RESEARCH PAPER

Comparative analysis of bone health according to sex and disease phenotype in children and adolescents with classic congenital adrenal hyperplasia

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Received: 04th June, 2026; Revised: 05th July, 2026; Accepted: 21th July, 2026; Available Online: 28th July, 2026

ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is classified into classic and non-classic forms based on the severity of the enzyme defect and the clinical presentation. The aim of this work was to compare the clinical characteristics, hormonal control, biochemical bone markers, vitamin D status, and bone mineral density according to sex and disease phenotype (salt-wasting (SW) and simple virilizing (SV)) in children and adolescents with congenital adrenal hyperplasia.

Methods: This study observational cross-sectional analytic study included 87 children and adolescents (aged 6–18 years) with clinically and biochemically confirmed classic congenital adrenal hyperplasia (21- OHD), including SW and SV forms. All patients were subjected to detailed history taking, thorough clinical examination, & bone health assessment including biochemical parameters as calcium, phosphorus, magnesium, ALP, 25-OH vitamin D3, PTH and radiological assessments through bone mineral density measurement by dual-energy X-ray absorptiometry (DXA) scan.

Results: Patients with the SW form of CAH were diagnosed at a significantly younger age than those with the SV form ($P < 0.001$). In addition, SW patients had significantly higher serum 17-hydroxyprogesterone (17-OHP) levels at the time of the study compared with SV patients ($P = 0.015$). A significantly greater proportion of SV patients achieved hormonal control compared with SW patients ($P = 0.038$). Bone health parameters were comparable across sexes and CAH phenotypes ($P < 0.05$).

Conclusions: These findings highlight the influence of sex and clinical phenotype on disease presentation and management, while suggesting that skeletal and biochemical profiles remain largely comparable across these patient groups.

Keywords: Phenotype-Related Differences; Clinical; Hormonal; Bone Health Characteristics; Adolescents; Congenital Adrenal Hyperplasia

How to cite this article: Hegazy F.A, Ashmawy A, Abdou D, Mahmoud R, Arafa N, Comparative analysis of bone health according to sex and disease phenotype in children and adolescents with classic congenital adrenal hyperplasia. 2026;16(72s): 359-364. DOI: 10.25258/ijddt.16.72s.41

Source of support: None

Conflict of interest: None

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a hereditary disorder that is distinguished by the inability to synthesize cortisol. The CYP21A2 gene abnormalities are responsible for 21-hydroxylase deficiency (21OHD), which is the cause of approximately 90% to 99% of CAH cases. This autosomal recessive disorder is distinguished by elevated androgen levels and reduced cortisol production [1].

The clinical presentation of CAH is contingent upon the severity of the enzyme deficiency and the patient's age and sex. The symptoms of this condition are diverse, ranging from severe neonatal adrenal crises to subtle signs of androgen excess in later life. The symptoms of classic CAH typically manifest in the neonatal period or early infancy, whereas non-classic forms may manifest in childhood, adolescence, or even adulthood [2, 3].

CAH caused by 21-OHD is categorised into classic and non-classic forms based on the clinical presentation and the severity of the enzyme defect [4]. The classic form includes two subtypes: salt-wasting (SW) and simple virilising (SV), and it accounts for the majority of severe cases. A milder, frequently late-onset variant is represented by the non-classic (NCCAH) form [2].

SW-CAH comprises 65-75% of the basic CAH patients. Hyperandrogenism and severe cortisol and aldosterone insufficiency are the hallmarks of these conditions, which manifest in infancy. SW-CAH typically exhibits a residual enzymatic activity of less than 1% [5].

The classic CAH is composed of 25-35% SV-CAH. In contrast to SW-CAH, this variant manifests later in life and is distinguished by severe cortisol deficiency, while

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aldosterone remains unaltered[6]. This variety of CAH has a residual enzymatic activity of 1-2% [2].

Chronic glucocorticoid exposure reduces bone mineral density (BMD). CAH patients, especially those receiving supraphysiologic GC doses, may develop osteopenia or osteoporosis, placing them at risk for fractures [1].

We conducted this study to compare the clinical characteristics, hormonal control, biochemical bone markers, vitamin D status, and bone mineral density according to sex and disease phenotype (SW and SV) in children and adolescents with congenital adrenal hyperplasia.

PATIENTS AND METHODS

This study observational cross-sectional analytic study included 87 children and adolescents (aged 6–18 years) with clinically and biochemically confirmed classic congenital adrenal hyperplasia (21-hydroxylase deficiency), including SW and SV forms.

All patients were receiving glucocorticoid replacement therapy and were regularly followed at the Endocrine Clinic, Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Cairo University Children's Hospital.

An informed written consent was obtained from relatives of the patients. The study was done after approval from the Ethical Committee Institutional Review Board of Kasr Al-Ainy Faculty of Medicine, Cairo University (IRB: MD-428-2023, 2 April 2024) in accordance with the principles of the Declaration of Helsinki between April 2024 and April 2025.

Exclusion criteria were patients with primary bone diseases, chronic systemic disorders affecting bone health (e.g., chronic kidney or liver disease, celiac disease, or endocrine disorders other than CAH), or poor treatment compliance and irregular follow-up.

Clinical assessment:

Demographic and clinical data were collected, including age, sex, age at diagnosis, disease duration, family history of consanguinity and similar conditions, CAH phenotype (SW or SV), history of hospital admissions, pubertal status, and current glucocorticoid and fludrocortisone replacement therapy. Glucocorticoid doses were expressed as hydrocortisone equivalents and normalized according to body surface area (mg/m²/day).

Laboratory investigations:

Serum 17-hydroxyprogesterone (17-OHP) levels at diagnosis and at the time of the study were retrieved from the patients' records. Hormonal control was assessed according to serum 17-OHP levels. In addition, serum calcium, phosphorus, magnesium, alkaline phosphatase (ALP), 25-hydroxyvitamin D, and intact parathyroid hormone (PTH) were measured for all participants.

Radiological assessment:

Bone age was assessed using a left hand and wrist radiograph according to the Greulich and Pyle atlas. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L1–L4) and left femoral neck. In pediatric patients, BMD results were interpreted using age- and sex-adjusted Z-scores, with low bone mineral density defined as a Z-score ≤ −2.0.

Statistical analysis

Sampling technique:

A convenience sampling method was employed. Eligible patients attending the
Endocrinology Clinic at the DEMPU, Cairo University Children's Hospital, were recruited
consecutively.

Sample size:

Sample size estimation was based on previously published data reported by **Garcia et al** [7].

Using the single-mean formula $n = [(Z_{1-\alpha/2} \times \sigma) / d]^2$, where ($Z = 1.96$, $\sigma = 1.09$, $d = 0.25$), the minimum required sample size was calculated to be 74 participants.

Data management:

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables (e.g., sex, CAH subtype, consanguinity, and fracture history) were summarized as frequencies and percentages. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data (e.g., age at study entry, hydrocortisone dose, and fludrocortisone dose) were expressed as mean ± standard deviation,
while non-normally distributed data (e.g., age at diagnosis) were presented as median (range). Correlations between BMD Z-scores (lumbar spine and femoral neck) and continuous variables (e.g., weight SDS, height SDS, 17-OHP, magnesium, and ALP) were assessed using Pearson's or Spearman's correlation coefficients, as appropriate. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

The study included 87 children and adolescents with congenital adrenal hyperplasia (CAH), with a mean age of 10.74 ± 3.15 years. Female patients were significantly older than male patients ($P = 0.005$), were diagnosed at a significantly younger age ($P = 0.001$), had a significantly longer disease duration ($P = 0.005$), and received a significantly higher current hydrocortisone dose ($P = 0.014$) than male patients. No statistically significant sex differences were observed regarding CAH phenotype, hormonal control, current hydrocortisone dose adjusted for body surface area, fludrocortisone dose, serum 17-hydroxyprogesterone, calcium, magnesium, phosphorus, alkaline phosphatase, vitamin D, parathyroid hormone levels, DXA Z-scores, or the distribution of biochemical parameters and bone mineral density categories (all $P > 0.05$). **Table 1**

Table 1: Comparison of demographic, clinical, biochemical, and bone health characteristics between male and female patients

Variable	Category	Male (n = 30)	Female (n = 57)	P value
Age (years)	**Mean ± SD**	9.42 ± 2.46	11.45 ± 3.26	**0.005***
	Median (Range)	8.71 (6.25–15.85)	11.83 (6.03–17.86)	
Age at diagnosis (days)	**Mean ± SD**	168.40 ± 288.72	169.49 ± 594.39	**0.001***
	Median (Range)	60 (7–1095)	15 (3–3650)	
Duration of disease (years)	**Mean ± SD**	8.60 ± 2.52	10.55 ± 3.46	**0.005***
	Median (Range)	8 (5–15)	11 (1–17)	
Current hydrocortisone dose (mg/day)	**Mean ± SD**	18.32 ± 6.65	22.23 ± 7.42	**0.014***
	Median (Range)	18.75 (7.5–30)	25 (6–32)	
Current hydrocortisone dose (mg/m²/day)	**Mean ± SD**	16.10 ± 5.06	17.51 ± 5.51	0.229
	Median (Range)	15.00 (7.6–27)	16.50 (8–38)	
Current fludrocortisone dose (mg/day)	**Mean ± SD**	0.06 ± 0.03	0.07 ± 0.03	0.328
	Median (Range)	0.05 (0.03–0.15)	0.05 (0.03–0.13)	
17-OHP (ng/mL)	**Mean ± SD**	8.44 ± 9.30	8.74 ± 8.23	0.568
	Median (Range)	3.14 (0.18–33)	5.80 (0.10–30)	
Total calcium (mg/dL)	**Mean ± SD**	10.52 ± 2.40	10.35 ± 1.98	0.399
Magnesium (mg/dL)	**Mean ± SD**	2.11 ± 0.67	1.92 ± 0.60	0.267
Phosphorus (mg/dL)	**Mean ± SD**	3.42 ± 1.32	3.84 ± 1.42	0.183
ALP (U/L)	**Mean ± SD**	224.37 ± 109.77	242.26 ± 113.09	0.478
25(OH) Vitamin D (ng/mL)	**Mean ± SD**	27.58 ± 14.80	28.18 ± 14.61	0.655
PTH (pg/mL)	**Mean ± SD**	15.29 ± 6.75	14.39 ± 6.89	0.389
DXA left femur Z-score	**Mean ± SD**	−0.04 ± 0.87	−0.11 ± 1.04	0.947
DXA lumbar spine (L1–L4) Z-score	**Mean ± SD**	−0.49 ± 1.46	−0.47 ± 1.51	0.936
Type of CAH	**Salt-wasting**	26 (86.7%)	54 (94.7%)	0.228
	Simple virilizing	4 (13.3%)	3 (5.3%)	
Hormonal control	**Controlled**	18 (60.0%)	34 (59.6%)	0.975
	Uncontrolled	12 (40.0%)	23 (40.4%)	
Total calcium status	**Normal**	7 (23.3%)	19 (33.3%)	0.675
	Low	5 (16.7%)	9 (15.8%)	
	High	18 (60.0%)	29 (50.9%)	
Magnesium status	**Normal**	12 (40.0%)	24 (42.1%)	0.551
	Low	7 (23.3%)	18 (31.6%)	
	High	11 (36.7%)	15 (26.3%)	
Phosphorus status	**Normal**	16 (53.3%)	32 (56.1%)	0.802
	Low	14 (46.7%)	25 (43.9%)	
ALP status	**Normal**	19 (63.3%)	42 (73.7%)	0.223
	Low	6 (20.0%)	4 (7.0%)	
	High	5 (16.7%)	11 (19.3%)	
Vitamin D status	**Sufficient**	11 (36.7%)	20 (35.1%)	0.694
	Insufficient	6 (20.0%)	16 (28.1%)	
	Deficient	13 (43.3%)	21 (36.8%)	
PTH status	**Normal**	22 (73.3%)	38 (66.7%)	0.523
	Low	8 (26.7%)	19 (33.3%)	
DXA left femur	**Normal BMD**	30 (100%)	55 (96.5%)	0.543
	Low BMD (Z ≤ −2)	0 (0%)	2 (3.5%)	
DXA lumbar spine (L1–L4)	**Normal BMD**	25 (83.3%)	50 (87.7%)	0.745
	Low BMD (Z ≤ −2)	5 (16.7%)	7 (12.3%)	

Data are presented as mean ± SD, Median (Range), or number (%) or. SD: standard deviation, CAH: congenital adrenal hyperplasia, 17-OHP: 17-hydroxyprogesterone, ALP: alkaline phosphatase, PTH: parathyroid hormone, DXA: dual-energy X-ray absorptiometry, BMD: bone mineral density. *: significant as P value < 0.05

Patients with the SW form of CAH were diagnosed at a significantly younger age than those with the SV form (P < 0.001). In addition, SW patients had significantly higher serum 17-hydroxyprogesterone (17-OHP) levels at the time of the study compared with SV patients (P = 0.015). A significantly greater proportion of SV patients achieved hormonal control compared with SW patients (P = 0.038). No statistically significant differences were observed between the two CAH

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phenotypes regarding age, current hydrocortisone dose, serum calcium, magnesium, phosphorus, alkaline phosphatase, vitamin D, parathyroid hormone levels, DXA Z-scores, or the distribution of biochemical parameters and bone mineral density categories (all P > 0.05). **Table 2**

Table 2: Comparison of demographic, clinical, biochemical, and bone health characteristics according to CAH phenotype

Variable	Category	Salt-wasting (n = 80)	Simple virilizing (n = 7)	P value
Age (years)	**Mean ± SD**	10.78 ± 3.11	10.35 ± 3.80	0.685
	Median (Range)	10.54 (6.03–17.01)	8.77 (6.58–17.86)	
Age at diagnosis (days)	**Mean ± SD**	47.85 ± 53.59	1555 ± 1107.11	**<0.001***
	Median (Range)	30 (3–240)	1095 (365–3650)	
Current hydrocortisone dose (mg/m²/day)	**Mean ± SD**	17.22 ± 5.42	14.79 ± 4.52	0.281
	Median (Range)	16 (8–38)	14.50 (7.6–20)	
17-OHP at study (ng/mL)	**Mean ± SD**	9.29 ± 8.63	1.22 ± 1.21	**0.015***
	Median (Range)	6.71 (0.1–33)	0.85 (0.2–3.7)	
Total calcium (mg/dL)	**Mean ± SD**	10.41 ± 2.15	10.31 ± 1.98	0.553
Magnesium (mg/dL)	**Mean ± SD**	2.00 ± 0.61	1.81 ± 0.77	0.425
Phosphorus (mg/dL)	**Mean ± SD**	3.65 ± 1.40	4.17 ± 1.26	0.310
ALP (U/L)	**Mean ± SD**	236.81 ± 111.49	227.86 ± 122.11	0.803
25(OH) Vitamin D (ng/mL)	**Mean ± SD**	27.79 ± 14.68	30.11 ± 14.46	0.492
PTH (pg/mL)	**Mean ± SD**	14.70 ± 6.89	14.73 ± 6.37	0.720
DXA left femur Z-score	**Mean ± SD**	-0.07 ± 0.99	-0.19 ± 0.96	0.864
DXA lumbar spine (L1–L4) Z-score	**Mean ± SD**	-0.51 ± 1.50	-0.13 ± 1.36	0.404
Hormonal control	**Controlled**	45 (56.3%)	7 (100%)	**0.038***
	Uncontrolled	35 (43.8%)	0 (0%)	
Total calcium status	**Normal**	21 (26.3%)	5 (71.4%)	0.076
	Low	14 (17.5%)	0 (0%)	
	High	45 (56.3%)	2 (28.6%)	
Magnesium status	**Normal**	35 (43.8%)	1 (14.3%)	0.195
	Low	21 (26.3%)	4 (57.1%)	
	High	24 (30.0%)	2 (28.6%)	
Phosphorus status	**Normal**	43 (53.8%)	5 (71.4%)	0.452
	Low	37 (46.3%)	2 (28.6%)	
ALP status	**Normal**	58 (72.5%)	3 (42.9%)	0.091
	Low	8 (10.0%)	2 (28.6%)	
	High	14 (17.5%)	2 (28.6%)	
Vitamin D status	**Sufficient**	29 (36.3%)	2 (28.6%)	0.608
	Insufficient	19 (23.8%)	3 (42.9%)	
	Deficient	32 (40.0%)	2 (28.6%)	
PTH status	**Normal**	55 (68.8%)	5 (71.4%)	1.000
	Low	25 (31.3%)	2 (28.6%)	
DXA left femur	**Normal BMD**	78 (97.5%)	7 (100%)	1.000
	Low BMD (Z ≤ −2)	2 (2.5%)	0 (0%)	
DXA lumbar spine (L1–L4)	**Normal BMD**	69 (86.3%)	6 (85.7%)	1.000
	Low BMD (Z ≤ −2)	11 (13.8%)	1 (14.3%)	

Data are presented as mean ± SD, Median (Range), or number (%) or. SD: standard deviation, CAH: congenital adrenal hyperplasia, 17-OHP: 17-hydroxyprogesterone, ALP: alkaline phosphatase, PTH: parathyroid hormone, DXA: dual-energy X-ray absorptiometry, BMD: bone mineral density. *: significant as P value < 0.05

DISCUSSION

In order to prevent adrenal crises and regulate hyperandrogenism, the management of classic CAH owing to 21-hydroxylase deficiency requires lifelong glucocorticoid (GC) therapy [6].

In the present study, we comprised 87 pediatric and adolescent patients with classic CAH due to 21-hydroxylase deficiency, with a mean age of 10.7 years. The majority of our patients (92%) presented with the salt-wasting form of CAH, and the median age was 10.74 ±3.15 years while mean age at diagnosis was 30 days, reflecting early clinical recognition of the disease. Moreover, a female predominance was observed in our study (65.5% female vs. 34.5% male), which is consistent with the higher likelihood of early detection in females due to atypical genitalia.

Also, a Brazilian study by Garcia Alves Junior et al., [7] comes in line with our findings regarding demographic characteristics. This cross-sectional study comprised 14 patients with classic CAH, with a mean age of 11.3 ± 3.6 years and a range of 5 to 19 years. The Brazilian study also revealed a female predominance, with 13 females (92.9%) and 1 male (7.1%). Their patient population consisted of 8 patients (57.1%) with salt-wasting form and 6 patients (42.9%) with simple-virilizing form. All patients initiated glucocorticoid treatment prior to the age of 4 months, which is consistent with our discovery of a median diagnosis age of 30 days, which indicates early identification through screening programs.

Conversely, ElBakry et al., [8] conducted a study in Egypt that demonstrates distinct demographic trends. The mean age of the 40 children with classic salt-losing CAH in their cross-sectional study was 5.8 ± 1.04 years, which is significantly younger than the 10.7 years in our analysis. Different gender distributions were observed in the Egyptian study, with 22 males (55%) and 18 females (45%). In addition, the median age at diagnosis in the Egyptian cohort was 3.5 ± 0.92 months.

Early diagnosis in females is expected because genital ambiguity at birth usually prompts immediate endocrine evaluation, whereas affected males often have normal external genitalia and may remain undiagnosed until adrenal crisis develops.

Subgroup analysis in our study has revealed that female patients received significantly higher absolute doses of hydrocortisone than their male counterparts, yet no corresponding difference in BMD Z-scores was observed. This may suggest a protective, anabolic effect from adrenal androgens that counteracts the higher glucocorticoid exposure. When comparing CAH subtypes, patients with simple virilizing CAH in our study had significantly poorer hormonal control than those with the salt-wasting type. This difference may be explained by the older age and longer disease duration among female patients, resulting in higher absolute glucocorticoid requirements, but this did not translate into a detectable difference in BMD.

A Lithuanian study by Navardauskaite et al., [9] provided a support for our androgen protection hypothesis. The study discovered a substantial correlation between dehydroepiandrosterone sulphate (DHEAS) levels and bone mineral density (BMD) in male CAH patients. This finding is consistent with the notion that adrenal androgens may exert a protective effect on bone density by influencing osteoblast function. The study observed that low BMD was associated with the failure to experience a physiological increase in DHEAS levels during adrenarche, and that glucocorticoid overdose had an impact on osteoblastic function and growth. This corroborates our observation that androgens may offer some protection against bone density loss, despite the fact that females experience a higher level of glucocorticoid exposure.

The assessment of disease management in our study indicated challenges in achieving optimal hormonal balance. Patients with the simple virilizing subtype demonstrated significantly different hormonal control compared with those with the salt-wasting subtype.

Our finding that 40.2% of the patients demonstrated poor hormonal control is consistent with the challenges highlighted in a recent review by Itonaga & Hasegawa, [10]. This comprehensive review on monitoring pediatric 21-hydroxylase deficiency emphasized that accurately calibrating glucocorticoid dosage is notoriously difficult. The authors reaffirm that both under treatment (risking hyperandrogenism) and overtreatment (risking iatrogenic Cushing) are common pitfalls.

In contrast, a large German/Austrian multicenter study by Hoyer-Kuhn et al., [11] illustrates distinct hydrocortisone administration patterns. This registry study comprised 1,288 patients (604 boys, median age 7.2 years, 817 salt-wasting, 471 simple-virilizing) who were taking hydrocortisone three times daily. The median daily dose was 14.4 mg/m² (12.3–16.7). The study demonstrated age-specific dosing, with mean concentrations of 19.4 mg/m² for patients under 3 months, 15.0 mg/m² for patients between 3 and 12 months, 14.0 mg/m² for patients between 1 and 5.9 years, 14.2 mg/m² for patients between 6 and 18 years, and 14.9 mg/m² for patients between 18 and puberty. The study discovered that 44.1% of patients received overdosage (>15 mg/m²). Significant differences were observed between treatment periods before and after 2005 (16.4 vs 14.6 mg/m², $p<0.0001$), evidence of the evolving treatment guidelines toward lower effective dosages.

Our study demonstrated that sex and CAH subtype influence several clinical characteristics of children with classic CAH, particularly age at diagnosis, hydrocortisone requirements, and hormonal control, whereas biochemical parameters and bone health remained largely comparable between the studied groups.

Overall, our findings suggest that bone health in pediatric CAH is multifactorial, reflecting the complex interaction between glucocorticoid therapy, disease control, adrenal androgen exposure, growth rather than sex or disease phenotype alone.

We recommended early diagnosis and regular clinical and biochemical follow-up are essential to optimize the management of children with classic congenital adrenal hyperplasia, particularly in male patients and those with the simple virilizing subtype who are at greater risk of delayed

diagnosis. Hydrocortisone therapy should be individualized according to age, body size, and disease severity to achieve optimal hormonal control while minimizing overtreatment. Further large-scale prospective multicenter studies are needed to validate sex- and subtype-related differences and to evaluate their impact on long-term clinical outcomes.
Limitations: The sample size was relatively small. The study was in a single center.

CONCLUSIONS

Children and adolescents with classic congenital adrenal hyperplasia demonstrated distinct clinical differences according to sex and disease subtype. These findings highlight the influence of sex and clinical phenotype on disease presentation and management, while suggesting that skeletal and biochemical profiles remain largely comparable across these patient groups.

Funding:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest:
The authors declare no financial or non-financial conflicts of interest related to this study.

Ethical Approval:
The study was approved by the Institutional Review Board of Kasr Al-Ainy Medical School (IRB: MD-428-2023; April 2, 2024) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients' legal guardians.

Consent to Participate:
Written informed consent was obtained from the parents/guardians of all participants before enrollment.

Authors' Contributions:
FAH contributed to study design, data collection, data interpretation, manuscript drafting, revision, and final approval. AA contributed to study design, data interpretation, manuscript revision, and final approval. DA contributed to study design, laboratory analysis, data interpretation, manuscript drafting and revision, and final approval. RM contributed to study design, DXA and bone age interpretation, manuscript drafting and revision, and final approval. NA contributed to study design, data interpretation, manuscript drafting and revision, and final approval.

Data Availability:
Data are available from the corresponding author upon reasonable request.

Acknowledgements:
The authors acknowledge the patients and their parents for their participation. We also sincerely thank all members of the Diabetes, Endocrine, and Metabolism Pediatric Unit, Children's Hospital, Cairo University, for their support in managing and following up the patients.

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