Jordan Journal of Applied Science
Natural Science Series

Research Article

Insulin-like growth factor1 and ghrelin's relationship with the nutritional status of children with short stature

Mohammed E. Moustafa[1*], Ezz E. Khalifa[2].
[1] Primary health care, Ministry of Health, Kuwait.
[2] Primary health care, Ministry of Health, Egypt.

ARTICLE INFO

Article history:
Received 20 Oct 2022
Accepted 5 Feb 2023
Published 30 Jun 2023

DOI: 10.35192/jjoas-n.v17i1.1809

***Corresponding author:**
Primary health care, Ministry of Health, Kuwait.
Email: drmohamed.ezzat@yahoo.com

Keywords:
Ghrelin
Insulin Growth Factor1
Nutrition
Short stature

ABSTRACT

Background: Pediatricians often encounter issues related to short stature, particularly in underdeveloped nations. Changes in total ghrelin (TG) or acylated ghrelin (AG) are thought to influence growth by affecting growth hormone secretion, which may subsequently impact the formation of insulin-like growth factor-1 (IGF-1) or through alterations in hunger and food consumption.
Aim: This study aims to improve the management of children with short stature and assess the outcomes associated with it.

Methods: Between March 2021 and October 2022, a cross-sectional descriptive study was conducted at the pediatric endocrine clinic of Mahala General Hospital. The study enrolled 48 participants. The patients were divided into two groups: Group A included children with growth hormone deficiency, while Group B comprised children with unexplained short stature. Ghrelin levels, IGF-1, growth hormone, thyroxine, triiodothyronine, and thyroid-stimulating hormone were all measured.

Results: There was a statistically significant decrease in IGF-1 in Group A compared to Group B. Additionally, Group A exhibited significantly higher ghrelin levels than Group B. Growth hormone showed a statistically significant negative correlation with ghrelin and a positive correlation with IGF-1.

Conclusion: The relationship between growth hormone, IGF-1, and ghrelin is negative; the short stature group has a lower body mass index (BMI) than the growth hormone deficiency group, indicating a lower nutritional status. Ghrelin may be a contributing factor in the etiology of idiopathic short stature.

Introduction

In the same ethnic group, short stature is defined as having a height less than the third percentile or two standard deviations below the mean height for that age and sex (1). Short stature might result from an illness or be a variation of average growth (2).

Familial (genetic) short height and delayed (constitutional) growth—standard, non-pathologic growth patterns—are the most prevalent reasons for short stature after the first year or two of life. Short stature can often be caused by endocrinological ailments involving hypercorticism, hypopituitarism (single anterior pituitary hormone shortage or numerous), hypothyroidism, and regular Laron syndrome (1). Being overweight, in terms of their height, outlines each of these. Along with several dysmorphic syndromes, small-for-gestational-age (SGA) births and intrauterine growth retardation (IUGR) can also result in short stature (2).

A deficiency of growth hormone results in short stature; it's a complex clinical situation requiring knowledge of the disease's history, experience, and careful assessment of all available treatment options in light of the best available scientific data, avoiding off-label or unproven therapies (3).

Finding the subgroup of kids with pathologic causes such as Turner syndrome, inflammatory bowel disease, or another underlying systemic condition—is the aim of evaluating a kid with short stature (such as growth hormone deficiency). To aid in decisions regarding intervention, if necessary, the evaluation also assesses the degree of the short stature and the expected growth trajectory (2).

Patients and Methods

Study design

A cross-sectional descriptive study was conducted at the pediatric endocrine clinic at Mahala General Hospital between March 2021 and October 2022. Interviews and lab tests were used to determine the patient's eligibility for this study. Before beginning the study, each participant provided written, informed consent. Group A: Growth hormone deficient child; Group B: Unexplained short stature.

Children aged 5 to 10 years, both male and female, who showed substantially short stature or short stature as measured by the Egyptian Growth Chart were included in the current research. The following conditions were not included in the study: skeletal dysplasia, hormonal deficiency rather than growth hormone (thyroid, for example), clinical syndromes (Turner, Cushing, silver russel, etc.), chronic disease (DM, chronic renal failure, etc.), and familial short stature.

Patient preparation

Taking a history involves providing personal details, medical history (with a focus on the existence of chronic illnesses), food and drug intake histories, and information about growth and development, including dental eruption, motor development, mental development, and mental development, as well as any family history of a condition similar to short stature or delayed puberty.

The clinical examination covers examinations of height with a stadiometer, weight with a Seca weighted scale, and body mass index (BMI) derived from a person's height in meters and weight in kilograms (kg/m2). Body mass index is determined using the WHO growth curves and z-scores. Each child's BMI was then calculated using the WHO Reference criteria. In addition to a local examination that included a chest, heart, and abdominal exam, a general examination was conducted to rule out the dysmorphic symptoms of syndromic short stature.

In a study conducted in a lab, Ghrelin levels, growth hormone, IGF-1, T3, T4, and thyroid stimulating hormone were all assessed.

Statistical Analysis of Data

Using SPSS version 21 (SPSS Inc., Chicago, USA), an IBM-compatible computer was used to arrange, tabulate, and statistically analyze the gathered data. Distributions of percent and frequency were computed for the qualitative data, and standard error (SE) and mean were computed for the quantitative data.

Results

The BMI and BMI percentile in the current study were almost similar for both groups. When Group I and Group II were compared, there was a substantial drop in height, height percentile, weight, and weight percentile in Group I. Group I had a considerable rise in triglycerides (TG) compared to Group II's TG. Low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (T-Ch) were almost similar in both groups. (Table 1).

GH, IGF-1, and Ghrelin were found to be statistically significantly lower in group I compared to group II, significantly higher in group I compared to group II, significantly decreased in free T4 in group I compared to group II, and significantly increased in TSH in group I compared to group II in the current study (Table 2).

Following clonidine induction, all growth hormone measures produced statistically significant results. The peak of the growth hormone-deficient group was almost five times greater than the same value in the other group (Table 3).

Comparing the ghrelin levels and insulin-like growth factor-1 between research groups revealed statistically significant variations. Ghrelin and insulin-like growth factor-1 have a statistically significant negative connection. The relationship between maximum growth hormone and insulin-like growth factor-1 is highly statistically significant (Figures 1-6)

Table 1. The analyzed cases' demographic information included their height, weight, BMI, percentiles, and lipid profiles.

	Group I	Group II	T-test	P value
Height (Cm)	87.19 ± 2.05	104.71 ± 2.86	4.98	<0.001*
Height percentile	10.24 ± 1.67	66.19 ± 3.57	14.2	<0.001*
Weight (Kg)	18.33 ± 0.61	23.62 ± 1.07	4.29	<0.001*
Weight percentile	11.67 ± 1.74	57.38 ± 4.62	9.26	<0.001*
BMI (kg/m2)	14.71 ± 0.38	13.97 ± 0.36	1.4	0.17
BMI percentile	47.62 ± 3.41	51.19 ± 3.65	0.72	0.48
TG (mg/dl)	83.91 ± 1.38	60.95 ± 1.06	10.85	<0.001*
T-Ch (mg/dl)	174.62 ± 3.17	167.71 ± 2.17	11.52	0.08
LDL (mg/dl)	86.05 ± 3.18	79.76 ± 2.66	1.51	0.14
HDL (mg/dl)	66.62 ± 2.63	68.62 ± 2.27	0.58	0.57

Table 2. Hematological parameter of the studied cases.

	Group I	Group II	T-test	P value
GH (ng/dl)	1.03 ± 0.19	4.8 ± 0.87	19.43	<0.001*
IGF-1 (ng/ml)	198.62 ± 35.02	310.19 ± 27.25	11.52	<0.001*
Ghrelin (pg/ml)	406.67 ± 33.76	315.38 ± 26.75	9.71	<0.001*
Free T4 (ng/dl)	0.85 ± 0.11	1.46 ± 0.3	8.62	<0.001*
TSH (ng/dl)	6.04 ± 0.42	3.78 ± 0.41	17.6	<0.001*

Table 3. Clonidine growth hormone induction results for the study groups

Group	Growth hormone deficient	Idiopathic short stature	p-value
Variables	Mean ± SD	Mean ± SD	
Basal (ng/ml)	0.9 ± 0.15	2.34 ± 0.5	<0.001
30 minutes (ng/ml)	1.6 ± 0.3	10.12 ± 1.09	<0.001
60 minutes (ng/ml)	1.8 ± 0.32	9.89 ± 0.79	<0.001
90 minutes (ng/ml)	1.03 ± 0.25	7.08 ± 1.22	<0.001
120 minutes (ng/ml)	0.51 ± 0.15	4.22 ± 1.14	<0.001
150 minutes (ng/ml)	1.25 ± 0.25	3.21 ± 1.19	<0.001
180 minutes (ng/ml)	0.77 ± 0.19	3 ± 0.75	<0.001
Maximum (ng/ml)	2.2 ± 0.25	12.3 ± 0.62	<0.001

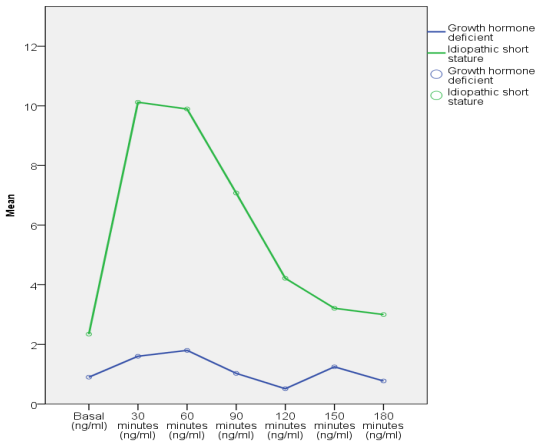


Figure 1 Graph comparing study groups' clonidine growth hormone induction results for the study groups

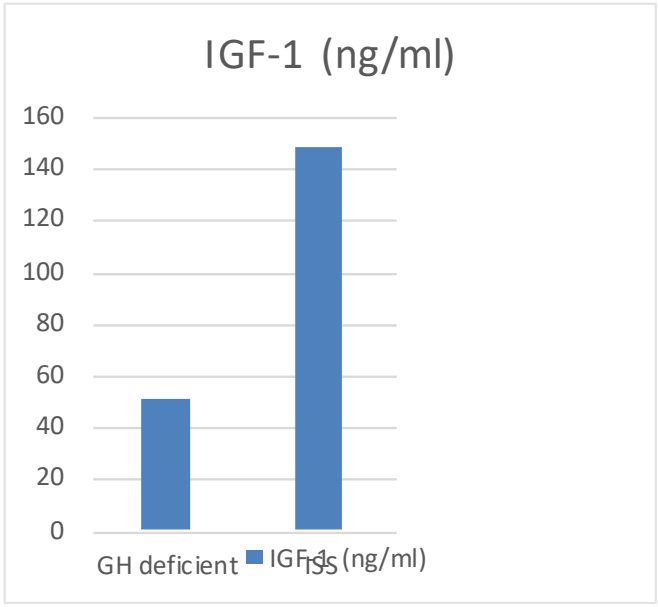


Figure 2. Graph comparing study groups' Insulin-like growth factor-1

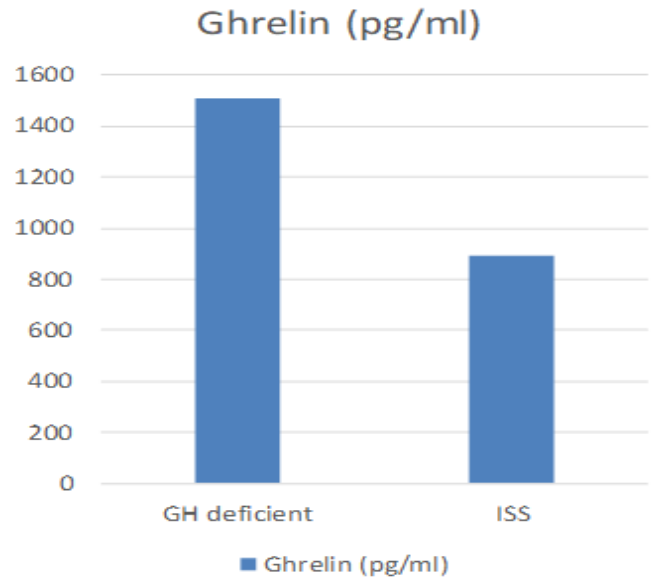


Figure 3. Graph comparing study groups' Ghrelin

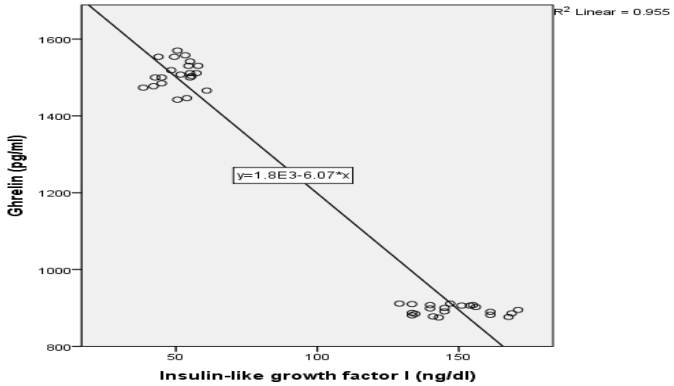


Figure 4. Scatterplot showing the relation between insulin-like growth factor-1 and ghrelin in the whole study population

Discussion

Our study's findings demonstrate that, regarding anthropometric measurements, children with GHD had significantly lower measurements than children with ISS, and group I had significantly smaller weights than group II. Additionally, the two groups' BMIs were remarkably identical.

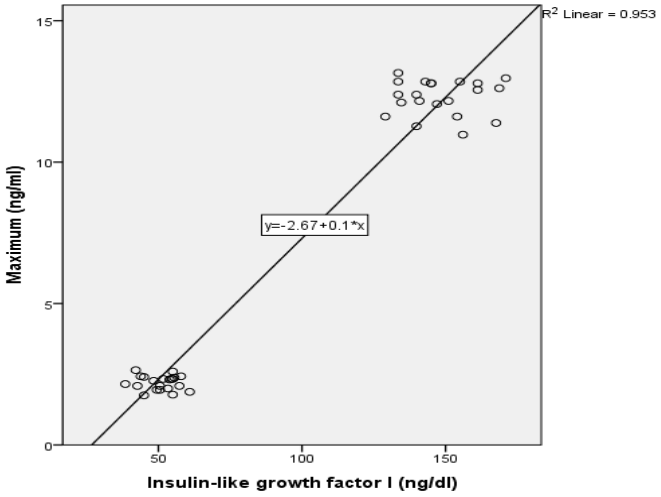


Figure 5. Scatterplot showing the relation between insulin-like growth factor-1 and maximal growth hormone measurement in the whole study population

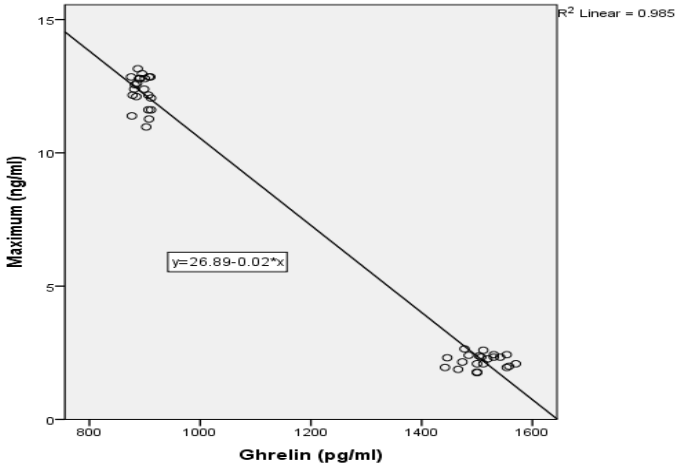


Figure 6. Scatterplot showing the relation between ghrelin and maximal growth hormone measurement in the whole study population

According to (4), children with growth hormone deficit (GHD) had lower weight and height measurements and percentiles. This change in food intake may respond to the increasing metabolic requirements brought on by GH treatment, as seen by the better appetite that matched with increases in weight, height, and energy expenditure throughout treatment. As compared to non-GHD patients, the GHD patients had a greater BMI upon diagnosis (5). Body composition alterations brought on by growth hormones are desirable. There has been a notable increase in the body mass index (BMI) in several research (6).

Our investigation indicates that the IGF-1 level was much lower in the GHD youngsters relative to the ISS group. Our data are compared with those of (7), who found no significant difference in IGF-1 levels between the control group and 41 prepubertal ISS, 25 prepubertal ISS, and pubertal ISS, respectively. According to Ibba et al. (8), 30 children with CDGD had significantly lower serum IGF−1 levels than the control group. Rather than being the result of GH insufficiency, low IGF-1 levels in children with CDGP were most likely caused by inadequate diet.

According to our study's findings, children with GHD had substantially higher levels of Ghrelin and statistically significantly lower levels of GH when compared to children with idiopathic short stature. According to Zhou and Du R (9) and Stawerska et al. (10), these findings reinforced the results. They reported that patients with growth hormone deficit (GHD) had greater levels of ghrelin than those with normal GH. In children with growth hormone deficit (GHD), GH and IGF-1 were shown to be lower, according to Yackobovitch-Gavana et al. (4). Improved appetite typically follows GH treatment, contributing to the enhanced growth rate in short children (11).

Interactions throughout the central nervous system and circulating hormones that regulate hunger determine how much food is consumed and how much appetite is controlled (12). The improved nutritional status of GH therapy enhanced the response to ghrelin stimulation. According to these results, lean and short children's nutritional condition is likely reflected rather than caused by ghrelin levels, most likely in a compensatory way (13).

A low level of serum IGF-1 in the absence of chronic illness and malnutrition is comparable to (45%) or superior to (37%) growth hormone stimulation test (GHST), according to 82% of those who replied to a survey on 387 citations covering the majority of guidelines and recommendations for the diagnosis of GHD (14). As provocative GH testing indicates (15), serum IGF-1 concentrations do not precisely translate with GH status. However, some individuals continue to believe that IGF-1 concentration may be a somewhat reliable test in detecting GHD due to GHST (16 – 17).

Our research demonstrates that in total patients, ghrelin is strongly associated negatively with IGF-1. No discernible relationship was found between the GHD and ISS groups. Amin et al.'s (18) study recruited 17 CDGP children, ages 6.5 to 15; 19 FSS children, ages 7 to 15.2; and 11 controls, ages 6.8 to 14.8. Low IGF-1 may have stimulatory effects on ghrelin, which could explain the negative association between ghrelin and IGF-1.

There was no relationship between ghrelin concentrations and IGF-I SDS, as demonstrated by Stawerska et al. (19), who assessed 134 prepubertal children who were categorized into four groups: normal height birth appropriate gestational age (AGA), just short AGA, normal-height SGA, and short SGA. Possible explanations of the data discrepancies include the substantial sample size and the assertion that SGA and AGA are not GHD patients. Our study revealed a negative correlation between BMI, weight, height, and Ghrelin in total patients. Ghrelin and BMI (SDS) had a non-significant statistically significant correlation in the idiopathic short-stature group and a substantially good statistically significant correlation in the growth-hormone deficient group.

We match the findings of Patro-Małysza et al. (20), who found that in 111 healthy children between the ages of 4 months and ten years, there was a negative connection between age and total ghrelin, acyl ghrelin and des-acyl ghrelin.

According to Amin et al. (18), in short-stature patients (CDGP and FSS) and controls, ghrelin was significantly linked with chronological years, bone age, weight, height, SDS, and BMI. Eleven controls, ages 6.8–14.8, 19 children with FSS, ages 7–15, and 17 children with CDGP, ages 6.5–15, participated in the study. Considering that the increased ghrelin levels were a compensatory response to the reduced height SDS caused by lower IGF-1 concentrations is reasonable. Another hypothesis for the compensatory rise of ghrelin as an orexigenic component could be that people with short stature have inferior dietary status, which results in reduced height SDS.

Ghrelin has been shown by El-Shumway et al. (21) to have a negative correlation with height, BMI, bone age, and weight (kg). The bone age latency (years) and ghrelin had a positive correlation. However, there was no discernible relationship between ghrelin and age in 23 CDGP children who were short-stature patients and controls. In 41 prepubertal and 116 prepubertal and pubertal children ISS, respectively, ghrelin was found to be inversely linked with weight SDS and height SDS, according to studies by Iñiguez et al. (7) and Stawerska et al. (10).

Lewiński et al. (22) found a substantial negative association between body weight, BMI SDS for HA, ghrelin concentration, and CA, HA, BA, and body weight. Regardless of the child's chronological age, thinner children have deeper ghrelin concentrations; nevertheless, no significant link has been shown between ghrelin concentration and BMI SDS for CA. However, in 15 GHD, 116 ISS pubertal and prepubertal children, and 19 controls, there were no significant associations observed between ghrelin concentrations and GH max in the entire group of children, either during the clonidine-provoking test or during the glucagon-stimulating test.

The findings of Willaschek et al. (23) indicate that there may be a negative feedback loop between ghrelin and GH similar, as there was a negative connection between circulating ghrelin and GH in 8 prepubertal short stature normal growth hormone (NGH) children. In ten prepubertal GHD children, no such changes were seen. The baseline ghrelin levels in NGH subjects negatively correlated with absolute body weight. The compensatory mechanism of ghrelin to alter the metabolic process has been proposed as the cause of this condition.

Our data also align with that of Stawerska et al. (19), who revealed statistically significant negative correlations between ghrelin and WT/SDS, BMI SDS for HA, and the ages of 134 prepubertal children, who were split into four groups: normal-height SGA, short SGA, average height born corresponding to gestational age (AGA), and short AGA.

In 28 anorexic patients and 33 controls of average weight,

Terra et al. (24) discovered a negative correlation between ghrelin and BMI. In this investigation, there was no discernible association with additional thyroid function metrics. According to Joanna et al., the T3 hormone and growth hormone levels in the serum were found to correlate positively for the group of people with short height. Thyroid hormone T3 is necessary for adequate skeletal development, and this finding confirmed the most commonly cited mechanism of changes in thyroid hormone levels: GH-mediated increase of peripheral T4 to T3 deiodination (25). Epiphyseal dysgenesis, delayed bone age, growth arrest, and low stature are the consequences of childhood hypothyroidism (26).

Ghrelin levels were negatively correlated with anthropometric measures in healthy children, including height, weight, BMI, waist circumference, and hip circumference (27). Relative to IGF1 and insulin-like growth factor binding protein-3 (IGFBP-3) and positively correlated with IGFBP-1, ghrelin levels in healthy children decline with age and puberty. These changes reduce the availability of IGF1 in the tissue (28). They hypothesized that the growth spurt during puberty is caused by the lowering of ghrelin with age and during puberty with increasing IGF1 levels. As a result of the neural circuits inducing a positive energy balance during fasting, ghrelin levels rise. By suppressing TSH levels and promoting the hypothalamic-pituitary -adrenal axis, ghrelin lowers energy expenditure via its effects on the hypothalamic-pituitary-thyroid axis (29). GH levels in anorexic patients are high, while GH secretion is reduced in obese patients; these differences may be explained by the fact that ghrelin is an endogenous agonist at the GH secretagogue receptor (30).

There are some limitations to our study. First, our study was a cross-sectional study. Second, the number of subjects in our study was relatively small. Third, we measured the total circulating ghrelin, including acyl and des acyl ghrelin, but not the active form.

Conclusion

There is a negative feedback loop between ghrelin and IGF-1 and GH, while positive feedback is with BMI. BMI, which is a reflection of nutritional status, is lower in the ISS group than in the GHD group. Despite that BMI is more affected in the ISS group, there is only a very weak positive non-significant correlation with ghrelin. Ghrelin may contribute to the pathogenesis of idiopathic short stature.

Declaration of Competing Interests

The authors declare no competing interests

Data sharing plans

Data will be available upon request

Funding

The authors received no financial support

References

1. Polidori N, Castorani V, Mohn A, Chiarelli F. Deciphering short stature in children. Ann Pediatr Endocrinol Metab. 2020 Jun;25 (2):69-79. doi: 10.6065/apem.2040064.032.
2. Maghnie M, Labarta JI, Koledova E, Rohrer TR. Short Stature Diagnosis and Referral. Front Endocrinol (Lausanne). 2018 Jan 11;8:374. doi: 10.3389/fendo.2017.00374.
3. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Front Endocrinol (Lausanne). 2021 Sep 1;12:720419. doi: 10.3389/fendo.2021.720419.
4. Yackobovitch-Gavan M, Gat-Yablonski G, Shtaif B, Hadani S, Abargil S, Phillip M, et al. Growth hormone therapy in children with idiopathic short stature - the effect on appetite and appetite-regulating hormones: a pilot study. Endocr Res. 2019 Feb-May;44 (1-2):16-26. doi: 10.1080/07435800.2018.1493598.
5. Lim HH, Kim YM, Lee GM, Yu J, Han HS, Yu J. Growth Responses During 3 Years of Growth Hormone Treatment in Children and Adolescents With Growth Hormone Deficiency: Comparison Between Idiopathic, Organic and Isolated Growth Hormone Deficiency, and Multiple Pituitary Hormone Deficiency. J Korean Med Sci. 2022 Mar 21;37(11):e90. doi: 10.3346/jkms.2022.37.e90.
6. Claessen KM, Appelman-Dijkstra NM, Adoptie DM, Roelfsema F, Smit JW, Biermasz NR, et al. Metabolic profile in growth hormone-deficient (GHD) adults after long-term recombinant human growth hormone (rhGH) therapy. J Clin Endocrinol Metab. 2013 Jan;98(1):352-61. doi: 10.1210/jc.2012-2940.
7. Iñiguez G, Román R, Youlton R, Cassorla F, Mericq V. Ghrelin plasma levels in patients with idiopathic short stature. Horm Res Paediatr. 2011 Feb;75(2):94-100. doi: 10.1159/000317429.
8. Ibba A, Corrias F, Guzzetti C, Casula L, Salerno M, di Iorgi N, et al. IGF1 for the diagnosis of growth hormone deficiency in children and adolescents: a reappraisal. Endocr Connect. 2020 Nov;9 (11):1095-1102. doi: 10.1530/EC-20-0347.
9. Zhou G, Du R. Dynamic Ghrelin and GH serum levels during combined simultaneous arginine clonidine stimulation test in children with dwarfism. Ital J Pediatr. 2019 Jan 28;45(1):17. doi: 10.1186/s13052-019-0610-5.
10. Stawerska R, Czkwianianc E, Smyczyńska J, Hilczer M, Lewiński A. Nutritional Status in Short Stature Children Is Related to Both Ghrelin and Insulin-like Growth Factor I Concentrations. J Pediatr Gastroenterol Nutr. 2017 May;64(5):812-817. doi: 10.1097/MPG.0000000000001387.
11. Zhang Z, Li F, Hannon BA, Hustead DS, Aw MM, Liu Z, et al. Effect of Oral Nutritional Supplementation on Growth in Children with Undernutrition: A Systematic Review and Meta-Analysis. Nutrients. 2021 Aug 30;13(9):3036. doi: 10.3390/nu13093036.
12. Young AA. Brainstem sensing of meal-related signals in energy homeostasis. Neuropharmacology. 2012;63(1):31-45. doi: 10.1016/j.neuropharm.2012.03.019.
13. Ibrahim Abdalla MM. Ghrelin - Physiological Functions and Regulation. Eur Endocrinol. 2015 Aug;11(2):90-95. doi: 10.17925/EE.2015.11.02.90.
14. Kanakis GA, Chrisoulidou A, Bargiota A, Efstathiadou ZA, Papanastasiou L, Theodoropoulou A, et al. The ongoing challenge of discrepant growth hormone and insulin-like growth factor I results in the evaluation of treated acromegalic patients: a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2016 Nov;85(5):681-688. doi: 10.1111/cen.13129.
15. Hamza RT, Ismail MA, Hamed AI. Growth hormone deficiency in children and adolescents with cerebral palsy: relation to gross motor function and degree of spasticity. Pak J Biol Sci. 2011 Apr 1;14(7):433-40. doi: 10.3923/pjbs.2011.433.440.
16. Cohen LE. Idiopathic short stature: a clinical review. JAMA. 2014 May 7;311(17):1787-96. doi: 10.1001/jama.2014.3970.
17. Smyczyńska J, Stawerska R, Lewiński A, Hilczer M. Do IGF-I concentrations better reflect growth hormone (GH) action in children with short stature than the results of GH stimulating tests? Evidence from the simultaneous assessment of thyroid function. Thyroid Res. 2011 Jan 13;4(1):6. doi: 10.1186/1756-6614-4-6.
18. Amin MK, Ahmed HG, Selmy M, Gad SS. Correlation of body mass index to Ghrelin and IGF-1 among children with short stature. J Pediatr (Rio J). 2022 May-Jun;98(3):276-281. doi: 10.1016/j.jped.2021.04.012.
19. Stawerska R, Szałapska M, Hilczer M, Lewiński A. Ghrelin, insulin-like growth factor I and adipocytokines concentrations in born small for gestational age prepubertal children after the catch -up growth. J Pediatr Endocrinol Metab. 2016 Aug 1;29(8):939-45. doi: 10.1515/jpem-2015-0463.
20. Patro-Małysza J, Trojnar M, Skórzyńska-Dziduszko KE, Kimber-Trojnar Ż, Darmochwał-Kolarz D, Czuba M, et al. Leptin and Ghrelin in Excessive Gestational Weight Gain-Association between Mothers and Offspring. Int J Mol Sci. 2019 May 15;20 (10):2398. doi: 10.3390/ijms20102398.
21. Hajishizari S, Imani H, Mehranfar S, Saeed Yekaninejad M, Mirzababaei A, et al. The association of appetite and hormones (leptin, ghrelin, and Insulin) with resting metabolic rate in overweight/ obese women: a case-control study. BMC Nutr. 2022 Apr 29;8(1):37. doi: 10.1186/s40795-022-00531-w.
22. Lewiński A, Karbownik-Lewińska M, Wieczorek-Szukała K, Stasiak M, Stawerska R. Contribution of Ghrelin to the Pathogenesis of Growth Hormone Deficiency. Int J Mol Sci. 2021 Aug 23;22 (16):9066. doi: 10.3390/ijms22169066.
23. Willaschek C, Meint S, Rager K, Buchhorn R. Modified Clonidine Testing for Growth Hormone Stimulation Reveals α2-Adrenoreceptor Sub Sensitivity in Children with Idiopathic Growth Hormone Deficiency. PLoS One. 2015 Sep 11;10 (9):e0137643. doi: 10.1371/journal.pone.0137643.

24. Terra X, Auguet T, Agüera Z, Quesada IM, Orellana-Gavaldà JM, Aguilar C, et al. Adipocytokine levels in women with anorexia nervosa. Relationship with weight restoration and disease duration. Int J Eat Disord. 2013 Dec;46(8):855-61. doi: 10.1002/eat.22166.
25. Witkowska-Sędek E, Kucharska AM, Rumińska M, Paluchowska M, Pyrżak B. Decreased Thyroxine Levels during rhGH Therapy in Children with Growth Hormone Deficiency. J Clin Med. 2021 Oct 30;10(21):5100. doi: 10.3390/jcm10215100.
26. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Front Endocrinol (Lausanne). 2021 Sep 1;12:720419. doi: 10.3389/fendo.2021.720419.
27. Fittipaldi AS, Hernández J, Castrogiovanni D, Lufrano D, De Francesco PN, Garrido V, et al. Plasma levels of ghrelin, des-acyl ghrelin and LEAP2 in children with obesity: correlation with age and insulin resistance. Eur J Endocrinol. 2020 Feb;182(2):165-175. doi: 10.1530/EJE-19-0684.
28. Devesa J. The Complex World of Regulation of Pituitary Growth Hormone Secretion: The Role of Ghrelin, Klotho, and Nesfatins in It. Front Endocrinol (Lausanne). 2021 Mar 11;12:636403. doi: 10.3389/fendo.2021.636403.
29. Serrenho D, Santos SD, Carvalho AL. The Role of Ghrelin in Regulating Synaptic Function and Plasticity of Feeding-Associated Circuits. Front Cell Neurosci. 2019 May 27;13:205. doi: 10.3389/fncel.2019.00205.
30. Wit JM, Joustra SD, Losekoot M, van Duyvenvoorde HA, de Bruin C. Differential Diagnosis of the Short IGF-I-Deficient Child with Apparently Normal Growth Hormone Secretion. Horm Res Paediatr. 2021;94(3-4):81-104. doi: 10.1159/000516407.