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Nutritional Status and Growth Outcomes in Pediatric Idiopathic Growth Hormone Deficiency: A Retrospective Study in Turkey

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ABSTRACT

Objective: Growth and development in children are significantly influenced by nutritional status. Nutritional deficiencies such as low hemoglobin (Hb), ferritin, vitamin B12, and vitamin D have been linked to impaired growth. This study aims to evaluate the impact of these nutritional markers on growth outcomes in children with idiopathic growth hormone deficiency (IGHD) undergoing recombinant growth hormone therapy (rhGH).

Material and Methods: A cross-sectional, retrospective study was conducted on 100 children with IGHD, aged under 16, diagnosed between 2000 and 2023. Data were collected from medical records, including height, body mass index (BMI), pubertal status, bone age, and nutritional markers [Hb, ferritin, vitamin B12, 25-hydroxy-vitamin D3 (25(OH)D3]. Growth parameters were assessed at the start and end of the first year of rhGH treatment.

Results: The cohort had a median age of 11.3 years; 30% were female, and 50% were prepubertal. The median height standard deviation score (SDS) was -2.8, and median BMI SDS was -0.7. Prevalence of nutritional deficiencies included 23% with low Hb, 31% with low ferritin, 44% with low 25(OH)D_3, and 15% with low vitamin B12. Despite these deficiencies, no significant differences were observed in height SDS or growth velocity when grouped by nutritional markers or supplementation status. Growth velocity showed a significant positive correlation with Hb levels and mid-parental height (MPH).

Conclusion: Nutritional deficiencies were common among IGHD patients; there was no significant difference in terms of growth-related metrics in the first year of the rhGH therapy in comparisons between the groups with and without common nutritional deficiencies. This finding underscores the resilience of growth in the presence of these deficiencies. In contrast, growth velocity correlated positively with Hb levels and MPH, suggesting that these factors may play a significant role in influencing growth. Further research with larger samples and extended follow-up is needed to explore the long-term impact of nutritional supplementation on growth in IGHD.

Keywords: Nutrition, idiopathic growth hormone deficiency, hemoglobin, ferritin, vitamin B12, 25-OH-vitamin-D_3, growth

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INTRODUCTION

Growth and development during childhood are critical for long-term health and well-being. Various factors, including nutritional status, hormonal balance, and genetic influences, play pivotal roles in determining growth patterns and final height outcomes. Malnutrition and deficiencies in essential nutrients have been widely recognized as significant contributors to impaired growth and development. For instance, deficiencies in iron, vitamin B12, and vitamin D are known to adversely affect hematologic and metabolic functions, potentially influencing growth trajectories (1).

Hemoglobin (Hb) levels, ferritin (an indicator of iron stores), vitamin B12, and 25(OH)D_3 levels are commonly assessed to evaluate nutritional status and its impact on growth. Recent studies have demonstrated that these parameters can be linked to growth parameters such as height and growth velocity (2).

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However, the impact of nutrient deficiencies on growth during recombinant growth hormone (rhGH) therapy in individuals with growth hormone deficiency (GHD), as well as the potential benefits of nutritional supplementation, continue to be important areas of ongoing research.

This study aims to examine the relationship between nutritional status indicators and growth outcomes in a pediatric population with idiopathic GHD (IGHD). By analyzing a cohort of 100 children with varying degrees of nutritional deficiencies, we seek to understand how these factors influence height, growth velocity, and other growth-related metrics within the Turkish population. Furthermore, we aim to assess the impact of nutritional supplementation on these growth parameters.

MATERIALS and METHODS

Study Design and Participants

This cross-sectional, retrospective and single-center study included 100 IGHD patients diagnosed between 2000-2023 years and data were recruited from medical records of our endocrinology clinic of Akdeniz University Hospital. This date range was selected to include the oldest patient for whom archival records are available and the newest patient who has completed at least one year of rhGH therapy. It encompasses all IGHD cases with complete medical data that were diagnosed and treated at our center during this period. The inclusion criteria included children under 16 years of age, with no other chronic illnesses or growth-affecting conditions that could potentially confound the results.Diagnosis of GHD and treatment procedure

The diagnosis of IGHD in patients was established based on specific consensus criteria. These criteria included (3):

1. Height and Growth Velocity: Patients needed to have a height below -2 Standard Deviation Scores (SDS) for their age, accompanied by inadequate growth velocity relative to their age group.

2. Growth Hormone (GH) Stimulation Tests: A peak GH concentration of less than 10 µg/L, measured during two separate GH stimulation tests, was required to confirm the diagnosis.

3. Bone Age Delay: There had to be at least a two-year delay in bone age compared to chronological age, indicating impaired skeletal maturation.

4. Imaging and Hormonal Evaluation: The diagnosis required that magnetic resonance imaging (MRI) of the brain showed no hypothalamic or pituitary lesions, and there was no evidence of other pituitary hormone deficiencies.

All patients diagnosed with IGHD were initially treated with rhGH administered subcutaneously at a starting dose of 0.1 units per kilogram per day, which is approximately 33 micrograms per kilogram per day. During follow-up evaluations, if the growth response or insulin-like growth factor-1 (IGF-1) levels were deemed inadequate, the dosage of rhGH was adjusted upward to better meet the treatment goals.

Data Collection

Height: Measured using a standard stadiometer with precision to the nearest 0.1 cm. Height SDS was calculated based on age and sex-specific reference standards (4).

Body Mass Index (BMI): Calculated as weight (kg) divided by height squared (m^2). BMI SDS was also derived using age and sex-specific reference data (4).

Pubertal Status: The pubertal stage was evaluated by Marshall and Tanner (5).

Bone Age and Predictive Adult Height (PAH): Determined through X-ray imaging of the left hand and wrist, assessed using the Greulich and Pyle method (6). For subjects with a bone age greater than 6 years, the PAH was determined using the Bayley-Pinneau method (7). In contrast, for those with a bone age of less than 6 years, the PAH was calculated using the Roche-Wainer-Thissen method (8).

The mid-parenteral height (MPH): It was calculated according to the formula: (height of mother + height of father – 13)/2 for girls and (height of mother + height of father + 13)/2 for boys.

Laboratory Tests: Hb levels are measured in g/dL, ferritin levels are assessed in µg/L, and vitamin B12 levels are measured in ng/L. Normal ranges are determined using age- and sex-specific scales (9,10,11). $25(OH)D_3$ levels are measured in µg/L, with $25(OH)D_3$ deficiency defined as <20 µg/L (12).

Ethics

This study was conducted in compliance with the principles outlined in the Declaration of Helsinki. The research protocol was reviewed and approved by the Akdeniz University Hospital ethics committee (approval number: TBAEK-570) and all procedures adhered to ethical standards to ensure the integrity and ethical conduct of the study.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Continuous variables were presented as means ± standard deviations (SD), and categorical variables were presented as frequencies and percentage. To assess the differences in growth parameters between groups (e.g., based on Hb levels, ferritin, vitamin B12, and 25-OH-D-vitamin levels), independent t-tests or Mann-Whitney U tests were used as appropriate. For categorical variables, chi-square tests were employed. Pearson or Spearman correlation coefficients were calculated to explore relationships between growth parameters (e.g., height SDS, growth velocity) and various nutritional markers. The strength of the relationship was interpreted based on the following r values: very weak (< 0.25), weak (0.26 to 0.49), medium (0.50 to 0.69), high (0.70 to 0.89), and very high (0.90 to 1.0). Statistical significance was considered at $p < 0.05$. Statistical analyses of our study were conducted using the Statistical Package for the Social Sciences program (version 23.0 for Windows, IBM Corp., Armonk, NY, USA).

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RESULTS

In this study, 100 children with a median age of 11.3 years were evaluated. Clinical and laboratory parameters of IGHD cases were expressed in Table 1. Of these children, 30% were female, and 50% were prepubertal. The median height was 128.1 cm, with a height SDS of -2.8. The average BMI was 16.0 kg/m², and the BMI SDS was -0.7. Hb levels averaged 12.6 g/dL, with 23% of the children having low Hb levels. The median ferritin level was 26.8 µg/L, and 31% had low ferritin levels. The median 25-OH-D-vitamin level was 22.1 µg/L, with 44% having low levels. Vitamin B12 levels averaged 393.5 ng/L, and 15% had low levels. 41% of the children were receiving at least one type of nutritional supplement (iron, B12, vitamin D, or multivitamin). During the first year of treatment, the height SDS was -2.2, and the annual growth velocity was 8.6 cm/year, with a growth velocity SDS of 1.4 (**Table 1**).

The characteristics based on Hb levels and growth-related metrics are presented in **Table 2**. When the cases were divided into groups based on Hb levels (low vs. normal), there were no significant differences in height SDS at the start of treatment, height SDS at the end of the first year of treatment, or growth rates. Similarly, when categorized based on ferritin, vitamin B12, and 25-OH-D-vitamin levels, no significant differences in height parameters were observed (**Tables 3, 4, 5**). Additionally, no significant differences were found in height SDS, height SDS at the end of the first year, or growth rates based on nutritional supplement use ($p > 0.05$).

Correlation analyses revealed that factors influencing height SDS at the end of the first year of treatment included initial height SDS, PAH, PAH SDS, and MPH. The growth velocity during the first year of treatment showed a significant positive correlation with hb levels, MPH, and MPH SDS (**Table 6**).

Table 1. Clinical and laboratory parameters of IGHD cases

	N=100
Age (year)	11.3 (5.6)
Sex (F) (n, %)	30 (30 %)
Pubertal status (prepubertal) (n, %)	50 (50 %)
Height (cm)	128.1 (29.4)
Height SDS	-2.8 (0.8)
BMI (kg/m^2)	16.0 (3.1)
BMI SDS	-0.7 (1.6)
Birth weight (kg)	3100 (600)
Hb (g/dl)	12.6 (1.3)
Low Hb (n, %)	23 (23%)
Ferritin (µg/L)	26.8 (25.1)
Low Ferritin (n, %)	31 (31%)
25(OH)D$_3$ (µg/L)	22.1 (11.3)
Low 25(OH)D$_3$ (n, %)	44 (44%)
Vitamin B12 (ng/L)	393.5 (285.5)
Low vitamin B12 (n, %)	15 (15%)
Nutritional replacement + (n, %)	41 (41%)
IGF1 (µg/L)	105 (117)
IGF1 SDS	-1.3 (1.4)
IGFBP3 (mg/L)	3400 (2450)
IGFBP3 SDS	-0.3 (1.9)
Hypophysis thickness (mm)	4.0 (2.0)
Peak GH (µg/L)	4.1 (4.0)
BA (year)	8.7 (5.6)
PAH (cm)	161.9 (13.8)
PAH SDS	-1.9 (1.1)
MPH (cm)	164.0 (14.5)
MPH SDS	-1.5 (1.2)
Height SDS (1st year)	-2.2 (0.7)
GV (1st year) (cm/year)	8.6 (2.3)
GV SDS (1st year)	1.4 (1.5)

Data are expressed as median (IQR) or number (percentage).
F: female; BMI: body mass index; SDS: standard deviation score; Hb: hemoglobin; 25(OH)D3: 25-hydroxy-vitamin D3; IGF1: insuline like growth factor 1; IGFBP3: insuline like growth factor binding protein 3; GH: growth hormone; BA: bone age; PAH: predictive adult height; MPH: midparental height; GV: growth velocity.

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Table 2. Clinical parameters according to hemoglobin level

	Low Hb (n=23)	Normal Hb (n=77)	*p*
Height	132.8 (16.8)	126.1 (30.8)	0.099
Height SDS	-2.8 (0.6)	-2.9 (1.2)	0.168
BMI	16.2 (5.6)	15.7 (3.0)	0.238
BMI SDS	-0.6 (1.8)	-0.7 (1.5)	0.811
Height SDS (1st year)	-2.1 (0.6)	-2.2 (0.7)	0.260
GV (1st year)	8.7 (1.8)	8.5 (1.6)	0.632
GV SDS (1st year)	1.1 (2.2)	1.4 (1.5)	0.981

Data are expressed as median (IQR).
Hb: hemoglobin; BMI: body mass index; SDS: standard deviation score; GV: growth velocity.

Table 3. Clinical parameters according to ferritin level

	Low Ferritin (n=31)	Normal Ferritin (n=69)	*p*
Height	124.3 (31.8)	127.2 (27.3)	0.974
Height SDS	-2.9 (0.9)	-2.8 (0.7)	0.785
BMI	16.0 (2.6)	15.6 (3.0)	0.847
BMI SDS	-0.8 (1.7)	-0.8 (1.4)	0.705
Height SDS (1st year)	-2.1 (0.6)	-2.2 (0.6)	0.833
GV (1st year)	9.4 (3.8)	8.5 (1.1)	0.400
GV SDS (1st year)	1.5 (1.7)	1.3 (1.4)	0.678

Data are expressed as median (IQR).
BMI: body mass index; SDS: standard deviation score; GV: growth velocity.

Table 4. Clinical parameters according to 25-hydroxy-vitamin D level

	Low 25(OH)D_3 (n=44)	Normal 25(OH)D_3 (n=56)	*p*
Height	117.5 (26.0)	126.5 (36.0)	0.543
Height SDS	-2.8 (0.6)	-2.9 (1.0)	0.570
BMI	15.3 (2.3)	15.5 (2.8)	0.908
BMI SDS	-0.8 (1.4)	-0.8 (1.7)	0.808
Height SDS (1st year)	-2.1 (0.6)	-2.2 (0.8)	0.666
GV (1st year)	8.3 (1.1)	8.5 (2.5)	0.520
GV SDS (1st year)	1.2 (1.0)	1.4 (1.9)	0.678

Data are expressed as median (IQR).
25(OH)D_3: 25-hydroxy-vitamin D3; BMI: body mass index; SDS: standard deviation score; GV: growth velocity.

Table 5. Clinical parameters according to vitamin-B12 level

	Low vitamin-B12 (n=15)	Normal vitamin-B12 (n=85)	
Height	128.4 (23.1)	127.8 (30.3)	0.456
Height SDS	-2.9 (0.2)	-2.8 (0.7)	0.286
BMI	16.1 (3.5)	15.7 (2.6)	0.634
BMI SDS	-0.8 (1.6)	-0.8 (1.7)	0.885
Height SDS (1st year)	-2.2 (0.2)	-2.2 (0.8)	1.000
GV (1st year)	8.8 (1.3)	8.5 (2.4)	0.497
GV SDS (1st year)	1.4 (1.2)	1.3 (1.5)	0.343

Data are expressed as median (IQR).
BMI: body mass index; SDS: standard deviation score; GV: growth velocity.

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Table 6. Correlational analyses of first year height SDS and growth velocith with clinical and laboratory parameters

	Height SDS (1st year)	GV (1st year)
Age	p:0.284 R:-0.111	p:0.206 R:0.131
Height	p:0.721 R:0.031	p:0.123 R:0.159
Height SDS	p<0.001* R:0.686	p:0.563 R:-0.060
BMI	p:0.455 R:0.077	p:0.178 R:0.139
BMI SDS	p:0.187 R:0.137	p:0.855 R:0.019
Birth weight	p:0.784 R:-0.033	p:0.175 R:0.162
Hb	p:0.944 R:-0.004	p:0.032* R:0.224
Ferritin	p:0.939 R:0.010	p:0.554 R:0.075
25(OH)D_3	p:0.951 R:-0.008	p:0.758 R:-0.040
Vitamin B12	p:0.767 R:-0.040	p:0.121 R:-0.208
Hypophysis thickness	p:0.153 R:-0.094	p:0.822 R:-0.031
Peak GH	p:0.266 R:-0.115	p:0.217 R:-0.228
BA	p:0.622 R:-0.051	p:0.221 R:0.127
PAH	p:0.008* R:0.269	p:0.354 R:0.096
PAH SDS	p:0.002* R:0.313	p:0.312 R:0.105
MPH	p:0.033* R:0.219	p:0.015* R:0.249
MPH SDS	p:0.062 R:0.192	p:0.003* R:0.304

*statistically significant correlation; R: correlation coefficient.

GV: growth velocity; BMI: body mass index; SDS: standard deviation score; Hb: hemoglobin; 25(OH)D3: 25-hydroxy-vitamin D3; GH: growth hormone; BA: bone age; PAH: predictive adult height; MPH: midparental height.

DISCUSSION

This study assessed 100 children with a median age of 11.3 years, evaluating their growth parameters and nutritional status. Our findings offer valuable insights into the relationship between nutritional factors and growth outcomes in children diagnosed with IGHD.

Nutritional Factors and Growth Parameters

Our data indicated that nutritional deficiencies, including low Hb, ferritin, vitamin B12, and 25-OH-D-vitamin levels, were prevalent among the study participants. Despite these deficiencies, statistical analyses showed no significant differences in height SDS, height SDS at the end of the first year, or growth velocity when categorized based on these nutritional markers. This suggests that, within the context of this study, these nutritional deficiencies might not have a significant direct impact on growth outcomes in IGHD patients, or the sample size might not have been sufficient to detect subtle effects.

In 1960, the potential link was explored firstly between 25(OH)D_3 and GH functions. Their research on patients with GHD undergoing rhGH revealed changes in calcium metabolism similar to those induced by 25(OH)D_3. Specifically, they observed increased calcium absorption in the gut, elevated urinary calcium excretion, and reduced urinary phosphorus excretion, all of which align with the effects typically associated with vitamin D supplementation (13). In recent years, numerous biological studies have delved into the intricate biochemical interactions between 25(OH)D_3 and the GH/IGF-1 axis (14). Emerging evidence suggests that 25(OH)D3 status may significantly influence the secretion of IGF-1 and insülin-like growth factor binding protein-3 (IGFBP-3) from the liver and modulate the expression of IGF-1 receptors across various tissues (15, 16). A recent prospective case–control study by Hamza et al. (17) further highlights the prevalence of vitamin D insufficiency among pediatric GHD patients. This study compared 50 prepubertal children newly diagnosed with IGHD and the findings revealed that 40% of the IGHD group had serum 25(OH)D_3 levels below 30 ng/mL, indicating insufficiency, while 44% had levels below 20 ng/mL, marking a total of 84% with vitamin D deficiency. In our study, individuals in the IGHD population with 25(OH)D3 levels <20 ng/mL were classified as having vitamin D deficiency, which was found at a rate of 44%, quite similar to previous findings. However, this study uniquely demonstrated a correlation between 25(OH)D_3 levels and height expressed as SDS at diagnosis. Notably, those with 25(OH)D_3 levels below 20 ng/mL were found to have the lowest heights, underscoring the potential impact of 25(OH)D3 status on growth outcomes according to their findings (17).

Recent studies have shown that Hb levels are closely linked to linear growth, with low Hb levels negatively impacting growth and development, particularly during early childhood (18-20). Additionally, a bidirectional relationship between Hb and GHD is being discussed. Studies have reported low Hb levels in children with GHD (21). On the other hand, growth is affected in children with low Hb levels. Ciresi et al. conducted a retrospective cohort study and found that the percentage of anemic patients among children with GHD who were treated with GH significantly decreased at the 3-year follow-up, and Hb levels increased significantly in both anemic and non-anemic children (22). GH promotes the clonogenicity of peripheral blood erythroid progenitor cells and enhances the cell cycle progression of hematopoietic progenitor cells mediated by IGF-I (23, 24). Interestingly, a study has shown a non-linear correlation between Hb levels and peak GH responses in GH stimulation tests. The authors emphasized that through threshold effect analysis, they identified an inflection point of Hb at 123 g/L. If the Hb value was below this inflection point, the correlation between Hb and GH peaks was not statistically significant (25). In our study, while no significant differences were found in height parameters between children with low and normal Hb levels, correlation analyses demonstrated a significant positive correlation between Hb levels and growth rates during the first year of treatment.

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Some studies have reported that vitamin B12 deficiency can affect the IGF-1/GH axis and lead to the development of GH resistance (26). However, another study found no change in taurine levels within the IGF-1/GH axis in children with B12 deficiency, and no increase in levels was observed following B12 therapy (27). There is limited research investigating the monitoring of B12 levels during rhGH treatment and the effect of B12 supplementation on growth velocity in GHD patients.

One possible reason for the lack of significant differences in growth outcomes despite prevalent nutritional deficiencies is that rhGH therapy may have the capacity to compensate for these deficiencies, leading to a favorable response from the body despite other negative factors associated with GH deficiency. However, since our study only includes a one-year follow-up, it is challenging to draw definitive conclusions about how the effectiveness of rhGH therapy might be impacted by inadequate nutritional reserves over a longer duration. Additionally, limitations in the measurement of nutritional markers may also influence this situation. For instance, serum levels may only reflect short-term nutritional status, while the effects on growth could be more closely related to long-term dietary habits. Consequently, the inadequacies of current measurement methods can hinder a broader evaluation of growth outcomes. These factors indicate that a deeper investigation is necessary to understand the impacts of nutritional deficiencies on growth.

Nutritional Supplementation

A notable finding was that 41% of the children were receiving some form of nutritional supplementation (iron, vitamin B12, vitamin D, or multivitamins). However, no significant differences in growth parameters were observed between those who received supplements and those who did not. This lack of significant effect may suggest that the initial supplementation doses were adequate or highlight the need for more individualized nutritional interventions based on specific requirements.

In a study that followed up for one year, it was reported that nutritional supplementation had a significant positive impact on height in short and lean prepubertal children, while it did not alter BMI (28). Our study, which includes a population with IGHD receiving rhGH therapy, complicates the isolation of the effect of nutritional support on growth. This is due to the interaction of several factors, including the severity of GHD, genetic factors, family height potential, and bone age. Therefore, assessing the isolated effect of nutritional support on growth in this context is challenging.

Growth Response and Predictive Factors

Correlation analyses identified that initial height SDS, PAH, PAH SDS, and MPH were significant factors influencing height SDS at the end of the first year of treatment. Studies also indicate that among the factors affecting growth rate during the first year of treatment, the peak GH response in stimulation tests and the severity of GHD are among the most influential (29). These findings underscore the importance of considering baseline growth metrics and familial height potential when evaluating treatment responses.

Additionally, the significant positive correlation between growth rate and Hb levels, MPH, and MPH SDS highlights the potential role of these factors in influencing growth velocity, although causality cannot be definitively established from correlation alone.

Limitations and Future Directions

This study has several limitations. Firstly, the relatively small sample size is a constraint. Although the sample size of the study is sufficient for statistical power analysis, the number of cases in some subgroups is low (for example, the group with low B12 levels, n=15), which reduces the statistical power of the study. Secondly, there is a lack of longitudinal data beyond the first year of treatment, including information on nutritional status at the end of the first year. Thirdly, as the study is retrospective and the data were obtained from medical records, we do not have detailed information on the exact dosage, duration, or adherence to the nutritional supplementation. Lastly, due to the retrospective nature of the study, important factors related to nutritional status, such as dietary habits and sociodemographic characteristics, may not have been recorded, and their potential effects remain unknown. Future studies with larger sample sizes, prospective nature and extended follow-up periods could provide more comprehensive insights into the long-term effects of nutritional supplementation on growth. Additionally, investigating other potential influencing factors, such as genetic markers and adherence to treatment protocols, as well as gathering brief survey data on dietary habits and family characteristics, could provide deeper insights into the growth patterns of children with IGHD.

CONCLUSION

Nutritional deficiencies were common among IGHD patients; there was no significant difference in terms of growth-related metrics in the first year of the rhGH therapy in comparisons between the groups with and without common nutritional deficiencies. This finding underscores the resilience of growth in the presence of these deficiencies. In contrast, growth velocity correlated positively with Hb levels and MPH, suggesting that these factors may play a significant role in influencing growth. Further research with larger samples and extended follow-up is needed to explore the long-term impact of nutritional supplementation on growth in IGHD.

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Ethical approval: The present study was conducted in strict in accordance with the principles outlined in the Declaration of Helsinki. Akdeniz University Hospital ethics committee (approval number: TBAEK-570)

Authors' Contribution

Conceptualization: ZD
Data curation: ZD, KÇ, YFB, EBÇ, BS, HT, MP
Formal analysis: ZD
Funding acquisition: No funds were received.
Investigation: ZD, KÇ, YFB, EBÇ, BS, HT, MP
Methodology: ZD
Project administration: ZD, MP
Resources: ZD, MP
Software: SPSS
Supervision: ZD, HT, MP
Validation: ZD
Visualization: ZD
Writing–original draft: ZD
Writing–review & editing: ZD, HT, MP

REFERENCES

1. Braun K, Erler N, Kiefte-de Jong J, Jaddoe V, van den Hooven E, Franco O, Voortman T. Dietary intake of protein in early childhood is associated with growth trajectories between 1 and 9 years of age. J Nutr. 2016;146(12):2361-7. doi: 10.3945/jn.116.237164.
2. Subhasish D, Sanchez J, Alam A, Haque A, Mahfuz M, Ahmed T, Long KZ. Dietary magnesium, vitamin D, and animal protein intake and their association with the linear growth trajectory of children from birth to 24 months of age: results from the MAL-ED birth cohort study conducted in Dhaka, Bangladesh. Food Nutr Bull. 2020;41(2):200-10. doi: 10.1177/0379572119892408
3. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990-3. doi: 10.1210/jcem.85.11.6984
4. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7(4):280-93. doi: 10.4274/jcrpe.2183
5. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291-303. doi: 10.1136/adc.44.235.291
6. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford (CA): Stanford University Press; 1959. p. 50-250.
7. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr. 1952;40(4):423-41. doi: 10.1016/s0022-3476(52)80205-7
8. Roche AF, Wainer H, Thissen D. The RWT method for the prediction of adult stature. Pediatrics. 1975;56(6):1027-33.
9. Brugnara C, Oski FA, Nathan DG. Diagnostic approach to the anemic patient. In: Orkin SH, Fisher DE, Ginsburg D, et al, editors. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: WB Saunders; 2015.
10. Flerlage J, Engorn B, editors. The Harriet Lane Handbook: A Manual for Pediatric House Officers. 20th ed. Philadelphia, Pa.: Saunders/Elsevier; 2015. p. 305.
11. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387(10021):907-14. doi: 10.1016/S0140-6736(15)60865-0
12. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol. 2009;19(2):73-8. doi: 10.1016/j.annepidem.2007.12.001.
13. Henneman PH, Forbes AP, Moldawer M, Dempsey EF, Carroll EL. Effects of human growth hormone in man. J Clin Invest. 1960;39(8):1223-38. doi: 10.1172/JCI104138.
14. Esposito S, Leonardi A, Lanciotti L, et al. Vitamin D and growth hormone in children: a review of the current scientific knowledge. J Transl Med. 2019;17:87. doi: 10.1186/s12967-019-1840-4.
15. Ameri P, Giusti A, Boschetti M, et al. Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. Eur J Endocrinol. 2013;169(6):767-72. doi: 10.1530/EJE-13-0510.
16. Matilainen M, Malinen M, Saavalainen K, Carlberg C. Regulation of multiple insulin-like growth factor binding protein genes by 1alpha,25-dihydroxyvitamin D3. Nucleic Acids Res. 2005;33(17):5521-32. doi: 10.1093/nar/gki872.
17. Hamza RT, Hamed AI, Sallam MT. Vitamin D status in prepubertal children with isolated idiopathic growth hormone deficiency: effect of growth hormone therapy. J Investig Med. 2018;66:1-8. doi: 10.1136/jim-2017-000618.
18. Mohammed SH, Esmaillzadeh A. The relationships among iron supplement use, Hb concentration, and linear growth in young children: Ethiopian demographic and health survey. Br J Nutr. 2017;118(9):730-6. doi: 10.1017/S0007114517002677.
19. Choy CC, Desai MM, Park JJ, et al. Child, maternal and household-level correlates of nutritional status: a cross-sectional study among young Samoan children. Public Health Nutr. 2017;20(7):1235-47. doi: 10.1017/S1368980016003499.
20. Allali S, Brousse V, Sacri AS, et al. Anemia in children: prevalence, causes, diagnostic work-up, and long-term consequences. Expert Rev Hematol. 2017;10(11):1023-8. doi: 10.1080/17474086.2017.1354696.
21. Eugster EA, Fisch M, Walvoord EC, et al. Low hemoglobin levels in children with idiopathic growth hormone deficiency. Endocrine. 2002;18(2):135-6. doi: 10.1385/ENDO:18:2:135.
22. Ciresi A, Piazza G, Radellini S, et al. Growth hormone and hematopoiesis: a retrospective analysis on a large cohort of children with growth hormone deficiency. Growth Horm IGF Res. 2018;42-43:8-13. doi: 10.1016/j.ghir.2018.07.005.
23. Merchav S, Tatarsky I, Hochberg Z. Enhancement of erythropoiesis in vitro by human growth hormone is mediated by insulin-like growth factor I. Br J Haematol. 1988;70(3):267-71. doi: 10.1111/j.1365-2141.1988.tb02480.x.
24. MP K, Stecewicz I, Piecyk K, et al. Effects of growth hormone therapeutic supplementation on hematopoietic stem/progenitor cells in children with growth hormone deficiency: focus on proliferation and differentiation capabilities. Endocrine. 2015;50(1):162-75. doi: 10.1007/s12020-015-0591-0.
25. Zhang T, Ban B, Zhang M, Ji B, Sun H, Sun B. Association between hemoglobin and growth hormone peak in Chinese children and adolescents with short stature: A cross-sectional study. Int J Gen Med. 2021;14:497-504. doi: 10.2147/IJGM.S292920.
26. Roman-Garcia P, Quiros-Gonzalez I, Mottram L, et al. Vitamin B_{12}-dependent taurine synthesis regulates growth and bone mass. J Clin Invest. 2014;124(7):2988-3002. doi: 10.1172/JCI75953.
27. Haliloglu B, Tuysuz G, Kaya A. The effect of vitamin B12 deficiency on the GH-IGF1 axis. Med Sci. 2017;6(3):496-7. doi: 10.5455/medscience.2017.06.8727.
28. Yackobovitch-Gavan M, Lebenthal Y, Lazar L, et al. Effect of nutritional supplementation on growth in short and lean prepubertal children after 1 year of intervention. J Pediatr. 2016;177:203-9. doi: 10.1016/j.jpeds.2016.08.100.
29. Donbaloğlu Z, Singin B, Acar S, et al. Evaluation of the growth response of children with growth hormone deficiency according to the peak growth hormone levels in provocation tests. Arch Pediatr. 2023;30(8):573-9. doi: 10.1016/j.arcped.2023.05.002.

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