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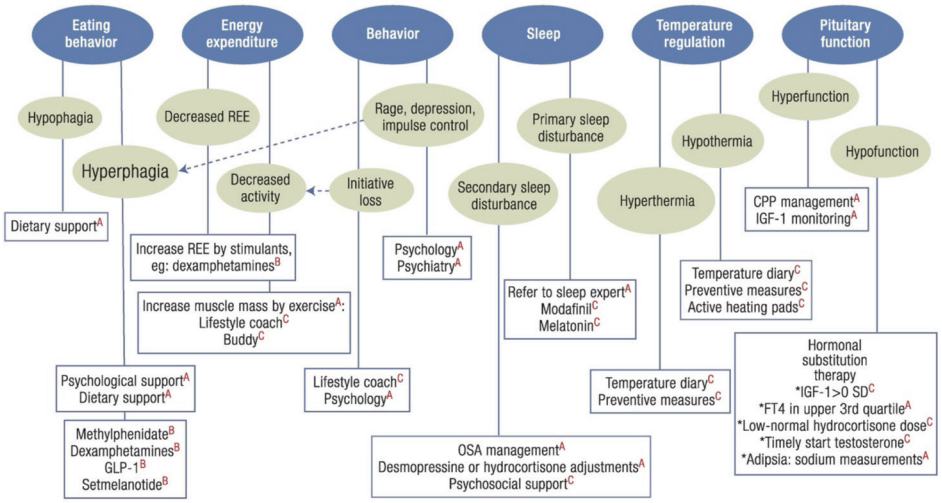

Current Approaches and Therapeutic Strategies for Hypothalamic Syndrome in Patients with Childhood-onset Craniopharyngioma

Hermann L. Müller.

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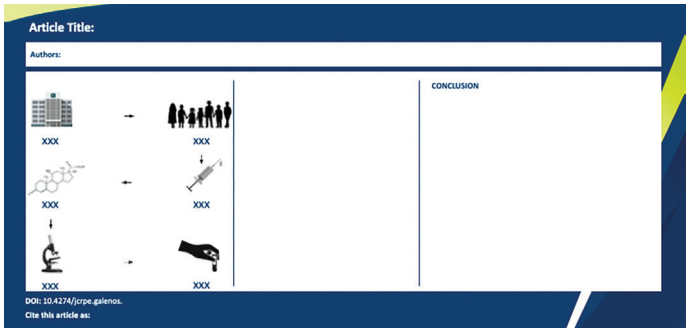

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Current Approaches and Therapeutic Strategies for Hypothalamic Syndrome in Patients with Childhood-onset Craniopharyngioma

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ABSTRACT

Patients diagnosed with craniopharyngioma often experience rapid and pronounced weight gain that can progress to severe hypothalamic obesity. This phenomenon is predominantly attributed to disruption of critical hypothalamic regulatory circuits, caused either by direct tumor infiltration or by treatment-related injury. Hypothalamic obesity is best conceptualized within the broader framework of hypothalamic syndrome, a complex clinical disorder encompassing multiple neuroendocrine deficits, impairments in circadian homeostasis, dysregulation of hunger, satiety, and thirst mechanisms, disturbances in thermoregulatory control, and a wide range of cognitive, sleep-related, and psychosocial abnormalities. Hypothalamic syndrome may also develop secondary to nonmalignant parasellar pathologies, including germ cell tumors, gliomas, Rathke's cleft cyst, and Langerhans cell histiocytosis, as well as traumatic hypothalamic injury following traumatic brain insult. Long-term prognosis is frequently poor, driven by elevated risks of metabolic syndrome, cardiovascular disease, diminished health-related quality of life, and increased rates of premature mortality. Management remains particularly challenging. Recently, a personalized and risk-stratified therapeutic framework has been proposed to guide clinical decision-making and optimize outcomes. Several pharmacologic interventions, such as centrally acting stimulants, glucagon-like peptide-1 receptor agonists, and the melanocortin-4 receptor agonist setmelanotide, have demonstrated potential in promoting weight reduction. Bariatric surgery may also yield clinical benefit; however, the use of irreversible procedures in pediatric populations presents substantial ethical and legal challenges. There remains an urgent need for therapeutic strategies that emphasize preservation of hypothalamic structure and function, alongside continued research into targeted and emerging interventions for more effective management of hypothalamic syndrome.

Keywords: Craniopharyngioma, obesity, metabolic syndrome, quality of life, hypothalamus, sequelae

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Introduction

Craniopharyngiomas (CPs) (1) are embryonic neoplasms exhibiting low-grade histological malignancy. Their annual incidence is estimated at 0.5-2.0 newly diagnosed cases per million individuals (2,3). In the 2021 World Health Organization classification of central nervous system tumors, adamantinomatous CP (aCP) and papillary CP (pCP) were formally designated as two distinct pathological subtypes (4). aCP predominantly occur in children and adolescents, whereas pCP almost exclusively arise in adults. Long-term prognosis is frequently compromised by tumor- and/or treatment-related injury to hypothalamic structures, which may lead to hypothalamic syndrome. Consequently, CP represents a prototypical disorder underlying hypothalamic dysfunction.

Molecular Pathology

In aCP, activating mutations in *CTNNB1* induce β-catenin accumulation and pathological activation of the WNT signaling cascade. Conversely, pCP is driven by the *BRAF*-V600E mutation, resulting in constitutive MAPK/ERK pathway activation. Recent evidence supports a senescence-mediated pathogenic mechanism in aCP. Senescent epithelial cells secrete pro-inflammatory and trophic factors [the senescence-associated secretory phenotype (SASP)], generating a tumor-supportive microenvironment through paracrine activity. Translational advances have facilitated the clinical application of BRAF/MEK inhibition in pCP, with early studies demonstrating substantial therapeutic efficacy. In parallel, pharmacological strategies targeting SASP mediators or selectively eliminating senescent cells (senolytic therapies) are under investigation for aCP (5).

Morbidity and Mortality

Patients with CP experience overall mortality rates that are three- to fivefold higher than those in the general population (6). Reported survival in pediatric cohorts ranges from 83% to 96% at 5 years (7), 65% to 100% at 10 years (8), and averages approximately 62% at 20 years of follow-up. While some studies suggest that younger patients demonstrate superior long-term survival, others indicate more favorable outcomes in older individuals. Findings regarding sex differences remain inconsistent: several reports describe increased mortality in female patients (6), whereas others observed no significant sex-related disparities. Late mortality is frequently linked to tumor- or treatment-related complications, including disease progression or recurrence, persistent hypothalamic dysfunction, endocrine insufficiencies, seizures, cerebrovascular events, and metabolic consequences, such as nonalcoholic fatty liver disease, which may evolve into cirrhosis (8,9). A recent review emphasized substantial long-term morbidity, citing standardized overall mortality ratios between 2.88 and 9.28. Cardiovascular mortality was 3- to 19-fold higher in CP patients than in the general population, with the highest risk observed in female patients (10). In childhood-onset (CO) CP, better baseline performance status has been associated with improved 10-year survival. The prognostic relevance of hydrocephalus at diagnosis remains debated (11). Importantly, Sterkenburg et al. (12) reported significantly reduced 20-year survival among patients with hypothalamic involvement and hypothalamic obesity. Conversely, the extent of surgical resection did not influence 20-year progression-free survival, reinforcing the view that aggressive gross-total resection does not confer a survival benefit with respect to preventing tumor recurrence in this population.

Hypothalamus and Hypothalamic Syndrome

The hypothalamus is a small yet phylogenetically conserved neuroendocrine center composed of multiple nuclei that coordinate essential physiological processes. It acts as a central integrator, governing pituitary hormonal output and influencing the autonomic nervous system, as well as modulating behavior through connections with other brain regions, including the frontal cortex. Hypothalamic disruption can produce a broad clinical phenotype encompassing (morbid) obesity (13), cachexia (14), hypopituitarism, adipsia, dysregulation of thermoregulation and circadian rhythms (15,16), reduced energy expenditure (17), and behavioral abnormalities (18).

The term hypothalamic syndrome refers to the constellation of symptoms arising from structural or functional compromise of hypothalamic nuclei. Although CPs constitute a leading cause, other etiologies include germ cell tumors, gliomas, Rathke's cleft cysts, Langerhans cell histiocytosis, and specific neurodevelopmental disorders such as Prader-Willi syndrome (PWS) and septo-optic dysplasia, as well as traumatic brain injury (19). Importantly, hypothalamic syndrome encompasses a broader construct than hypothalamic obesity alone and varies considerably between individuals. According to van Santen et al. (20), five major clinical domains characterize hypothalamic syndrome in CO CP: disordered eating, behavioral abnormalities, sleep disturbances, thermoregulatory dysfunction, and endocrine impairments.

Management of Hypothalamic Syndrome

An individualized management approach for CO CP patients with hypothalamic syndrome was initially proposed by van Iersel et al. (21). A recent update shifts emphasis from isolated obesity treatment to addressing the full spectrum of hypothalamic dysfunction (22,23) (Figure 1). This more comprehensive framework aims to improve not only body mass index (BMI) but also overall vitality and daily functioning. Findings by van Schaik et al. (26) underscore the benefits of centralized care (24,25): following national centralization of CP treatment in the Netherlands, the incidence of hypothalamic obesity in children with CP fell from 33% to 12%.

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Hypothalamic and Pituitary Function

Hypothalamic nuclei exert regulatory control over the pituitary gland by producing releasing hormones. Damage to hypothalamic structures may therefore lead to multiple pituitary hormone deficiencies, including hypogonadotropic hypogonadism, growth hormone (GH) deficiency, central hypothyroidism, and adrenocorticotropic hormone (ACTH) deficiency. In addition, the hypothalamus secrets arginine vasopressin (AVP), which is stored and released from the posterior pituitary gland.

GH Deficiency

Insufficient endocrine replacement therapy can result in severe consequences, such as impaired growth (27). GH replacement in patients with confirmed GH deficiency does not increase the risk of CP recurrence or progression (28). Unlike malignant tumors, no mandatory waiting period is required between completion of oncological therapy and initiation of GH treatment in CP. Early GH replacement may assist with weight regulation and improve quality of life (QoL) (29). A recent consensus statement from the Growth Hormone Research Society concluded that GH therapy is safe in CP (28). Although GH does not correct hypothalamic obesity, it supports healthier body composition and reduces metabolic complications (29).

Adrenocorticotropin Deficiency

ACTH deficiency, typically resulting from tumor-associated damage or therapeutic interventions, necessitates hydrocortisone replacement with stress-adjusted dosing. Cortisol deficiency may clinically present with headaches, nausea, or reduced stress tolerance, and can progress to life-threatening adrenal crisis. Excessive glucocorticoid administration increases obesity risk. While perioperative corticosteroid therapy may cause short-term weight gain, it has not been linked to long-term obesity (30). Physiological dosing of hydrocortisone substitution should not elevate obesity risk.

Hypothyroidism

Central hypothyroidism may be overlooked if free thyroxine (T4) levels remain in the lower half of the reference interval. A reduction of >20% in free T4 should prompt suspicion and consideration of levothyroxine therapy (31). Replacement should maintain free T4 concentrations in the mid-to-upper reference

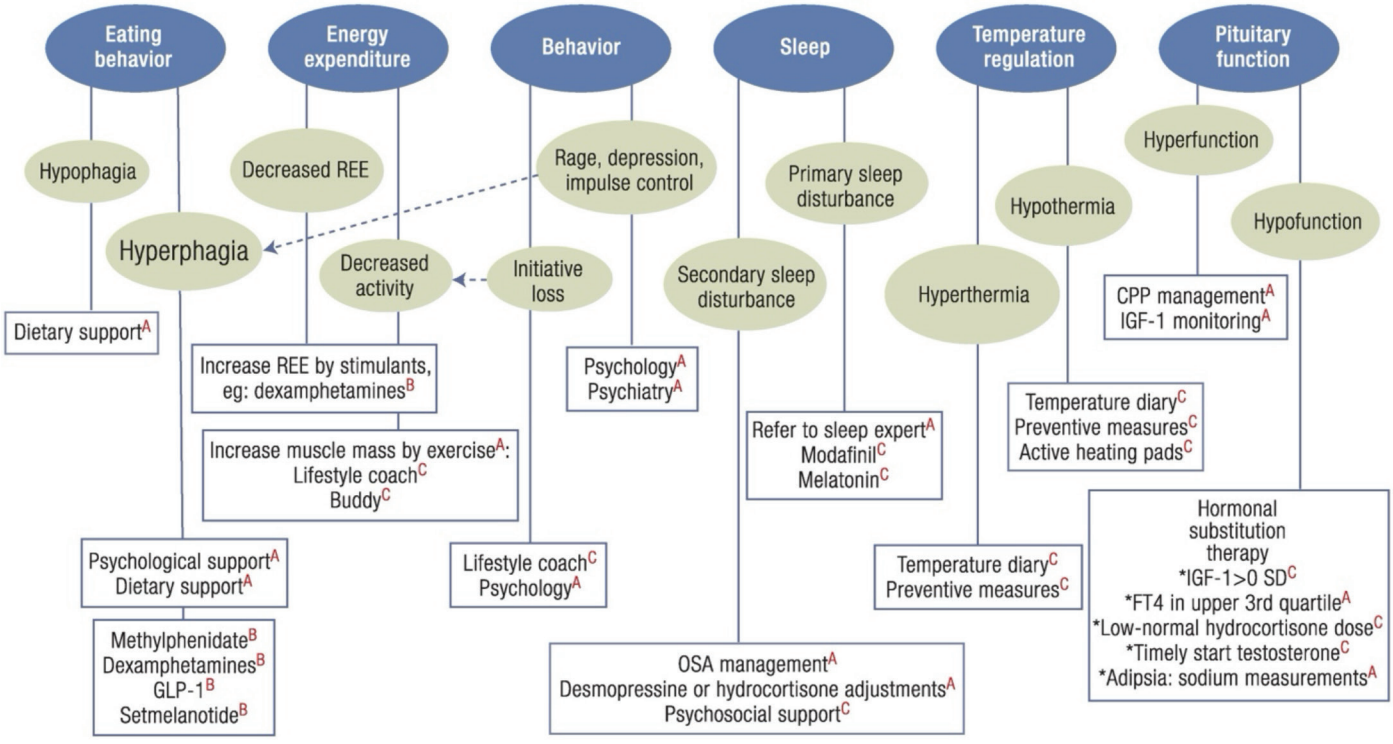

Figure 1. Algorithm for the management of (acquired) hypothalamic dysfunction. Hypothalamic dysfunction may lead to different signs and symptoms that may all contribute to the development of hypothalamic overweight or obesity and feelings of fatigue. By evaluating all 6 different clinical domains of hypothalamic dysfunction, with a step wise approach, a personalized approach is enabled improving feelings of fatigue and decreasing obesity. Suggested interventions are categorized as existing guidelines A, clinical trial or case series data B, and expert opinion C. (Reproduced from van Santen and Müller, Endocr Rev, 2025 (22), with kind permission of Illustration Presentation ENDOCRINE SOCIETY).

CPP, central precocious puberty; OSA, obstructive sleep apnea; REE, resting energy expenditure

range. Insufficient replacement may contribute to weight gain, emphasizing the need for optimal dosing.

Gonadotropin Deficiency

Gonadotropin deficiency often requires induction of puberty and, in some cases, assisted reproductive techniques (32). Adults treated for CP in childhood show high rates of psychosexual dysfunction and reduced sexual activity (32). In males, low testosterone is associated with adverse metabolic profiles and increased mortality risk. Adequate testosterone replacement can improve body composition through reduction of fat mass and increase in lean mass.

Oxytocin

Oxytocin deficiency in CP arises primarily from hypothalamic injury, contributing to hypothalamic syndrome. Compared with healthy individuals, CP patients show reduced basal and stimulated salivary oxytocin levels (33,34,35,36). Lower levels correlate with increased anxiety and impaired social cognition. Individuals with anterior hypothalamic lesions exhibit the lowest oxytocin concentrations and respond most favorably to single-dose intranasal oxytocin compared with patients with posterior lesions or healthy controls (34,35). These data indicate potential for oxytocin-based interventions to treat neuropsychological symptoms of hypothalamic syndrome (37).

AVP Deficiency (AVP-D)

AVP-D commonly results from posterior hypothalamic injury and predisposes to hypothalamic obesity. It therefore serves both as a marker of hypothalamic damage and an independent risk factor for obesity and reduced QoL (38). When thirst regulation is also impaired, adipsic AVP-D may occur, carrying substantial risk for sodium imbalance and systemic instability.

Sleep Disorders

Children with CP and hypothalamic syndrome may develop primary hypothalamic sleep disturbances, including hypersomnia (15), narcolepsy (39) and circadian rhythm dysregulation (16). Secondary sleep problems can arise from tumor therapy, severe obesity, or visual impairment. These include psychosocial stressors, obstructive sleep apnea, poorly controlled AVP-D with nocturia, and other comorbidities. Sleep-wake disruption and circadian disturbances are hallmark manifestations of hypothalamic syndrome (40). Hypersomnia is defined by excessive daytime sleepiness (EDS) despite adequate nighttime sleep. Affected individuals often struggle to remain awake during daily activities (40). In a cohort of 115 CO CP patients, Müller et al. (39) reported EDS in 30% of cases, including hypersomnia and secondary narcolepsy. Central stimulants such as modafinil or methylphenidate improved alertness and daily functioning (39).

Temperature Regulation

Thermoregulation is governed by interconnected hypothalamic circuits, including the arcuate nucleus (thermogenesis), the preoptic area-dorsomedial hypothalamic circuit (temperature sensing), and the ventromedial hypothalamus (cold-induced thermogenesis) (41). Hypothalamic injury can impair these pathways, resulting in hypothermia (<36 °C) or hyperthermia (>37.5 °C) (42,43). Some patients maintain normal core temperatures but experience subjective thermal dysregulation. Management is largely supportive: external warming for hypothermia and light clothing for hyperthermia. Hydrocortisone stress dosing should be considered when temperatures fall below 35.5 °C or exceed 38 °C.

Behavioral Problems

As the hypothalamus is tightly connected to limbic structures, hypothalamic dysfunction may cause diverse neurobehavioral abnormalities. Anxiety disorders are common, potentially due to perturbations of the Papez circuit (44), and memory impairments may also occur (18,45). Lesions involving the nucleus accumbens have been associated with addictive behaviors, obsessive tendencies, hoarding, and compulsive eating (18). Combined with disrupted satiety signaling, these alterations contribute to severe obesity (20,46). Cognitive dysfunction may also be present (47).

Neurocognitive Outcome

Studies of childhood CP survivors reveal wide variability in psychosocial and physical outcomes ranging from excellent functioning in most patients to significant impairment in nearly half (8,48,49,50). Social and emotional functioning are frequently affected, with many patients rating psychosocial health lower than physical well-being (8). Challenges include learning difficulties, emotional dysregulation, peer relationship problems, and body-image concerns (51,52). Worse outcomes are associated with preoperative impairment, younger age at CP diagnosis, hypothalamic involvement, larger tumors, and certain treatment strategies. Surgery alone yields poorer results than limited resection followed by radiotherapy; repeated surgeries also worsen long-term outcomes. Endocrine, neurological, and ophthalmological sequelae further diminish QoL (8,48). Hypothalamic dysfunction exerts the greatest negative effect on social functioning, physical capacity, and body image (7,8,48).

Long-term survivors frequently experience cognitive deficits, particularly in episodic memory, executive functions, and attention (8,51,52). Ozyurt et al. (53) demonstrated that hypothalamic injury disrupted medial prefrontal cortex mechanisms during memory retrieval, indicating reduced executive control efficiency. Incomplete tumor resection followed by radiotherapy was associated with psychological and educational difficulties (52). Although most patients retain

normal overall intelligence, visual memory is frequently impaired despite preserved visuospatial skills (51,52). Early deficits in attention often predict poor academic performance.

Psychosocial Functioning

At a median follow-up age of 29 years, adults with CO CP reported similar psychosomatic and emotional well-being when compared to controls (54). Social interaction scores were comparable, though social integration appeared less adequate in patients. Educational attainment was slightly lower in the CP group, and employment rates were reduced (48% vs 62%), although unemployment benefits were similar. Notably, 14% of CP survivors, but none of the controls, were on long-term sick leave or disability pension. Dekkers et al. (55) reported reduced QoL in a mixed adult- and CO cohort with a mean follow-up of 20 years. Greater QoL impairment in adults may reflect a heightened sense of loss when diagnosis occurs later in life. In children, Müller et al. (49) found reduced QoL at 4.5 years post-diagnosis, particularly in those with hypothalamic involvement (Table 1). Some studies suggest that outcomes improve over time due to psychological adaptation. However, CO CP survivors with hypothalamic damage consistently report reduced satisfaction with social participation and overall health, alongside lower educational and employment attainment, and constitute all cases receiving disability pension or long-term sick leave (54).

Despite extensive documentation of neurocognitive and psychosocial difficulties in CP survivors, targeted interventions remain scarce. Recent case studies have piloted cognitive rehabilitation for executive dysfunction and behavioral instability (56). One program combining goal-management therapy with structured workplace tasks yielded improvements in tasks requiring organization. Additional behavioral difficulties, including aggression, are common (8). In some individuals, behavioral analysis followed by reinforcement strategies and extinction techniques reduced aggressive

Table 1. Health-related quality of life after craniopharyngioma. Selected publications (2019-2025). Modified from Müller HL, 2025, biomedicines (1) with kind permission of mdpi

Diagnosis	Pat. no.	Age at cranio-pharyngioma diagnosis (years)	Follow-up interval (years)	Treatment	Quality of life/outcome	Authors/year of publication
CO CP with presurgical grade 2 HI	109	Median 9.5 (range: 1.3-17.9)	Mean 6.1 (range: 3.0-10.2)	Surgery leading to 23 grade 0 HL 29 grade 1 HL 57 grade 2 HL	Worse PEDQOL for grade 3 patients in terms of physical, social and emotional functionality when compared with HL grade 0 and 1.	Bogusz et al. (95), 2019
CO CP	131	Median 9.7 (range: 1.3-17.6)	3 years	21 (18%) complete resection; 94 (82%) incomplete resection	Grade 2 HI, grade 2 HL and complete surgical resection were associated with low QoL.	Eveslage et al. (94), 2019
Hypothalamic dysfunction + CO CP	290	n.a.	n. a.	n. a.	Worldwide online survey: Obesity (51%) and fatigue (48%). Needs for improvement in the domains of obesity, fatigue and lifestyle.	Van Roessel et al. (99), 2020
CO CP	78	Mean: 10.8±3.11 SD	n. a.	56 surgical resections 16 catheter implantations	Poorer parental-reported QoL; AVP-D directly predicted greater global executive functioning impairment.	Niel et al. (100), 2021
Caregivers of CO CP patients	106	<18 years	n. a.	48 RT 134 surgical interventions	Online survey: reduced social functioning.	Craven et al. (101), 2022
CO CP	48	GTR: Median 6.4 (range: 2.2-16.8) PR+RT: Median 8.5 (range: 3.8-16.4)	10 years	21 GTR, 22 PR+RT	No differences in the trajectory of intellectual functioning or QoL scale scores between the two groups (GTR vs. PR + RT).	Aldave et al. (102), 2023
Caregivers of CO CP patients	82	Mean 9.3±4.5 SD	Duration of caregiving: mean 7.4 (SD: 6.0), median: 5.5, (range: <1-28) years	52.4 % GTR	Survivor poly-symptomatology predicted caregiver burden. The study separated hyperphagia and obesity and identified hyperphagia and other hypothalamic dysfunction symptoms as understudied issues.	Kayadjanian et al. (103), 2023

Table 1. Continued

Diagnosis	Pat. no.	Age at cranio-pharyngioma diagnosis (years)	Follow-up interval (years)	Treatment	Quality of life/outcome	Authors/year of publication
CO CP and parents/ caregivers	120	Median 10.0 (range: 1.3 -16.8)	3 years	25 complete resections 95 incomplete resections 61 RT	Reduced autonomy was found three years after diagnosis in self-assessments and parental assessments of QoL (PedQol).	Sowithayasakul et al. (104), 2023
CO CP with RT	99	Median 9.5 (range: 1.6-17.9)	Median 6.4 (range: 0.9-14.7)	64 PBT 35 photon-based RT	No significant difference between PBT and photon-based RT in terms of QoL (PedQol), functional capacity (FMH), and body mass index.	Friedrich et al. (105), 2023
CO CP	87	Mean 7.39±3.67 SD	Median 6.54 (IQR: 3.11-10.69)	25% complete resection 44% incomplete resection 30% cyst drainage 46% RT	BMI at diagnosis and grade of HL were associated with hypothalamic obesity.	Van Schaik et al. (26), 2023
CO CP	709	< 2 years: 3% 2-5 years: 16% 56-11 years: 46% 12-18 years: 35%	Median 8.37 (range, 0.04 to 38.87)	33% RT: 35% PBT; 46% photon-based 27% GTR	BMI>3SD in 45%; risk factor for obesity: HI and HL Patients <2yrs at dgx: low functional capacity (FMH); Patients >12 yrs at dgx: low QoL (PedQol); Lower EFS in younger age groups	Beckhaus et al. (57), 2023
AO CP: 90% CO CP: 10%	109	Median 40.0 (range: 28.5-56.0)	Median 10.0 (range: 2.5-24.0)	25.6%: surgery 4.6%: RT	SF-36: impaired QoL compared with general population. MCS, GAD7, PHQ9: adverse effect of AVP-D in multivariate linear regression. AVP-D risk factor for developing depressive symptoms.	Lin et al. (38), 2024
CO CP from a lower-middle-income country	29	Mean 13.5±4.2 SD	Mean: 4.4±2.2 SD	15 GTR 11 Debulking 3 Reservoir and biopsy	PedsQL: GTR 56.6±7.12 Debulking: 93.8±3.37 Biopsy: 83.3±5.69	Baqai et al. (106), 2024
CO OP	92	Mean 10.5±4.0 SD	n. a.	PBT after surgical intervention	Fatigue, QoL, and brain tumor symptoms improved over time during proton beam therapy.	Mandrell et al. (107), 2024
CO CP	11	Median 15.2 years (IQR: 9.7-17.9)	Mean 5.3±3.2 (SD)	73% surgery 82% RT	PEDS-QL4.0: Worse QoL in global, physical, emotional, and psychosocial dimensions linked to HI. Irradiated patients had worse global QoL.	Pereira Neto et al. (108) 2024
CO CP	66	Median 5 (IQR: 3-8)	Median 7.4 (IQR: 2.8-9.7).	100% surgery 44% RT 24% intracystic therapy	PedsQL: QoL was impaired by repeated surgeries, RT, and longer follow-up interval.	Perez-Torres et al. (109) 2024
CO CP	119	Median 12 (range: 2-17)	Mean 10 (range: 1-39)	CR in 34 (29%) 6 HL grade 0 23 HL grade 1 55 HL grade 2	QoL (EORTC QLQ-C30) was negatively correlated with daytime sleepiness (ESS), highest ESS in patients with HL grade 2.	Mann-Markutzyk et al. (15), 2025
CO CP with PBT	47	Median 9.7 (range: 2.4-22.1)	Median 11.2 (range: 1.3-17.3)	55% surgery 100% RT (PBT)	PedsQL: PPR and CSR TCS lower than normal controls at last follow-up, and lower in patients with AVP-D, sex hormone deficiency, and hyperphagia	Rose et al. (110) 2025

AO CP, adult-onset craniopharyngioma; CO CP, childhood-onset craniopharyngioma; QoL, quality of life; GTR, gross total resection; HI, presurgical hypothalamic involvement; HL, surgical hypothalamic lesions; PR, partial resection; RT, radiotherapy; PBT, proton beam therapy; dgn, diagnosis; AVP-D, arginine vasopressin deficiency; n. a., data not available; IQR, interquartile ratio; SD, standard deviation; ESS, Epworth Sleepiness Scale; pat, patients; FMH, functional ability scale Münster Heidelberg; GAD7, Generalized Anxiety Disorder Questionnaire scale; PHQ9, Patient Health Questionnaire Depression; SF-36, Short Form 36; PEDS-QL4.0., Pediatric Quality of Life Inventory; PPR, parent-proxy reports; CSR, Child-self report; TCS, total core scores

episodes by >88% and increased adaptive behaviors (56). These observations indicate that structured rehabilitation may enable survivors of CO CP to develop compensatory strategies for neurocognitive and psychosocial deficits.

Quality of Life

Beckhaus et al. (57) analyzed the largest cohort reported to date (n=709) of individuals with CO CP, assessing clinical features at presentation and long-term outcomes including QoL. The study specifically examined whether age at diagnosis affected disease characteristics, therapeutic management, and prognosis. At final follow-up, severe obesity [BMI >3 standard deviation score (SDS)] was documented in 45.4% of patients. Posterior hypothalamic involvement and structural hypothalamic damage were identified as independent predictors of both reduced event-free survival and the presence of obesity at follow-up. Although overall survival did not vary by age at diagnosis, younger age (<12 years) was associated with an increased risk of disease progression and recurrence. Notably, children diagnosed before 6 years of age demonstrated lower event-free survival but reported higher QoL compared with those diagnosed at ≥6 years. Lower functional capacity percentiles were associated with higher BMI SDS at final assessment and with diagnosis before 2 years of age. These observations suggest that differences in management strategies such as the timing or modality of radiotherapy or intrinsic tumor biology may account for age-related outcome variability. Despite these disparities, overall survival remained comparable across age groups, implying that re-irradiation and surgical reintervention were effective in controlling tumor recurrence or progression. Functional capacity, reflecting performance in daily activities, differed substantially between age subgroups, with younger age at diagnosis predicting poorer long-term functional outcomes. Paradoxically, QoL scores based on both patient and parent reports were less favorable among those diagnosed at an older age, particularly regarding body image. Developmental factors may help explain this finding. In very young children, neurological and endocrine impairments heavily shape overall development. Conversely, older children and adolescents, whose brain maturation is more advanced, may experience fewer disruptions to developmental trajectories but are more capable of perceiving and evaluating changes in QoL compared with their pre-diagnosis baseline. Consequently, adolescents may be more sensitive to alterations in body image. Body shape and appearance constitute central determinants of QoL in adolescence.

Energy Balance

Energy homeostasis is maintained through the dynamic interaction between energy intake and energy expenditure, orchestrated by hypothalamic nuclei that integrate central and peripheral signals within complex neural circuits (21,41). Energy intake is regulated by three principal processes: initiation of eating, cessation of eating, and food selection. The hypothalamus modulates these processes via orexigenic mediators such as orexin A/B, ghrelin, and neuropeptide Y and anorexigenic mediators, including adiponectin, leptin, brain-derived neurotrophic factor, and insulin. While gastrointestinal satiety signals contribute to terminating meals, food preference is influenced by the mesolimbic reward system and by prefrontal-amygdala networks that interact with hypothalamic centers. Energy expenditure consists of resting metabolic rate (60-75%), activity-related thermogenesis (~20%), and diet-induced thermogenesis (10-15%), all of which are modulated by sympathetic nervous system activity under hypothalamic regulation. Damage to the hypothalamus may disrupt parasympathetic control, leading to hyperinsulinemia and promoting adipose tissue deposition, thereby increasing the risk of obesity. The extent and nature of hypothalamic impairment depend on factors such as age at onset, tumor-related characteristics, and comorbidities, and may affect endocrine axes, neuroendocrine pathways, or inter-regional neural connections to varying degrees.

A key pathway in appetite control is the melanocortin system. Following food intake, leptin binds to its receptors on pro-opiomelanocortin neurons, stimulating the release of α- and β-melanocyte-stimulating hormones (α/β-MSH). These peptides activate melanocortin-4 receptors (MC4R), increasing satiety and energy expenditure. Disruption of this system contributes to hyperphagia and obesity (58). In addition, hypothalamic efferent pathways regulate sympathetic outflow, thereby influencing energy expenditure. Among 67 children with hypothalamic syndrome, 67.2% demonstrated a measured resting energy expenditure (mREE) below 90% of predicted REE (pREE) values, with the lowest mREE/pREE ratios observed in patients with severe or posterior hypothalamic injury, corresponding to higher rates of hypothalamic obesity (59). REE is also closely associated with muscle mass, which is metabolically more active than fat mass. Physical activity increases REE both directly, through muscle hypertrophy, and indirectly, via enhanced thermogenesis. In contrast, children with hypothalamic obesity typically exhibit reduced muscle mass due to low activity levels.

Physical Activity and Energy Expenditure

Accelerometry studies show that patients with CO CP engage in substantially less physical activity than BMI-matched controls (13). Reduced activity levels persist into adulthood (17). Patients report diminished participation in recreational physical activity year-round, and pedometer data corroborate lower daily step counts compared with healthy individuals. Severe hypothalamic obesity is commonly accompanied by EDS (60). CP survivors also exhibit reduced morning and nighttime salivary melatonin levels, which correlate with daytime somnolence

and hypothalamic obesity. Melatonin supplementation (6 mg/day) can normalize melatonin profiles and transiently improve sleepiness and activity, though long-term benefit remains uncertain (61). Polysomnographic assessments in CP patients with pronounced hypothalamic obesity frequently reveal hypersomnia or secondary narcolepsy, including frequent sleep-onset REM periods. In such cases, central stimulants (e.g., methylphenidate, modafinil) significantly ameliorate daytime sleepiness and enhance activity (39).

Management strategies should emphasize increasing REE, for example through structured physical training, testosterone therapy to augment muscle mass, and active warming when hypothermia is present. Optimization of endocrine replacement (GH, thyroid hormone) is also essential. Pharmacological measures, such as dexamphetamine, may be appropriate in selected patients to further elevate energy expenditure (62,63). Measurement of REE using ventilated-hood calorimetry offers clinically valuable insights into weight trajectories and informs individualized nutritional planning (59).

Hypothalamic Obesity and Disordered Eating

Under normal physiological conditions, satiety and body-weight regulation arise from a balanced interaction between anorexigenic and orexigenic signaling pathways. In hypothalamic obesity, this tightly coordinated network becomes impaired due to structural or functional disruption of key hypothalamic regions (58), resulting in dysregulated appetite control and inappropriate food intake (21). In patients with CP, increased parasympathetic activity mediated by heightened vagal tone contributes to hyperinsulinemia and persistent hunger, thereby promoting excessive weight gain (21). Concurrently, diminished sympathetic activity reduces total energy expenditure and lipolysis. Many individuals with hypothalamic obesity also exhibit reduced concentrations of α-MSH, a neuropeptide involved in driving energy expenditure.

A recently proposed consensus definition for acquired hypothalamic obesity (64) included the following diagnostic criteria:

- A traumatic event or oncologic disease resulting in hypothalamic damage detectable on magnetic resonance imaging;

- A rapid (within 12 months of surgery/diagnosis), persistent (for at least 24 months), and clinically significant increase in BMI (≥5% increase in adults; ≥1.0 SDS increase in children) beginning within 12 months after the onset of hypothalamic injury, with clinical and anthropometric monitoring at 3-month intervals;

- Development of obesity meeting defined thresholds (BMI SDS≥+2.0 SD in children; BMI≥25 kg/m^2 or ≥30 kg/m^2 in adults, with adjustment for racial and ethnic factors).

Long-term follow-up showed that approximately half of CO CP patients with hypothalamic lesions developed hypothalamic obesity (7,65). In a study by Rovani et al. (66), 54% of CP survivors were overweight or obese, with risk factors including female sex, hypothalamic involvement, and baseline BMI>+2 SDS. Beckhaus et al. (67) further demonstrated that familial susceptibility, reflected by elevated maternal and paternal BMI at the patient's time of diagnosis, was strongly associated with the development of severe hypothalamic obesity. In a mixed AO/CO cohort, the prevalence of excessive weight gain or hyperphagia increased from 39% at 10 years to 67% at 20 years post-diagnosis. Once severe obesity is established, weight reduction becomes extremely difficult (21) and many patients reach a high but stable BMI plateau (27). Currently, no uniformly effective therapy exists (58). Therapeutic efforts therefore focus on preventing hypothalamic injury through hypothalamus-sparing surgical techniques, precision radiation modalities (e.g., proton beam therapy), and emerging pharmacologic treatments specifically targeting hypothalamic obesity (5). In pCP harboring the *BRAF* V600E mutation, targeted therapy with BRAF inhibitors has also demonstrated encouraging results (68).

Hyperphagia

Hyperphagia in children with hypothalamic obesity may be profound, sometimes necessitating strict household controls to prevent food seeking and food theft. However, hyperphagia is not universally present in all affected individuals (43). When designing dietary interventions, it is important to recognize that hypothalamic dysfunction is typically lifelong rather than transient. A systematic review evaluating lifestyle and dietary interventions for hypothalamic obesity included 12 studies involving 118 patients with CP, monogenic obesity, PWS, or rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation syndrome. Four studies concluded that dietary interventions were feasible but reported multiple challenges. Among the seven studies assessing efficacy, both balanced hypocaloric diets (30% fat, 45% carbohydrates, 25% protein) and more stringent regimens (8-10 kcal/cm/day) were associated with stabilization or reduction of body weight (69).

Hypophagia

Although less common, hypophagia can also occur in individuals with hypothalamic dysfunction. In CO CP, anorexia or reduced intake is unusual but has been documented, especially in younger children. The German KRANIOPHARYNGEOM cohort reported that 11 of 485 patients initially presented with anorexia (14). In infants with PWS, atypical eating behavior has been linked to altered ghrelin acylation patterns. Management is primarily dietary. But given the potential transition from hypophagia to hyperphagia over time, continuous monitoring and timely intervention are crucial.

Treatment of Hypothalamic Obesity

Lifestyle Interventions

Lifestyle approaches have typically produced only short-term reductions in BMI, indicating that sustained weight control requires long-term, structured behavioral support (Table 2). A stable and supportive home environment is essential, particularly given the persistent combination of hyperphagia, pituitary hormonal deficits, and behavioral challenges (70). Data from the German KRANIOPHARYNGEOM cohort (n=291) showed that BMI at final follow-up strongly correlated with maternal and paternal BMI at diagnosis (67) underscoring the need for family-centered obesity management. Engaging caregivers and family members is therefore critical to achieving durable therapeutic outcomes.

Antidiabetic Medications

Multiple antidiabetic agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, diazoxide, fenofibrate, pioglitazone, and various combination regimens (71) have demonstrated potential benefits in limiting weight gain and enhancing insulin sensitivity in individuals with hypothalamic obesity. Among these, metformin appears particularly advantageous when used alongside lifestyle modification, as it offers moderate weight stabilization with a generally favorable safety profile (72). Nevertheless, the long-term efficacy and safety of metformin specifically for hypothalamic obesity have not yet been fully characterized (73).

GLP-1 receptor agonists

A small study including 26 adults with hypothalamic obesity reported that all but one patient achieved weight reduction during semaglutide therapy, with an average weight loss of 13.4 kg and a corresponding BMI decrease of 4.4 kg/m^2 after one year (74). Consistent with these findings, a systematic review of 10 studies concluded that GLP-1 receptor agonists may represent a safe and effective intervention for weight management in this population (75). Despite encouraging results, the therapeutic effect of GLP-1 receptor agonists in adults with hypothalamic obesity remains under discussion. Several investigations have documented improved glycemic control and reductions in food intake (75,76), yet Shoemaker et al. (76) observed an unexpected decline in total energy expenditure following weekly exenatide administration, out of proportion to weight loss and unrelated to physical activity or leptin levels. Conversely, Perez et al. (77) reported that individuals with more extensive hypothalamic injury experienced greater adiposity reductions under the same exenatide dose. The GLP-1 analogue liraglutide, approved for long-term management of general obesity, has been used in adults with CP-related hypothalamic obesity, leading to weight reductions of 9-22 kg (78). Semaglutide is similarly approved

Table 2. Therapeutic approaches for treating acquired hypothalamic obesity and effects on weight development/obesity. Modified from Müller HL, biomedicines, 2025 (1), with kind permission of mdpi

	Intervention	#	Age (years)	BMI/weight at intervention	BMI/weight change during / after intervention	Authors/year of publication
Pharmacological agent	Dextroamphetamine	19	12.3±4.0	BMI 3.58±0.85 SD	ΔBMI SDS -0.14	van Schaik et al. (63), 2022
	Dextroamphetamine	7	0.5, 11.1, 11.8, 12.5, 14.7, 14.8, 21.0	BMI +3.17±0.9 SD Range: +1.9 to +4.4 SD	Mean BMI SDS decelerated to -0.18±0.12/year during the 1st year of treatment and stabilized at +0.05±0.32/year during the 2nd year of treatment.	Denzer et al. (62), 2019
	Diazoxide/metformin	9	15.4±2.9	BMI +1.8-+2.96 SD	ΔBMI -0.3±2.3 kg/m^2	Hamilton et al. (111), 2011
	Octreotide (RCT)	10	13.8±1.2	BMI 37.1±1.3 kg/m^2	ΔBMI -0.2±0.2 kg/m^2 (*vs* placebo +2.2±0.5 kg/m^2)	Lustig et al. (89), 2003
	Semaglutide	26	52 (18-65)	BMI 38 (28-58) kg/m^2	Mean TWL 13.4 kg (95% CI 10.3-16.5 kg)	Svendstrup et al. (74), 2024
	Semaglutide	4	22, 44, 57, 69	BMI 48.0 (35.0-55.5) kg/m^2	ΔBMI 7.9 BMI (6.7-10.1); weight loss of 17.0% (11.3-22.4%)	Gjersdal et al. (112), 2024
	Exenatide / liraglutide	9	46 (22-49)	BMI 37.6±7.2 kg/m^2	Exenatide: ΔBMI -6.1 to -2.8 kg/m^2; liraglutide: Δweight -22 to -9 kg	Zoicas et al. (78), 2013
	Exenatide	8	27.5±7.8	BMI 47.5±10.8 kg/m^2	Mean Δweight -1.4 kg	Lomenick et al. (113), 2016
	Tesomet (tesofensine and metoprolol)	18	45.4±13.3	BMI 37.3±5.6 kg/m^2	Δweight: -6.3% (tesomet -6.6% vs. placebo -0.3%)	Huynh et al. (88), 2022

Table 2. Continued

	Intervention	#	Age (years)	BMI/weight at intervention	BMI/weight change during / after intervention	Authors/year of publication
	Setmelanotide	18	15.0±5.3	BMI 38·0±6·5 kg/m^2	ΔBMI: -15% (SDS 10%) after 4 mo; Extension 12 mo (12 patients): -26% (12 SDS)	Roth et al. (81), 2024
	Setmelanotide	120	19.9 (4 - 66)	≥18 years: BMI 41.2 (95% CI: 38.4 - 44.0 kg/m^2; <18 years: BMI Z score 3.61 SDS (95% CI: 3.21-4.00SD).	RCT: mean BMI reduction of 16.5% after 52 weeks in the treatment group (n=81), compared to a 3.3% increase in the placebo group (n=39). Good tolerability: adverse events leading to treatment discontinuation in 7.4% (setmelanotide) and 7.7% (placebo)	Roth et al. (86), 2025
Lifestyle modification	Regular visits at a comprehensive care clinic	39	13.4 (4.3-18.2)	BMI 1.93 (0-3.2) SD	Median ΔBMI rate +4.5 kg/m^2/y (-17.8 to+8.4); Median ΔBMI SDS rate 0.0/y (-5.2 to +0.5)	Rakhshani et al. (114), 2010
Bariatric surgery	SG (n=3); RYGB (n=5)	8	33.4±13.6	BMI 43.3 ± 4.1 kg/m^2	SG (n=3): mean Δweight -10%; RYGB (n=5): mean Δweight -25%	Wijnen et al. (115), 2017
	LAGB (n=4)	4	13, 17, 21, 23	BMI +7.3-+12.3 SD	ΔBMI +1.7 to +8.7 kg/m^2	Müller et al. (116,117) 2007, 2011
	SG (n=2); RYGB (n=2)	4	24, 30, 43, 51	BMI 37.6, 37.7, 43.7, 51.0 kg/m^2	ΔBMI: SG -10, -3.6; RYGB: -6.2, +11.3 kg/m^2	Gatta et al. (118), 2013
	LAGB (n=6); SG (n=4); RYGB (n=2)	9	17 (12-30)	BMI 44.7 (40.2-61.6) kg/m^2	LAGB: no change; SG: no change; RYGB: mean Δweight -30%	Weismann et al. (119), 2013
	LAGB (n = 6); SG (n = 8); RYGB (n = 6); BPD (n = 1)	21	24 (12-54)	BMI 49.6 kg/m^2	TWL (%) LAGB: 10.5%; SG: 20.7%; RYGB: 20.2%; BPD: 24.8%	Bretault et al. (91), 2013
	SG	3	21, 22, 24	BMI 49.2 (41.6-58.1) kg/m^2	Mean ΔBMI -13.9 kg/m^2; Δweight -17.6%, -25.0%, -41.1%	Trotta et al. (120), 2017
	SG (n=2), RYGB (n=3)	5	38 (27-47)	BMI 41.3 (37.9-46.3) kg/m^2	ΔTWL (%) -14.7% (23.7; 5.8)	Garrez et al. (121), 2020
	RYGB (n=12), SG (n=4)	16	26±12	BMI 46±8 kg/m^2	Mean Δweight: -22% after 5 years	van Santen et al. (122), 2021
	SG (39%), RYGB (61%)	23	35 (25-43)	BMI 44.2 (40.7-51.0) kg/m^2	ΔTWL (%) - 39.0% (14.0; 53.3)	Faucher et al. (123), 2022
Vagotomy	Truncal vagotomy	1	19	BMI 43.0 kg/m^2	Δweight -7.0 kg	Smit et al. (124), 1983
DBS	Nucleus accumbens DBS	1	19	BMI 52.9 kg/m^2	ΔBMI -5.2 kg/m^2	Harat et al. (125), 2016

#, patient number; TWL, total weight loss; BMI, body mass index; SDS, standard deviation score; LAGB, laparoscopic adjusted gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; DBS, deep brain stimulation; RCT, randomized controlled trial; n. a., data not available.

for obesity treatment in adolescents, achieving a median BMI reduction of approximately 17%. Early evidence suggests that semaglutide and exenatide may hold therapeutic value for weight control in hypothalamic obesity (79).

Setmelanotide

Setmelanotide, a MC4R agonist, has shown marked effectiveness in children with monogenic obesity syndromes such as Bardet-Biedl syndrome. Originally developed for congenital hypothalamic obesity caused by proopiomelanocortin or leptin receptor deficiency (80), setmelanotide activates remaining MC4R-expressing neurons within the hypothalamus. Impairment of this pathway leads to profound hyperphagia and subsequent hypothalamic obesity. In a phase 2 study including pediatric and adult participants with acquired hypothalamic obesity, setmelanotide resulted in a mean BMI decrease of 15±10%, together with notable improvements in hyperphagic symptoms and QoL (81).

Preliminary data from a prospective, placebo-controlled clinical trial (NCT05774756) involving 120 affected individuals revealed that 52-week treatment produced a mean BMI reduction of 16.5% in the setmelanotide group (n=81), compared with a 3.3% BMI increase in the placebo cohort (n=39). Furthermore, 80% of treated patients achieved at least a 5% BMI reduction at 52 weeks (82). Collectively, these findings indicate that setmelanotide might represent a promising pharmacologic therapy for hypothalamic obesity (83) (Table 2).

Combination of oral phentermine and topiramate (Ph/T)

Phentermine is a sympathomimetic amine, while topiramate is a GABAergic agent commonly used as an anticonvulsant. Given that patients with hypothalamic obesity frequently exhibit diminished sympathetic nervous system activity (84), they may theoretically benefit from the appetite-suppressing effects of central stimulants (85,86). The combination of oral phentermine and topiramate (Ph/T) is approved by the U.S. Food and Drug Administration for use in individuals aged 12 years and older with obesity (87). Nevertheless, the efficacy and safety of Ph/T have not yet been systematically investigated in patients with confirmed hypothalamic obesity.

Tesofensine

Tesofensine is a centrally acting triple monoamine reuptake inhibitor that may counter the reduced sympathetic tone commonly observed in hypothalamic obesity. By blocking presynaptic reuptake of dopamine, serotonin, and noradrenaline and inhibiting the dopamine active transporter, tesofensine reduces caloric intake and promotes weight loss. To attenuate potential adrenergic adverse effects, it is administered in combination with the beta-blocker metoprolol. A randomized, double-blind, placebo-controlled phase 2 trial involving 21 individuals assessed Tesomet (tesofensine plus metoprolol) for hypothalamic obesity (88). Patients in the treatment arm exhibited reductions in body weight, waist circumference, and blood glucose relative to placebo.

Somatostatin and the autonomic nervous system

Lustig et al. (89) proposed that patients with CO CP may experience a loss of hypothalamic inhibitory control, resulting in increased vagal output and overstimulation of pancreatic β-cells. This leads to hyperinsulinemia and contributes to severe obesity. Based on this model, they tested the somatostatin analogue octreotide, which suppresses β-cell activity (89). However, its clinical utility has been limited by modest efficacy and frequent adverse effects, including gastrointestinal symptoms and gallstone formation. Other studies have implicated reduced sympathetic activity in decreased physical activity and pronounced obesity. Supporting this, Roth et al. (84) reported lower urinary catecholamine metabolite levels, correlating with both severity of obesity and reduced activity.

Central stimulating agents

A range of central nervous system stimulants, including methylphenidate, phentermine, dextroamphetamine, mazindol, caffeine, and ephedrine, has been used off-label in hypothalamic obesity (62,63,85). Two small pediatric case series documented that dexamphetamine therapy resulted in reductions in BMI, increased REE, and improved energy levels among affected children (62).

Oxytocin treatment

Oxytocin, a neuropeptide playing a central role for social behavior and reproduction, also influences appetite regulation and satiety. It has been shown to reduce food intake and suppress hunger. In CP patients, altered salivary oxytocin responses to food and exercise have been associated with differences in BMI and disordered eating behaviors (90). These findings suggest potential therapeutic utility for oxytocin in hypothalamic obesity. However, the mechanisms underlying its metabolic effects in the setting of hypothalamic injury remain poorly defined, and optimal dosing, delivery approaches, and long-term safety require further investigation.

Bariatric Interventions

Bariatric surgery has demonstrated meaningful weight-loss efficacy and safety in individuals with CP (Table 1). In an individual-level meta-analysis of 21 cases, Bretault et al. (91) reported total weight loss of -0.9% at 6 months and -15.1% at 12 months post-operatively, with the greatest reductions observed after Roux-en-Y gastric bypass (RYGB). In children and adolescents, irreversible bariatric procedures such as RYGB remain ethically and legally challenging, and their use is

generally restricted to clinical trial settings (92). The Endocrine Society's Clinical Practice Guideline (93) recommends considering bariatric surgery only for adolescents with morbid obesity, who have reached advanced pubertal maturation and near final or final adult height, and who have demonstrated adherence to lifestyle interventions.

Prevention of Hypothalamic Dysfunction through Hypothalamus-Sparing Approaches

Eveslage et al. (94) demonstrated that preoperative hypothalamic involvement and intraoperative damage to anterior and posterior hypothalamic nuclei are associated with reduced QoL and increased BMI in CP survivors. Complete surgical resection was linked to worse BMI and QoL outcomes compared with subtotal surgery (94) (Figure 2). Lesions confined to the anterior hypothalamus tended to produce fewer adverse effects, whereas injury to posterior regions markedly increased the risk of hypothalamic syndrome and impaired QoL (95). Consequently, surgical strategies should emphasize preservation of posterior hypothalamic structures. These hypothalamus-sparing techniques may increase the likelihood of tumor recurrence or progression. Radiotherapy therefore plays a pivotal role in managing residual disease and preventing relapse, forming a central component of hypothalamus-preserving treatment paradigms for CP (2,96).

Conclusion

Hypothalamic syndrome substantially affects morbidity and QoL in patients with CP, and current therapeutic outcomes remain unsatisfactory. The heterogeneity of hypothalamic syndrome indicates that a standardized treatment approach is unlikely to be effective. Accordingly, personalized management algorithms have been proposed to improve care (20,21). Treatment decisions that prioritize the preservation of hypothalamic, neuroendocrine, and visual function should be made within experienced multidisciplinary teams. Establishing multicenter reference networks is essential to ensure standardized, high-quality care and access to specialized expertise (97). Future strategies to improve outcomes should include deeper investigation into the molecular pathogenesis of CP, facilitating the development of targeted therapies that address tumor progression and hypothalamic involvement. Advances in surgery and radiotherapy should focus on hypothalamus-sparing approaches to limit long-term neuroendocrine and metabolic

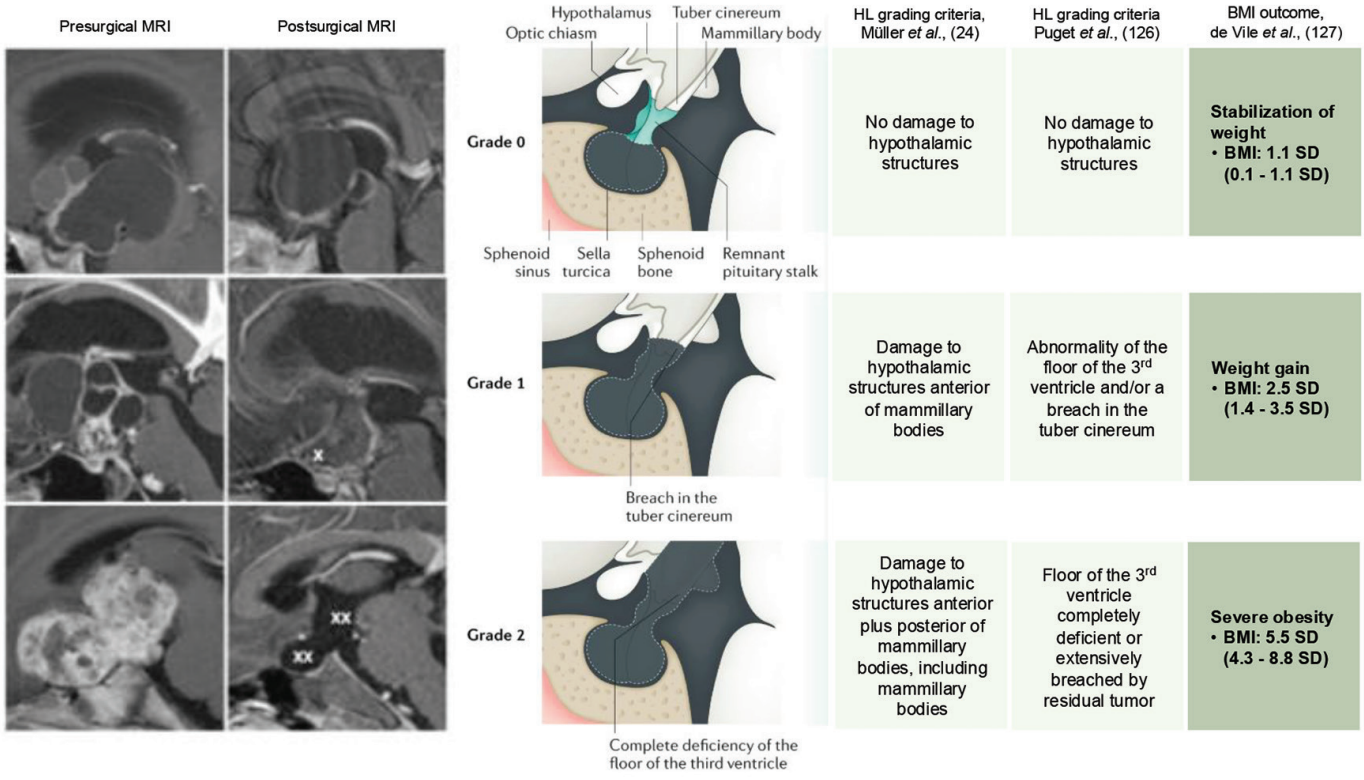

Figure 2. Hypothalamic lesions (HL) in craniopharyngioma: pre- and postoperative grading on MRI and outcome/body mass index (BMI). Definition of different grades of hypothalamic lesions based on postsurgical magnetic resonance imaging (MRI) as published by Puget at al. (126), de Vile et al. (127), and Müller et al. (24). Outcome (BMI) SDS according to de Vile et al. (127) in terms of weight gain and the development of hypothalamic obesity with regard to grade of hypothalamic lesion. Median BMI and interquartile ranges are shown for BMI SDS. X indicates anterior hypothalamic area, XX indicate anterior and posterior hypothalamic area.

consequences (98). In addition, policy-level initiatives are needed to define and implement quality standards for comprehensive multidisciplinary management of CP.

Footnotes

Competing Interests: HLM has received reimbursement of participation fees for scientific meetings and continuing medical education events, and reimbursement of travel expenses and lecture honoraria from Rhythm Pharmaceuticals.

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REVIEW

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Genetics of Idiopathic Hypogonadotropic Hypogonadism

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ABSTRACT

Idiopathic hypogonadotropic hypogonadism (IHH) comprises a group of disorders characterized by deficient secretion or action of gonadotropin-releasing hormone (GnRH), leading to impaired pubertal development and infertility. Traditionally, IHH is classified into Kallmann syndrome, associated with anosmia, and normosmic IHH, in which olfactory function is preserved. The condition exhibits marked genetic heterogeneity. Advances in next generation sequencing have significantly expanded the genetic landscape of IHH, with pathogenic variants identified in over 60 genes, accounting for up to 50% of cases. Oligogenic inheritance is increasingly recognized, occurring in 10-20% of individuals. The potential for spontaneous or treatment-induced clinical recovery in a subset of patients, along with phenotypic overlap with constitutional delay of growth and puberty, presents additional diagnostic challenges. Despite these complexities, genetic studies of IHH have provided critical insights into fundamental neuroendocrine processes, most notably the recent elucidation of the Kisspeptin, Neurokinin B, Dynorphin neurons as the GnRH pulse generator. These discoveries have also informed the development of targeted therapies, exemplified by the recent FDA approval of fezolinetant, a neurokinin B receptor antagonist, for the treatment of menopausal vasomotor symptoms.

Keywords: Hypogonadotropic hypogonadism, delayed puberty, genetics, etiology

Introduction

In vertebrates, gonadotropin releasing hormone (GnRH)-secreting neurons develop outside the central nervous system, originating from the nasal placode. They migrate along olfactory-derived vomeronasal axons to their final location in the hypothalamus (1).

The activity of the hypothalamic-pituitary-gonadal (HPG) axis demonstrates significant variability across the human lifespan (2). During early adolescence, a gradual reactivation of this neuroendocrine axis initiates the development of secondary sexual characteristics and the maturation of the reproductive system, marking the onset of puberty. This complex developmental process typically starts around 10 to 11 years of age in girls and boys respectively and spans from two to five years. Epidemiological data suggest that approximately 50% to 75% of the variation in the age at onset of puberty is influenced by genetics (3). The failure to undergo pubertal progression results in sexual immaturity and infertility, a clinical state referred to as hypogonadism. When this condition arises from anatomical malformations or functional impairments that compromise the secretion of GnRH or the subsequent release of pituitary gonadotropins, it is specifically classified as hypogonadotropic hypogonadism (HH).

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Idiopathic Hypogonadotropic Hypogonadism

The term idiopathic HH (IHH) refers to a condition characterized by delayed or absent sexual maturation due to deficient secretion or action of GnRH, in the absence of any identifiable anatomical or functional cause. IHH is traditionally categorized into two main forms: Kallmann syndrome (KS), which is associated with anosmia or hyposmia, and normosmic IHH (nIHH), in which olfactory function remains intact. IHH may be either congenital or acquired, with congenital cases comprising the majority of those that have a hereditary basis. In female individuals, clinical signs typically do not become evident until the early adolescent years. In contrast, male infants may exhibit signs of reproductive dysfunction at birth due to the critical activity of the HPG axis between the sixteenth and twenty-second weeks of gestation, a period during which androgen production is essential for the proper virilization of the male fetus with a 46,XY karyotype. As a result, congenital IHH in males may present with micropenis and/or undescended testes (cryptorchidism) at birth. In some cases, the degree of under-virilization is sufficient to warrant evaluation for a "disorder of sexual development". The brief reactivation of the HPG axis during early infancy, commonly referred to as "minipuberty", occurring approximately between four and sixteen weeks of life, presents a valuable diagnostic window during which both male and female infants with congenital IHH may be identified (4). KS is typically attributed to aberrant embryonic development and/or disrupted migration of GnRH-secreting neurons. During embryogenesis, these GnRH neurons originate from the nasal placode and migrate along olfactory axons to reach the hypothalamus. Consequently, the close developmental association between GnRH and olfactory neurons underlies the characteristic clinical presentation of HH accompanied by anosmia or hyposmia. In addition to reproductive and olfactory deficits, individuals with KS frequently exhibit a spectrum of non-reproductive congenital anomalies, including cleft palate, unilateral renal agenesis, limb malformations such as split hand/foot malformation and shortened metacarpals, sensorineural hearing loss, and mirror movements (synkinesia) (5). In contrast nIHH refers to those IHH cases in which patients have an intact sense of smell (6). nIHH arises from dysfunction of the GnRH neurons that are properly located within the hypothalamus. These cases typically lack any associated congenital anomalies.

Caution is warranted when employing the classifications of KS and nIHH, as the distinction between these entities can be ambiguous. This is exemplified by mutations in the *FGFR1* gene, which could be associated with either phenotype. Mutations in *CCDC141* or *IGSF10*, although typically associated with nIHH, have been shown *in vitro* to impair the migration of GnRH neurons, an abnormality more commonly linked to the KS phenotype. These findings underscore the complexity of the underlying molecular mechanisms and challenge the traditional dichotomy between KS and nIHH (7,8).

Pubertal delay is the most typical presentation of IHH. Pubertal delay is defined as absence of breast development (Tanner breast stage 1) in a girl at age 13 years or failure to achieve a testicular volume of 4 mL in a boy by age 14 years (9). By far the most common cause of delayed puberty is constitutional delay in growth and puberty (CDGP), also known as self-limited delayed puberty, which is not a disease *per se* but a maturational delay in development at the extreme of the population standards. CDGP accounts for pubertal delay in two third of boys and one third of girls (10). As CDGP is a diagnosis of exclusion, it must be carefully considered in the differential diagnosis of IHH. Differentiating between these two conditions frequently necessitates prolonged clinical observation and extensive diagnostic evaluation.

Studies have shown that some variants in established puberty-related genes, including *TAC3* and *TACR3*, are present in both individuals with nIHH and those with CDGP within the same families. These findings suggest that CDGP may represent a milder, transient manifestation of the same genetic defect underlying IHH, indicating a shared pathophysiological continuum between the two conditions (11). Clinicians often initiate a low-dose sex steroid regimen to "jump-start" pubertal development in patients suspected of having CDGP. It is now well established that approximately 10-20% of individuals with IHH experience clinical recovery, occurring either spontaneously or, more commonly, following sex steroid replacement therapy (12,13). These observations suggest that CDGP and IHH may share underlying pathophysiological mechanisms. This supports the concept of a phenotypic continuum ranging from normal pubertal timing to severe forms of IHH, with CDGP representing an intermediate point along this spectrum. On the other hand, a recent study found that the common genetic variants associated with pubertal timing in the general population contribute substantially to the genetic basis of CDGP, but only minimally to that of IHH (14). Furthermore, a more recent study involving 71 CDGP subjects revealed no mutations in genes associated with nIHH, such as *GNRHR, TAC3,* and *TAC3R*. This study revealed new candidate genes for CDGP, most notably *INHBB*, encoding the beta B subunit of inhibin, which is associated with age at menarche (15). In yet another study *MC3R* loss-of-function variants were overrepresented in patients with CDGP in comparison to IHH (16). Collectively, these recent studies suggest that the genetic architecture underlying CDGP and IHH may be distinct. Currently identified genetic defects explain up to 50% of all IHH cases (5,17). To date, mutations in nearly 60 genes have been implicated in the pathogenesis of IHH. A comprehensive list of currently known IHH-associated genes

is presented in Table 1. In a subset of patients or pedigrees, more than one pathogenic variant in different IHH-associated genes is identified, a phenomenon referred to as oligogenic inheritance or etiology. This mode of inheritance is estimated to account for 10-20% of all IHH cases (18,19,20,21). With the increased application of comprehensive, unbiased genetic approaches, such as whole exome sequencing (WES), it has become evident that oligogenic inheritance is more prevalent in Mendelian disorders than previously recognized (22). From the diagnostic point of view designing a panel of genes for targeted exome sequencing may prove to be practical in aiding timely differential diagnosis of delayed puberty. Such gene panels may prioritize genes more commonly implicated in patients with IHH or CDGP, and in our view, should at minimum include *FGFR1, ANOS1, CHD7, PROKR2, GNRHR, KISS1R, TAC3, TACR3, FGF8, FGF17, PROK2, CCDC141, SEMA3A, IGSF10, INHBB, MC3R*, and *IL17RD (5,15,16,23,24)*.

Genes Associated with IHH

Kallmann syndrome (KS) associated genes

X-linked recessive, autosomal dominant (AD), and autosomal recessive (AR) inheritance patterns have all been described in association with KS. However, KS frequently occurs as a sporadic condition. Even in familial cases, considerable intrafamilial phenotypic variability is commonly observed, with individuals harboring the same genetic mutation exhibiting a wide range of clinical manifestation (25,26,27). Based on the presence of specific associated clinical features, genetic screening can be prioritized for particular gene(s): synkinesia (*ANOS1*), dental agenesis (*FGF8/FGFR1*), digital bony abnormalities (*FGF8/FGFR1*) and hearing loss (*CHD7*, *SOX10*) (28). A shared pathophysiological mechanism among genes implicated in KS involves the interaction of fibroblast growth factor signaling, prokineticin signaling, and Anosmin-1 with heparan sulfate glycosaminoglycan moieties within extracellular signaling complexes. These interactions are thought to facilitate the proper migration of GnRH neurons during embryonic development (29,30).

Table 1. The list of genes associated with idiopathic hypogonadotropic hypogonadism

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
AMH	464	Anti-Müllerian hormone	Persistent Mullerian duct syndrome, type I	261550
AMHR2	465	Anti-Müllerian hormone receptor type 2	Persistent Mullerian duct syndrome, type II	261550
ANOS1	6211	Anosmin 1	Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1)	308700
ARHGAP5	675	Rho GTPase activating protein 5		
ARHGAP35	4591	Rho GTPase activating protein 35		
AXL	905	AXL receptor tyrosine kinase		
CCDC141	26821	Coiled-coil domain containing 141		
CHD7	20626	Chromodomain helicase DNA binding protein 7	Hypogonadotropic hypogonadism 5 with or without anosmia	612370
			CHARGE syndrome	214800
CPE	2303	Carboxypeptidase E	BDV syndrome	619326
DCC	2701	DCC netrin 1 receptor	Colorectal cancer, somatic	114500
			Esophageal carcinoma, somatic	133239
			Gaze palsy, familial horizontal, with progressive scoliosis, 2	617542
			Mirror movements 1 and/or agenesis of the corpus callosum	157600
DLG2	2901	Discs large MAGUK scaffold protein 2		
DMXL2	2938	Dmx like 2	Deafness, autosomal dominant 71*	617605
			Polyendocrine-polyneuropathy syndrome*	616113
			Developmental and epileptic encephalopathy 81	618663
DUSP6	3072	Dual specificity phosphatase 6	Hypogonadotropic hypogonadism 19 with or without anosmia	615269
FEZF1	22788	FEZ family zinc finger 1	Hypogonadotropic hypogonadism 22, with or without anosmia	616030
FGF8	3686	Fibroblast growth factor 8	Hypogonadotropic hypogonadism 6 with or without anosmia	612702

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Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
FGF17	3673	Fibroblast growth factor 17	Hypogonadotropic hypogonadism 20 with or without anosmia	615270
FGFR1	3688	Fibroblast growth factor receptor 1	Hypogonadotropic hypogonadism 2 with or without anosmia	147950
			Encephalocraniocutaneous lipomatosis, somatic mosaic	613001
			Hartsfield syndrome	615465
			Jackson-Weiss syndrome	123150
			Osteoglophonic dysplasia	166250
			Pfeiffer syndrome	101600
			Trigonocephaly 1	190440
FLRT3	3762	Fibronectin leucine rich transmembrane protein 3	Hypogonadotropic hypogonadism 21 with anosmia	615271
FSHB	3964	Follicle stimulating hormone subunit beta	Hypogonadotropic hypogonadism 24 without anosmia	229070
GNRH1	4419	Gonadotropin releasing hormone 1	Hypogonadotropic hypogonadism 12 with or without anosmia*	614841
GNRHR	4421	Gonadotropin releasing hormone receptor	Hypogonadotropic hypogonadism 7 without anosmia	146110
HESX1	4877	HESX homeobox 1	Growth hormone deficiency with pituitary anomalies	182230
			Pituitary hormone deficiency, combined, 5	182230
			Septooptic dysplasia	182230
HS6ST1	5201	Heparan sulfate 6-O-sulfotransferase 1	Hypogonadotropic hypogonadism 15 with or without anosmia	614880
IGSF10	26384	Immunoglobulin superfamily member 10		
IL17RD	17616	Interleukin 17 receptor D	Hypogonadotropic hypogonadism 18 with or without anosmia	615267
IRF2BPL	14282	Interferon regulatory factor 2 binding protein like	Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures	618088
KISS1	6341	KiSS-1 metastasis suppressor	Hypogonadotropic hypogonadism 13 with or without anosmia*	614842
KISS1R	4510	KISS1 receptor	Hypogonadotropic hypogonadism 8 with or without anosmia	614837
			Precocious puberty, central, 1*	176400
KLB	15527	Klotho beta		
LEP	6553	Leptin	Obesity, morbid, due to leptin deficiency	614962
LEPR	6554	Leptin receptor	Obesity, morbid, due to leptin receptor deficiency	614963
LHB	6584	Luteinizing hormone subunit beta	Hypogonadotropic hypogonadism 23 with or without anosmia	228300
NDNF	26256	Neuron derived neurotrophic factor	Hypogonadotropic hypogonadism 25 with anosmia	618841
NHLH2	7818	Nescient helix-loop-helix 2	Hypogonadotropic hypogonadism 27 without anosmia*	619755
NR0B1	7960	Nuclear receptor subfamily 0 group B member 1	46XY sex reversal 2, dosage-sensitive	300018
			Adrenal hypoplasia, congenital	300200
NSMF	29843	NMDA receptor synaptonuclear signaling and neuronal migration factor	Hypogonadotropic hypogonadism 9 with or without anosmia	614838
NTN1	8029	Netrin 1	Mirror movements 4	618264
OTUD4	24949	OTU deubiquitinase 4		

Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
PCSK1	8743	Proprotein convertase subtilisin/kexin type 1	Obesity, susceptibility to, BMIQ12	612362
			Endocrinopathy due to proprotein convertase 1/3 deficiency	600955
PLXNA1	9099	Plexin A1	Dworschak-Punetha neurodevelopmental syndrome	619955
PLXNA3	9101	Plexin A3		
PLXNB1	9103	Plexin B1		
PNPLA6	16268	Patatin like domain 6, lysophospholipase	Laurence-Moon syndrome*	245800
			Boucher-Neuhauser syndrome	215470
			Oliver-McFarlane syndrome	275400
			Spastic paraplegia 39, autosomal recessive	612020
POLR3A	30074	RNA polymerase III subunit A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism	607694
			Wiedemann-Rautenstrauch syndrome	264090
POLR3B	30348	RNA polymerase III subunit B	Charcot-Marie-Tooth disease, demyelinating, type 1I	619742
			Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism	614381
POU6F2	21694	POU class 6 homeobox 2	Wilms tumor susceptibility-5	601583
PROK2	18455	Prokineticin 2	Hypogonadotropic hypogonadism 4 with or without anosmia	610628
PROKR2	15836	Prokineticin receptor 2	Hypogonadotropic hypogonadism 3 with or without anosmia	244200
RAB18	14244	RAB18, member RAS oncogene family	Warburg micro syndrome 3	614222
RAB3GAP1	17063	RAB3 GTPase activating protein catalytic subunit 1	Martsolf syndrome 2	619420
			Warburg micro syndrome 1	600118
RAB3GAP2	17168	RAB3 GTPase activating non-catalytic protein subunit 2	Martsolf syndrome 1	212720
			Warburg micro syndrome 2	614225
RNF216	21698	Ring finger protein 216	Cerebellar ataxia and hypogonadotropic hypogonadism	212840
SEMA3A	10723	Semaphorin 3A	Hypogonadotropic hypogonadism 16 with or without anosmia	614897
SEMA3E	10727	Semaphorin 3E		
SEMA3F	10728	Semaphorin 3F		
SMCHD1	29090	Structural maintenance of chromosomes flexible hinge domain containing 1	Bosma arhinia microphthalmia syndrome	603457
			Facioscapulohumeral muscular dystrophy 2, digenic	158901
SOX2	11195	SRY-box transcription factor 2	Microphthalmia, syndromic 3	206900
			Optic nerve hypoplasia and abnormalities of the central nervous system	206900
SOX3	11199	SRY-box transcription factor 3	Intellectual developmental disorder, X-linked, with isolated growth hormone deficiency	300123
			Panhypopituitarism, X-linked	312000
SOX10	11190	SRY-box transcription factor 10	PCWH syndrome	609136
			Waardenburg syndrome, type 2E, with or without neurologic involvement	611584
			Waardenburg syndrome, type 4C	613266
SOX11	11191	SRY-box transcription factor 11	Intellectual developmental disorder with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism	615866

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Table 1. Continued

Gene	HGNC ID	Approved name	OMIM phenotype	Phenotype MIM number
SPRY4	15533	Sprouty RTK signaling antagonist 4	Hypogonadotropic hypogonadism 17 with or without anosmia	615266
SRA1	11281	Steroid receptor RNA activator 1		
STUB1	11427	STIP1 homology and U-box containing protein 1	Spinocerebellar ataxia 48	618093
			Spinocerebellar ataxia, autosomal recessive 16	615768
TCF12	11623	Transcription factor 12	Hypogonadotropic hypogonadism 26 with or without anosmia	619718
			Craniosynostosis 3	615314
TAC3	11521	Tachykinin precursor 3	Hypogonadotropic hypogonadism 10 with or without anosmia	614839
TACR3	11528	Tachykinin receptor 3	Hypogonadotropic hypogonadism 11 with or without anosmia	614840
TBC1D20	16133	TBC1 domain family member 20	Warburg micro syndrome 4	615663
WDR11	13831	WD repeat domain 11	Hypogonadotropic hypogonadism 14 with or without anosmia	614858
			Intellectual developmental disorder, autosomal recessive 78	620237

ANOS1

The first gene identified as causative for KS is *ANOS1* (31). Formerly known as *KAL1* it is located on the short arm of the X chromosome (Xp22.3) (OMIM: 300836) (32). Ten to 20 percent of males with KS carry *ANOS1* mutations or intragenic microdeletions are present (33, 34). The extracellular glycoprotein it encodes, anosmin-1, plays a role in the adhesion of GnRH cells and axon migration during organogenesis (35). Anomin-1 exerts its biological effects mainly through signal modulation of *FGFR1* via its third fibronectin-like type 3 (FnIII) domain and the N-terminal region (36). The migratory defect of olfactory and GnRH neurons is the central mechanism underlying the clinical features of *ANOS1* mutations (37). In its first observation, in a 19-week-old male human fetus with a deletion in *ANOS1*, GnRH neurons could not migrate to their normal positions in the brain (38). In KS cases associated with *ANOS1* mutations, penetrance has been reported to be almost complete (39,40). Additional clinical findings include bimanual synkinesis, unilateral renal agenesis, vas deferens agenesis, and deafness (28,41).

FGFR1, *FGF8* and related genes (*FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, *FLRT3*, and *KLB*)

FGFR1 encodes a receptor belonging to the tyrosine kinase superfamily. It regulates central developmental processes, such as neuronal proliferation, differentiation, and migration critical for embryonic development. *FGFR1* is the first gene in which mutations were identified for the AD form of KS (42). However, over time, *FGFR1* has also been found to be associated with nIHH (43,44). Around 10% of patients with KS were found to have inactivating mutations in *FGFR1* (29,43,45). Loss-of-function mutations in *FGFR1* were detected in 7% of 134 nIHH patients (46). To date numerous insertions/deletions, missense, and nonsense mutations have been reported with AD, AR, *de novo*, and oligogenic inheritance (29,47,48). Loss of *FGFR1* function elicit reproductive abnormalities ranging from severe AD KS through fully penetrant nIHH to delayed puberty (43,44,45,49,50). *FGFR1* mutations have been associated with cleft palate, synkinesis, and tooth agenesis, and asymptomatic carriers have been reported in some familial cases (5,51).

FGF8 and *FGF17* are *FGFR1* ligands with similar sequence structures that play a role in GnRH neuron ontogenesis. Mutations in these genes have been reported in IHH patients with varying olfactory functions (52,53). Mice homozygous for the hypomorphic *Fgf8* allele exhibited absent olfactory bulbs and lacked GnRH neurons in the hypothalamus (52). IHH patients harboring *FGF8* variants have also been reported to exhibit additional phenotypic features, including cleft lip and/or palate, a flat nasal bridge, and camptodactyly (54,55). Further screening for *FGF8*-related genes in a group of 388 congenital IHH patients revealed inactivating variants in *FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, and *FLRT3* (53).

KLB encodes β-Klotho, a co-receptor essential for *FGF21* signaling via *FGFR1*. In one study, over 300 IHH patients were screened, identifying 13 individuals with loss-of-function *KLB* variants. Most of these patients exhibited metabolic abnormalities, including insulin resistance or dyslipidemia. Notably, *Klb* knockout mice displayed a milder hypogonadal phenotype compared to the human presentation (56).

HS6ST1

heparan sulfate 6-O-sulfotransferase 1 (HS6ST1) is directly involved in the sulfation of heparan sulfate proteoglycans, which are critical modulators of FGF signaling. The 6-O-sulfation of heparan sulfate chains, catalyzed by *HS6ST1*, is required for optimal binding and activation of FGF ligands (such as *FGF8* and *FGF17*) to their receptor *FGFR1* (57). This interaction is essential for the development, migration, and survival of GnRH neurons during embryogenesis. Mutations in *HS6ST1*, often co-occurring with variants in other known KS genes, have been reported in seven families (58).

PROKR2 and *PROK2*

PROK2 and *PROKR2* encode prokineticin 2, an 81-amino acid peptide, and its G protein-coupled receptor, respectively. Both play critical roles in the development of neuronal precursors and are essential for processes such as olfactory bulb morphogenesis and sexual maturation (59). This ligand-receptor pair has been identified as a strong candidate for the pathogenesis of KS as *PROK2* (60,61) or *PROKR2* knockout mice had defective olfactory bulbs and failed migration of GnRH neurons (62). Subsequent studies identified inactivating variants in *PROKR2* and *PROK2* in patients with KS. The majority of these mutations have been identified in the heterozygous state, although both homozygous and compound heterozygous variants have also been reported (63). Patients with *PROK2* or *PROKR2* mutations have considerable phenotypic variability (61,64,65), ranging from KS to nIHH. A variety of associated clinical features has been reported in affected individuals, including fibrous dysplasia, synkinesia, epilepsy, and Crohn's disease (66). Mutations in *PROKR2* and *PROK2* are frequently identified in combination with variants in other genes, supporting an oligogenic mode of inheritance in IHH.

CHD7

CHARGE syndrome is a multisystem disorder that includes **C**oloboma, Heart anomalies, choanal Atresia, growth Retardation, Genital defects and Ear anomalies (67). *CHD7* mutations are present in the majority of patients with CHARGE syndrome. *CHD7* is a chromatin-remodeling protein essential for the ontogeny of GnRH neurons and the proper targeting of olfactory axons during embryogenesis. Pathogenic *CHD7* mutations disrupt these developmental processes, resulting in a reduced number of hypothalamic GnRH neurons and defective GnRH secretion. There is a range of abnormalities in the GnRH neuron migration pathway in mice with *CHD7* deficiency (68,69). While large *de novo* deletions are noted in classical CHARGE syndrome patients, inherited or *de novo* point mutations may result in KS/nIHH (48,70,71). Thus, IHH patients should be carefully examined for possible clinical features of CHARGE syndrome, such as abnormal ears, deafness, semicircular canal hypoplasia, and coloboma (67).

WDR11

WDR11 in partnership with EMX1, a homeodomain transcription factor, is essential for normal Hedgehog (Hh) signaling and ciliogenesis, both of which are critical for the embryonic development and migration of GnRH neurons. Mutations in *WDR11* disrupt Hh pathway signaling, impairing the formation and function of primary cilia, which are required for the proper migration of GnRH and olfactory neurons (72). By positional cloning, heterozygous mutations were discovered in several patients with KS (73).

CCDC141

CCDC141 encodes a coiled-coil domain containing protein that is expressed in GnRH neurons. We have reported inactivating *CCDC141* variants in four separate families with IHH. Affected individuals exhibit normal olfaction and anatomically normal olfactory bulbs (74). In a rodent nasal explant model, knockdown of Ccdc141 led to impaired embryonic migration of GnRH neurons without affecting olfactory axon outgrowth, thereby producing a nIHH phenotype distinct from other genes implicated in GnRH neuronal migration (7). *CCDC141* Mutations have been identified as a recurrent finding in individuals with CDGP. Among a cohort of 193 patients with CDGP, 21 individuals (6%) were found to carry predicted deleterious variants in *CCDC141* (75).

FEZF1

The protein product of *FEZF1* facilitates the penetration of olfactory receptor neuron axons through the basal lamina of the central nervous system in murine models. As a subset of these axons serves as a migratory scaffold for GnRH neurons, *FEZF1* deficiency results in failed entry of GnRH neurons into the brain (76,77). Through autozygosity mapping and WES of 30 individuals with KS, we discovered homozygous loss-of-function mutations in *FEZF1* in two separate consanguineous families, each with two affected siblings (78). *FEZF1* mutations are apparently extremely rare as no new KS cases have been reported to date.

IGSF10

IGSF10, a member of the immunoglobulin superfamily, was implicated in delayed puberty by Howard et al. (8), who analyzed WES data from over 100 affected individuals and identified pathogenic mutations in six families. Knockdown studies demonstrated reduced GnRH neuronal migration in the GN11 cell line. Despite this impaired migration, patients harboring *IGSF10* mutations exhibited a normal sense of smell. The authors proposed that a reduced number or delayed arrival of GnRH neurons to the hypothalamus results in a milder disruption of the GnRH neuronal network, manifesting as delayed puberty rather than permanent IHH. Notably, *IGSF10* mutations were also identified in adults with functional hypothalamic amenorrhea, a condition considered a mild and reversible form of HH (8).

SEMA3A and related genes (*SEMA3E, SEMA3G, SEMA3F, PLXNA1, PLXNA3 etc)*

The precise targeting of GnRH neurons and olfactory/vomeronasal projections relies on the coordinated activity of axonal guidance cues, including semaphorins which are a large and heterogeneous family of secreted and membrane-bound proteins (79). Mutations in class-3 semaphorin family members, including *SEMA3A*, *SEMA3E*, and *SEMA3G*, have been implicated in the pathogenesis of IHH (80,81,82). *SEMA3* proteins exert their biological functions by binding to Neuropilin co-receptors, forming heteromeric complexes with *PlexinA1-4 (PLXNA1-4)* receptors, thereby initiating plexin-mediated signal transduction pathways (83). Non-synonymous heterozygous variants in *PLXNA1* have been identified in KS individuals (84). More recently we have identified deleterious variants in *SEMA3F* and *PLXNA3* that caused IHH (85).

SEMA3F and *PLXNA3*

SEMA3F and its coreceptor *PLXNA3* play a role in cell migration and axonal guidance (86). WES of 216 patients with IHH identified rare *SEMA3F* and *PLXNA3* variants in 15 individuals. Over half (54%) also carried mutations in other known IHH genes, highlighting the disorder's oligogenic nature. *SEMA3F* variants followed AD inheritance with variable penetrance, while *PLXNA3* variants were X-linked recessive. Six patients exhibited impaired olfaction. The study provided clinical, genetic, and cellular evidence supporting the role of *SEMA3F* signaling deficiency in IHH pathogenesis (85).

PLXNA1

Plexin-A1, a transmembrane coreceptor for semaphorin 3 signaling, is encoded by *PLXNA1* (87). Heterozygous *PLXNA1* variants were identified in 15 of 237 unrelated patients with KS, and impaired plexin-A1 signaling has been linked to oligogenic inheritance in KS (84). Subsequently, by screening the WES data of 215 IHH patients, we identified rare heterozygous *PLXNA1* variants in KS and nIHH patients carrying additional variants in known IHH genes. Thus, the contribution of *PLXNA1* to the oligogenicity of both forms of IHH was confirmed (88).

PLXNB1

The receptor for semaphorin 4D, plays a critical role in GnRH neuronal development. In murine models, disruption of *Sema4D/PLXNB1* signaling results in abnormal GnRH ontogeny. In a cohort of 336 patients with IHH, we were able to detect six rare *PLXNB1* variants in eight individuals with the nIHH (89).

SMCHD1

SMCHD1 encodes an epigenetic repressor that is expressed in the human olfactory epithelium. Shaw et al. (90) identified inactivating mutations in *SMCHD1* as the underlying cause of congenital arhinia in 41 cases. Notably, 97% of affected individuals also exhibited hypogonadal features, including cryptorchidism, microphallus, or amenorrhea, alongside absent olfactory structures and anosmia (90).

SOX10

Inactivating mutations in *SOX10* are responsible for Waardenburg syndrome, a rare condition marked by pigmentation defects and sensorineural hearing loss. In a subset of KS patients presenting with deafness, *SOX10* mutations were identified in about one-third of cases. Consistent with these findings, *Sox10* knockout mice exhibit a complete absence of olfactory ensheathing cells along the olfactory nerve pathway, highlighting the critical role of this gene in olfactory system development (91). A large cohort study of 1309 IHH patients reported that developmental problems due to *SOX10* variants may encompass a phenotypic line from KS to nIHH (92).

SOX2

SOX2 encodes the SRY-related, HMG-box 2 transcription factor protein. A study involving eight IHH patients with heterozygous *SOX2* variants who had severe eye defects found that pathogenic *SOX2* variants were linked to both anosmic and normosmic forms of IHH. Functional analyses indicated that *Sox2* was highly expressed in the hypothalamus of adult mice. The study emphasized that screening for *SOX2* variants should be performed in patients, regardless of the presence of ocular defects, when conducting genetic evaluations for IHH (93).

NDNF

NDNF is a secreted neurotrophic factor involved in the migration of GnRH neurons and is a member of the fibronectin type III (FN3) superfamily. Screening for rare variants in FN3 domain-containing proteins identified three protein-truncating and one missense heterozygous *NDNF* variant among patients with KS. In *NDNF*-null mice, a reduced number of GnRH neurons reached their final destination compared to wild-type $NDNF^{+/+}$ mice (94). More recently, we identified a homozygous protein-truncating variant in *NDNF* in a consanguineous family with KS, highlighting that, in addition to the previously described dominant inheritance, NDNF-related disease can also follow an AR pattern (95).

AMH and *AMHR2*

Anti-Müllerian Hormone (AMH) is expressed in migrating GnRH neurons in mouse and human fetuses during embryonic development and functions as a promotility factor (96). *AMHR2*-deficient mice exhibit aberrant development of the peripheral olfactory system and impaired embryonic migration of GnRH neurons. In humans, heterozygous inactivating variants in *AMH* or *AMHR2* have been associated with IHH. These findings indicate

the critical role of *AMH/AMHR2* signaling in GnRH neuronal migration and its contribution to the pathogenesis of IHH (97).

AXL

AXL receptor tyrosine kinases, members of the TAM (TYRO3/AXL/MERTK) family, play a role in GnRH neuron migration and survival. Studies of sexual maturation in *AXL* null mice reported that TAM function was impaired (98). *AXL* variants have been identified in both anosmic and normosmic IHH probands.

NTN1

Netrin-1, encoded by the *NTN1* gene, plays a crucial role in central nervous system development by guiding axonal and neuronal migration through its receptor DCC. In *DCC*$^{-/-}$ and *NTN1*$^{-/-}$ mouse embryos, GnRH neurons exhibited aberrant trajectories and failed to reach the medial preoptic area, highlighting the importance of NTN1/DCC signaling in proper GnRH neuronal migration (99,100). WES of a cohort of 133 individuals with IHH identified pathogenic variants in *NTN1* and the gene for its receptor, *DCC*. Five heterozygous *DCC* variants were detected in six probands, five of whom had KS and one with nIHH. In addition, co-occurring variants in both *DCC* and *NTN1* were identified in two KS patients, supporting an oligogenic basis for disease pathogenesis (101).

nIHH Associated Genes

Genes implicated in nIHH are particularly informative for understanding the regulation of the HPG axis and the timing of puberty. Genetic analyses of familial nIHH cases have significantly advanced this understanding. In a study of 22 consecutive multiplex families with nIHH, mutations were identified in five genes, *GNRHR*, *TACR3*, *TAC3*, *KISS1R*, and *KISS1*, in 77% of families. Among these, *GNRHR* and *TACR3* mutations were the most frequently observed, each accounting for approximately one-third of the genetically resolved cases (24).

GNRHR and *GNRH1*

GNRH1 and *GNRHR* are the most obvious candidate gene in the etiology of IHH. In 1997, de Roux et al. (102) identified compound heterozygous mutations in *GNRHR* in two siblings with partial nIHH, showing that Gln106Arg impaired GnRH binding while Arg262Gln reduced IP3 signaling. The male sibling exhibited normal gonadotropin levels and LH pulse frequency but reduced pulse amplitude, consistent with partial GnRH receptor dysfunction. Shortly after, Layman et al. (103) reported a family with four siblings carrying compound heterozygous *GNRHR* mutations (p.Arg262Gln and p.Tyr284Cys), further supporting the role of biallelic *GNRHR* mutations in IHH without anosmia or developmental anomalies (103). Subsequent studies found *GNRHR* variants in approximately 5-6% of nIHH cases (104). This relatively high prevalence of *GNRHR* was confirmed in subsequent studies (105). To date over 60 distinct mutations have since been reported (106).

Genotype-phenotype correlations have been observed for specific *GNRHR* mutations. The genetic makeup (homozygous, compound heterozygous, or monoallelic variants) broadly correlates with clinical severity, ranging from complete IHH to milder forms, such as CDGP and functional hypothalamic amenorrhea (104). The homozygous R139C missense mutation in the conserved DRS motif of the GnRH receptor causes complete IHH by severely impairing receptor trafficking to the plasma membrane, a defect reversible with the pharmacological chaperone IN3 (107). In contrast, the heterozygous Gln106Arg mutation is linked to adult-onset IHH (AOHH), where normal pubertal development precedes nIHH. Homozygosity for p.Gln106Arg has also been associated with the fertile eunuch variant of nIHH, characterized by hypogonadism with preserved testicular size and partial virilization (108). These findings highlight how specific *GNRHR* mutations contribute to a broad spectrum of GnRH deficiency phenotypes (5,106).

GNRH1 encodes the GnRH preprohormone. Deletion of *GNRH1* in murine models was shown to result in complete absence of GnRH synthesis, a finding reported well before analogous mutations were identified in humans (109,110). Over a decade after the initial discovery of *GNRHR* mutations, pathogenic *GNRH1* variants were reported in humans (111,112). Bouligand et al. (111) demonstrated that pulsatile GnRH administration for two weeks resulted in synchronous LH pulses, increased levels of estradiol, and a single dominant ovarian follicle. These findings confirmed the hypothalamic origin and pivotal role of GnRH in human reproduction. Affected individuals frequently present with micropenis and cryptorchidism (111,112,113).

KISS1R and *KISS1*

In 2003, kisspeptin emerged as a pivotal central regulator of GnRH neuronal activity following the identification of mutations in a previously little-characterized G protein-coupled receptor, initially termed *GPR54* and later renamed *KISS1R* (kisspeptin receptor) (106). In 2003, two independent research groups concurrently reported homozygosity mapping in familial cases of IHH, resulting in the first identification of pathogenic mutations in *KISS1R* (114,115). Mutant *KISS1R* constructs exhibited impaired receptor function in *in vitro* assays, and *KISS1R*-knockout mice recapitulated the human hypogonadotropic phenotype, confirming the essential role of the kisspeptin signaling pathway in pubertal and reproductive regulation across mammals (114). In a mutational screening study, only five out of 166 (3%) probands with nIHH were found to have rare variants in *KISS1R* (116). The rarity of mutations in *KISS1* and *KISS1R* may be attributed to evolutionary selection pressures, given the critical roles of kisspeptin in placentation, reproductive

function, and metastasis suppression, which likely constrain the transmission of deleterious variants within populations (106). Studying a large, consanguineous family with four sisters with nIHH, we found inactivating mutations altering the 4th amino acid of Kisspeptin-10. Overnight frequent LH sampling did not reveal any LH pulsatility, further confirming the essential role of kisspeptin signaling in the GnRH pulse generator (117). Coutant et al. (118) recently identified homozygous frameshift mutations in *KISS1* within a consanguineous family (118). Molecular analyses confirmed a complete absence of kisspeptin protein. Affected male siblings exhibited congenital gonadotropin deficiency, including bilateral cryptorchidism, micropenis, and absent spontaneous puberty. However, the two older brothers later showed spontaneous reversal of hypogonadism, with normalization of testicular volume and spermatogenesis. These findings indicate that complete kisspeptin deficiency does not preclude delayed GnRH activation or pubertal maturation, highlighting the redundancy and adaptability of upstream neuroendocrine pathways (118). The potential involvement of alternative *KISS1R* ligands, neuroendocrine plasticity, or compensatory pathways, such as neurokinin B (NKB) or glutamatergic signaling, requires further investigation.

TACR3 and *TAC3*

Tachykinin receptor 3, encoded by *TACR3*, mediates the biological actions of neurokinin B (NKB), which is encoded by *TAC3*. Through autozygosity mapping aimed at discovering novel regulators of the HPG axis, we identified homozygous non-synonymous mutations in the coding regions of *TAC3* or *TACR3* in nine individuals from four families presenting with an nIHH phenotype (119). With the additional cases identified in our cohort, it became clear that *TACR3* mutations are almost as common as *GNRHR* mutations (24,120). Similar findings regarding the prevalence of *TACR3* mutations have been reported by other research groups. Gianetti et al. (121) found 19 among 345 (5.5%) cases while a very similar rate (5.2%) was observed by Francou et al. (122) from a cohort of 173 cases of familial and sporadic nIHH. The frequent occurrence of micropenis and cryptorchidism in male patients with *TACR3* mutations suggests that functional *TACR3* signaling is essential for normal fetal gonadotropin secretion, which in turn regulates testicular development, descent, and penile growth (4).

Clinical reversibility, characterized by spontaneous pubertal progression, often following a period of exogenous sex steroid therapy, was observed in approximately 10% of an unselected cohort with nIHH (12). Gianetti et al. (121) reported a significantly higher rate of reversibility of 83% in their cohort of patients with *TAC3*/*TACR3* mutations. In our cohort, four patients from three unrelated and ethnically diverse families exhibited clinical recovery, representing 25% (4/16) of the cases. Notably, all of these families carried the same *TACR3* mutation (p.Thr177Lys). Given the relatively high rate of reversibility, it was hypothesized that CDGP might represent a mild form of IHH linked to *TACR3* mutations. To investigate this, Vaaralahti et al. (123) screened *TAC3* and *TACR3* in 146 Finnish individuals with CDGP but identified no pathogenic variants associated with the phenotype.

Additional clinical studies have enhanced our understanding about the regulation of the HPG axis by Neurokinin B signaling. Young et al. (124) showed that patients with null mutations in *TAC3* could achieve pubertal levels of gonadotropins and sex steroids following repeated administration of exogenous GnRH. This finding indicates that neurokinin B acts at a hypothalamic level, upstream of GnRH secretion, rather than directly influencing pituitary function (124). Furthermore, a genome-wide association study identified a significant association between age at menarche, a surrogate marker of pubertal start, and a single nucleotide polymorphism (rs3733631) located immediately upstream of *TACR3*, supporting a role for neurokinin B signaling in the regulation of pubertal timing at the population level (125).

IRF2BPL (*EAP1*)

Pubertal onset is postulated to be regulated in part by transcriptional factors such as EAP1 (126). In a cohort with familial CDGP, two rare *EAP1* variants (p.Ala221del and p.Asn770His) were identified, both impairing GnRH promoter activation through distinct molecular mechanisms. These findings provide the first link between *EAP1* mutations and CDGP (127).

LEP and *LEPR*

Leptin deficiency with mutations in either *LEP* (encoding leptin) or *LEPR* (encoding the leptin receptor) is associated with IHH (128,129). Administration of leptin in individuals with *LEP* deficiency restores normal pubertal development but does not induce precocious puberty in prepubertal children. This suggests that leptin functions as a permissive, rather than initiatory, factor in the onset of puberty in humans (130). These patients are readily distinguishable from other individuals with IHH due to the characteristic presentation of early-onset obesity and hyperphagia.

NR0B1 (*DAX1*)

NR0B1 belongs to the nuclear receptor superfamily and is classified as an orphan receptor due to the absence of a known endogenous ligand. Mutations in *NR0B1* are known to cause adrenal hypoplasia congenita in combination with IHH (131,132,133,134,135). Adrenal hypoplasia typically presents as adrenal insufficiency during infancy, whereas IHH becomes manifest in affected males who survive into the second decade of life. Nuclear receptors, such as SF-1 and LRH-1, involded in

adrenal and gonadal phyiology and development, are regulated in their transcriptional activity by coregulatory molecules (136). *DAX-1*, lacks a DNA-binding domain and functions exclusively as a coregulator (137). Notably, Dax-1 is predominantly expressed in the arcuate nucleus (ARC) of the hypothalamus. In adult female mice, *DAX-1* is present in at least 70% of Kiss1 neurons within the ARC, which is associated with pubertal development, whereas it is found in fewer than 5% of Kiss1 neurons in the AVPV nucleus, which is exclusively linked to the menstrual cycle (138). These findings suggest that *DAX-1* is selectively involved in the regulation of pubertal onset and the sustained function of the HPG axis. As mentioned earleir, mutations in *NR0B1* result in adrenal hypoplasia congenita together with IHH (131,132). Paradoxically, *NR0B1* mutations can also result in the opposite phenotype, precocious puberty, even within the same kindred (133,134,135). The genetic mechanisms underlying these divergent phenotypic outcomes remain poorly understood, highlighting intriguing genotype-phenotype correlations. This paradox suggests a complex, context-dependent role for *DAX-1* in regulating the HPG axis and pubertal timing.

SRA1

SRA1 was the first gene demonstrated to exert its function through both its protein product and a non-coding, functional RNA transcript (139). These proteins serve as co-regulators for nuclear receptors, including sex steroid receptors, and play a critical role in modulating the activity of SF-1 and LRH-1, the principal regulators of steroid hormone biosynthesis. *SRA1* is required for the synergistic enhancement of SF-1 transcriptional activity by *DAX-1 (NR0B1*), mutations in which also cause IHH (140). We and others have reported nIHH patients with inactivating *SRA1* mutations (141,142,143).

PNPLA6

Gordon Holmes syndrome (GDHS) is characterized by cerebellar ataxia/atrophy and nIHH, while the related Boucher-Neuhäuser syndrome also includes chorioretinal dystrophy. *PNPLA6*, which encodes neuropathy target esterase (NTE), a key regulator of phospholipid metabolism, was found to carry loss-of-function mutations in six GDHS patients from three unrelated families via autozygosity mapping and WES. Functional studies showed that NTE inhibition in LβT2 gonadotroph cells impaired LH exocytosis in response to GnRH. These findings suggest that NTE dysfunction in GDHS disrupts phospholipid homeostasis, contributing to both neurodegeneration and impaired LH secretion, resulting in nIHH (144).

OTUD4 and *RNF216*

Ubiquitination-related *OTUD4* encodes a deubiquitinase, while *RNF216* encodes a ubiquitin E3 ligase. *OTUD4* and *RNF216* mutations have been identified in patients with GDHS. Patients have progressive ataxia, dementia, and neuronal losses are observed in the cerebellar pathway and hippocampus. Functional studies have shown that knockout of *OTUD4* and *RNF216* in zebrafish causes defects in the eye and cerebellum and that suppression of the two genes together worsens these phenotypes. Hence, inactivating mutations in *OTUD4* and *RNF216* cause neurodegeneration and reproductive failure through dysregulated ubiquitination (145).

STUB1

STUB1 encodes C-terminus of HSC70-inactivating protein, which functions as a E3 ubiquitin ligase. Pathogenic variants of *STUB1* have been associated with GDHS (146).

POU6F2

POU6F2 belongs to a gene family characterized by a bipartite DNA-binding domain, comprising a POU-specific domain and a POU homeodomain. Members of this family function as transcriptional regulators involved in cell type–specific differentiation. Several POU domain–containing proteins have been implicated in the regulation of GnRH neuron expression (147,148). Using WES data from two independent IHH cohorts (331 nIHH, 85 KS; 416 patients in total and 677 nIHH, 632 KS; 1309 patients in total), 12 rare missense variants of *POU6F2* were identified in 15 patients. Functional studies of two different isoforms encoded by *POU6F2* were performed, and the function of isoform 1 was proven as a transcriptional regulator of GNRH1 expression. Thus, pathogenic *POU2F6* variants were shown to be involved in IHH pathogenesis by disrupting normal GnRH migration (149).

DLG2

DLG2 encodes a scaffolding protein that interacts with N-methyl-D-aspartate (NMDA) receptors, which have been implicated in the regulation of sexual maturation in animal models. WES identified a rare missense variant in *DLG2* in a large family with delayed puberty. Functional studies demonstrated that this variant reduces *GnRH* expression *in vitro*, suggesting a potential mechanistic link between *DLG2* and pubertal timing (150). A subsequent study screened the WES data of 336 IHH probands from 290 independent families for rare *DLG2* variants. A total of one homozygous and two heterozygous missense variants were identified in three independent normosmic patients (151).

NHLH2

NHLH2, a basic helix-loop-helix transcription factor family member, mediates leptin-induced activation of POMC in the leptin-melanocortin pathway. Screening of WES data in a large IHH cohort revealed obese patients with rare disease-causing sequence variants. *In silico* and *in vitro* analyses of the findings showed that *NHLH2* binding to the Mc4r promoter

and KISS1 transactivation were reduced, supporting a critical role for *NHLH2* in human puberty and body weight control (152). Remarkably, *NHLH2* knockout mice exhibit a phenotype closely resembling that of patients with rare inactivating *NHLH2* variants, characterized by nIHH and late-onset obesity (153).

CPE

CPE encodes an enzyme responsible for processing neuropeptides, including GnRH, into their biologically active forms within the hypothalamus. Inactivating mutations in *CPE* result in a syndrome characterized by severe obesity, intellectual disability, disrupted glucose homeostasis, and IHH, a phenotype consistent with observations in *CPE* knockout mouse models (154). A subsequent study detected a homozygous non-sense *CPE* mutation in three obese siblings with mental retardation and IHH (155). Comparison with previously reported cases led to the delineation of a distinct clinical entity termed Blakemore-Durmaz-Vasileiou (BDV) syndrome, which is an extremely rare AR disorder characterized by a combination of impaired intellectual development, hyperphagia, and IHH (156).

POLR3A and *POLR3B*

RNA polymerase III regulates fundamental cellular processes through the transcription of small RNAs. Its catalytic core is composed of multiple subunits, including *POLR3A* and *POLR3B*. Pathogenic variants in these subunits have been associated with 4H syndrome (also known as POLR3-related leukodystrophy), a rare disorder characterized by hypomyelination, hypodontia, and IHH (157,158). Mice studies have shown that missense mutations in *POLR3A* and *POLR3B* can variably disrupt development and Pol III function (159). It is still unclear how inactivating mutations in those genes cause IHH.

Small GTPase related genes (*RAB18, RAB3GAP1, RAB3GAP2, TBC1D20,* and *DMXL2*)

Mutations in several genes related to small GTPases that include *RAB18, RAB3GAP1, RAB3GAP2, TBC1D20,* and *DMXL2*, have been implicated in IHH, often in conjunction with neurodegenerative features. Small GTPases are critical regulators of intracellular trafficking, particularly in endocytosis and exocytosis. RAB18 is a member of the Ras-related GTPases that play a role in apical endocytosis/recycling between the plasma membrane and early endosomes (160). Mutations in *RAB18* or in any of its essential regulators, *RAB3GAP1, RAB3GAP2,* and *TBC1D20* (161,162,163), are associated with Warburg micro syndrome type 3 (164). Warburg micro and Martsolf syndromes are overlapping clinical entities characterized by IHH, progressive spasticity, severe developmental delay, microcephaly, cortical visual impairment, hypotonia, and optic nerve atrophy. *DMXL2* encodes for rabconnectin-3a, which is a regulator of another intracellular GTPase, RAB3A. Rabconnectin-3a is expressed in exocytosis vesicles in GnRH axons in the median eminence of the hypothalamus (165). Furthermore, inactivating *DMXL2* mutations cause a novel complex syndrome that features IHH and a neurodegenerative phenotype, including cerebellar ataxia and demyelinating polyneuropathy, among other clinical features (165).

ARHGAP35 and *ARHGAP5*

ARHGAP35 which codes for Rho GTPase activating protein 35 and *ARHGAP5* which codes for Rho GTPase activating protein 5 are Rho GTPase activating protein genes. Rare protein-truncating variants (PTVs) in *ARHGAP35* have been reported to result in IHH. Zebrafish modeling has shown that neuronal areas are reduced in mutant embryos lacking the *ARHGAP35* paralog *ARHGAP35*. No changes were observed in the *ARHGAP35* paralog in functional studies, and it was identified as an IHH candidate. These observations suggest a novel role for the p190 RhoGAP proteins in GnRH neuronal development and integrity (166).

FSHB

FSHB encodes the beta subunit of follicle-stimulating hormone (FSH). A homozygous deletion of *FSHB* has been reported in a patient with nIHH, primary amenorrhea, and infertility due to isolated pituitary FSH deficiency (167). Studies have reported mutations in compound heterozygous, missense, and non-sense types (168,169). Mouse studies show that *FSHB*-/- female mice are sterile and hypogonadal (170).

LHB

Luteinizing hormone (LH), encoded by *LHB*, is a glycoprotein hormone essential for the regulation of gonadal function. A homozygous mutation in *LHB* was first identified in a patient with nIHH caused by biologically inactive LH (171,172). Subsequent studies have reported missense mutations, non-sense mutations, and small deletions in *LHB* associated with nIHH (173,174,175). In animal models, targeted disruption of *LHB* in mice resulted in reduced testicular size and decreased testosterone levels in males, while females exhibited a hypogonadal phenotype (176).

Scientific Significance of Identifying Ihh-Associated Genes

Undoubtedly, the most impactful contribution of IHH-associated gene studies has been the elucidation of the long-sought GnRH pulse generator, advancing our fundamental understanding of reproductive neuroendocrine regulation (177,178,179,180). A surge of research into kisspeptin and neurokinin B signaling, catalyzed by the discovery of inactivating mutations in familial cases of nIHH, has led to the characterization of the elusive GnRH pulse generator. Current understanding centers on a population of sex steroid-responsive neurons within the arcuate (infundibular) nucleus that co-express Kisspeptin, NKB, Dynorphin (KNDy), and estrogen receptor alpha (ERα), collectively termed KNDy neurons. Within this network, stimulatory signals from NKB initiate action potentials, which are subsequently attenuated by inhibitory dynorphin signaling. When dynorphin-mediated inhibition is overcome, a new cycle of NKB-induced excitation

ensues, resulting in rhythmic, intermittent action potentials. Each burst drives pulsatile kisspeptin release onto GnRH neuron terminals in the median eminence, thereby triggering GnRH secretion into the portal circulation and ultimately stimulating pituitary gonadotropes. The synchronization of KNDy neuronal activity is thought to be mediated by NKB-neurokinin-3 receptor (NK3R) signaling via ipsilateral and contralateral projections within the KNDy network (178,181,182).

Clinical Significance of Identifying IHH-Associated Genes

A major impact stemming from IHH-associated gene studies may be the translation into new therapeutic modalities. The first therapeutic oppurtunities linked to the identification of IHH genes stemmed from the discovery of *TAC3* and *TACR3* mutations in patients with nIHH (183). Antagonism of neurokinin B signaling has been used in the development of pharmacological therapies targeting two of the most common reproductive health disorders in women globally: menopausal hot flushes and polycystic ovary syndrome (PCOS).

In menopausal women, the decline in ovarian estrogen levels reduces negative feedback on KNDy neurons, causing them to become hypertrophied and to overproduce neurokinin B. KNDy neurons project to the *TACR3*-expressing median preoptic nucleus within the hypothalamus, a key region involved in thermosensory processing and heat-defense mechanisms (184,185). Building on these observations, the Rance laboratory demonstrated that ablation of KNDy neurons in rats leads to a reduction in tail-skin temperature, indicating that NKB promote cutaneous vasodilation, a key physiological component of hot flushes (186). Following clinical trials, fezolinetant, which is a selective *NK3R* antagonist, was approved for the treatment of vasomotor symptoms in menopausal women in 2023 (187,188).

NK3R antagonists also have potential for the treatment of PCOS. In premenopausal women, NK3R antagonism decreases the GnRH pulse frequency leading to reduced basal LH secretion, lower LH/FSH ratio, and the modulation of the temporal dynamics of ovarian sex hormone production over the menstrual cycle (189). The NK3R antagonist, MLE4901, was demonstrated to reduce LH pulse frequency, as well as serum LH and testosterone levels, in women with PCOS (190). These hormonal findings were validated in a recent study involving fezolinetant. However, no significant improvement was observed in menstrual cycle regularity or clinical outcome scores (187). The investigators noted that the 12-week treatment duration in this trial may have been insufficient to elicit measurable changes, as favorable clinical outcomes in PCOS trials are typically observed after 6 to 9 months of therapy (187,191). The use of an NK3R antagonist as a therapeutic agent for PCOS remains a promising strategy, given its potential to modulate the neuroendocrine dysregulation underlying the condition.

Concluding Remarks

Currently, approximately half of the genes underlying IHH remain unidentified. The complexity of genotype-phenotype correlations in IHH, largely due to the established phenomena of oligogenic inheritance and spontaneous or treatment-induced clinical reversibility, poses significant challenges to gene discovery. Nevertheless, advances in next-generation sequencing technologies are expected to drive continued progress in uncovering the genetic basis of IHH. These investigations not only enhance our understanding of fundamental biological processes, such as the recent elucidation of the GnRH pulse generator, but also inform the development of targeted therapeutics, exemplified by the approval of fezolinetant for the treatment of menopausal hot flushes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A. Kemal Topaloğlu, Concept: A. Kemal Topaloğlu, Design: A. Kemal Topaloğlu, Data Collection or Processing: A. Kemal Topaloğlu, Analysis or Interpretation: A. Kemal Topaloğlu, Literature Search: A. Kemal Topaloğlu, Leman Damla Kotan, Writing: A. Kemal Topaloğlu, Leman Damla Kotan.

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Type 1 Diabetes Mellitus and Transfer from Pediatric to Adult Care: A Single-Center Experience

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ABSTRACT

Objective: Type 1 diabetes mellitus (T1DM) requires lifelong follow-up, and the transition from pediatric to adult care may influence clinical outcomes. To evaluate sociodemographic, clinical, and laboratory characteristics associated with the transition process in patients with T1DM and to compare two different transition models.

Methods: Patients with T1DM transferred to an adult outpatient clinic between 2001 and 2022 were retrospectively assessed. Demographic data, metabolic parameters, complications, and treatment modalities before and after transition were assessed. Transition was performed either as a single-session model (Model 1) or as a gradual process over 4-6 months (Model 2).

Results: A total of 64 patients transitioned over the 21 year study period. The annual number of follow-up visits was significantly lower in adult care (3.0±0.9 vs. 2.1±1.8 visits/year; p=0.009). HbA1c levels were also lower in adulthood (8.9% vs. 8.3%; p=0.007). Total insulin dose was lower (0.95 vs. 0.75 IU/kg/day; p=0.009), whereas the basal insulin ratio was higher (43.1% vs. 52.8%; p<0.0001). Although mean body mass index slightly decreased, obesity prevalence increased. No significant differences were observed between the two transition models in terms of glycemic outcomes, insulin requirements, or complication rates.

Conclusion: A structured transition process was associated with improved glycemic control and treatment adaptation in T1DM, regardless of whether it is implemented as a single-session or gradual model. The absence of major differences between models may support the importance of individualized, patient-centered transition strategies.

Keywords: Type 1 diabetes mellitus, transition, diabetes care

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What is already known on this topic?

Transitioning from pediatric to adult care is a challenging period for patients with type 1 diabetes mellitus (T1DM), often resulting in poor glycemic control and increased dropout rates. Effective transition models are essential to ensure continuity of care and reduce complications.

What this study adds?

This study shows that, regardless of the transition model, patients experienced improvements in hemoglobin A1c levels and insulin management during adult care follow-up. These findings highlight the importance of supporting adolescents with T1D during the transition period with coordinated care models tailored to their individual needs.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease that usually starts in childhood and adolescence, and requires lifelong follow-up and treatment. The transition process refers to the transfer of an individual with diabetes from pediatric care to adult care, and this process may be a difficult period for individuals. Significant changes take place in their school lives, working and financial situations during this process. Perhaps more importantly, they will be struggling with the psychological and physiological changes of adolescence (1). It is also a period in which they gradually take responsibility for their illness from their families. These changes in patients' personal lives and medical care may disrupt diabetes follow-up and treatment (2,3,4). A poorly planned transition has been shown to lead to 60% of these patients dropping out of follow-up (5). Studies have shown that glycemic control worsens during the transition from childhood to adulthood (6). The time when hemoglobin A1c (HbA1c) levels are the highest coincides with the transition period, that is, late adolescence and early adulthood. Poor glycemic control is associated with an increased risk of chronic complications and mortality (7,8). Approximately 50% of young adults with T1DM develop diabetes-related complications such as retinopathy, neuropathy and hypertension in their 20s (9). Shifting from pediatric to adult follow-up is important for enhancing patient compliance and, consequently, improving long-term patient monitoring and health outcomes. The transition from pediatric to adult follow-up should ideally be seamless and well coordinated, and take into account the social and psychological development of the patient (10). The American Diabetes Association recommends that preparations for adult follow-up begin one year before transition and that patients should be encouraged and educated about their diabetes responsibilities during adolescence (11).

To strengthen the support provided to young adults with T1DM, it is essential to determine factors associated with successful transition and continuity of care. In our study, the aim was to retrospectively analyze the sociodemographic, medical, and laboratory features of individuals with T1DM who transitioned from pediatric to adult care at our hospital, and to compare the outcomes of two different structured transition models. We hypothesized that structured and gradual transition models would be associated with better metabolic outcomes and treatment adherence compared to single-session transfers.

Methods

Research Design

This study was conducted as a retrospective cohort analysis to examine the sociodemographic, clinical, and laboratory characteristics of patients with T1DM who transitioned from pediatric follow-up to the adult endocrinology outpatient clinic at Istanbul University, Istanbul Faculty of Medicine, and to compare different transition models. A total of 73 T1DM patients who completed pediatric care and were transferred to adult follow-up between 2001 and 2022, and whose medical records were accessible, were initially considered for inclusion. However, five patients who were lost to follow-up after a single visit and four patients who had only recently been transferred were excluded from the final analysis. As a result, complete pediatric and adult electronic medical records of 64 patients were included in the study. Exclusion criteria were: missing data, discontinuation of care before transfer to adult follow-up, and a diagnosis of type 2 diabetes mellitus. Due to the retrospective nature of the study and the wide time frame (2001-2022), the duration of adult follow-up varied significantly. While some patients had only recently transitioned, others had been under adult care for more than a decade. This variability resulted in a broad follow-up range, from a few months to over 20 years. Sociodemographic characteristics, clinical data, and laboratory findings were obtained retrospectively from patient files. A detailed flowchart illustrating the sample selection process is provided in Figure 1.

Transition Models

In Model 1 (n=36), the transition was conducted through a single structured meeting lasting 90 minutes in the pediatric endocrinology clinic, where the clinical evaluation was carried out by the pediatric endocrinology team. This session was attended by pediatric endocrinologists, adult endocrinology and metabolism specialists, pediatric and adult diabetes nurses and diabetes

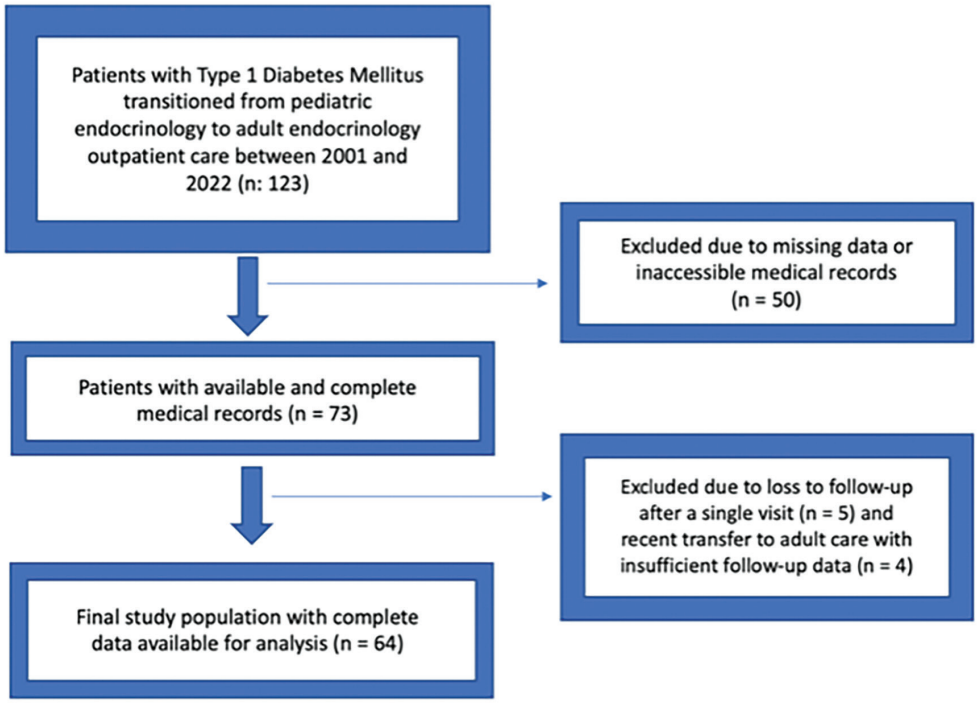

Figure 1. Flowchart of patient screening and selection for the study

dietitians along with the patient and their family. During the meeting, patients received comprehensive education covering: (a) detailed explanation of adult clinic expectations and procedures, including appointment scheduling and emergency protocols; (b) assessment of current clinical status and self-care competencies; and (c) personalized transition goal setting.

In Model 2 (n=24), the transition process involved two structured meetings (60-90 minutes each) conducted over a 4-6 month period by a multidisciplinary team comprising pediatric and adult endocrinologists and dietitians. The first meeting was held in the pediatric endocrinology clinic, while the second took place in the adult endocrinology outpatient clinic. The number of visits was increased in individuals with low cooperation. Specifically, for two patients who were considered not yet ready to assume full responsibility for diabetes self-management, the number of structured visits was increased to three. These additional sessions aimed to enhance self-care competency and support a smoother transition into adult services. These sessions were designed to: (a) provide graduated education on autonomous disease management; (b) reinforce self-monitoring skills and complication prevention strategies; and (c) administer final competency evaluations before adult care transfer. Both meetings incorporated individualized care planning based on continuous glucose monitoring (CGM) data and HbA1c trends.

All transition meetings systematically addressed three core domains: (1) clinical status evaluation, including glycemic control metrics and complication screening; (2) self-management capacity building emphasizing medication adherence and problem-solving skills; and (3) healthcare system navigation training, covering insurance transition and adult service utilization.

During the coronavirus disease-19 pandemic period, four patients were transferred directly to the adult endocrinology outpatient clinic as face-to-face transition meetings could not be held. Instead, these patients received information regarding the transition process via telephone consultation. Since their transfer procedures did not align with the structured models and could introduce bias in group-based statistical comparisons, they were excluded from the model analyses.

Data Collection and Definitions

Sociodemographic data included sex, age, body mass index (BMI) and diabetes education status of the patients. The duration of the disease, number of medical appointments during the transition period, average number of annual visits in pediatric and adult follow-up, insulin treatment dose, use of continuous subcutaneous insulin infusion (CSII) therapy, diabetes-related acute (number of emergency admissions with diabetic ketoacidosis) and chronic complications (retinopathy, neuropathy, hypertension), comorbidities, and HbA1c levels

were also evaluated. Data on the screening, diagnosis, and treatment of microalbuminuria, neuropathy, retinopathy and dyslipidemia were collected for each patient prior to and after the transition. HbA1c levels were evaluated based on the mean values recorded during pediatric and adult follow-up visits. For hyperlipidemia, low density lipoprotein (LDL) ≥100 mg/dL and statin use were recorded as dyslipidemia. Patients with a urine microalbumin/creatinine ratio of ≥30 mg/g were considered to have microalbuminuria. The pre- and post-transition examination records were evaluated for retinopathy and peripheral neuropathy.

Ethical Considerations

The study was approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval no.: 2023/785, date: 15.05.2023).

Statistical Analysis

The data obtained in the study were analyzed using SPSS software, version 23 (IBM Inc., Armonk, NY, USA). Descriptive statistics (mean, standard deviation and frequency) and comparative analysis methods (t-test and chi-square test) were used to assess variations between the groups. For statistical significance, a threshold of $p<0.05$ was applied.

Results

Population Characteristics

The study included the medical records of 64 patients with T1DM who transitioned during the study period. Among the patients enrolled in the study, 43.7% were female, and the median age at diagnosis was 9.25 years (range 0.8-17.5 years). At their last pediatric visit, the mean age of the patients was 19.4±1.2 years (range: 16.6-21.9). The mean age at the time of transition to adult care was 20.2±1.4 years (range: 17.7-23.1), and the mean age at the last adult visit was 23.2±4.2 years (range: 18.4-39.5). The median follow-up duration after transition to adult care was 3.3 years (range 0.3-20.9). Furthermore, 32.8% were seen within the first six months, 51.6% within the first two years, and 75% within four years. BMI decreased from 24.1±1.7 kg/m² at transition to 23.6±3.5 kg/m² at the last adult visit. While the prevalence of obesity was 1.6% (n=1) in the pediatric follow-up, this rate increased to 9.3% (n=6) at the last visit in adult care. Although mean BMI slightly decreased, the proportion of participants classified as obese increased during adult follow-up (Table 1).

Clinical Outcomes

Routine control visits in diabetes care were more frequent during pediatric follow-up (3.0±0.9 vs. 2.1±1.8, p=0.009). Total insulin doses at the time of transition were significantly higher compared to the last visit in adult care (0.95 IU/kg/day at transition vs. 0.75 IU/kg/day in adult care; p=0.009). The proportion of basal insulin was higher in the adult care group (43.1% in pediatric follow-up, 52.8% in adult care; p<0.0001). Although CSII was used more frequently in the adult care group (12.5% vs. 4.7%), this difference was not significant (p=0.11). The mean HbA1c levels were significantly lower in the adult period (8.9% in pediatric follow-up vs. 8.3% in adult care; p=0.007) (Table 2).

To minimise the potential bias introduced by very long adult follow-up times, we re-analysed outcomes in a subgroup with ≤4 years of adult follow-up (n=48; 75% of the study cohort). The direction and magnitude of the main findings remained unchanged. HbA1c decreased from 8.85±1.63% to 8.36±1.86% (p=0.047), daily insulin requirement declined (0.87±0.27 vs. 0.80±0.27 IU/kg; p<0.001), and the basal-insulin ratio increased (44.2±12.4% vs. 51.2±11.6 %; p<0.001). Visit frequency was still lower in adulthood (2.9±0.7 vs. 2.3±0.7 visits/year; p=0.039). Detailed results are provided in Supplementary Table S1.

Table 1. Comparison of demographic and anthropometric data before and after the transfer in individuals with type 1 diabetes mellitus

Demographics and anthropometry	Last pediatric evaluation (n=64)	Post-transition evaluation (n=64)
Gender n (%)		
Female	28 (43.7%)	
Male	36 (56.3%)	
Age (years) (mean±SD)	19.36±1.29	23.3±4.2
Body weight (kg) (mean±SD)	68.5±13.5	71.7±22.0
Body mass index (kg/m²) (mean±SD)	24.1±1.65	23.6±3.5
Body mass index categories n (%)		
Normal	43 (67.2%)	44 (68.7%)
Overweight	20 (31.2%)	14 (21.8%)
Obese	1 (1.6%)	6 (9.3%)

Data are presented as mean±standard deviation or frequency. This table provides descriptive comparisons between the last pediatric evaluation and the last adult visit.
SD: standard deviation

Complications and Comorbidities

There was no difference in the frequency of autoimmune thyroiditis and celiac disease between pediatric and adult care. Microvascular and macrovascular complications were observed more frequently during adult care. However, no significant statistical variation was observed in acute or chronic complications (Table 3).

No significant differences were observed between the two groups in mean HbA1c, annual visit frequency, BMI, insulin dose, carbohydrate-counting knowledge or practice, CSII/multiple daily injections/CGM use, or the prevalence of nephropathy and neuropathy (Supplementary Table S2). The same overall pattern was confirmed in a sensitivity analysis restricted to the sub-group of participants with ≤4 years of adult follow-up (Supplementary Table S3). The only between-model significant differences were a slightly higher pediatric visit frequency and a larger reduction in visit rate after transfer in Model 1 (p=0.025 and p=0.014, respectively).

Discussion

The transition from pediatric to adult care is a difficult process in many respects, and patients with diabetes are currently prepared for the transition period from pediatric to adult care in limited centers (12). For patients to undergo a smooth transition, the distinctions between pediatric and adult care should be appropriately addressed. In the present study, patients with T1DM who switched from pediatric to adult follow-up were examined using pre- and post-transition data, and two different transition models were compared. Our findings show that the mean age at the time of transition to adult care was 20.2±1.4 years (range 17.7-23.1). Early transition age may be advantageous for individual adaptation; however, many authors suggest that transition occur after psychosocial maturity (13). Therefore, transition age should be determined in relation to the patient's social and clinical status, and pediatric endocrinologists should make individualized decisions based on these factors.

Table 2. Comparison of clinical parameters between pediatric and adult follow-up periods

Clinical parameters	Pediatric follow-up (n=64)	Adult follow-up (n=64)	p value
Follow-up duration (years) (mean±SD)	10.6±4.1	3.1±4.2	<0.0001
Number of visits/year (mean±SD)	3.0±0.9	2.1±1.8	0.009
HbA1c (last year) (%) (mean±SD)	8.95±1.6	8.3±1.6	0.007
Knows carbohydrate counting n (%)	34 (53.1%)	35 (55.6%)	0.78
Practices carbohydrate counting n (%)	25 (39.7%)	24 (38.1%)	0.85
Insulin dose (IU/kg/day) (mean±SD)	0.95±0.3	0.75±0.34	<0.0001
Basal insulin ratio (%) (mean±SD)	43.1±10.8	52.8±11.3	<0.0001
Insulin therapy modality			
Multiple daily doses n (%)	61 (95.3%)	56 (87.5%)	0.011
Continuous subcutaneous insulin infusion therapy n (%)	3 (4.7%)	8 (12.5%)	

Follow-up duration and annual number of visits represent average values across the pediatric and adult care periods. HbA1c refers to the mean of the final year in each period. Knowledge and practice of carbohydrate counting, insulin treatment model, insulin dose, and basal insulin ratio were assessed based on the last recorded visit in each setting.
SD: standard deviation, HbA1c: hemoglobin A1c.

Table 3. Evaluation of comorbidities and complications before and after the transition in individuals with type 1 diabetes mellitus

Comorbidities	Before transition	After transition	p value
Celiac disease n (%)	2 (3.1%)	2 (3.1%)	0.96
Hashimoto thyroiditis n (%)	15 (23.4%)	14 (21.9%)	0.75
Complications	**Before transition**	**After transition**	**p value**
Nephropathy n (%)	8 (12.5%)	11 (18%)	0.389
Retinopathy n (%)	1 (1.6%)	3 (4.9%)	0.286
Neuropathy n (%)	2 (3.1%)	4 (6.6%)	0.369
Hyperlipidemia n (%)	8 (12.5%)	13 (21.3%)	0.187
DKA episodes per year (mean±SD)	0.2±0.64	0.2±0.64	0.103

DKA: diabetic ketoacidosis

In the present study, a comparison of patients' mean HbA1c levels before and after transfer demonstrated a significant (p=0.007) reduction in HbA1c levels during the adult period. Young people have been reported to make up the largest proportion among groups with poor diabetes management (HbA1c≥9.5%), and high HbA1c levels have been detected in 25% of patients older than 12 years (14,15). In a review, HbA1c improved significantly after transition to adult care in five of the eight studies examined. Although care centers and transition methods differed in these studies, it was thought that the transition facilitated adult care (16). In adult care, individuals assuming greater responsibility for disease management and engaging more in follow-up and treatment may contribute to the decrease in HbA1c levels (15,17). However, in a retrospective study by Walch et al. (18), no notable alteration in HbA1c levels was detected after the transition to adult care. Another study examined standard and intervention transition methods, enrolling 101 patients under routine care and 102 individuals in the intervention-based transition group. Although HbA1c levels were similar 12 and 18 months after transition, participation in health services was higher in the intervention transition group (19). Our findings are in line with the systematic review by DeLacey et al. (20), which highlighted that while structured transition programs or provider-led interventions may yield modest improvements in glycemic control after transfer, the overall evidence base remains limited and inconsistent. Most existing studies lack long-term follow-up or standardized outcome reporting, making it difficult to draw strong conclusions regarding the effectiveness of transition strategies (20).

Differences in insulin treatment were observed in adult care compared to those before transition. During the adult care period, the total daily insulin dose was noticeably lower than the dose at the time of transition (0.75 IU/kg/day vs. 0.95 IU/kg/day p=0.009). This decrease in insulin dose after transition to adult care may reflect age-related changes in insulin requirements and improvements in self-management during adulthood (1,21,22). A structured transition process can support improved glycemic control in T1DM management, whether implemented through single-session or stepped models. Our protocolized transition approach, which features standardized training modules, multidisciplinary team involvement, and competency assessments, was associated with clinically meaningful HbA1c reduction and decreased insulin requirements, though whether this reflects the transition process itself or improved care quality in the adult setting cannot be determined from our retrospective data. In our cohort, we found a significantly increased basal insulin ratio in the adult group (p<0.0001) and this finding is consistent with the literature, which reports that basal insulin requirements in children usually do not exceed 30-45% of the total daily insulin dose, whereas this ratio usually exceeds 50% in adults. This is noteworthy in view of the fundamental changes in the insulin regimen during the transition to adulthood (23,24,25,26). This increase in basal insulin rate may be due to the need for more frequent insulin dose adjustments at meals and higher bolus insulin requirements during childhood (25,27,28). Positive effects of CSII on glycemic control have been reported in the literature (29). We found that the rate of CSII use in adult care was relatively higher than in pediatric care, suggesting that access to emerging technologies and individualized treatment options in diabetes care may be more prevalent in adult patients. Moreover, time passing while patients were growing up was concordant with more widespread use of this technology. Our finding was not significant but this result should be re-evaluated with a larger sample groups. Furthermore, although follow-up durations varied widely in our cohort, a sensitivity analysis limited to patients with ≤4 years of adult follow-up did not alter the main findings for HbA1c, insulin requirements, or the other key outcomes. Nevertheless, it remains possible that very long follow-up periods could partially obscure the true impact of the transition process.

Studies on the effect of transition on the frequency of follow-up in T1DM have yielded variable results (30,31). In a study comparing interventional transition with standard transition, 104 patients were included in the transition program, while 101 patients underwent a standard transition plan. Follow-up frequency and patient satisfaction were found to be higher in the intervention transition group. However, these benefits were not sustained in the 12-month period after the completion of the intervention and it was suggested that strategies are needed to sustain long-term benefits (3). In an Australian study involving 60 participants in the intervention group and 60 in the control group, no difference was found in the average frequency of appointments between the two groups over 12 months. Although the number of visits decreased in adult follow-up, HbA1c was found to be lower in the present study (30). Our findings are consistent with the study by Busse et al. (31), who observed a decrease in outpatient visits during adulthood and interpreted this as adults taking responsibility for their own care.

Diabetes-related complications before and after transition have been investigated less frequently. Walch et al. (18) retrospectively analyzed the medical records of 54 patients with T1DM. Complications including hypertension, dyslipidemia, nephropathy, and neuropathy were examined in patients who switched from pediatric care to adult follow-up, and no significant difference was found in the rate of complications before and after transition (18). A study conducted in Canada showed that the frequency of retinopathy screening did not change before and after transition, while at the same time, there was no significant difference in the rate of hospitalization due to diabetes before and after transition (32). Although micro- and macrovascular complications were observed more frequently

in adult care in our study, the difference between acute and chronic complications in the pre-transition period was not significant. This may be due to the longer pediatric follow-up period (10.6±4.1 years) compared to the adult follow-up period (3.1±4.2 years). The shorter follow-up period in adult care suggests that some complications may not have fully emerged in these young adult patients, or that complications may not have been recognized early. Future research with an extended monitoring period is required to validate these results. Furthermore, given the wide range in adult follow-up durations (from less than one year to over 20 years), complication-related outcomes should be interpreted with caution. In patients with shorter follow-up durations, chronic complications may not have had sufficient time to manifest or be detected.

Research has shown that single-session transitions can increase patient satisfaction and engagement. In one study, a single-session transition clinic model positively affected patient and parent satisfaction and made the transition process more effective (33). However, for some patients, this rapid transition can be stressful. In contrast, gradual transitions have been shown to facilitate patient compliance and increase treatment adherence, but it has also been emphasized that such gradual transitions require more resources. For the gradual transition model, it has been reported that this method can facilitate the adaptation process of young people. A study by the American Diabetes Association found that young people prefer a delayed or gradual transition to adult care. In this research, young people expressed that they found it more comfortable to transition to adult care with a longer transition period, especially due to their relationship and commitment to pediatric care providers (34,35). However, in our study there was no difference with respect to transition models. In the ≤4-year sensitivity comparison, we found no clinically meaningful differences between the two structured transition models in metabolic control or complication rates. The only divergence was a slightly higher pediatric visit frequency and a more pronounced decline in visit rate after transfer in Model 1, a pattern that did not translate into any adverse clinical outcomes.

Study Limitations

The single-center design and the restricted patient cohort (64 patients) were two limitations of our study. This may limit the applicability of the findings to larger or more diverse populations. Moreover, because structured transition care has been mandatory for all young people with T1DM at our centre since 2000, it was impossible to assemble a control group that underwent an unstructured transfer. The absence of such a comparator limits our ability to quantify the added value of the transition models. In addition, our study did not include assessments of psychosocial readiness, patient satisfaction, or family involvement, which are increasingly recognized as critical components of successful transition. This limits our ability to capture the broader patient experience and evaluate non-medical outcomes related to the transition process. Finally, adult BMI is reported as mean±SD together with weight-status categories because a validated adult BMI-SDS reference is not available and paediatric SDS could not be calculated uniformly for all participants; this will hinder direct comparison with studies that report z-scores.

Conclusion

Considering the difficulties and varying outcomes of transitioning from pediatric to adult care, developing individualized approaches can significantly improve patient experiences and long-term diabetes management. However, transition outpatient clinics present several challenges in daily practice, including resource limitations, multidisciplinary work, compliance and additional time for both healthcare professionals and patients. Therefore, further research is required to evaluate the long-term impact of transition outpatient clinics and to assess the effectiveness of different models in managing blood glucose levels, preventing complications, and enhancing patient experience, improving the transition process and ultimately improving patient health outcomes.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval no.: 2023/785, date: 15.05.2023).

Informed Consent: Retrospective cohort analysis study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Betul Yigit Yalcin, Ummahan Tercan, Hulya Hacisahinogullari; Concept: Gulsah Yenidunya Yalin, Nurdan Gul, Ozlem Soyluk Selcukbiricik, Ayse Kubat Uzum, Sukran Poyrazoglu, Firdevs Bas, Kubilay Karsidag, Ilhan Satman, Feyza Darendeliler; Design: Melek Yildiz, Hulya Hacisahinogullari; Data Collection or Processing: Betul Yigit Yalcin, Ummahan Tercan; Analysis or Interpretation: Melek Yildiz, Firdevs Bas, Ilhan Satman; Literature Search: Betul Yigit Yalcin, Ummahan Tercan, Ayse Kubat Uzum, Sukran Poyrazoglu; Writing: Betul Yigit Yalcin, Ayse Kubat Uzum, Feyza Darendeliler.

Conflict of Interest: One author of this article, Feyza Darendeliler, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she was not involved in any stage of the editorial decision process for this manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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Supplementary Tables: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/20508f89-22f5-47d0-871b-f454f6145583.pdf

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Isolated Hypoglycemia in Children with Cystic Fibrosis: Role of Pancreatic Insufficiency and Glucagon Response

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ABSTRACT

Objective: Hypoglycemia is one of the comorbidities that adversely affects the quality of life in patients with cystic fibrosis (CF). Isolated hypoglycemia (IsoHypo) is poorly described in patients with CF and its etiopathogenic significance is unclear. To investigate the etiopathogenesis of IsoHypo and the role of pancreatic insufficiency (PI) in IsoHypo in children with CF.

Methods: The blood glucose, insulin, and glucagon responses of patients with CF and healthy controls were evaluated during a 3-hour oral glucose tolerance test. Based on the results, the patients were categorized into 5 groups: 1) normal glucose tolerance (NGT); 2) IsoHypo; 3) hypoglycaemia with abnormal glucose tolerance (Hypo+AGT); 4) AGT; and 5) CF-related diabetes. IsoHypo and NGT were sub-classified according to the presence of PI as PI(+) or PI(-). Hypoglycemia was defined as blood glucose <70 mg/dL.

Results: A total of 44 patients with CF and 9 controls. Hypoglycaemia was observed in 21 of 44 patients (47.7%), predominantly as IsoHypo (29.5%). Hypo+AGT was found in eight patients (18.2%). The IsoHypo group exhibited undelayed and higher insulin secretion than the Hypo+AGT group, with IsoHypo PI(-) being less impaired compared to IsoHypo PI(+). Both IsoHypo and Hypo+AGT groups exhibited a blunted rise in glucagon at 180 minutes, with the deficiency being more pronounced in the Hypo+AGT group. Insulin and glucagon responses to oral glucose load in IsoHypo PI(+) were similar to Hypo+AGT, whereas they were less impaired in IsoHypo PI(-) patients who had early and higher insulin secretion.

Conclusion: IsoHypo is common in children with CF and may precede Hypo+AGT in those with PI(+). The abnormal insulin and glucagon responses to glucose appear to be the most significant contributors to the development of IsoHypo in CF.

Keywords: Cystic fibrosis, hypoglycemia, insulin, glucagon, children

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What is already known on this topic?

The possible mechanisms of hypoglycemia in cystic fibrosis (CF) are delayed and prolonged insulin secretion and/or impaired counterregulatory hormone function. However, CF patients in these studies had hypoglycemia with abnormal glucose tolerance (Hypo+AGT) and pancreatic insufficiency (PI).

What this study adds?

Isolated hypoglycemia in CF patients with pancreatic insufficiency (IsoHypo, PI+) is associated with delayed insulin secretion and impaired glucagon response. However, IsoHypo without pancreatic insufficiency is associated with early and exaggerated insulin secretion with relatively preserved but still insufficient glucagon response to hypoglycemia. IsoHypo PI(+) may be a predecessor to Hypo+AGT, whereas IsoHypo PI(-) appears to represent a milder impairment of glucose homeostasis in CF.

Introduction

In recent years, spontaneous or reactive hypoglycemia has been increasingly recognized in individuals with cystic fibrosis (CF), both during oral glucose tolerance test (OGTT) and in daily life. The reported prevalence varies widely, ranging from 7% to 69%, depending on the definition of hypoglycemia and the duration of OGTT (1,2,3,4,5,6,7). It is more frequently observed in 3-hour OGTTs, affecting approximately 45% to 65% of CF patients (6,7,8,9,10). One of the key pathophysiological features observed during OGTT in CF is a disruption of the biphasic insulin secretion pattern. The early (first phase) insulin response is often delayed, and this is followed by a prolonged and dysregulated insulin release. Recent studies suggest that this delayed and sustained hyperinsulinemia may predispose to postprandial or reactive hypoglycemia (8,9,10,11). In addition to beta-cell dysfunction, impaired suppression and a dysregulated response to glucose loading, rather than an absolute reduction, have been described in CF patients with abnormal glucose tolerance (AGT) and pancreatic insufficiency (PI). Furthermore, an inadequate glucagon increase in response to hypoglycemia (inappropriate response) may also contribute to the development of reactive hypoglycemia in these patients (8,9,11). Most studies investigating hypoglycemia in CF have focused on individuals with PI and have not included healthy control groups. Moreover, participants experiencing hypoglycemia in these studies often exhibited AGT (8,9,10,11).In our previous research, we identified cases of isolated hypoglycemia (IsoHypo) during OGTT in some children with CF who had normal glucose tolerance (4). The aim of the present study was to explore the mechanisms underlying IsoHypo and to assess the impact of PI on hypoglycemia in CF. We examined glucose, insulin, and glucagon responses to a three-hour OGTT in CF patients with and without PI, as well as in healthy controls.

Methods

Participants

Participants with CF aged 10-18 years, who had been regularly followed in the pediatric pulmonology and endocrinology departments, were invited to participate in this study (NCT05700604). Individuals on corticosteroid therapy, those who had experienced an acute exacerbation in the last three months, or those with a prior diagnosis of diabetes were excluded from the study. PI was defined as the need for enzyme replacement therapy due to clinical symptoms or a fecal elastase level below 200 µg/g stool and all patients with PI were receiving enzyme replacement therapy. All patients included in the study were receiving inhaled therapies because of underlying pulmonary involvement. None of the patients were on CFTR modulatory treatments and none had overt liver disease. The data collected from participants with CF included height, weight, body mass index (BMI), forced expiratory volume in one second (FEV1), molecular etiology, and the presence of PI.The control group consisted of age-matched healthy, non-diabetic siblings of children with type 1 diabetes, who were under follow-up at our clinic. All controls tested negative for pancreatic β-cell autoantibodies, including anti-glutamic acid decarboxylase, islet cell antibodies, and insulin antibodies. The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 09.2019.933, date: 01.11.2019), and written informed consent was obtained from participants or their parents.

Procedures

A 3-hour OGTT was performed in the morning following overnight fasting of at least 8 hours. All participants received oral glucose solution (1.75 g/kg; max: 75 g). Blood samples were collected at 0, 30, 60, 90, 120, 150 and 180 minutes for glucose and insulin, and at 0, 60, 120, 150 and 180 minutes for glucagon measurement. In addition, hemoglobin A1c (HbA1c) and C-reactive protein

(CRP) levels were measured at baseline to evaluate glucose metabolism and systemic inflammation, respectively. OGTT results were classified based on ISPAD guidelines (12). Participants with indeterminate glucose tolerance (INDET) or impaired glucose tolerance (IGT) without hypoglycemia were categorized as AGT. The terminology of "isolated hypoglycemia" (IsoHypo) was used for those who experienced hypoglycemia with normal glucose tolerance (NGT). The term "Hypo+AGT" was applied to the participants who had both hypoglycemia and AGT. According to the International Hypoglycaemia Study Group (IHSG) position statement, hypoglycemia is defined as any venous glucose level below 70 mg/dL (13). Although, in individuals not receiving glucose-lowering treatments, the threshold for defining hypoglycemia is recommended to be <54 mg/dL, venous glucose level below 70 mg/dL was chosen as the study hypoglycemia threshold, since the physiological counterregulatory glucagon response to falling glucose levels is known to begin at approximately 68 mg/dL (2). Following the initial analysis, participants with IsoHypo and NGT were further classified based on the presence of PI to evaluate the effect of PI on hypoglycemia (Figure 1). The NGT PI(-) group was selected as the reference group for hormonal comparisons, as these patients had both NGT and preserved pancreatic function, making them the relatively healthiest CF subgroup in terms of blood glucose homeostasis. This group was therefore considered the most appropriate baseline for evaluating the pathophysiology of isolated hypoglycemia.

Plasma Glucose, Insulin and Glucagon Analysis

Blood samples were collected in EDTA tubes and immediately centrifuged on-site after collection. Glucose and insulin measurements were performed on the same day in the laboratory. Glucose was analyzed using the glucose hexokinase method on the Cobas c701/702 (Roche, Uniq İstanbul, Türkiye), while insulin was measured by ECLIA on the Cobas e801 (Roche, Uniq İstanbul, Türkiye). For glucagon analysis, plasma was separated after centrifugation and stored at 4 °C until the OGTT was completed (180 minutes). Immediately afterward, all glucagon samples were transferred to -80 °C for long-term storage. Plasma glucagon levels was measured using a direct sandwich ELISA technique (Mercodia Glucagon ELISA, cat. no. 10-1271-01, lot no. 29870, Uppsala, Sweden) following the standard manufacturer's protocol. Insulin and glucagon responses were considered "inappropriate" if, during venous glucose concentrations below 70 mg/dL, insulin levels were not suppressed, and/or an increase in glucagon failed to raise venous glucose above 70 mg/dL.

Statistical Analysis

All analyses were made using SPSS, version 20 (IBM Inc. Armonk, NY, USA) and graphical figures were produced with GraphPad Prism, V5.0 software (GraphPad Software Inc., San Diego, California, USA). For groups with fewer than five patients (CF-related diabetes and AGT), data are summarized using only median and min-max values; and they are not included in the comparisons, although data is shown on Table 1. For all other

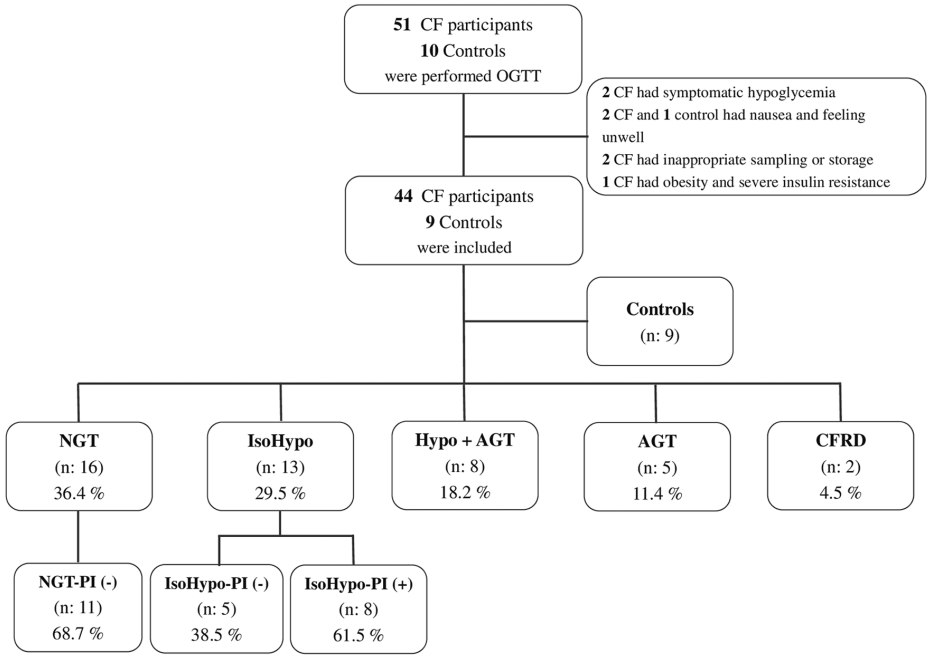

Figure 1. The distribution of the OGTT results
CF: cystic fibrosis, NGT: normal glucose tolerance, OGTT: oral glucose tolerance test, IsoHypo: isolated hypoglycemia

groups, both mean±SD and median (min-max) are reported due to the overall limited sample sizes.Data normality was assessed using Q-Q plot, the Shapiro Wilk test, and the Kolmogorov-Smirnov tests. Depending on normality, group comparisons were performed using either repeated ANOVA or the Kruskal-Wallis test. Post-hoc analysis for ANOVA were conducted using Tukey's or Tamhane's T2 test depending on the homogeneity of variances. For the Kruskal-Wallis test, post-hoc comparisons were performed using Kruskal-Wallis one-way ANOVA (k samples) test. Statistical significance was set at $p<0.05$.

Results

Baseline Characteristics and Prevalence of Hypoglycaemia

A total of 61 participants (51 with CF and 10 healthy controls) were recruited. Two CF participants experienced symptomatic hypoglycemia, necessitating the early termination of their OGTT. In addition, two CF participants and one control were unable to complete the OGTT because of nausea and discomfort. One CF participant with obesity and severe insulin resistance was also excluded. Samples from two CF participants were removed

Table 1. Demographic features and OGTT results of the participants

	Hypoglycemia (+)		**Hypoglycemia (-)**				
	Isolated Hypo (n=13)	**Hypo+AGT (n=8)**	**NGT (n=16)**	**AGT (n=5)**	**CFRD (n=2)**	**Control (n=9)**	**p**
Age, mean±SD	13.5±1.6	13.1±1.8	13.7±2.2	13.3±1.5	15.3 (12.6-17.9)	13.2±1.8	NS
Male, n (%)	10 (77)	4 (50)	9 (56)	3 (60)	1 (50)	4 (44)	NS
BMI SDS	-0.3±1.1 0.0 (-2.1-1.7)	-0.4±1.0 -0.2 (-1.6-1.0)	-0.1±0.8 0.0 (-1.6-1.0)	-0.6±0.5 -0.6 (-1.2-0.2)	-0.0 (-0.2-0.1)	0.0±0.7 -0.4 (-0.8-1.6)	NS
HbA1c, %	5.7±0.3 5.7 (5.1-6.0)	5.7±0.2 5.8 (5.4-6.1)	5.5±0.3 5.6 (4.8-6.0)	5.9±0.3 6.1 (5.6-6.3)	6.7 (5.9-7.5)	5.2±0.2 5.3 (4.9-5.6)	**0.004**[§,&,P]
CRP (mg/dL)	6.7±9.6 3.2 (3.1-38)	6.9±8.6 3.1 (3.1-27.6)	3.4±0.9 3.1 (3.1-6.8)	6.3±7.1 3.1 (3.1-19.1)	5.0 (3.1-6.9)	0.5±1.0 0.2 (0.1-2.9)	**<0.001**[§,&,P]
FEV1, %	86±29 94 (34-126)	88±18 87 (53-117)	92±9 94 (68-106)	77±28 77 (58-97)	99 (76-123)		NS
Genotype, n (%)							
ΔF508/ΔF508	1 (8)	2 (25)	1 (6)	1 (20)	1 (50)		NS
ΔF508/nonΔF508	5 (38)	2 (25)	3 (19)	2 (40)			NS
nonΔF508/nonΔF508	7 (54)	4 (50)	12 (75)	2 (40)	1 (50)		NS
PI, n (%)	8 (62)	8 (100)	5 (31)	5 (100)	2 (100)		0.005
OGTT							
Glucose (mg/dL) mean±SD and median (min-max)							
0. min	85±5 86 (75-93)	92±13 91 (80-116)	87±5 84 (80-98)	97±5 97 (91-103)	96 (91-102)	83±4 81 (79-89)	NS
30th min	170±28 173 (93-210)	178±27 174 (153-238)	143±25 138 (83-195)	181±46 195 (116-228)	187 (173-201)	133±16 129 (115-163)	**<0.001**[**,§,#,&]
60th min	152±43 162 (50-198)	229±21 230 (204-267)	125±29 118 (85-189)	201±53 202 (119-260)	266 (218-315)	126±26 119 (98-170)	**<0.001**[*,#,&]
90th min	120±37 129 (68-167)	177±40 168 (133-250)	105±17 104 (77-137)	173±22 164 (148-202)	292 (221-363)	120±27 112 (93-174)	**0.003**[#,&]
120th min	100±23 108 (58-125)	133±35 118 (99-190)	105±12 105 (78-126)	146±27 142 (120-177)	301 (228-375)	101±20 103 (64-130)	NS
150th min	77±20 79 (42-105)	91±23 91 (46-125)	102±17 98 (80-155)	128±30 121 (100-171)	237 (177-297)	90±17 90 (62-110)	**0.025**[**]
180th min	68±16 67 (46-98)	60±10 66 (42-68)	93±17 90 (70-128)	117±26 114 (84-154)	132 (75-190)	87±14 89 (59-102)	**<0.001**[**,#,&]

Table 1. Continued

	Hypoglycemia (+)		Hypoglycemia (-)				
Insulin (mIU/mL) mean±SD and median (min-max)							
0. min	8.3±6.1 6.2 (1.7-24.0)	5.9±5.1 4.4 (1.9-18.0)	8.0±4.3 8.6 (1.3-18.4)	8.3±1.5 8.1 (6.4-10.4)	14.3 (4.1-24.5)	10.9±7.5 8.6 (3.0-23.4)	NS
30th min	72.2±75.9 48.0 (8.4-243.0)	20.0±16.1 16.0 (4.4-55.0)	68.3±28.9 68.0 (16.0-113.0)	39.2±19.0 43.0 (8.0-58.0)	16.5 (15.0-18.0)	38.2±30.1 26.0 (3.9-108.0)	**0.002**[#]
60th min	93.3±91.0 58.0 (14.1-299.0)	63.5±71.1 45.0 (15.5-235.0)	59.5±36.7 46.7 (24.6-140.0)	46.4±28.1 41.9 (15.0-80.6)	22.2 (3.2-41.3)	51.5±25.4 47.3 (18.8-102)	NS
90th min	59.8±55.3 46.0 (2.4-181.0)	72.0±45.1 60.3 (34.2-166.0)	46.1±29.8 37.0 (17.0-103.0)	50.1±19.3 54.0 (28.0-71.0)	24.0 (3.0-45.0)	54.9±49.0 48.0 (3.4-169.0)	NS
120th min	39.5±22.2 38.2 (12.3-89.2)	35.1±13.9 37.4 (6.0-51.1)	41.9±22.4 35.7 (18.6-89.2)	49.5±16.0 41.6 (34.9-73.7)	24.8 (3.0-46.7)	49.2±35.5 48.3 (13.8-135.0)	NS
150th min	16.5±7.1 14.8 (1.3-31.1)	17.5±11.1 18.0 (4.6-31.3)	34.6±17.0 28.1 (12.2-73.6)	37.8±10.7 37.1 (21.9-43.9)	46.4 (11.2-81.6)	31.5±35.3 24.1 (1.1-119.0)	**0.013**[**]
180th min	12.3±8.8 10.0 (0.9-29.0)	8.2±6.1 7.3 (1.5-18.7)	29.2±24.4 20.6 (7.0-105.2)	23.1±11.1 24.5 (4.6-32.1)	40.1 (20.1-59.4)	23.5±18.2 20.4 (6.1-68.4)	**0.004**[#]
Glucagon (pmol/L) mean±SD and median (min-max)							
0. min	6.1±5.6 4.0 (1.7-22.4)	5.7±2.9 5.7 (2.1-9.7)	4.9±2.2 4.4 (1.3-9.3)	9.7±6.1 10.4 (1.3-16.3)		7.2±3.7 6.4 (3.7-15.8)	NS
60th min	3.4±1.5 3.0 (1.8-6.7)	5.8±5.1 4.2 (0.1-16.7)	2.8±2.3 2.1 (0.4-7.1)	5.5±5.0 4.9 (0.3-11.0)	5.0 (4.2-5.8)	1.7±1.2 1.7 (0.2-3.5)	**0.037**[&]
120th min	3.8±2.1 3.0 (1.7-8.1)	4.2±3.3 3.2 (1.4-11.6)	3.0±2.0 2.6 (0.1-8.4)	4.2±2.9 4.9 (0.4-6.9)	18.3 (3.2-33.3)	1.3±1.1 1.2 (0.1-3.3)	**0.009**[§,&]
150th min	4.1±3.0 3.8 (1.4-11.7)	4.0±2.5 3.3 (1.9-9.6)	2.6±1.6 2.0 (0.8-6.0)	4.3±2.9 4.1 (0.6-8.8)	5.0 (3.0-7.0)	2.1±2.3 1.3 (0.5-7.6)	**0.031**[&]
180th min	6.4±5.9 4.7 (0.6-21.8)	5.1±4.0 4.4 (0.1-11.2)	2.7±1.6 2.2 (0.4-6.6)	2.5±1.4 2.9 (0.3-4.0)	8.7 (4.8-12.6)	5.4±6.6 3.3 (1.0-21.2)	NS

Analyses were performed only for groups with more than five patients; AGT and CFRD groups were excluded. Data are presented as mean±SD and median (min-max). [*]IsoHypo vs Hypo+AGT, [**]IsoHypo vs NGT, [§]IsoHypo vs Controls, [#]Hypo+AGT vs NGT, [&]Hypo+AGT vs Controls, [P]NGT vs Controls

from the analysis because of improper sampling or storage. The final study cohort consisted of 53 participants (44 with CF and 9 controls) and these were included in the final analysis (Figure 1).

Based on the OGTT results, the patients were categorized into 5 groups: 1) normal glucose tolerance (NGT; n=16); 2) isolated hypoglycemia (IsoHypo; n=13); 3) hypoglycemia with abnormal glucose tolerance (Hypo+AGT; n=8); 4) AGT (n=5); and 5) CF-related diabetes (n=2).

The frequency of hypoglycemia in participants with CF was 47.7% (21/44) and 22.2% (2/9) in the healthy controls (p>0.05). The mean HbA1c and CRP levels were higher in all CF groups compared to the controls (p=0.004 and p<0.001, respectively) but no difference was observed between CF groups. There was also no difference in FEV1 and CFTR genotype between the CF groups (Table 1). There was a significant difference in the frequency of PI between OGTT groups in CF participants (p=0.005) (Table 1). Hypoglycemia was significantly worse in CF participants with PI(+) than PI(-) (p=0.006).

Differences in OGTT Characteristics between IsoHypo, Hypo+AGT, NGT in the CF and Healthy Control Groups

While the time of peak glucose was at 30 min in the IsoHypo group, similar to the NGT and control groups, it was delayed in Hypo+AGT to 60 min.Glucose level at 30 minutes was statistically higher in both IsoHypo and Hypo+AGT than in NGT and controls (p<0.001), whereas high glucose levels at 60 and 90 minutes persisted only in Hypo+AGT (p<0.001 and p=0.003, respectively). Glucose at 180 minutes was similar in IsoHypo and Hypo+AGT and lower than NGT and controls (p<0.001). Compared to IsoHypo, Hypo+AGT exhibited a delayed insulin peak, whereas IsoHypo demonstrated the highest peak insulin levels among all groups. Although, the insulin levels at 150 and 180 min in IsoHypo and Hypo+AGT were significantly

lower than NGT (p=0.013 and p=0.004, respectively), they were inappropriately high in the context of lower glucose.In relation to glucagon, both the IsoHypo and Hypo+AGT groups exhibited inadequate suppression in response to glucose increase during the OGTT. This insufficiency was statistically significant in the Hypo+AGT group (p=0.037). In the IsoHypo group, it remained comparable to NGT and controls, even though glucose levels were significantly higher, suggesting an inadequate suppression. Furthermore, despite the presence of hypoglycemia at 180 minutes in the Hypo+AGT and IsoHypo groups, glucagon levels were comparable to those observed in the NGT and control groups (p=0.192) (Figure 2 and Table 1).

3.3. Effect of Pancreatic Insufficiency (PI) in IsoHypo Group

The participants with IsoHypo and NGT were also sub-classified according to the presence of PI as either PI(+) or PI(-). Glucose level was higher at 30 min (p=0.002) and lower at 180 min (p=0.008) in IsoHypo PI(+) compared to NGT PI(-) and controls, but not in IsoHypo PI(-) (Figure 2 and Table 2).

The insulin response to an oral glucose load in the IsoHypo PI(+) group was lower compared to the IsoHypo PI(-) group and was more akin to the response observed in the Hypo+AGT group (Figure 2). Similarly, the glucagon response pattern to the oral glucose load in IsoHypo PI(+) mirrored that of the Hypo+AGT group, demonstrating insufficient suppression and significantly elevated levels despite the glucose increase at 60 minutes during the OGTT (p=0.045). The glucagon response to declining glucose levels at 150 and 180 minutes in IsoHypo PI(+) was weak and inappropriate. In IsoHypo PI(-) group, glucagon levels at 120 and 150 minutes were significantly higher in comparison to the control group (p<0.05), while glucose levels were declining (Figure 2). Nevertheless, the glucagon response in IsoHypo PI(-) was inadequate to prevent mild hypoglycemia.

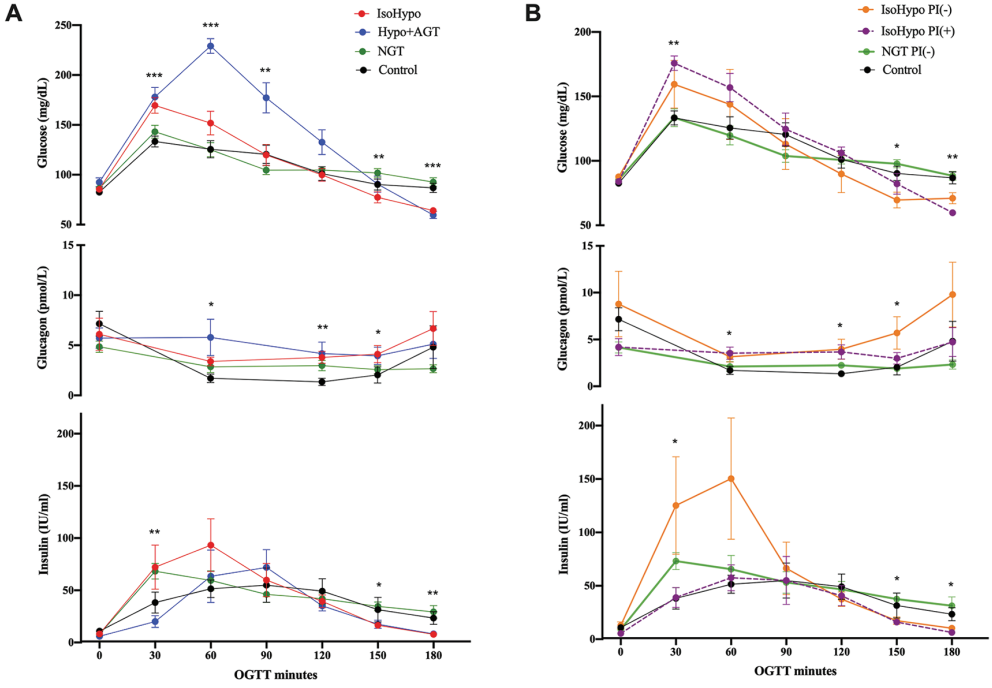

Figure 2. Glucose, insulin, and glucagon changes of the groups during OGTT. In graph A, red line shows the participants with isolated Hypoglycemia (IsoHypo), blue line shows the participants with hypoglycemia with abnormal glucose tolerance (Hypo+AGT), dark green line shows the participants with normal glucose tolerance (NGT), black line shows the healthy controls. Data are presented mean±SE. In graph B, purple line shows the participants with IsoHypo with pancreatic insufficiency [IsoHypo PI(+)], orange line shows the participants with IsoHypo without pancreatic insufficiency [IsoHypo PI(-)], light green line shows the participants with NGT without pancreatic insufficiency [NGT PI(-)], black line shows the healthy controls. Data are presented mean±SE. Statistical significance is indicated as *<0.05, **<0.01, ***<0.001

Table 2. Demographic features and OGTT results of the participants with IsoHypo and NGT according to the presence of pancreatic insufficiency

	IsoHypo PI (-) (n=5)	IsoHypo PI (+) (n=8)	NGT PI (-) (n=11)	Control (n=9)	p
Age (mean)	14.4 ± 1.3	13.0 ± 1.6	14.2 ± 2.4	13.2±1.8	ns
Male, n (%)	5 (100)	5 (63)	5 (45)	4 (44)	0.167
BMI SDS	0.3±1.1 0.4 (-1.4-1.7)	-0.7±0.9 -0.7 (-2.1-0.3)	-0.0±0.7 0.0 (-1.2-1.0)	0.0±0.7 -0.4 (-0.8-1.6)	ns
HbA1c, %	5.6±0.2 5.7 (5.3-5.9)	5.7±0.3 5.8 (5.1-6.0)	5.4±0.3 5.3 (4.8-5.8)	5.2±0.2 5.3 (4.9-5.6)	**0.010**[§,&]
CRP (mg/dL)	3.2±0.1 3.1 (3.1-3.3)	8.9±12 3.6 (3.1-38)	3.5±1.1 3.1 (3.1-6.8)	0.5±1.0 0.2 (0.1-2.9)	**<0.001**[§,&,P]
FEV1, % (mean)	98±16 96 (75-118)	78±35 80 (34-126)	95±6 95 (88-106)		ns
Genotype, n (%)					
ΔF508/ΔF508	-	1 (12.5)	-		ns
ΔF508/nonΔF508	3 (60)	2 (25)	2 (18)		
nonΔF508/nonΔF508	2 (40)	5 (62.5)	9 (82)		
OGTT					
Glucose (mg/dL) mean±SD and median (min-max)					
0. min	88±3 88 (84-91)	84±6 84 (75-93)	85±5 84 (80-97)	83±4 81 (79-89)	ns
30th min	159±41 167 (93-201)	176±16 173 (161-210)	134±22 136 (83-167)	133±16 129 (115-163)	**0.002** [#,&]
60th min	144±61 164 (50-194)	157±31 161 (110-198)	120±24 118 (85-164)	126±26 119 (98-170)	ns
90th min	113±44 109 (68-167)	125±33 142 (77-155)	104±16 106 (77-126)	120±27 112 (93-174)	ns
120th min	90±32 84 (58-125)	106±13 110 (81-122)	101±10 103 (78-112)	101±20 103 (64-130)	ns
150th min	70±14 76 (53-83)	82±23 91 (42-105)	98±10 98 (80-114)	90±17 90 (62-110)	**0.029** [**]
180th min	75±13 81 (57-90)	63±16 59 (46-98)	88±11 86 (70-105)	87±14 89 (59-102)	**0.008** [#,&]
Insulin (mIU/mL) mean±SD and median (min-max)					
0. min	12.9±7.6 14.4 (5.3-24.0)	5.4±2.5 5.7 (1.7-8.6)	9.2±4.5 9.7 (1.3-18.4)	10.9±7.5 8.6 (3.0-23.4)	ns
30th min	125.2±101.9 63.0 (33.1-243.0)	39.0±26.3 34.5 (8.4-89.0)	73.2±25.2 71.0 (35.2-113.1)	38.2±30.1 26.0 (3.9-108.0)	**0.013** [P]
60th min	150.4±126.9 132.6 (14.2-299.0)	57.6±34.4 56.6 (17.4-123)	65.5±42.7 43.9 (24.6-103.0)	51.5±25.4 47.3 (18.8-102)	ns
90th min	66.4±54.8 57.0 (12.3-152.0)	55.1±59.6 36.0 (2.4-181.0)	53.1±32.1 44.5 (18.0-103.0)	54.9±49.0 48.0 (3.4-169.0)	ns
120th min	37.5±15.2 38.3 (12.3-50.6)	40.8±26.7 33.0 (13.2-89.2)	46.7±24.8 39.2 (18.9-89.2)	49.2±35.5 48.3 (13.8-135.0)	ns
150th min	17.3±7.9 14.7 (11.2-31.1)	16.0±7.1 16.6 (1.3-23.8)	37.6±18.5 28.2 (12.2-73.6)	31.5±35.3 24.1 (1.1-119.0)	**0.027** [#]
180th min	17.0±9.3 16.2 (5.2-29.0)	9.3±7.6 7.6 (0.9-26.5)	31.4±27.3 22.5 (9.9-105.0)	23.5±18.2 20.4 (6.1-68.4)	**0.021** [#]

Table 2. Continued

	IsoHypo PI (-) (n=5)	IsoHypo PI (+) (n=8)	NGT PI (-) (n=11)	Control (n=9)	p
Glucagon (pmol/L) mean±SD and median (min-max)					
0. min	8.8±7.8 5.6 (3.5-22.4)	4.2±2.4 3.7 (1.7-8.6)	4.2±1.9 4.1 (1.3-8.9)	7.2±3.7 6.4 (3.7-15.8)	ns
60th min	3.2±1.3 2.9 (1.9-5.0)	3.5±1.7 3.1 (1.8-6.7)	2.1±1.8 1.8 (0.4-6.9)	1.7±1.2 1.7 (0.2-3.5)	**0.045** &
120th min	3.9±2.4 3.1 (2.1-8.1)	3.7±2.0 2.7 (1.7-6.7)	2.2±1.0 2.4 (0.1-3.5)	1.3±1.1 1.2 (0.1-3.3)	**0.011** §
150th min	5.7±3.9 4.7 (1.5-11.7)	3.0±1.6 2.0 (1.4-5.7)	1.9±0.8 1.7 (0.8-4.1)	2.1±2.3 1.3 (0.5-7.6)	**0.047** §
180th min	10.3±7.7 9.6 (1.9-21.8)	4.0±2.9 3.7 (0.6-9.9)	2.3±1.6 2.1 (0.4-6.6)	5.4±6.6 3.3 (1.0-21.2)	ns

Data are presented mean±SD and median (min-max). *IsoHypo PI(-) vs IsoHypo PI(+), **IsoHypo PI(-) vs NGT PI(-), § IsoHypo PI(-) vs Controls, # IsoHypo PI(+) vs NGT PI(-), & IsoHypo PI(+) vs Controls, PNGT PI(-) vs Controls

Discussion

Over the past decade, postprandial or reactive hypoglycemia has been increasingly recognized in patients with CF, although its underlying causes are not fully understood. This study assessed pediatric CF patients with isolated hypoglycemia and explored the role of PI in this condition. The results suggest that isolated hypoglycemia is prevalent among pediatric CF patients and is linked to dysregulated insulin secretion, which involves early and excessive insulin release. Moreover, there was a weakened glucagon response, with insufficient suppression following glucose elevation and an inadequate increase during hypoglycemia. Our findings also suggest that isolated hypoglycemia appears to be an early indicator of hypoglycemia accompanied by abnormal glucose tolerance (Hypo+AGT), but only in individuals with PI. In contrast, isolated hypoglycemia in those with pancreatic sufficiency appears to arise from a distinct mechanism.

The frequency of hypoglycemia observed in this study was comparable to that seen in other 3-hour OGTT studies (6,7,8,10). However, previous research did not differentiate between IsoHypo and Hypo+AGT. In the present study, the frequency of IsoHypo was 61.9%, which is similar to the 66.6% found in our previous pediatric cohort (4). IsoHypo appears to be more common in pediatric CF populations than adult studies, suggesting it may serve as an early indicator of future glucose regulation abnormalities. Delayed and prolonged insulin secretion, along with impaired counterregulatory response, has been proposed as a key factor contributing to reactive hypoglycemia in CF studies (8,9,10,11). In those studies, most hypoglycemic patients had both AGT and PI. In such populations, the delayed and prolonged insulin secretion and/or impaired counterregulatory response are likely causes for hypoglycemia due to the association of AGT with PI. Consistent with this, we also observed β-cell dysfunction in Hypo+AGT group, as reported in other studies on hypoglycemia (8,9,11). However, this mechanism may not apply to CF patients with pancreatic sufficiency (15,16). A critical point in understanding whether other factors, aside from PI, contribute to hypoglycemia is to examine CF patients with isolated hypoglycemia with or without PI. Given that the CFTR mutation distribution in our country differs significantly from that of European and North American cohorts, this genetic variability likely contributes to the higher prevalence of pancreatic sufficiency observed in our cohort. This, in turn, enabled us to evaluate the impact of PI on hypoglycemia more effectively. In the present study, the robust insulin response seen at 30 min during the OGTT in the IsoHypo group indicated a relatively hyperinsulinemic state. When analyzed further, based on the presence of PI, this early and elevated insulin release was found only in the IsoHypo PI(-) subgroup. In contrast, the IsoHypo PI(+) subgroup exhibited a delayed and prolonged insulin secretion, similar to response observed in the Hypo+AGT group.

Glucagon secretion from α-cells has been found to exhibit impaired suppression and a dysregulated response to glucose loading in CF patients with AGT and PI, rather than an absolute reduction (21,22). Recent studies have also reported a diminished glucagon response in individuals with NGT and PI(+), while those with NGT but no PI displayed normal glucagon responses, similar to healthy controls (15). In the present study, both the IsoHypo and Hypo+AGT groups exhibited inadequate glucagon suppression at 60 and 120 min following glucose intake during the OGTT, with the deficiency being more pronounced in the Hypo+AGT group. Subgroup analysis indicated that the IsoHypo PI(+) group had a more pronounced impairment in glucagon suppression, resembling that seen in the Hypo+AGT group, whereas the IsoHypo PI(-) group demonstrated relatively preserved suppression. Furthermore, despite the occurrence of lower glucose at 180 min in both the Hypo+AGT and IsoHypo

groups, glucagon levels at 180 min did not significantly differ from those observed in the NGT and control groups, suggesting an inappropriate glucagon response. When subgroups were compared by the presence or absence of PI, glucagon response to meaningful low glucose at 180 min was weak and insufficient in the IsoHypo PI(+), whereas it remained comparable to the control group in IsoHypo PI(-) (Figure 2B). However, in both groups, the glucagon response was not strong enough to prevent mild hypoglycemia.

Kilberg et al. (8,11) hypothesized that hypoglycemia in PI(-) may reflect a physiological phenomenon similar to that observed in general healthy population, rather than a distinct pathological feature of CF8. In our control group, although the frequency of hypoglycemia was not significantly different from the CF group, the severity was lower than in the IsoHypo PI(-) group. Moreover, two hypoglycemic healthy participants exhibited normal early insulin secretion. Therefore, we believe this effect warrants further investigation in relation to impaired insulin and glucagon secretion in pancreatic-sufficient CF patients. Another possible explanation is the inflammation of islet cells, which has primarily been studied in CF patients with PI (21,22,27). In our cohort, IsoHypo PI(-) and NGT PI(-) groups also had significantly higher CRP levels than healthy controls, suggesting systemic inflammation. This inflammatory condition may contribute to functional abnormalities of islet cells, even in patients with sufficient pancreatic function.

Study Limitations

The main limitations of this study include the lack of frequent sampling for glucagon levels during the early period of the OGTT, which may have resulted in missing important fluctuations. Although our total sample size was relatively large compared with previously published studies in this area, the small number of participants within each subgroup, due to the high number of subgroups analyzed, as well as small sample size of the control group, may limit the generalizability of the findings.

Conclusion

This study provides further evidence suggesting that dysregulated insulin secretion and impaired glucagon response may contribute to hypoglycemia in CF, and that these abnormalities can be observed even in the absence of PI. Isolated hypoglycemia in pediatric CF patients appears to be common and may represent a predecessor Hypo+AGT in pancreatic insufficient CF patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 09.2019.933, date: 01.11.2019).

Informed Consent: Written informed consent was obtained from participants or their parents.

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Prior Presentation: This study was presented at 2nd National Symposium on Pediatric and Adolescent Diabetes (2021).

Footnotes

Authorship Contributions

Concept: Belma Haliloğlu, Abdullah Bereket, Design: Belma Haliloğlu, Serap Demircioğlu Turan, Abdullah Bereket, Data Collection or Processing: Belma Haliloğlu, Tuba Seven Menevşe, Yasemin Gökdemir, Ela Erdem, Bülent Karadağ, Analysis or Interpretation: Belma Haliloğlu, Seda Güleç Yılmaz, Tuba Akdeniz, Büşra Gürpınar Tosun, Turgay İşbir, Literature Search: Belma Haliloğlu, Tuba Seven Menevşe, Writing: Belma Haliloğlu, Tülay Güran, Abdullah Bereket.

Conflict of Interest: One author of this article, Abdullah Bereket, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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Association with Metabolic Syndrome in Children Diagnosed with Type 1 Diabetes Mellitus: A Cross-Sectional Study

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ABSTRACT

Objective: To evaluate the prevalence of metabolic syndrome (MetS) in children with type 1 diabetes mellitus (T1DM) and to determine the predictive value of simple anthropometric measurements, in particular neck circumference (NC) and waist circumference (WC), for identifying MetS.

Methods: Children (aged 6-18 years) and diagnosed with T1DM were included in this cross-sectional study. Anthropometric [NC, WC, hip circumference (HC), body mass index (BMI), tri-ponderal mass index (TMI)] and laboratory parameters, including lipid profile and hemoglobin A1c (HbA1c) were recorded. MetS diagnosis was established using the International Diabetes Federation criteria. Receiver operating characteristic (ROC) curve analysis and Least Absolute Shrinkage and Selection Operator (LASSO) regression were employed to identify key predictors.

Results: A total of 168 children with T1DM participated, among whom the prevalence of MetS was 8.9%. Children with MetS had significantly higher BMI, WC, NC, HC, and TMI values compared to non-MetS counterparts. ROC analysis identified WC Z-score having the highest discriminative power [area under the curve (AUC)=0.954], followed by NC Z-score (AUC=0.906). LASSO regression identified NC Z-score and BMI percentile as the most robust predictors. A strong positive correlation was observed between NC and WC ($r=0.812$, $p<0.001$), and there was a mild inverse correlation between NC and high-density lipoprotein cholesterol.

Conclusion: NC and WC are simple, non-invasive, and reliable tools for early detection of MetS risk in pediatric T1DM patients. Their routine measurement may enhance risk stratification and guide preventive interventions targeting obesity and dyslipidemia. These findings support incorporating NC and WC into standard clinical assessments to improve long-term cardiometabolic outcomes in children with T1DM, with NC $z>1.04$ or WC $z>1.41$ as actionable thresholds.

Keywords: Anthropometric measurements, metabolic syndrome, neck circumference, type 1 diabetes mellitus

What is already known on this topic?

Cardiovascular risk is increased by metabolic syndrome (MetS) in children with type 1 diabetes mellitus (T1DM) but further studies are needed to determine its prevalence and predictors among these children. Neck circumference (NC) shows promise as an anthropometric indicator of central obesity and metabolic risk in T1DM but is not routinely used in T1DM care.

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What this study adds?

Based on International Diabetes Federation criteria, the study found MetS in 8.9% of a Turkish cohort of children with T1DM. A strong correlation was found between NC, waist circumference (WC), and body mass index and NC emerged as an independent predictor of MetS predictor. The strong discriminatory ability of NC and WC Z-scores suggests their inclusion in standard pediatric T1DM evaluations for early cardiometabolic risk detection may be warranted.

Introduction

Recent decades have witnessed a dramatic shift in the management of type 1 diabetes mellitus (T1DM) in children, from an acute, life-threatening disease to a chronic condition characterized by long-term complications and metabolic complications (1,2). Despite improvements in survival because of widespread availability of insulin therapy and self-monitoring, pediatric T1DM patients are experiencing increased rates of overweight, obesity, and related cardiovascular risks (3,4,5). These trends parallel the global childhood obesity epidemic, contributing to a higher risk of metabolic syndrome (MetS), a cluster of metabolic issues that increase the risk of type 2 DM (T2DM), cardiovascular disease, and early mortality (3,6,7).

MetS in children is diagnosed with central obesity and at least two of these: elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, hypertension, and/or impaired fasting glucose (1,2). The International Diabetes Federation (IDF) criteria are widely used in pediatrics because of pragmatic cut-off values for waist circumference (WC) based on age and sex (2). T1DM children experience worsened MetS risk due to poor glycemic control, insulin-related weight gain, and a proinflammatory state (4,6,8,9). MetS prevalence in this group shows variability, ranging from 3.2% to 29.9%, with IDF criteria-based rates of 8-10% (4,10). The extent of this variability emphasizes the requirement for practical, early screening tools in identifying cardiometabolic risk.

Anthropometric indices provide readily available alternatives to assess adiposity and cardiovascular risk in children. Body mass index (BMI) is most commonly employed to classify overweight and obesity. However, BMI does not distinguish between lean and fat mass or capture fat distribution (11). Measurements of central adiposity, such as WC and waist-to-height ratio (WHtR), more accurately reflect visceral fat and its metabolic effects, despite needing standardized methods and age/sex-specific references (12,13).

A simple anthropometric marker, neck circumference (NC), indicates upper-body subcutaneous adiposity and its metabolic implications (14,15,16). In contrast to WC, NC measurement shows less sensitivity to respiration and posture changes, proving more socially suitable in specific contexts. ACFIES (Association between Cardiorespiratory Fitness, Muscular Strength and Body Composition with Metabolic Risk Factors in Colombian Children) study data (14) revealed that NC levels in school-aged children correlated positively with fasting glucose, triglycerides, blood pressure, insulin, and Homeostatic Model Assessment for Insulin Resistance, but inversely with HDL (14). These findings suggest that using NC alongside current methods could enhance pediatric MetS screening, especially in situations requiring rapid assessment or where WC measurement is difficult.

The relationship between NC, WC, BMI, and MetS prediction in T1DM children, especially within the Turkish pediatric population, is understudied, despite a growing body of work on general pediatric anthropometric indices. Children with T1DM face unique metabolic challenges, including insulin-induced weight gain, autoimmune-related inflammation, and glycemic variability, that increase susceptibility to dyslipidemia, hypertension, and central obesity (2,10,17,18). In Türkiye, about 10.5% of children with T1DM meet the IDF criteria for MetS, a rate higher than that in age-matched healthy peers (19). This increased rate highlights the importance of integrating simple, reliable physical measurements into routine healthcare for early detection and prompt intervention in children with T1DM.

The aim of this study was to examine the connections between NC, WC, BMI, and MetS markers in Turkish children with T1DM. Our ultimate goal was to identify easy-to-use, evidence-based tools for early cardiometabolic risk detection in children with T1DM by investigating the contributions of various anthropometric measures to MetS risk stratification.

Methods

Study Design and Population

The study was cross-sectional and investigated the relationships between physical measurements, laboratory results, and MetS in children with T1DM. Written informed consent was obtained from all participants and their parents or guardians, and ethical approval was obtained from the Gaziantep University Clinical Research Ethics Committee approval (approval no.: 2021/356, date: 03.11.2021). The study included participants who were between 6 and 18 years old. Inclusion criteria were a confirmed diagnosis of T1DM for at least one-year, regular follow-up for at least six months in a pediatric endocrinology clinic, evaluated and monitored for MetS components and the availability of complete clinical and laboratory data. Participants with T2DM, monogenic DM, syndromic obesity, other secondary causes of

obesity, incomplete anthropometric data, or missing laboratory records were excluded.

The presence of MetS was the key outcome. Secondary outcomes included the evaluation of risk factors, such as obesity, dyslipidemia, and distortion of anthropometric measurements associated with MetS, focusing on anthropometric and laboratory markers. Predictor variables included NC, WC, BMI, tri-ponderal mass index (TMI), and lipid profile components.

Data Collection

Demographic, clinical, and anthropometric data were collected during routine clinic visits and recorded.

1. Anthropometric Measurements

An experienced individual took anthropometric measurements, including weight in kilograms (kg), height in centimeters (cm), WC in cm, NC in cm, and hip circumference (HC) in cm. All measurements were taken with the subjects standing upright, facing forward, and shoulders relaxed. Further anthropometric parameters were derived from these measurements, including waist-to-hip ratio (WHR) and WHtR.

• **NC (cm):** Measured with a non-elastic tape at the level of the thyroid cartilage, which is the most prominent part of the subject's neck in an upright position, with the eyes forward and the head in a horizontal plane.

• **WC (cm):** Measured with a non-elastic 150 cm tape measure. The measurement was taken with the patient standing in anatomical position, midway between the iliac crest and lowest rib.

• **HC (cm):** Measured by circling the hips at their widest point with a tape, ensuring the tape remained level and parallel to the ground.

• **WHR:** Calculated by dividing WC (cm) by HC (cm). A higher WHR signifies greater central obesity and has been connected to elevated risks of cardiovascular and metabolic complications.

• **WHtR:** Derived by dividing WC (cm) by height (cm).

• **BMI:** Calculated as weight in kg divided by height in m squared (kg/m^2).

• **TMI:** Computed using the formula: weight (kg) divided by height cubed (kg/m^3). TMI has established cutoff values of 16.0 kg/m^3 for overweight boys and 16.8 kg/m^3 for overweight girls (20).

• **Blood pressure:** Measured in a seated position using an automated sphygmomanometer after 10 minutes of rest. Hypertension was identified when systolic or diastolic blood pressure exceeded the 95th percentile for age, sex, and height, based on international guidelines (21).

Height (cm), weight (kg), blood pressure and BMI standard deviation (SD) score (SDS) were calculated according to Turkish Pediatric Endocrinology and Diabetes Association official formula list 2017: ÇEDD Çözüm/Child Metrics (www.ceddcozum.com, www.childmetrics.org data) (21).

2. Obesity Definitions (4)

• **BMI Percentiles**

- Underweight=BMI<5th percentile

- Normal weight=BMI between the 5th and 85th percentiles

- Overweight=BMI between the 85th and 95th percentiles

- Obesity=BMI≥95th percentile

• **WC classification:** The WC classification for abdominal obesity was determined using population-specific standards, where a WC at or above the 90th percentile for age and sex was obese.

• **WHtR:** A WHtR≥0.5 was also considered a marker of central obesity, in line with guidelines.

3. MetS Diagnosis: Based on IDF criteria (2), MetS diagnosis involved abdominal obesity (WC≥90th percentile) and at least two of the following:

• Elevated triglycerides (TG) [≥150 milligram (mg)/deciliter (dL)]

• Decreased HDL cholesterol (<40 mg/dL)

• Elevated blood pressure (above the 95th percentile for age, sex, and height)

• Fasting glucose≥100 mg/dL or pre-existing diabetes diagnosis.

Individuals in this study were classified as having MetS if they met the criteria set by the IDF, while those who met none or only some criteria were considered not to have MetS.

Laboratory and Other Analyses

Venous blood samples, drawn after an overnight fast, were analyzed for:

• **Lipid profile:** The lipid profile included measurements of total cholesterol (TC), low-density lipoproteins (LDL) cholesterol, HDL cholesterol, and TG. Plasma TG, HDL, LDL, and TC were analyzed using standard enzymatic methods on the AU 5800 Series AU model biochemistry analyzers (Beckman Coulter, Brea, CA, USA).

• **Fasting glucose and glycated hemoglobin A1c (HbA1c) levels:** High-performance liquid chromatography was used to measure

fasting glucose and HbA1c levels. Poor T1DM control was defined as HbA1c levels greater than 8% (22).

Dyslipidemia was defined as one of the following (4): 1) TC>200 mg/dL, 2) TG≥100 mg/dL between the ages of 0-9 years, 3) TG: ≥130 mg/dL between the ages of 10-19 years, 4) LDL≥130 mg/dL increase, and 5) HDL<40 mg/dL decrease (4).

Patient medical records were reviewed to extract clinical and demographic data, including age, sex, duration of diabetes, daily insulin dose (expressed as units/kg/day), co-morbidities, and current therapeutic regimens.

Statistical Analysis

All data analysis was conducted using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Data management and visualization were performed using R packages. Based on their distribution, continuous variables are presented either as the mean with SD or the median and range (minimum to maximum). Frequencies and percentages were used to represent categorical variables.

Continuous data were analyzed using Independent Samples t-tests (normal distribution) or Mann-Whitney U tests (non-normal distribution), while categorical data were analyzed using chi-square tests. The associations between anthropometric measurements and laboratory parameters were assessed using Pearson or Spearman correlation coefficients, depending on data distribution. To account for age- and sex-related variability, NC and WC values were standardized into Z-scores using reference LMS parameters derived from Turkish pediatric populations (16,23). Z-scores were calculated using the LMS method formula:

$Z=((X/M)^{L}-1)/(L\times S)$ when $L\neq 0$, or $Z=\ln(X/M)/S$ when $L=0$.

The predictive value of both raw and standardized NC and WC measures for MetS was examined through receiver operating characteristic (ROC) curve analysis. Optimal cut-off points were identified using the Youden index, and corresponding sensitivity, specificity, and area under the curve (AUC) values were reported at 95% confidence intervals (CIs). As there were a limited number of outcome events (n=15), to prevent overfitting, a penalized logistic regression model using the Least Absolute Shrinkage and Selection Operator (LASSO) was employed for variable selection. The optimal penalty parameter (λ) was determined using 10-fold cross-validation with the glmnet package in R. Two models were considered: λmin, which minimizes cross-validated binomial deviance, and λ1 standard error (SE), the most parsimonious model within one SE of the minimum. Variables included in the penalized model were age, sex, NC Z-score, BMI percentile, and TG levels. At λmin, NC Z-score (β=0.589) and BMI percentile (β=0.038) were retained as predictors, while age, sex, and triglycerides were shrunk to zero. The final model thus included the most significant predictors, addressing multicollinearity and accounting for the limited number of events per variable. Two-tailed tests were used, with $p<0.05$, signifying statistical significance.

Results

Demographic and Anthropometric Characteristics of Participants

The study included 168 children with T1DM, 84 male and 84 female (50% each) (Table 1). The mean age of participants was 12.5±2.9 years, and the median T1DM duration was 4 (0-15) years. Participants' mean NC and WC were 30.8±3.2 cm and 68.6±8.3 cm. The mean BMI [SD score (SDS)] of participants was -0.24 (-3.43-2.63) kg/m^2, with 12.5% (n=21) being overweight and 2.4% (n=4) being obese. The laboratory results showed a median HbA1c level of 9.4% (5.7-16.5%), while median lipid values were: TC 180.0 (95-314) mg/dL; LDL cholesterol 108.5 (47-214) mg/dL; HDL cholesterol 57.0 (26-132) mg/dL; and TG 92.0 (27-544) mg/dL. The IDF definition identified MetS in 15 (8.9%) of the sample.

Comparing Children with and without MetS

Median daily insulin dose was 0.94 (0.31-1.58) units/kg/day, with no significant difference between MetS and non-MetS groups (p=0.391). Table 2 compares anthropometric and clinical parameters between children with MetS and children without MetS. Children with MetS had significantly greater weight, BMI, BMI SDS, NC, WC, and HC than those without MetS ($p<0.05$ for all). HDL levels were significantly lower (p=0.038) in children with MetS. Anthropometric variables and their connections with MetS are illustrated in Table 2. Increased WC was present in all participants with MetS, but only 6.5% of those without MetS ($p<0.001$). Similarly, the MetS group showed a considerably higher prevalence of increased NC compared to the non-MetS group (93.3% vs. 34%, respectively; $p<0.001$). Elevated WHtRs were also significantly associated with MetS ($p<0.001$).

Correlations Between Anthropometric and Laboratory Variables

Significant correlations were found between various anthropometric measures (Table 3). Strong positive correlations between NC and WC (r=0.812, $p<0.001$), and NC and HC (r=0.786, $p<0.001$) suggest that NC is an effective measure of central obesity. Moderate positive correlations were found between WHtR and WC (r=0.482, $p<0.001$) and TMI and WC (r=0.321, $p<0.001$). HDL levels were weakly inversely correlated with NC (r=-0.190, p=0.015), suggesting higher NC may be associated with a less favorable lipid profile.

Table 1. Demographic variables of participants (n=168)

	Total (n=168) n (%)		Total (n=168) n (%)
		MetS (based on IDF)	
Age*	12.5±2.9	No	153 (91.1)
		Yes	15 (8.9)
Sex			
Female	84 (50)	**NC (cm)***	30.8±3.2
Male	84 (50)		
T1DM duration (years)	4.0 (0-15)	**NC classification**[¥]	
		Normal	96 (57.1)
		High	66 (39.3)
Median insulin dose (units/kg/day)*	0.94 (0.31-1.58)	**WC (cm)***	68.6±8.3
Median insulin dose (units/kg)*	41.0 (9.0-105.0)	**WC classification**	
		Normal	143 (85.1)
		High	25 (14.9)
Family T1DM history	22 (13.1)	**HC (cm)***	85.6±11.4
Family T2DM history	51 (30.4)	**WHR***	0.81 (0.65-1.15)
Height (cm)*	150.3±16.6	**WHtR***	0.45 (0.38-0.60)
Height (SDS)*	-0.21 (-3.78-2.65)	**TMI (kg/m^3)***	12.8±2.2
Weight (kg)*	44.1±14.3	**HbA1c (%)**	9.4 (5.7-16.5)
Weight (SDS)*	-0.37 (-3.77-2.63)	**Total cholesterol (mg/dL)***	180.0 (95-314)
BMI (kg/m^2)*	19.0±3.3	**LDL (mg/dL)***	108.5 (47-214)
BMI (SDS)*	-0.24 (-3.43-2.63)	**HDL (mg/dL)***	57.0 (26-132)
BMI percentile	40.5 (0.03-98.64)	**Triglyceride (mg/dL)***	92.0 (27-544)
BMI percentile classification			
Underweight	21 (12.5)	**Puberty**	
Normal	122 (72.6)		
Overweight	21 (12.5)	**No**	100 (59.5)
Obese	4 (2.4)	**Pubertal**	68 (40.5)

Numeric variables are presented as median (minimum-maximum) or mean±SD. [¥]NC measurements could not be made in four patients in the MetS negative group.
BMI: body mass index; cm: centimeter; dL: deciliter; HbA1c: glycated hemoglobin A1c; HC: hip circumference; HDL: High-density lipoproteins; kg: kilogram; IDF: International Diabetes Federation; LDL: low-density lipoproteins; m: meter; MetS: metabolic syndrome; mg: milligram; NC: neck circumference; SD: standard deviation; SDS: standard deviation score; TMI: tri-ponderal mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio.

Table 2. Components of metabolic syndrome according to International Diabetes Federation (IDF) criteria in children with type 1 diabetes mellitus

	Based on the IDF criteria		
	MetS (-) n=153	**Mets (+) n=15**	**p value**
Age (years)*	12.6±2.9	11.9±2.8	0.363
Sex			
Female	75 (49.0)	9 (15.0)	0.416
Male	78 (51.0)	6 (40.0)	
T1DM duration (years)	4.0 (0-15)	4.0 (1-12)	0.905
Median insulin dose (units/kg/day)*	0.94 (0.31-1.58)	1.01 (0.43-1.28)	0.391
Median insulin dose (units/kg)*	40.0 (9.0-90.0)	49.0 (30.0-105.0)	***0.026***
Family T1DM history	20 (13.1)	2 (13.3)	0.977

Table 2. Continued

	Based on the IDF criteria		
	MetS (-) n=153	**Mets (+) n=15**	**p value**
Family T2DM history	46 (30.1)	5 (33.3)	0.794
Height (cm)*	149.8 ±16.5	155.5±17.1	0.209
Height (SDS)*	-0.26 (-3.78-2.17)	0.49 (-2.90-2.65)	0.068
Weight (kg)*	43.0±13.3	55.6±19.1	**0.001**
Weight (SDS)*	-0.43 (-3.77-2.244)	1.15 (-1.37-2.63)	**<0.001**
BMI (kg/m^2)*	18.7±3.1	22.7±3.6	**<0.001**
BMI (SDS)*	-0.34 (-3.43-1.92)	1.10 (-1.07-2.21)	**<0.001**
BMI percentile	36.7 (0.03-97.3)	86.4 (14.23-98.64)	**<0.001**
BMI percentile classification			
Underweight	21 (13.7)	0 (0.0)	**<0.001**
Normal	117 (76.5)	5 (33.3)	
Overweight	3 (8.5)	8 (53.3)	
Obese	2 (1.3)	2 (13.3)	
NC (cm)*	30.5±3.1	33.1±3.3	**0.002**
NC classification[¥]			
Normal	95 (62.1)	1 (6.7)	**<0.001**
Increased	52 (34.0)	14 (93.3)	
WC (cm)*	67.6±7.6	78.6±9.2	**<0.001**
WC classification			
Normal	143 (93.5)	0 (0.0)	**<0.001**
Increased	10 (6.5)	15 (100.0)	
HC (cm)*	83.6±11.0	94.3±11.4	
WC classification			
Normal	143 (93.5)	0 (0.0)	**<0.001**
Increased	10 (6.5)	15 (100.0)	
WHR*	0.80 (0.65-1.5)	0.83 (0.71-0.97)	0.195
WHtR*	0.45 (0.38-0.59)	0.51 (0.42-0.60)	0.186
WHtR			
Normal	128 (83.7)	4 (26.7)	<0.001*
Increased	25 (16.3)	11 (73.3)	
TMI (kg/m^3)*	12.7±2.1	14.4±1.9	**0.004**
TMI (kg/m^3)			
Normal	147 (96.1)	13 (86.7)	0.102
Increased	6 (3.9)	2 (13.3)	
Dyslipidemia + HT	36 (25.3)	5 (33.3)	0.414
HbA1c (%)	9.2 (5.7-15.8)	9.7 (6.4-16.5)	0.332
Total cholesterol (mg/dL)*	180.0 (95-314)	171.5 (100-294)	0.416
LDL (mg/dL)*	109.0 (47-211)	107.0 (59-214)	0.791
HDL (mg/dL)*	58.0 (26-132)	51.0 (36-79)	**0.038**
Triglyceride (mg/dL)*	88.0 (27-544)	119.0 (44-289)	0.248

Table 2. Continued

	Based on the IDF criteria		
	MetS (-) n=153	Mets (+) n=15	p value
Puberty			
Prepubertal	91 (59.5)	9 (60.0)	0.969
Pubertal	62 (40.5)	6 (40.0)	

Numeric variables are presented as median (minimum-maximum) or mean±SD. ¥NC measurements could not be made in four patients in the MetS negative group.
BMI: body mass index; cm: centimeter; dL: deciliter; HbA1c: glycated hemoglobin; HC: hip circumference; HDL: high-density lipoproteins; kg: kilogram; IDF: International Diabetes Federation; LDL: low-density lipoproteins; m: meter; MetS: metabolic syndrome; mg: milligram; NC: neck circumference; SD: standard deviation. SDS: standard deviation score; TMI: tri-ponderal mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio.

ROC-Based Comparison of Neck and WC Metrics for Predicting MetS

To determine the ability of raw and Z-scored anthropometric measures to identify MetS, ROC curve analysis was performed (Figure 1, Table 4). For NC (cm), the AUC was 0.718 (SE=0.063; p=0.005; 95% CI, 0.595-0.841), with an optimal cut-off of 30.25 cm yielding 80.0% sensitivity and 52.4% specificity. The AUC for WC (cm) was 0.809 (SE=0.065; p<0.001; 95% CI, 0.682-0.935), with an optimal cutoff of 73.5 cm corresponding to 73.3% sensitivity and 74.2% specificity. The AUC was 0.906 for the NC Z-score (SE=0.032; p<0.001; 95% CI: 0.854-0.959) with an optimal threshold of 1.041, giving 93.3% sensitivity and 80.0% specificity, while the WC Z-score achieved an AUC of 0.954 (SE=0.019; p<0.001; 95% CI: 0.915-0.992) at an optimal threshold of 1.408, with 100% sensitivity and 80.0% specificity.

Penalized Regression Model for Risk Factors

Table 5 presents penalized logistic regression analysis revealing several independent predictors of MetS. The model exhibiting optimal performance, identified via minimization of the penalty parameter (λ_min), indicated that NC Z-score (β=0.589) and BMI percentile (β=0.038) significantly predicted MetS. In contrast, age, sex, and triglyceride levels were penalized to zero, showing minimal additional predictive value. Anthropometric indicators, especially the NC Z-score, demonstrated superior predictive validity for MetS within this cohort compared to conventional demographic or biochemical markers. Supplementary Figure 1 provides further elucidation of these findings by illustrating the coefficient shrinkage path across λ values.

Table 3. Correlation analysis of anthropometric measurements and laboratory values

	NC (cm)	WC (cm)	HC (cm)	WHR	WHR	TMI (kg/m³)	HbA1c (%)	HDL (mg/dL)
NC (cm)	1	0.812	0.786	-0.102	0.174	0.184	0.034	-0.190
WC (cm)	0.812	1	0.823	0.111	0.482	0.321	0.075	-0.125
HC (cm)	0.786	0.823	1	-0.466	0.139	0.254	-0.015	-0.140
WHR	-0.102	0.111	-0.466	1	0.487	0.071	0.122	0.050
WHtR	0.174	0.482	0.139	0.487	1	0.643	0.086	-0.053
TMI (kg/m³)	0.184	0.321	0.254	0.071	0.643	1	-0.064	-0.094
HbA1c (%)	0.034	0.075	-0.015	0.122	0.086	-0.064	1	0.131
HDL (mg/dL)	-0.190	-0.125	-0.140	0.050	-0.053	-0.094	0.091	1

NC: neck circumference; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; TMI: tri-ponderal mass index; HbA1c: glycated hemoglobin; HDL: high-density lipoproteins; WHtR: waist-to-height ratio.

Table 4. Diagnostic performance of anthropometric measurements in predicting MetS in children with type 1 diabetes mellitus

Variable	AUC	p value	95% CI	Optimal cut-off	Sensitivity (%)	Specificity (%)
NC	0.718	**0.005**	0.595-0.841	30.25	80.00	52.38
WC	0.809	**<0.001**	0.682-0.935	73.50	73.33	74.15
NC Z-score	0.906	**<0.001**	0.854-0.959	1.041	93.33	80.00
WC Z-score	0.954	**<0.001**	0.915-0.992	1.408	100.00	80.00

AUC: area under the curve; CI: confidence intervals; MetS: metabolic syndrome; NC: neck circumference; WC: waist circumference.

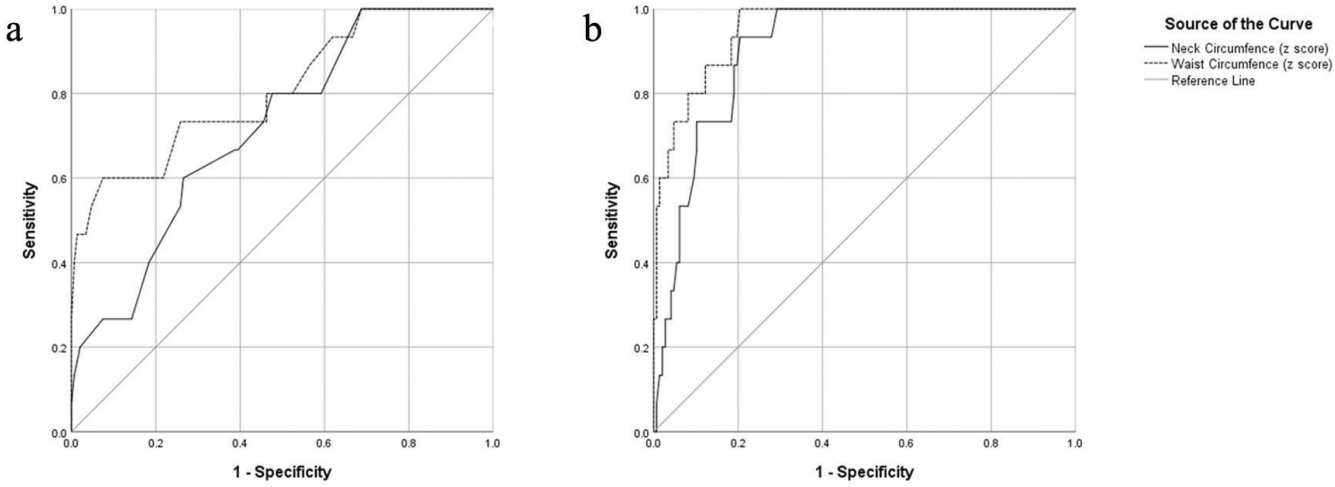

Figure 1. ROC analysis of the NC, WC, NC (Z-score), and WC (Z-score). a) ROC analysis of the NC and WC. b) ROC analysis of the NC (Z-score) and WC (Z-score)

Notes: For clarity in grayscale printing, NC and WC are represented with solid and dashed lines, while Z-score curves are shown with dotted lines and circle markers.

ROC: receiver operating characteristic; NC: neck circumference; WC: waist circumference; HC: hip circumference.

Table 5. Multivariate LASSO regression analysis of risk factors associated with metabolic syndrome in children with type 1 diabetes mellitus

Variable	Coefficient at λ_{min}	Coefficient at λ_{1SE}
(Intercept)	-5.673	-3.886
Age	0.000	0.000
Sex (F:M)	0.000	0.000
NC Z-score	**0.589**	0.296
BMI (percentile)	**0.038**	0.018
TG (mg/dL)	0.000	0.000

BMI: body mass index; dL: deciliter; mg: milligram; F: female; M: male; NC: neck circumference; TG: triglyceride.

Discussion

This research investigated the complex relationships between anthropometric measures, MetS, and laboratory findings in children with T1DM. Using IDF criteria, MetS was identified in 8.9% of participants with T1DM. Anthropometric measures (NC, WC, HC, BMI, and TMI) and lipid profiles were significantly elevated in children with MetS. WC Z-score showed the highest power to discriminate, followed by NC Z-score. NC Z-score and BMI percentile were strong predictors of MetS. This study highlights the utility of straightforward anthropometric measures, especially NC and WC, for detecting increased cardiometabolic risk in T1DM children.

Early identification and evaluation of MetS in individuals with T1DM is important to prevent or ameliorate the development of both major and minor complications. Despite limited research, studies into MetS in T1DM patients indicate an incidence ranging between 3.2% and 29.9% (4,5,9,10). Several factors contribute to the discrepancies observed between studies, including variations in MetS diagnostic criteria, study population characteristics, participant age, and country-specific differences in the prevalence of obesity/overweight.

Pediatric T1DM is increasingly associated with MetS, largely due to the obesity epidemic and inherent disease factors. Our cohort showed an 8.9% prevalence of MetS, consistent with previous pediatric studies (2,4,19,24). Conversely, general population rates vary between 2.1% and 11.2%, contingent on criteria and location (5). Despite limited data on T1DM prevalence, some studies report rates up to 29.9% in similar age groups (10). Weight gain and fat redistribution, especially abdominal adiposity, and increased MetS risk are potential side effects of insulin therapy, despite its essential role in glycemic control (3,25,26). Moreover, chronic hyperglycemia and oxidative stress lead to dyslipidemia and hypertension (26,27). Concurrently, T1DM-associated inflammation fosters insulin resistance, a central feature of MetS. In addition, chronic hyperglycemia and oxidative stress contribute to dyslipidemia and hypertension (9). These metabolic abnormalities are further complicated by diet and physical inactivity (28,29). According to Messiah et al. (18), early metabolic problems in T1DM may persist despite optimal glycemic control, increasing long-term cardiovascular risk.

Practical screening tools for MetS in children with T1DM now include anthropometric indices, with a focus on NC and WC measurements. We found significantly increased NC, WC, HC, BMI, and TMI in participants with MetS. This data confirms earlier studies which highlighted the significant role of overweight

and obesity in the development of MetS among adolescents with T1DM (11,20,30). In multivariate LASSO regression, NC z-score and BMI percentile emerged as a robust predictors (31). Adolescent metabolic risk showed independent associations with TMI and BMI percentile, as observed by Sun et al. (30). Notably, NC includes upper-body subcutaneous fat, an adipose tissue related to metabolic dysfunction by releasing pro-inflammatory adipokines, thus measuring anthropometric changes that are missed if only BMI is measured (11,14,15,29). Consequently, despite its minimal invasiveness and reproducibility, NC is a preferred clinical measurement, particularly when WC measurement variability is problematic (16).

The hallmarks of MetS in T1DM are dyslipidemia and inflammatory processes. Lower HDL cholesterol was observed in MetS children in our study, consistent with the effects of central adiposity on lipid metabolism (32). Although NC weakly inversely correlated with HDL and showed no significant triglyceride relationship, WC's inverse association with HDL highlights the importance of central adiposity (33). These moderate correlations are consistent with findings reported by Ma et al. (12), who showed an inverse relationship between WHtR and HDL in adolescents. Besides, the strong positive correlations between HC and NC (r=0.786) and HC and WC (r=0.823) suggest that generalized adiposity levels often change together across different body parts. Despite this, LASSO analyses identified NC and BMI percentile as independent predictors of MetS, with NC highlighting the crucial role of upper-body fat distribution in cardiometabolic risk assessment.

Free fatty acids and inflammatory mediators released from adipose tissue underlie the pathophysiology of these anthropometric-metabolic associations (14,16,23,29,33). Upper-body subcutaneous fat, as measured by NC, releases free fatty acids into the hepatic portal vein, worsening hepatic insulin resistance and dyslipidemia (14,16,32). Increased central adiposity (WC) promotes visceral fat accumulation, leading to metabolic dysfunction due to its lipolytic and pro-inflammatory effects (29,33). Autoimmune β-cell destruction, in addition to weight gain and sedentary behavior, causes insulin resistance in T1DM, fostering a milieu in which adiposity-driven inflammation amplifies metabolic disturbances (34). In the present study, significant correlations found between NC, WC, and TMI indicate the strong relationship between adipose tissue stores, necessitating comprehensive anthropometric assessment.

ROC analysis further illustrated the superior discriminative power of the WC Z-score (AUC=0.954) versus the NC Z-score (AUC=0.906). The optimal WC z-score threshold of 1.408 yielded 100% sensitivity and 80% specificity, whereas an NC z-score cutoff of 1.041 achieved 93.3% sensitivity and 80% specificity. The acceptable WC AUCs and moderate NC performance in predicting pediatric MetS, reported by Masquio et al. (13) and Formisano et al. (35), are consistent with our results but we achieved much improved performance after conversion to Z-scores. The rise in childhood obesity, particularly in insulin-treated children, suggests that combining NC and WC measurements and converting them to Z-scores could allow for early identification of at-risk individuals, leading to prompt lifestyle interventions (11,13,14,35).

Routine NC and WC measurements during pediatric endocrinology visits may be appropriate as they are relatively easy and simple to implement in clinical settings and, especially when converted to Z-scores, are useful for identifying T1DM children at heightened MetS risk. Given the identification of NC z-score as an independent predictor and WC's excellent AUC, incorporating both measures into screening protocols could optimize risk stratification before laboratory testing. Children surpassing NC or WC cut-offs could receive tailored counseling, such as dietary and physical activity promotion. Moreover, the observed but weak inverse correlation between HDL and anthropometric measures suggests that comprehensive cardiometabolic evaluations, including fasting lipid panels, may be appropriate in high-risk children. Collaborative, interdisciplinary teams (endocrinologists, dietitians, and exercise physiologists) will be important for integrating weight and cardiometabolic risk management into standard T1DM care, personalizing interventions to minimize obesity-related complications (34).

Study Limitations

Several limitations must be acknowledged. Our cross-sectional design precludes causal inferences; longitudinal studies are needed to confirm whether elevated NC and WC predict incident MetS in T1DM children. Generalizability and statistical power may be limited by the small sample of 168, including just 15 (9%) MetS-positive participants. While LASSO regression promoted model parsimony through penalization, the model suffered from a lack of key variables, such as physical activity levels. Predictive models should be improved in future research by including objective activity measurements (like accelerometry). Despite standardization of NC and WC measurements, precision remained susceptible to intra- and inter-observer variability. It is also important to note that cut-off values for NC and WC might differ according to sex and pubertal status. Future studies should perform stratified analyses by sex and Tanner stage to refine these thresholds and to produce robust data for calculating Z-scores.

Conclusion

Simple anthropometric indices, especially NC and WC, were found to be useful for screening for MetS in children with T1DM. The different metabolic processes in T1DM, such as weight

changes from insulin and autoimmune inflammation, suggest that adding NC and WC measurements to regular checkups may help identify children with a higher chance of cardiovascular problems earlier. Then lifestyle interventions, thorough lipid monitoring, and including weight management in T1DM treatment plans might reduce future cardiometabolic disease. Globally, rising childhood obesity rates among those with T1DM highlight the need for preventive strategies using simple and readily available anthropometric markers with the aim of improving long-term health for children with T1DM.

Ethics

Ethics Committee Approval: The study protocol was approved by the Gaziantep University Clinical Research Ethics Committee (approval no.: 2021/356, date: 03.11.2021).

Informed Consent: Written informed consent was obtained from all participants and their parents or guardians.

Footnotes

AI Statement: The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work but did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

Authorship Contributions

Concept: Ahmet Yıldırım, Design: Serpil Albayrak, Mehmet Keskin, Data Collection or Processing: Serpil Albayrak, Analysis or Interpretation: Murat Karaoğlan, Writing: Serpil Albayrak.

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Supplementary Figure: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/02ae3f9a-00c5-49b5-bc71-c33b226aaf5a.pdf

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Real-World Efficacy of Weekly Somatrogon on Growth and Bone Health in Pediatric Growth Hormone Deficiency: A 12-Month Retrospective Cohort Study

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ABSTRACT

Objective: Growth hormone deficiency (GHD) in children results in short stature and impaired bone health. While daily growth hormone (GH) injections are effective, they are associated with adherence challenges. Somatrogon, a long-acting, recombinant human GH (rhGH), allows weekly administration, potentially improving treatment compliance.

Methods: This retrospective cohort study included prepubertal children with GHD treated with weekly Somatrogon at Al Jalila Children's Hospital, Dubai. Diagnosis was based on clinical, biochemical, and radiological criteria, including height standard deviation score (SDS) <-2.0, subnormal growth velocity, and subnormal peak GH in one stimulation test (<10 ng/mL), supported by low IGF-1 and/or abnormal cranial magnetic resonance imaging. Growth outcomes and bone health indices were assessed over 12 months using auxology, insulin-like growth factor 1 (IGF-1) levels, and BoneXpert-derived bone health index (BHI) SDS and Metacarpal Index (MCI) SDS.

Results: The study cohort consisted of 39 children with GHD. After 12 months of therapy, mean height SDS improved significantly from -2.16±0.80 to -1.65±0.71 ($p<0.001$). IGF-1 SDS rose from -1.38±1.02 to 0.88±1.57 ($p<0.001$). Adult predicted height and BHI SDS also improved significantly ($p=0.005$ and $p<0.001$, respectively). No significant changes were observed in bone age SDS or MCI SDS.

Conclusion: Weekly Somatrogon significantly improved linear growth, IGF-1 levels, and measures of cortical bone health without advancing bone age in children with GHD. These findings support the efficacy of this form of long-acting GH therapy and its potential to optimize growth and skeletal outcomes in clinical practice.

Keywords: Growth hormone deficiency, somatrogon, bone health, IGF-1, children

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What is already known on this topic?

Daily growth hormone (GH) therapy is effective but often limited by poor adherence. Weekly Somatrogon offers a convenient alternative, with early data showing comparable growth outcomes. Effects on bone health as measured by bone age or bone health index (BHI) remain underreported.

What this study adds?

Weekly Somatrogon improved height and insulin-like growth factor 1 standard deviation score over 12 months in prepubertal patients with GH deficiency (GHD). Somatrogon increased BHI without advancing bone age or metacarpal index. Somatrogon appears to be a safe, effective, once-weekly GH-therapy option.

Introduction

Growth hormone deficiency (GHD) in children is characterized by short stature, reduced growth velocity, and failure to achieve normal adult height, negatively impacting quality of life and future outcomes (1,2).

Growth hormone replacement has enabled children with GHD to achieve height within the normal accepted adult range (1). However, agents used for conventional daily growth hormone therapy have a short half-life (3) and require frequent injections (4), which contribute to caregiver burden (5) and poor adherence (6). This leads to frequent missed doses (7) and eventually a poorer clinical outcome (8).

Efforts have focused on developing long-acting GH formulations to improve convenience, reduce injection burden, and enhance clinical outcomes (9,10). Somatrogon (Ngenla®) is a long-acting rhGH with three C-terminal peptide extensions, designed to extend half-life and enable weekly dosing. Clinical trials have demonstrated that Somatrogon achieves growth outcomes comparable to daily GH therapy (11,12).

GHD also impairs bone health, leading to reduced bone mineral density (BMD), as shown by dual-energy X-ray absorptiometry (DXA) (13) and computed tomography studies (14). GH replacement promotes osteoblast activity, new bone formation, and improved BMD (15,16).

The bone health index (BHI), derived from hand radiographs using the automated BoneXpert® software (Visiana ApS, Fremtidsvej 1, 2970 Hørsholm, Denmark), serves as a robust indicator of cortical bone strength in children (17). Prior studies have demonstrated that daily GH treatment is associated with significant improvements in BHI (18).

The metacarpal index (MCI), another parameter generated through radiogrammetry, estimates cortical thickness and has been validated as a predictor of fracture risk (19,20). Both BHI and MCI are calculated from metacarpal dimensions: BHI is defined as the cortical area divided by width$^{1.33}$ multiplied by length$^{0.33}$, while MCI is calculated as cortical area divided by width^2. These indices correlate strongly with DXA findings and provide a reliable, non-invasive means of assessing skeletal integrity in growing children (21,22).

The aim of the present study was to evaluate the real-world effects of weekly Somatrogon therapy on growth outcomes, including height velocity, adult predicted height (APH), and IGF-1 stability, as well as the bone health indices, BHI and MCI, in children with GHD.

We hypothesised that weekly Somatrogon would improve linear growth and bone health in prepubertal children with GHD.

Methods

This retrospective cohort study assessed pre- and post-treatment outcomes over 12 months in children diagnosed with GHD who received Somatrogon therapy at Al Jalila Children's Hospital in Dubai, UAE. The Institutional Review Boards of Al Jalila Children's Hospital and Mohammed Bin Rashid University approved the study. Participants were consecutively recruited from January 2023 to June 2024.

The study population included children who received Somatrogon therapy at a dose of 0.66 mg/kg/week (11), all patients remained on the same dose throughout the 12 months of the study. Their age was between 3.0 and 10.0 years for girls and 3.0 and 11.0 years for boys. All were prepubertal, defined as Tanner stage 1 on physical examination (23,24). All patients remained prepubertal (Tanner stage 1) throughout the entire 12-month study period.

The diagnosis of GHD was established through an integrated approach combining clinical, radiological, and biochemical evidence. An auxological assessment was performed, with growth failure defined as a height standard deviation score (SDS) below -2.0 for age and sex or a growth velocity 1 SD below the mean for chronological age over the 12 months prior to treatment (25,26).

Participants were included if they exhibited a peak GH <10 ng/mL in one stimulation test, supported by either: (1) height

SDS <-2.0 + growth velocity <-1 SDS, or (2) low IGF-1/IGFBP-3 (insulin-like growth factor binding protein-3), or (3) abnormal cranial MRI. This approach is consistent with guidelines for severe phenotypes (27,28).

Exclusion criteria included previous exposure to growth-promoting agents, abnormal thyroid function, or other significant medical conditions. Data was collected anonymously using medical record numbers to ensure confidentiality.

Auxologic Measurements

Height was measured using a wall-mounted stadiometer [Seca216® (Seca GmbH & Co. KG, Hammer Steindamm 9-25, 22089 Hamburg, Germany)]. Height SDS was calculated using CDC 2000 references (29).

Laboratory Investigations

GH measurements were performed using the Siemens Immulite® assay (Siemens Healthineers, Llanberis, Gwynedd, United Kingdom); (sensitivity: 0.01 ng/mL). Serum IGF-1 was measured at baseline and 96 hours after the most recent Somatrogon dose to reflect weekly pharmacokinetics (30) using the Roche Elecsys® ECLIA (Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany); (range: 0.25-1600 ng/mL; CV<5%) (31). IGF-1 values were expressed as SDS based on age- and sex-specific norms; eligible patients had baseline IGF-1 at least 1 SD below the mean (11,31).

Radiographic Assessments

An automated radiographic analysis of the left hand and wrist radiographs was performed using BoneXpert® software before the initiation of Somatrogon therapy and after 12 months of treatment. This automated analysis determined bone age, BHI, and MCI.

Bone age assessment using the BoneXpert® method is based on the Greulich-Pyle bone age standard, and it analyzes the image completely automatically using artificial intelligence (AI). It has been shown to provide accurate data on a patient's bone age, in addition to analysis of BHI and MCI (32).

BoneXpert® offers an automated assessment of both bone age and cortical bone geometry using radiographic measurements. Specifically, it evaluates the width (W), cortical thickness (T), and length (L) of the second, third, and fourth metacarpal bones. From these parameters, it calculates key indices:

Cortical area (A): Computed using the formula $A=\pi\times W\times T\times(1-T/W)$, representing the area of the cortical bone cross-section.

Metacarpal index (MCI): Defined as $MCI=A/W^2$, this index expresses cortical bone thickness relative to the overall bone width.

Bone health index (BHI): Calculated as $BHI=A/(W^{1.33}\times L^{0.33})$, this index integrates bone dimensions to reflect cortical bone robustness.

These indices provide a detailed profile of cortical bone structure and are interpreted against standardized reference values for bone age. Although BoneXpert's normative dataset is based on Caucasian populations (33), it remains the most widely validated tool for pediatric skeletal assessment. To mitigate ethnic bias, we report results as SDS relative to each patient's bone age rather than relying on raw values.

APH was calculated using BoneXpert® software, which applies the Bayley-Pinneau method to deliver accurate and standardized predictions of final adult height, minimizing variability associated with manual calculations (34).

Sample Size

The sample size was calculated based on Horikawa et al. (11) study, in which Somatrogon increased height SDS in children with GHD by 0.94 after 12 months of treatment. Therefore, at a significance level of 0.05 and power of 80%, a total of 30 subjects were required to test our hypothesis.

Ethical Considerations

This study was approved by the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority, and the Institutional Review Board of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU IRB-2024-562; Ref: DSREC-SR-11/2024_04). Given the retrospective design, the requirement for informed consent was waived.

Statistical Analysis

Statistical analysis was done using SPSS, version 29 (IBM, Armonk, NY, USA). Continuous variables were assessed for normality using Shapiro-Wilk tests. Paired t-tests compared pre/post outcomes for parametric data. Continuous variables were summarized as means with SDs and/or medians with minimum and maximum values, as appropriate. Categorical data were presented as frequencies and percentages within the study cohort. To assess the primary endpoint, annual height velocity, comparisons between baseline and the end of therapy were conducted using a t-test, with statistical significance set at a *p*-value of less than 0.05.

Results

The study included 39 patients with a mean age of 9.63 years, of whom 64% were male (Table 1). Height SDS improved significantly from a mean of -2.16±0.80 at baseline to -1.65±0.71 after 12 months of treatment ($p<0.001$) (Figure 1). When analysed separately by sex, both boys and girls demonstrated a similar

and significant increase in absolute height over 12 months. In boys (n=27), mean height increased from 123.73±8.74 cm to 132.06±8.55 cm (mean change +8.33 cm, p<0.001). In girls (n=12), mean height increased from 122.23 ± 14.88 cm to 130.97±13.82 cm (mean change +8.73 cm, p<0.001).

APH improved from 161.86±7.2 cm to 164.88±6.4 cm (p<0.001) (Figure 2). Bone age SDS showed no change (p=0.269) (Table 2).

The IGF-1 SDS improved significantly from a mean of -1.38±1.02 at baseline to 0.88±1.57 after treatment (p<0.001) (Figure 3). BHI SDS improved from –1.29±1.50 to -0.83±1.41 (Δ= +0.46; p<0.001). MCI SDS showed no significant change (-1.33±1.18 to -1.16 ±1.07; Δ= +0.17; p=0.106) (Table 2).

Table 1. Characteristics of patients in the study at baseline

Number	**39**
Age, years Mean±SD	9.63±2.19
Males n (%)	27 (64)
Bone age, years Mean±SD	7.5±2.37
Bone age SDS Mean±SD	-1.53±1.30
Mean height SDS Mean±SD	-2.16± 0.80
Mean APH, cm Mean±SD	161.73± 7.60

APH: adult predicted height; N: number; SDS: standard deviation score.

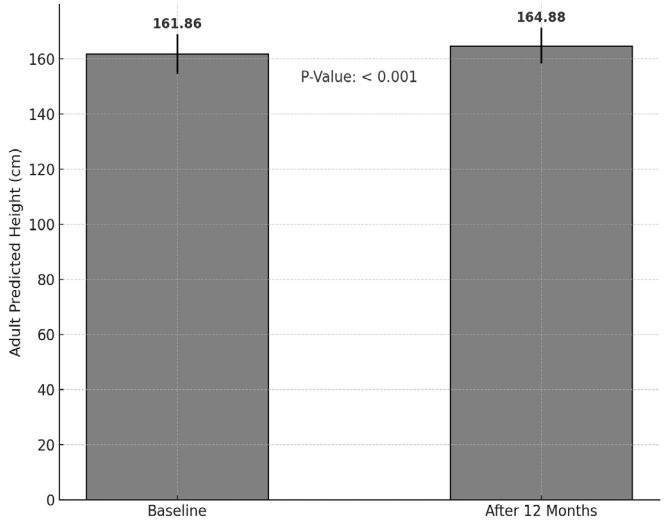

Figure 2. Change in adult predicted height (APH) before and after 12 months of weekly Somatrogon therapy in children with growth hormone deficiency. p<0.001.

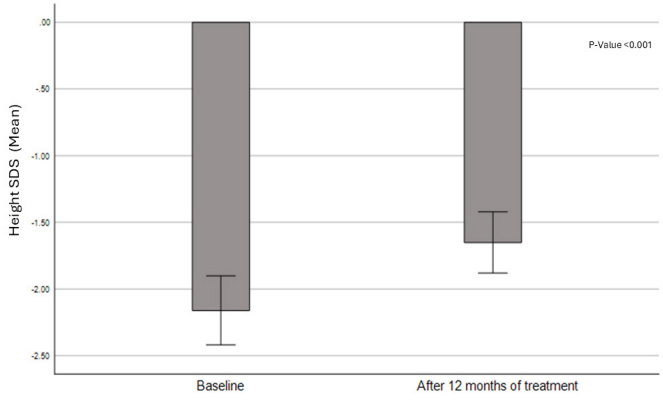

Figure 1. Change in height SDS before and after 12 months of weekly Somatrogon therapy in children with growth hormone deficiency. p<0.001.
SDS, standard deviation score.

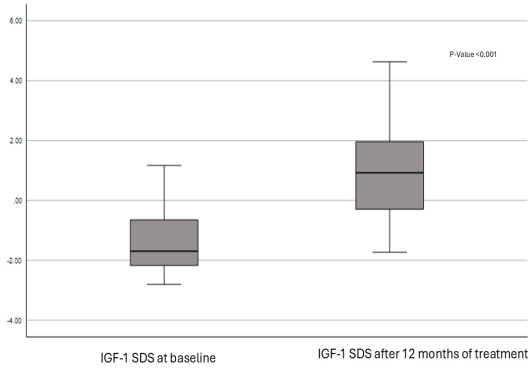

Figure 3. Change in IGF-1 SDS before and after Somatrogon treatment. p<0.001.
IGF-1, insulin-like growth factor-1; SDS, standard deviation score.

Table 2. Effect of Somatrogon on bone geometry after 12 months of treatment

Variable	**Baseline (Mean±SD)**	**After 12 months of Somatrogon treatment (Mean±SD)**	**p value**
Bone age SDS	-1.53±1.30	-1.44±1.28	0.269
BHI SDS	-1.29±1.50	-0.83±1.41	<0.001
MCI SDS	-1.33±1.18	-1.16±1.07	0.106

p values calculated using paired t-tests comparing baseline and 12-month post-treatment values.
BHI: bone health index; MCI: metacarpal index; SDS: standard deviation score.

Discussion

In our real-world setting, treatment with Somatrogon significantly increased height SDS, APH, and IGF-1 SDS levels after one year of treatment. In addition, Somatrogon treatment for one year was associated with improved BHI without significant change in bone age or MCI.

The significant height SDS gain observed aligns with findings from Deal et al. (12), where Somatrogon demonstrated non-inferiority to daily somatropin in terms of height velocity and height SDS with the least squares mean (LS mean) treatment difference: 0.06 (95% confidence interval, -0.01, 0.13). Horikawa et al. (11) similarly reported robust growth outcomes with Somatrogon in rhGH naïve prepubertal children where the LS mean change in height SDS from baseline to 12 months was greater in the Somatrogon group (0.94) compared to the daily GH group (0.52) (11). Our height SDS improvement (Δ0.51) closely mirrors daily GH outcomes in Deal et al. (12) (Δ0.52).

The observed increase in IGF-1 SDS in our cohort is consistent with previous findings. Deal et al. (12) reported similar findings, noting that IGF-1 profiles with Somatrogon were higher compared to daily GH regimens, where the mean IGF-1 SDS was -1.95 at baseline and increased to 0.65 at 12 months post-baseline. Similarly, Horikawa et al. (11) reported significant increase in IGF-1 SDS in Japanese children with GHD after treatment with Somatrogon (11).Improvements in BHI observed in our study with Somatrogon treatment are consistent with findings from Wydra et al. (35), which emphasized the anabolic effects of GH on bone mineralization. Another study showed that in short-statured children, daily GH treatment significantly improved BHI, where BHI SDS increased from -0.97 to -0.17 after 1 year of GH ($p<0.001$). The BHI increased initially with GH treatment and plateaued over time, suggesting sustained improvement in bone health (18).

The absence of significant bone age advancement in our study differs from results commonly observed with previous studies, where Deal et al. (12) in a phase 3 study comparing Somatrogon to daily rhGH found significant bone age progression after one year of treatment, which was comparable to bone age progression rates seen on daily rhGH. Similarly, Horikawa et al. (11) reported significant bone age advancement on Somatrogon treatment. This discrepancy may be explained by the different methods used to assess bone age. In our study, bone age was determined using an automated AI-based analysis, whereas the previous studies relied on manual evaluation.

However, the lack of significant improvement in the MCI was notable. This is consistent with findings from Bettendorf et al. (36) and Radetti et al. (37), which reported no substantial alteration in metacarpal proportions during GH therapy. However, the findings diverge from Martin et al. (38), who also used BoneXpert and observed significant improvement in MCI within the first year of daily GH therapy (22). The discrepancy with the results reported by Martin et al. (38) could stem from differences in GH regimens. Daily GH therapy may exert a more consistent anabolic effect on bone geometry compared to the intermittent stimulation provided by weekly Somatrogon.

While BoneXpert software represents a validated and widely-used automated tool for bone health assessment in pediatric populations, it is important to acknowledge that its reference standards are derived from a Dutch Caucasian population (33). To address this potential limitation in our ethnically diverse cohort, we employed SDS relative to bone age rather than absolute values, a recommended approach that helps normalize for population differences (39). Although ethnic variations in BMD and skeletal architecture have been documented in pediatric populations, BoneXpert has demonstrated acceptable performance and has undergone validation across diverse populations (40). The BHI provided by BoneXpert has been shown to reflect cortical BMD effectively in pediatric and adolescent patients (17), and the use of SDS values in our analysis provides a standardized approach that accounts for individual variation, allowing for meaningful clinical interpretation of bone health parameters (38). While population-specific reference data would be ideal for Middle Eastern children, BoneXpert remains the most extensively validated automated tool available for pediatric bone health assessment, and our findings using SDS-based analysis provide valuable real-world evidence of skeletal outcomes following Somatrogon therapy (41). In addition, the paired design of our analysis, where each participant served as their own control, further mitigates the influence of any systematic bias in the reference data.

The observed improvement in the BHI, despite the absence of significant changes in the MCI or bone age, suggests a nuanced shift in cortical bone geometry. Given that MCI is calculated as the ratio of cortical area (A) to the square of bone width (W^2), its stability implies that any increase in cortical area occurred proportionally to changes in bone width. In contrast, BHI incorporates both width and bone length in the denominator with lower exponents ($W^{1.33}$ and $L^{0.33}$), making it more sensitive to subtle increases in cortical area. The improvement in BHI, therefore, likely reflects a disproportionate increase in cortical thickness relative to width, resulting in a net gain in cortical area that was not substantial enough to affect MCI. Moreover, the lack of advancement in bone age suggests that these structural changes occurred independently of accelerated skeletal maturation.

Study Limitations

This study has several limitations. Its retrospective cross-sectional design, absence of a daily GH control group, and relatively small

sample size may restrict the generalizability of the results. DXA, the gold standard for assessing BMD, was not employed (42). Bone age assessments were conducted using BoneXpert, which, while the most practical and validated tool available in the absence of local reference data, may be less accurate in a cohort with diverse ethnic backgrounds (33). In addition, systematic safety data were not collected due to the retrospective nature of the study.

Conclusion

In a real-world setting, the results of our study add to the growing body of evidence showing that Somatrogon is an effective option for GHD treatment. Weekly Somatrogon therapy led to significant improvements in growth parameters and IGF-1 levels, as well as enhancements in the BHI. However, the nuanced effects on cortical bone geometry underscore the need for further research. Future studies should include the assessment of bone health using DXA to provide a more comprehensive evaluation of skeletal outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority, and the Institutional Review Board of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU IRB-2024-562; Ref: DSREC-SR-11/2024_04).

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Concept: Mohammad Hosny Awad, Rania Eladl, Zulf Mughal, Manal Mustafa, Design: Mohammad Hosny Awad, Rania Eladl, Zulf Mughal, Manal Mustafa, Data Collection or Processing: Mohammad Hosny Awad, Reham Ghanim, Rania Eladl, Zulf Mughal, Manal Mustafa, Analysis or Interpretation: Mohammad Hosny Awad, Manal Mustafa, Literature Search: Mohammad Hosny Awad, Manal Mustafa, Writing: Mohammad Hosny Awad, Manal Mustafa.

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Challenges in Sex Assignment in 46,XX Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency and 11β-hydroxylase Deficiency in Developing Countries: Insights from an Expert Center in Indonesia

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ABSTRACT

Objective: The absence of newborn screening, insufficient knowledge among medical professionals, and poor treatment adherence in congenital adrenal hyperplasia (CAH) in Indonesia causes late diagnosis. This study presents two decades of experience in gender assignment and diagnosis of 46,XX CAH.

Methods: A cohort study was carried out at a CAH referral center in Central Java, Indonesia. Data regarding clinical outcomes, molecular analysis, and sociodemographic information were taken from medical records. Participants were grouped based on current social gender, females and males. Gender at diagnosis, age at first presentation, age at first diagnosis, age at present, CAH types, virilization, puberty, birth attendant, and gender at birth decision maker significantly predict current gender identity.

Results: Among 131 individuals with 46,XX CAH, 52 (39.7%) with a sex assignment incongruent with their karyotype were included. The majority (49/52; 94.2%) had 21-hydroxylase deficiency (21OHD), while three (5.8%) had 11 beta-hydroxylase deficiency (11OHD). Individuals assigned as males at birth (3/52) had severe virilization. A change of gender occurred in 46 of 52 patients (88.46%). Midwives were the most frequent birth attendants (24/51), while pediatricians were the major decision-makers (19/51) of sex assignment.

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Conclusion: In Indonesia, many 46,XX individuals with CAH were initially assigned as males due to late diagnosis, primarily caused by low awareness among healthcare professionals and exacerbated by limited medical resources and a lack of clear guidelines on sex assignment. Therefore, targeted education and standardized guidelines involving a multidisciplinary team are crucial to ensure appropriate sex assignment and care.

Keywords: Congenital adrenal hyperplasia, sex assignment, developing country, newborn screening

What is already known on this topic?

Gender assignment in virilized 46,XX congenital adrenal hyperplasia (CAH) is challenging, considering many interplaying factors, such as biological function, sociocultural factors, family beliefs, and psychological outcomes. In the absence of newborn screening, many CAH individuals are late-diagnosed, leading to various practices of gender assignment across countries. The lack of knowledge regarding CAH among healthcare professionals and the absence of newborn screening added to the complexity of gender assignment of CAH individuals in Indonesia.

What this study adds?

This study presented the gender assignment practices in the only CAH center in Indonesia, highlighting the importance of timely and accurate CAH diagnosis to determine an optimal assignment for each individual. Moreover, the gender assignment approach of two types of CAH, 21-hydroxylase deficiency and 11β-hydroxylase deficiency, was presented.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive conditions caused by enzymatic defects in steroid synthesis. Approximately 90-99% of CAH cases are caused by 21-hydroxylase deficiency (21OHD), although other causes includes 11 β-hydroxylase deficiency (11OHD), 17-hydroxylase deficiency (17OHD), *HSD3B2* deficiency, *CYP11A1* mutation, *STAR* mutation, and P450 oxidoreductase (POR) deficiency (1,2). Both 21OHD and 11OHD result in excessive adrenal androgen synthesis and cortisol deficiency leading to virilization of the external genitals in 46,XX individuals while 46,XY individuals are typically normal (3). CAH is the most frequent cause of 46,XX disorders/differences of sex development (DSD) (4).

The incidence of 21OHD (OMIM #201910) varies geographically and ethnically, with the highest rates in regions with a high degree of consanguinity. Globally, 1 in 14,000-18,000 live newborns are affected (5). 21OHD results from homozygous or compound heterozygous mutation in the *CYP21A2* genes manifesting as a clinical spectrum, from the most severe classic salt wasting (SW) type associated with cortisol and aldosterone deficiency to mild non-classic type (NCCAH), presenting with mild signs of hyperandrogenism (3). 11OHD (OMIM #202010), caused by mutations in the *CYP11B1* gene, is less common, accounting for approximately 0.2-8% of cases; hence the incidence is 1 in 100,000-200,000 live births (6,7). Similarly, 11OHD causes androgen excess, but aldosterone is unaffected. Instead, aldosterone precursors accumulate, leading to various degrees of hypertension (8).

Prenatal androgen exposure, particularly between 8-24 weeks of gestation and the early neonatal period, has long-lasting organizational effects on neurobehavioral sexual differentiation, resulting in male-typical behavior in females with 21OHD or 11OHD (9). Increased androgen also causes various degree of virilisation in females (10). The Pediatric Endocrine Society (PES) advises female assignment in 46,XX CAH newborns to maintain fertility and reproductive functionality (11). However, recent studies propose male sex of rearing for severely virilized individuals, representing an evolving perspective considering both the importance of biological functional and psychosocial factors, including family dynamics, culture, prenatal androgen exposure, and sexual function, in accordance with the Chicago Consensus (12,13).

In many Western countries, newborn screening (NBS) has enabled early CAH diagnosis and intervention to prevent life-threatening adrenal crisis and minimizing comorbidities, such as short stature, infertility, and psychological adversity (14). Nevertheless, in many developing countries, CAH diagnoses remain delayed due to the absence of NBS (15,16). Furthermore, poor awareness among many healthcare professionals leads to confusion about gender assignment. Poor infrastructure and limited transportation in Indonesia, as well as parents' fear of stigmatization and educational barriers, further delay presentation to the healthcare facilities (17).

In Indonesia, birth attendants, which may include midwife, general physician, OB/GYN, pediatrician, or traditional midwife (*paraji*), assign sex primarily based on the external genital appearance. As only "male" or "female" is legally recognized in Indonesia, ambiguous genitalia present an additional burden. Physicians often suggested giving a unisex name to avoid delay in birth registration, which must occur within 60 days. The birth certificate is vital for civil status and state recognition,

according to the Constitution of 1945. In the past, many severely virilized, late-diagnosed 46,XX CAH had to undergo a legal trial to change their gender. As a Muslim majority country, the Indonesian Ulama Council (MUI) exerts a major influence on the management of DSD individuals by issuing a *fatwa*, a religious ordinance, that does not hold constitutional power but has a significant moral impact within the Muslim society, to prohibit transsexuals from having sex reassignment surgery, but legalized gender reassignment DSD (*khuntsa*) individuals. Although the MUI's fatwa is not legally binding, it significantly shapes court decisions and medical practices (18).

Gender assignment among DSD individuals is a complex process; hence, it is obligatory to involve a multidisciplinary team consisting of at least pediatric endocrinologists, surgeons or urologists, gynecologists, geneticists, psychologists and medical ethicists. Nevertheless, not all medical centers in Indonesia have applied this approach. It has caused various sex assignments and adverse psychological outcomes, including gender dysphoria, anxiety, stress, and depression, among these individuals. This study presents two decades of experience in gender assignment and diagnosis of 46,XX CAH individuals at a single CAH referral center in a developing country, emphasizing the importance of timely and accurate diagnosis to ensure appropriate treatment in future cases.

Methods

Research Design

A retrospective cohort study was conducted on patients referred to the CAH clinic in Semarang, Central Java. The patients' data were collected from medical records between July 2004-December 2024.

Samples and Participants

All patients diagnosed by pediatric endocrinologists with CAH due to 21OHD based on clinical manifestations and 17-hydroxy progesterone (17-OHP) levels were included in this study. Patients with 11OHD CAH were diagnosed based on clinical manifestations and genetic test results. Patients with other etiologies of ambiguous genitalia were excluded.

Data Collection

The following patients' data were obtained from medical records. The diagnosis of CAH was made by an experienced pediatric endocrinologist (AU) based on: (1) clinical manifestations, including genital ambiguity, vomiting, diarrhea, and failure to thrive; (2) biochemical analyses, including levels of 17-OHP; and (3) chromosomal analysis conducted in Center for Biomedical Research (CEBIOR), Faculty of Medicine, Universitas Diponegoro, Indonesia.

The diagnosis was confirmed by mutation analysis. DNA samples were sent to the Department of Human Genetics, Radboud University Medical Centre (Radboudumc), Nijmegen, the Netherlands, for multiplex ligation-dependent probe amplification and Sanger sequencing to analyze the *CYP21A2* gene and the *CYP11B1* gene for 21OHD and 11OHD CAH, respectively. If available, genetic evaluations were considered to confirm the type of CAH and to provide genetic counselling. In 11 individuals genetic tests were not conducted, thus, electrolyte levels, showing hyponatremia and hypokalemia, were considered to differentiate between CAH types, 21OHD and 11OHD, and a history of previous hospitalization for adrenal crisis for SW CAH.

Sex Assignment

Patients presenting with a clinical suspicion of CAH, with symptoms that may have included vomiting, diarrhea, dehydration, failure to thrive, and virilization, were physically examined by a pediatric endocrinologist in our center. The degree of virilization and puberty were assessed using the Prader and Tanner stage, respectively. The patients would be referred for a biochemical investigation of electrolytes and 17OHP, to confirm CAH diagnosis. To determine the patient's karyotype, karyotyping was performed.

A psychological evaluation regarding gender assignment was not conducted for newborns, infants, and toddlers (<2 years) because the child had not developed a gender identity yet. The attending pediatric endocrinologist would explain the results and diagnosis. Based on the medical information provided by the pediatric endocrinologist, the parents made a decision regarding their child's gender.

A gender evaluation for children aged 2-7 years was conducted by a psychologist, who interviewed parents about the child's gender behavior, the child's gender preferences, and parental expectations regarding the child's gender. As gender development is dynamic and influenced by social factors, and considering the brain gender of the child, the psychologist will usually advise parents to continue observation of the child's gender behavior and preferences until adolescence, particularly concerning the possibility of the development of gender dysphoria. In most cases, girls with CAH developed masculine gender behavior and preferences, but without any confusion or dissatisfaction with the assigned gender. Children, adolescents, and adults who were late-diagnosed were referred for a psychological evaluation regarding gender assignment. A clinical psychologist and a psychiatrist conducted the assessment simultaneously and wrote a report independently to assess the individual's gender identity, gender role, and sexual orientation. Gender assignment of children aged 8 years or older was conducted using questionnaires and interviews with the patients and parents. If gender was doubted or matched with gender dysphoria according to the

DSM-5 criteria, typically triggered by the appearance of external genital or primary and secondary sexual characteristics, an interdisciplinary team meeting was held to discuss the results, outcomes, and planned management with consideration of the individual's overall well-being. A justification for gender change could not be made solely on gender behavior, such as clothing choices, playmates' preferences, and roles within a society. Instead, the individual's desire to be the opposite gender was the basis of the decision. The outcomes of the meeting, along with the consequences of choosing a certain gender, were delivered by the attending physician directly to the adult individuals and to the parents in the case of children and adolescents. Parents were given adequate time and space to make informed decisions in the best interest of their child. If a gender change was decided, it was a shared decision-making process between the team, patients, and parents.

CAH treatment was given immediately in 46,XX CAH patients assigned as females, i.e., patients with SW and simple virilizing (SV) type were given hydrocortisone (HC) combined with fludrocortisone (FC) for SW CAH and HC for SV CAH, respectively, whereas patients with 11OHD CAH were administered HC. Regular monitoring was conducted, consisting of gender satisfaction and disease evaluation control, which included signs of adrenal and SW crisis, reproductive health, and metabolic control (Figure 1).

Some of the individuals included in this study have already been reported by Ediati et al. (18) and Utari et al. (16), specifically, some who were reassigned as males and were siblings, respectively.

Ethical Considerations

All parents or caregivers provided written informed consent prior to the study, and the Diponegoro University Faculty of Medicine Health Research Ethics Committee approved the study (approval no.: 682/EC/KEPK/FK-UNDIP/XII/2024, date: 19.12.2024), guaranteeing that it complied with the 1975 Declaration of Helsinki's ethical standards.

Statistical Analysis

The categorization of the 46,XX CAH individuals were based on the current gender identity. Descriptive data are presented as frequency and percentages. Analysis was performed using SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Bivariate analysis using Fisher's exact test was conducted to determine the association between variables, including clinical characteristics and social factors. Statistical significance was defined as p value <0.05.

Results

Gender Assignment Practices

Among 131 46,XX 21OHD and 11 OHD patients managed in our center, 83 were assigned as female after birth, while 30 (22.9%) individuals received sex assignments after birth inconsistent with the karyotyping result, and 18 (13.7%) individuals were undecided (Figure 2). There were 12 individuals (23.1%) who consented to be males and refused medication after receiving information regarding the CAH condition.

Six (11.54%) were late-diagnosed and identified themselves as males who chose not to take HC or FC. Two were diagnosed with SW CAH based on genetic test results. One individual was diagnosed at the age of 3 months and received treatment until the age of 1 year. He started to be re-treated at the age of 6 years, but his treatment was irregular. At the age of 8.5 years, a re-evaluation was conducted, and he wished to remain as a male. Another individual remained untreated/chose not to be treated and was assigned as male because his parents wanted a son despite a history of adrenal crisis. The parents had been fully informed about the impact of untreated CAH, which could be life-threatening. In addition, he had precocious puberty and attained skeletal maturity at the age of ten with a final height of 135.9 cm.

Upon diagnosis of CAH, three (5.77%) individuals initially assigned as females at birth refused to take medication and chose to live as males. Their gender was reassigned at the ages of 3, 7, and 45 years. One individual was assigned and reared as female, but at age 3 years transitioned to male due to social pressure regarding the appearance of the external genitals looking more like a male's. Another individual, originally assigned as female at birth, then independently transitioned and gained real-life experience as a male, visited the center only to confirm his gender. Later, he married a woman and reported a satisfying personal life.

From a total of 18 individuals whose gender was undecided at birth, three were siblings with 11OHD who were reassigned as males. They presented with severe virilization (Prader 5) at ages 1.7, 8.5, and 2.1 years; their gender was initially undecided but re-assigned as males after the diagnosis based on their father's decision and degree of virilization. Upon diagnosis, they refused to change their gender to female. They continued to live as men, had female partners, and were employed in physically demanding jobs, including construction work and driving.

The majority (49/52; 94.23%) had pathogenic *CYP21A2* variants, of which 43 (87.76%) had SW CAH. Three individuals had died after an adrenal crisis, after multiple hospitalizations due to frequent vomiting and dehydration. Almost half (24/51; 47.1%) of the CAH patients' births were attended by midwives, followed by OB/GYN (21/51; 41.2%) and traditional midwives (6/51; 11.8%). The largest proportion of sex assignments at birth were decided by pediatricians (19/51; 37.25%). The data on birth attendants and the person in charge of the birth sex assignment of one patient were not available in the medical record.

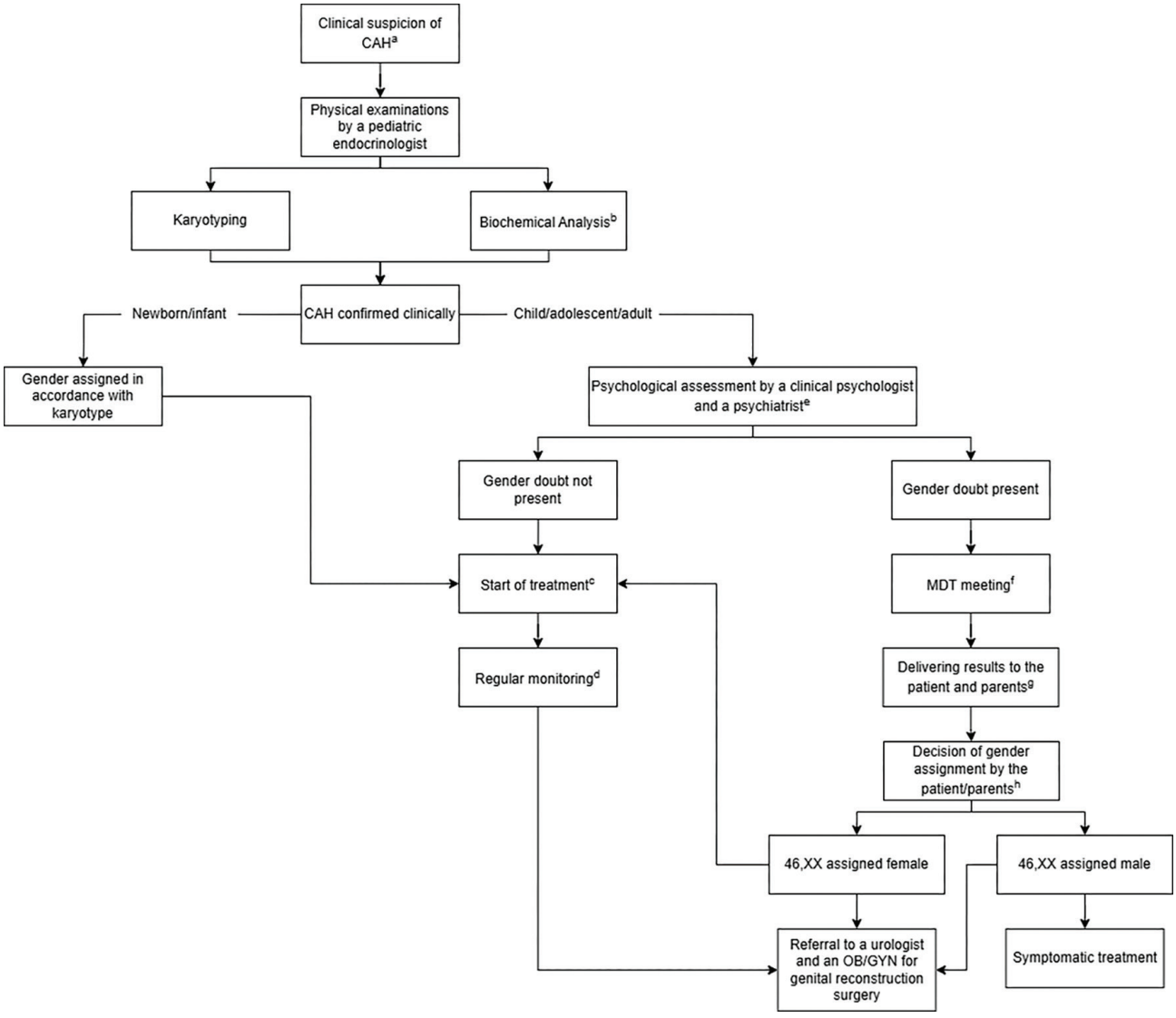

Figure 1. Flowchart of the sex assignment procedure of CAH individuals at our center

[a]Clinical suspicion of CAH includes vomiting, diarrhea, genital ambiguity, hyperpigmentation, and failure to thrive in newborns and infants. [b]Electrolytes, i.e., sodium, potassium, and chloride, and 17-OHP levels were measured. [c]Treatment comprised of hormonal, i.e., glucocorticoid and mineralocorticoid, and symptomatic, i.e., antihypertensive for 11OHD and NaCl for CAH SW. [d]Symptoms of adrenal insufficiency, menstrual cycle, libido and erection, sexual health, pubertal development, height, body mass index, blood pressure, bone age, and scrotal or ovarian ultrasound were monitored as indicated. [e]Psychological assessment of the individual's gender identity, gender role, and sexual orientation was conducted by a clinical psychologist and a psychiatrist. Reports were made independently. [f]A multidisciplinary team consisted of a pediatric endocrinologist, a geneticist, a clinical psychologist, a psychiatrist, a urologist, an OB/GYN, and a genetic counsellor. [g]Results were delivered to the patients and parents of children or adolescents. For adults, the results were received solely by them. [h]The gender decision was made by the parents considering the child's well-being. Adults with CAH made their own decision. 11OHD, 11β-hydroxylase deficiency; 17-OHP, 17-hydroxyprogesteron; CAH, congenital adrenal hyperplasia; MDT, multidisciplinary team.

Predictors of Gender at Present

Table 1 shows a significant difference in age at diagnosis between females and males with 46,XX CAH, in which 87.5% of females (n=40) were diagnosed at age <1 year, compared to 8.3% in the male group (n=12) (p<0.001). In contrast to 62.5% females presenting with Prader 3, severely virilized individuals were significantly more likely to have male gender identity (p<0.008), as evidenced by 41.7% and 25.0% males presenting with Prader 4 and 5, respectively. The involvement of healthcare professionals at the birth of CAH individuals significantly predicted their current gender (p<0.001), in which all females were attended by either a midwife or OB/GYN, and 54.5% of males were attended by non-healthcare professionals (i.e., traditional midwives). Due to the limited sample size, sensitivity analysis of the present gender subgroups was not conducted.

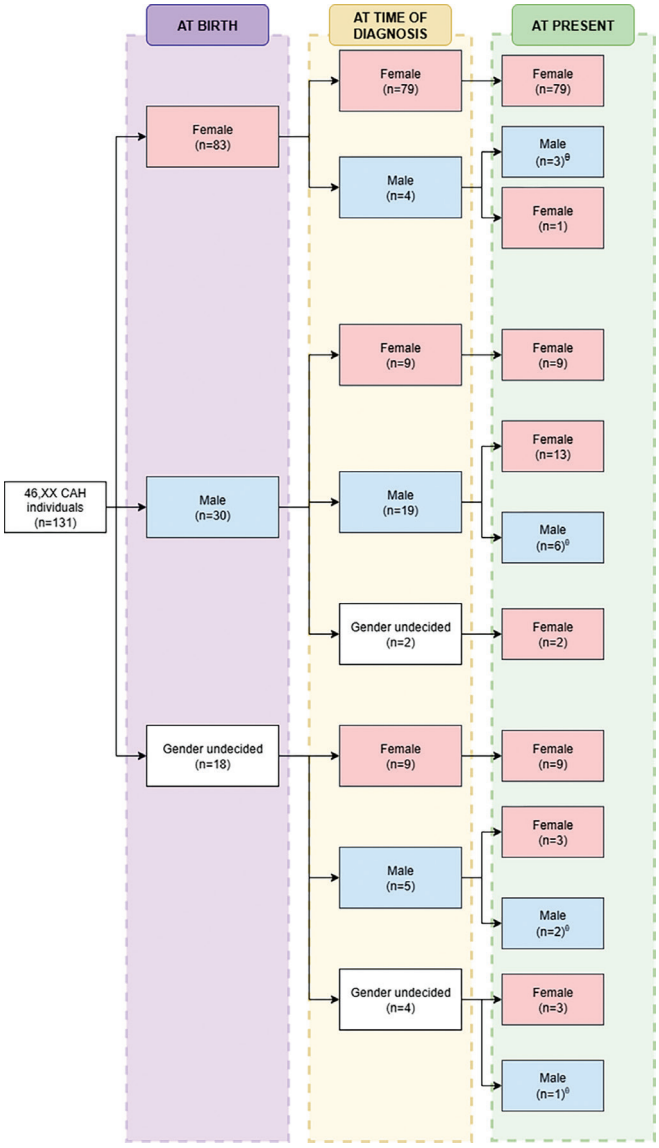

Figure 2. Gender assignment odyssey of 46,XX CAH individuals in Indonesia

θCAH individuals who were reassigned as males gave informed consents not to take medication, i.e., HC and FC, due to their wish to remain as males.

Discussion

Various gender assignment practices in CAH individuals remain common in Indonesia, even after two decades of experience. The majority of 46,XX CAH individuals in this study were late-diagnosed, which is comparable to a previous study in the context of lack of NBS for CAH (19). In Indonesia, the pilot project of CAH NBS only started in 2024 and expanded nationally at the beginning of 2025. Individuals who received earlier recognition were mostly attended by healthcare professionals, midwives and OB/GYN, and depicted an increasing tendency to be assigned as females. According to the Decree of the Minister of Health, uncomplicated spontaneous birth was prioritized to be assisted in primary healthcare facilities, such as sub-district health centers (*Puskesmas*), midwife private practices, and primary doctor clinics, attended by midwives or general physicians (20). Although the Indonesian government increased the number of midwives at the community level and healthcare facilities in both urban and rural areas, only 55.2% of mothers sought help with childbirth from healthcare professionals, such as general physicians, midwives, hospitals, maternity homes, or other health centers (21). This indicates a significant reliance on non-medical professionals, including traditional midwives (*paraji*) who lack formal medical training.

The majority of 46,XX CAH individuals in Indonesia had the most severe SW type. Children with CAH were usually born with an uncomplicated pregnancy and spontaneous labor, hence, most children born in primary and secondary healthcare facilities were not immediately referred to the central hospital to receive an appropriate diagnosis and treatment. Referrals typically occurred after frequent episodes of vomiting and dehydration without improvement after receiving treatment, which are the characteristics of the most severe SW type (16,22,23). Delayed referral is a common challenge found in developing countries, as reported from Bangladesh, Sri Lanka, and Malaysia (24,25,26). Many Indonesian healthcare professionals lack knowledge about CAH, including the atypical presentation of external genital, clinical manifestation of adrenal insufficiency, genetic etiology, laboratory workup, and management (27). For example, genetics was only included in the list of midwives' standard competencies in 2020 (28).

Some 46,XX individuals with CAH were initially treated, but due to a lack of compliance, their conditions were poorly controlled. Upon monitoring, they were offered continuation of medication, but, despite understanding the impending adrenal crisis, chose not to take medication which may lower androgen levels, because they would like to remain as males. Our data showed that adherence to treatment remained an issue, despite the increased availability of CAH medications (29). CAH individuals in a developing country had to travel considerable distances and a spend a substantial amount of time to receive care at the tertiary hospital (30). The need for lifelong medications might reduce individuals' motivation to adhere to treatment. Adding to the complexity were inadequate information and myths about the side effects of taking lifelong medications, which are commonly believed in developing countries (31,32). Conversely, a previous study in Sweden reported good treatment adherence in children and adults with CAH, with better adherence observed in SW, the most severe CAH (33).

Table 1. Sex assignment practices in 46,XX CAH individuals

	Current gender		p value
	Female n (%)	Male n (%)	
Sex at birth (n=52)			0.064
Male	24 (60.0)	6 (50.0)	
Female	1 (2.5)	3 (25.0)	
Undecided	15 (37.5)	3 (25.0)	
Gender at diagnosis (n=52)			**0.004***
Male	17 (42.5)	11 (91.7)	
Female	18 (45.0)	1 (8.3)	
Undecided	5 (12.5)	0 (0.0)	
Age at first presentation (n=52)			**<0.001***
<1 y	37 (92.5)	0 (0.0)	
1-5 y	2 (5.0)	3 (25.0)	
5-11 y	1 (2.5)	5 (41.7)	
11-18 y	0 (0.0)	2 (16.7)	
>18 y	0 (0.0)	2 (16.7)	
Age at first diagnosis (n=52)			**<0.001***
<1 y	35 (87.5)	1 (8.3)	
1-5 y	4 (10.0)	3 (25.0)	
5-11 y	1 (2.5)	4 (33.3)	
11-18 y	0 (0.0)	2 (16.7)	
>18 y	0 (0.0)	2 (16.7)	
Age at present (n=46)			**<0.001***
<1 y	33 (82.5)	0 (0.0)	
1-5 y	6 (15.0)	2 (33.3)	
5-11 y	1 (2.5)	3 (50.0)	
11-18 y	0 (0.0)	0 (0.0)	
>18 y	0 (0.0)	1 (16.7)	
CAH types (n=52)			**<0.001***
SW	39 (97.5)	4 (33.3)	
SV	1 (2.5)	5 (41.7)	
11OHD	0 (0.0)	3 (25.0)	
Degree of virilization (n=52)			**0.008***
Prader 1	0 (0.0)	0 (0.0)	
Prader 2	2 (5.0)	1 (8.3)	
Prader 3	25 (62.5)	3 (25.0)	
Prader 4	13 (32.5)	5 (41.7)	
Prader 5	0 (0.0)	3 (25.0)	
Puberty at diagnosis (n=52)			**<0.001***
Yes	0 (0.0)	9 (75.0)	
No	40 (100.0)	3 (25.0)	

Table 1. Continued

	Current gender		p value
	Female n (%)	Male n (%)	
Treatment status (n=52)			**<0.001***
Treated (hormonal treatment)	36 (90.0)	0 (0.0)	
Untreated	0 (0.0)	10 (83.3)	
Loss to follow-up	1 (2.5)	2 (16.7)	
Died	3 (7.5)	0 (0.0)	
Birth attendant (n=51)†			**<0.001***
Midwife	20 (50.0)	4 (36.4)	
OB/GYN	20 (50.0)	1 (9.1)	
Traditional midwife (*paraji*)	0 (0.0)	6 (54.5)	
Decision maker of gender at birth (n=51)††			**0.011***
Midwife	12 (30.0)	4 (36.4)	
OB/GYN	2 (5.0)	0 (0.0)	
Pediatrician	18 (45.0)	1 (9.1)	
General physician	1 (2.5)	0 (0.0)	
Traditional midwife (*paraji*)	0 (0.0)	3 (27.3)	
Parents	7 (17.5)	3 (27.3)	
Genetic variants (n=82)§			
R356W	53.1	13.6	
I2G	28.1	31.8	
Exon 1-7 del	6.3	0.0	
P30L	6.3	0.0	
W22X	3.1	0.0	
p.Trp406*	3.1	0.0	
p.Trp20*	0.0	4.5	
I172N	0.0	4.5	
Exon 1-3 del	0.0	4.5	
p.Ile386del	0.0	4.5	
p.Gln196*	0.0	4.5	
R356W/Microconversion in the promoter region (c.-126T; c.-113G>A; c.-110T>C; c.-103A>G) [~80% less active transcript]	0.0	4.5	
p.Val252fs (CYP11B1)	0.0	27.3	

*Statistically significant (p<0.05)
@There were 6 individuals who were assigned male at birth and stayed as males.
#Puberty was determined by pubarche (Tanner P2).
†Data were unavailable from 1 male patient due to loss to follow-up.
††Data were unavailable from 1 male patient due to loss to follow-up.
§Allele frequency was calculated from the genetic test results of 41 individuals. Allele frequency was presented in percentage. No comparative analysis for the allele frequency variable was conducted.
¶Individuals were siblings. Their father decided their sex based on the male-like appearance of their external genitalia.
N/A: not available; 11OHD: 11 β -hydroxylase deficiency; CAH: congenital adrenal hyperplasia; SV: simple virilizing; SW: salt wasting.

Individuals with CAH in developing countries missed receiving timely diagnosis and treatment. The lack of laboratory analysis facilities in Indonesia, especially outside of Java, hindered diagnosis in our cohort. With prolonged time to diagnosis, CAH individuals were exposed to extended periods of elevated androgen levels which affected permanent neural organizational changes in the brain and, as a consequence, caused male-typical behaviors and toy choices in females with CAH (34). The masculinization effect from the androgen persisted and played a role in the establishment of male gender identity in 46,XX CAH (35). Therefore, after thorough evaluation with a clinical psychologist, individuals diagnosed in childhood or beyond determined to remain males owing to the androgen masculinizing effect on their gender behavior and identity. This finding was in accordance with a prior study that illustrated a mid-childhood conversion to male in late-diagnosed 46,XX CAH individuals in Bangladesh (36). In contrast, transition to male in 46,XX individuals with CAH has rarely been reported in developed countries due to early diagnosis and adequate access to medication. Nevertheless, this presented a complex situation because assigning a 46,XX CAH individual as male could deprive them of the opportunity of having children; the reproductive function would be preserved in 46,XX CAH females who were treated promptly and appropriately (3).

Gender identity issues and distress were commonly observed in DSD individuals, which led to gender dysphoria (37). Late-identified DSD individuals have reported experiencing more emotional and behavioral issues, including social isolation, particularly in adult women (38). Compared to children with DSD who were raised as boys, those who were raised as girls showed a high level of gender confusion. The same study also reported that women with DSD who received no treatment exhibited behavior inconsistent with their gender roles and were presumably more dissatisfied with their gender identity (18). Findings from some Sri Lankan and Indian 46,XX CAH populations revealed that a subset of individuals raised as females had gender dysphoria (25,39). Nonetheless, a meta-analysis found that the prevalence of gender identity issues was higher in CAH-raised males compared to females (40).

The majority of 46,XX CAH individuals reassigned as female were diagnosed before the age of one year. At this age, the primary social interactions were within the family where parents had the strongest impact on gender role development in their children (41). Later, children start forming stereotypes for both sexes at the age of two to three years, where they begin socializing beyond the family (42). Social stereotypes and pressure may influence the child's emerging gender identity, as seen in one of the individual within the "assigned male and remained as male" group.

However, a study by Dessens (43) revealed that some previously misassigned females with CAH at birth had difficulty with society's acceptance of gender reassignment. This was aggravated by preconceived notions and fear of social rejection. These stereotypes of how someone should behave to conform to a certain gender increased the burden on females with CAH, particularly if they were late-diagnosed and priorly assigned as males. In some cases, societal values further complicate the decision of gender assignment. In our society that prefers male children over females, some parents still choose to raise their 46,XX child as a male, even after diagnosis. Having a son was considered superior to having a daughter because, although a male is infertile, he can still hold a high place in a community and get a better job compared to a female. This was a common practice in Indonesia as patriarchal beliefs were still held by many, especially in rural areas (44).

Most 46,XX CAH in our cohort came with a moderate to severe degree of virilization (Prader 3-5), and more than half were assigned as male at birth. The appearance of external genitalia had a great impact on the gender assignment process, in which Prader 1-3 were more likely to be assigned females, but Prader 4-5 were apt to be assigned males, particularly due to the complexity of feminizing surgery, which may include worse outcomes, more complications, and greater assessment challenges (45). Both DSD and controls in a study by Chowdhury et al. exhibited a more masculine identity when they had more severely virilized external genitalia (46).

The development of one's gender is a fluid process with various factors interplaying, including potential for future fertility, hormonal therapy, feminizing or masculinizing surgery, psychological implications, and sociocultural factors (3). The latter were very diverse between populations, hence an individualized and measured approach needs to be considered (15,24,25,44). In the CAH Clinical Guidelines, an infant born with 46,XX CAH should be assigned female. This recommendation was made reflecting the condition in developed countries where early diagnosis was possible due to the availability of NBS (5). Previous studies reported that male assignment in 46,XX CAH could be an option in severely masculinized individuals, as they showed a good quality of life (QoL) (12). An emphasis on social and cultural preferences needed to be considered in assigning a person's gender, for example in Middle and Far Eastern countries, where males were considered to have a higher status than females (47). According to the Clinical Guidelines for the Management of Disorders of Sex Development in Childhood, the management of a person with a DSD condition must be individually tailored. A patient-centered care approach from a multidisciplinary team should consider the uniqueness of each person; hence, the best decision needs to be made in the patient's best interest (48). A psychologist or a psychiatrist trained in DSD care played an

integral part in gender assignment or reassignment, decision regarding surgery or hormonal treatment, and assessment of short or long-term outcomes. However, the DSD multidisciplinary team was only available in Semarang, Indonesia, bringing challenges to the provision of holistic and comprehensive care for the patients and their families (49).

Due to its potential to be life-threatening, CAH must be ruled out in every child born with genital ambiguity, and the attendants should contact healthcare professionals familiar with the disease. Although genital ambiguity is present only in 46,XX CAH, male gender assignment was common in a region without NBS (5). Several studies reported that only a small portion of severely virilized 46,XX CAH raised females reported dissatisfaction with their gender. Stigmatization related to cross-gender behavior and atypical physical appearance has been identified as a stress predictor in both adults with DSD and parents of children with DSD (23). In India, DSD individuals were labelled as "*hijra*" and received discrimination, which resulted in lower QoL (50). In developing countries, fertility and future marriage remained a concern for parents of female CAH (30).

A guideline for sex assignment in CAH individuals in Indonesia has not been established. The beginning of CAH NBS in Indonesia in 2025 represents a significant advance, offering a promising opportunity for early identification and treatment for affected individuals, thereby anticipating serious outcomes such as adrenal crisis, delayed sex assignment, and gender dysphoria. Nevertheless, national CAH guidelines for sex assignment need to be established. Furthermore, the development of effective education strategies for healthcare professionals will improve the knowledge and skills of healthcare professionals regarding CAH. Thus, its implementation should be made at primary, secondary, and tertiary care levels. Future research on the long-term evaluation of the psychological and social impact of late diagnosis should be conducted in resource-limited settings.

Study Limitations

This was a descriptive study in a single national DSD referral center, but it can provide useful insights into the past and changing practice concerning individuals with CAH. This study relied on retrospective data, which may be affected by incomplete medical records. Moreover, findings from a single referral center may not fully represent the sex assignment practices of CAH individuals in Indonesia. This study was not able to report the impact of sex assignment on the CAH individuals. Hence, future studies are needed to provide broader insights into CAH sex assignment practices in developing countries.

Conclusion

Various sex assignment practices affecting 46,XX CAH individuals in Indonesia remain, caused by low awareness among healthcare professionals and a lack of laboratory facilities, leading to late diagnosis. Gender at diagnosis, age at first presentation, at first diagnosis, and at gender reassignment, types of CAH, degree of virilization, puberty status, state of treatment, birth attendant, and decision maker for gender at birth were significant predictors of gender at present. Treatment compliance issues exposed these individuals to excessive androgen levels, causing male-gender behavior. Cultural, religious, and family values played an important role in shaping gender identity. In Indonesia, development of national CAH sex assignment guidelines and targeted education for healthcare professionals is necessary to ensure better long-term outcomes for individuals affected by CAH.

Ethics

Ethics Committee Approval: Diponegoro University Faculty of Medicine Health Research Ethics Committee approved the study (approval no.: 682/EC/KEPK/FK-UNDIP/XII/2024, date: 19.12.2024).

Informed Consent: All parents or caregivers provided written informed consent prior to the study.

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Footnotes

Authorship Contributions

Concept: Irene Astrid Larasati, Agustini Utari, Tri Indah Winarni, Design: Irene Astrid Larasati, Agustini Utari, Tri Indah Winarni, Data Collection or Processing: Irene Astrid Larasati, Agustini Utari, Annastasia Ediati, Analysis or Interpretation: Irene Astrid Larasati, Agustini Utari, Annastasia Ediati, Hedi L. Claahsen - van der Grinten, Tri Indah Winarni, Literature Search: Irene Astrid Larasati, Agustini Utari, Writing: Irene Astrid Larasati, Agustini Utari, Annastasia Ediati, Hedi L. Claahsen - van der Grinten, Tri Indah Winarni.

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Pediatric Complete Androgen Insensitivity Syndrome (CAIS): Clinical Presentation, Hormonal Profiles, and Gonadal Management

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ABSTRACT

Objective: Complete androgen insensitivity syndrome (CAIS) is caused by mutations in the *androgen receptor (AR)* gene, leading to androgen resistance. Early recognition is critical for optimal management. To evaluate clinical presentations, hormonal profiles, genetic characteristics, and decisions regarding gonadectomy in pediatric CAIS. Factors influencing gonadectomy, including malignancy risk, gonadal function, and psychological well-being were assessed.

Methods: Medical records of 16 children with genetically confirmed CAIS patients, aged 3 days-18 years, diagnosed between 2004 and 2024 at a tertiary referral center were retrospectively reviewed. Clinical, hormonal, genetic, and histological data were analyzed.

Results: Twelve patients (75%) were diagnosed prepubertally, most commonly due to inguinal hernia. Familial recurrence occurred in four cases (25%). Novel pathogenic AR variants not previously reported in public databases were identified in three patients. Prepubertal patients with hormone data (n=5) demonstrated Anti-Müllerian hormone>150 pM. Pubertal patients (n=9) had markedly elevated testosterone levels [median at 1361.3 ng/dL, range 367-3460 ng/dL]. Gonadal biopsy was performed in three cases (19%). Gonadal preservation was recommended in 11 children (69%), while five (31%) underwent gonadectomy followed by estrogen replacement therapy.

Conclusion: Most CAIS cases in this pediatric cohort were detected early through inguinal hernia or family screening. Delayed gonadectomy allowed spontaneous pubertal development and feminization. While gonadectomy results in lifelong hormone dependence and may raise identity-related concerns, surveillance-based gonadal preservation appears safe during childhood. The identification of novel *AR* variants expands the mutational spectrum of CAIS and highlights the need for multicenter registries and improved biomarkers to optimize individualized care.

Keywords: Androgen-insensitivity syndrome, amenorrhea, castration

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What is already known on this topic?

Complete androgen insensitivity syndrome (CAIS) arises from *androgen receptor (AR)* gene mutations in 46,XY individuals, causing a female phenotype with common presentations of inguinal hernia in infancy and primary amenorrhea in adolescence. Prophylactic gonadectomy timing is debated because of the low prepubertal malignancy risk and benefits of spontaneous pubertal development.

What this study adds?

This cohort of 16 pediatric CAIS patients shows that delaying gonadectomy until after spontaneous puberty under structured surveillance yielded no malignancies, supported natural estrogenization, and enhanced psychological outcomes. Familial AR mutation inheritance patterns and detailed hormonal profiles inform personalized gonadal management.

Introduction

Complete androgen insensitivity syndrome (CAIS) is a condition classified as a difference of sex development (DSD) caused by mutations in the X-linked *androgen receptor* (*AR*) gene (1). The disorder is primarily inherited from a heterozygous carrier mother, though *de novo* mutations occur in about 30% of cases (2,3). These mutations lead to a loss of function, preventing the androgen receptor from responding to androgens, primarily testosterone (T) and dihydrotestosterone (DHT). As a result, individuals with a 46,XY karyotype develop a female phenotype (4,5). Globally, the prevalence of CAIS is estimated at 1 in 20,000 to 1 in 100,000 live births (4,6). Due to androgen resistance, the Wolffian ducts fail to develop into male internal and external genitalia, Anti-Müllerian hormone (AMH) which acts independently, prevents the formation of typical female reproductive structures like the uterus and fallopian tubes, and the upper part of the vagina (7,8). The testes are typically undescended and may be located in various positions along the path of normal testicular descent, failing to descend into the scrotum. Common locations for undescended testes in CAIS include the abdomen, inguinal canal, suprapubic area, or labia majora, which may mimic labial swelling (2,9). During puberty, high levels of T produced by Leydig cells, are converted to oestradiol, resulting in the development of a phenotypic female with breast development. Peripheral androgen resistance limits the development of pubic and axillary hair (5,10).

The diagnosis of CAIS may first be suspected in infancy or early childhood, especially when inguinal hernias are observed in individuals with a female phenotype (4). In such cases, patients are referred for diagnostic hormonal evaluation and may require surgical intervention, occasionally including gonadal biopsy. In adolescence, clinicians should consider CAIS in patients presenting with primary amenorrhea, a shortened vagina, absence of a uterus and sparse body hair (11). CAIS can also be diagnosed prenatally when there is a discrepancy between the phenotypic sex and a 46,XY karyotype identified during foetal screening (9). Definitive confirmation of CAIS is achieved through molecular genetic testing, which identifies a hemizygous mutation in the *AR* gene on the X chromosome in individuals with a 46,XY karyotype. This molecular confirmation is vital for establishing the clinical diagnosis of CAIS. However, the optimal management of gonadal tissue in CAIS remains a matter of debate. The aim of this study was to evaluate the clinical presentation, hormonal profile, and genetic characteristics of genetically confirmed CAIS patients and assess the impact of gonadectomy decisions, considering oncological risks, endocrine function, and psychological well-being (2,3).

Methods

This retrospective study analysed a cohort of CAIS patients managed at the Department of Endocrinology and Diabetology at The Children's Memorial Health Institute, Warsaw, Poland, between 2004 and 2024. The aim was to characterize the clinical presentation, hormonal profile, and genetic findings in individuals with CAIS and evaluate the factors influencing gonadal management decisions, including the rationale for gonadectomy, histological findings, and long-term outcomes. In addition, the study explored the endocrine and psychological aspects related to gonadal preservation. Inclusion criteria included a confirmed diagnosis of CAIS based on genetic testing (46,XY karyotype with a pathogenic *AR* gene mutation) and clinical features. Eligible patients exhibited at least one of the following clinical characteristics: (1) typical female external genitalia at birth despite a 46,XY karyotype; (2) primary amenorrhea in adolescence; (3) inguinal hernia containing gonadal tissue in infancy or childhood; (4) absence of Müllerian structures (uterus, fallopian tubes) on imaging; and/or (5) elevated AMH levels within the male reference range during infancy or prepuberty.

Medical records were reviewed to collect data on key clinical parameters, including age at presentation, reasons for endocrine consultation, history of surgical interventions (particularly inguinal hernias and gonadectomies), and family history of similar conditions. These data were used to assess trends in clinical presentation and decision-making regarding gonadal management.

Clinical examination included final height measurements using a stadiometer, expressed in standard deviations (SD) compared to the mean height of both adult females and males and in comparison to height predictions based on mid-parental height. Psychological outcomes and quality of life were assessed retrospectively from clinical follow-up notes and patient/parent reports, including emotional well-being, self-acceptance of CAIS diagnosis, body image perception, and concerns related to fertility and gender identity. No validated psychometric questionnaires were applied. Moreover, clinical follow-up notes were reviewed for reports of anxiety, depression, or psychosocial distress associated with gonadal management decisions.

Laboratory investigations were categorized into three age ranges: first six months of life; prepubertal (six months to breast development at Tanner stage 2); and pubertal (Tanner stage 2 and higher). Hormonal evaluations were conducted using immunoassays to measure levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), T, estradiol (E2), dehydroepiandrosterone sulfate, 17-hydroxyprogesterone (17-OHP), and AMH. AMH levels typically exceeded the maximum detection limit, so the highest measured value was recorded. Given the limited assay sensitivity at high AMH concentrations, the potential variability in extreme values was acknowledged in data interpretation.

A human chorionic gonadotropin (hCG) stimulation test was performed in selected cases to assess the presence of functional Leydig cells. The test protocol included intramuscular administration of 2000 units of hCG/m^2, with blood samples collected before injection and 96 hours post-stimulation to measure T levels. A rise above 60 ng/dL was considered indicative of Leydig cell function.

All patients underwent ultrasound (US) examinations to assess gonadal position and morphology. In selected cases, magnetic resonance imaging was performed to further characterize gonadal structures, delineate size and composition, and assess their relation to adjacent anatomical structures.

For patients who underwent gonadectomy, detailed data were collected, including age at surgery, histological analysis of gonadectomy specimens, and details of hormone replacement therapy (HRT).

The study protocol was approved by the Research Ethics Committee of The Children's Health Memorial, Warsaw, Poland on 25.04.2024 (approval no.: 12/KBE/2024). Written informed consent was obtained from the parents or legal guardians of underage patients, and from the patients themselves if they were adults.

Statistical Analysis

All statistical analyses were descriptive in nature. Quantitative variables were assessed for distribution; data following a normal distribution were presented as mean values with SD, while non-normally distributed variables were summarized using medians and interquartile ranges. Categorical data were reported as frequencies and percentages. No formal hypothesis testing or inferential statistical procedures were applied due to the small sample size and retrospective design of the study. All analyses were performed using Microsoft Excel for Microsoft 365, Version 2405 (Microsoft Corporation, Redmond, Washington, USA).

Results

Clinical Manifestations

This study included 16 patients: 8 infants, 4 prepubertal children, and 4 pubertal patients. The age at the time of first medical consultation ranged from 5 days to 18 years, with an average age of 5.3 years at the start of diagnostic assessment.

There were four affected families within the studied cohort: in two both offspring were 46,XY diagnosed with CAIS, another two families had both children diagnosed with CAIS, and included a 46,XX *AR* mutation carrier.

The diagnosis of CAIS was established based on a combination of clinical features, hormonal findings, and genetic confirmation. The following clinical indicators prompted further evaluation for CAIS:

Mismatch between prenatal karyotype and phenotype: One case (6.3%) involved a mismatch between a prenatal 46,XY karyotype and a postnatal female phenotype.

Presence of inguinal hernia with testicles: This was the most common initial symptom of CAIS, observed in seven cases (43.7%). The age at surgical intervention for inguinal hernia ranged from 5 days to 4.5 years, with an average age of 1.7 years. During surgery, the presence of gonads was confirmed in four cases, along with the absence of the uterus, fallopian tubes, and ovaries. Gonadal biopsies were performed in three cases, showing microscopic structures corresponding to testicular tissue. In one case, a patient who underwent surgery for an inguinal hernia at 3.5 years of age experienced a recurrence three weeks later. A revision surgery of the inguinal canal unexpectedly revealed a gonad, prompting further investigations (Table 1).

Primary amenorrhea: Primary amenorrhea led to the diagnosis of CAIS in four patients (25%). The age at diagnosis ranged from 13.5 to 16.8 years, with a mean of 15.2 years. All presented with normal breast development but sparse pubic and axillary

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Table 1. Clinical and molecular characteristics of CAIS cases

Patient no	Age at diagnosis [years]	Reason for consultation	Base change aminoacid change	Maternal carriers	Other family members affected	Final height* [cm]	Final height [SD] Female/Male	Final length of vagina* [cm]	Location of gonads
1	0.1	Familial *AR* mutation	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
2	0.5	Inguinal hernia	c.239_240delAA	Yes	No	NA	NA	NA	Inguinal canal
3	3	Inguinal hernia	c.3387C>G p.Leu763Val	Yes	No	NA	NA	NA	Inguinal canal/ Abdomen
4	4.8	Inguinal hernia	c.2513A>T p Glu 838 Val *novel mutation*	Yes	No	NA	NA	NA	Inguinal canal
5	0.2	Familial *AR* mutation	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
6	0.4	Inguinal hernia	c.175C>T Gln59Ter	Yes	Sister	NA	NA	NA	Inguinal canal
7	4	Inguinal hernia	c.2728G>A Gly910Arg	Yes	No	171.4	1.0/-1.1	3	Inguinal canal
8	0.6	Familial *AR* mutation	N705S	Yes	Sister	183.7	3.0/0.8		Inguinal canal
9	0.1	Karyotype mismatch	c.589C>T p.(Gln197*) *novel mutation*	Yes	No	178.8	2.2/0.1		Abdomen
10	0.6	Inguinal hernia	Deletion after exon 6 – no binding – complete AR defect**	de novo	No	169.1	0.6/-1.5	7	Inguinal canal
11	17	Primary amenorrhea Familial *AR* mutation	c.2599 G>A Val/867 Met	Yes	Sister	169.1	0.6/-1.5	5.6	Inguinal canal
12	17.5	Primary amenorrhea	c.1567G>T *novel mutation*	Yes	No	171.2	0.9/-1.1		Inguinal canal
13	16	Primary amenorrhea	c.2599 G>A Val/867 Met	Yes	Sister	179	2.2/0.1	4.5	Inguinal canal
14	0.4	Familial *AR* mutation	N705S	Yes	Sister	171.4	1.0/-1.1	5.6	Inguinal canal/ Abdomen
15	1.6	Inguinal hernia	N705S	Yes	Sister	172.4	1.3/-1	NA	Inguinal canal/ Abdomen
16	18	Primary amenorrhea	CGA-> CCCGA Arg -> Pro, stop 788	Yes	No	173.5	1.5/-0.9	6.3	Inguinal canal

*Data only shown for those who had achieved final height
NA, not available; CAIS, complete androgen insensitivity syndrome; *AR*, *androgen receptor*; SD, standard deviation

hair. Pelvic US confirmed the absence of a uterus and ovaries, and laboratory evaluation showed markedly elevated T within the male reference range. In two patients, genetic testing was performed promptly after initial hormonal work-up, while in the remaining two, the diagnosis was delayed until further imaging and gonadal biopsy.

Familial presence of *AR* mutation: A family history of CAIS prompted evaluation in four patients (25%). These children were siblings of individuals previously diagnosed at our center. The age at diagnosis ranged from 3 days to 7 years. In two cases, genetic testing was performed shortly after birth due to known maternal carrier status, leading to early confirmation. In the other two, diagnosis followed clinical referral after inguinal hernia repair in an older sibling. All four patients had typical female external genitalia and absent Müllerian structures on imaging.

Physical examinations of the patients revealed typically female external genitalia without any distinctive anomalies. Pubertal patients displayed normally developed breasts but had little to no axillary and pubic hair growth.

The mean final height in patients who reached adult height (n=9/16; 56%) was 171.4 cm (±4.88 cm), which is +0.97 SD according to the standard for Polish women and -1.1 SD compared to the standard for Polish men.

Hormonal and Imaging Evaluation

During the first six months of life, measured gonadotropin and E2 levels in patients fell within the expected mini-puberty ranges (FSH 0.73-4.8 IU/L, LH <0.15-2.17 IU/L, E2 <8.2-17.3 pg/mL), while T varied between 2.5 and 299 ng/dL. In three cases, T was elevated within the typical male range (Table 2).

To further evaluate Leydig cell function, five patients underwent a hCG stimulation test. Post-stimulation, T levels increased significantly, ranging from 209 ng/dL to 884 ng/dL.

AMH levels during minipuberty were consistently above 150 pM in all cases, with a range of 181 pM to over 350 pM. This elevation of AMH, observed across all age groups, indicated normal Sertoli cell function.

During puberty, hormonal analysis showed significantly elevated T levels, ranging from 367 ng/dL to 3460 ng/dL, with a median value of 1361.3 ng/dL. LH levels were also elevated, ranging from 9.6 IU/L to 27.6 IU/L, with a median of 15.7 IU/L.

Pelvic US examinations confirmed the absence of a uterus, fallopian tubes, and ovaries in all patients. Undescended testes were predominantly located in the inguinal region in 10 patients. In one case, the testes were located within the abdominal cavity, while in three cases, the testes were found unilaterally in the inguinal region and unilaterally within the abdominal cavity (Table 1). Assessments of vaginal length revealed a shortened, blind-ending vaginal canal, with post-pubertal lengths ranging from 3 cm to 8.5 cm.

Genetic Testing

In the studied group, chromosomal analysis confirmed a 46,XY karyotype in all patients, as is typical for CAIS. Of note, one patient had a prenatal karyotyping that showed a 46,XY karyotype. This finding, combined with a normal female phenotype observed postnatally, led to an early diagnosis of CAIS.

Genetic testing of the *AR* gene identified various pathogenic mutations (see Table 1). To confirm these findings, Sanger sequencing was performed and successfully verified a hemizygous pathogenic mutation in the *AR* gene in all cases. Variant nomenclature followed the Human Genome Variation Society recommendations, based on the *AR* reference transcript NM_000044.6. Subsequent maternal molecular analysis showed that nearly all mothers (10 out of 11 families) were heterozygous carriers of the mutation. Among the identified variants, 13 had been previously reported, whereas three mutations (c.2513A>T, c.589C>T, c.1567G>T) were novel and have not been described in published databases to date. These novel variants are highlighted in Table 1.

For families with a history of the condition, Sanger sequencing was also extended to the patients' siblings. This analysis identified three families in which the hemizygous variant was inherited from the mother to more than one child. Notably, in one family with four children, three were found to have a 46,XY karyotype and were affected by the mutation, while one subject with a 46,XX karyotype was an asymptomatic carrier of the mutation (Table 1).

Gonadal Biopsy and Gonadectomy

Gonadal biopsy was performed in three cases during inguinal hernia surgery in response to intraoperative findings that suggested the presence of testicular tissue in girls undergoing the procedure. Microscopic examination revealed tissue consistent with testicular structure, showing numerous small tubules lined with immature germinal epithelium, consisting of Sertoli cells and germ cells, while Leydig cells were present in the interstitium (Table 3).

In our cohort, bilateral gonadectomy was performed in five patients (31.3%). The earliest surgery was conducted at nine months of age, while the remaining four patients underwent the procedure post-puberty, between the ages of 14.5 and 18.7 years. In four cases, the surgery was recommended as a prophylactic measure, while in one case, the gonads were removed at the patient's request. Histopathological examination of the gonadal tissue revealed Sertoli and Leydig cell hyperplasia

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in two cases (Table 3), with no evidence of malignancy. Tissue analysis from the other three patients revealed testicular tissue predominantly composed of Sertoli cells, with no evidence of mature spermatogenesis or microscopic signs of invasive testicular cancer.-Post-pubertal patients who underwent bilateral gonadectomy required estrogen replacement therapy. Most of these patients were prescribed oral estrogen pills, although one patient opted for a transdermal spray.

Tumour Risk Assessment

In our cohort of patients with CAIS, a tumour surveillance protocol was followed to monitor the risk of gonadal malignancies, which are a recognized concern in this population. Tumour markers, specifically alpha-fetoprotein (AFP) and β-hCG, were measured annually, while routine US examinations were conducted every 2-3 years to detect any potential morphological changes in the gonads.

Table 2. Characteristics of hormonal evaluation in studied cohort of CAIS individuals, considering the age group division

Patient no	LH in mini-puberty [IU/L]	FSH in mini-puberty [IU/L]	E2 in mini-puberty [pg/mL]	Testosterone in mini-puberty [ng/dL]	Testosterone in hCG stimulation test [ng/dL]	AMH [pM/L]	Pubertal LH [IU/L]	Pubertal T [ng/dL]	Pubertal E2 [pg/mL]
1	-	-	-	-	-	>150 (1076)	-	-	-
2	1.6	1.5	17.3	2.5	-	>150	-	-	-
3	-	-	-	-	-	>150	-	-	-
4	-	-	-	-	-	>150	-	-	-
5	0.59	0.73	-	2.5	255.3	>150	-	-	-
6	2.17	4.09	-	13.3	884	>150	-	-	-
7	-	-	-	-	209	>160	12.2	1491	50.1
8	-	-	-	299	-	>150	27.6	1235.8	95.4
9	<0.15	1.52	<8.2	4.3	504.8	>150	9.6	1279	34
10	-	-	-	-	-	>350	-	-	25.9
11	-	-	-	-	-	>150	17.16	3460	68
12	-	-	-	-	-	-	15.8	1688	22.6
13	-	-	-	-	-	-	11	1701.8	53.1
14	0.6	4.8	-	185.3	-	-	10,7	367	14.8
15	-	-	-	-	310.6	>150	17.4	568	34.9
16	-	-	-	-	-	-	18.4	461	20

AMH, Anti-Müllerian hormone; E2, oestradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; -, not available; T, testosterone

Table 3. Gonadal histopathology in study group

Patient no	Type	Age at the time of surgery	Gonadal histopathology
2	Biopsy	6 months	Structure of the testicle Numerous small tubules lined with immature spermatogenic epithelium.
6	Biopsy	8 days	Structure of the testicle Sertoli cells visible in the tubules
15	Biopsy	19 months	Structure of the testicle
10	Gonadectomy	9 months	Structure of the testicle
13	Gonadectomy	17.9 years	Sertoli cell adenoma Few spermatogonia, Leydig cells
14	Gonadectomy	14.5 years	Sertoli cell adenoma Hyperplasia of Leydig cells
15	Gonadectomy	16.75 years	Sertoli cell adenoma Hyperplasia of Leydig cells
16	Gonadectomy	18.7 years	Structure of the testicle Sertoli cell adenoma.

Remarkably, throughout the surveillance period, there were no instances of elevated AFP or β-hCG levels in any of the patients. Furthermore, no US examination revealed any abnormalities suggestive of malignancy.

Psychosexual Care

Sexual identity in all patients was female. Psychological outcomes and quality of life were assessed retrospectively from clinical follow-up notes and patient/parent reports, including emotional well-being, self-acceptance of the CAIS diagnosis, body image perception, and concerns related to fertility and gender identity. No validated psychometric questionnaires were applied. Detailed psychological and psychiatric evaluations were available in 9 out of 16 children (56%), as the remaining patients were too young at the time of assessment to provide reliable psychosexual evaluation. In this subgroup, eight patients demonstrated age-appropriate psychological functioning and good adaptation to the diagnosis. Only one patient was diagnosed with an anxiety disorder requiring psychological follow-up. These findings suggest that, within the limits of the available data, most CAIS patients adapted well psychosocially during childhood and adolescence.

Discussion

Clinical Presentation and Diagnosis

Inguinal hernia was the most common presentation (43.7%), followed by primary amenorrhea (25%) and family history of CAIS (25%), consistent with earlier studies (12,13,14,15). These findings confirm that early diagnosis often results from surgical findings or cascade genetic testing. Prenatal karyotype-phenotype discordance was rare but contributed to early detection in one case (4,5).

Hormonal and Imaging Evaluation

Our hormonal results reflect the characteristic profile of CAIS across developmental stages. During mini-puberty, baseline T ranged from 2.5 to 299 ng/dL, consistent with the transient activation of the hypothalamic-pituitary-gonadal (HPG) axis and variable timing of sampling (16). In contrast to typical 46,XY infants, patients with CAIS do not consistently exhibit a physiological LH-testosterone surge during mini-puberty. This observation aligns with the findings of Bouvattier et al. (17), who demonstrated that activation of the mini-puberty axis required functional androgen receptor signalling, and its absence results in a blunted rise of LH and testosterone despite intact Leydig cell capacity (16).

In our cohort, Leydig cell responsiveness was confirmed by a marked testosterone increase following hCG stimulation, and Sertoli cell function was preserved, as evidenced by uniformly elevated AMH concentrations. Importantly, AMH remains a valuable biomarker to distinguish CAIS from gonadal dysgenesis, where AMH is typically reduced (8,18).

Final height in our cohort averaged 171.4 cm (±4.88), approximately +0.97 SD above the female reference population. This supports previous evidence that delayed bone age and absence of androgen-driven epiphyseal closure contribute to increased adult height in CAIS patients.

Pelvic imaging confirmed the absence of Müllerian structures in all patients, and a shortened, blind-ending vagina (3-8.5 cm) was documented in post-pubertal individuals. These findings reflect the effect of persistent AMH secretion from Sertoli cells, which suppresses Müllerian development during fetal life.

Genetic Testing

Most AR mutations identified in our cohort have been previously described, confirming the heterogeneous but partially recurrent spectrum of pathogenic variants in CAIS. Importantly, three novel *AR* mutations were detected, expanding the mutational landscape and potentially contributing to improved genotype-phenotype interpretation in future cases.

Gonadal Management and Tumor Risk

The timing of gonadectomy remains a key controversy in CAIS management. Historically, early removal of gonads was recommended; however, contemporary studies show malignancy risk in children is low (0.8-2%), increasing gradually to ~14% in adulthood.

In our cohort, 31% (n=5) underwent gonadectomy. Two had benign Sertoli or Leydig cell hyperplasia, and in one case the procedure was patient-driven due to psychological distress. The remaining 11 patients retained their gonads, allowing spontaneous puberty and endogenous estrogen production via aromatization.

Gonadal surveillance included annual AFP and β-hCG testing and US every 2-3 years (median follow-up 7.5 years). No malignant changes were detected. However, consistent with the literature, tumor markers and US have limited sensitivity for early neoplasia, highlighting the need for improved biomarkers.

Our data therefore support the strategy of delaying gonadectomy until after puberty, provided that careful surveillance is in place.

Clinical Decisions and Gonadal Management

Of the five patients who underwent gonadectomy, in four the procedure followed previous standard recommendations, while in one it was performed due to psychological distress. Histology revealed only benign changes (Sertoli cell adenoma and/or Leydig cell hyperplasia).

The remaining 11 patients retained their gonads, which enabled spontaneous puberty and aromatization of testosterone to estrogen, eliminating the need for immediate hormone replacement. Delaying gonadectomy allowed patients to participate in decision-making once mature, which is important given lifelong hormonal consequences and potential psychological impact.

Current Tumor Monitoring Strategies

Tumor surveillance in CAIS most commonly includes serum AFP, β-hCG and lactate dehydrogenase (LDH), although their sensitivity for early malignancy is limited, as elevations may also occur in non-gonadal or benign conditions. Therefore, these markers should not be used as standalone screening tools.

In patients who retain their gonads, recent recommendations suggest a structured surveillance protocol, including clinical self-examination, periodic pelvic/inguinal US, and consideration of targeted gonadal biopsy in late adolescence to detect GCNIS (11,19).

Historically, prophylactic early gonadectomy was advised, but current practice supports delaying removal until after puberty, provided careful follow-up is ensured.

Study Findings Regarding Tumor Surveillance

In our cohort, all patients underwent annual AFP and β-hCG monitoring and US every 2-3 years, and no abnormalities were detected. However, as no routine histological assessment was performed in patients who retained their gonads, subclinical lesions cannot be completely excluded. Isolated reports of germ cell neoplasia *in situ* and Sertoli cell tumors in pediatric CAIS highlight the need for continued surveillance, despite the overall low malignancy risk. Further progress in this area will depend on the development of more sensitive biomarkers and imaging techniques for early detection.

Psychological Aspects of CAIS

All patients were raised as females and identified as such. Although most adapted well, previous studies report that up to 36% may experience reduced certainty of gender identity or femininity. Psychological support is therefore essential, particularly around puberty and disclosure of diagnosis (20,21,22).

Therapeutic Considerations and Long-term Outcomes

HRT remains essential after gonadectomy. In our cohort, some patients required HRT, while others with preserved gonads experienced spontaneous puberty.

Beyond our data, the existing literature explores potential differences between estrogen and T therapy. Auer et al. (23) conducted a randomized, double-blind crossover trial showing comparable metabolic profiles but differential effects on sexual functioning, with T possibly enhancing well-being through neurosteroid activity.

Study Limitations

This study has limitations. Its retrospective design may lead to documentation bias and incomplete data. The small sample size inherent to the rarity of CAIS, limits generalizability and prevents statistical testing. Psychological assessments were based on clinical notes and patient-reported impressions rather than validated psychometric tools. Finally, the long study period (2004-2024) may involve changes in diagnostic and therapeutic practices over time, introducing variability in management.

Conclusion

The management of CAIS remains a subject of ongoing debate, particularly regarding the timing of gonadectomy. Our study supports the importance of an individualized, multidisciplinary approach, balancing the benefits of spontaneous pubertal development and endogenous estrogen production against the potential risk of malignancy. While our findings support delaying gonadectomy in asymptomatic patients under structured surveillance, the lack of sensitive biomarkers for early neoplastic transformation remains a significant limitation. Long-term, standardized follow-up protocols are essential to refine risk stratification and optimize clinical outcomes. Future research should focus on improving tumor surveillance strategies and assessing the long-term impact of gonadal retention on metabolic and bone health.

Ethics

Ethics Committee Approval: The study protocol was approved by the Research Ethics Committee of The Children's Health Memorial, Warsaw, Poland (approval no.: 12/KBE/2024, date: 25.04.2024).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of underage patients, and from the patients themselves if they were adults.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Elzbieta Marczak, Maria Szarras-Czapnik, Concept: Elzbieta Marczak, Maria Szarras-Czapnik, Design: Elzbieta Marczak, Data Collection or Processing: Elzbieta Marczak, Maria Szarras-Czapnik, Agata Skórka, Kinga Kowalczyk, Gabriela Grochowska, Malgorzata Walewska-Wolf, Barbara Antoniak, Katarzyna Bajszczak, Elżbieta Moszczyńska, Analysis or Interpretation: Elzbieta Marczak, Maria Szarras-Czapnik, Agata Skórka, Gabriela Grochowska, Barbara Antoniak, Literature Search: Elzbieta Marczak, Elżbieta Moszczyńska, Writing: Elzbieta Marczak, Maria Szarras-Czapnik, Katarzyna Bajszczak, Elżbieta Moszczyńska.

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Mucopolysaccharidosis or Skeletal Dysplasia? Clinical and Radiologic Clues for Differential Diagnosis Based on Difficult Cases

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ABSTRACT

Objective: The skeletal abnormalities of mucopolysaccharidosis (MPS) and skeletal dysplasia (SD) may be similar and even indistinguishable. This study aims to elucidate clinical clues and overlapping features that may assist in the different diagnosis.

Methods: The clinical features of patients who were first referred to endocrinology or rheumatology department for short stature or joint abnormalities were addressed and signs were examined upon different diagnosis.

Results: Three patients (I, II and III) were diagnosed with SD with overlapping and also distinguishing skeletal features compared with MPS. An atypical presentation defined in patient IV who was diagnosed with Morquio syndrome. Patients V and VI were diagnosed with MPS with early onset and typical skeletal features accompanied with additional systemic manifestations uncommon in SD.

Conclusion: In conclusion, this study emphasizes the clinical and radiological evaluation and nuances distinctions in clinical presentations that will highlight the challenges and guide to distinguishing different diagnosis of MPS and SD in atypical presentations for achieving the accurate diagnosis.

Keywords: Mucopolysaccharidosis, skeletal dysplasia, orthopedics, radiology, genetics

What is already known on this topic?

Mucopolysaccharidosis and skeletal dysplasia are genetic bone disorders mostly presented by short stature and joint abnormalities. Clinical and radiological assessments consist the main steps for diagnosis.

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What this study adds?

This study highlights the clinical and radiological clues for distinguishing different diagnosis in patients with short stature or joint abnormalities for accurate diagnosis even in atypical presentations.

Introduction

Mucopolysaccharidoses (MPS) are a group of inborn metabolic diseases caused by mutations in genes encoding lysosomal hydrolases required for degradation of mucopolysaccharides, resulting in skeletal abnormalities described as dysostosis multiplex (1,2). Skeletal dysplasias (SD) are a group of genetic disorders characterized by short stature, bone and cartilage abnormalities. Common pathogeneses leading to similar clinical manifestations have been classified into different SD groups (3).

Some overlapping signs and symptoms of both disease groups make the correct diagnosis difficult and often lead to diagnostic delay (4). Currently, the use of gene panels including both *MPS* and *SD* genes has become widespread for distinguishing differential diagnoses in patients with short stature and skeletal manifestations (5). However, appropriate and detailed clinical and radiological assessment can provide more accurate and rapid guidance. The distinguishing clinical and radiological criteria for these two groups of disorders are illustrated in this report through the presentation of illustrative patient examples.

Methods

Six patients, three with SD and three with MPS were enrolled in the study. Patients who were initially referred to the endocrinology or rheumatology department due to short stature or joint anomalies and were followed up by these departments with other diagnoses were included in the study to address the difficulty of differential diagnosis. In addition, two patients who were initially referred to other departments despite having distinct features of MPS were included to underline the overlapping clinical symptoms. Patients I, II, III, V and VI were first referred to the endocrinology department, but patient IV first attended the rheumatology department.

All patients had final diagnosis and follow-up as MPS or SD in Departments of Inborn Metabolic Disease and Pediatric Genetic between 2010 and 2024. Symptoms leading to referral, medical history, radiological assessment, enzyme activity analysis results and molecular analysis results were obtained from the patients' medical records. This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Gazi University (approval no.: 12, date: 09.07.2024). Informed consent forms were obtained from patients or their parents. No statistical analysis was performed.

Results

Patients' demographic data, genotypes, clinical and radiological assessments are listed in Table 1. Patients' radiological abnormalities are presented in Figure 1.

Discussion

Recognizing distinguishing clues from radiological findings is the first step to establish the diagnosis of SD or MPS. The clinical picture of MPS and SD may vary by disease severity and atypical presentations are not unusual (6).

As in our cases, one of the most common presentations of MPS and SD was short stature. Several patients with short stature were first admitted to the pediatric endocrinology department. Careful family history and family growth patterns constitute the first step for evaluating constitutional delay or familial short stature, both with near-normal growth velocity during childhood, in contrast to both MPS or SD. In addition to laboratory tests for primary endocrinopathies, detailed physical examination plays a key role in recognizing genetic disorders presenting with short stature (7). Facial dysmorphism is more frequently observed in MPS and is often noted during the initial assessment, but may also be associated with SD as in Patients I and II (8). In the diagnostic algorithm for short stature, radiological assessment is not routinely recommended. However, skeletal survey should be performed especially in the presence of disproportionate short stature or short stature associated with facial dysmorphism or any skeletal deformities (7,9). Short stature with a short trunk is a common finding in MPS due to severe spinal involvement but atypical cases, such as patient IV, may present with normal proportions without short trunk. Furthermore, achievement of normal growth may be seen in attenuated forms of MPS, thus normal height for age should not exclude MPS (10).

Another common manifestation of attenuated types of MPS is joint stiffness and contractures. Those clinical findings are prominent in rheumatologic diseases, such as rheumatoid arthritis. It has been suggested that patients with joint involvement, particularly affecting the hands should be screened for MPS I. Moreover, MPS must be considered in the differential diagnosis of rheumatoid arthritis, especially when morning stiffness, elevated erythrocyte sedimentation rate or

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Table 1. Patients' demographic data, genotypes, clinical and radiological assessments

Patients	I	II	III	IV	V	VI
Gender	F	M	M	M	F	F
Age at diagnosis	14 y	2 y	14 m	17 y	18 m	20 m
Diagnosis	SEMD	SEMD	SED	MPS IVA	MPS IVA	MPS I
Enzyme activity/ genotype (nucleotide change)	*TONSL* Compound heterozygous c.122-4_126del (LP: PVS1, PM2) and c.344G>A (VUS: PM2)[α]	*COL2A1* Homozygous c.1339G>C (LP: PM1, PP2, PM2, PM5, PP3)[α]	*ACAN* Homozygous c.548C>T (VUS: PM2)[α]	N-Acetylgalactosamine 6-sulphatase <0.1 nmol/h/ prot (1.53-10.6)[β] *GALNS* Homozygous c.1249 G>T (VUS: PM2, PP2)[α]	N-Acetylgalactosamine 6-sulphatase <0.1 nmol/h/prot (1.53-10.6)[β]	Alpha-iduronidase :2.27 nmol/h/ mg protein (19-41)
Parental consanguinity	No	Yes	No	No	Yes	No
Symptoms at referral	Short stature skeletal deformities	Short stature skeletal deformities	Short stature macrocephaly	Short stature joint pain	Short stature	Spine deformities hepatosplenomegaly
Physical examination	Short stature (Height SDS: -8.1) Depressed nasal bridge Bulbous nose Prognathism Frontal bossing Scoliosis Increased lumbar lordosis Genu valgum	Short stature (Height SDS: -3.2) Depressed nasal bridge Frontal bossing Pectus excavatum Short limbs Genu varum	Short Stature (Height SDS: -2.0) Coarse face Acquired Macrocephaly Brachydactyly Proximal shortness of limbs	Short stature (Height SDS: -2.3) Pectus Carinatum Genu varum Broad joints of his hands and limitation of extension at all joints	Short stature (Height SDS: -2.1) Joint laxity Genu valgum	Short stature (Height SDS: -2.0) Coarse face Acquired Macrocephaly Prominent metopic suture Pectus carinatum Thoracal kyphosis Splint for hip dysplasia Brachydactyly Large Mongolian spot
Additional condition	No	No	No	Diagnosed as JRA and FMF Treated with etanercept	No	Adenoid hypertrophy and recurrent low respiratory tract infection Motor development delay
Radiological assessment at diagnosis	J-shaped sella Kyphoscoliosis Biconcave vertebral bodies Decreased interpeduncular distance Osteopenia Flattened capital femoral epiphysis Broadening of ribs at sternal ends	Kyphoscoliosis Increased lumbar lordosis Platyspondyly Ovoid configuration and irregular vertebral endplates Metaphyseal and proximal femoral epiphysial irregularities	J-shaped sella Irregular vertebral endplates Ovoid configuration and beaking of vertebral bodies Epiphysial irregularity in distal femur	Thickened skull Oar-shaped ribs Epiphyseal and metaphyseal irregularities of proximal femur Deformities in vertebral endplates	Kyphosis Genu valgum Vertebral beaking Platyspondyly Oar-shaped ribs Round shaped iliac bone Coxa valga Irregular acetabular border and femoral head	J-shaped sella Thoracolumbar kyphosis Oar-shaped ribs Posterior scalloping and inferior beaking of vertebral bodies Round shaped iliac bones Coxa valga Bullet-shaped metacarpal bones

[α]Patients were performed exome sequencing [β]Multiple sulfatase deficiency was excluded

y: years, m: months, SEMD: spondyloepimetaphyseal dysplasia, SED: spondyloepiphyseal dysplasia, JRA: juvenil rheumatoid arthritis, FMF: Familial Mediterranean Fewer, LP: likely pathogenic VUS: Variant of uncertain significance upon ACMG classification, PVS1: Pathogenic very strong (null variant), PM2: extremely low frequency in gnomAD population databases, PM1: Non-truncating non-synonymous variant is located in a mutational hot spot, PP2: Missense variant in a gene with low rate of benign missense mutations, PM5: Different amino acid change as a known pathogenic variant, PP3: For a missense or a splicing region variant, computational prediction tools unanimously support a deleterious effect on the gene

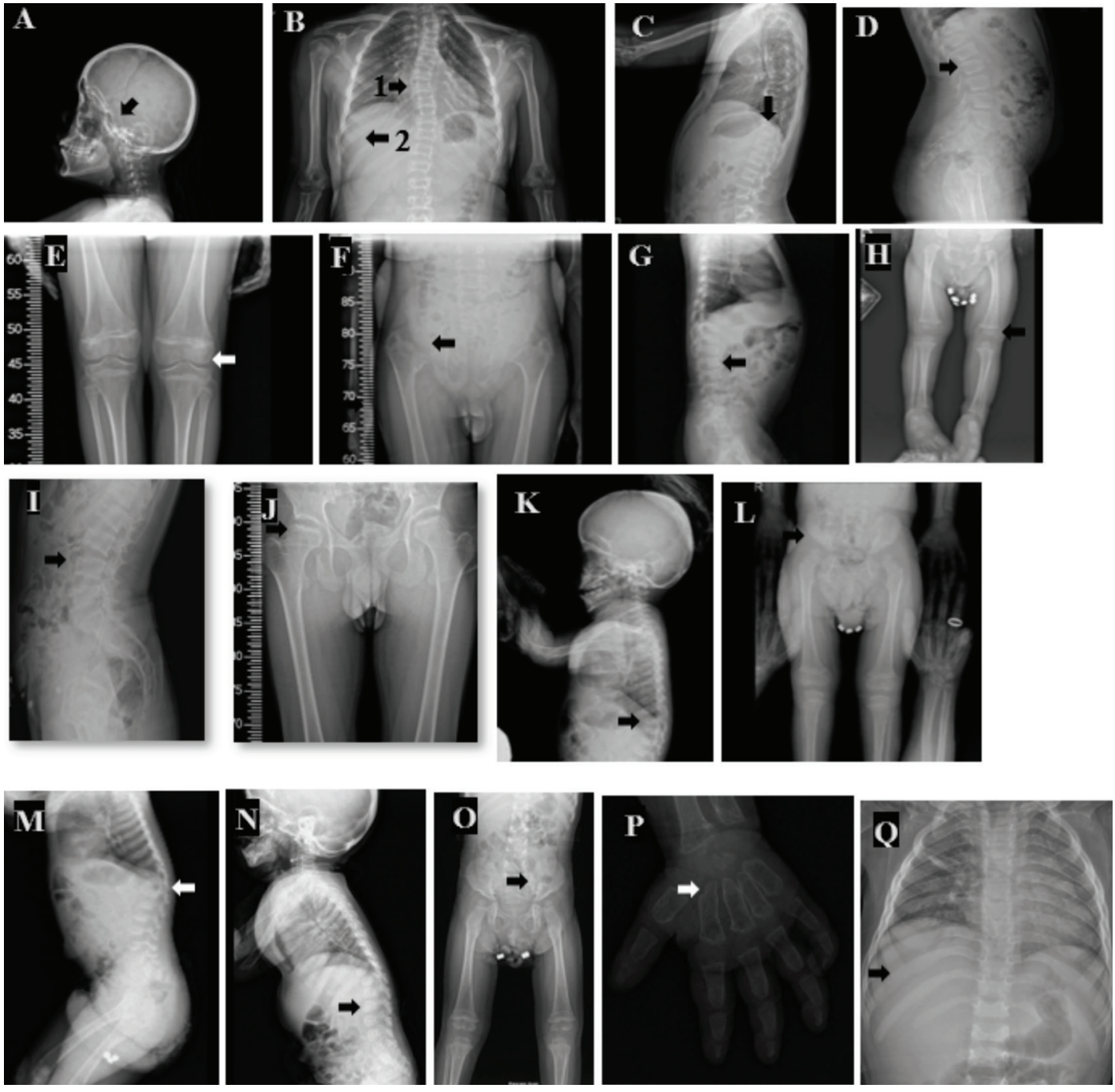

Figure 1. Patients' radiological abnormalities. **A)** J-shaped sella of P1, **B)** Scoliosis (1), broadening of ribs at the sternal ends (2) of P1 **C)** Biconcave vertebral bodies of P1. **D)** Platyspondyly, ovoid configuration and irregular vertebral endplates of P2. **E)** Metaphyseal irregularities of P2 **F)** Delayed epiphysial ossification/ Irregular borders of femoral head and acetabulum of P2 **G)** Ovoid configuration and beaking of vertebral bodies of P3 **H)** Epiphysial irregularity of P3 **I)** Irregularities in vertebral endplates of P4 **J)** Epimetaphyseal irregularities of proximal femur of P4. **K)** Anterior beaking in vertebral bodies, platyspondyly of P5 **L)** Round shaped iliac bone, coxa valga, irregular acetabular border and femoral head of P5 **M)** kyphosis of P5 **N)** posterior scalloping and inferior beaking of vertebral bodies of P6 **O)** rounded iliac wings, inferior tapering of the ilea, coxa valga of P6 **P)** bullet-shaped metacarpal bones of P6 **Q)** Oar-shaped ribs of P6

C-reactive protein levels and response to nonsteroidal anti-inflammatory drugs are absent (11,12).

In the presence of findings of skeletal deformity, and during the clinical examination, some accompanying clinical signs, such macrocephaly, corneal clouding, and/or umbilical hernia can provide clues for a diagnosis of MPS. In addition, hearing impairment, recurrent respiratory tract and middle ear infections, cardiac abnormalities, and/or development delay are other extra-skeletal manifestations that should raise suspicion of storage disorders like MPS (13,14,15).

Patient I presented with short stature and facial dysmorphism may be supposed to be an attenuated form of MPS. Although J-shaped sella and oar-shaped ribs were observed, beaking of vertebral bodies that is strongly expected in MPS patients was absent. In Patient IV, vertebral deformities were also not typical for MPS as they resembled the biconcave vertebral bodies observed in Patient I. Patient IV was provisionally diagnosed as SD because of the lack of the typical short stature with short trunk and beaking of vertebral bodies, but surprisingly was finally diagnosed as MPS IV. It should be noted that imaging findings may be mild or atypical in early childhood or in attenuated form of MPS that have a later onset with slower progression (16). Patient II also exhibited flattened vertebral bodies, with a similar appearance of the vertebral bodies seen in Patient IV. Therefore, considering those atypical or mild presentations it is not surprising that in several studies it has been showed that about half of the MPS IV patients were misdiagnosed with spondyloepiphyseal dysplasia (SED), based on radiographic interpretations (13).

It is important to accurately interpret vertebral abnormalities to distinguish between the two entities, MPS and SD. The presence of superior notched vertebra in addition to scoliosis and/or kyphosis is a common finding in SED while platyspondyly or humping of vertebral bodies is not consistently present (13). Moreover, one of the most significant findings on spinal radiograph in MPS is beaking of vertebrae and in SD are tongue-like projections, for example in pseudo achondroplasia. Although these features may appear similar, the thicker and wider shape of tongue-like projection is a helpful distinction (17,18). In addition to the spinal deformities, the deposition of glycosaminoglycans in the soft tissues contributes to cervical cord compression that occurs in MPS rather than SD. However, it should be noted that the incidence of myelopathy caused by atlantoaxial subluxation is present in nearly one third of patients with SED congenita (19,20).

The pelvic radiograph may also be useful in revealing distinctive radiological findings for SD and MPS. The square ilium is commonly associated with the achondroplasia group or Ellis-van Creveld syndrome, but is not usually present in MPS. The pelvic pattern in MPS is one of hypoplasia of the lower half of the ilium, which narrows and tapers inferiorly (21,22,23). Although the pelvic manifestations of MPS IV, SD and atypical phenotypes may overlap, distinguishing and features found only in MPS IV of all the MPS subtypes, such as genu valgum and joint laxity, may also contribute to earlier and correct diagnosis (4).

Patients V and VI are typical presentations of MPS IV and MPS I, respectively. Radiological findings are evident, even in infancy. However, early onset skeletal deformities in SD, such as ovoid configuration and beaking of vertebral bodies, as observed in Patient III, may mimic MPS. The central tongue of ossified bone extends anteriorly from the vertebral body in MPS IV patients. With a little distinction from MPS IV, MPS I is associated with inferior beaking of vertebral body. Another striking feature to help to identify the MPS subtype is that in MPS I, the L1 and L2 hypoplastic vertebral bodies commonly have posterior scalloping with dorsal gibbus, while in MPS IV platyspondyly and central beaking is widespread in the thoracolumbar vertebral bodies, as seen in Patient V (13,24). Furthermore, pelvic radiographic investigation may also assist in subtyping of MPS subtypes. In a patient with MPS IV, epiphyseal dysplasia of the caput femoris would accompany the tapered ilium, unlike in MPS I (4).

Radiological examination following by an enzyme activity assays will establish the initial diagnostic workflow and provide data to perform targeted molecular genetic tests. Although molecular genetic tests are essential tools for diagnosis, clinical confirmation remains necessary in some SDs because of an autosomal dominant inheritance pattern and variants of unknown significance.

Study Limitations

This was a retrospective study and so different radiological or biochemical analyses were not performed that might be requested for the differential diagnosis of patients.

Conclusion

Awareness of comprehensive clinical and radiological evaluation that guide an appropriate approach for distinguishing between MPS and SD is essential for establishing an accurate and timely diagnosis. This report has presented a summary of such distinguishing features which it is hoped will facilitate diagnosis by highlighting clues present at clinical presentations and on radiological imaging.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Gazi University (approval no.: 12, date: 09.07.2024).

Informed Consent: Informed consent forms were obtained from patients or their parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ayşe Akyüz, Hakan Atalar, Kübra Çilesiz, Aslı İnci, Concept: Fatih Ezgü, Design: Ayşe Akyüz, Fatih Ezgü, Data Collection or Processing: Ayşe Akyüz, Hakan Atalar, Kübra Çilesiz, Aslı İnci, Analysis or Interpretation: Ayşe Akyüz, İlyas Okur, Leyla Tümer, Fatih Ezgü, Literature Search: Ayşe Akyüz, İlyas Okur, Leyla Tümer, Fatih Ezgü, Writing: Ayşe Akyüz.

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Near Final Height in Males treated with Aromatase Inhibitors

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ABSTRACT

Objective: Data on the impact of aromatase inhibitor (AI) therapy on final or near-final adult height (FNFH) in males with short stature is limited. This study investigated whether AI therapy improved FNFH in males with advanced or rapidly advancing bone age (ABA) and compromised predicted adult height.

Methods: Data were collected through retrospective chart review. Descriptive statistics were used to characterize the study cohort. Fisher's exact test and the Wilcoxon rank-sum test were used to compare outcomes.

Results: Of 72 patients reviewed, 59 (82%) received anastrozole, 11 (15%) received letrozole, and 2 (2.8%) switched from anastrozole to letrozole. Median treatment duration was 25 [interquartile range (IQR): 18-32] months. Most common diagnoses included growth hormone (GH) deficiency (31%), early puberty and premature adrenarche (18%), idiopathic short stature (15%), overweight/obesity (14%). GH was used in 66%. The overall median gain in height (FNFH minus initial predicted height) was 1.2 cm (IQR: -1.9-4.2). Letrozole-treated patients showed a greater median height gain (4.2 cm, IQR: 0.6-13) compared to the anastrozole group (0.8 cm, IQR: -2.6-3.5; p=0.013) and reached a FNFH closer to mid-parental height (p=0.031). Longer duration of treatment, therapy at earlier puberty stages, and GH therapy were all significantly associated with greater gain in height (p values=0.005, 0.012, and 0.022, respectively).

Conclusion: Our findings suggest that letrozole is associated with greater gain in height compared to anastrozole in males with ABA. Other factors associated with greater gains are treatment at earlier stages of puberty, longer duration of treatment and concurrent GH therapy.

Keywords: Near final height, aromatase inhibitor, anastrozole, letrozole, advanced bone age, compromised height prediction

What is already known on this topic?

Aromatase inhibitors (AIs) are prescribed off-label in boys with accelerated bone maturation and reduced predicted adult height. Current literature offers limited and conflicting evidence regarding their effect on near-final or final height.

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What this study adds?

Letrozole was associated with greater gain in height compared to anastrozole (mean 4.2 vs 0.8 cm) in males with advanced bone age. Other factors associated with greater gains are treatment at earlier stages of puberty, longer duration of treatment and concurrent GH therapy.

Introduction

Aromatase, a member of the P450 enzyme family, catalyzes the conversion of androgens into estrogens by removing a methyl group at the carbon 19 position of the androgen molecule. This process results in the formation of phenolic 18-carbon estrogens. Aromatase Inhibitors (AIs) act by binding to aromatase and inhibiting its action, thereby decreasing estrogen production. They are FDA-approved for the treatment of hormone receptor-positive breast cancer as well as male gynecomastia (1). In the United States, commonly used AIs include letrozole and anastrozole.

Estrogen is known to play a significant role in growth plate senescence and epiphyseal fusion in both males and females, ultimately leading to cessation of linear bone growth after puberty (2,3). Genetic disorders that cause estrogen deficiency or resistance can disrupt the normal growth plate closure and lead to continued growth into adulthood. Aromatase mutations can result in decreased estrogen production, leading to delayed or incomplete growth plate fusion (4) Similarly, mutations in the estrogen receptor can lead to impaired estrogen signaling, preventing growth plate closure, whereas early exposure to estrogen, such as in early/precocious puberty, can lead to early growth plate fusion and short stature (5). AIs have been used off label in the treatment of males with short stature as it is believed that they can postpone growth plate closure and extend the period of linear bone growth, thus improving adult height.

Previous studies have demonstrated the potential of AI therapy to enhance the predicted adult height (PAH) of males undergoing treatment for various conditions, including idiopathic short stature (ISS), growth hormone (GH) deficiency (GHD) and constitutional delay of growth and puberty (CDGP). Mauras et al. (6,7) showed that anastrozole, when used concurrently with GH in males with GHD, resulted in a significant increase of the PAH, with a 4.5 +/- 1.2 cm increase after 24 months and a 6.7 +/- 1.4 cm increase after 36 months of therapy. In a separate study, the same group also showed that 24 months of anastrozole therapy led to a 0.5 increase in height standard deviation score (SDS) in boys with ISS (6,7). Hero et al. (8,9) studied 31 boys diagnosed with ISS, treated with either letrozole or placebo and documented a 5.9 cm increase in the PAH of boys in the letrozole group. In a different study, they found that boys with CDGP treated with letrozole attained a higher mean near-final height, which did not significantly differ from their mid parental height (MPH) compared to boys on placebo (8,9). More recently, Yackobovitch-Gavan et al. (10) reported that AI treated pubertal boys with short stature achieved greater adult heights when compared to both untreated controls and their baseline PAH.

Anastrozole and letrozole are both third-generation, highly potent, non-steroidal AIs. However, studies in postmenopausal women with breast cancer have shown that letrozole is more effective in suppressing total body aromatization and lowering estrogen levels compared to anastrozole (11). Results from pediatric studies comparing their impact on growth potential have been mixed. Pedrosa et al. (12) compared children treated with letrozole or anastrozole with or without GH and found that the letrozole + GH group had an increase in PAH that was significantly higher than the other groups. In contrast, Zegarra et al. (13) reported a minimal 1.3 cm increase in the PAH of patients treated, with no significant differences between the two drug groups. When comparing hormonal changes the letrozole group had a greater increase in the testosterone levels and a greater decrease in the estradiol levels (13). Studies investigating AI safety and particularly their impact on bone health have also produced equivocal data. Hero et al. (14) found no significant differences in the bone mineral density (BMD) between boys with ISS treated with letrozole or placebo 12 months after completing treatment. However, vertebral deformities were reported in 6 out of 13 boys in the letrozole group and 4 out of 11 boys in the placebo group. On the other hand, Zegarra et al. (13) reported a significant decrease in whole body and lumbar spine BMD Z-scores among boys treated with AIs, with a greater reduction in the letrozole group.

Collectively, these studies highlight the potential of AIs to delay the bone age progression and enhance PAH. However, further studies are warranted to assess their efficacy in improving final adult height among males with other diagnoses associated with compromised height potential and accelerated bone age. In addition, data comparing the efficacy and safety of the two different available agents, anastrozole and letrozole, remain limited. Therefore, the aim of the present study was to analyze data of male patients treated with AIs who have attained final or near-final adult heights (FNFH).

Methods

Study Design

This study was a retrospective chart review of male patients treated with AIs (anastrozole, letrozole) in the pediatric endocrinology clinic at Weill Cornell Medicine (WCM) between

2007 and 2022. Patients were selected based on predefined inclusion and exclusion criteria. The study was conducted in accordance with the guidelines and protocols approved by the Institutional Review Board (IRB) and all research procedures adhered to the ethical standards and regulations set forth by the IRB. The study protocol was reviewed and approved by the Weill Cornell Medicine Research Integrity IRB and determined to qualify for exemption per the Code of Federal Regulations on the Protection of Human Subjects (WRG submission number: 23-08026421-02, FWA number: FWA00000093, date: 29.12.2023). Data was collected and managed in REDCap.

Inclusion and Exclusion Criteria

Male patients treated with AIs for a height prediction below their MPH or more than 2 SD below the population mean and advanced or rapidly advancing bone age (ABA) were included in the study. Exclusion criteria included: duration of AI treatment of less than one year; initiation of treatment before age nine years; nonadherence to therapy (as documented on follow up notes reviewed during chart review); concurrent treatment with a luteinizing hormone-releasing hormone analogue; or lack of data on final or near final height (NFH). NFH was defined as a bone age ≥16 years or growth velocity <2 cm/yr.

Data and Outcomes

Data collected from medical records included patient demographics (race/ethnicity, insurance status), anthropometric measurements including height (cm) and height SDS at treatment initiation and during therapy, weight and BMI percentiles at the same time points, PAH at baseline and during treatment, bone age results, laboratory findings, duration of AI therapy, primary diagnosis, concurrent treatments and testicular volume at the start of treatment. Bone ages were interpreted by the senior pediatric endocrinologists of the WCM clinic. PAH were calculated according to the Bailey and Pinneau method, applying the reference tables for "average" boys to avoid the significant overestimation of adult height that has been shown to occur in children with advanced bone age when the accelerated reference tables are used (15).

Primary outcomes included: gain in height (defined as the difference between FNFH and baseline PAH); gain in predicted height (defined as the difference between the final PAH and baseline PAH); and the final height discrepancy (defined as the difference between FNFH and MPH). Secondary outcomes included: change in bone age over time; occurrence of medication-related adverse effects; and associations between treatment efficacy and these variables - type of AI used, underlying diagnosis, age, pubertal stage at treatment initiation, duration of therapy and presence or absence of concurrent growth hormone therapy. Patients who transitioned from one AI type to the other were excluded from the analyses comparing the efficacy between the two AI types to avoid confounding.

Statistical Analysis

Descriptive statistics were used to characterize the study cohort. Categorical variables are represented as frequency (percent), and continuous variables are represented as median (interquartile range; 25th-75th percentile). The Fisher's exact test and Wilcoxon rank-sum test were used to examine the association between clinical variables of interest and outcome measures. The difference in bone age across time points and between treatment groups was assessed using the Skillings-Mack test, which accounts for the missingness in follow-up. Multivariable linear regression was performed for gain in height with treatment (letrozole vs anastrozole) and receipt of GH treatment (yes vs. no) as predictors. Adjusted betas and 95% confidence intervals (CIs) were estimated from the multivariable model. All p values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

A total of 72 patients treated with AIs were included. Of these, 59 patients (82%) received anastrozole only, 11 (15%) received letrozole only, and 2 (2.8%) transitioned from anastrozole to letrozole during the course of treatment due to persistently rapid advancement of bone age despite anastrozole therapy following chart review. Anastrozole was prescribed at 1 mg daily and letrozole at 2.5 mg daily with no dose adjustments during the treatment course. The majority of patients identified as White (62%) and were privately insured (94%). The median duration of AI therapy was 25 (18-32) months.

The overall median height and BMI at initiation of treatment were 154 (148-158) cm or -0.92 (-1.50 to 0.14) SD and 63rd (38th-89th) percentile respectively, while the overall median FNFH and final BMI were 169 (165-174) cm or -0.71 (-1.31 to -0.14) and 74th (50th-86th) percentile respectively. There was no significant difference in baseline median height in the anastrozole and letrozole groups (155 cm, IQR: 148-159 versus 151 cm, IQR: 143-158, p=0.33 or -0.92 SD, IQR: -1.53 to 0.12 versus -0.77 SD, IQR: -1.16 to 0.31, p=0.91). However, the FNFH in cm was significantly higher in the letrozole group (168 cm, IQR: 165-172 versus 173 cm, IQR: 168-179, p=0.042). FNFH SD did not differ between the two groups (-0.82 SD, IQR: -1.35 to -0.21 versus -0.15 SD, IQR: -0.56-0.26, p=0.1). No significant differences were observed between the two groups in median BMI at treatment initiation or at final follow-up (treatment initiation BMI 61st percentile,

IQR: 38th-89th versus 73rd percentile IQR: 35th-96th, p=0.51 and final BMI 70th percentile, IQR: 50th -87th versus 77th percentile, IQR: 43rd-82nd, p=0.98).

The median chronological age at treatment initiation was 13.3 (12.3-14.2), and 15.5 (14.8-16.2) years at the end of treatment. The median bone age at treatment initiation was 14 (13-14.3) years, with a median final bone age of 15.5 (15-16) years. Median testicular volume at treatment initiation was 12 (8-15) mL.

Diagnoses included GHD) (31%), early or rapid progression of puberty and premature adrenarche (18%), ISS (15%), overweight/obesity (14%), short stature not meeting criteria for ISS (13%), small for gestational age (9.9%), ABA only (9.9%), congenital adrenal hyperplasia (CAH) (4.2%) and other conditions (14%). All patients with GHD had isolated GHD, confirmed by two-agent GH stimulation testing. Among the 10 patients with overweight/obesity, 6 had concurrent GHD, and 4 were treated for ABA with compromised adult height prediction only.

Concurrent GH therapy was used for 47 patients (66%) with an overall median treatment duration of 42 (27-65) months. The median starting GH dose was 0.29 (0.25-0.30) mg/kg/week and the median maximum dose was 0.34 (0.3-0.37) mg/kg/week. There was no significant difference between the two groups in GH treatment duration or starting or maximum dose (41 vs 43 months, p=0.70; 0.29 vs 0.29 mg/kg/wk, p=0.60; and 0.34 vs 0.33 mg/kg/wk, p=0.86, respectively).

Outcomes

The overall median gain in height was 1.2 (-1.9 to 4.2) cm, while the median gain in predicted height was 3 (0-6) cm. The overall median final height discrepancy was -4.8 (-7.8 to -0.1) cm. Letrozole-treated patients showed a greater median gain in height of 4.2 (0.6 to 13) cm compared to those treated with anastrozole who gained 0.8 (-2.6 to 3.5) cm; p=0.013), as well as a smaller final height discrepancy [0.5 (-3.1 to 1.4) cm versus -5.8 (-8.0 to -2.3; p=0.036) cm] (Table 1). When adjusting for GH therapy, letrozole patients had on average a 7.5 cm greater gain in height (95% CI: 1.8 to 13) compared to anastrozole patients (p=0.011).

Longer treatment duration (p=0.005), earlier pubertal stage at treatment initiation (p=0.012) and concurrent GH therapy (p=0.022) were all associated with greater gain in height. Longer treatment duration and concurrent GH therapy were also associated with smaller final height discrepancies (p=0.002 and p<0.001, respectively) (Table 2A-C). Patients who received concurrent GH therapy had on average a 5.9 cm greater gain in height (95% CI: 1.4, 10, p=0.012), adjusting for treatment type. No significant differences in gain in height, gain in PAH and final height discrepancy were observed across the different diagnosis groups. AI therapy showed slower bone age advancement across treatment groups (p=0.025), but no difference was found between treatment groups over time (Figure 1A, 1B).

Adverse Effects/Laboratory Changes

Patient reported adverse effects included acne in 30 individuals, mental health concerns reported by six, including aggressive behavior, anger issues, and anxiety and depression, and hair loss in two. Laboratory abnormalities were also noted and included elevated liver function tests with six patients experiencing AST elevation, three patients ALT elevation and nine patients total bilirubin elevation. Elevations in AST and ALT resolved on repeat testing or after discontinuation of therapy in 5 out of 7 patients. One patient discontinued anastrozole due to elevated liver function tests but he was already nearing the end of his treatment course at the time of discontinuation. Among those with bilirubin elevations, two had elevated bilirubin at baseline that continued throughout treatment, while four showed normal levels on follow-up testing after completion of therapy. Testosterone levels increased compared to baseline during treatment follow-up (Table 3). No significant difference was noted on adverse effects and laboratory changes between the anastrozole and letrozole groups.

Discussion

Data on the off-label use of AIs to improve adult height in males with compromised PAH and ABA remain limited and inconsistent. Some studies suggest that boys with ISS with a PAH <-2.5 SD treated with a combination of GH and anastrozole

Table 1. Anastrozole vs. letrozole

	n	Overall	Anastrozole (n=59)	Letrozole (n=11)	p value
Gain in height (cm)	69	1.2 (-1.9-4.2)	0.8 (-2.6-3.5)	4.2 (0.6-13)	**0.013**
Gain in predicted height (cm)	68	3 (0-6)	2 (0-5)	7 (3-19)	**0.011**
FNFH-MPH (cm)	64	-4.8 (-7.8 to -0.1)	-5.8 (-8 to -2.3)	0.5 (-3.1-1.4)	**0.036**
Predicted height/MPH	64	0.97 (0.94-0.98)	0.97 (0.95-0.98)	0.95 (0.92-0.98)	0.41
FNFH/MPH	64	0.97 (0.96-0.99)	0.97 (0.95-0.98)	1 (0.98-1)	**0.031**

Median (25th-75th percentile), gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height.
MPH: mid-parental height

Table 2A. Treatment duration

		Treatment duration			
	n	**<24 mo (n=24)**	**24-36 mo (n=31)**	**>36 mo (n=14)**	**p value**
Gain in height (cm)	69	0.6 (-1.1-3.6)	1 (-3-2.9)	10.7 (0.2-13)	**0.005**
Gain in predicted height (cm)	68	2 (1-4)	2 (-2-5)	15 (5-17)	**<0.001**
FNFH-MPH (cm)	65	-5.7 (-10.8 to -2.3)	-5.9 (-7.8 to -3.9)	0.5 (-1.9-4.1)	**0.002**
Predicted height/MPH	65	0.97 (0.93-0.98)	0.97 (0.96-0.98)	0.96 (0.93-0.98)	0.26
FNFH/MPH	65	0.97 (0.94-0.99)	0.97 (0.96-0.98)	1 (0.99-1.02)	**0.001**

Median (25th-75th percentile)-gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height-gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height.
FAH: final adult height, MPH: mid-parental height

Table 2B. Testicular volume

		Testicular volume at initiation			
	n	**1-3 mL (n=2)**	**4-8 mL (n=19)**	**15-25 mL (n=26)**	**p value**
Gain in height (cm)	66	14.1(13-15.1)	4.3 (-1.2-10)	0.2 (-1.8-2.9)	**0.012**
Gain in predicted height (cm)	65	17 (14-21)	5 (4-11)	1 (-2-4)	**<0.001**
FNFH-MPH (cm)	61	4.1 (4-4.1)	-5.8 (-7.8-1.1)	-4.6 (-6.9 to -3.9)	0.14
Predicted height/MPH	61	0.95 (0.94-0.95)	0.96 (0.94-0.98)	0.97 (0.97-0.99)	0.12
FNFH/MPH	61	1.02 (1.02-1.02)	0.97 (0.96-1)	0.97 (0.96-0.98)	0.11

Median (25th-75th percentile), gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height.
FAH: final adult height, MPH: mid-parental height

Table 2C. Growth hormone therapy

	n	**GH therapy n=47**	**No GH therapy n=24**	**p value**	
Gain in height (cm)	71	2.7 (-1.8-6.3)	0.2 (-2.3-1.6)	**0.022**	
Gain in predicted height (cm)	70	4 (0-10)	2 (0-5)	0.20	
FAH-MPH (cm)	66	-4 (-6.1-0.8)	-7.7 (-10.8 to -4.9)	**<0.001**	
Predicted height/MPH	66	0.97 (0.945-0.98)	0.97 (0.94-0.98)	0.97	
FAH/MPH	66	0.98 (0.965-1)	0.96 (0.94-0.97)	**0.002**	

Median (25th-75th percentile)-gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height.
FAH: final adult height, MPH: mid-parental height, GH: growth hormone

Table 3. Testosterone levels

	n	**Overall**	**Anastrozole n=59**	**Letrozole n=11**	**p value**
Initial testosterone (ng/dL)	45	218 (89-334)	234 (102-365)	167 (8-190)	**0.037**
Testosterone at 1 year (ng/dL)	51	546 (272-637)	540 (287-615)	699 (272,-841)	0.20
Testosterone at 2 years (ng/dL)	30	476 (329-605)	438 (285-579)	575 (452-917)	0.18
Final testosterone (ng/dL)	52	495 (355-608)	482 (355-567)	592 (488-821)	0.10

Median (25th-75th percentile)

attain greater adult height compared to those receiving GH alone (7,16). In contrast, Varimo et al. (17) found that two years of letrozole monotherapy in pre- and early-pubertal boys with ISS did not significantly improve adult height compared to placebo. Among boys with GHD, combined GH and anastrozole therapy was associated with improved PAH versus GH alone, particularly with longer treatment durations (6). Similarly, Wickman et al. (18) reported a 5.1 cm increase in PAH among boys with CDGP treated with letrozole compared to placebo or no treatment (p=0.004). Neely et al. (19) observed a 4.2 cm increase in PAH with anastrozole in boys with short stature, whereas letrozole showed no significant benefit in the same cohort. In contrast, a retrospective study by Shams et al. (20) found no significant PAH improvement in boys with rapid pubertal progression, bone age ≥13 years, and short stature following short-term AI therapy.

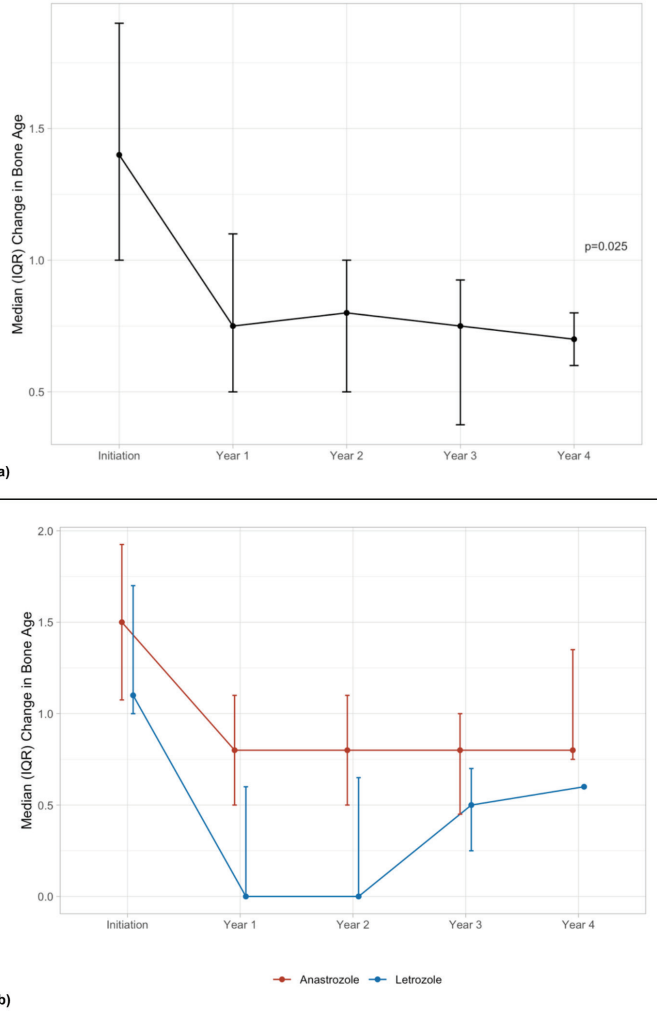

Figure 1. Change in bone age over time. a) Overall median change in bone age over time. b) Median change in bone age over time in the two treatment groups.

In our study, we assessed the impact of AI therapy on the FNFH of boys with a variety of underlying diagnoses, all of whom had predicted heights below their MPH and ABA. Overall, the gain in height observed was lower than what has been reported in prior studies. However, this may reflect an underestimation, as final adult height data were not available for all subjects with NFH used instead. This interpretation is supported by the more substantial gain in predicted height noted, which was based on patients' final available bone age results.

Since the purpose of AI treatment is to slow down bone age advancement by reducing estrogen, it is important to note that bone age advancement significantly slowed during treatment compared to the period prior to treatment initiation, when the mean bone age advancement was faster than chronological progression. The Bayley-Pinneau method used to calculate the PAH assumes an average bone age advancement and average growth velocity. Patients with a rapidly ABA would likely not reach their PAH as calculated by the above method. Thus, without intervention, patients may have achieved adult heights lower than their baseline PAH, although this remains speculative.

In contrast to the studies by Neely et al. (19) and Zegarra et al. (13), patients in our study who were treated with letrozole achieved a greater gain in height and FNFH closer to their MPH than those treated with anastrozole. This difference persisted even after adjusting for GH therapy. However, it is important to note that there were only eleven subjects in the letrozole group in our study, which was substantially fewer than the anastrozole group (which may introduce bias); thus the statistical difference between the two groups for gain in height must be interpreted with caution. This smaller sample size reflects the fact that letrozole has largely fallen out of favor in our clinical practice due to safety concerns, including reports of spinal deformities and a more pronounced decline in BMD Z-scores compared to anastrozole (13,14).

Consistent with previous studies, longer duration of treatment was associated with greater gain in height and a FNFH closer to MPH. Our study also showed that initiation of treatment at earlier stages of puberty (testicular volume ≤8 mL) resulted in greater gains in height, which is likely due to the substantial increase in testosterone production as puberty progresses. Moreover, concurrent treatment with GH was associated with a significantly higher median gain in height.

While prior studies have focused on the effect of AI therapy on height outcomes of patients treated for specific diagnoses including ISS, GHD or CDGP, our study included a broader patient population with a variety of diagnoses including the above as well as SGA, overweight/obesity, CAH, premature adrenarche and early puberty. No significant differences in the

treatment outcomes were observed based on the underlying diagnosis.

Adverse effects were generally mild. Acne was the most commonly reported side effect. Mental health concerns were evaluated and noted in 8.5% of the patients, though it is unclear whether systematic mental health screening was performed at follow up visits. Laboratory monitoring revealed increased testosterone levels and mild elevations of liver function tests, which mostly resolved on repeat testing, with no significant difference between the two treatment groups. This contrasts prior studies that reported greater testosterone increases with letrozole compared to anastrozole (13,19). Patients in our study did not undergo DXA scans during or after treatment with AIs, so the impact on BMD Z-scores remains unknown.

Study Limitations

Limitations of our study include the study design as a retrospective chart review with limited control over available data, particularly on the final adult height of patients included. Another limitation is the relatively small sample size, particularly in the letrozole group, though the sample was larger than in several prior studies on this topic.

Conclusion

This study supports the efficacy of AI therapy and particularly letrozole in improving the final adult height of males with compromised PAH and ABA, irrespective of the underlying

diagnosis. Patients treated with letrozole, at earlier pubertal stages, for longer duration and receiving concurrent treatment with GH attained better final height outcomes. Nonetheless, concerns about the safety of use persist, particularly regarding their potential impact on bone health.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Weill Cornell Medicine Research Integrity IRB and determined to qualify for exemption per the Code of Federal Regulations on the Protection of Human Subjects (WRG submission number: 23-08026421-02, FWA number: FWA00000093, date: 28/12/2023).

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

Footnotes

Presented in: Part of the content of this manuscript was previously presented as a poster presentation at the Pediatric Endocrine Society Annual Meeting (PES 2025, National Harbor, MD).

Authorship Contributions

Concept: Athanasia Bouliari, Oksana Lekarev, Karen Lin-Su Design: Athanasia Bouliari, Karen Lin-Su, Data Collection or Processing: Athanasia Bouliari, Analysis or Interpretation: Athanasia Bouliari, Anjile An, Karen Lin-Su, Literature Search: Athanasia Bouliari, Karen Lin-Su Writing: Athanasia Bouliari, Oksana Lekarev, Karen Lin-Su.

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Peer Victimization and Psychological Outcomes in Adolescents with Pubertal Gynecomastia: A Case-Control Study

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ABSTRACT

Objective: Pubertal gynecomastia is associated with psychosocial consequences including anxiety, depression, and body image disturbances. However systematic examination of bullying experiences and their psychological correlates in adolescents with gynecomastia remains limited. The aim of this study was to investigate peer victimization prevalence and its relationship with psychological outcomes in this vulnerable population.

Methods: This case-control study included male adolescents aged 10-17 years, comprising half with gynecomastia and half healthy controls. Gynecomastia diagnosis and severity were assessed using clinical examination and Rohrich classification. Participants completed validated Turkish versions of the Olweus Bully/Victim Questionnaire, Rosenberg Self-Esteem Scale, and Revised Child Anxiety and Depression Scale.

Results: A total of 155 adolescents were included, with 78 (50.3%) having gynecomastia and the remaining 77 being healthy. Adolescents with gynecomastia demonstrated significantly higher peer victimization rates compared to controls (34.6% versus 16.9%, p=0.012), with markedly increased victim-perpetrator status (12.8% versus 1.3%, p=0.005). Gynecomastia diagnosis increased victimization risk 2.63-fold (95% confidence interval: 1.076-6.436, p=0.034). Victimized participants exhibited elevated anxiety and depression scores across multiple symptom domains ($p<0.05$). Behavioral modifications were prevalent, including altered clothing preferences (58.9%), changing room avoidance (44.8%), and swimming avoidance (41.0%).

Conclusion: Adolescents with gynecomastia experienced substantially elevated peer victimization with consequential psychological impact in this cohort. These findings suggest the importance of routine bullying assessment during clinical evaluation and implementation of comprehensive psychosocial screening protocols with early intervention strategies.

Keywords: Pubertal gynecomastia, peer victimization, bullying, adolescents, anxiety, depression

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What is already known on this topic?

Pubertal gynecomastia affects approximately 1% of adolescents and is associated with psychosocial difficulties. Physical appearance differences increase bullying risk in adolescents. Limited research has systematically examined bullying experiences in adolescents with gynecomastia.

What this study adds?

Adolescents with gynecomastia experience 2.63-fold increased peer victimization risk. Victimized adolescents show significantly elevated anxiety and depression across multiple domains compared with non-gynecomastic peers. Routine bullying assessment should be integrated into clinical evaluation of gynecomastia patients.

Introduction

Pubertal gynecomastia (PG), defined as the benign enlargement of male breast tissue, represents one of the most common endocrine conditions encountered during puberty, affecting an estimated 1.08% of male adolescents aged 12-15 years according to recent population-based data (1). The condition typically manifests between the ages of 13-14 years, corresponding to Tanner stages 3-4, with bilateral involvement observed in approximately 90% of cases (2,3). While pubertal gynecomastia is largely physiological and resolves spontaneously within 1-3 years in most cases, persistent enlargement occurs in approximately 10% of adolescents by age 17 years, necessitating medical or surgical intervention (4). PG develops due to transient imbalances between androgens and estrogens during pubertal development, is idiopathic in over 95% of patients, although pathological causes including endocrine disorders, medications, and genetic syndromes account for less than 5% of cases (5,6).

PG represents a physical condition affecting adolescent males, yet its effects extend far beyond anatomical changes to encompass significant psychosocial consequences. Controlled research demonstrated that adolescents with gynecomastia exhibit impairments in social functioning, mental health, and self-esteem parameters compared to their healthy peers (7). The psychosocial manifestations include shame, anxiety, social isolation, body image disturbance, and excessive self-consciousness. PG is frequently associated with avoidance behaviors affecting physical activities and a decline in academic performance (7,8). Clinical studies have revealed elevated rates of anxiety disorders, depression, social phobia, disordered eating behaviors, and adjustment disorders among this population (7,9,10,11). Follow-up studies conducted after surgical intervention demonstrate improvements in patients' self-esteem, social functioning, and quality of life scores. These findings demonstrate the importance of early diagnosis and appropriately timed therapeutic interventions (10,12).

Peer victimization and bullying during adolescence have emerged as major public health concerns, with recent meta-analyses indicating that approximately 36% of adolescents worldwide experience some form of bullying victimization (13). The relationship between differences in physical appearance and increased bullying risk has been extensively documented (14,15). Beyond immediate psychological effects, systematic reviews demonstrate that bullying experiences have lasting consequences into adulthood, including depression, anxiety, self-harm behaviors, and suicidal ideation (16). Appearance-based bullying in particular shows particularly high correlations with body image issues, and low self-esteem in adolescent populations (14). The occurrence of different physical appearance and peer victimization may result in a complex and heterogeneous multifactorial situation that results in individual psychological distress. As such, this challenging occurrence warrants careful investigation in vulnerable populations, such as adolescents with medical conditions affecting appearance.

Despite the well-established psychological impact of gynecomastia and the documented relationship between appearance differences and bullying victimization, limited research has systematically examined the intersection of these phenomena. This lack of evidence is particularly concerning given that adolescents with visible physical differences may be at heightened risk for peer victimization, potentially amplifying the already significant psychological burden associated with gynecomastia. The aim of the present study was to investigate the prevalence of peer victimization among adolescents with gynecomastia compared to healthy controls, examine the relationship between bullying experiences and psychological outcomes, including self-esteem, anxiety, and depressive symptoms, and identify predictive factors for victimization within this vulnerable population. Through comprehensive assessment of both bullying experiences and psychological wellbeing, this research sought to inform evidence-based approaches to clinical care and intervention strategies for adolescents with gynecomastia.

Methods

This case-controlled study was conducted between June 2023 and January 2024 at University of Health Sciences Türkiye,

Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Türkiye. The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: KAEK/2023.06.254, date: 2023) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their parents or legal guardians prior to enrollment.

The study included male adolescents aged 10-17 years, divided approximately into half with gynecomastia and half healthy controls. Case group participants were recruited from patients presenting to the pediatric endocrinology outpatient clinic with a confirmed diagnosis of gynecomastia. Diagnosis of gynecomastia was established through clinical examination by a pediatric endocrinologist and severity assessed using the Rohrich classification (3). Control group participants were recruited from healthy adolescents attending routine pediatric check-ups or accompanying siblings to medical appointments.

Inclusion criteria for the gynecomastia group included being male, aged 10-17 years and with clinical diagnosis of gynecomastia confirmed by a pediatric endocrinologist. In addition, gynecomastia duration was ≥6 months, and participants had capacity to complete questionnaires in Turkish. Control group inclusion criteria included healthy male adolescents aged 10-17 years with no clinical evidence of gynecomastia, no history of chronic medical conditions, no current psychiatric disorders requiring treatment, and age-matching to the gynecomastia group.

Exclusion criteria for both groups included presence of serious psychiatric disorders, such as psychosis, cognitive impairment preventing questionnaire completion, chronic medical conditions affecting psychological wellbeing, current use of psychotropic medications, and refusal to participate or provision of incomplete data.

Sample size was determined using G*Power software (version 3.1.9.2, Heinrich-Heine-Universität Düsseldorf, Germany) based on anticipated differences in peer victimization prevalence between groups. Given the limited literature on bullying in adolescents with gynecomastia, we assumed a medium effect size (Cohen's $h=0.5$) for the primary outcome, with $\alpha=0.05$ and power $(1-\beta)=0.80$, yielding a required sample size of 64 participants per group. To ensure adequate power, we recruited in excess of this number for both case and control groups.

Clinical Assessment

All participants underwent comprehensive clinical evaluation, including measurement of height, weight, and calculation of body mass index (BMI) standard deviation scores (SDS) using Turkish reference standards (17). Gynecomastia severity was assessed using the Rohrich classification system. Pubertal development was evaluated according to Tanner staging. Additional clinical data collected included family history, medication use, and presence of any concurrent medical conditions.

For participants with gynecomastia, detailed clinical characteristics were documented including laterality (unilateral or bilateral), Rohrich grade, and associated behavioral modifications. The Rohrich classification is a clinically useful system developed to categorize the severity of gynecomastia based on the degree of breast hypertrophy and the degree of breast ptosis. It defines four grades: Grade 1 refers to minimal hypertrophy (<250 g) without ptosis; Grade 2 involves moderate hypertrophy (250-500 g) without ptosis; Grade 3 indicates severe hypertrophy (>500 g) with Grade 1 ptosis; and Grade 4 includes severe hypertrophy with more advanced ptosis (Grade 2 or 3). Higher grades therefore reflect greater breast enlargement and skin redundancy. In the present study, severity was graded clinically by a pediatric endocrinologist according to the degree of hypertrophy and ptosis, and the diagnosis of gynecomastia itself was established by clinical examination rather than by this grading scale (3). Specific behavioral modifications assessed included social avoidance behaviors, clothing preference changes favoring loose-fitting garments, avoidance of changing rooms, and avoidance of swimming pools or beaches.

Psychological Assessment Instruments

Peer Victimization Assessment

Bullying and victimization experiences were evaluated using the validated Turkish adaptation of the Olweus Bully/Victim Questionnaire (18,19). This comprehensive instrument consists of 39 items designed to assess various forms of peer aggression and victimization occurring within the preceding month. The questionnaire employs a frequency-based classification system, where participants reporting experiences occurring two to three times or more frequently are categorized into distinct groups: pure victims, pure perpetrators, bully-victims (individuals who both perpetrate and experience bullying), or uninvolved participants. The Turkish version has demonstrated satisfactory psychometric properties with internal consistency coefficients of $\alpha=0.81$ in adolescent populations.

Self-Esteem Measurement

Global self-esteem was assessed using the ten-item self-esteem subscale from the Turkish adaptation of the Rosenberg Self-Esteem Scale (20,21). This widely utilized instrument evaluates overall self-worth and self-acceptance through items addressing personal satisfaction, self-respect, and perceived adequacy. Responses are recorded on a four-point Likert format ranging from strongly disagree to strongly agree, with higher composite scores reflecting enhanced self-regard. The Turkish version of this

subscale has demonstrated robust psychometric characteristics with validity coefficients of r=0.71 and test-retest reliability indices of r=0.75 in adolescent populations.

Anxiety and Depression Symptomatology

Psychological distress was measured using the Turkish version of the Revised Child Anxiety and Depression Scale (RCADS), a DSM-IV-aligned assessment tool comprising 47 items (22,23). The instrument evaluates six distinct symptom domains through dedicated subscales: generalized anxiety (6 items), separation anxiety (7 items), panic symptomatology (9 items), obsessive-compulsive features (6 items), social anxiety manifestations (9 items), and major depressive symptoms (10 items). Response options range across a four-point continuum from 0 (never experienced) to 3 (always experienced), with elevated scores indicating greater symptom severity. The Turkish adaptation has demonstrated excellent internal reliability with overall Cronbach's alpha coefficients of 0.95.

Data Collection Procedure

Data collection was conducted in a quiet, private room within the hospital setting. All questionnaires were administered by trained research personnel in a standardized manner. Participants completed the questionnaires individually, with research staff available to provide clarification when needed. The assessment session lasted approximately 20-45 minutes for each participant. Demographic information was collected through a structured interview with both the participant and accompanying parent or guardian.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences), version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics including frequencies and percentages were calculated for categorical variables; as continuous variables were not normally distributed, they were summarized as medians with minimum-maximum ranges. The normality of continuous variables was assessed using the Shapiro-Wilk test. Since the data did not meet normality assumptions, non-parametric tests were employed for group comparisons.

Categorical variables were compared between groups using chi-square tests or Fisher's exact test when appropriate. Continuous variables were compared using the Mann-Whitney U test for independent groups. Statistical significance was set at $p<0.05$ for all analyses.

Binary logistic regression analysis was performed to identify predictors of peer victimization. The overall model included group status (gynecomastia vs control), age, BMI-SDS, self-esteem scores, and total anxiety-depression scores as independent variables. A separate logistic regression analysis was conducted within the gynecomastia group to identify specific predictors of victimization among affected adolescents. Model fit was assessed using the Omnibus test, and the explained variance was reported using Nagelkerke R-squared values.

Results

Participant Characteristics

This case-control study included 155 male adolescents aged 10-17 years, with 78 (50.3%) participants diagnosed with gynecomastia and 77 healthy controls. The groups were well-matched for demographic characteristics, with no significant differences observed in grade level distribution, educational levels, or family income status (all $p>0.05$).

Anthropometric measurements revealed significant differences between groups. Participants with gynecomastia demonstrated significantly higher weight SDS and BMI-SDS (p=0.001) compared to controls. However, no significant differences were found in age, pubertal stage, height SDS, or daily screen time between the two groups.

The clinical presentation of gynecomastia was bilateral in 89.7% of participants. Distribution according to Rohrich grading system revealed that 34.6% were classified as Grade 2, 30.7% as 3, and 19.2% as 4. The physical changes associated with gynecomastia resulted in substantial behavioral modifications among affected adolescents. Social avoidance behaviors were reported by 43.5% of participants, while 58.9% experienced changes in clothing preferences, specifically favoring loose-fitting garments. In addition, 44.8% reported avoiding changing rooms and 41.0% avoided swimming pools or beaches, indicating significant impact on daily activities and social participation (Table 1).

Peer Victimization Outcomes

The primary analysis revealed markedly higher rates of peer victimization among adolescents with gynecomastia compared to controls. Overall victimization prevalence reached 34.6% in the gynecomastia group versus 16.9% in the control group (p=0.012), representing a significant two-fold increase. Furthermore, participants with gynecomastia demonstrated elevated rates of perpetrating bullying behaviors (15.4% vs 5.2%, p=0.037) and were significantly more likely to exhibit dual victim-perpetrator status (12.8% vs 1.3%, p=0.005) (Table 2).

Psychological Well-being Measures

Assessment of self-esteem using the Rosenberg Self-Esteem Scale revealed no significant difference between groups (p=0.064). Similarly, overall psychological symptoms measured by the RCADS showed comparable total scores between groups (p=0.569). Individual subscale analyses revealed no significant between-group differences for any RCADS domain (all $p>0.05$) (Table 3).

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Impact of Victimization Within the Gynecomastia Group

Among participants with gynecomastia, those who experienced peer victimization demonstrated significantly elevated psychological distress across multiple domains compared to their non-victimized counterparts. Victimized adolescents showed markedly higher total RCADS scores (p=0.001).

Detailed analysis of symptom domains revealed significant elevations in social phobia (p=0.004), obsessive-compulsive symptoms (p=0.001), panic disorder (p=0.001), generalized anxiety (p=0.006), and depression (p=0.001). Despite these pronounced differences in psychological symptoms, self-esteem scores remained comparable between victimized and non-victimized participants with gynecomastia (p=0.695) (Table 4).

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Gynecomastia group (n=78)	Control group (n=77)	p value
Age, years	14.13±1.87	13.97±1.82	0.661
Grade level, n (%)			0.797
Primary school	1 (1.3)	2 (2.6)	
Middle school	36 (46.2)	37 (48.1)	
High school	41 (52.6)	38 (49.4)	
Weight SDS	1.07±1.54	0.14±1.09	**0.001***
Height SDS	0.42±1.26	0.07±1.26	0.123
BMI SDS	1.01±1.34	0.16±0.93	**0.001***
Pubertal stage			0.975
Stage 2	10 (12.8)	11 (14.2)	
Stage 3	20 (25.6)	19 (24.6)	
Stage 4	16 (20.5)	17 (22)	
Stage 5	32 (41.0)	30 (38.9)	
Gynecomastia-specific characteristics			
Laterality n (%)			
Unilateral	8 (10.3)	-	-
Bilateral	70 (89.7)	-	-
Rohrich grade n (%)			
Grade 1	12 (15.4)	-	-
Grade 2	27 (34.6)	-	-
Grade 3	24 (30.7)	-	-
Grade 4	15 (19.2)	-	-
Behavioral modifications n (%)			
Social avoidance	34 (43.5)	-	-
Clothing preference changes	46 (58.9)	-	-
Changing room avoidance	35 (44.8)	-	-
Swimming/beach avoidance	32 (41.0)	-	-
Screen time, hours/day	4.97±2.97	4.15±2.75	0.061
Family income, n (%)			0.835
Below minimum wage	16 (20.5)	14 (18.2)	
Minimum wage - 2x	42 (53.8)	47 (61.0)	
2x-3x minimum wage	14 (17.9)	11 (14.3)	
>3x minimum wage	6 (7.7)	5 (6.5)	

*p<0.05; SDS: standard deviation score; BMI: body mass index

Predictive Factors for Peer Victimization

Logistic regression analysis across the entire sample identified two significant predictors of peer victimization. The presence of a diagnosis of gynecomastia emerged as the strongest predictor, increasing victimization risk by 2.63-fold (OR=2.631, 95% CI: 1.076-6.436, p=0.034). In addition, psychological symptom severity, as measured by total anxiety and depression scores, showed a dose-response relationship with victimization risk, with each unit increase associated with a 4% increase in victimization probability (OR=1.040, 95% CI: 1.021-1.060, p=0.001). This comprehensive model explained 24.2% of the variance in victimization status (Nagelkerke R^2=0.242).

Table 2. Peer victimization patterns by group

Victimization type	Gynecomastia group (n=78)	Control group (n=77)	p value
Overall victimization, n (%)	27 (34.6)	13 (16.9)	**0.012***
Victim only, n (%)	17 (21.8)	12 (15.6)	0.322
Perpetrator only, n (%)	2 (2.6)	3 (3.9)	0.639
Victim-perpetrator, n (%)	10 (12.8)	1 (1.3)	**0.005***
No involvement, n (%)	49 (62.8)	61 (79.2)	**0.025***

*p<0.05; chi-square test

Table 3. Psychological measures by group

Measure	Gynecomastia group (n=78)	Control group (n=77)	p value
Rosenberg self-esteem scale	24 (14-34)	23 (15-29)	0.064
RCADS total score	26 (0-120)	27 (1-87)	0.569
RCADS subscales			
Separation anxiety	2 (0-15)	3 (0-15)	0.476
Social phobia	7 (0-26)	8 (0-26)	0.793
Obsessive-compulsive	4 (0-18)	4 (0-15)	0.993
Panic disorder	2 (0-23)	3 (0-25)	0.199
Generalized anxiety	4.5 (0-18)	6 (0-16)	0.384
Major depression	4 (0-27)	5 (0-24)	0.399

Data presented as median (minimum-maximum); RCADS: revised child anxiety and depression scale; Mann-Whitney U test; p<0.05

Within the gynecomastia subgroup, a more nuanced pattern emerged. Higher total anxiety and depression scores remained a significant predictor of victimization (OR=1.080, 95% CI: 1.036-1.125, p=0.001), while elevated separation anxiety subscale scores demonstrated a protective association (OR=0.718, 95% CI: 0.529-0.974, p=0.033). This gynecomastia-specific model demonstrated enhanced explanatory power, accounting for 36.5% of the variance in victimization among affected adolescents (Nagelkerke R^2=0.365). Age, BMI SDS, self-esteem levels, and gynecomastia-related behavioral modifications did not emerge as significant predictors in either analytical model (Table 5).

Table 4. Psychological outcomes by victimization status within gynecomastia group

Measure	Victimized (n=27)	Non-victimized (n=51)	p value
Rosenberg self-esteem scale	24 (19-31)	24 (14-34)	0.695
RCADS total score	46 (4-103)	21 (0-120)	**0.001***
RCADS subscales			
Separation anxiety	3 (1-11)	2 (0-15)	0.124
Social phobia	11 (0-26)	7 (0-23)	**0.004***
Obsessive-compulsive	6 (0-18)	3 (0-15)	**0.001***
Panic disorder	6 (0-17)	1 (0-23)	**0.001***
Generalized anxiety	7 (1-16)	4 (0-18)	**0.006***
Major depression	11 (0-27)	3 (0-26)	**0.001***

Data presented as median (minimum-maximum); RCADS: revised child anxiety and depression scale; Mann-Whitney U test; *p<0.05

Discussion

This study employed a case-control design to examine the prevalence of peer victimization among adolescents with pubertal gynecomastia and its relationship with psychological outcomes, including self-esteem, anxiety, and depressive symptoms. Our findings indicate that adolescents with gynecomastia experienced significantly higher rates of peer victimization than healthy controls, and that victimized adolescents showed elevated anxiety and depressive symptoms across multiple domains. However, overall self-esteem, anxiety, and depression scores did not differ significantly between the two groups. These findings extend the limited existing literature by quantifying peer victimization and its psychological correlates in adolescents with gynecomastia using validated instruments and a matched control group.

Differences in physical appearance have been extensively shown to be significant risk factors for peer victimization (24,25,26,27). Thus, gynecomastia constitutes an important risk factor for bullying as a condition that significantly affects physical appearance during adolescence. Although studies examining bullying experiences in adolescents with gynecomastia remain limited, existing data support this relationship. Karpinski et al. (12) reported that 95.7% of adolescents with gynecomastia had a history of bullying, teasing, or shame related to their

Table 5. Logistic regression analysis: predictors of peer victimization.

Overall sample analysis				
Variable	**β**	**OR**	**95% CI**	**p value**
Gynecomastia diagnosis	0.967	2.631	1.076-6.436	**0.034***
Age	-0.066	0.936	0.747-1.173	0.566
BMI-SDS	0.140	1.151	0.812-1.631	0.430
Self-esteem score	-0.023	0.978	0.861-1.110	0.727
RCADS total score	0.039	1.040	1.021-1.060	**0.001***
Model: χ^2=27.774, p=0.001; Nagelkerke R^2=0.242 *p<0.05; OR: odds ratio; CI: confidence interval; BMI: body mass index; SDS: standard deviation score; RCADS: revised child anxiety and depression scale				
Gynecomastia group analysis				
Variable	**β**	**OR**	**95% CI**	**p value**
Age	-0.152	0.859	0.610-1.210	0.385
BMI SDS	0.374	1.454	0.896-2.359	0.130
Self-esteem score	0.013	1.013	0.851-1.206	0.881
RCADS total score	0.077	1.080	1.036-1.125	**0.001***
RCADS separation anxiety	-0.331	0.718	0.529-0.974	**0.033***
Clothing preference change	-0.507	0.602	0.187-1.945	0.397
Model: χ^2=23.568, p=0.001; Nagelkerke R^2=0.365 *p<0.05; OR: odds ratio; CI: confidence interval; BMI: body mass index; SDS: standard deviation score; RCADS: revised child anxiety and depression scale				

breast appearance. In a study published by Isik et al. (28) in 2025, adolescents with gynecomastia experienced significantly more teasing and attacks on personal belongings compared to controls, with an observed trend toward increased overall bullying scores. Our findings strengthen these data with our findings of 34.6% overall bullying prevalence and 2.63-fold increased risk ratio confirming that bullying risk is significantly elevated in adolescents with physical differences. The variation in prevalence rates across studies underscores the importance of methodological approaches used in bullying assessment. The 95.7% rate reported by Karpinski et al. (12) differs substantially from our finding of 34.6%. This difference likely reflects what was measured rather than a true discrepancy in prevalence: Karpinski et al. (12) retrospectively evaluated any lifetime ("ever") history of bullying, teasing, or shame related to breast appearance whereas our study used the Olweus questionnaire to capture current victimization occurring at a defined frequency threshold of two to three times per month or more. These two figures therefore correspond to different time frames—lifetime experience versus recent, recurrent victimization—which largely accounts for the difference in reported rates rather than reflecting a true discrepancy in bullying prevalence.

The complex relationship between psychological symptoms and bullying experiences has been comprehensively examined in the literature. As demonstrated in Reijntjes et al. (29) in a longitudinal meta-analysis, internalizing problems can serve as both antecedents and consequences of bullying. Cook et al. (30) published a meta-analytic study showing that children with elevated anxiety and depression symptoms have increased risk of bullying victimization. Similarly, bullying experiences have been documented to lead to long-term psychological consequences by Moore et al. (16) in a systematic review. In our study, each unit increase in RCADS total score increased bullying risk by 4%, demonstrating that this dose-response relationship is also valid in adolescents with gynecomastia. The gynecomastia group-specific analysis model demonstrated higher explanatory power compared to the general sample and was able to explain 36.5% of the variance in bullying. This indicates that bullying risk factors are more distinct and predictable in adolescents with gynecomastia. Therefore, early recognition and intervention for psychological symptoms in adolescents with gynecomastia may be important for reducing bullying risk.

The clinical significance of adolescents exhibiting a mixed bully-victim profile has been documented in comprehensive research in recent years. Ariani et al. (31) undertook a global meta-analysis published in 2025, which examined 116 studies and 603,231 participants; the prevalence of adolescents with a mixed bully-victim profile was reported as 16%. Cook et al. (30) suggested that bullying experiences can serve as both antecedents and consequences, creating a complex cycle. In our study, the proportion of adolescents with a bully-victim profile in the gynecomastia group was 10 times higher compared to the control group (12.8% versus 1.3%), indicating that adolescents with physical differences were overrepresented in this category. This suggests that adolescents with gynecomastia may not only experience bullying victimization but may also exhibit bullying behaviors themselves, emphasizing the necessity for comprehensive psychosocial assessment and multidimensional intervention strategies.

Systematic reviews and meta-analyses have shown that bullying victimization is associated with various mental health problems including emotional distress, loneliness, anxiety, depression, suicidal ideation, and self-harm behaviors. In many cases, these effects persist beyond adolescence into adulthood (16,31,32). The findings from our study are consistent with this and demonstrate the effects of bullying on adolescents with gynecomastia. Adolescents with gynecomastia who experienced bullying exhibited higher scores on anxiety and depression subscales compared to their peers with gynecomastia who had no bullying victimization. Increases were particularly prevalent in social phobia, obsessive-compulsive symptoms, panic disorder symptoms, and depressive symptoms. Given these findings, we further suggest that bullying history should be routinely assessed during psychiatric evaluation of adolescents with gynecomastia. Evaluating bullying experiences in adolescents with gynecomastia who present with psychological symptoms is of critical importance for developing effective intervention strategies.

The literature has reported patient statements and clinical observations indicating that adolescents with gynecomastia prefer loose clothing to conceal their breasts and avoid social settings where the upper body is exposed, such as changing rooms and swimming (6,11,33). However, systematic and quantitative data regarding the prevalence of these behaviors have remained limited to date. Our study addresses this by revealing that approximately 60% of participants made changes in clothing preferences (favoring looser and more concealing garments), 44% avoided changing rooms, and 41% avoided swimming or beach activities. Therefore, our findings demonstrate that these behavioral adaptation strategies, previously mentioned only as possible outcomes, are quite prevalent and are possibly clinically significant in adolescent gynecomastia.

Previous research reports inconsistent psychological outcomes in adolescents with gynecomastia, with some studies demonstrating elevated anxiety, depression, and impaired self-esteem (10,12,34), while others found no differences (35). In our regression analysis, the absence of significant effects of age, BMI, self-esteem, and behavioral modifications on bullying victimization risk meant that gynecomastia diagnosis

was the strongest determining factor in the general sample, with anxiety-depressive symptom levels contributing as an independent risk factor. In the gynecomastia group-specific analysis, while anxiety-depressive symptom levels increased bullying risk, separation anxiety was unexpectedly identified as a protective factor (OR=0.718, p=0.033), suggesting that family closeness may have a protective effect against bullying. The literature has documented that adolescents with gynecomastia may exhibit extreme avoidance behaviors including withdrawal from social environments, peer exclusion, and even thoughts of dropping out of school due to severe bullying (9,36). Therefore, adolescents with high separation anxiety may have reduced their bullying victimization risk by avoiding social risks with the motivation to preserve the psychological safety of their family environment. The absence of significant differences in baseline anxiety, depression, and self-esteem levels between gynecomastia and control groups suggests that the pronounced psychological elevations observed in bullied adolescents with gynecomastia may be a consequence of the bullying experience.

Study Limitations

Several methodological limitations warrant consideration when interpreting these findings. The cross-sectional design prevents establishment of causal relationships between gynecomastia, psychological symptoms, and bullying experiences. While the sample size was adequate for detecting the primary outcome based on power analysis, the relatively modest sample size—which, when divided across Rohrich grades 1-4, yields small subgroups—limits generalizability and precludes definitive conclusions regarding any specific severity grade. Assessment of psychological symptoms relied exclusively on self-report measures rather than clinical diagnostic interviews, potentially compromising the depth and reliability of psychological evaluations. Single-center recruitment from a tertiary care facility may introduce selection bias, potentially overrepresenting individuals seeking medical intervention. The study did not assess detailed characteristics of bullying experiences, including frequency, duration, or specific types of victimization. Furthermore, the study did not evaluate family or school context variables, such as family support, parenting styles, teacher support, and peer relationships, which could strongly influence bullying experiences and psychological outcomes. Finally, the absence of longitudinal follow-up prevents examination of temporal relationships and long-term psychosocial outcomes.

Conclusion

This investigation demonstrated that adolescents with gynecomastia experienced significantly elevated rates of peer victimization, with prevalence reaching 34.6% compared to 16.9% in healthy controls. The 2.63-fold increased risk, particularly in dual victim-perpetrator categories, highlighted the complex bullying dynamics affecting this population. Victimized adolescents with gynecomastia showed substantial psychological burden across multiple anxiety and depressive symptom domains. These findings indicate that while gynecomastia may not invariably precipitate clinical-level psychological disorders, it imposes considerable psychosocial burden during the already challenging period of adolescence, characterized by social difficulties and avoidance behaviors. The results imply the necessity of routine bullying assessment during clinical evaluation and implementing comprehensive psychosocial screening protocols with early intervention strategies. Future studies should focus on developing and implementing school-based bullying prevention programs and evaluating the effectiveness of integrated mental health interventions for this high-risk population. Future research with larger samples across all gynecomastia severity levels and incorporating longitudinal designs will help the understanding of these psychosocial dynamics and the development of targeted intervention strategies for this vulnerable adolescent population.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: KAEK/2023.06.254, date: 2023).

Informed Consent: Written informed consent was obtained from all participants and their parents or legal guardians prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Zümrüt Kocabey Sütçü, Emel Hatun Aytaç Kaplan, Concept: Yasin Çalışkan, Zümrüt Kocabey Sütçü, Design: Yasin Çalışkan, Data Collection or Processing: Yasin Çalışkan, Emel Hatun Aytaç Kaplan, Analysis or Interpretation: Yasin Çalışkan, Emel Hatun Aytaç Kaplan, Literature Search: Yasin Çalışkan, Zümrüt Kocabey Sütçü, Writing: Yasin Çalışkan, Zümrüt Kocabey Sütçü, Emel Hatun Aytaç Kaplan.

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Single-Center Experience in Five Patients Diagnosed with Lipoid Congenital Adrenal Hyperplasia due to *Steroidogenic Acute Regulatory Protein (STAR)* Gene Variants: A Rare Cause of Adrenal Insufficiency

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ABSTRACT

Lipoid congenital adrenal hyperplasia (LCAH) is the rarest and most severe form of congenital adrenal hyperplasia (CAH), characterized by impaired adrenal and gonadal steroidogenesis. This case series presents our clinical experience with five pediatric patients diagnosed with LCAH due to mutations in the *steroidogenic acute regulatory protein (STAR)* gene. Clinical and laboratory data from five patients diagnosed with LCAH and followed at the Pediatric Endocrinology Clinic of Akdeniz University Faculty of Medicine Hospital between January 2020 and May 2025 were retrospectively reviewed. The patients, aged 7 days to 6 months, all exhibited a female phenotype and presented with vomiting and feeding difficulties. Three showed hyperpigmentation. Severe hyponatremia, hyperkalemia, elevated adrenocorticotropic hormone and renin activity, and low cortisol were observed. Aldosterone and 17-hydroxyprogesterone were normal; testosterone and precursors were low. Imaging showed bilateral adrenal lipoid infiltration and hyperplasia. Karyotypes included 46,XX (n=3) and 46,XY (n=2). *STAR* gene mutations identified were c.505G>A, c.33del, and c.288G>T. All received hydrocortisone and fludrocortisone and all survived without morbidity. LCAH is a rare genetic disorder that can present with life-threatening adrenal insufficiency. However, as demonstrated in these cases, early diagnosis and appropriate treatment can lead to excellent outcomes.

Keywords: lipoid congenital adrenal hyperplasia, steroidogenic acute regulatory protein, adrenal insufficiency, disorders of sex development

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What is already known on this topic?

Lipoid congenital adrenal hyperplasia (LCAH) represents the most severe and rarest form of congenital adrenal hyperplasia, resulting from mutations in the *steroidogenic acute regulatory protein (STAR)* gene. The disorder is characterized by impaired adrenal and gonadal steroidogenesis, leading to life-threatening adrenal insufficiency and disorders of sex development. Timely diagnosis and glucocorticoid/mineralocorticoid replacement therapy are essential to prevent morbidity and mortality.

What this study adds?

This case series provides detailed clinical, biochemical, radiological, and genetic data from five pediatric patients with genetically-confirmed, classical LCAH followed at a single tertiary care center. It describes the presence of three distinct homozygous pathogenic variants in the *STAR* gene (c.505G>A, c.33del, and c.288G>T), expanding the genotypic spectrum observed in LCAH. The case series illustrates that in LCAH, despite the severity of the condition, early recognition and appropriate hormone replacement therapy can result in favorable clinical outcomes, including survival without morbidity. These cases also reiterate the importance of multidisciplinary care and individualized management, particularly in patients with disorders of sex development.

Introduction

Lipoid congenital adrenal hyperplasia (LCAH, OMIM #201710) is the most severe and rarest form of congenital adrenal hyperplasia (CAH), characterized by impaired synthesis of all adrenal and gonadal steroid hormones (1,2). The most common cause is mutations in the gene encoding the steroidogenic acute regulatory (STAR) protein, which plays a critical role in intracellular cholesterol transport for steroid hormone synthesis.

In classical LCAH, patients typically present with severe adrenal insufficiency within the first few months of life, although symptoms may occasionally appear in later infancy. Common presenting features include vomiting, diarrhea, hyponatremia, hyperkalemia, metabolic acidosis, and hypoglycemia. If left untreated, the condition can be fatal. However, survival into adulthood is possible with early and appropriate mineralocorticoid and glucocorticoid replacement therapy (3,4,5).

Affected 46,XY individuals generally present with female external genitalia due to impaired testicular androgen production (6,7,8). In contrast, 46,XX individuals are born with normal female genitalia and may occasionally experience spontaneous pubertal development. Unlike the adrenal and testicular steroidogenic tissues, the fetal ovary lacks significant steroidogenic enzyme activity and remains unstimulated until puberty. As a result, cholesterol esters do not accumulate during infancy, and ovarian damage is initially avoided (8,9). Consequently, affected 46,XX females may develop secondary sexual characteristics and experience menstrual bleeding. However, over time, progressive accumulation of cholesterol esters in the ovaries leads to the loss of follicular steroidogenic capacity, resulting in anovulatory cycles due to insufficient progesterone synthesis. Eventually, patients develop progressive hypergonadotropic hypogonadism in adolescence or adulthood (10,11).

Defects in either *steroidogenic acute regulatory protein* (*STAR*) or *CYP11A1* (which encodes P450scc) disrupt the initial steps of steroidogenesis, leading to the clinical picture of LCAH (7). Steroid biosynthesis begins with cellular uptake of low-density lipoprotein-derived cholesterol (8,10,12). STAR mediates cholesterol transport into the mitochondria, where it is converted into pregnenolone by the P450scc enzyme (2,6,8,10,12,13). The pathophysiology of LCAH has been explained by a “two-hit” model. The first hit involves impaired cholesterol transport due to STAR mutations. The second hit results from progressive cellular damage caused by the accumulation of cholesterol esters and toxic cholesterol oxidation products within lipid droplets (6,8,13). Decreased cortisol production weakens negative feedback inhibition on the pituitary gland, leading to increased adrenocorticotropic hormone (ACTH) secretion. Elevated ACTH levels contribute to hyperpigmentation and adrenal cortical hyperplasia (14).

The human *STAR* gene is located on chromosome 8p11.2 and consists of seven exons (15,16). Most mutations that cause classical LCAH are located in the C-terminal region, between exons 5 and 7, which encodes the STAR-associated lipid transfer domain. These mutations usually result in no measurable STAR activity and are found in either homozygous or compound heterozygous states involving mutations with similarly reduced function (8). To date, more than 40 pathogenic STAR mutations associated with classical LCAH have been described (8,12,17,18). Although STAR mutations have been identified in diverse ethnic groups, they are more prevalent in Japan, Korea, and certain isolated populations. In Korea and Japan, the most common variant protein is p.Gln258X, accounting for 92.3% and 70% of cases, respectively. The p.Leu260Pro mutation is prevalent in Switzerland, p.Arg182His in Eastern Saudi Arabia, and p.Arg182Leu among Palestinian Arabs (7,8,19,20).

Mutations in *CYP11A1* can also result in a clinical phenotype similar to that of STAR mutations, due to P450scc enzyme deficiency, although adrenal hyperplasia is typically absent in these cases. While adrenal enlargement is a hallmark of classical LCAH, small adrenals have also been reported and are not pathognomonic (18,21).

A milder form of LCAH, referred to as non-classical or atypical LCAH, is associated with STAR mutations that partially preserve protein function (10,22). In such cases, mineralocorticoid secretion is less severely affected, resulting in a milder adrenal insufficiency that manifests later in life. Individuals with a 46, XY karyotype may present with mild disorders of sex development, such as hypospadias and/or micropenis, or even with entirely normal male external genitalia (7,22,23,24,25). Adrenal hyperplasia is typically absent in these patients (22,23).

Early diagnosis, appropriate hormone replacement therapy, close monitoring of sex development, and genetic counseling for the family are essential components of the management of this disorder. This case series presents our experience in the diagnosis, management, and follow-up of five patients with LCAH caused by mutations in the *STAR* gene.

Methods

This retrospective, single-center case series included five patients who were diagnosed with LCAH and followed at the Pediatric Endocrinology Department of Akdeniz University Faculty of Medicine Hospital between January 2020 and May 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (approval no: KAEK-629, date: 31.07.2025). Written informed consent was obtained from the parents of all participants.

Clinical and laboratory data were retrieved retrospectively through a review of the hospital's electronic medical records system. The collected data included demographic information, presenting symptoms, physical examination findings, hormonal profiles, adrenal imaging results, and genetic analyses.

Laboratory parameters assessed in the study included serum electrolytes, bicarbonate, glucose, blood gas pH, serum cortisol, ACTH, aldosterone, plasma renin activity (PRA), 17-OHP, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), estradiol (E2), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4).

Chromosomal analysis and pathogenic variants of the *STAR* gene were investigated using DNA extracted from peripheral blood samples. Genetic testing was performed using a multi-gene panel targeting exon regions, and analyzed via next-generation sequencing. Variant analysis was conducted using Seq Analysis software (version 15.p; JSI Medical Systems, Ettenheim, Germany) and the Ensembl annotation database (26). The pathogenicity of the variants was evaluated according to the guidelines of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) (27).

In addition, imaging findings obtained from pelvic ultrasonography (USG) and magnetic resonance imaging (MRI), performed to assess internal genital structures and adrenal morphology, were also included in the study.

Case Reports

Case 1

A 49-day-old infant presented with vomiting, diarrhea, and difficulty in feeding. Blood pressure was low and tachycardia was present (Table 1). System examinations were normal, external genitalia were phenotypically female with separate urethral and vaginal openings. Birth and family histories are given in Table 2. Laboratory tests revealed hyponatremia (Na 125 mEq/L), hypochloremia (Cl 84 mEq/L), hyperkalemia (K 6.5 mEq/L), and hypoglycemia (38 mg/dL). Complete blood count, renal and liver function tests, infection parameters, and urinalysis were within normal limits. ACTH levels and PRA were markedly elevated. Serum cortisol levels were low, while 17-OHP levels were within the normal range. Hormonal values at admission are summarized in Table 3. The patient was admitted to the intensive care unit with a preliminary diagnosis of primary adrenal insufficiency. Treatment included intravenous dextrose bolus, supraphysiological doses of hydrocortisone (100 mg/m²/day), sodium-rich intravenous fluid replacement, and fludrocortisone. USG revealed absence of uterus and ovaries, with a hyperplastic appearance of the adrenal glands (Table 2). Pelvic MRI showed no Müllerian structures or gonads. Chromosomal and fluorescence in situ hybridization (FISH) analysis revealed a 46,XY SRY (+) normal male karyotype. Genetic analysis identified a homozygous pathogenic variant *c.288G>T* (p.Trp96Cys) in the *STAR* gene (Table 1).Multidisciplinary council evaluation led to cystoscopy and vaginoscopy, showing a normal urethra and a vaginal length of 3 cm but the cervix was not visualized. Diagnostic laparoscopy revealed absence of uterus and fallopian tubes, with bilateral vas deferens, epididymis, and testes present. Bilateral gonadal biopsy was consistent with immature testicular tissue. A diagnosis of classic LCAH was established. At the last follow-up at 3.5 years old, the patient's height was 94.1 cm [-1.2 standard devitaion score (SDS)], weight 14 kg (-0.6 SDS), and body mass index (BMI) 15.8 kg/m² (0.26 SDS). The patient remains on hydrocortisone (10 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment with stable clinical status and normal electrolytes. Psychological follow-up is ongoing, and the patient continues to be raised as female. Future multidisciplinary assessments are planned.

Table 1. Genetic and clinical characteristics of five patients with lipoid congenital adrenal hyperplasia

	Case 1	Case 2	Case 3	Case 4	Case 5
City of origin	Silopi/Şırnak/ Türkiye	Yüreğir/Adana/ Türkiye	Elmalı/Antalya/ Türkiye	Yüreğir/Adana/Türkiye	Elmalı/Antalya/ Türkiye
Karyotype	46,XY	46,XX	46,XX	46,XX	46,XY
STAR gene variant	c.288G>T (p.Trp96Cys) homozygous pathological variant	c.505G>A (p.GLu169Lys) homozygous pathological variant	c.33 del (p.Ser12Alafs*9) homozygous pathological variant	c.505G>A (p.GLu169Lys) homozygous pathological variant	c.33 del (p.Ser12Alafs*9) homozygous pathological variant
Age of onset (days)	49	7	60	10	180
Vital signs					
Blood pressure (mmHg)	50/28	35/20	55/34	40/25	50/30
Heart rate (per minute)	162	184	168	190	162
Respiratory rate (per minute)	38	44	40	68	30
Oxygen saturation (%)	99	98	98	85	100
Temperature (C°)	36.5	36.6	38.6	38.2	36.6
Clinical findings	Inadequate oral intake, vomiting, diarrhea	Skin hyperpigmentation, inadequate oral intake, vomiting, icterus	Skin hyperpigmentation, inadequate oral intake, vomiting	Inadequate oral intake, vomiting, dyspnea, tachypnea	Skin hyperpigmentation, inadequate oral intake, vomiting, coma
Genital examination EGS	Normal female EGS: 0	Female genitalia, mild posterior labial synechia EGS: 1.5	Normal female EGS: 0	Normal female EGS: 0	Female genitalia, bilateral inguinal palpable gonads EGS: 1

STAR: steroidogenic acute regulatory; EGS: external genitalia scores

Table 2. Perinatal history, family background, ımaging findings, and treatment characteristics in patients with lipoid congenital adrenal hyperplasia

	Case 1	Case 2	Case 3	Case 4	Case 5
Perinatal history					
Birth weight (g, percentile)	3750 (85th)	3000 (40th)	2800 (45th)	3050 (25th)	3530 (45th)
Birth length (cm, percentile)	51 (75th)	49 (50th)	49 (65th)	50 (50th)	51 (50th)
Head circumference (cm, percentile)	36 (85th)	34 (40th)	34 (60th)	35 (60th)	35 (45th)
Gestational age (w)	38	38	37	40	41
Mode of delivery	NSVY	C/S	C/S	NSVY	NSVY
Newborn CAH screening (Heel prick)	Normal	Normal	Normal	Normal	Normal
Family history					
Parental consanguinity	No	No	No	Second-degree cousins	Second-degree cousins
CAH/SIDS/DSD	None	+/−/−	None	+/−/−	None
Adrenal imaging	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia
Maintenance treatment	Hydrocortisone (10 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (10 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (8 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (8 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (12 mg/m^2/d), fludrocortisone (0.2 mg/d)

CAH: congenital adrenal hyperplasia; SIDS: sudden infant death syndrome; DSD: disorders of sex development; g: gram; cm: centimeters; w: weeks; d: day; NSVY: normal spontaneous vaginal delivery; C/S: Cesarean section; mg: milligram; m2: square meters; +: present; −: absent

Table 3. Biochemical results and hormonal profiles of patients with lipoid congenital adrenal hyperplasia at ınitial presentation

Laboratory test results	Case 1	Case 2	Case 3	Case 4	Case 5	Reference range
Serum Sodium (mmol/L)	125	126	126	124	95	135-145
Serum Potassium (mmol/L)	6.5	7.0	8.0	7.8	7.2	3.5-5.1
Serum Cloride (mmol/L)	84	88	90	85	68	98-107
Serum Glucose (mg/dL)	38	70	82	76	45	60-100
Hormones						
ACTH (ng/L)	1588	>2000	>2000	>2000	>2000	7.2-63.3
Cortisol (ug/dL)	0.31	0.63	1.0	0.89	0.63	Newborn: 2.0-11 Infant: 2.8-23
PRA (ng/mL/h)	11	18.7	10.9	10.7	7.7	0.1-6.5
17-OHP (ng/mL)	0.1	0.23	0.13	0.80	0.17	0.10-1.78
Aldosterone (ng/dL)	4.2	11.9	6.5	13.1	6.7	7-30
Testosterone (ng/dL)	<0.03	<0.03	<0.03	<0.03	<0.03	0.14-0.76
Androstenedione (ng/mL)	<0.02	1.25	0.26	0.30	<0.02	0.3-3.2
DHEA-S (ug/dL)	<0.2	1.1	5.28	4.83	<0.2	31.6-431
TSH (mIU/L)	2.43	3.70	3.22	2.85	3.64	0.72-11
fT3 (ng/L)	3.42	3.45	3.82	2.96	3.52	1.95-6.04
fT4 (ng/dL)	1.66	1.21	1.53	1.18	1.34	0.89-2.2
LH (IU/liter)	1.25	1.34	1.94	1.26	1.17	
FSH (IU/liter)	9.2	9.5	7.87	6.83	4.27	
Estradiol	<5	<5	<5	<5	<5	

ACTH: adrenocorticotropic hormone; PRA: plasma renin activity; 17-OHP: 17-hydroxyprogesterone; DHEA-S: dehydroepiandrosterones sulfate; TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine.

Case 2

A 7-day-old neonate presented with pathological jaundice, vomiting, and difficulty in feeding. Systemic examinations were normal. The external genitalia were phenotypically female. The patient had significant hyperpigmentation compared to family members. Scleral icterus was evident. Blood pressure was low and tachycardia was noted, with other vital signs within normal limits for age (Table 1). Birth and family histories are given in Table 2. Phototherapy was planned and the patient was admitted to the neonatal intensive care unit. Laboratory tests revealed hyponatremia (Na 126 mEq/L) and hyperkalemia (K 7 mEq/L). Complete blood count, renal and liver function tests, infection parameters, and urinalysis were normal. Both ACTH and PRA were elevated, while serum cortisol was low and 17-OHP was normal. Additional hormone levels are listed in Table 3. Treatment included supraphysiological doses of hydrocortisone, sodium-rich intravenous fluid replacement, and fludrocortisone. USG showed uterus and bilateral ovaries, with bilateral adrenal hyperplasia (Table 2). Chromosomal analysis revealed a 46,XX normal female karyotype. Genetic testing identified a homozygous pathogenic variant *c.505G>A* (p.Glu169Lys) in the *STAR* gene, confirming classic LCAH diagnosis (Table 1). Under hydrocortisone (10 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment, the patient's skin hyperpigmentation significantly decreased. Clinical condition remained stable with regular follow-up.

Case 3

A 2-month-old infant presented to an external center with vomiting and difficulty in feeding and was hospitalized with a preliminary diagnosis of gastroenteritis. The patient appeared severely dehydrated, characterized by dry mucous membranes, prolonged capillary refill time (4 seconds), and decreased skin turgor due to fluid loss. External genitalia were phenotypically female with double openings and mild posterior labial synechia. The patient exhibited significant hyperpigmentation compared to family members. Birth and family histories are given in Table 2. Due to clinical deterioration and resistant hyponatremia (126 mEq/L) and hyperkalemia (8.0 mEq/L), the patient was referred to our center for further evaluation and treatment. Leukocytosis (26,320/mm³) and elevated C-reactive protein (48 mg/L, normal: 0-5) were present. Laboratory results showed ACTH and PRA elevated, low cortisol and normal 17-OHP levels. Additional hormonal values are shown in Table 3. On admission to the intensive care unit, the patient presented with hypotension, tachycardia, and fever, while other vital signs were within normal

limits for age (Table 1). Treatment included supraphysiological doses of hydrocortisone, sodium-rich intravenous fluid replacement, fludrocortisone, and antibiotic therapy (ampicillin and cefotaxime). USG revealed uterus and bilateral ovaries with bilateral adrenal hyperplasia (Table 2). Chromosomal analysis was 46,XX female karyotype. Genetic testing identified a homozygous pathogenic *c.33 deletion* (p.Ser12Alafs*9) variant in the *STAR* gene, confirming LCAH diagnosis (Table 1). The patient continued hydrocortisone (8 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment. Clinical status remained stable with regular follow-up.

Case 4

A 10-day-old neonate presented to the emergency department with fever, tachypnea, dyspnea, desaturation, vomiting, and difficulty in feeding. On physical examination, the patient demonstrated significant intercostal retractions, with rales and rhonchi audible on auscultation. The external genitalia were phenotypically female (Table 1). Birth and family histories are given in Table 2. The patient was admitted to neonatal intensive care with a diagnosis of congenital pneumonia. Hyponatremia (Na 124 mEq/L) and hyperkalemia (K 7.8 mEq/L) were detected. Leukocytosis (24,000/mm³) and elevated C-reactive protein (29 mg/dL, normal: 0-5) were present. Other laboratory results showed ACTH and PRA elevated, low cortisol and normal 17-OHP levels. Additional hormonal values are given in Table 3. Chest X-ray showed bilateral pneumonic infiltrates. The patient developed respiratory failure with severe acidosis on blood gas analysis and received intravenous antibiotics (ampicillin and cefotaxime) and five days of non-invasive mechanical ventilation. Treatment with supraphysiological hydrocortisone, sodium-rich intravenous fluids, and fludrocortisone was started (Table 2). After two weeks of neonatal intensive care, acute phase reactants and electrolyte imbalances improved and the patient was discharged. USG showed uterus and bilateral ovaries, and adrenal glands appeared bilaterally hyperplastic. Chromosomal analysis revealed a 46,XX normal female karyotype. Genetic testing showed a homozygous pathogenic *c.505G>A* (p.Glu169Lys) variant in *STAR* gene, confirming LCAH diagnosis (Table 1). The patient's parents of this case were second degree cousins and were related to the father of Case 2. Segregation analysis revealed heterozygous variants in both parents. The patient is on hydrocortisone (8 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment with normal growth and development at last follow-up at age 5 years. Height was 100.2 cm (0.13 SDS), weight 19 kg (0.16 SDS), BMI 15.6 (0.15 SDS). The patient is actively participating in ballet and regular swimming exercises.

Case 5

A 6-month-old infant was referred to our center with difficulty in feeding, vomiting, and coma. Blood pressure was low and tachycardia was present, while other vital signs were within age-appropriate limits (Table 1). Systemic examinations were unremarkable. The external genitalia were phenotypically female, with palpable bilateral inguinal gonads, presence of two urogenital openings, and skin hyperpigmentation. Birth and family histories are given in Table 2. Laboratory tests showed severe hyponatremia (Na 95 mEq/L), hyperkalemia (K 7.2 mEq/L), and hypoglycemia (45 mg/dL). Complete blood count, renal and hepatic function tests, infection markers, and urinalysis were all within normal limits. Laboratory testing revealed markedly elevated ACTH and PRA levels. Serum cortisol was decreased, while 17-OHP levels remained within the normal range. Hormonal values on admission are summarized in Table 3. Treatment included intravenous dextrose bolus, supraphysiological hydrocortisone, sodium-rich intravenous fluids, and fludrocortisone. USG did not reveal uterus or ovaries, however bilateral inguinal masses consistent with testes were identified. Adrenal MRI showed bilateral adrenal lipoid infiltration and hyperplasia (Table 2). Chromosomal/FISH analysis confirmed 46,XY SRY(+) normal male karyotype. Next-generation sequencing identified a homozygous pathogenic *c.33 deletion* (p.Ser12Alafs*9) variant in the *STAR* gene (Table 1). Classic LCAH diagnosis was made.The patient continued mineralocorticoid and glucocorticoid replacement therapy. Segregation analysis revealed heterozygous variants in both parents. The parents of this case and Case 3 originate from the same district, suggesting a possible founder effect. Vaginoscopy and cystoscopy revealed intact anatomical structures. Diagnostic laparoscopy showed absence of uterus and ovaries. Bilateral inguinal gonads were visualized and biopsy confirmed immature testicular tissue. No significant hormonal response was observed on human chorionic gonadotropin (hCG) stimulation test. The multidisciplinary council decision, based on psychological evaluation and family preference, was to raise the patient as female. Bilateral gonadectomy was performed at 4 years of age. The patient showed no complications during follow-up, with neurodevelopment appropriate for age. At last follow-up at 4.5 years, height was 103.5 cm (-0.55 SDS), weight 17 kg (-0.13 SDS), BMI 15.8 (0.33 SDS). The patient continues hydrocortisone (12 mg/m²/day) and fludrocortisone (0.2 mg/day) treatment and has ongoing psychological monitoring.

Discussion

In this case series, we present the clinical management experience of five pediatric patients diagnosed with LCAH. In order to contribute to the understanding of the natural history of LCAH, the initial presentations, clinical characteristics, diagnostic processes, and treatment courses of these cases are described in detail.

CAH encompasses a group of autosomal recessive disorders characterized by enzymatic defects in steroidogenesis. LCAH represents the most severe form of CAH due to disruption of the initial step of steroid biosynthesis (7). Since all steps of steroidogenesis are affected, accumulation of steroid hormone precursors does not occur. Therefore, as observed in our series, newborn screening results are usually negative (21). Mutations in the *STAR* gene demonstrate a broad clinical spectrum. Consistent with the literature (8,28), all patients in this case series exhibited vomiting and feeding difficulties; one patient presented in a coma, one with jaundice, another with diarrhea, and one with respiratory distress.While some affected infants exhibit immediate signs of mineralocorticoid and glucocorticoid deficiency, others may remain asymptomatic for several months (8,29). In this case series, two patients presented during the neonatal period, whereas the remaining three were admitted with manifestations of adrenal crisis in early infancy. The latest presenting case (Case 5) survived without hormone replacement therapy until six months of age. Similarly, Bose et al. (8) reported a patient remaining asymptomatic up to six months without hormonal intervention. The ability of some LCAH patients to survive for several months without treatment is attributed to the persistence of normal placental steroidogenesis (8). Severe electrolyte disturbances, including hyponatremia, hypochloremia, and hyperkalemia, are commonly observed in patients with classic LCAH, as demonstrated in our series. Signs of adrenal insufficiency, such as hypoglycemia and hypotension, may also be evident (8,28). In this case series, all patients were hypotensive at initial presentation, with two exhibiting hypoglycemia. In non-classic LCAH cases, salt loss is either delayed in onset or minimal to absent (22).

Review of the literature reveals that patients with LCAH, exhibit elevated plasma ACTH and renin levels, similar to our case series, whereas serum cortisol and testosterone levels are variable (1,8). Due to high intrauterine ACTH exposure, hyperpigmentation is an expected finding, though it is not present in all cases (8). Zheng et al. (30) reported hyperpigmentation in 28 of 30 classic LCAH patients. Likewise, the study of Bose et al. (8) which included 15 LCAH cases from 10 countries, documented hyperpigmentation in 13 patients. In contrast, only three patients in our series exhibited notable skin hyperpigmentation compared to their parents. This variation may be attributable to inter-individual differences in melanocyte number and structure, as well as genetic and structural factors.

As expected in classic LCAH, two of our patients with male karyotypes presented with fully female external genitalia. On physical examination, additional findings included mild posterior labial synechia in Case 1 and palpable bilateral inguinal gonads in Case 5. However, in non-classic LCAH patients with a 46,XY karyotype, external genitalia may be completely male-typical or mildly affected (22).

While most LCAH cases are caused by variants in the *STAR* gene, mutations in the *CYP11A1* gene are a much rarer cause (12,31,32). The incidence of this disorder is low, with only approximately 200 cases harboring *STAR* gene variants reported worldwide (33). The *STAR* gene variants identified in our patients have been previously reported as pathogenic in association with LCAH, and all cases were classified as classic LCAH.

The homozygous pathogenic variant *c.288G>T* (p.Trp96Cys) found in Case 1 has also been described in a Portuguese infant presenting with adrenal crisis at two months, normal female genitalia, and a 46,XY karyotype (34). The *c.505G>A* (p.Glu169Lys) variant identified in Cases 2 and 4 has been clearly associated with LCAH in the study by Yüksel et al. (35). The homozygous *c.33 deletion* (p.Ser12Alafs*9) observed in Cases 3 and 5 was included among LCAH-related variants in a national study reporting rare primary adrenal insufficiency cases by Guran et al. (36).

In 46,XY patients harboring pathogenic STAR variants, impaired fetal testicular steroidogenesis results in normal female external genitalia (8). Since Müllerian structures are absent on pelvic imaging, the diagnosis in 46,XY individuals is more likely (1). Consistent with this, pelvic USG performed in Cases 1 and 5 at presentation did not reveal Müllerian structures. Therefore, even prior to genetic results, *STAR* gene mutation, *CYP11A1* mutation, and P450 oxidoreductase deficiency were considered highly probable differential diagnoses.

All cases exhibited adrenal enlargement on imaging, consistent with classic LCAH. Phadte et al. (6) performed a systematic review of 292 cases with classic and non-classic LCAH and demonstrated significantly more pronounced adrenal hyperplasia in classic LCAH patients, who also presented with earlier and more severe clinical features. Thus, the degree of adrenal hyperplasia may serve as a valuable marker of disease severity (6).

In our case series, all patients presented with adrenal crisis and were initially managed with an intravenous bolus of hydrocortisone (100 mg/m²/day) in combination with sodium-rich intravenous fluid replacement. Maintenance therapy was subsequently initiated. All patients received oral fludrocortisone (100-200 µg/day) along with additional supportive measures when clinically indicated. Similar management strategies for adrenal insufficiency in LCAH have been reported in the literature (28,30).

According to the Diagnosis and Treatment of Primary Adrenal Insufficiency guidelines by Bornstein et al. (37), the recommended initial treatment for pediatric patients presenting with adrenal insufficiency consists of intravenous hydrocortisone at 50-100 mg/m²/day, oral fludrocortisone at 100 µg/day, and sodium-rich intravenous fluids containing dextrose. Consistent with this, the Turkish Neonatal and Pediatric Endocrinology and Diabetes Society's consensus statement also advises hydrocortisone

replacement at 50-100 mg/m²/day for infants presenting with adrenal crisis (38).

Zhang et al. (28) described a patient with LCAH who was started on supraphysiological doses of intravenous hydrocortisone, tapered over three days (200 mg/day, 100 mg/day, and 50 mg/day), followed by maintenance therapy with oral prednisone (28). In our series, maintenance therapy consisted of hydrocortisone at 8-12 mg/m²/day, divided into three doses, in combination with 100-200 µg/day of fludrocortisone.

Similarly, in a report of three Chinese patients with LCAH harboring *STAR* gene variants, supraphysiological doses of intravenous hydrocortisone and sodium-rich intravenous fluids were initially administered, followed by hydrocortisone replacement at 10-14 mg/m²/day (7). Çamtosun and Sangün (39) also recommended maintenance hydrocortisone therapy at 8-12 mg/m²/day, divided into three doses. In a case reported by Bizzarri et al. (1) involving an Italian infant with LCAH, high-dose intravenous hydrocortisone and rehydration were provided until clinical stabilization was achieved, after which maintenance therapy with 16 mg/m²/day of hydrocortisone and 100 µg/day of fludrocortisone was continued.

Conclusion

Patients with classical LCAH typically present in early infancy with symptoms of primary adrenal insufficiency and female external genitalia. Due to the defect occurs at the first step of steroidogenesis, cortisol precursors do not accumulate, making detection by CAH newborn screening programs very unlikely. However, when identified early and treated with appropriate hormone replacement therapy, patients typically achieve favorable outcomes, including no recurrent adrenal crises, appropriate growth, development, and neurodevelopment progression. Genetic counseling for families and comprehensive multidisciplinary monitoring of LCAH patients, especially those with a 46,XY karyotype presenting with disorders of sex development, are essential components in effective disease management.

Ethics

Ethics Committee Approval: This study was approved by the by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (approval no: KAEK-629, date: 31.07.2025).

Informed Consent: Written informed consent was obtained from the parents of all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Kürşat Çetin, Concept: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan, Design: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan, Data Collection or Processing: Kürşat Çetin, Yasemin Funda Bahar, Ali Tırtar, Mesut Parlak, Analysis or Interpretation: Kürşat Çetin, Zeynep Donbaloğlu, Sezin Yakut Uzuner, Hale Tuhan, Literature Search: Kürşat Çetin, Yasemin Funda Bahar, Ali Tırtar, Mesut Parlak, Writing: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan.

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The Relationship between Hemoglobin A1c and the Glucose Management Indicator and Glucose Metrics in Children and Adolescents with Type 1 Diabetes Mellitus Using Automated Insulin Delivery Systems

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ABSTRACT

Objective: Hemoglobin A1c (HbA1c) remains the standard biomarker for long-term glycemic control in type 1 diabetes mellitus (T1D), butis incapable of capturing short-term glucose variability and acute excursions. This limitation is especially relevant in children with T1D who use continuous glucose monitoring systems (CGMS) and automated insulin delivery (AID) systems. The objective of this study was to evaluate the temporal relationship between HbA1c and the glucose management indicator (GMI), and any further associations with CGMS-derived glycemic parameters over a 12 weeks in youth with T1D using AID.

Methods: This retrospective, cross-sectional, observational study, included children and adolescents with T1D using the Medtronic MiniMed 780G™ system. CGMS data covering the 12 weeks prior to HbA1c measurement were analyzed in two-week intervals. Correlations between HbA1c, GMI, and CGMS metrics were assessed.

Results: The study cohort numbered 81; 46 (57%) were female. Median age at T1D diagnosis was 8.1 (interquartile range: 4.3-10.8) years. HbA1c correlated positively with all GMI values, with the strongest correlation observed for the last six-week GMI ($r=0.728$, $p<0.001$). The mean difference between HbA1c and last 12-week GMI was 0.57% (95% confidence interval: -1.13 to 2.27). GMI demonstrated stronger correlations than HbA1c with time in range (TIR), time above range (TAR) and time below range (TBR). Notably, in individuals with similar TIR (~70%), HbA1c values varied widely (6.6-9.6%/48-81 mmol/mol), while GMI remained stable (6.8-7.1%).

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Conclusion: The strongest correlation between HbA1c and the most recent 6-week GMI suggests that HbA1c reflects relatively recent glycemic trends. GMI also showed closer alignment with CGMS-derived indices such as TIR, TAR and TBR, suggesting better sensitivity in capturing day-to-day glycemic variability. We suggest GMI offers a more sensitive and clinically actionable estimate of glycemic control, supporting its integration into routine care for children with T1D using AID.

Keywords: T1D, AID, CGMS, GMI, sampling period

What is already known on this topic?

Hemoglobin A1c (HbA1c) remains the most widely used biomarker for long-term glycemic control, but it does not fully reflect short-term glucose variability or continuous glucose monitoring systems (CGMS)-derived parameters in children with type 1 diabetes mellitus.

What this study adds?

HbA1c showed the strongest correlation with glucose management indicator (GMI) calculated over the last six weeks ($r=0.728$, $p<0.001$), suggesting that HbA1c mainly reflects recent rather than cumulative glycemic trends. GMI demonstrated stronger associations than HbA1c with key CGMS-derived metrics, including time in, above and below range [time in range (TIR), time above range and time below range, respectively]. Compared with HbA1c, GMI values were more stable across similar TIR levels, supporting its reliability for personalized diabetes management. Incorporating GMI alongside CGMS-derived parameters may provide a more accurate and clinically actionable assessment of glycemic control in pediatric automated insulin delivery users.

INTRODUCTION

Type 1 diabetes mellitus (T1D) is the most common chronic autoimmune disorder in childhood, characterized by insulin deficiency and persistent hyperglycemia. Achieving and maintaining optimal glycemic control is crucial to reduce the risk of both acute and long-term complications, particularly microvascular damage (1,2).

Glycosylated hemoglobin A1c (HbA1c) remains the primary indirect measuring method for glycemic control, and its correlation with microvascular complications is well-established (3). Although HbA1c is widely used as a predictor of glucose exposure in the three months preceding sampling, using HbA1c alone not sensitive enough to optimize and personalize treatment decisions. HbA1c cannot capture short-term glucose fluctuations or provide information about glycemic variability, hypoglycemic episodes, or postprandial excursions (3). Moreover, its accuracy may be compromised in individuals with conditions, such as anemia, iron deficiency, or hemoglobinopathies, which are not uncommon in many pediatric populations (4). The increasing use of continuous glucose monitoring systems (CGMS) systems has highlighted these limitations of HbA1c.

CGMS systems assess glucose levels in the interstitial compartment, which closely correlate with plasma glucose, thereby enabling continuous evaluation of glycemic patterns (5,6,7). CGMS provides real-time data on glucose dynamics, including time in range (TIR), time below range (TBR), time above range (TAR), and glycemic variability. In response to these advances, the glucose management indicator (GMI) was introduced to estimate average glucose levels based on CGMS data. GMI is determined using a method that generates a regression line from a plot of mean glucose concentration points on the x-axis and HbA1c values on the y-axis [calculated via the standardized formula: GMI (%)=3.318+0.006094×(mean glucose in mg/dL) or GMI (mmol/mol)=12.71+4.7058×(mean glucose in mmol/L)]. While GMI and HbA1c are intended to represent similar aspects of glycemic control, studies have shown that they often differ substantially, and this discrepancy appears to remain relatively stable for individuals over time (8). Several physiological factors contribute to the divergence between HbA1c and GMI, including interindividual differences in erythrocyte lifespan, rates of glycation, and glucose exposure. The commonly assumed erythrocyte lifespan of 120 days is not universally applicable, and newer evidence suggests that the average age of circulating erythrocytes may be significantly shorter, particularly in individuals with higher mean glucose levels.

Although a 14-day CGMS sampling period is considered sufficient to estimate glycemic patterns in adults, there is limited evidence supporting this recommendation in pediatric populations using advanced technologies such as automated insulin delivery (AID) systems. It remains unclear how well HbA1c reflects mean blood glucose (MBG) over time, and how closely GMI aligns with HbA1c and other CGMS metrics, particularly in children with T1D (9).

In this study, the objective was to examine the relationship between HbA1c and GMI, explore the temporal evolution of this relationship, and assess their associations with CGMS-derived

parameters in children and adolescents with T1D using an AID system. By analyzing biweekly CGMS data over a 12-week period, we sought to clarify the clinical relevance and reliability of these metrics in the context of modern diabetes management.

Methods

In this retrospective cross-sectional observational study, children and adolescents with T1D on Medtronic MiniMed 780G™ were enrolled. A sample size was not calculated because the study was designed to include all children and adolescents with T1D who are monitored in the Department of Pediatric Endocrinology and Diabetes, Ege University Faculty of Medicine and use AID. The data of children and adolescents with T1D who met the inclusion criteria and accepted to participate in the study were retrospectively examined during a six-month study period.

Inclusion criteria were: age between 2 and 18 years (inclusive); diagnosis of T1D for at least one year; at least six months of current use of an AID system with MiniMed 780G™- The Guardian™ Sensor (Medtronic Türkiye, İstanbul, Türkiye) (3). Exclusion criteria were: people with T1D with a diagnosis of concurrent chronic disease, including glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathies such as thalassemia or Sickle cell disease, and/or anemia of any cause.

Data for this study were obtained from a dataset approved by the Ege University Medical Research Ethics Committee (approval no.: 24-9T/38, date: 05.09.2024). This dataset was obtained retrospectively from children and adolescents with T1D using advanced hybrid closed-loop. Another study derived from this dataset discussing the temporal relationship of TIR and time in tight range (TITR) is currently in the process of being published in a journal.

The parents of all people with diabetes and from people with diabetes over 18 years of age provided written informed consent. We confirm that this study complied with the Declaration of Helsinki.

Anthropometric data (height, weight) and HbA1c levels were collected from the files of the people with diabetes. Height was measured to the nearest millimeter with Seca 264® (Seca GmbH & Co. KG, Hamburg, Germany) stadiometer and weight to the nearest 100 grams by an electronic scale (Desis Model KW®, ETS Elektronik Tartı Sistemleri, Tekirdağ, Türkiye). Standard deviation (SD) scores (SDS) for weight, height, and body mass index (BMI) were calculated, based on age and gender (10). Normal weight was defined as BMI-SDS≥-1 to <+1 for children and adolescents and a BMI of 18.5-24.9 kg/m^2 for young adults. HbA1c was measured using a turbidimetric inhibition immunoassay (TINIA, Roche cobas c513, Tina-quant HbA1c Gen.3, Roche Diagnostics Türkiye, İstanbul, Türkiye). This method is traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference system and NGSP-certified. Previous comparative studies have shown excellent agreement between the Roche TINIA method and IFCC-aligned High-Performance Liquid Chromatography (HPLC) systems for the measurement of HbA1c (r>0.98, mean bias <0.2% HbA1c).

Glucose ranges are presented in mg/dL with SI unit equivalents (mmol/L) given in parentheses. CGMS data for the entire study duration from each person with T1D were extracted from CareLink™. TIR 70-180 mg/dL, TAR>180 mg/dL, and TBR<70 mg/dL, mean glucose, mean glucose SD and CV and GMI were defined as per the 2024 international consensus guidance on TIR and other CGMS metrics (11).

Data Analysis

Six CGMS reports for the three months prior to the HbA1c measurement were obtained. For each CGMS report, a minimum sensor wear time of 80% was required. People with T1D who did not have at least five valid reports fulfilling this criterion were excluded from the study. Each report covered two-week intervals, beginning from the date of the HbA1c measurement. The first CGMS report included data from the two weeks leading up to the HbA1c measurement, the second CGMS report covered data from weeks three and four, and the third CGMS report captured data from weeks five and six. We then restructured the data to display a continuous timeline leading up to the HbA1c measurement date defined for study purposes as GMILastTwoWeeks, GMILastFourWeeks, and GMILastSixWeeks that represent the 2-, 4-, and 6-week periods immediately preceding the HbA1c measurement, respectively). A timeline diagram has been included as supplementary material to provide clearer clarification of the definitions.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). The significance level was defined as $p<0.05$. Categorical variables are represented as counts and percentages. Normal distribution of quantitative variables was assessed. Continuous variables with normal or skewed distributions are presented as mean ± SD or median [interquartile range (IQR)], respectively. Group differences were assessed using the independent t-test for normally distributed data and the Mann-Whitney U test for skewed data. We analyzed the differences in repeated measures using the repeated measures ANOVA for normally distributed data and the Friedman test for skewed data. The 12-week data from each sampling period were used to compare the values with the squared value of the Pearson correlation coefficient (R2). We evaluated the concordance between the 12 weeks of CGMS data and each of the six biweekly CGMS reports using Bland-Altman

plots and linear regression. The correlation between TIR values of GMI and HbA1c was assessed using the Williams' t-test for testing the significance of two related correlations. To control for multiple comparisons, p-values were adjusted using the Benjamini-Hochberg false discovery rate correction.

Results

The study included 81 people with diabetes; 46 (57%) were female. There were 12 (14.8%) patients with T1D who used the AID system off-label because they were under 7 years old. The median age at diagnosis was 8.1 years (IQR: 4.3-10.8), the median age at AID initiation was 11.4 years (IQR: 9.3-15.2), and the median age at the time of the study was 13.6 years (IQR: 11.3-17). At the time of AID initiation, median BMI SDS was 0.21 (IQR: -0.37/0.74). All CGMS data, with the exception of TBR, exhibited a normal distribution (Table 1).

To evaluate the reliability of our findings, a post-hoc power analysis was conducted based on the observed effect sizes. This analysis revealed a statistical power of 87% (α=0.05), indicating that the study was sufficiently powered to detect the differences observed and supporting the robustness of our results.

GMI values ($GMI_{Last\ two\ weeks}$, $GMI_{Last\ four\ weeks}$, $GMI_{Last\ six\ weeks}$, $GMI_{Last\ eight\ weeks}$, $GMI_{Last\ ten\ weeks}$, and $GMI_{Last\ twelve\ weeks}$) had a strong correlation with each other, and there was no significant difference between these correlations (p=0.26) (Table 2). HbA1c showed a strong positive correlation with all GMI values. HbA1c and $GMI_{Last\ twelve\ weeks}$/$GMI_{Last\ six\ week}$ measurements were compared using the Bland-Altman statistical method. An average difference of 0.57 units was found between HbA1c and $GMI_{Last\ twelve\ weeks}$ (95% CI: between -1.13 and 2.27, p<0.001), and average difference of 0.51 units was found between HbA1c and $GMI_{Last\ six\ weeks}$ (95% CI: between -0.61 and 1.12, p<0.001). These plots suggest that the discrepancy between these two parameters increases, particularly among individuals with poor glycemic control. A multiple linear regression analysis was performed to identify the factors influencing the difference between HbA1c and GMI values (HbA1c-GMI difference). The model was statistically significant [F(6,70)=6.43, p<0.001], explaining 35.5% of the variance (R^2=0.355, adjusted R^2=0.300). Higher TITR (β=-0.415, p=0.025) was significantly associated with a smaller HbA1c-GMI difference.

The relationship between HbA1c and $GMI_{Last\ two\ weeks}$ showed the weakest association (r=0.595, p<0.001) (Table 2). The strongest association between HbA1c and GMI was observed for the last six weeks value (r=0.728, p<0.001). The correlation of HbA1c with $GMI_{Last\ six\ weeks}$ was significantly stronger than with $GMI_{Last\ two\ weeks}$ (t=3.51; p<0.001) (Figure 1).

Table 3 summarizes the correlations between CGMS data and both HbA1c and GMI. All CGMS parameters, except for CV, showed a correlation with both HbA1c and GMI. In each of these associations, GMI exhibited a stronger correlation coefficient. The correlation between TBR and HbA1C was not significant, but both $GMI_{Last\ two\ weeks}$ and $GMI_{Last\ twelve\ weeks}$ showed a negative correlation with TBR. The correlation coefficients for the last two weeks with HbA1c and GMI indicated a significantly stronger correlation (t=2.81, df=78, p=0.014; 95% CI for r_1-r_2 = 0.05 to 0.29) between TIR and GMI (Figure 2). In cases with a TIR of approximately 70%, HbA1c levels ranged from 6.6% to 9.6%, while GMI values varied from 6.8% to 7.1%. The correlations of $GMI_{Last\ twelve\ weeks}$ with $TIR_{Last\ twelve\ weeks}$ (t=5.20, df=78, p<0.001; 95% CI for r_1-r_2=0.17 to 0.37) and $TAR_{Last\ twelve\ weeks}$ (t=6.00, df=78, p<0.001; 95% CI for r_1-r_2=0.20 to 0.40) were significantly higher than the correlation between $GMI_{Last\ two\ weeks}$ and these parameters. $TBR_{Last\ twelve\ weeks}$ showed a moderate negative correlation with both $GMI_{Last\ two\ weeks}$ (r=-0.415, p=0.007) and $GMI_{Last\ twelve\ weeks}$ (r=-0.5, p<0.001). Furthermore, no significant difference was observed between the strengths of these two correlations (p>0.47) (Table 3).

There were no clinically significant correlations between CV and HbA1c or any GMI measures (r=0.15-0.17, p=0.15-0.22).

Table 1. Summary of CGM data

Number of patients: 81	Mean±SD	Median, IQR
HbA1c, %	7.26±0.67	
$MBG_{Last\ two\ weeks}$, mg/dL	139.2±12.3	
$MBG_{Last\ twelve\ weeks}$, mg/dL	140.0±11.3	
Sensor usege rate, %	90.8±8.3	
$GMI_{Last\ two\ weeks}$, %	6.6±0.29	
$GMI_{Last\ twelve\ weeks}$, %	6.6±0.25	
$TIR_{Last\ two\ weeks}$, %	77.4±7.3	
$TIR_{Last\ twelve\ weeks}$, %	76.8±7.0	
*$TBR_{Last\ two\ weeks}$, %		2 (1-4)
*$TBR_{Last\ twelve\ weeks}$, %		2 (1-4)
$TAR_{Last\ two\ weeks}$, %	17.2±4.7	
$TAR_{Last\ twelve\ weeks}$, %	16.9±5.1	
$CV_{Last\ two\ weeks}$, %	34.5±3.8	
$CV_{Last\ twelve\ weeks}$, %	35.2±4.9	

*: Non-normally distributed parameters are presented as median and IQR.
CGM: continuous glucose monitoring system; SD: standard deviation; IQR: interquartile range; HbA1C: glycosylated hemoglobin; MBG: mean blood glucose; GMI: glucose management indicator; TIR: time in range; TBR: time below range; TAR: time above range; CV: coefficient of variation

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Table 2. Correlation HbA1c and GMIs of different periods

Number of patients: 81	$GMI_{Last\ two\ weeks}$	$GMI_{Last\ four\ weeks}$	$GMI_{Last\ Six\ weeks}$	$GMI_{Last\ eight\ weeks}$	$GMI_{Last\ ten\ weeks}$	$GMI_{Last\ twelve\ weeks}$
HbA1c	r=0.595* **p<0.001***	r=0.697* **p<0.001***	r=0.728* **p<0.001***	r=0.714* **p<0.001***	r=0.718* **p<0.001***	r=0.704* **p<0.001***
$GMI_{Last\ two\ weeks}$	1	r=0.892* **p<0.001***	r=0.890* **p<0.001***	r=0.848* **p<0.001***	r=0.819* **p<0.001***	r=0.776* **p<0.001***
$GMI_{Twelve\ weeks}$	r=0.776* **p<0.001***	r=0.916* **p<0.001***	r=0.949* **p<0.001***	r=0.973* **p<0.001***	r=0.989* **p<0.001***	1

*To control for multiple comparisons, p-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction.
Reinterpreted combined datasets:
- $CGMS_{Last\ two\ weeks}$: 0 → -2 weeks
- $CGMS_{Last\ four\ weeks}$: 0 → -4 weeks
- $CGMS_{Last\ six\ weeks}$: 0 → -6 weeks
- $CGMS_{Last\ eight\ weeks}$: 0 → -8 weeks
- $CGMS_{Last\ ten\ weeks}$: 0 → -10 weeks
- $CGMS_{Last\ twelve\ weeks}$: 0 → -12 weeks
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator

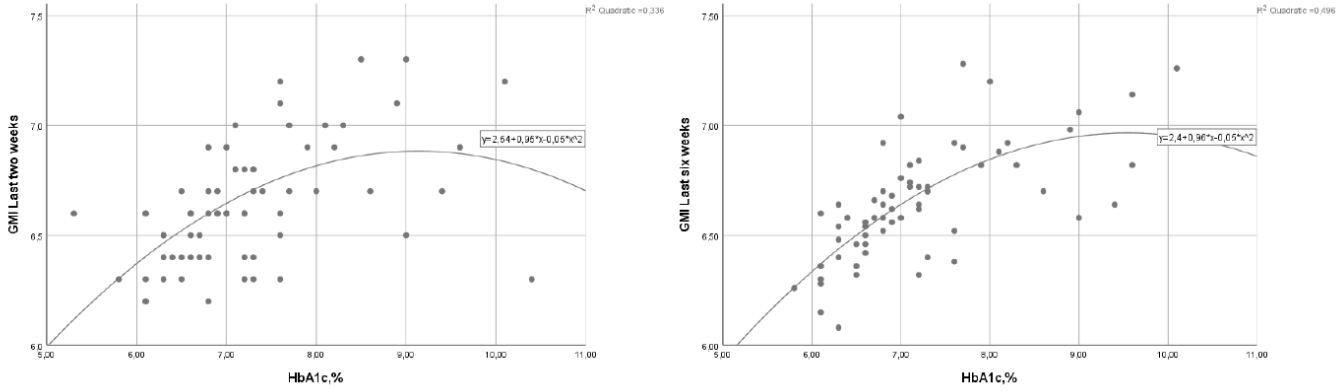

Figure 1. Comparison of HbA1c with GMILast two weeks and GMISix weeks (t=3.51; p<0.001). HbA1c shows a strong correlation with both GMILast two weeks and GMISix weeks. When these two correlations are compared using the method of testing the significance of two related correlations, it is observed that GMISix weeks correlates better with HbA1c (t=2.9, p=0.037)
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator

Table 3. Correlation HbA1c and GMI with other CGM data

Number of patients: 81	$MBG_{Last\ two\ weeks}$	$MBG_{Last\ twelve\ weeks}$	$TIR_{Last\ two\ weeks}$	$TIR_{Last\ twelve\ weeks}$	$TAR_{Last\ two\ weeks}$	$TAR_{Last\ twelve\ weeks}$	$TBR_{Last\ two\ weeks}$	$TBR_{Last\ twelve\ weeks}$	$CV_{Last\ two\ weeks}$	$CV_{Last\ twelve\ weeks}$
HbA1c	r=0.635* **p<0.001***	r=0.721* **p<0.001***	r=-0.583* **p<0.001***	r=-0.558* **p<0.001***	r=0.558* **p<0.001***	r=0.532* **p<0.001***	r=-0.12 p=0.31	r=-0.283* p=0.013	r=0.15 p=0.22	r=0.07 p=0.52
$GMI_{Last\ two\ weeks}$	r=0.993* **p<0.001***	r=0.777* **p<0.001***	r=-0.762* **p<0.001***	r=-0.473* **p<0.001***	r=0.831* **p<0.001***	r=0.605* **p<0.001***	r=-0.533* **p<0.001***	r=-0.415* **p= 0.007***	r=0.168 p=0.18	r=0.028 p=0.8
$GMI_{Last\ Twelve\ weeks}$	r=0.803* **p<0.001***	r=0.987* **p<0.001***	r=-0.647* **p<0.001***	r=-0.749* **p<0.001***	r=0.706* **p<0.001***	r=0.845* **p<0.001***	r=-0.397* **p<0.001***	r=-0.500* **p<0.001***	r=0.173 p=0.15	r=0.194 p=0.11

*To control for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction.
Reinterpreted combined datasets:
- $CGMS_{Last\ two\ weeks}$: 0 → -2 weeks
- $CGMS_{Last\ four\ weeks}$: 0 → -4 weeks
- $CGMS_{Last\ six\ weeks}$: 0 → -6 weeks
- $CGMS_{Last\ eight\ weeks}$: 0 → -8 weeks
- $CGMS_{Last\ ten\ weeks}$: 0 → -10 weeks
- $CGMS_{Last\ twelve\ weeks}$: 0 → -12 weeks
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; CGM: continuous glucose monitoring system; MBG: mean blood glucose; TIR: time in range; TAR: time above range; TBR: time below range; CV: coefficient of variation

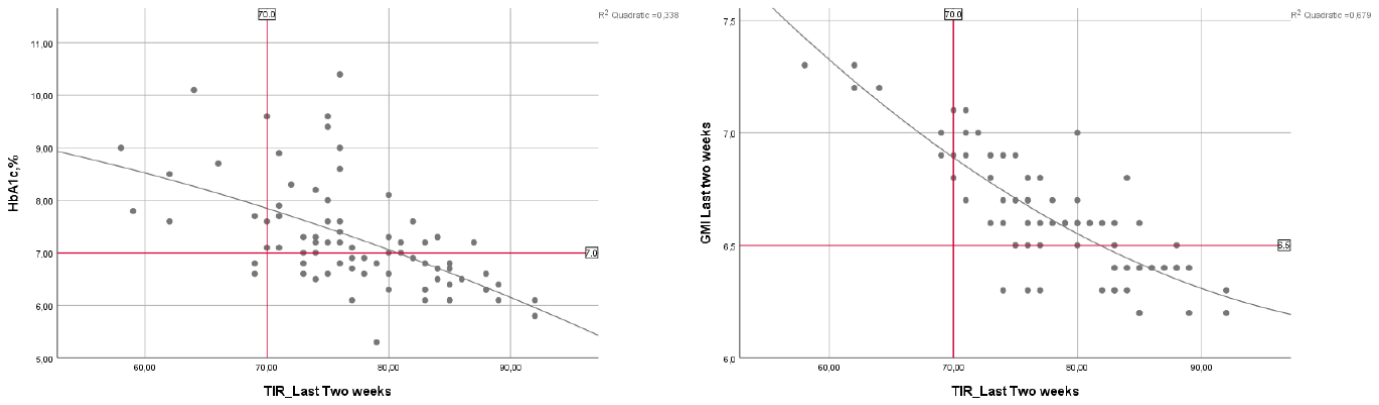

Figure 2. Comparison of TIRLast two weeks with HbA1c and GMILast two weeks (t=2.81; p=0.014). The correlation of TIRLast two weeks with HbA1c and GMILast two weeks were compared. The graph shows that TIRLast two weeks has a better correlation with GMILast two weeks (t=2.81; p=0.014)
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; TIR: time in range

Discussion

This study demonstrated that the last six weeks of GMI correlated well with HbA1c, but the 12-week GMI exhibited a lack of similar consistency with HbA1c. GMI demonstrated a narrower variability than HbA1c and showed stronger correlations with metrics reflecting good glycemic control, such as TIR, TITR, and TBR, emphasizing its value as an indicator of optimal glycemic management.

GMI is determined using a method that generates a regression line from a plot of mean glucose concentration points on the x-axis and HbA1c values on the y-axis. Minimed Medtronic 780G™ continuous insulin infusion system calculates GMI by combining data from two trials that lasted an average of 48 days (with a range of 13 to 89 days) (3,12). The regression equation for calculating GMI (%) is 3.31+0.02392×[mean glucose in mg/dL], or GMI (mmol/mol)=12.71+4.70587×[mean glucose in mmol/L glucose]. In a study where 528 people with diabetes were included, 19% of GMI and HbA1c levels were the same, while 51% diverged by 0.3% or more, and 28% differed by 0.5%(3). In the study by Perlman et al. (13), which predominantly included adults with T1D, the discrepancy between GMI and HbA1c reached ≥0.5% in approximately half of the people with diabetes, and exceeded 1% in nearly 22%. Our data revealed a significant difference of 0.57% between HbA1c and GMI after twelve weeks, confirming the suggestion that HbA1c does not accurately reflect 12-week blood glucose in real-life conditions. Furthermore, while HbA1c exhibited a strong correlation with all GMIs, the magnitude of these correlations varied significantly (t: 3.51; p<0.001). There was a strong correlation between GMIs reflecting different periods, and there was no significant difference between the magnitude of these correlations (Table 2). Therefore, we attributed the difference in correlations between HbA1c and GMI values obtained for different periods to the fact that HbA1c did not reflect the 12-week period as well as other periods. Although numerous studies have examined the correlation between HbA1c and GMI, few have investigated how this relationship changes over time. A recent large cohort study in individuals with T1D evaluated correlations between HbA1c and CGMS data collected over last 4- and 12-week periods, demonstrating strong associations in both time frames, findings consistent with our results (14). However, because the study did not directly compare the strength of the correlations between HbA1c and the last 4- and 12-week CGMS datasets, a potential temporal difference in this relationship may have gone unnoticed. By identifying this difference, our study provides a more nuanced understanding of the time-dependent nature of the HbA1c-GMI relationship.

Several studies have suggested that the difference between GMI and HbA1c varies considerably among individuals and may be influenced by factors such as pubertal stage, the type of CGMS device used, and the mode of insulin therapy (12,13,14,15). Although no consensus has been established regarding what constitutes a clinically meaningful GMI-HbA1c discrepancy, Lenters-Westra et al. (15) recently suggested that differences of 0.8% or greater should be interpreted with caution (15). In our study, we suggest that differences of 0.55% or greater (as presented in Figure 3) should prompt more cautious interpretation of glycemic control.

$GMI_{Last\ \ six\ \ weeks}$ showed the strongest correlation with HbA1c, suggesting that blood glucose significantly influenced circulating red blood cells in the final six weeks. The fact that HbA1c did not consistently reflect the 12-week period lends credence to the hypothesis that GMI reflects temporal changes in average blood glucose better than HbA1c. The literature shows that the

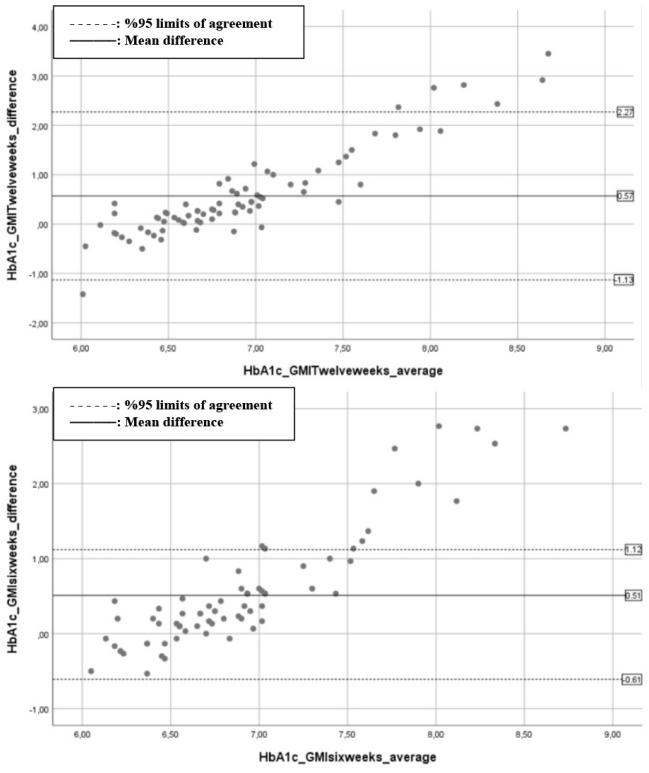

Figure 3. Comparing HbA1c and GMItwelve weeks and GMIsix weeks with the Bland-Altman Plots test. HbA1c and GMItwelve weeks / GMIsix week measurements were compared using the Bland-Altman statistical method. Average difference of 0.57 units was found between HbA1c and GMItwelve weeks (95% CI: between -1.13 and 2.27, p<0.001), and average difference of 0.51 units was found between HbA1c and GMIsix weeks (95% CI: between -0.61 and 1.12, p<0.001). These plots suggest that the discrepancy between these two parameters increases particularly among individuals with poor glycemic control

HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; CI: confidence interval

difference between HbA1c and GMI remains relatively constant for each individual over time, possibly due to the individuals having a different erythrocyte lifespan or erythrocyte glycation rate than the average, making GMI useful in personalized diabetes treatment (3,8,16). Recent research has shown that erythrocyte lifespan varies greatly, even in healthy people (17,18,19). The homogenous erythrocyte survival model, which predicts an erythrocyte lifespan of about 120 days, has led to a misunderstanding of HbA1c. Beltran Del Rio et al. (20) created HbA1c-MBG curves with the probability of maximum erythrocyte lifespan (MEL) in circulation being 90-117 and 140 days. Individuals with higher MBG have a shorter MEL (90 days), whereas those with lower MBG have a longer MEL (140 days). The authors interpreted this as hyperglycemia having a shortening effect on erythrocyte lifetimes, leading to clinically significant variations in HbA1c interpretation. They also suggested that the variability in HbA1c at the same MBG value may be larger than previously reported (19). Cohen et al. (16) found that while the MEL was 117±12 days, the average lifespan of erythrocytes was 80±11 days, much shorter than the widely recognized 120 days. They presented this as evidence that age does not affect the clearing of erythrocytes from circulation. The study found that age-related clearance accounted for only 38±9.6% of erythrocytes from circulation and reached MEL. The average age of circulating erythrocytes was 49±6 days, and the authors estimated the HbA1c half-life to be 25-35 days (16). A lot of people agree that the changing relationship between HbA1c and MBG is due in part to reticulocyte glycation in the bone marrow, the rate at which glucose separates from hemoglobin, and how high blood sugar affects the lifespan of circulating erythrocytes (16,20). In our study, HbA1c had the strongest correlation with $GMI_{\text{Last six weeks}}$, which is consistent with the findings of these two studies. The finding that HbA1c shows the strongest correlation with the last 6-week data will contribute to the interpretation of which time frame for glycemic control HbA1c may best reflect in routine clinical practice. In addition, it will raise the discussion on the clinical value of evaluating 6-week CGM data instead of 2-week CGM data.

Many investigations have demonstrated that, despite a strong association between TIR and HbA1c, a wide range of HbA1c for the same TIR value leads to inaccurate case prediction (21,22). Bosoni et al. (22) observed that a lower TIR maintained the HbA1c ≤7% in a subgroup of patients whereas another subgroup needed a high TIR to achieve the same result. In our study, given identical TIR values, HbA1c had a substantially broader distribution than GMI. We interpret this to show that human factors have less influence on GMI, allowing GMI to predict the TIR within a tighter range. Furthermore, as shown in Figure 3, the widening gap between GMI and HbA1c in individuals with suboptimal glycemic control further illuminates the necessity of personalized diabetes management using CGMS data, particularly GMI, in this population. As demonstrated in the present study, GMI correlates more strongly with TIR, TAR, and TBR than HbA1c, indicating that GMI is superior to HbA1c in measuring glycemic control. Though the use of CGMS technology in children with T1D is increasing, the efficient use of CGMS data remains low (23). This is primarily due to the difficulty in interpreting CGMS data and the lack of standardization (24). To achieve consistency, a recently published international agreement on the use of CGMS proposed that CGMS be sampled for 10 to 14 days, with glycemic control targets of TIR>70%, TAR<25%, and TBR<4% (9,25). Based on research indicating that a longer sampling period does not increase correlation, this guideline recommended a 14-day sampling period. However, it's important to note that these studies primarily involved adults with diabetes with minimal use of insulin infusion pumps. Several studies have found that a 14-day sampling interval might be highly deceptive, especially when monitoring hypoglycemic objectives (26,27,28). In our study,

GMI data from CGMS reports from different sampling periods revealed a significant correlation. However, $TIR_{Last\ twelve\ weeks}$ and $TAR_{Last\ twelve\ week}$ had differing levels of correlation with $GMI_{Last\ two\ weeks}$ and $GMI_{Last\ twelve\ weeks}$, highlighting the need to evaluate the reliability of the 14-day sampling period.

Another area in which CGMS shows a clear advantage over HbA1c is its ability to facilitate remote monitoring through telemedicine, thereby enabling more frequent and responsive evaluation of glycemic control. During the coronavirus disease-2019 pandemic, Kaushal et al. (29) observed significant improvements in mean CGMS glucose and GMI among youth with T1D despite a reduction in face-to-face encounters. In addition, Plachy et al. (30) demonstrated that telemedicine follow-up was non-inferior to traditional in-person visits for maintaining glycemic outcomes, while allowing continuous assessment of CGMS-derived indices such as TIR. Moreover, Ferber et al. (31) reported short-term improvements in TIR and GMI following both telemedicine and on-site consultations, showing the stability of glycemic management when CGMS data are accessible remotely. Collectively, these findings suggest that CGMS metrics, particularly GMI, enable real-time remote evaluation and timely treatment adjustments, an advantage that is inherently absent in HbA1c-based assessment.

Study Limitations

This study has limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Second, all individuals were using the same AID system, and results may not extend to those using other insulin delivery methods. Although HbA1c was measured using the TINIA method rather than HPLC, both assays are IFCC-aligned, and their results are considered interchangeable within clinically acceptable limits. Therefore, potential assay-related bias is unlikely to have affected the main findings.

Conclusion

Our findings further highlight the limitations of HbA1c as a standalone measure of glycemic control in children and adolescents with T1D, particularly those using AID systems. Although HbA1c remains a widely available and used clinical tool, its variability and limited sensitivity to glycemic fluctuations reduce its reliability for personalized diabetes care. In contrast, GMI, derived from CGMS data, demonstrated more stable and consistent associations with key glycemic metrics, including TIR and TITR. GMI was less influenced by physiological variability and more accurately reflected recent glucose exposure, particularly over the six- to twelve-week period.

Incorporating GMI and other CGMS-based metrics into routine clinical assessment may enhance treatment decisions and optimize outcomes, especially in pediatric populations using advanced diabetes technologies. Future guidelines should consider greater emphasis on CGMS-derived measures alongside or in place of HbA1c to support individualized, data-driven management strategies in T1D.

Ethics

Ethics Committee Approval: Data for this study were obtained from a dataset approved by the Ege University Medical Research Ethics Committee (approval no.: 24-9T/38, date: 05.09.2024).

Informed Consent: The parents of all people with diabetes and from people with diabetes over 18 years of age provided written informed consent.

Footnotes

Prior Presentation: This study was presented at the Turkish National Pediatric Endocrinology Congress in May 2024.

Availability of Data and Materials: The datasets generated and analyzed during the current study are not publicly available due to institutional and ethical restrictions but are securely stored on the personal computers of the corresponding author (Damla Gökşen) and co-author (Emrullah Arslan). The de-identified summary dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Authorship Contributions

Surgical and Medical Practices: Emrullah Arslan, Deniz Özalp Kızılay, Damla Gökşen, Concept: Emrullah Arslan, Samim Özen, Şükran Darcan, Damla Gökşen, Design: Emrullah Arslan, Samim Özen, Şükran Darcan, Damla Gökşen, Data Collection or Processing: Emrullah Arslan, Hanife Gül Balkı, Günay Demir, Damla Gökşen, Analysis or Interpretation: Emrullah Arslan, Günay Demir, Samim Özen, Şükran Darcan, Literature Search: Emrullah Arslan, Hanife Gül Balkı, Deniz Özalp Kızılay, Writing: Emrullah Arslan, Damla Gökşen.

Conflict of Interest: Two authors of this article, Samim Özen and Damla Gökşen, are member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, they did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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Once-Weekly Somatrogon in Pediatric Growth Hormone Deficiency: Real-World Efficacy, Safety, and Quality-of-Life Findings

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ABSTRACT

Objective: To report real-world 6- and 12-month outcomes in children with growth hormone deficiency (GHD) treated with somatrogon or somatropin, including those who transitioned from somatropin to somatrogon.

Methods: Eligible patients were categorized into three groups [somatrogon-naïve (naïve), somatrogon-switch (switch), and somatropin only] and were followed for 6 or 12 months. Bioimpedance analysis, as well as a standardized, age-appropriate assessment of the Pediatric Quality of Life Inventory (PedsQL), the Child Behavioural Checklist (CBCL) and the Multidimensional Scale of Perceived Social Support (MSPSS), were conducted at baseline and month 6 in the naïve and switch groups. Psychiatric evaluations were also performed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria.

Results: A total of 58 patients (58.6% male) were included (naïve: n=20; switch: n=18; somatropin: n=20). Mean ages were 11.1±3.0, 9.7±3.4, and 10.5±3.2 years, respectively. After 12 months, mean changes in height standard deviation score (Δheight SDS) were 0.6±0.3, 0.7±0.3, and 0.7±0.4; and height velocities were 10.0±1.9, 9.1±1.7, and 9.8±1.9 cm/year, respectively. Corresponding increases in IGF-1 SDS (ΔIGF-1 SDS) were 2.2±1.2, 0.9±1.2, and 1.3±1.0, respectively. Among the 38 patients receiving somatrogon, 15.8% (n=6; 3 naïve, 3 switch) developed IGF-1 SDS >+2 during follow-up, managed successfully with observation or dose adjustment. No serious adverse events were observed. Bioimpedance analyses demonstrated a favorable but non-significant trend toward improved body composition in somatrogon-naïve children. At six months, PedsQL domains, CBCL scales, and MSPSS scores remained stable (all p>0.05).

Conclusion: Once-weekly somatrogon demonstrated efficacy and safety comparable to daily somatropin with stable quality-of-life and psychosocial outcomes in children with GHD.

Keywords: Children, growth hormone, growth hormone deficiency, long-acting growth hormone

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What is already known on this topic?

Somatropin is the standard treatment for growth hormone deficiency (GHD), but daily injections may reduce adherence and quality-of-life. Somatrogon, a once-weekly long-acting growth hormone analog, has demonstrated non-inferior efficacy and comparable safety to somatropin in clinical trials. Real-world data on somatrogon use in clinical practice, especially in children switching from somatropin, remain limited.

What this study adds?

This real-world study compared somatrogon and somatropin over 6 and 12 months in children with GHD. Somatrogon demonstrated comparable growth outcomes, insulin-like growth factor-1 dynamics, and safety to somatropin. Bioimpedance analyses suggested favorable changes in body composition, quality-of-life scores remained stable, supporting the potential of somatrogon to reduce treatment burden without compromising efficacy or safety.

Introduction

Growth hormone (GH) deficiency (GHD) is characterized by inadequate production or secretion of GH, resulting in decreased height velocity (HV), impaired linear growth, and short stature (1). Beyond its impact on physical development, GHD may adversely affect emotional and social well-being and is associated with metabolic disturbances, including dyslipidemia, insulin resistance, and increased cardiovascular risk (1,2). GH and insulin-like growth factor-1 (IGF-1) also contribute to hematopoiesis, promoting platelet formation and erythropoiesis through stimulation of renal erythropoietin production (3).

Recombinant human GH (rhGH) has been the standard treatment for nearly four decades, effectively improving growth parameters, optimizing adult height, reducing metabolic risk, and enhancing quality-of-life (QoL) (4,5,6). However, conventional rhGH regimens require daily subcutaneous injections, imposing a significant treatment burden (4). A systematic review reported that up to 71% of children demonstrate suboptimal adherence to therapy, potentially compromising treatment outcomes (7). In recent years, long-acting GH (LAGH) preparations have been developed to improve adherence and treatment satisfaction. Several of these formulations have now received regulatory approval (8). Somatrogon, a once-weekly rhGH analog approved for use in children aged three years and older with GHD, has demonstrated efficacy and safety comparable to daily somatropin, with additional benefits in treatment satisfaction and QoL (1,4).

Despite encouraging results from randomized clinical trials, real-world evidence concerning somatrogon use remains limited. Such data are essential to evaluate treatment adherence, effectiveness, and safety in routine clinical settings. Therefore, the primary objective of this study was to present 6- and 12-month real-world outcomes in children with GHD who initiated somatrogon, switched from daily somatropin to somatrogon, or continued somatropin.

Methods

Study Design and Population

This single-center study was conducted at the Clinic of Pediatric Endocrinology, Aydın Adnan Menderes University Faculty of Medicine. The analysis was conducted using a retrospective review of prospectively collected data, allowing consistent follow-up and standardized assessments. Between June 1, 2024, and June 1, 2025, children aged 3-18 years with a confirmed diagnosis of GHD who either newly initiated somatrogon therapy, transitioned from somatropin to somatrogon, or continued somatropin treatment were enrolled. Follow-up evaluations were performed at baseline, 6 months, and 12 months.

Inclusion and Exclusion Criteria

Inclusion criteria: Confirmed GHD diagnosis; chronological age ≥3 years; peak GH ≤10 ng/mL in two stimulation tests (clonidine and L-dopa); bone age (BA) delay ≥2 years in prepubertal children at the initiation of GH therapy or BA ≤ chronological age in pubertal children; normal karyotype in females; annual HV standard deviation score (SDS) <-0.7 SDS at the initiation of GH therapy; and IGF-1 SDS ≤-1 at the initiation of GH therapy.

The peak GH ≤10 ng/mL cut-off was based on the diagnostic criteria applied in routine clinical practice during the study period and is consistent with thresholds used in pivotal phase 3 growth hormone trials (4). Although lower thresholds have been suggested in more recent guidelines, this criterion was maintained to ensure methodological consistency across retrospectively and prospectively included patients.

Exclusion criteria: age <3 or >18 years; chromosomal abnormalities or syndromic conditions (e.g., Turner syndrome, Prader-Willi syndrome, Noonan syndrome, Silver-Russell syndrome, SHOX mutations/deletions, ACAN mutations, skeletal dysplasias); chronic illnesses (e.g., chronic kidney disease, celiac disease); malignancy, radiotherapy, or chemotherapy; history of being born small for gestational age; Body mass index (BMI) <-2 SDS; positive anti-rhGH antibodies; or psychosocial dwarfism.

Group Allocation

Participants were categorized into three groups based on treatment status:

Somatrogon-naïve group: Treatment-naïve patients who initiated once-weekly somatrogon therapy.

Somatrogon-switch group: Patients who transitioned from somatropin to once-weekly somatrogon.

Somatropin group: Patients who continued daily somatropin therapy.

Treatment Protocol

Somatrogon was administered at a dose of 0.66 mg/kg/week on a fixed weekly schedule, whereas the somatropin dose was 0.025-0.035 mg/kg/day. Both treatments were delivered using multidose prefilled pens equipped with 31G, 5 mm disposable pen needles. Missed somatrogon doses were administered within three days or omitted if more than three days had elapsed. Doses were adjusted based on body weight and IGF-1 SDS targeting levels between -2 to +2 (ideally near 0). In cases of persistently elevated IGF-1 >+2 SDS, the dose was reduced by 15% and reassessed after 4-8 weeks.

Follow-up and Assessments

At each visit, vital signs, auxological parameters (height, weight, BMI, HV cm/year, HV SDS), pubertal staging according to Tanner criteria (9,10), adverse events, and laboratory results were recorded. Laboratory evaluations included complete blood count, liver and kidney function tests, electrolytes, hemoglobin A1c (HbA1c), fasting glucose, insulin, C-peptide, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, free thyroxine, thyroid-stimulating hormone, cortisol, calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, IGF-1, and IGF binding protein-3 (IGFBP3).

Height was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, UK) and weight with a calibrated digital scale. SDS values for height, weight, BMI, and HV were calculated based on national reference data using the Child Metrics system (www.ceddcozum.com) (11,12).

Bone age was assessed at baseline, 6, and 12 months using the Greulich and Pyle digital atlas (13) by a single experienced pediatric endocrinologist to ensure consistency and minimize interobserver variability, and BA SDS was calculated using the BA software (14).

IGF-1 and IGFBP3 concentrations were measured using a chemiluminescence immunoassay (CLIA) with the IMMULITE 2000 XP Immunoassay System (Siemens Healthineers, Erlangen, Germany; Siemens Healthcare Sağlık A.Ş. İstanbul, Türkiye) IGF-1 SDS values were calculated based on age- and sex-specific reference ranges. In the somatrogon naïve and switch groups, blood sampling for IGF-1 measurement was standardized at 96 hours post-injection. When samples were drawn outside this time window, appropriate time-adjusted corrections were applied during SDS calculation (15).

Bioelectrical impedance analysis (InBody 230, Biospace Co., Seoul, South Korea) was conducted at baseline and at 6 months in the somatrogon naïve and switch groups to assess body composition parameters, including body fat percentage and skeletal muscle mass percentage.

QoL and Psychosocial Measures

Turkish versions of the Pediatric QoL Inventory (PedsQL), the Child Behavior Checklist (CBCL), and the Multidimensional Scale of Perceived Social Support (MSPSS), each supported by original development studies and Turkish validation studies, were administered at baseline and after six months, under the supervision of a child and adolescent psychiatrist (16,17,18,19,20,21). For children aged 3-7, the PedsQL and CBCL were completed by parents, with the PedsQL additionally administered as a structured interviewer-assisted child form in the 5-7 years age-group. For children aged ≥8 years, PedsQL was collected via both child self-report and parent proxy, while CBCL remained parent-reported. MSPSS was self-reported in children aged ≥8 years. The PedsQL items were reverse-coded and linearly transformed (0/1/2/3/4→100/75/50/25/0), with higher scores indicating better QoL. The PedsQL is a tool designed to assess physical, emotional, social, and school functioning in children and adolescents (16,17). The CBCL utilises a structured assessment approach, evaluating a range of syndrome scales and broad-band composites. These include scales such as Anxiety/Depression, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking, and Aggressive Behaviours. Higher CBCL scores are indicative of a greater number of problematic behaviours (18,19). MSPSS provided Family, Friends, Significant Other, and Total scores (20,21). At 0 and 6 months, child and adolescent psychiatrist performed DSM-5-TR clinical evaluations (e.g., ADHD, ASD, intellectual disability, developmental language disorder). These diagnoses informed pre-specified sensitivity analyses (excluding any psychiatric diagnosis) and descriptive subgroup summaries. The somatropin group consisted of patients whose first-year treatment data were included retrospectively as part of the overall comparative evaluation of growth and safety outcomes. QoL and psychosocial questionnaires were not routinely administered during the earlier somatropin treatment period; therefore, retrospective QoL data were not available

for the somatropin group. QoL analyses were conducted prospectively in the naïve and switch groups using within-group paired comparisons (baseline vs. 6 months), and change scores were compared between these two groups.

Ethical Considerations

The study was approved by the Institutional Ethics Committee of Aydın Adnan Menderes University (approval no.: 2025/23, date: 30.01.2025) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from parents or legal guardians and assent was obtained from pediatric participants when appropriate, in accordance with age and national regulations. Where applicable, written informed consent for publication was also obtained.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as frequencies and percentages for categorical variables, and as means with standard deviations for continuous variables with normal distribution. For non-normally distributed continuous variables, data are presented as medians with minimum and maximum values. The normality of continuous variables was assessed using descriptive statistics, Skewness and Kurtosis coefficients, histograms, and the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical variables. For comparisons between two independent groups, the independent samples t-test and Cohen's d were applied when criteria for normality were met, and the Mann-Whitney U test and Cliff's delta were used otherwise. A Type I error rate of 5% was considered acceptable, and $p<0.05$ was regarded as statistically significant.

Results

A total of 58 patients were included: somatrogon-naïve (n=20), somatrogon-switch (n=18), and somatropin (n=20) groups. Age, sex distribution, and pubertal status were comparable among the three groups (Table 1). Significant differences were observed in height SDS, HV, HV SDS, IGF-1 SDS, L-dopa peak GH response, and starting dose. Height SDS, HV, HV SDS, and IGF-1 SDS were

Table 1. Baseline characteristics of the study groups

Characteristic	Somatrogon-naïve (n=20)	Somatrogon-switch (n=18)	Somatropin (n=20)	p value
Age (years)	11.1±3.0	9.7±3.4	10.5±3.2	0.411
Sex (F/M), n (%)	10/10 (50)	5/13 (27.8/72.2)	9/11 (45/55)	0.351
Prepubertal/Pubertal, n (%)	9/11 (45/55)	11/7 (61.1/38.9)	9/11 (45/55)	0.525
Height SDS	-3.0±0.8	-1.8±0.6	-2.7±0.5	<0.001
Weight SDS	-2.0±1.0	-1.4±0.8	-1.6±1.3	0.258
BMI SDS	-0.4±0.9	-0.6±0.9	-0.2±1.2	0.381
Target height SDS	-1.0±0.7	-1.0±0.9	-1.1±1.0	0.952
Bone age (years)	9.0±3.3	7.9±3.5	8.2±3.4	0.606
Bone age SDS	-2.3±1.0	-1.9±0.8	-2.4±1.0	0.214
Height velocity (cm/year)	2.9±1.1	6.9±2.2	2.5±0.8	<0.001
Height velocity SDS	-2.0±0.8	0.5±1.3	-2.4±1.3	<0.001
IGF-1 (ng/mL)	105.9±59.5	151.0±89.2	115.7±73.0	0.159
IGF-1 SDS	-1.9±0.9	-0.9±0.9	-1.8±0.6	<0.001
IGFBP-3 (µg/mL)	4.1±1.6	4.3±1.7	NA	0.845
Clonidine peak GH (ng/mL)	4.2±2.9	5.5±2.2	4.9±3.1	0.380
L-dopa peak GH (ng/mL)	2.6±2.5	5.0±3.0	3.1±1.9	0.010
Pituitary MRI, normal, n (%) **MRI, abnormal, n (%)***	17 (85) 3 (15)	13 (72.2) 5 (27.8)	16 (80) 4 (20)	0.661
Panhypopituitarism, n (%)	0 (0)	0 (0)	1 (5)	1.000
Starting dose	0.66 mg/kg/week	0.66 mg/kg/week	0.030±0.003 mg/kg/day	<0.001

Values are presented as mean ± SD unless otherwise indicated. In the somatrogon-switch group, auxological and IGF-1 data represent values recorded at the time of switching from daily somatropin to once-weekly somatrogon. Growth hormone stimulation test results, including clonidine and L-dopa peak GH responses, represent diagnostic values obtained before initiation of any growth hormone treatment. Starting doses are presented according to the dosing schedule of each treatment: mg/kg/week for somatrogon and mg/kg/day for somatropin.

*Abnormal findings included empty sella (n=4), ectopic posterior pituitary (n=3), stalk interruption (n=2), pituitary hypoplasia (n=2), and adenoma (n=1).

F, female; M, male; n (%), number (percentage); SDS, standard deviation score; BMI, body mass index; IGF-1, insulin-like growth factor-1; ng/mL, nanogram per milliliter; IGFBP-3, Insulin-like growth factor binding protein-3; µg/mL, microgram per milliliter; NA, not available; GH, growth hormone; MRI, magnetic resonance imaging

higher in the somatrogon-switch group, which consisted of patients who had previously received daily somatropin treatment before switching to once-weekly somatrogon. Therefore, baseline auxological and IGF-1 data in the somatrogon-switch group refer to the time of somatrogon initiation rather than treatment-naïve status. Growth hormone stimulation test results, including clonidine and L-dopa peak GH responses, represent diagnostic values obtained before the initiation of any growth hormone treatment. Mean weight and BMI SDS values were within the expected ranges for children with GHD. Pituitary MRI findings are detailed in Table 1. Most patients (79.3%) had normal pituitary MRI scans, while isolated structural abnormalities, including empty sella, ectopic posterior pituitary, stalk interruption, and pituitary hypoplasia, were observed in a minority of cases. The mean starting dose was 0.66 mg/kg/week for somatrogon in both the naïve and switch groups and 0.030±0.003 mg/kg/day for somatropin in the somatropin group. The difference in starting dose reflects the distinct dosing schedules of once-weekly somatrogon and daily somatropin. Baseline demographic, auxological, biochemical, and radiological characteristics of the study groups are presented in Table 1.

Treatment Outcomes at 6 and 12 Months

Changes in height SDS, HV (cm/year) and IGF-1 SDS for all three study groups (somatrogon-naïve, somatrogon-switch, and somatropin) at baseline, week 6, and months 3, 6, 9, and 12 are illustrated in Figures 1, 2, and 3. Based on these data, 6- and 12-month outcomes were analyzed; the primary comparison was performed between the somatrogon-naïve and somatropin groups. As summarized in Table 2, both the somatrogon-naïve and somatropin groups demonstrated comparable improvements in growth parameters at 6 and 12 months. Accordingly, in the paired values presented below, the first value refers to the somatrogon-naïve group and the second value refers to the somatropin group. At 6 months, increases in height SDS (0.4±0.3 vs 0.5±0.3; p=0.25), HV (10.8±2.5 vs 11.3±3.0 cm/year; p=0.61), and IGF-1 SDS (1.9±1.3 vs 1.4±0.9; p=0.16) were similar between

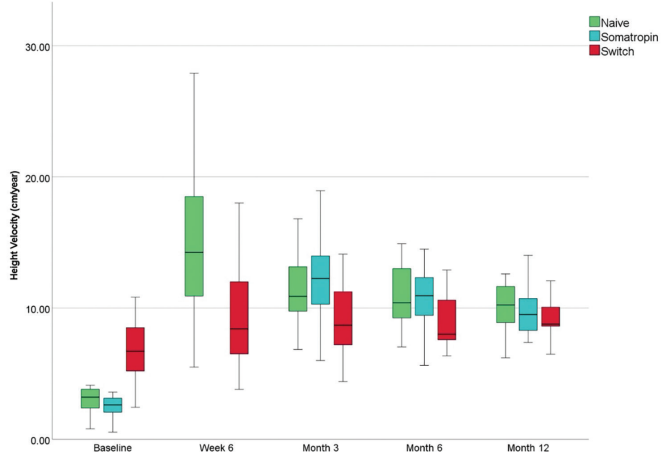

Figure 2. Height velocity (cm/year) at baseline, week 6 and months 3, 6, 9, and 12 in the three study groups. Median values are shown as horizontal lines, and mean values are indicated by diamond symbols naive, treatment-naïve patients who initiated somatrogon; somatropin, patients who continued daily somatropin treatment; switch, patients who transitioned from somatropin to somatrogon

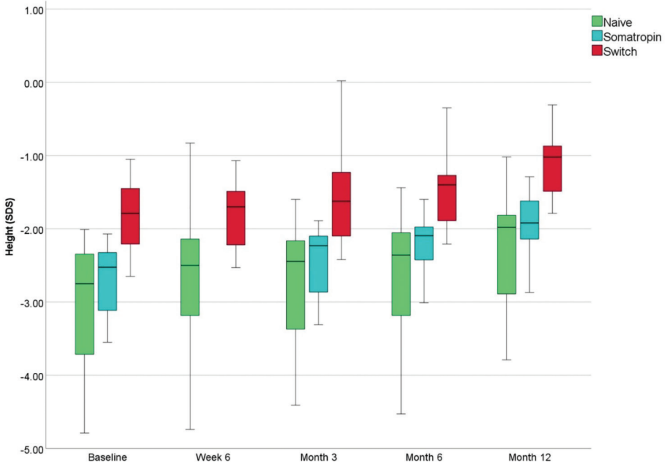

Figure 1. Height SDS at baseline, week 6 and months 3, 6, 9, and 12 in the three study groups. Median values are shown as horizontal lines, and mean values are indicated by diamond symbols

SDS, standard deviation score; naive, treatment-naïve patients who initiated somatrogon; somatropin, patients who continued daily somatropin treatment; switch, patients who transitioned from somatropin to somatrogon

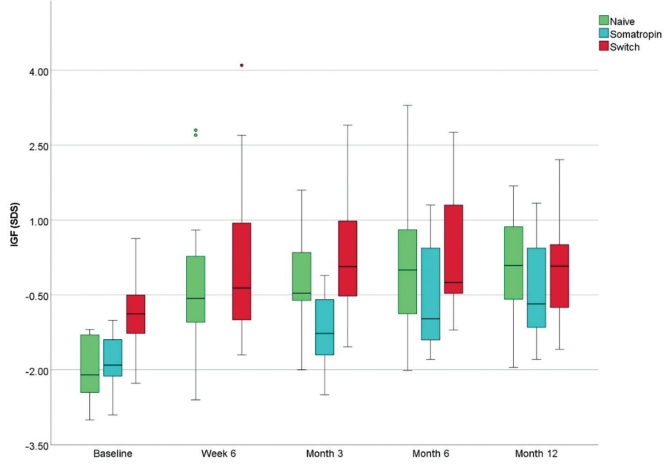

Figure 3. IGF-1 SDS at baseline, week 6 and months 3, 6, 9, and 12 in the three study groups. Median values are shown as horizontal lines, and mean values are indicated by diamond symbols

IGF-1, insulin-like growth factor-1; SDS, standard deviation score; naive, treatment-naïve patients who initiated somatrogon; somatropin, patients who continued daily somatropin treatment; switch, patients who transitioned from somatropin to somatrogon

groups. At 12 months, Δheight SDS (0.6±0.3 vs 0.7±0.4; p=0.78), HV (10.0±1.9 vs 9.8±1.9 cm/year; p=0.73), and ΔBA SDS (0.6±0.5 vs 0.6±0.7; p=0.91) remained comparable, whereas the increase in IGF-1 SDS was significantly greater in the somatrogon-naive group (2.2±1.2 vs 1.3±1.0; p=0.03).

No significant differences were observed between groups regarding BMI SDS, BA SDS, pubertal progression, or safety outcomes. A sensitivity analysis was performed excluding the naïve patient with an IGF-1 SDS value >+2 at year 1. After exclusion, the between-group difference was attenuated and no longer reached conventional statistical significance (p=0.051). However, the mean ΔIGF-1 SDS in the naïve group remained 2.1±1.0, and the effect size remained moderate-to-large (Cohen's d=0.733).

Switch Group Outcomes

In the switch group, treatment outcomes during the first year on daily somatropin were compared with those from the first year after transitioning to once-weekly somatrogon (Table 3). Growth and biochemical responses were comparable across both treatment periods. Mean HV remained unchanged (9.1±2.1 vs 9.1±1.7 cm/year; p=0.45), as did HV SDS (2.0±1.6 vs 2.0±0.9; p=1.00). Changes in height SDS (0.8±0.7 vs 0.6±0.3; p=0.99), IGF-1 SDS (0.9±1.0 vs 0.9±1.2; p=0.53), and BA SDS (0.6±1.5 vs 0.2±0.5; p=0.45) were also similar between phases.

QoL, Emotional-Behavioral, and Social Support

Paired analyses from baseline to 6 months demonstrated no significant change after Holm correction in PedsQL Total or domain scores in either the naïve or switch groups. A trend towards improvement was observed for the PedsQL Psychosocial Health Summary in the naïve subgroup (Δ≈+6.2 points; *p*=0.058), which did not survive multiplicity. The CBCL syndrome scales (anxiety/depression, social withdrawal, somatic, social problems, thought problems, attention, rule-breaking, aggression), and broad-band internalizing/externalizing totals demonstrated no significant change (p>0.05). The MSPSS scores for family/friends/significant other and total also did not change materially from the baseline (p>0.05). Sensitivity analyses that excluded children with any psychiatric diagnosis yielded similar point estimates and inferences, indicating that stable QoL/CBCL/MSPSS findings were not driven by comorbidity. In the naïve group, 85.0% (17/20) had no psychiatric diagnosis; 10.0% (2/20) had ADHD; and 5.0% (1/20) had moderate intellectual disability. Within the switch group, 88.9% (16/18) had not received a diagnosis; 5.6% (1/18) had been diagnosed with ADHD; and 5.6% (1/18) had been diagnosed with developmental language disorder. No significant differences in change scores from baseline to 6 months were observed between the naïve and switch groups.

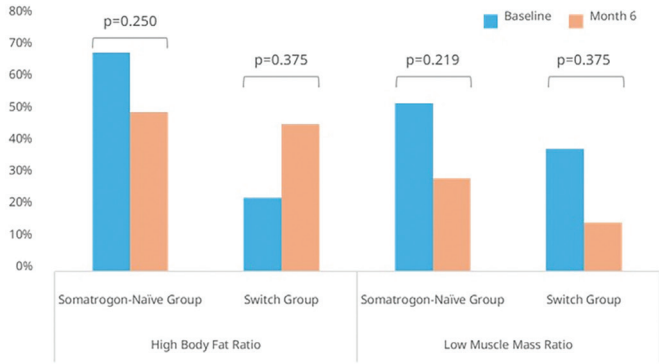

Figure 4. Body composition changes at baseline and month 6 in the somatrogon-naïve and switch groups (p values shown above bars). p<0.05 was considered statistically significant. Somatrogon-naïve, treatment-naïve patients who initiated somatrogon; switch, patients who transitioned from somatropin to somatrogon

Table 2. Comparison of treatment outcomes at 6 and 12 months in the naïve and somatropin groups

Timepoint	Outcome	Naïve	Somatropin	p value	Effect size Cohen's d
6 months	ΔHeight SDS	0.4±0.3 (n=20)	0.5±0.3 (n=20)	0.253	0.367
	HV (cm/year)	10.8±2.5	11.3±3.0	0.614	0.161
	HV SDS	2.8±1.8	2.9±2.3	0.799	0.050*
	ΔIGF-1 SDS	1.9±1.3	1.4±0.9	0.155	0.472
	ΔBA SDS	0.2±0.3	0.2±0.3	0.620	0.092*
12 months	ΔHeight SDS	0.6±0.3 (n=16)	0.7±0.4 (n=19)	0.783	0.094
	HV (cm/year)	10.0±1.9	9.8±1.9	0.728	0.116
	HV SDS	2.4±1.4	2.2±1.5	0.589	0.098*
	ΔIGF-1 SDS	2.2±1.2	1.3±1.0	0.025	0.836
	ΔBA SDS	0.6±0.5	0.6±0.7	0.909	0.108

Values are presented as mean±SD. Δ Indicates change from baseline. p<0.05 was considered statistically significant. *Cliff's delta
n, number; SDS, standard deviation score; HV, height velocity; IGF-1, insulin-like growth factor-1; BA, bone age

Table 3. Switch group outcomes: somatropin first year compared to somatrogon first year

Parameter	Somatropin 1st year	Somatrogon 1st year post-switch	p value	Effect size
HV (cm/year)	9.1±2.1	9.1±1.7	0.453	0.311
HV SDS	2.0±1.6	2.0±0.9	0.995	0.003
ΔHeight SDS	0.8±0.7	0.6±0.3	0.989	0.006
ΔIGF-1 SDS	0.9±1.0	0.9±1.2	0.530	0.043
ΔBA SDS	0.6±1.5	0.2±0.5	0.445	0.317

Values are presented as mean±SD. Δ indicates change from baseline. $p<0.05$ was considered statistically significant
HV, height velocity; SDS, standard deviation score; IGF-1, insulin-like growth factor-1; BA, bone age

Body Composition Outcomes

In the somatrogon-naïve group, bioimpedance analyses demonstrated a favorable but non-significant trend toward improved body composition: the proportion of patients with high body fat decreased from 68.8% to 50% (p=0.25), while those with low muscle mass declined from 52.9% to 29.4% (p=0.22). In the switch group, high body fat was observed in 23.1% of patients at baseline, increasing to 46.2% at month 6 (p=0.38), whereas low muscle mass decreased from 38.5% to 15.4% (p=0.38) (Figure 4).

Safety and Tolerability

Among 38 patients receiving somatrogon, 15.8% (n=6; 3 naïve, 3 switch) developed IGF-1 SDS values >+2 during follow-up. Four cases were detected at week 6; two normalized spontaneously by month 3, while two required sequential 15% dose reductions, achieving normalization by month 12. In two cases, elevated levels were detected at month 12, with spontaneous normalization observed six weeks later. No deaths occurred during the study, and overall treatment adherence was high. One patient in the naïve group discontinued treatment at month 6 due to personal choice. No treatment-related adverse events were reported in the somatropin group (n=20). Among patients treated with somatrogon, treatment-related adverse events were observed in 50% (n=19), most commonly injection-site pain (n=10), followed by lipoatrophy (n=3), injection-site pruritus (n=2), minor bleeding (n=2), localized swelling (n=2), myalgia (n=1), and headache (n=1). All events were mild and transient. Lipoatrophy developed in patients who consistently injected into the same anatomical region, particularly the upper arm. Discontinuing injections at the affected site and rotating to alternative regions (thighs, abdomen, or buttocks) resulted in complete resolution within 3 months. No treatment interruptions or discontinuations were necessary because of adverse events.

Discussion

This single-center study provides real-world evidence on the use of once-weekly somatrogon in children with GHD. Somatrogon demonstrated efficacy comparable to that of daily somatropin, as reflected by similar gains in height SDS and HV at both 6 and 12 months. Biochemical outcomes, including ΔIGF-1 SDS and ΔBA SDS, also showed parallel trends between treatment groups.

Our findings align closely with phase 3 randomized controlled trials demonstrating that once-weekly somatrogon was non-inferior to daily somatropin in efficacy and safety (4,22). Those trials reported comparable improvements in height SDS, HV, ΔIGF-1 SDS, and ΔBA SDS after 12 months, findings mirrored in our real-world cohort. Long-term extension studies have further confirmed the sustained efficacy and safety of somatrogon over five years, supporting its role as a durable therapeutic option (23). Furthermore, in the switch group, growth and biochemical responses observed during the first year of somatrogon therapy were comparable to those achieved in the preceding year of somatropin treatment, highlighting the feasibility, safety, and clinical stability of transitioning patients from daily to once-weekly dosing.

Beyond clinical trials, systematic reviews and meta-analyses have shown that LAGH analogs achieve comparable growth outcomes to daily GH while improving adherence and treatment satisfaction (24,25). Economic modeling from Spain further suggested potential cost-effectiveness through improved compliance and reduced treatment burden (26). Likewise, global surveys of physicians participating in phase 3 trials highlighted high satisfaction with once-weekly somatrogon, particularly due to convenience and reduced injection frequency (27). In our cohort, adherence and satisfaction were uniformly high, with only one patient electing to discontinue therapy at month 6.

Clinical trial data have emphasized the importance of IGF-1 surveillance during somatrogon treatment. Phase II and III studies reported dose-dependent increases in IGF-1 SDS, occasionally exceeding +2 SDS and necessitating dose adjustment, particularly in the Japanese phase III trial, while such elevations were not observed with somatropin (4,22,28). Transient IGF-1 elevations (IGF-1 SDS >+2) were observed in 15.8% (6/38) of patients treated with somatrogon in the present study, most frequently during the initial weeks of therapy. In four patients, levels normalized spontaneously or following minor dose adjustment, whereas two additional cases identified

at 12 months were scheduled for reassessment. These findings indicate that short-term IGF-1 fluctuations are not uncommon but can be effectively managed through routine biochemical monitoring and timely titration. In addition, although a greater increase in IGF-1 SDS was observed in the naïve group, sensitivity analysis excluding a single elevated value attenuated statistical significance while preserving a moderate-to-large effect size, suggesting that the overall trend was not solely driven by an outlier. However, the long-term clinical significance of these transient elevations remains uncertain, underscoring the need for continued surveillance to clarify their potential impact on metabolic outcomes and overall treatment safety. Of note, one patient in our cohort maintained low IGF-1 SDS despite adequate growth velocity. Although neutralizing antibody testing was unavailable, prior long-term studies suggest that non-neutralizing antibodies do not compromise clinical efficacy (23).

The overall safety profile in this study was consistent with the existing literature with all adverse events being mild and transient (4,22,23,28). Injection-site pain was the most frequently reported complaint, while lipoatrophy was observed in three somatrogon-treated patients, all instances of which were related to repeated injections into the same anatomical region, and these resolved fully after rotation of injection sites. Similar cases have been described with both daily rhGH and somatrogon therapy (29,30), reiterating the importance of patient education on injection technique and site rotation. No treatment interruptions or discontinuations were required.

Recent research has also focused on the broader dimensions of GH therapy, including psychosocial and metabolic well-being (1,31). In this context, our bioimpedance analysis provides additional insight into body composition changes in somatrogon-treated naïve children and revealed favorable trends. The concomitant increase in both muscle and fat mass in the switch group may be related to the short follow-up duration and the small sample size. Evaluating the long-term effects in a larger population would help clarify this finding. Although QoL measures remained stable, longer follow-up may be needed to capture potential benefits of reduced injection burden on emotional and social functioning, not only for children themselves but also for their parents/caregivers and possibly other family members. Collectively, evidence from randomized trials, systematic reviews, and real-world data, including the present study, supports somatrogon as a safe, effective, and well-tolerated alternative to daily GH therapy. Our findings extend existing evidence by incorporating exploratory parameters, such as body composition and QoL assessments in children receiving somatrogon treatment, including both somatrogon-naïve and somatrogon-switch patients. Although body composition changes did not reach statistical significance, these data provide preliminary insight into the broader effects of somatrogon treatment and should be interpreted cautiously and confirmed in larger studies with longer follow-up.

In this cohort, once-weekly somatrogon was found to maintain QoL and psychosocial stability over a period of six months, as determined by the administration of age-appropriate, validated instruments under the supervision of a psychiatrist. The absence of deterioration on PedsQL and CBCL is consistent with reports that LAGH can reduce treatment burden without adversely affecting psychosocial functioning (1,8,31). Standardized psychiatric evaluations and sensitivity analyses mitigate the concern that unmeasured comorbidity may obscure true change. The near-significant trend in PedsQL Psychosocial domain scores among naïve patients may be indicative of a patient-perceived benefit that warrants testing in larger, longer studies with 12-month QoL endpoints.

Study Limitations

This study has several limitations. It was conducted in a single center with a relatively small sample size, limiting generalizability. The follow-up duration was short, and longer-term data are required to confirm durability of efficacy and safety. Neutralizing antibody testing was unavailable, precluding assessment of potential immunogenicity. Finally, QoL and body composition analyses were exploratory, warranting confirmation in larger and longer studies. However, the study has several strengths. It represents a real-world evaluation of once-weekly somatrogon in pediatric GHD, including both treatment-naïve and switch populations. The inclusion of standardized follow-up visits, bioimpedance analysis, and validated QoL assessments provided a comprehensive evaluation of treatment effects beyond traditional growth parameters. Furthermore, all patients were managed in a single tertiary center by the same multidisciplinary team, ensuring consistency in clinical practice.

Conclusion

In this real-world study, once-weekly somatrogon demonstrated growth outcomes comparable to daily somatropin over 6 and 12 months. Within the limitations of this single-center study with a relatively small sample size and limited follow-up duration, short-term safety findings were comparable between treatments. Transient IGF-1 elevations were managed through observation or dose adjustment, and no serious adverse events were observed during the study period. Bioimpedance analyses suggested favorable changes in body composition, while QoL outcomes remained stable. These findings suggest that somatrogon may represent a clinically effective and well-tolerated alternative to daily GH therapy in pediatric GHD. However, larger multicenter studies with longer follow-up are required to confirm long-term efficacy and safety.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Aydın Adnan Menderes University (approval number: 2025/23, date: 30.01.2025).

Informed Consent: Written informed consent was obtained from parents or legal guardians and assent was obtained from pediatric participants when appropriate, in accordance with age and national regulations. Where applicable, written informed consent for publication was also obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Kübra Şen Küçük, Ahmet Anık, Concept: Kübra Şen Küçük, Ahmet Anık, Design: Ahmet Anık, Data Collection or Processing: Kübra Şen Küçük, Sebla Güneş, Mustafa Dinçer, Tolga Ünüvar, Ahmet Anık, Analysis or Interpretation: Kübra Şen Küçük, Mustafa Dinçer, Sercan Öztürk, Ahmet Anık, Literature Search: Kübra Şen Küçük, Mustafa Dinçer, Ahmet Anık, Writing: Kübra Şen Küçük, Mustafa Dinçer, Sercan Öztürk, Ahmet Anık.

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A Comparative Assessment of Large Language Models in Congenital Hypothyroidism: Reliability, Quality and Readability

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ABSTRACT

Objective: To comparatively evaluate the reliability, quality, and readability of responses generated by widely used large language model (LLM)-based chatbots to congenital hypothyroidism (CH)-related patient questions.

Methods: Forty frequently asked questions (FAQs) about CH, derived from clinician-reviewed patient education resources, were submitted under standardized conditions (December 2025) to Chat Generative Pre-Trained Transformer-4 (ChatGPT-4), ChatGPT-5.2, Gemini, and Copilot. The modified DISCERN (mDISCERN) instrument was used to assess reliability, whereas the Global Quality Score (GQS) was used to evaluate quality. Readability was evaluated using Flesch Reading Ease (FRE), Flesch-Kincaid Grade Level (FKGL), Gunning Fog Index (GFI), Coleman-Liau Index (CLI), and Simple Measure of Gobbledygook (SMOG). Scores were compared using Friedman tests with Bonferroni-corrected post-hoc analyses.

Results: Median mDISCERN scores were 5.0 for ChatGPT-4, ChatGPT-5.2, and Gemini, and 4.0 for Copilot. Median GQS scores were 5.0 for ChatGPT-4, ChatGPT-5.2, and Gemini, and 4.0 for Copilot. Differences among models were significant for both mDISCERN and GQS ($p<0.001$), with ChatGPT-5.2 outperforming others in key pairwise comparisons. Readability differed significantly across all indices (all $p<0.001$). ChatGPT-5.2 demonstrated the highest FRE and lowest FKGL, whereas Gemini produced the most complex text. However, all models exceeded the recommended sixth-grade reading level.

Conclusion: LLM-based chatbots produced generally moderate-to-high quality CH information, but readability remains suboptimal for patient education. ChatGPT-5.2 showed the best overall performance. LLM outputs may support patient information needs but should complement, not replace, clinician-provided counseling.

Keywords: Artificial intelligence, ChatGPT, congenital hypothyroidism, copilot, Google Gemini, large language models

What is already known on this topic?

Large language model (LLM)-based chatbots are increasingly used by patients to obtain medical information. Previous studies have shown variable reliability, quality, and readability of LLM-generated health content, but most materials exceed the recommended sixth-grade reading level for patient education.

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What this study adds?

This study is the first to evaluate four LLMs in the context of congenital hypothyroidism using parent-centered questions, assessing reliability, quality, readability, and source accuracy. Although all models demonstrated good levels of reliability and quality, ChatGPT-5.2 showed superior overall performance compared with the others. These findings suggest that, as LLMs continue to evolve, they hold increasing potential to generate more reliable and readable health information.

Introduction

Primary congenital hypothyroidism (CH) is the most common congenital endocrine disorder, with an estimated incidence of approximately 1 in 1,000-3,000 live births worldwide. If left untreated, CH may lead to severe and irreversible intellectual disability, however, this adverse outcome can largely be prevented through neonatal screening programs and early initiation of treatment. In countries where newborn screening programs are effectively implemented, the majority of patients with CH demonstrate neurodevelopmental outcomes within normal limits (1,2,3,4,5,6,7).

Abnormal findings on newborn screening necessitate confirmatory biochemical testing to establish or exclude the diagnosis of hypothyroidism. Measurement of thyrotropin [thyroid-stimulating hormone (TSH)] together with free thyroxine (free T4), or alternatively total T4 and triiodothyronine (T3) uptake, is recommended for this purpose. The presence of elevated serum TSH levels accompanied by low free T4 concentrations confirms the diagnosis of primary hypothyroidism and requires urgent initiation of treatment (8). Oral levothyroxine is the treatment of choice, and both the timing and dosage of thyroid hormone replacement are critical determinants of clinical outcomes (9,10). In term infants, the recommended initial dose is 10-15 µg/kg/day, a range that has been associated with optimal neurocognitive outcomes, normal growth, and improved school performance (10,11).

Currently, patients and parents of patients frequently rely on the internet to access health-related information. Previous reports indicate that approximately 90% of adults use the internet, and nearly 75% search for health-related information before seeking medical care, highlighting the importance of evaluating the accuracy and readability of online medical content (12). Medical content is disseminated to broad audiences through digital and social media platforms such as Google, Facebook, and Twitter (13). In recent years, the use of artificial intelligence (AI) technologies in the field of healthcare has increased rapidly (14). AI refers to the ability of computer systems to perform functions that typically require human intelligence, including decision-making, learning from experience, natural language understanding, and problem-solving.

In addition to traditional citation metrics, alternative metrics such as Altmetric scores provide valuable insight into the dissemination and societal impact of scientific publications. Bibliometric analyses not only illustrate the historical development of a research field but also identify highly interactive studies that shape academic visibility. Recent bibliometric studies highlight the growing role of digital engagement in the dissemination of medical knowledge, including the importance of evaluating online information sources in contemporary healthcare environments (13).

In this context, AI-driven large language models (LLMs) have emerged as novel and easily accessible sources of information for individuals seeking health-related knowledge. AI-based chatbots are capable of interacting with patients, answering questions, and providing basic medical information (15). Chat Generative Pre-Trained Transformer (ChatGPT) version 3.5 was released in 2022, rapidly gained a large user base, and was subsequently followed by more advanced versions (16). In addition to ChatGPT, other LLM-based chatbots, such as Microsoft Copilot and Google Gemini, have also been developed. These models were selected because they represent the most widely used and publicly accessible LLM-based chatbots at the time of the study and have been frequently been evaluated in previous healthcare-related research, allowing comparability with existing literatüre.

Access to AI enables patients to obtain health-related information quickly and easily. However, health literacy plays a central role in patient understanding and engagement, and the readability, reliability, and quality of this information are thus of critical importance (17). The National Institutes of Health (NIH), the American Medical Association (AMA), and the United States Department of Health and Human Services recommend that web-based patient education materials be written at or below a sixth-grade reading level (18,19,20,21). In addition, LLMs may occasionally cite non-existent sources or generate biased or inaccurate information, raising concerns regarding patient safety (22). Improved patient knowledge regarding disease mechanisms and treatment has been shown to enhance adherence to medical recommendations and improve clinical outcomes (23).

The aim of this study was to conduct a comparative evaluation of the responses generated by four AI-based chatbots, ChatGPT-4, ChatGPT-5.2, Gemini, and Copilot, to frequently asked questions (FAQs) related to CH, with respect to readability, reliability, and quality.

Methods

Study Design

This study was designed as a cross-sectional analytical study evaluating the reliability, quality, and readability of responses generated by AI-based LLMs regarding CH.

This study did not involve human participants or patient-level data. All evaluated responses were obtained from publicly accessible AI platforms. Therefore, ethics committee approval was not required.

Question Sources and Initial Screening

Questions related to CH were developed using patient education content from internationally recognized, reliable, evidence-based websites that are reviewed by clinicians, including the Cleveland Clinic, Mayo Clinic, and the United Kingdom National Health Service. These sources were selected because they are widely regarded as trustworthy in patient and caregiver education and include questions that are frequently asked by patients and their families.

Initially, 60 questions related to CH were identified. Questions that were repetitive, highly similar in wording, overlapping in meaning, or not directly related to CH were excluded through a screening process. Following this refinement, 40 questions were selected for the final analysis. The complete list of questions is provided in the Supporting Information section. The screening and selection of questions were independently performed by two pediatric endocrinologists with clinical experience in CH, and any disagreements regarding inclusion or exclusion were resolved by consultation with a third pediatric endocrinologist, with final decisions made by consensus.

Question Categorization

The final set of questions was categorized into six clinically meaningful domains reflecting the topics most frequently sought by parents of children with CH. These domains included basic information; symptoms and clinical features; diagnosis and screening; treatment and monitoring; risks, side effects, and complications; and recovery and outlook.

AI Models and Interaction Procedure

The selected questions were submitted to multiple LLM-based chatbot platforms, including ChatGPT-4 and ChatGPT-5.2 (free and paid versions; OpenAI; December 2025 and December 2025), Gemini (free version; Google; November 2025), and Copilot (Microsoft; December 2025), all of which were publicly accessible at the time of the study. All evaluations were conducted in December 2025 using identical prompts and standardized conditions. All searches were performed using a web browser in incognito mode without logging into any personal accounts to minimize personalization bias.

To ensure that each response was generated independently and to prevent contextual memory bias, the conversation history was cleared prior to each question, and a new chat session was initiated. To assess response consistency, the same set of questions was resubmitted to each chatbot one week later under the same conditions. No additional prompts, follow-up questions, response regeneration commands, or clarifications were used, except for requesting references when they were not initially provided by the chatbot.

All responses and cited references were recorded and stored for subsequent analysis. The existence, accessibility, and academic credibility of the cited sources were systematically verified and documented. All cited references were systematically verified using PubMed, Google Scholar, CrossRef, and official journal websites. A reference was classified as fabricated if it could not be identified in these databases or if inconsistencies were detected in authorship, journal name, publication year, volume, page numbers, or DOI information. In addition, references that were retrievable but unrelated to the topic or that did not support the statements made in the chatbot response were classified as inaccurate citations. All references were independently reviewed by two pediatric endocrinologists, and disagreements were resolved by consensus. Source usage and citation behavior were incorporated into the modified DISCERN (mDISCERN) (24,25) and Global Quality Scale (GQS) (26,27) assessments, and misleading, fabricated, or non-academic references were systematically identified and recorded.

Expert Evaluation Process

All chatbot responses were independently evaluated by two pediatric endocrinologists with clinical experience in the management of CH. In cases of disagreement regarding scoring, the responses were re-assessed by a third pediatric endocrinologist, and a final decision was reached by consensus. Inter-rater agreement exceeded 0.80 (Cohen's κ), indicating excellent agreement.

Reliability Assessment

The mDISCERN instrument was used to assess reliability. This scale consists of five criteria, with each criterion scored as 1 if fulfilled and 0 if not fulfilled. Higher total scores (out of five) indicate greater reliability. The reliability and validity of the DISCERN instruments have been previously established (24,25). The mDISCERN scale evaluates the following five criteria using a yes/no format: clear statement of aims; reliability of information sources; balance and absence of bias; provision of additional sources of information; and discussion of uncertainties.

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Quality Assessment

The quality of the chatbot responses was evaluated using the GQS, which has been applied in similar studies (26,27). GQS is a five-point Likert scale designed to assess the usability, quality, and flow of online health information. A score of 1 represents the lowest quality, whereas a score of 5 indicates the highest quality. Scores of 2 reflect low quality with limited usefulness, 3 indicate moderate quality with limited usefulness, and 4 represent good quality and usefulness (Table 1).

Readability Assessment

The readability of the responses generated by the chatbots was analyzed using multiple established readability indices to evaluate textual complexity and the required reading level. These indices included the Flesch Reading Ease (FRE), Flesch-Kincaid Grade Level (FKGL), Gunning Fog Index (GFI), Coleman-Liau Index (CLI), and the Simple Measure of Gobbledygook (SMOG). Readability scores were calculated using an online tool with automated computation functions (28).

The FRE score ranges from 0 to 100, with lower scores indicating more difficult text. Scores between 0 and 30 correspond to very difficult texts requiring college-level reading skills; scores between 31 and 50 indicate difficult texts appropriate for grades 13-16; scores between 51 and 60 represent relatively difficult texts at the 10th-12th grade level; scores between 61 and 70 indicate plain English suitable for grades 8-9; scores between 71 and 80 correspond to fairly easy texts at the 7th-grade level; scores between 81 and 90 indicate easy texts appropriate for the 6th-grade level; and scores between 91 and 100 represent very easy texts that can be understood by an average 11-year-old student.

The FKGL score represents the grade level required to understand a text, with scores of 10 or higher indicating that the material is appropriate for readers at the high school level or above. According to recommendations from the AMA and the NIH, patient education materials should be written at a sixth-grade reading level or lower (18,19,20,21).

Table 1. Global quality scale (GQS) criteria
1. Poor quality, poor flow of the site, most information missing, not at all useful for patients
2. Generally poor quality and poor flow, some information listed but many important topics missing, of very limited use to patients
3. Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4. Good quality and generally good flow, most of the relevant information is listed, but some topics not covered, useful for patients
5. Excellent quality and excellent flow, very useful for patients

The CLI measures the reading level corresponding to grade levels in the United States. The SMOG score indicates the number of years of education required to understand a text. In the GFI, which evaluates textual complexity based on sentence length and the proportion of long words, scores above 12 indicate more difficult texts.

Acceptable readability thresholds were defined as an FRE score of ≥80 and ≤6 for the other four indices. Materials exceeding these thresholds were considered more difficult to read than the levels recommended for the general population (23,29,30,31,32).

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). Continuous and ordinal variables were assessed for normality using the Shapiro-Wilk test. As the outcome scores did not follow a normal distribution, results were summarized as median and interquartile range. Differences in scores across the compared chatbot models were evaluated using the Friedman test. When the Friedman test indicated a statistically significant difference, post hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction. A Bonferroni-corrected p value of <0.008 was considered statistically significant. Effect sizes for the Friedman tests were calculated using Kendall's W and interpreted as small (≈0.1), moderate (≈0.3), and large (≥0.5). This approach was used to complement p-values and to provide information on the magnitude of differences between models.

Results

The response performance of ChatGPT-4, ChatGPT-5.2, Gemini, and Copilot was evaluated using CH-related FAQs grouped into six domains. These domains comprised Basic Information; Symptoms and Clinical Features; Diagnosis and Screening; Treatment and Monitoring; Risks, Side Effects, and Complications; and Recovery and Outlook.

The reliability of the LLMs was assessed using mDISCERN. The median mDISCERN score was 5.0 (4.0-5.0) for ChatGPT-4, 5.0 (5.0-5.0) for ChatGPT-5.2, 5.0 (4.0-5.0) for Gemini, and 4.0 (3.0-4.0) for Copilot (Table 2).

The quality of the responses was evaluated using GQS. The median GQS score was 5.0 (4.0-5.0) for both ChatGPT-4 and Gemini, 5.0 (5.0-5.0) for ChatGPT-5.2, and 4.0 (3.0-4.0) for Copilot (Table 2).

The readability of the responses to the FAQs was evaluated using multiple indices. The highest FRE score was observed for ChatGPT-5.2 at 57.2 (39.4-66.8), whereas the lowest FRE score was recorded for Gemini at 38.2 (31.1-46.8). The lowest FKGL score was also obtained for ChatGPT-5.2 at 8.4 (7.0-12.0), while

the highest FKGL score was found for ChatGPT-4 at 13.3 (11.9-14.5). ChatGPT-5.2 demonstrated the lowest SMOG, GFI, and CLI scores, whereas Gemini had the highest values for these indices (Table 3).

Gemini and Copilot provided references and direct links to the cited sources after each response. ChatGPT-4 and ChatGPT-5.2 did not provide sources by default but supplied references when explicitly requested; ChatGPT-5.2 included hyperlinks, whereas ChatGPT-4 did not. Regarding the accuracy of the cited sources, ChatGPT-5.2 achieved a rate of 100%, ChatGPT-4 and Gemini each demonstrated an accuracy of 95%, and Copilot showed an accuracy rate of 60%.

All LLMs provided additional information beyond the direct answers and indicated what further details they could offer upon request. In addition, ChatGPT-5.2 presented brief summary sections for parents (e.g., "short answer for parents") for some questions. The responses generated by ChatGPT-4 were generally longer than those of the other models.

Reliability and Quality

All LLMs differed significantly in terms of mDISCERN scores ($p<0.001$). The Friedman test yielded $\chi^2(3)=22.653$ ($p<0.001$), with a Kendall's W of 0.19, indicating a small-to-moderate effect size. In pairwise comparisons, significant differences were observed between ChatGPT-5.2 and ChatGPT-4 and between ChatGPT-5.2 and Copilot ($p=0.002$ and $p<0.001$, respectively) (Table 2). ChatGPT-5.2 achieved higher reliability scores than the other models.

With respect to content quality, GQS scores also differed significantly between all LLMs ($p<0.001$). The effect size was small-to-moderate [$\chi^2(3)=22.393$, $p<0.001$; Kendall's W=0.19]. In pairwise comparisons, the GQS score of ChatGPT-5.2 was significantly higher than those of the other three models ($p=0.001$, $p=0.001$, and $p<0.001$, respectively) (Table 2). No significant differences in reliability or quality scores were observed across the different question categories.

Readability

Significant differences were observed between the AI models across all readability indices (SMOG, FKGL, GFI, CLI, and FRE; all $p<0.001$). Effect size analysis demonstrated large effects for FKGL (W=0.59), SMOG (W=0.55), CLI (W=0.58), and FRE (W=0.49), and a very large effect for GFI (W=0.86), indicating substantial differences in textual complexity across models (Table 3). ChatGPT-5.2 demonstrated significantly higher FRE scores and significantly lower FKGL, SMOG, GFI, and CLI scores compared with all other models (Table 4), indicating superior readability.

In pairwise comparisons between ChatGPT-4, Gemini, and Copilot, mixed results were observed depending on the index. No significant difference was found between ChatGPT-4 and Copilot for the CLI score, or between Gemini and Copilot for the SMOG score ($p=0.624$) (Table 4).

FRE

Significant differences were observed between the models ($p<0.001$). Copilot was more readable than ChatGPT-4 and

Table 2. Comparison of mDISCERN and GQS scores across AI models

AI Model	mDISCERN Median (Q1-Q3)	vs ChatGPT-5 (p)	vs Gemini (p)	GQS Median (Q1-Q3)	vs ChatGPT-5 (p)	vs Gemini (p)
ChatGPT-4	5.0 (4.0-5.0)	**0.002**	0.655	5.0 (4.0-5.0)	**0.001**	0.721
ChatGPT-5.2	5.0 (5.0-5.0)	Reference	-	5.0 (5.0-5.0)	Reference	-
Gemini	5.0 (4.0-5.0)	0.008	Reference	5.0 (4.0-5.0)	**0.001**	Reference
Copilot	4.0 (3.0-4.0)	**<0.001**	0.036	4.0 (3.0-4.0)	**<0.001**	0.021

Values are presented as median [interquartile range (Q1-Q3)]. Overall differences between AI models were assessed using the Friedman test. Post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test with Bonferroni correction ($p<0.008$). Asterisks (*) indicate statistically significant differences

Table 3. Comparison of readability scores across AI models

Readability index	ChatGPT-4	Gemini	Copilot	ChatGPT-5.2	p
FRE	41.2 (36.3-48.9)	38.2 (31.1-46.8)	46.9 (39.8-52.8)	57.2 (39.4-66.8)	**<0.001**
FKGL	13.3 (11.9-14.5)	11.9 (11.0-13.9)	10.2 (8.8-12.8)	8.4 (7.0-12.0)	**<0.001**
SMOG	12.6 (11.3-13.9)	13.9 (12.4-15.8)	13.2 (12.0-14.6)	9.8 (7.4-13.5)	**<0.001**
GFI	14.0 (12.8-15.8)	15.8 (13.6-17.2)	14.6 (13.4-16.3)	10.2 (7.9-14.9)	**<0.001**
CLI	12.9 (11.8-14.7)	14.2 (12.4-16.8)	12.9 (11.8-14.1)	9.1 (7.3-13.9)	**<0.001**

Values are presented as median [interquartile range (Q1-Q3)]. Comparisons across AI models were performed separately for each readability index using the Friedman test. Statistically significant differences ($p<0.05$) are shown in bold.
FRE: Flesch Reading Ease; FKGL: Flesch-Kincaid Grade Level; SMOG: Simple Measure of Gobbledygook; GFI: Gunning Fog Index; CLI: Coleman-Liau Index

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Table 4. Post-hoc Wilcoxon signed-rank test results for readability indices

Comparison	FRE p	FKGL p	SMOG p	GFI p	CLI p
ChatGPT-4 vs Gemini	0.013	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ChatGPT-4 vs Copilot	**0.002**	**<0.001**	**0.002**	**<0.001**	0.624
Gemini vs Copilot	**<0.001**	**<0.001**	0.014	**0.001**	**<0.001**
ChatGPT-4 vs ChatGPT-5.2	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.001**
Gemini vs ChatGPT-5.2	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Copilot vs ChatGPT-5.2	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

All p values were obtained using the Wilcoxon signed-rank test with Bonferroni correction. Adjusted significance level was set at p<0.008.
FRE: Flesch Reading Ease; FKGL: Flesch-Kincaid Grade Level; SMOG: Simple Measure of Gobbledygook; GFI: Gunning Fog Index; CLI: Coleman-Liau Index

Gemini (p=0.002 and p<0.001, respectively). ChatGPT-5.2 was more readable than all other models (all p<0.001).

FKGL

Significant differences were again evident between the models (p<0.001). Copilot was more readable than ChatGPT-4 and Gemini, and Gemini was more readable than ChatGPT-4 (all p<0.001). ChatGPT-5.2 demonstrated significantly better readability than all other models (all p<0.001).

SMOG

Significant differences were detected across all models, once more (p<0.001). ChatGPT-4 had lower SMOG scores than Gemini and Copilot (p<0.001 and p=0.002, respectively). ChatGPT-5.2 once again performed better on SMOG scores than all other models (all p<0.001).

GFI

GFI scores ranked from lowest to highest were ChatGPT-5.2, ChatGPT-4, Copilot, and Gemini, with all pairwise comparisons being statistically significant.

CLI

Based on CLI scores, ChatGPT-4 and Copilot were more readable than Gemini (both p<0.001). ChatGPT-5.2 had significantly lower CLI scores than all other models (p=0.001 vs. ChatGPT-4; p<0.001 vs. Gemini and Copilot) (Tables 3 and 4).

Discussion

In this study, the quality, reliability, and readability of responses provided by four popular AI chatbots, ChatGPT-4, ChatGPT-5.2, Gemini, and Copilot, to some of the most FAQs about CH were evaluated. To the best of our knowledge, this is the first study to compare the responses of four different LLMs to CH-related FAQs.

CH is now usually diagnosed during the neonatal period, most commonly through heel-prick blood screening. If early treatment is not initiated, it can lead to irreversible intellectual disability and developmental delay, making it a major source of anxiety for parents of newborns (8). For this reason, many parents seek information about CH through LLMs. These systems have been reported to assist healthcare professionals in areas such as disease diagnosis, treatment planning, prognostic assessment, and public health management, and they may also influence patient decision-making in healthcare (33). By comparing the quality, reliability, and readability of LLMs, the present study provided insight into their suitability for use by parents.

We found the reliability and quality of all LLMs to be in the moderate-to-high range, but with significant differences between them. Ranked from lowest to highest, the models were Copilot, ChatGPT-4 and Gemini, and ChatGPT-5.2. ChatGPT-5.2 was significantly more reliable than ChatGPT-4 and Copilot and demonstrated higher quality than ChatGPT-4, Gemini, and Copilot. Consistent with our findings, a previous study evaluating ChatGPT, Perplexity, ChatSonic, and Microsoft Bing AI reported that the information quality of the responses was moderate to high (34). Gül et al. (14) found lower mDISCERN scores for ChatGPT and Gemini and higher scores for Perplexity. Another study reported that Gemini achieved higher GQS scores compared with other chatbots (35). The superior performance of ChatGPT-5.2 in our study may be attributed to its concise and accurate responses and the high accuracy of the sources it provided, while Gemini's provision of references and direct links alongside its answers likely contributed to its relatively high scores.

Recent studies have shown that the accuracy, quality, and clinical appropriateness of LLM responses depend largely on the clarity and specificity of user prompts. Sarangi and Mondal (36) showed that LLMs, such as ChatGPT, Google Bard, and Microsoft Bing, perform better when prompted with clear and well-defined queries. Therefore, the questions were developed from internationally recognized, evidence-based patient education materials that were specifically designed for patients and caregivers, written in an understandable language, and reviewed by healthcare professionals. Within the scope of the validated assessment tools used in this study, all evaluated LLMs demonstrated generally high levels of reliability and quality.We also evaluated the readability level of the responses in our study.

In the United States, the average literacy level corresponds to approximately the 7th-8th grade; however, according to the AMA, health education materials should be written at the 6th-grade level. This recommendation is based on the fact that patients' comprehension decreases when they are dealing with illness and psychological stress, and therefore even complex medical conditions should be explained in very simple language (27). Nevertheless, previous studies have shown that a substantial proportion of online patient education materials exceed the recommended readability levels, which is considered inappropriate from a public health perspective (19,20,21,24).

While significant differences were observed across models, effect size analysis showed that reliability and quality differences were at most small-to-moderate, whereas readability differences were large to very large. This suggests that although overall content quality was relatively comparable among models, substantial variability existed in textual complexity, which may have a meaningful effect on patient comprehension and overall health literacy.

In the present study, the responses generated by ChatGPT-5.2 were found to correspond approximately to a 9th-10th grade reading level, whereas those of Copilot corresponded to a 12th-14th grade level, ChatGPT-4 to a 13th-14th grade level, and Gemini to a 14th-16th grade level. ChatGPT-5.2 was significantly more readable than all other LLMs. Pairwise comparisons among ChatGPT-4, Gemini, and Copilot yielded variable significant differences depending on the readability index used.

Momenaei et al. (37) reported that understanding ChatGPT's responses on retinal disease surgery required a university-level education. Similarly, another study found that responses provided by ChatGPT, Bard, and Microsoft Bing Chat to palliative care-related questions were written at approximately a 10th-grade reading level (38). Although studies directly comparing ChatGPT, Gemini, Copilot, and particularly ChatGPT-5.2 in terms of readability are limited, existing evidence, consistent with our findings, indicates that the readability of LLM-generated content generally exceeds the recommended 6th-grade level. Previous studies have demonstrated that ChatGPT versions can reduce readability levels when provided with specific instructions (39,40,41). These findings suggest that incorporating tailored prompts aimed at simplifying language could enhance readability in future applications. The superior readability of ChatGPT-5.2 observed in our study may also be attributed to its more advanced language model architecture compared with the other LLMs.

In a study evaluating the knowledge levels of caregivers of children with CH, insufficient knowledge was identified as a major barrier to effective follow-up. It was suggested that healthcare professionals providing information about CH, which is one of the leading preventable causes of intellectual and developmental disability, should use clear, simple, and patinet-appropriate understandable language (42). Education is a key component of disease management (43), and studies have shown that providing patients and caregivers with personalized information improves adherence to medical recommendations and leads to better health outcomes (44).

The use of LLMs by caregivers, in addition to the education provided by healthcare professionals, has become increasingly common with the recent expansion and widespread use of AI-based applications. Although the use of LLMs is known to enhance access to healthcare information, concerns remain regarding the potential for misleading content, variability in quality, and readability levels that may exceed those appropriate for the general population (14,45). Therefore, AI-based tools should be used cautiously, and consultation with healthcare professionals should be encouraged when necessary. Reassuringly, all LLMs evaluated in our study included warning statements advising users to consult a physician or noting that the information provided should **not** be used as a substitute for medical decision-making. Previous research into digital platforms such as YouTube and web-based resources, that represent other major sources of health information for patients, have demonstrated considerable variability in the readability, reliability, and quality of such content, highlighting the importance of ongoing evaluation of online health information (18,46)

Study Limitations

The analysis was limited to English-language responses, as English is the most commonly used language in general online information seeking. Therefore, the findings cannot be directly generalized to content generated in other languages. In addition, the use of a single readability calculator may have introduced minor variability in readability estimates, although the tool employed has been widely used in previous studies (35). Furthermore, the findings are based on chatbot responses obtained in December 2025; given the continuous updating of LLMs, these results will change over time and may improve further. LLM-generated responses are not fully deterministic and may vary across sessions or over time due to model updates and probabilistic generation mechanisms. Therefore, exact reproducibility of responses cannot be fully guaranteed.

Strengths

This study represents the first comprehensive evaluation of multiple LLMs specifically about CH. The use of validated and widely accepted assessment tools, standardized prompts, and expert evaluation enhances the methodological robustness and objectivity of the findings, enabling a reliable comparison across models.

Conclusion

The present study showed that although all four chatbots produced CH-related content with moderate to good reliability and quality, ChatGPT-5.2 outperformed the others in reliability, quality, and readability, despite overall readability exceeding the recommended sixth-grade level. The potential of AI-based tools to provide accurate, understandable, and reliable information about CH, which is screened for in a large proportion of neonates in many countries, to parents and caregivers is of great importance. To minimize the risk of misinformation and improve user experience, both continued model development and appropriate prompt formulation remain important factors influencing the quality, reliability, and readability of LLM-generated responses. Nevertheless, regardless of how advanced LLMs become, they are currently a long way from replacing face-to-face medical consultations and clinical evaluation of patients by physicians.

Ethics

Ethics Committee Approval: This study did not involve human participants or patient-level data. All evaluated responses were obtained from publicly accessible artificial intelligence platforms. Therefore, ethics committee approval was not required.

Informed Consent: Informed consent was not required.

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Footnotes

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The complete list of FAQs included in the analysis is available in the Supporting Information.

Authorship Contributions

Concept: Ebru Barsal Çetiner, Design: Ebru Barsal Çetiner, Berna Singin, Data Collection or Processing: Ebru Barsal Çetiner, Berna Singin, Analysis or Interpretation: Ebru Barsal Çetiner, Berna Singin, Literature Search: Ebru Barsal Çetiner, Writing: Ebru Barsal Çetiner, Berna Singin.

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CASE REPORT

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Acute Kidney Injury after Thyroid Hormone Withdrawal in an Adolescent with Papillary Thyroid Carcinoma

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ABSTRACT

We report a patient with papillary thyroid carcinoma (PTC) who developed acute kidney injury (AKI) and elevated creatine kinase (CK) after thyroid hormone withdrawal (THW) prior to radioiodine therapy. A 12-year-old female patient who had undergone total thyroidectomy for PTC one year previously, presented with leg pain for the past two days. Following THW three weeks earlier, she had received 70 mCi radioiodine treatment six days before this presentation. Serum creatinine [1.53 mg/dL, normal range (NR): 0.3-1.1], aspartate aminotransferase (102 IU/L, NR: 0-40) and CK (3451 IU/L, NR: 26-174) levels were elevated. Thyrotropin level was elevated (µIU/mL, NR: 0.51-4.3), and free T4 level was decreased (0.05 ng/dL, NR: 0.98-1.63). Serum creatinine and CK levels decreased after intravenous hydration and levothyroxine treatment. In PTC cases with thyroidectomy, kidney function and CK elevation should be assessed after THW and dehydration should be prevented.

Keywords: Papillary thyroid carcinoma, thyroid hormone withdrawal, rhabdomyolysis, acute kidney injury, radioactive iodine therapy

What is already known on this topic?

Differentiated thyroid cancer is the most common thyroid cancer in children. The standard treatment is total thyroidectomy. Radioactive iodine (RAI) therapy is indicated for patients with pulmonary metastases or small-volume, unresectable residual cervical disease. During RAI therapy, having a thyrotropin above 30 µIU/mL facilitates ^{131}I uptake, which may usually be achieved by thyroid hormone withdrawal (THW) for ≥14 days in children.

What this study adds?

Patients who have undergone thyroidectomy may experience creatine kinase (CK) elevation and acute kidney injury may occur as a result of THW prior to RAI treatment. Kidney function tests and CK levels should be assessed in cases with THW and dehydration should be prevented.

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Introduction

Differentiated thyroid cancer (DTC) is the most common thyroid cancer in children. A previous history of radiotherapy used in treatment regimens for other malignancies is a risk factor for the development of thyroid cancer (1). However, less than 2% of all thyroid cancers develop in childhood and adolescence most commonly in female adolescents aged 15–19 years (1,2). Papillary thyroid carcinoma (PTC), a subtype of DTC, accounts for 90% of pediatric cases. At the time of diagnosis, approximately 50% of children with PTC have cervical lymph node metastasis (1).

Total thyroidectomy is the standard surgical approach for pediatric DTC due to the higher frequency of bilateral or multifocal involvement in children compared to adults (3). In cases with central cervical lymph node involvement, central lymph node dissection should be performed along with total thyroidectomy (2). Radioactive iodine (RAI) therapy is indicated for patients with pulmonary metastases or small-volume, unresectable residual cervical disease (2,3). During RAI therapy, having thyrotropin (TSH) levels above 30 µIU/mL facilitates ^{131}I uptake and this can usually be achieved by thyroid hormone withdrawal (THW) for ≥14 days in children (3).

In patients with DTC, short-term hypothyroidism during THW causes an increase in serum creatinine levels of approximately 30% (4). Thyroid hormones have direct and indirect effects on the cardiovascular system and hemodynamic conditions in the kidney. The decrease in cardiac output and increase in peripheral resistance seen in hypothyroidism may decrease renal blood flow. Decreased renal perfusion and glomerular filtration rate (GFR) will lead to decreased water excretion and increased creatinine levels.

Hypothyroidism may also precipitate rhabdomyolysis. The diagnosis of rhabdomyolysis is based on medical history and laboratory findings. For the diagnosis of rhabdomyolysis, the serum creatine kinase (CK) level should be greater than five times the upper limit of normal or greater than 1000 IU/L when the serum myoglobin >150 ng/mL. Acute kidney injury (AKI) is a common and serious complication of rhabdomyolysis. It has been reported that 13-46% of patients with rhabdomyolysis develop AKI. Rhabdomyolysis causes kidney damage due to fluid sequestration in injured skeletal muscle, activation of the renin-angiotensin system and sympathetic nervous system, antidiuretic hormone release, and renal vasoconstriction. AKI is thought to be the result of salt and water retention and tubular damage due to myoglobin-induced oxidative damage (5).

In this case report, we describe a patient with PTC who developed AKI and elevated CK after planned THW prior to RAI therapy.

Case Report

A 12-year-old female patient who had undergone total thyroidectomy and cervical lymph node dissection for PTC one year previously presented with leg pain of two days duration. She had received L-thyroxine and cholecalciferol treatment for iatrogenic hypoparathyroidism after the operation. Following THW for three weeks, she had received 70 mCi radioiodine treatment six days before the current presentation. No infections, metabolic disorders, or recent medication use were noted in her medical history. Physical examination revealed tenderness in the thigh muscles without other symptoms. The urine output was 3.15 mL/kg/h. Previous examinations showed normal complete blood count and serum creatinine value [0.44 mg/dL, normal range (NR): 0.3-1.1]. However, on admission, laboratory tests revealed increased levels of serum creatinine (1.53 mg/dL, NR: 0.3-1.1) and the estimated GFR was 52 mL/min/1.73m^2. Uric acid (7.3 mg/dL, NR: 2-5.5) and aspartate aminotransferase (AST) 102 IU/L (NR: 0-40) levels were elevated, while CK levels were significantly elevated at 3451 IU/L (NR: 26-174), 19.8 times the upper limit of normal. Electrolyte levels, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) levels were normal. TSH level was elevated (>100 µIU/mL, NR: 0.51-4.3), and free T4 level was low (0.05 ng/dL, NR: 0.98-1.63). The urinalysis showed low urine specific gravity (1005, NR: 1010-1030), with no blood and no protein on dipstick. Urine microalbumin/creatinine ratio (0.015 mg/g, NR: <30 mg/g) and urine β2-microglobulin level (0.16 mg/L, NR: 0.02-0.25 mg/L) were within the NR. Thyroid ultrasonography did not show any signs of disease relapse. She received an intravenous infusion of normal saline (0.9% NaCl) at a rate of 2000 mL/m^2/day for five days and oral L-thyroxine at 100 µg/day was initiated. Serum creatinine (0.47 mg/dL, NR: 0.3-1.1) and CK (136 IU/L, NR: 26-174) levels decreased after hydration and L-thyroxine treatment (Figure 1).

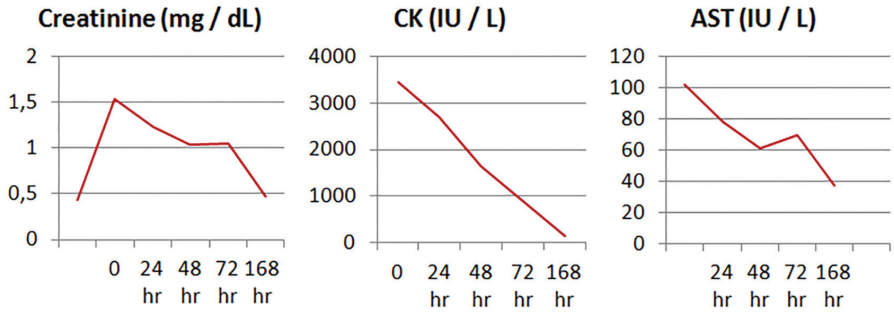

Figure 1. Serum creatinine, CK and AST levels of the patient
CK: creatine kinase, AST: aspartate aminotransferase, hr: hour

Discussion

In patients with PTC who undergo thyroidectomy, temporary hypothyroidism-induced rhabdomyolysis may occur after THW. Although AKI from rhabdomyolysis is a rare complication in children and adolescents, the severity of the side-effect may be variable. The management varies depending on the patient and severity. We report our experience with a patient diagnosed with PTC who developed rhabdomyolysis and AKI associated with THW prior to RAI therapy.

Causes of rhabdomyolysis include excessive muscle activity, trauma or injury, inherited muscle enzyme disorders, infections, drugs and toxins, as well as metabolic and endocrine disorders (5). The severity of rhabdomyolysis due to hypothyroidism ranges from minimal CK elevation to acute renal failure (6,7). In patients with Graves' disease and PTC, CK elevation and rhabdomyolysis have been reported following THW before RAI therapy (8,9). During THW for RAI therapy, serum lipid, creatinine, CK, AST, ALT, GGT, and LDH levels increase (4).

AKI resulting from hypothyroidism-associated rhabdomyolysis is rarely reported in children and adolescents. Saroufim et al. (7) reported a 16-year-old male adolescent with AKI attributed to rhabdomyolysis secondary to acquired hypothyroidism. In another case, a 10-year-old girl with hypothyroidism secondary to autoimmune thyroiditis was reported by Galli-Tsinopoulou et al. (10). She presented with rhabdomyolysis, pericardial effusion, renal failure, and acquired von Willebrand disease. Both of these cases were successfully treated with thyroid replacement therapy and hydration (7,10). In addition, Comak et al. (11) reported the administration of 24 sessions of hemodialysis in a 13-year-old girl with acute renal failure due to hypothyroidism secondary to thyroid hypoplasia. Hemodialysis and thyroid replacement therapy resulted in the recovery of kidney function (11). In our case, a three-fold increase in serum creatinine from baseline was defined as stage 3 AKI according to the KDIGO criteria (12). CK had increased to 20-fold the normal level, AST level was slightly elevated but GGT, ALT, and LDH levels were normal. After one week of hydration and L-thyroxine treatment, serum creatinine and CK levels decreased in our patient.

In hypothyroidism, reduced cardiac output leads to reduced renal blood flow and prerenal AKI (3). When muscle cells break down, they release myoglobin into the bloodstream and in cases of significant muscle damage, the increased load of myoglobin may lead to impaired kidney function. High concentrations of myoglobin in the kidneys can lead to acute tubular necrosis because of the combination of the direct toxic effects of myoglobin and the obstruction of renal tubules (5). However, kidney function is important for iodine excretion (3). Adequate hydration is required to increase ^{131}I clearance which can be hazardous for the renal tubules if clearance is decreased. Therefore, if necessary, additional supportive care with stool softeners, laxatives, and antiemetics may be considered to increase ^{131}I clearance (3). In addition, the effect of ^{131}I on the renal tubules has been associated with early complications of RAI therapy. These include radiation thyroiditis, xerostomia, ocular dryness, taste changes, sialadenitis, nausea, and vomiting which may increase the degree of dehydration (1,3). We speculate that AKI may be due to tubular damage associated with rhabdomyolysis as a result of THW and possible ^{131}I toxicity due to dehydration (9,13).

The main goal in the management of rhabdomyolysis is the preservation of kidney function and prevention of AKI. Early recognition is important to prevent AKI, and treatment consists of aggressive intravenous fluid resuscitation with correction of electrolyte abnormalities. Adjunctive therapies, including the urinary alkalization of urine, diuretics, and continuous renal replacement therapy, have been discussed but the benefits of these treatment modalities are controversial (5). Increased serum creatinine and CK levels can be reversed simultaneously with thyroid replacement therapy and intravenous fluid resuscitation (9).

Data on the use of recombinant human thyrotropin (rhTSH) in children are limited. It is reported that rhTSH is clinically safe and

provides adequate TSH stimulation in children and adolescents with DTC (14). However, its use is recommended in adults with endogenous hypothyroidism who are at risk of comorbidity (congestive heart failure, coronary artery disease, or psychiatric disorders) or in whom THW does not provide an adequate TSH response (TSH deficiency) (3). While THW for the preparation of RAI therapy causes a significant transient decrease in kidney function by reducing GFR, rhTSH injection is recommended for the preparation of RAI therapy without risking kidney function in patients at risk (15). Therefore, rhTSH could be considered as an alternative to THW in children who are going to receive RAI therapy (9).

Conclusion

Complications of short-term THW include cognitive, cardiovascular, affective, renal clearance, and lipid abnormalities. A significant complication of hypothyroidism is rhabdomyolysis and associated AKI. Kidney function and CK level should be assessed in cases with THW and dehydration should be prevented. Recombinant human TSH can be used in selected patients instead of THW, despite insufficient evidence for its use in the pediatric and adolescent population.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Yavuz Özer, Rüveyda Gülmez, Oya Ercan, Concept: Yavuz Özer, Oya Ercan, Design: Yavuz Özer, Oya Ercan, Data Collection or Processing: Yavuz Özer, Rüveyda Gülmez, Hande Turan, Gürkan Tarçın, Dilek Bingöl Aydın, Olcay Evliyaoğlu, Oya Ercan, Analysis or Interpretation: Yavuz Özer, Oya Ercan, Literature Search: Yavuz Özer, Rüveyda Gülmez, Oya Ercan, Writing: Yavuz Özer, Rüveyda Gülmez, Oya Ercan.

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CASE REPORT

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Identification of a Novel *IGSF1* Variant in Two Malaysian Male Siblings with Central Hypothyroidism and Macroorchidism

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ABSTRACT

Immunoglobulin superfamily member 1 (IGSF1) mutation is the commonest cause of mild to moderate isolated central congenital hypothyroidism and has an X-linked recessive inheritance, primarily affecting males. Other notable clinical features are macro-orchidism with delayed pubertal testosterone rise, large birth weight, increased body mass index, low prolactin andtransient growth hormone deficiency. Two male siblings with central hypothyroidism were found to have a novel *IGSF1* c.3467T>A variant that was likely pathogenic based on the family segregation study. The proband, aged 3 years, presented at 18 days old with prolonged jaundice while his 16-year-old brother was only shown to have central hypothyroidism after the genetic analysis result of the proband was known. Both siblings were obese, had large birth weights, macro-orchidism and low prolactin. The proband's brother had intellectual disability while the proband had normal development. This case study highlights the importance of evaluation for *IGSF1* variants in patients with unexplained central hypothyroidism, especially when accompanied by X-linked inheritance and macro-orchidism. Family segregation analysis will facilitate detection of other affected family members or carriers who may also benefit from thyroxine treatment.

Keywords: *IGSF1* variant, central hypothyroidism, macroorchidism

What is already known on this topic?

Immunoglobulin superfamily member 1 (IGSF1) mutation is the most common cause of X-linked recessive mild to moderate isolated central hypothyroidism. It is associated with macro-orchidism with delayed pubertal testosterone rise, high birth weight, increased body mass index, low prolactin and transient growth hormone deficiency.

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What this study adds?

A novel *IGSF1* c.3467T>A variant was found in two siblings with central hypothyroidism accompanied by macro-orcidism, the first report from South East Asia. Genetic evaluation for *IGSF1* variants is important in patients with unexplained isolated central hypothyroidism +/- macro-orchidism to enable early detection and treatment of hypothyroidism in the proband and other similarly affected family members.

Introduction

Central congenital hypothyroidism (CCH) is a thyroid disorder that is not readily detected by thyroid stimulating hormone (TSH)-based neonatal screening programmes due to low levels of both TSH and free thyroxine hormone (FT4). CCH is caused by a mutation in transcription factor genes that mediate pituitary gland development in most (60%) cases, including *POU1F*, *PROP1*, and *HESX1*, resulting in multiple pituitary hormone deficiencies (1,2). Isolated CCH is rare and can be due to genetic defects in the β-subunit of TSH and thyrotropin-releasing hormone (TRH) receptor (1,2,3). More recently, three other genes have been implicated in isolated central CH, namely, *IGSF1*, *TBL1X* and *IRS4*, all of which are of X-linked inheritance (1).

The *IGSF1* gene resides on X-chromosome (Xq26.2) and is expressed in the pituitary gland, hypothalamus, and testes (1,2,4). It encodes a plasma membrane immunoglobulin superfamily glycoprotein that may be involved in TRH receptor expression in the pituitary gland, and regulates TSH secretion via TRH signaling (1,2). Loss-of-function mutations in *IGSF1* cause TSH deficiency and X-linked recessive mild to moderate central hypothyroidism (OMIM: #300888), primarily affecting males. Other reported clinical features are macro-orchidism with delayed pubertal testosterone rise, delayed adrenarche, low prolactin, large birth weight and obesity (2,5). TSH and prolactin response to TRH stimulation is normal or reduced (1). The phenotype of carrier females ranges from being asymptomatic to having minor manifestations (5).

The *TBL1X* protein forms part of the thyroid hormone receptor corepressor complex. *TBL1X* mutation results in hypothalamus and pituitary gland resistance to low FT4 levels and a negative shift of the FT4 setpoint (1). TSH and prolactin response to TRH test is however normal (1). Hemizygous males with *TBL1X* pathogenic variants have mild to moderate hypothyroidism and some affected individuals also have hearing deficits (1). Patients with *IRS4* gene mutation have isolated CCH which is only mild with a blunted TSH response and normal/slightly low prolactin response to TRH (1). Individuals with *TBL1X* and *IRS4* pathogenic variants do not exhibit the other clinical features of *IGSF1* variants, such as macro-orchidism with delayed adrenarche or large birth weight. As with *IGSF1* mutation, heterozygous females with *TBL1X* and *IRS4* mutations are usually asymptomatic and have low-normal FT4 levels (1).

Case Presentation

A 3-year-old boy was diagnosed with central hypothyroidism at 18 days old during a workup for prolonged jaundice. He was the sixth child of non-consanguineous parents. His newborn screening cord TSH was 3.997 mIU/L (normal). He was a term infant with a birth weight of 4.3 kg born to a mother with gestational diabetes. He required five days of invasive respiratory support at birth for respiratory distress syndrome. He was later readmitted at 18 days old for nosocomial pneumonia and was found to have prolonged jaundice. A thyroid function test (TFT) performed at that time revealed a normal TSH of 4.3 mIU/L (1.7-9.1 mIU/L) and a low normal FT4 of 10.8 pmol/L (10.5-30 pmol/L). Serial monitoring of thyroid function showed a declining trend in FT4 down to 7.8 pmol/L, with TSH 3.5 mIU/L at 48 days old. He was commenced on L-thyroxine 4 mcg/kg/day daily at two months of age. His thyroxine dose was gradually weaned down from five months of age as his TSH was very low (<0.5 mIU/L) with FT4 levels at the upper range of normal. Thyroxine was later stopped at one year of age due to low thyroxine requirement (1 mcg/kg/day). However, it was restarted one month later as FT4 fell to 9.4 pmol/L (10-17.6 pmol/L) with a lack of TSH response (TSH 5.08 mIU/L) without thyroxine replacement, suggesting central hypothyroidism.

His developmental milestones were normal. Serial growth monitoring revealed weight following the 97th percentile since infancy while height was on the 50th percentile. His calorie intake was excessive for his age and consisted of rice/noodles with meat and vegetables for his three main meals with three servings of snacks (biscuits/bread/ fresh milk) in a day. His present height, weight and body mass index (BMI) at 3 years of age are 93.9 cm (-0.28 SD), 17.8 kg (+1.82 SD) and 20.2 kg/m^2 (+2.71 SD) respectively. Bilateral testicular enlargement (≥4 mL) was observed as early as 2.2 years of age. The right testis increased to 10 mL while the left enlarged to 6 mL at 3 years of age. There were no other signs of puberty. He had no midline defects or other system abnormalities. His hormonal profile was prepubertal with unstimulated luteinizing hormone (LH) of <0.12 IU/L, follicle stimulating hormone (FSH) 2.21 IU/L and serum testosterone <0.45 nmol/L). His serum prolactin was low 57.2 mIU/L (72-592 mIU/L). Peak cortisol was 656.8 nmol/L (normal >500 nmol/L) post synacthen test. Genetic testing by whole-exome sequencing by a commercial diagnostic genetic laboratory (3billion, South Korea), identified a novel hemizygous

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missense variant c.3467T>A (p.Val1156Glu) in the *IGSF1* gene (NM_001555.5) of uncertain significance.

Family Segregation Study

Seven family members (the proband's parents and five siblings) consented to genetic testing. Blood samples were taken for DNA extraction for targeted Sanger sequencing (by 1st BASE, Malaysia) and screening TFT. The genotype and phenotype of the family pedigree are presented in Figure 1.

The proband's 16-year-old elder brother (II2) was found to carry the same c.3467T>A variant (Figure 1). His screening TFT revealed central hypothyroidism. Like the proband, he was relatively large at birth and had normal newborn cord blood TSH screening. He had speech delay and psychomotor retardation since preschool age. He was a slow learner and had poor social interaction with others. His present height, weight and BMI are 168.8 cm (-0.62 SD), 100.4 kg (+2.39 SD) and 35.2 kg/m^2 (+2.43 SD) respectively at 16 years of age. His Tanner puberty staging was genitalia 4, public hair 3, and both testes were enlarged (>25 mL). He had normal pubertal levels of LH (2.13 IU/L), FSH (9.67 IU/L), and serum testosterone (16.64 nmol/L). Serum prolactin was also low at <17.22 mIU/L (72-592 mIU/L). His fasting lipid profile and fasting blood glucose were normal. He was commenced on L-thyroxine 1 mcg/kg/day daily upon diagnosis of central hypothyroidism. Since then, he has shown improvement in his mental processing and social functioning with normalization of FT4.

The probands' mother (I2) and 8-year-old sister (II5) who were carriers for the same *IGSF1* variant, c.3467T>A, had normal TFT but were also obese (BMI 35.9 kg/m^2 and 21.5 kg/m^2 (+1.74 SD), respectively. Other siblings (II1, II3, II4) who did not carry the *IGSF1* variant had normal TFT but variable weight status. His 17-year-old sister (II1) was overweight (BMI 28.5 kg/m^2), while his 14-year-old brother (II3) and 12-year-old sister (II4) had normal BMI. The proband's unaffected siblings had lower birth weights, ranging from 3.0-3.9 kg. The detected *IGSF1* variant (c.3467T>A) was reclassified as likely pathogenic based on the American College of Medical Genetics and Genomics criteria and cosegregation data interpretation in pathogenicity classification (Table 1) (6,7).

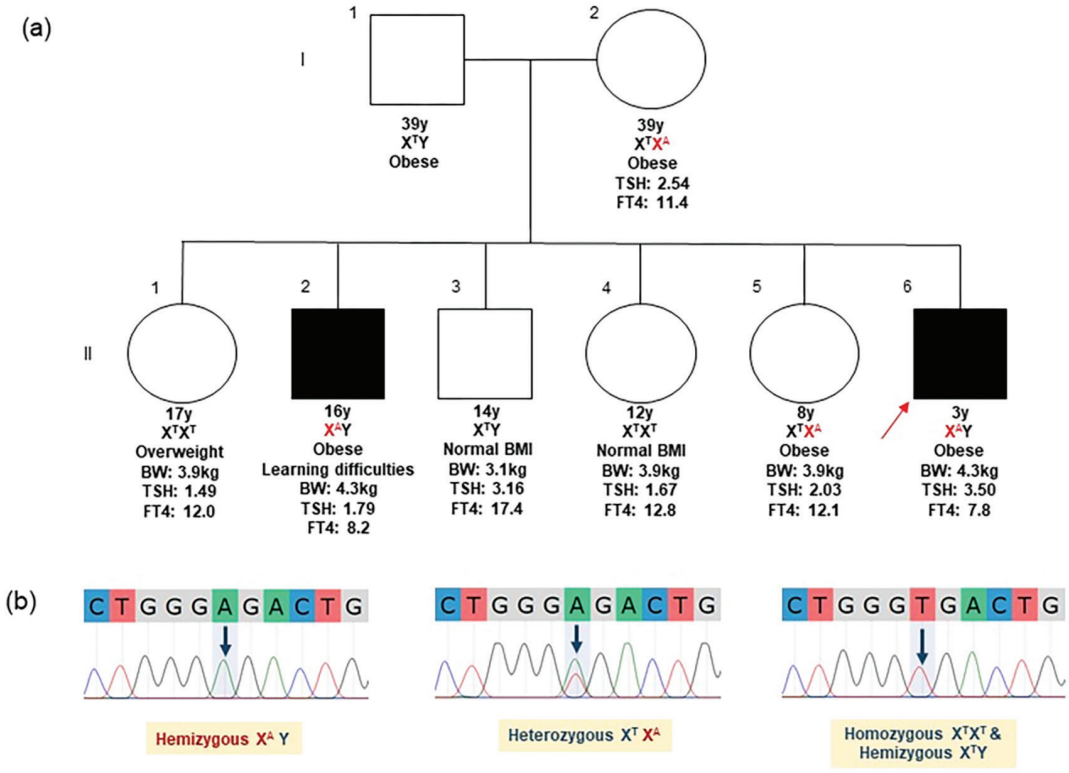

Figure 1. (a) Family pedigree. Filled black symbols represent individuals affected by central hypothyroidism. The present age in years (y) is shown below the symbols. The genotype is shown below the present age. BW, birth weight; BMI, body mass index; TSH, thyroid stimulating hormone (mIU/L); FT4, free thyroxine (pmol/L). A red arrow indicates the proband. (b) Representative chromatograms for targeted Sanger sequencing of the *IGSF1* gene variants identified in the family.

Table 1. *IGSF1* (c.3467T>A) classification according to American College of Medical Genetics and Genomics criteria

Evidence	Category	Description
PM2	Moderate	Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
PP1	Strong	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease.
Classification: Likely pathogenic by fulling American College of Medical Genetics and Genomics criteria		

Discussion

The first cases of *IGSF1* variant were reported among 11 unrelated families in 2012 who exhibited central hypothyroidism, testicular enlargement, and prolactin deficiency (8). Hitherto, this was the most common cause of mild to moderate isolated CCH among males and females and has an incidence rate of approximately 1:100000 (1,9). Patients with *IGSF1* variants have been reported to express a broad spectrum of clinical manifestations (5,10,11). Central hypothyroidism of variable severity is the main finding in all males with *IGSF1* variant, presenting with symptoms of hypothyroidism at different stages in life (5,10,11). The proband (II6) had mild to moderate CCH when he presented in early infancy with prolonged jaundice. The proband's brother (II2) had a later presentation with speech delay and psychomotor retardation at preschool age, and was only found to have moderate CCH in his teens.

Both siblings share the classical phenotype of the *IGSF1* variant-induced syndrome reported in the literature, including increased birth weight, obesity, macro-orchidism and prolactin deficiency (5). Other studies have reported these patients to be overweight or obese despite thyroid hormone replacement (5,12). The mechanism of increased birth weight and obesity is unknown. The relatively high FSH levels in the proband and untreated hypothyroidism in the affected brother may have contributed to the macro-orchidism (13). As *IGSF1* is also expressed in the testes, it is postulated that loss-of-function mutations in *IGSF1* cause the testicular enlargement (13).

Hyperprolactinemia associated with *IGSF1* mutation is yet to be understood but it can affect adrenal function (13). Prolactin receptors are expressed in the adrenal gland and work synergistically with adrenocorticotropin hormone (ACTH) to augment adrenal androgen secretion (14). Delayed adrenarche is a finding often associated with *IGSF1* mutation with prolactin deficiency (5). However, the pituitary-adrenal axis in *IGSF1* mutation is usually intact with adequate cortisol response on ACTH stimulation test, as shown by the proband (5). The affected brother (II2) did not have an ACTH stimulation test but he had no history to suggest adrenal insufficiency. Fertility has reportedly been preserved in individuals with *IGSF1* mutations (5). Clinical and biochemical monitoring for adrenarche and puberty would be required for the proband.

The degree of central hypothyroidism varies in individuals with *IGSF1* mutation, and it is unclear at what FT4 levels patients are affected by hypothyroidism. While some untreated adults generally have normal cognitive functioning with normal height, children with prolonged jaundice, obesity, dyslipidemia, and poor growth respond to the initiation of thyroxine therapy (5). In the case of II2, improvement in mental processing and social functioning was observed after thyroxine replacement as per parental report. As for the proband, his normal development is likely attributed to the early initiation of treatment. It is recommended that treatment be started in all male children with *IGSF1* variant and a treatment trial be given to all male adults and female carriers with low FT4 concentrations (5).

Conclusion

This case study describes the phenotype of two male siblings with a novel *IGSF1* variant, c.3467T>A, that is likely pathogenic based on the family segregation study. The report highlights the importance of genetic testing for *IGSF1* variants in patients with unexplained central hypothyroidism, especially when X-linked inheritance, macro-orchidism without pubarche, high birth weight, obesity or prolactin deficiency are present. Furthermore, a detected *IGSF1* variant on genetic testing of a proband should prompt screening of other seemingly asymptomatic family members who may also benefit from thyroxine replacement.

Ethics

Informed Consent: The proband's family have given written consent for the family segregation study and to publish their case.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Yee Lin Lee, Tzer Hwu Ting, Concept: Yee Lin Lee, Tzer Hwu Ting, King Hwa Ling, Design: Yee Lin Lee, Data Collection or Processing: Yee Lin Lee, Chong Teik Lim, Karuppiah Thilakavathy, Nurul Huda Musa, King Hwa Ling, Analysis or Interpretation: Yee Lin Lee, Tzer Hwu Ting, Chong Teik Lim, Karuppiah Thilakavathy, Nurul Huda Musa, King Hwa Ling, Literature Search: Yee Lin Lee, Tzer Hwu Ting, Writing: Yee Lin Lee, Tzer Hwu Ting, Chong Teik Lim, Karuppiah Thilakavathy, King Hwa Ling.

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CASE REPORT

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Exploring Multiple Endocrinological Issues and Dysautonomia in a Rare Case: Hypoparathyroidism in MIRAGE Syndrome

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ABSTRACT

MIRAGE syndrome is a rare multisystemic disorder characterized by the following manifestations: myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy. Dysautonomia has also been reported, but rarely. We present a 6.5-year-old girl, who was first admitted with short stature. On follow-up, she exhibited multiple endocrinological issues, including transient hypothyroidism, primary hypoparathyroidism and dysautonomia, along with multisystem involvement. Further investigations revealed recurrent moniliasis, low IgM levels, and transient monosomy 7 in the bone marrow. Whole exome sequencing revealed a heterozygous pathogenic variant of *SAMD9* (c.2159del; p.Asn720ThrfsTer35). Additional complications observed during follow-up included medullary nephrocalcinosis, hypomagnesemia, hypomagnesuria, hypophosphatemia, decreased glomerular filtration rate, and nephrotic proteinuria. The patient also developed hyperglycemia, which was managed with low-dose insulin. This case highlights the diagnostic challenges and the diverse phenotypic presentation that may occur in MIRAGE syndrome.

Keywords: Dysautonomia, hypoparathyroidism, MIRAGE syndrome, monosomy 7, *SAMD9*

What is already known on this topic?

MIRAGE syndrome is a rare, multisystemic disorder It is characterized by myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy. The syndrome is associated with pathogenic variants in *SAMD9*.

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What this study adds?

This case report describes a 3.5-year-old girl with a previously reported *SAMD9* variant (c.2159del; p.Asn720ThrfsTer35). The case report highlights the presence of primary hypoparathyroidism and diabetes mellitus in a patient with MIRAGE syndrome, which expands the spectrum of associated endocrinological issues. Dysautonomia is a relatively rare finding in MIRAGE syndrome and further emphasizes the heterogeneity of clinical presentations in MIRAGE syndrome. Finally, the diagnostic challenges associated with MIRAGE syndrome are illustrated, as its diverse phenotypic presentation can make it difficult to recognize and diagnose the condition rapidly and accurately.

Introduction

MIRAGE syndrome is a rare multisystemic disorder characterized by Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy. MIRAGE is a recently described autosomal dominant disorder caused by gain-of-function (GOF) mutations in the *SAMD9* gene located on chromosome 7q21.2 (1). MIRAGE syndrome is typically diagnosed in early childhood. While the classical features have been well-documented, autonomic dysfunction, such as insensitivity and anhidrosis, has been infrequently reported (2-5). Only 44 affected individuals with MIRAGE syndrome have been documented (6).

Variants in *SAMD9* may cause structural and functional changes in the endosome system. This may result in defective recycling of plasma membrane epidermal growth factor receptors and the accumulation of giant vesicles in adrenocortical cells. These alterations may disrupt normal cellular processes and contribute to developing growth restriction, dysautonomia, and other symptoms observed in MIRAGE syndrome.

Moreover, the loss of chromosome 7 carrying the *SAMD9* mutation may be associated with developing myelodysplastic syndrome (MDS) in some patients (1). Monosomy 7 significantly impacts the survival of individuals with MIRAGE syndrome. Survival in MIRAGE syndrome is generally poor, with a median age of mortality of three years. Around 60% of deaths are caused by infectious diseases. While there have been isolated reports of individuals with MIRAGE syndrome reaching the age of 20 years, the overall survival rates for this condition remain low (6).

Here, we present a case of MIRAGE syndrome with the additional clinical features of primary hypoparathyroidism and dysautonomia, highlighting the diagnostic challenges, clinical manifestations, and multidisciplinary management. To the best of our knowledge, primary hypoparathyroidism and diabetes have not been reported within the endocrine phenotype of MIRAGE syndrome previously.

Case Report

A female infant was born to healthy, non-consanguineous parents at 39 weeks of gestation, with a birth weight of 2790 g. She had unremarkable antenatal ultrasound findings. She exhibited normal neurodevelopmental milestones. However, at 15 days of age, she was diagnosed with compensated congenital hypothyroidism [thyroid stimulating hormone 88.47 mIU/L, fT4 14.52 pmol/L (13.9-26.19), urine iodine 95 mcg/L (100-200), thyroid ultrasound normal with right lobe 11x6x4 mm, left lobe 16x6x5 mm isthmus 1.5 mm; total volume 0.39 mL (-1.3 standard deviation (SD))]. Levothyroxine (LT4) treatment was initiated at 8 mcg/kg/day.

At one year of age, the patient developed thrombocytopenia and neutropenia, which led to a diagnosis of monosomy 7 (45, XX, -7[45]/46, XX[5]) based on bone marrow and peripheral blood tests. However, subsequent bone marrow aspiration at 16 months of age revealed a normal karyotype and normal hemogram, suggesting transient monosomy 7.

At 3.5 years of age, the patient presented to our clinic with short stature and hand stiffness. Physical examination revealed a short stature of 88 cm (-2.8 SD) and a low body mass index (BMI) of 14 kg/m^2 (-1.3 SD). The patient was prepubertal and exhibited dysmorphic facial features, including a short and narrow forehead, synophrys, prominent supraorbital folds, narrow nasal bridge, bulbous nose, full cheeks, high palate, thin lips, and a hypoplastic clitoris. Systemic examinations revealed a 1/6 murmur. Biochemical evaluation showed abnormal levels of calcium (Ca) 6.4 mg/dL (8.5-10.5), phosphorus 7.36 mg/dL (3.8-6.5), parathyroid hormone 8.9 pg/mL with normal magnesium (Mg) 2 mg/dL (1.7-2.1), alkaline phosphatase 217 U/L (142-335), urine Ca/creatinine clearance ratio: 0.24 and 25-hydroxyvitamin D of 53 mcg/L. The patient was diagnosed with primary hypoparathyroidism. Medical history revealed that the daily Ca intake was approximately 850-1000 mg. Recurrent moniliasis and low IgM levels (64.8 mg/dL, reference range: 78-261) were also observed. Di George Syndrome was ruled out through fluorescence *in situ* hybridization (FISH) test. An atrial septal defect was detected and normal hearing was reported. Tests for polyglandular autoimmune syndrome type 1, including adrenocorticotropic hormone (ACTH) levels of 32.1 pg/mL and cortisol levels of 11.12 ng/dL, showed normal results. Furthermore, tests for anti-21-hydroxylase antibody, anti-gliadin antibody (total IgA 0.893 g/L, reference range: 0.39-1.7), anti-thyroid peroxidase antibody, and anti-thyroglobulin antibody were negative. A standard dose ACTH stimulation test was also normal (stimulated cortisol 26.3 mcg/dL). Hypoparathyroidism was successfully managed with calcitriol treatment.

The patient underwent laboratory and imaging evaluations for short stature. Hemogram, biochemical parameters, liver and kidney function, blood glucose, tissue transglutaminase IgA autoantibody, serum total Ig A level, and urine analysis were normal. Insulin-like growth factor 1 (IGF-1) was 280 ng/mL (reference range: 84-447), IGFBP3 was 1700 ng/mL (reference range: 1400-4250), and L-Dopa was 4 ng/mL. The bone survey showed normal dense ivory epiphysis, and pituitary MRI revealed no abnormalities in pituitary size (4.3 mm, reference range: 4±0.7 mm). Although the patient was monitored and evaluated for growth hormone deficiency, growth hormone treatment was avoided due to the patient's history of transient monosomy 7 and the potential risk of developing malignancies.

At the age of four years, treatment with LT4 was discontinued. During the follow-up periods, thyroid function tests were normal. In addition, the patient's cognitive function and neurodevelopmental milestones were assessed during these visits and were within the normal range.

During the follow-up at 4 years and 2 months of age, the patient presented with progressive sensorineural hearing loss and was subsequently diagnosed with hyperglycemia. The fasting blood sugar was 106 mg/dL, while the insulin level was 3 µIU/mL, and the C-peptide was 0.524 ng/mL. The random blood glucose was 332 mg/dL, and HbA1C was 8.3%. Autoantibody tests, including anti-glutamic acid decarboxylase (0.55 U/mL, reference range: 0-1), anti-insulin antibody (4.3%, reference range: 0-5.5%), and anti-islet antibody, were negative. Parents fasting blood glucose (FBG), and HbA1c (maternal FBG 83 mg/dL, HbA1c 5.5%; paternal FBG 92 mg/dL HbA1c 5.4%) were all normal.

Low-dose insulin therapy (0.6 U/kg/day) was initiated for glycemic control. Renal ultrasonography detected medullary calcinosis, but no other renal anomalies were observed. Laboratory investigations for mitochondrial cytopathy, including blood amino acid levels, tandem mass spectrometry analysis of organic acids in urine, serum lactate level (15.38 mg/dL, reference range: 10-14), and serum pyruvate level (0.45 mg/dL, reference range: 0.5-1), did not reveal any pathological findings. Mitochondrial DNA sequencing analysis was normal.

Due to the involvement of multiple systems and severe short stature, microarray analysis was assessed and was reported normal. Considering the patient's history of transient monosomy 7 and significant short stature, MIRAGE syndrome was initially suspected. However, since there was no adrenal insufficiency and the presence of endocrinopathies such as hypoparathyroidism and diabetes mellitus, which are not typically associated with MIRAGE syndrome, whole-exome sequencing (WES) was performed. WES analysis identified a heterozygous variant (c.2159del; p.Asn720ThrfsTer35) in *SAMD9*, classified as likely pathogenic. Consequently, the patient was diagnosed with MIRAGE Syndrome. Segregation analysis revealed that the mother carried the heterozygous mutation in *SAMD9*, while the father had a normal genotype. The patient's gonadal hormone levels were assessed for potential accompanying hypogonadism associated with MIRAGE syndrome. Follicle-stimulating hormone was 4.4 mIU/mL, luteinizing hormone (LH) was 0.4 mIU/mL, estradiol was 5 pg/mL, and anti-Müllerian hormone (AMH) at 8.85 pmol/L (normal range: 1.5-12.6 pmol/L), indicating a prepubertal status. No data from the mini puberty period were available.

During follow-up, the patient experienced several hospital admissions due to intractable vomiting episodes related to dysautonomia. Episodes of hypotension, tachycardia, feeding difficulties, and absence of tears were observed. Body temperature regulation was normal. She recovered with symptomatic supportive treatment in episodic periods. At 4 years and 7 months of age, the patient presented with hypomagnesemia (serum Mg levels of 1.23 mg/dL, reference range: 1.7-2.1 mg/dL) and hypermagnesiuria (FeMg 12%). A decreased glomerular filtration rate (GFR) of 85 mL/min/1.73 m^2 and nephrotic proteinuria (9 mg/m^2/day) were also observed. Mg supplementation was initiated, and the patient was put under close nephrology follow-up.

At 6 years of age, the patient demonstrated developmental milestones such as independent walking and the ability to navigate stairs. However, a comprehensive evaluation revealed a delay in gross motor development and increased support needs compared to peers. Her gross motor development was judged to be -2 SD, indicating a developmental delay. Cognitive development was in the low normal range.

On the last follow-up at the age of 6.5 years, the patient's height was 94 cm (-5 SD), and BMI was 12.5 kg/m^2 (-2.5 SD).

On follow-up, ACTH stimulation test was normal. Adrenal insufficiency has not been confirmed. The most recent ACTH level was 25 pg/mL, while the cortisol level was 17.7 mcg/dL. The patient is on basal insulin therapy at 0.2 U/kg/day with regulated blood glucose and is supplemented with calcitriol and Mg. A multidisciplinary team is closely monitored to ensure comprehensive care and follow-up (Table 1, Figure 1).

Discussion

The protein product of *SAMD9* affects the endosome system, yet its precise mechanisms remain inadequately elucidated. *SAMD9*/*SAMD9L* disrupts protein translation and causes MIRAGE syndrome, involving many systems and is generally associated with a poor prognosis (1,6).

We describe the diagnostic challenges and various clinical manifestations associated with MIRAGE syndrome. Typically,

Table 1. Features, manifestations, and treatment of a patient with MIRAGE syndrome

Features	Manifestation	Age at diagnosis	Treatment
Myelodysplasia	Incident thrombocytopenia and neutropenia during routine laboratory evaluation, led to a diagnosis of monosomy 7 (45, XX, -7[45]/46, XX[5]).	1 year of age	Providing blood transfusion to manage severe cases of anemia and thrombocytopenia
Infection	Not observed yet	-	-
Growth restriction	Weight, height/length, and head circumference <-2.0 SD despite the sufficient caloric intake	3.5 years of age	Adequate caloric intake
Adrenal deficiency	Not observed yet	-	-
Genital anomalies	Hypoplastic clitoris	3.5 years of age	-
Enteropathy	Not observed yet	-	-
Autonomic dysfunction	Episodes of hypotension, intractable vomiting, feeding difficulties, and absence of tears	4 years and 7 months of age	Symptomatic supportive treatment

SD: standard deviation

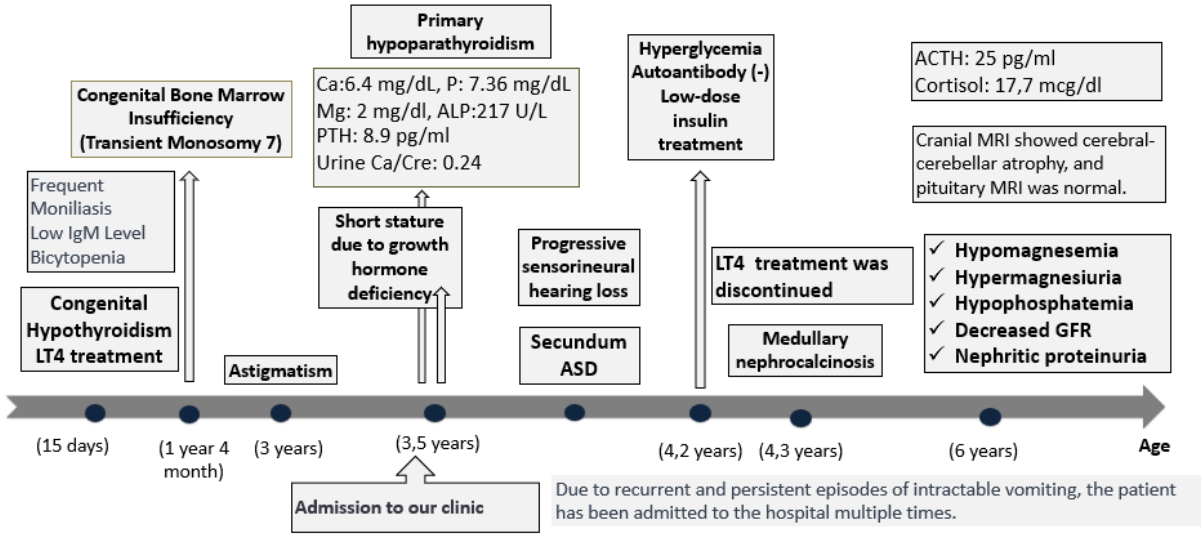

Figure 1. Timeline of the patient's clinical presentation
Ca: calcium, Mg: magnesium, PTH: parathyroid hormone, P: phosphorus, ALP: alkaline phosphatase, Ca/Cre: Ca/creatinine clearance ratio, ACTH: adrenocorticotropic hormone, MRI: magnetic resonance imaging, LT4: levothyroxine, ASD: atrial septal defect, GFR: glomerular filtration rate

MIRAGE syndrome manifests with bicytopenia during infancy (1,3,6,7). Adrenal hypoplasia is a well-known endocrinopathy associated with MIRAGE syndrome. It is frequently detected in investigations to determine the underlying causes of adrenal insufficiency, particularly in individuals with a history of intrauterine growth restriction, postnatal growth retardation, and extra-adrenal involvement. In our case, a standard dose ACTH stimulation test showed sufficient peak cortisol levels, and treatment initiation has not yet been initiated. Upon reviewing the existing literature, adrenal insufficiency was identified in 70% of the 50 reported cases, indicating a relatively low sensitivity for this particular finding (1,6). Although adrenal hypoplasia was absent in our case, the patient displayed rare manifestations within the endocrine system, which is a noteworthy observation.

Due to the rarity of the disease, it is difficult to define the phenotype-genotype relationship. An individual with the same *SAMD9*:c.2159del variant, which was classified as likely pathologic in genetic databases (Franklin by Genoox, ClinVar) is reported. However, we could not find a published case report. To the best of our knowledge, only one case of MIRAGE syndrome has been reported from Türkiye with the variant c.2920G>A (p.E974K) in *SAMD9*. This patient presented with adrenal hypoplasia on the 15th day of life (7). Considering the rarity of the disease and the limited number of diagnosed cases worldwide, the phenotype-genotype relationship may differ on a variant-specific basis, which suggests that adrenal hypoplasia might not have developed yet or may never develop in our case. One patient with c.2318T>C in *SAMD9* has been reported who

developed adrenal hypoplasia at the age of 10 years (8). The effect of the variant in our case may be observed at a later age; hence close monitoring of the patient is ongoing.

This case report contributes to the existing literature by presenting a case of MIRAGE syndrome with additional clinical manifestations, including a previously unreported endocrine representation of primary hypoparathyroidism. The presence of primary hypoparathyroidism might be related to the clinical spectrum of the syndrome.We excluded other conditions that could cause hypoparathyroidism through clinical and laboratory investigations and detailed genetic analyses, including FISH, WES, and microarray analysis. The patient also exhibited subtle findings of clitoral hypoplasia. Since histological examination was not performed due to its invasive nature, ovarian dysgenesis could not be confirmed. However, the AMH level was in the normal range for her age. Close monitoring is also maintained to assess for potential gonadal insufficiency that may occur during puberty.

The *SAMD9* gene product plays a crucial role in regulating cell growth and differentiation, and GOF mutations in this gene have been implicated in the pathogenesis of MIRAGE syndrome (1,6). This mechanism may explain the severe short stature observed in our case. Interestingly, the patient also developed hyperglycemia at around four years of age, requiring low-dose insulin therapy. We initially diagnosed the patient with diabetes while there were still beta cell reserves in the pancreas. We observed decreased C-peptide levels during follow-up, indicating a loss of beta cell reserves, as laboratory tests showed. Despite the depletion of beta cell reserves, it was intriguing to see that blood sugar regulation was achieved under low-dose insulin therapy without any dose increase. Diabetes autoantibodies were also negative. No variants were shown in mitochondrial DNA analysis. This clinical exhibition was different from the classic presentation of type 1 diabetes mellitus and may be linked to the as-yet-undisclosed mechanisms of the syndrome. To the best of our knowledge, diabetes has not been reported in MIRAGE syndrome until now. Although the exact mechanism underlying this glucose dysregulation is not fully understood, it may be related to the underlying genetic abnormalities and the dysregulation of multiple organ systems observed in MIRAGE syndrome. Further research is needed to elucidate the pathophysiological mechanisms linking MIRAGE syndrome and abnormalities in glucose metabolism.

GOF mutations in *SAMD9* generally cause MIRAGE syndrome. The excessive antiproliferative effect by *SAMD9* of-function GOF variants induce various genetic alterations, including loss of chromosome 7 or its long arm (monosomy 7/7q), second-site loss-of-function (LOF) variants in cis or trans configuration, as well as uniparental disomy for the long arm of chromosome 7. However, the involvement of compensatory mechanisms is not clear (9). While inheritance of *SAMD9*-linked MIRAGE from an asymptomatic mother has been reported by Roucher-Boulez et al. (10), these instances were attributed to a reversion mechanism observed in the mother. She carried the GOF variant involved in MIRAGE, alongside another stop mutation in cis, which appeared *in utero* in her but was not transmitted to her child. Variable expressivity and incomplete penetrance in MIRAGE syndrome are consistent with an autosomal dominant inheritance pattern (1,6,11). Segregation analysis revealed that the mother was heterozygous for the c.2159del(p.Asn720ThrfsTer35) variant in *SAMD9*, while the father was normal. Variable age of onset, incomplete penetrance, and expressivity differences are frequently observed in autosomal dominant inherited diseases (11). Therefore, it is common to find cases where children are affected, but parents do not show clinical symptoms. These factors may explain the absence of the disease phenotype in the mother. However, a frameshift variant was detected in our patient, which cause quiet likely a LOF variant. Mehawej et al. (9) reported a case of autosomal recessive MIRAGE-like disease, who had bi-allelic LOF variants in the *SAMD9*. The discovery of a heterozygous LOF in the patient exhibiting a MIRAGE-like phenotype suggested the potential presence of another heterozygous LOF variant inherited from the father, which might have been undetected. This speculation would explain why the mother remained asymptomatic due to the same heterozygous LOF variant. Genetic counseling was provided to the family to elucidate potential inheritance patterns and assist in understanding the risk of recurrence.

MIRAGE syndrome involving *SAMD9* and *SAMD9L* mutations, some of which exhibit transient monosomy 7, has been suggested to be a clonal event followed by somatic correction through uniparental disomy for chromosome 7q (UPD7q) with double wildtype *SAMD9L* (12). Transient monosomy 7 has also been reported in pediatric patients with MDS. Typically, patients with MDS die due to subsequent infections (1,6,7,12,13). *SAMD9* variants may cause syndromic or non-syndromic MDS. Therefore, there may be children who may have isolated enteropathy, isolated immune deficiency, or isolated genital anomalies, as reported by Narumi et al. (1). The presented patient is being closely monitored for the development of MDS.

In recent years, there have been reported cases demonstrating both dysautonomia and proteinuria (5,6,7). Our patient has exhibited proteinuria from the age of 4 years and 7 months. Furthermore, clinical manifestations indicative of autonomic dysfunction have been observed, including frequent episodes of hypotension, feeding difficulties, and absence of tears. Although specific diagnostic tests, such as contractions with the methacholine eye drop test, evaluation of catecholamine metabolite levels, and a histamine intradermal reaction test

have not been conducted, the patient's clinical presentation aligns with symptoms commonly associated with dysautonomia. In addition to the multisystemic manifestations, the patient has experienced recurrent and intractable vomiting episodes, which are indicative of potential dysautonomia symptoms. A case series on hereditary sensory and autonomic neuropathies underscores the presence of autonomic dysfunction (2,3,4,5). Therefore, we suggest that recurrent vomiting episodes should be considered indicative of dysautonomia in MIRAGE syndrome.

Renal involvement in MIRAGE syndrome warrants consideration, as evidenced by the development of medullary nephrocalcinosis, hypomagnesemia, hypomagnesuria, hypophosphatemia, decreased GFR, and nephritic proteinuria, which have been reported in other cases with renal involvement in MIRAGE syndrome (5,6,8).

Hematopoietic stem cell transplantation is the established curative approach. However, syndrome-specific comorbidities may impede treatment success and cause additional challenges, such as possible adverse outcomes and potential complications (14). The CRISPR/Cas9 system holds promise as a future treatment modality for MIRAGE (15). Thus, it becomes imperative to understand the clinical manifestations and molecular mechanisms associated with germline *SAMD9* variants to facilitate the effective management of the disease.

In conclusion, this case report expands the multisystemic nature of MIRAGE syndrome and highlights the diagnostic challenges associated with this rare disorder. The presented case of MIRAGE syndrome is the first description of primary hypoparathyroidism in a patient with MIRAGE. Additional complications such as symptoms of dysautonomia symptoms, glucose dysregulation, and renal and hematological abnormalities highlight the need for multidisciplinary management in individuals with MIRAGE syndrome. Further research is warranted to elucidate the underlying mechanisms linking *SAMD9* variants to the clinical features of MIRAGE syndrome and to develop targeted therapeutic interventions for this rare condition.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Hasan Fatih Çakmaklı, Gizem Şenyazar, Zehra Aycan, Concept: Sirmen Kızılcan Çetin, Fatih Çakmaklı, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Gizem Şenyazar, Zehra Aycan, Serdar Ceylaner, Analysis or Interpretation: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Literature Search: Zeynep Şıklar, Gizem Şenyazar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Writing: Elif Özsu, Zeynep Şıklar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu.

Conflict of Interest: One author of this article, Merih Berberoğlu is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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CASE REPORT

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Hereditary Severe Insulin-resistance Syndrome and Acanthosis Nigricans Caused by Novel Mutations in the *INSR* Gene

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ABSTRACT

Most cases of hereditary severe insulin-resistance syndrome (H-SIRS) are linked to mutations in the insulin receptor (*INSR*) gene. Patients with H-SIRS typically manifest symptoms of hyperinsulinemia, insulin resistance, and diabetes mellitus. Other symptoms include impaired glucose regulation, hyperandrogenism, and the presence of acanthosis nigricans (AN). In this report, we present two cases of H-SIRS in female children exhibiting various symptoms, including hyperinsulinemia, fasting hypoglycemia, postprandial hyperglycemia, overweight, fatty liver, hyperandrogenism, and varying degrees of AN. One patient also presented with mental retardation. Gene sequencing identified specific mutations in the *INSR* gene for both patients: c.2663A > G (p.Tyr888Cys) in Patient 1 and c.38_61del (p.Pro13_Ala20del) in Patient 2. These mutations both have the potential to disrupt the interaction between the insulin receptor, *INSR*, and insulin, leading to abnormal insulin signaling, insulin resistance, and various clinical manifestations.

Keywords: Insulin receptor, insulin resistance, hyperinsulinemia, hyperandrogenism, impaired glucose regulation, acanthosis nigricans.

What is already known on this topic?

Hereditary severe insulin-resistance syndrome (H-SIRS) is an extreme form of insulin resistance caused by mutations in the insulin receptor (*INSR*) gene. Acanthosis nigricans (AN) is a cutaneous manifestation of H-SIRS. AN demonstrates an 81% positive predictive value for insulin resistance.

What this study adds?

This study reports two cases of H-SIRS in female children. Genetic testing showed a c.2663A>G (p.Tyr888Cys) missense mutation in one patient and a c.38_61del (p.Pro13_Ala20del) frameshift mutation in *INSR* in the other patient. Both mutations have the potential to impact the binding of *INSR* to its ligand, insulin.

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Introduction

Insulin resistance is defined as a decrease in the sensitivity of target organs to the normal physiological effects of insulin. Its characteristics include impaired glucose uptake in muscle and adipose tissue, increased hepatic gluconeogenesis and glycogen breakdown, increased risk of obesity, impaired glucose tolerance, abnormal blood lipid levels, and endothelial dysfunction (1). Hereditary severe insulin-resistance syndrome (H-SIRS) is an extreme form of insulin resistance, accounting for approximately 0.1% to 0.5% of hospitalized patients with diabetes. H-SIRS caused by mutations in the insulin receptor (*INSR*) gene can be classified into Donahue syndrome (DS), Rabson-Mendenhall syndrome (RMS), and type A insulin resistance syndrome (A-IR), while type B insulin resistance is associated with the production of insulin autoantibodies (2,3). The clinical phenotypes of H-SIRS include hyperinsulinemia, abnormalities in glucose homeostasis, dyslipidemia, and acanthosis nigricans (AN). It is also characterized by ovarian dysfunction and excessive androgen levels in women. Most DS or RMS patients have bi-allelic gene variations resulting in abnormalities in the *INSRα* subunit, resulting in more severe symptoms, such as intrauterine and postnatal growth retardation, reduced subcutaneous fat, hirsutism, and characteristic facial changes. A-IR patients have heterozygous variations in the intracellular tyrosine kinase domain of the β subunit (2,3).

Patients with AN typically exhibit pigmentation and excessive keratinization in skin folds, resulting in darkening, roughness, or a velvety texture in localized areas. In certain instances, it may progress to nipple- or wart-like patches. Furthermore, the presence of AN correlates with insulin resistance, metabolic syndrome, and polycystic ovary syndrome (PCOS) in overweight and obese children (4). A single-center study conducted among teenagers in the UK reported that patients with AN exhibited significantly higher median fasting insulin levels, average fasting blood glucose levels, and median insulin resistance index scores in comparison to the control group (215 pmol/L vs. 126 pmol/L; 4.7 mmol/L vs. 4.5 mmol/L; 6.4 vs. 3.7). AN has been reported to have an 81% positive predictive value for insulin resistance, suggesting its utility as a marker for type 2 diabetes mellitus (T2DM) in teenagers (5). The present study contributes two cases of adolescent H-SIRS patients with AN resulting from two novel *INSR* mutations, thereby expanding the genotype and phenotype spectrum of this disease.

Patients and Research Methods

Case Introduction

Patient 1

The medical history of Patient 1 was as follows. She was a 12 years old and initially presented to The First Hospital of Lanzhou University because of thickening of the skin of the neck, armpits, groin, and popliteal fossa with hyperpigmentation which had been evident for eight years. She was a full-term delivery, but birth weight and length were unknown. There was no history of complications during pregnancy, but she had exhibited an introverted personality since childhood, she had suspected intellectual disability, and had not started menstruation. There was no history of similar diseases in the family.

On physical examination she was 159 cm (75th-90th percentile for same age and gender), weight was 65 kg (over 97th percentile for same age and gender), body mass index (BMI) was 25.71 kg/m^2 (over 97th percentile for same age and gender) (6). Examination showed skin thickening with hyperpigmentation in the neck, armpits, groin, and popliteal fossa, appearing velvety with no skin tags, normal subcutaneous fat, no excessive body hair (Ferriman-Gallwey Score: 4) (7) and no striae. She had no physical deformities, had Tanner stage 2 breast development, there was no lactation, and she had normal external female genitalia with no clitoromegaly.

Oral glucose tolerance (OGTT) and insulin stimulation tests revealed fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia (Table 1). In addition, her karyotype was 46,XX. She had normal liver function, kidney function, blood lipid, and no relevant autoantibodies (Table 2). However, there was elevated serum uric acid and elevated testosterone levels with normal follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, prolactin androstenediol, and dehydroepiandrosterone. Moreover, normal adrenocorticotropic hormone (ACTH), cortisol rhythm and 24-hours urinary free cortisol level were all normal. Abdominal ultrasonography suggested a fatty liver, and hand radiography for bone age assessment indicated an advanced bone age (between the ages of 15 and 17 years) greater than the actual age (12 years old).

Patient 2

This girl first presented to the First Hospital of Lanzhou University at the age of 10 years due to the discovery of thickening of the skin of the neck, armpits, groin, and popliteal fossa with hyperpigmentation which had been present for five years. She was also a full-term delivery with a birth weight of 2.8 kg. Of note, menstruation had occurred twice when she was nine years old, with light red color, no dysmenorrhea, no blood clots, and lasted about 3-4 days each time. At the time of presentation there was no menstruation. There was no history of similar diseases in the family.

At presentation her height was 155 cm (over 97th percentile for same age and gender), and weight was 60 kg (over 97th percentile for same age and gender), resulting in a BMI of 24.97 kg/m^2 (over 97th percentile for same age and gender)(6).

Table 1. Oral glucose tolerance test and islet function determination of the patients

Glucose levels and pancreatic island function	Patient 1	Patient 2	Reference ranges
Glu (0 min) (mmol/L)	4.46	3.98	3.9-6.1
Glu (30 min) (mmol/L)	6.53	10.69	
Glu (60 min) (mmol/L)	7.63	11.12	
Glu (120 min) (mmol/L)	8.39	11.10	
Glu (180 min) (mmol/L)	6.97	11.23	
Ins (0 min) (mIU/L)	84.90	95.03	1.9-23
Ins (30 min) (mIU/L)	>300.00	>300.00	
Ins (60 min) (mIU/L)	>300.00	>300.00	
Ins (120 min) (mIU/L)	>300.00	>300.00	
Ins (180 min) (mIU/L)	>300.00	>300.00	

Glu: glucose; Ins: insulin

Table 2. Summary table of the clinical data of the patients

Inspection item		Patient 1	Patient 2	Reference ranges
Gender		Female	Female	
Age (year)		12	10	
Chromosome		46, XX	46, XX	
BMI (kg/m^2)		25.71	24.97	Overweight: greater than or equal to the 85th percentile of BMI specific to age and gender (10 years female BMI≥19.60; 12 years female BMI≥21.12). Obesity: greater than or equal to 90th percentile for age and sex specific BMI (10 years female BMI≥22.60; 12 years female BMI≥24.89) (7).
Laboratory investigations	AST (U/L)	25	14	14-44
	ALT (U/L)	28	16	7-30
	Scr (μmol/L)	52.1	47.90	27-66
	SUA (μmol/L)	103	337	125-420
	TC (mmol/L)	2.63	3.74	3.6-5.7
	TG (mmol/L)	1.42	1.18	0.8-1.8
	LDL-c (mmol/L)	1.62	2.46	1.55-3.7
	HDL-c (mmol/L)	0.79	0.86	0.8-1.8
Abdominal ultrasound		**Fatty liver**	**Fatty liver**	
GH (ng/mL)			0.36	0.123-8.050
IGF-1 (ng/mL)			543.00	123.0-427.0
IGFBP-3 (ng/mL)			5310	3116-6761
Autoantibodies	ANA	Negative	Negative	Negative
	AMA	Negative	Negative	Negative
	ANuA	Negative	Negative	Negative
	AHA	Negative	Weakly positive	Negative

Table 2. Continued

Inspection item		Patient 1	Patient 2	Reference ranges
Sex hormones	FSH (mIU/mL)	5.41	3.47	Follicullar phase: 3.50-12.50; Ovulatory period: 4.70-21.50; Luteal phase: 1.70-7.70; Menopause: 25.80-134.80
	LH (mIU/mL)	8.04	9.05	Follicullar phase: 2.40-12.60; Ovulatory period: 14.00-95.60; Luteal phase: 1.00-11.40; Menopause: 7.70-58.50
	E2 (pg/mL)	24.50	25.20	Follicullar phase: 12.40-233.00; Ovulatory period: 41.00-398.00; Luteal phase: 22.30-341.00; Menopause: 0-138.00; Early pregnancy: 154.00-3243.00; Middle pregnancy: 1561.00-21280.00; Late pregnancy: 8525.00-30000.00
	PROG (ng/mL)	0.200	0.420	Follicullar phase: 0.057-0.893; Ovulatory period: 0.121-12.00; Luteal phase: 1.83-23.90; Menopause: 0-0.126; Early pregnancy: 11.00-44.30; Middle pregnancy: 25.40-83.30; Late pregnancy: 58.70-214.00
	PRL (ng/mL)	7.49	16.80	4.79-23.30
	T (ng/dL)	41.70	70.90	Tanner by stages: 1: 0-6.10 2: 0-10.40 3: 0-23.70 4: 0-26.80 5: 4.60-38.30
	DA (ng/mL)	1.67	3.18	0.3-3.5
	DHEA (μg/dL)	64.60	79.20	35-430
Cortisol and ACTH rhythm	ACTH (8 am) (pg/mL)	47.80	39.50	7.20-63.30
	ACTH (4 pm) (pg/mL)	19.10	38.80	
	ACTH (0 am) (pg/mL)	8.85	10.60	
	Cor (8 am) (μg/dL)	11.70	7.25	6.02-18.40
	Cor (4 pm) (μg/dL)	4.40	6.89	2.68-10.50
	Cor (0 am) (μg/dL)	1.07	0.74	
	24 h UHC (μg/24 h)	365.52	264.84	75.0-520.0

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Scr: serum creatinine; SUA: serum uric acid; TC: total cholesterol; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; GH: growth hormone; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor binding protein 3; ANA: antinuclear antibody; AMA: anti-mitochondrial antibody; ANUA: anti-nucleosome antibody; AHA: anti-histone antibody; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol 2; PROG: progesterone; PRL: prolactin; T: testosterone; AD: androstendione; DHEA: dehydroisoandrosterone; ACTH: adrenocorticotropic hormone; Cor: cortisol; UFC: urinary-free cortisol

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She exhibited thickened and pigmented skin at the neck, armpits, groin, and armpits. There were nipple-like nodules in the neck and armpits with pigmentation, mostly in joint folds, scattered papules on her back like millet grains with normal skin in between the areas of rash, accompanied by itching, increased body hair (Ferriman-Gallwey Score: 9) (7), no striae and no skin tags. She was bilateral Tanner B2 with no lactation. Of note, she exhibited enlarged female external genitalia with an enlarged clitoris (about 2-3 cm) (Figure 1).

OGTT and insulin release test suggested fasting hypoglycemia, diabetes, and hyperinsulinemia (Table 1). Her karyotype was 46,XX. Laboratory testing reported normal liver function, kidney function, blood lipids, and blood uric acid. Glycosylated hemoglobin was 7% and she had weakly positive histone antibody (1:100) but was negative for anti-islet cell antibody and anti-glutamic acid decarboxylase antibody. This patient also exhibited elevated testosterone level, while FSH, LH, estradiol, progesterone, prolactin, androstenediol, and dehydroepiandrosterone were all normal. ACTH and cortisol rhythms were normal, and 24-hours urine free cortisol level was also normal. She had elevated growth hormone and insulin-like growth factor-1, and insulin-like growth factor binding protein-3 was normal. Abdominal ultrasonography suggested fatty liver.

Based on the symptoms of hyperinsulinemia, fasting hypoglycemia, postprandial hyperglycemia, overweight, fatty liver, and hyperandrogenemia in two patients, as well as various degrees of manifestations of AN, a preliminarily diagnosis of insulin resistance syndrome was made.

It is worth noting that these two girls were not related.

Methods

Gene Sequencing

Peripheral venous blood (4 mL) was collected from both patients. Genomic DNA was extracted using the Qiagen FlexiGene DNA Kit (Qiagen, Germany) and stored at -20 °C for future use. This study adhered to the ethical principles outlined in the Declaration of Helsinki, and both patients' guardians/parents signed written informed consent forms approved by the Ethics Committee of the First Hospital of Lanzhou University (approval no.: LDYYLL-2023-487).

The DNA samples were fragmented using an ultrasonic disruptor, resulting in DNA fragments of 150-300 bp. Adapters were added to both ends of the fragmented genome, followed by PCR library amplification and purification to repair the sticky ends. Subsequently, the post-library amplified DNA underwent

Figure 1. Pedigree of Patient 2 and photos of pioneer. Patient 2 has thickening of the skin with pigmentation in the neck, axilla, groin, and axilla, and nipple-like nodules can be seen in the neck and axilla

hybridization and amplification with probes (Agilent, SureSelect probe enrichment system, No.3 Wangjing North Road, Chaoyang District, Beijing, China). The resulting products were purified and quantified. For the gene testing package for diabetes and insulin resistance genes, including *INSR*, 6q24 region (*PLAGL1*), 11p15 region (*INS*, *KCNJ11*), 6p22 region (*ZFP57*), *HNF4A*, *GCK*, *HNF1A*, and *HNF1B* genes using MLPA large fragment detection (Beijing Beijing Kangxu Medical Testing Institute, 2nd Floor, Building 10, Zone C, Yiyuan Cultural and Creative Industry Base, 65 Xingshikou Road, Haidian District), Illumina's NextSeq500-amplified products (12th-13th floors, Building 23, Science and Technology Oasis, No.1999 Yishan Road, Minhang District, Shanghai, China) were utilized for paired-end sequencing. Modified DNA polymerase and dNTPs with four fluorescent labels were added, and the fluorescence signal results were counted to obtain Fastaq-formatted data. The CASAVA (1.8.2) software converted the raw data into recognizable base sequences, followed by alignment, SNP, and DIP analyses to obtain information on mutation sites in the target region. Finally, SIFT (http://sift.jcvi.org), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), and Mutation Taster (http://www.mutationtaster.org) were employed for protein functional change analysis to qualitatively predict the probability of the results. This process helped identify mutation sites requiring further validation. Gene sequences for the identified mutation sites were retrieved from the GenBank human genome database, and primers were designed and synthesized using the Primer Z website (http://genepipe.ncgm.sinica.edu.tw/primerz/primerz4.do). PCR amplification was performed on the mutation sites, and the obtained sequences were aligned with previous sequences to exclude false-positive sites in second-generation sequencing.

Gene Sequencing Results

Patient 1, harboring a mutation in exon 13 of the *INSR* gene, was found to have a c.2663A>G mutation. This was a heterozygous missense mutation where the A nucleotide at position 2663 is substituted with a G nucleotide, resulting in the amino acid at position 888 of the β-subunit of *INSR* being converted from a tyrosine to a cysteine (p.Tyr888Cys) (Figure 2). Protein functional analysis using SIFT, PolyPhen, and MutationTaster indicated that the p.Tyr888Cys mutation was predicted to be "pathogenic" by SIFT (score: 0, disease prediction: Deleterious), PolyPhen2_HVAR software (score: 1, disease prediction: Deleterious), and MutationTaster (score: 1, disease prediction: Deleterious).

Patient 2 manifested an in-frame mutation in exon 1 of the *INSR* gene, resulting in a 24-base pair deletion between the 38th and 61st bases (c.38_61del). This deletion leads to the fusion of the original 37th base C with the 62nd base T, causing the loss of eight amino acids: Pro13 (P13), Leu14 (L14), Leu15 (L15), Val16 (V16), Ala17 (A17), Val18 (V18), Ala19 (A19), and Ala20 (A20) (p.Pro13_Ala20del). Notably, the translation of the amino acids preceding and following the deletion, Ala12 (A12) and Leu21 (L21), respectively, remained unaltered (Figure 3).

Treatment and Follow-up

Two patients received metformin at a dosage of 500 mg twice daily to address insulin resistance and facilitate weight control. Subsequently, blood sugar levels were effectively managed and maintained within the normal range. Additionally, a noticeable reduction in skin pigmentation was observed (Table 3).

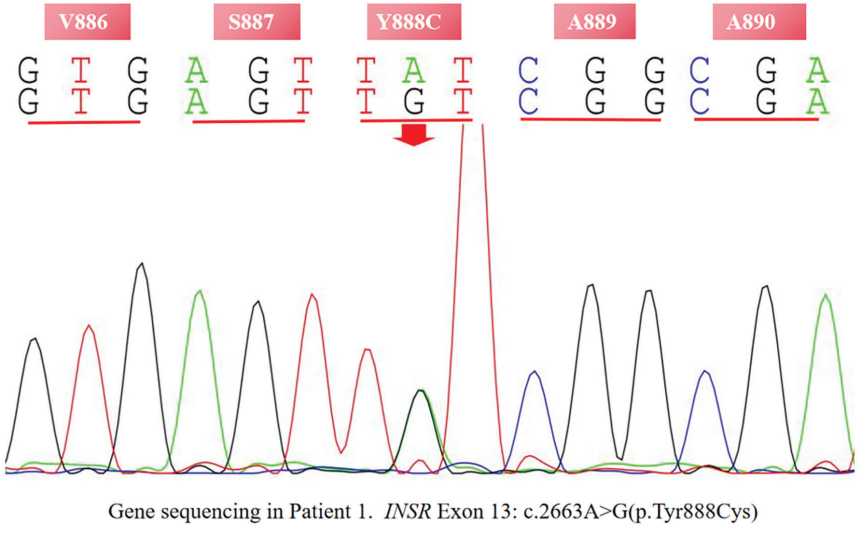

Figure 2. Gene sequencing in Patient 1. *INSR (NM_000208):* Chromosome location: chr19:7141707, Exon13; Nucleotide change: c.2663A>G; Amino acid change: p.Tyr888Cys; Mutation type: missense mutation; Validation result: heterozygous

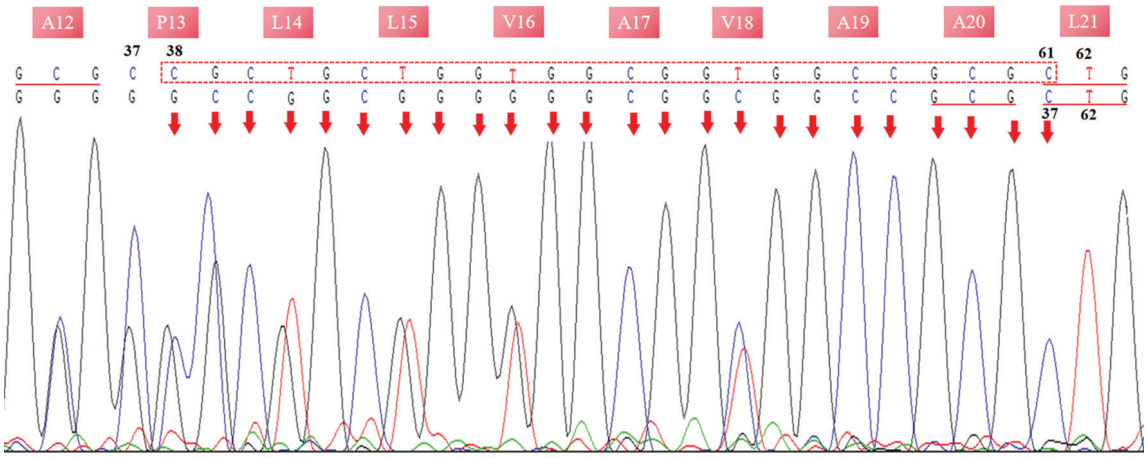

Figure 3. Gene sequencing in Patient 2 and her parents. *INSR (NM_000208):* Chromosome location: chr19:7293842, Exon1, nucleotide change: c.38_61del; amino acid change: p.Pro13_Ala20del; mutation type: in-frame mutation, verification result: heterozygous

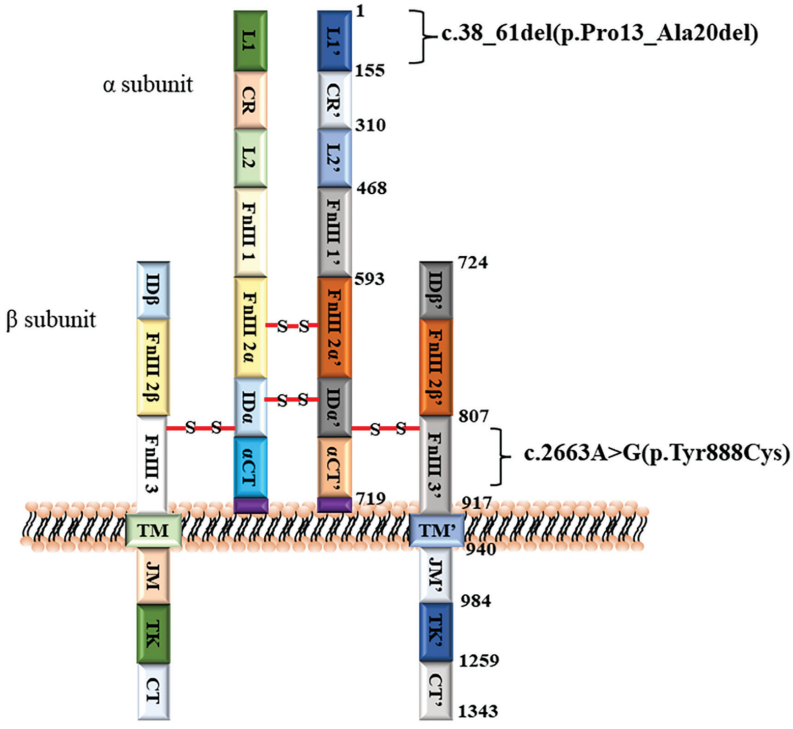

Figure 4. Insulin receptor structural model and mutation site localization. The INSR is composed of two α subunits and two β subunits connected by disulfide bonds (-s-s-). The INSRα subunit acts as the ligand-binding site and consists of a leucine-rich repeat-1 (L1), a cysteine-rich region (CR), a leucine-rich repeat-2 (L2), two fibronectin type III domains (FnIII-1 and FnIII-2α), an insert domain α (IDα), and an α-helical C-terminal domain (αCT). The INSRβ subunit includes an extracellular insert domain β (IDβ), fibronectin type III domains (FnIII-2β and FnIII-3), a transmembrane helix (TM), an intracellular juxtamembrane region (JM), a tyrosine kinase domain (TK), and a C-terminal tail (CT). Based on the genetic sequencing results of two patients reported in our study, the c.2663A>G mutation may affect the transmembrane signaling of insulin, and the c.38_61del mutation may affect the binding of insulin to the receptor

Table 3. Results of follow-up examinations

Glucose levels and pancreatic island function	Patient 1	Patient 2	Reference ranges
Glu (0 min) (mmol/L)	3.82	3.77	3.9-6.1
Glu (120 min) (mmol/L)	-	4.48	
Ins (0 min) (mIU/L)	37.00	54.68	1.9-23
Ins (120 min) (mIU/L)	-	>300.00	
T (ng/dL)	54.00	40.40	Tanner by stages: 1: 0-6.10 2: 0-10.40 3: 0-23.70 4: 0-26.80 5: 4.60-38.30

Glu: glucose; Ins: insulin; T: testosterone

Discussion

Here, we present findings from two unrelated female pediatric patients who exhibited hyperinsulinemia, fasting hypoglycemia, and postprandial hyperglycemia during OGTT and insulin release tests. Both patients displayed characteristic symptoms of AN. Both also presented with hyperandrogenism, overweight, and fatty liver. Notably, our genetic sequencing revealed specific heterozygous mutations in the *INSR* gene for each patient.

In patient 1, a heterozygous missense mutation, c.2663A>G, in exon 13 of *INSR* was identified, resulting in the amino acid at position 888 of the β-subunit of the INSR being changed from a tyrosine to a cysteine (p.Tyr888Cys) (Figure 2). Patient 2, in contrast, exhibited a deletion of 24 base pairs between positions 38 and 61 in exon 1 of *INSR*, leading deletion of eight amino acids between proline at position 13 and alanine at position 20 in the α-subunit of INSR (p.Pro13_Ala20del) (Figure 3). Consequently, considering the clinical phenotypes and laboratory results of both cases, we diagnosed these patients with H-SIRS.

Most mutations causing H-SIRS have been identified in the *INSR* gene. Ardon et al. (8) summarized 132 pathogenic variants of *INSR* mutations, including missense, non-sense, insertion, deletion, and complex rearrangements. Recently, new mutation sites have been identified. You et al. (9) recently reported a patient with hyperinsulinemia associated with AN, and gene sequencing revealed a novel variant, c.3472C>T (p.Arg1158Trp), in the index case and his father's *INSR* gene. Poon et al. (10) reported a case of hyperinsulinism and hypoglycemia in an infant who did not respond to diazoxide treatment. It was later found that she carried a heterozygous *INSR* gene mutation, c.1246C>T, leading to the replacement of the arginine codon at position 416 with a stop codon.

Different types of *INSR* gene mutations can affect the molecular structure of the *INSR*, leading to varying pathotypes. Zhou et al. (11) reported two cases of A-IR and one case of DS: the proband with A-IR and his sister had compound heterozygous mutations c.3670G>A and c.3614C>T in the *INSR* gene, while the patient with DS had mutations c.749_751del and c.3355C>T. The impact of these new variants on *INSR* function was determined by expressing the mutant receptors in Chinese hamster ovary (CHO) cells. The results showed that Thr250 and Val1224 are located in the cysteine-rich region and tyrosine kinase domain of *INSR*, respectively. The new variant c.749_751del (p.Thr250del) in the α subunit reduced the expression of mature *INSR* protein and severely impaired *INSR* function. In contrast, although protein function analysis suggested that the c.3670G>A (p.Val1224Met) mutation was pathogenic, the new variant in the β subunit did not affect the expression and phosphorylation of *INSR*. The tyrosine kinase activity of *INSR* is crucial for insulin action *in vivo*, with the α subunit containing the insulin binding site and the β subunit containing the tyrosine kinase domain. Phosphorylation of the *INSR* β subunit is necessary for mediating insulin action. The translation products of *INSR* mutations lacking kinase activity do not mediate the promotion of glycogen synthesis, glucose uptake, cell proliferation, or gene transcription by insulin (12).

The two *INSR* gene mutations we report have not been presented in previous studies, therefore, the molecular structure and function resulting from these two mutations are unknown. However, mutant sites at adjacent positions in the *INSR* gene have been reported previously. Qin et al. (13) reported a case of c.62T > G (p.L21R) and c.2563G > T (p.V855F) mutations in the *INSR* gene, in which the patient presented with thickening of the skin of the neck and trunk accompanied by hyperpigmentation, roughness of the face, enlargement of the head, thickness of the lips, generalized hirsuitism, reduction of subcutaneous fat, and a severe speech disorder. Molecular dynamics simulations showed that the c.62T > G missense mutation located in the α-subunit led to functional defects in the signal peptide, and the c.2563G > T missense mutation was located in the cysteine-rich

structural domain of the β-subunit, which completely altered the tertiary conformation of *INSR*, led to inactivation of the *INSR*, and interfered with *INSR* binding to the ligand. In addition, Brierley et al. (14) evaluated the impact of *INSR* gene mutations using a cell culture model. The results indicated that when the *INSR* mutation site is located on the cell surface, the binding of *INSR* to insulin and signal transduction are impaired. When the aspartic acid placement at position 707 on the β-subunit of the *INSR* is replaced by an alanine, this mutation is located near the cysteine residue, which may affect disulfide bond formation as well as the autophosphorylation of the *INSR* and its binding to substrates.

The two *INSR* gene mutations identified in this study, with the c.2663A>G (p.Tyr888Cys) mutation site located at the junction between the α and β subunits, may affect transmembrane signaling of insulin. In contrast, the c.38_61del (p.Pro13_Ala20del) mutation site located in the α subunit may affect insulin binding to the receptor (Figure 4), but the specific mechanism still needs further basic research confirmation.

Gene mutations severely impaired the sensitivity of the *INSR* to insulin, leading to hyperinsulinemia and reduced affinity for peripheral tissue insulin receptors, further promoting insulin resistance. This results in pancreatic beta cells secreting more insulin compensatively, resulting in a vicious cycle. Over time, pancreatic cell function eventually declined, increasing the risk of chronic complications, such as diabetes (3). The main histological features of AN included hyperkeratosis and epidermoid cyst disease, along with mild or absent acanthosis and excessive basal pigmentation (15). Insulin promotes cell proliferation, and hyperinsulinemia should lead to elevated circulating levels of insulin-like growth factor 1 (IGF-1), causing overactivation of IGF-1 receptors on fibroblasts and keratinocytes and driving excessive cell proliferation and differentiation. Therefore, AN could be considered a cutaneous manifestation of insulin resistance (16). In addition, both patients had hyperandrogenemia. The cause might be the cross-reactivity between high concentrations of insulin and IGF-1 receptors in the ovaries, leading to excessive secretion of androgens (17).

The treatment of AN depends on the underlying conditions. In cases of insulin resistance, weight control or weight loss surgery can improve symptoms. In addition, the indications for metformin in T2DM have been extended to include PCOS and AN. Limited data are available regarding cosmetic interventions such as melatonin, urea cream, vitamin D analogs, or topical tretinoin. In the early stages, lifestyle changes and improvement of insulin resistance should be started, along with the use of keratolytic agents (such as α hydroxy acids and salicylic acid) in combination with depigmenting agents (such as hydroquinone or azelaic acid). Topical tretinoin can be administered when velvety skin changes are observed (15).

There are limitations to this study. The present study did not investigate the effect of the mutant site on the molecular structure and function of the *INSR*. These changes in *INSR* remain to be further investigated by *in vivo* or *in vitro* experiments in the future.

Conclusion

Our study reports two cases of H-SIRS in female children, both presenting with hyperinsulinemia, fasting hypoglycemia, postprandial hyperglycemia, fatty liver disease, hyperandrogenism, and varying degrees of hirsutism. Patient 1 exhibited suspected intellectual disability. Genetic testing revealed the presence of a c.2663A>G (p.Tyr888Cys) missense mutation in Patient 1 and a c.38_61del (p.Pro13_Ala20del) frameshift mutation in *INSR* in Patient 2. These mutations have the potential to impact the binding of *INSR* to its ligand, insulin, thereby disrupting insulin receptor binding and resulting in abnormal insulin signaling. This disruption leads to insulin resistance and other associated clinical manifestations. Hyperinsulinemia and insulin resistance are relatively common in clinical practice, but their causes are diverse. Therefore, genetic testing is important to determine the etiology of insulin resistance.

Ethics

Informed Consent: Each participants provided written informed consent.

Authorship Contributions

Surgical and Medical Practices: Chen Chongyang, Zhao Yangting, Li Kai, Lv Xiaoyu, Wang Yawen, Zhen Donghu, Fu Songbo, Ma Lihua, Zhou Liyuan, Liu Jingfang, Concept: Chen Chongyang, Zhao Yangting, Liu Jingfang, Design: Chen Chongyang, Zhao Yangting, Liu Jingfang, Data Collection or Processing: Chen Chongyang, Zhao Yangting, Li Kai, Lv Xiaoyu, Wang Yawen, Zhen Donghu, Fu Songbo, Ma Lihua, Zhou Liyuan, Liu Jingfang, Analysis or Interpretation: Chen Chongyang, Zhao Yangting, Liu Jingfang, Literature Search: Chen Chongyang, Zhao Yangting, Liu Jingfang, Writing: Chen Chongyang, Zhao Yangting, Liu Jingfang.

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LETTER TO THE EDITOR

JCRPE Journal of Clinical Research in Pediatric Endocrinology

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Internal Inconsistency Between the Reported 50th Percentile Value and the LMS Median Parameter

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Cite this article as: Teksan A. Internal inconsistency between the reported 50th percentile value and the LMS median parameter. J Clin Res Pediatr Endocrinol. 2026;18(2):368

Keywords: Z-score, anthropometric index, children, guidelines

To the Editor,

We read with interest the article by Neyzi et al. entitled "Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children," published in J Clin Res Pediatr Endocrinol, which presents percentile values together with corresponding LMS parameters for weight in Turkish children (1).

Upon independent recalculation, we identified an internal inconsistency between the 50th percentile (P50) value for weight reported in Table 1 and the median (M) parameter for weight presented in Table 5 for 8-year-old boys.

By definition, the M parameter represents the median of the distribution and should therefore correspond to the 50th percentile. However, the M value (23.9) reported in Table 5 does not match the 50th percentile value (25.9) provided in Table 1. Recalculation using the published LMS parameters resulted in an approximate deviation of 0.5 standard deviation score.

When the 50th percentile value reported in Table 1 was used as the M parameter, internal mathematical consistency was restored and recalculated Z-score values corresponded to the published percentile data. This finding was reproducible upon repeated recalculation.

Given the widespread implementation of LMS parameters in digital growth assessment tools, even a localized discrepancy between the reported median and percentile values may have implications for automated percentile and Z-score calculations.

We respectfully request clarification regarding the reported LMS median parameter to ensure consistency between the published percentile and LMS data.

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LETTER TO THE EDITOR

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J Clin Res Pediatr Endocrinol 2026;18(2):369

Response to the Letter Regarding "Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children"

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Keywords: Z-score, anthropometric index, children, guidelines

We thank the author for the careful review of our publication entitled "Reference values for weight, height, head circumference, and body mass index in Turkish children" (1) and for drawing attention to the inconsistency in the LMS parameter table for boys' weight at 8 years of age (2).

Upon re-examination of the published material, we confirm that the M value for 8-year-old boys was incorrectly reported as 23.9 kg in the LMS parameter table. The correct median (M) value is 25.9 kg. This value is consistently reflected in the percentile tables and in the graphical growth curves presented in the same publication. It is also in agreement with the earlier reference studies based on the same dataset (2,3).

According to the LMS methodology, the 50th percentile corresponds directly to the M parameter. Therefore, use of the incorrectly printed M value for SDS calculations may lead to a deviation of up to 0.5 SD at this specific age (8 years) in boys' weight; this applies only to weight and not to height or body mass index.

It should be emphasised that the percentile curves and graphical growth charts for all auxological parameters were generated using the correct LMS output values.

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LETTER TO THE EDITOR

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Sleep Hygiene in Pediatric Patients with Steatotic Liver Disease

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Cite this article as: Finsterer J. Sleep hygiene in pediatric patients with steatotic liver disease. J Clin Res Pediatr Endocrinol. 2026;18(2):370-371

Keywords: Gastrointestinal symptoms, hepatic steatosis, liver disease, sleep quality, childs sleep habits questionnaire

We appreciated to read the article by Ozkan et al. (1) on a cross-sectional study on the prevalence of sleep disturbances in children with gastrointestinal symptoms due to metabolic steatosis-related liver disease (MASLD). The study demonstrated that sleep disturbances are more common in MASLD patients and are associated with gastrointestinal symptoms (1). The study is appealing but has some limitations.

Firstly, the sleep of children with MASLD depends not only on the liver disease but on numerous other influencing factors that were not adequately considered in the analysis (1). Disruptive factors affecting children's sleep quality are listed in Table 1. As long as these interfering factors that affect sleep have not been included in the analysis, the results may remain unreliable.

The second point concerns the use of the Child's Sleep Habits Questionnaire (CSHQ) to assess the sleep quality of the included children (1). The CSHQ has several limitations (2,3). These include limited validation using polysomnography or actigraphy, subjectivity because of its reliance on parental reports, and low internal consistency of the subscales. The CSHQ is not diagnostic on its own, and its structure cannot be consistently replicated across different cultural contexts or age groups. Polysomnography or actigraphy should have been used for an objective assessment of sleep quality and duration. Only objective measurement methods can reliably determine whether sleep is normal or disturbed.

The third point concerns the lack of brain imaging in the included patients (1). Since sleep disturbances can be caused by central nervous system (CNS) disease, it is important to know whether a CNS disorder was present that could explain the sleep disturbance. CNS disorders that particularly affect sleep include stroke, extrapyramidal disease, traumatic brain injury, central sleep apnea syndrome, and narcolepsy.

The fourth point is that MASLD can be complicated by hepatic encephalopathy (4), which itself can be further complicated by sleep disturbances (5). Therefore, it is important to know how many patients had elevated serum ammonia levels and in how many cerebral MRI findings indicated hepatic encephalopathy.

In summary, sleep disturbances in children with MASLD cannot be attributed solely to steatosis of the liver until all factors influencing sleep have been excluded as alternative explanations.

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Table 1. Factors that can disrupt children's sleep (6)
Genetic constitution
Personality type
Stress management strategies
Comorbidities (pain, seizure, anxiety, depression, neuroses, psychosis, bedwetting, attention deficit hyperactivity disorder)
Sleep habits (fixed or variable bedtimes, sleep aids (autosuggestion, reading, TV, relaxing music, airing out the bedroom)
Devices that emit electromagnetic radiation
Stress (school requirements, noise, light, vibrations, drafts, insects, pets, earthquakes, bed quality, snoring of bed neighbours, indoor tobacco smoke levels, indoor and outdoor air pollution, nighttime light pollution, cell phone towers, electromagnetic radiation, relationship problems with parents, siblings, or friends, parental socioeconomic status, local, regional, national, and geopolitical conditions)
Diet
Late last meal or drinking
Stimulating medications or drinks

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LETTER TO THE EDITOR

JCRPE Journal of Clinical Research in Pediatric Endocrinology

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Response to Letter to the Editor "Sleep hygiene in pediatric patients with steatotic liver disease"

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Cite this article as: Ozkan B, Akbulut UE. Response to Letter to the Editor "Sleep hygiene in pediatric patients with steatotic liver disease". J Clin Res Pediatr Endocrinol. 2026;18(2):372-373

Keywords: Gastrointestinal symptoms, hepatic steatosis, liver disease, sleep quality, childs sleep habits questionnaire

Dear Editor,

We thank Josef Finsterer for his constructive comments about our manuscript entitled "Association Between Gastrointestinal Symptoms and Sleep Habits in Children with Metabolic Dysfunction-Associated Steatotic Liver Disease: a Cross-Sectional Study" (1). We appreciate the opportunity to address the points raised.

The correspondent lists numerous potential sleep disruptors, including genetic factors, personality, comorbidities, sleep habits, environmental stressors, diet, late meals, and extreme factors such as earthquakes. While we acknowledge the multifactorial nature of sleep, it is methodologically not feasible to adjust for every conceivable confounder in a cross-sectional design. Our selection of covariates was guided by established evidence, and we believe that the listed factors such as earthquakes or geopolitical events are unlikely to have systematically biased our stable, single-center cohort. We have, however, acknowledged the potential for residual confounding in our limitations section (2).

Regarding the Children's Sleep Habits Questionnaire (CSHQ), the correspondent argues that polysomnography (PSG) or actigraphy should have been used. Our study aimed to screen parent-reported sleep habits in a large sample, not to diagnose sleep disorders (2). For epidemiological screening, validated questionnaires are widely accepted. The CSHQ has been validated in Turkish children (Cronbach's α=0.78) and has a well-established clinical cut-off (3). PSG or actigraphy are resource-intensive, impractical for 176 children, and capture only a single night. We agree that objective methods are valuable and stated in our limitations that future studies should incorporate them. The citation of Markovich et al. (4) does not invalidate the CSHQ as a screening tool; it simply highlights that questionnaire and objective measures capture different aspects of sleep.

Respectfully, we do not agree with the suggestion of routine brain imaging. None of the enrolled children had clinical signs of structural CNS disease, and performing brain MRI on asymptomatic children without neurological red flags would be neither ethical nor indicated by any current guideline.

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Finally, the correspondent raises the possibility of hepatic encephalopathy (HE) as a confounder, suggesting that serum ammonia or cerebral MRI for HE should have been performed. Hepatic encephalopathy occurs almost exclusively in patients with cirrhosis and advanced liver failure (5). Our study included children with MASLD, none of whom had clinical or biochemical evidence of cirrhosis (normal albumin, no ascites, no jaundice). Citing articles on HE in cirrhotic patients is not applicable to our non-cirrhotic pediatric population. Therefore, routine measurement of serum ammonia or cerebral imaging for HE in asymptomatic, non-cirrhotic pediatric MASLD patients is not indicated by current guidelines (6).

In summary, none of the raised criticisms invalidate our main findings: gastrointestinal symptoms are independently associated with sleep disturbances in children with MASLD, and low family income and insulin resistance are significant predictors. We maintain that the additional investigations suggested by the correspondent are not warranted in our asymptomatic, non-cirrhotic pediatric cohort, and we have clearly acknowledged the inherent limitations of a cross-sectional design in our manuscript. We thank Dr. Finsterer for his comments, which have allowed us to further clarify the scope of our study.

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