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Changes in body composition, adipokines, ghrelin, and FGF23 in growth hormone-deficient children during rhGH therapy

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Abstract

Introduction: Beyond growth acceleration, growth hormone (GH) therapy improves body composition of GH-deficient (GHD) children due to the interaction of GH with lipid and carbohydrate metabolism, possibly mediated by adipokines secreted by adipose tissue and ghrelin. To promote linear growth, it is essential to have normal phosphate homeostasis. Fibroblast growth factor 23 (FGF23) is a known regulator of serum phosphorus and may be responsible for the increased renal phosphorus reabsorption observed during GH therapy. This study aimed to assess the impact of one-year GH therapy on body composition, adipokines, acylated/unacylated ghrelin (AG/UAG), and FGF23 in GHD children.

Material and methods: A prospective observational study of 42 prepubertal, non-obese GHD children followed up in the first year of GH replacement therapy, investigating changes in adipokine profiles, AG/UAG, FGF23, and body composition. Data before therapy onset were compared with measurements obtained after 6 and 12 months of GH therapy.

Results: All children with a mean age of 9.2 ± 2.6 years grew at an accelerated pace. Total body fat decreased significantly, while the lipid profile improved, and total bone mineral density (BMD) significantly increased over the 12 months of treatment. Leptin and UAG levels decreased significantly, whereas adiponectin and AG values increased. A significant increase in plasma FGF23 and insulin growth factor 1 (IGF1) was accompanied by increased serum phosphate. Changes in FGF23 concentration did not have an impact on BMD. The strong association of FGF23 with IGF1 and height standard deviation (SD) could reveal a role of FGF23 in linear growth. In regression analysis models, GH therapy influences the changes of leptin and adiponectin, but not ghrelin, independently of body composition — lean or fat mass.

Conclusions: GH replacement therapy improves body composition and adipokine profile in GHD children and directly impacts leptin and adiponectin concentrations independently of body composition. Also, GHD children have increased serum phosphate, correlated with upregulation rather than with suppression of FGF23, an unexpected observation given the phosphaturic role of FGF23. Further research is needed to identify the molecular mechanisms by which the GH/IGF1 axis influences adipokines secretion and plasma changes of FGF23. **(Endokrynol Pol 2024; 75 (3): 291–299)**

Key words: *GH deficiency; adipokines; ghrelin; IGF1; body composition; FGF23*

Introduction

Linear growth can be affected by numerous factors, including nutrition, genetics, metabolism, and hormones. Growth hormone (GH)/insulin-like growth factor 1 (IGF1) axis, calcium-phosphorus homeostasis, and bone-kidney endocrine system mediated by the novel phosphaturic hormone fibroblast growth factor 23 (FGF23) play critical roles in appropriate bone and growth plate mineralisation [1–3]. Children with growth hormone deficiency (GHD) have a smaller stature and reduced longitudinal bone growth [4], an altered body composition and metabolic profile, with a lower bone mineral density (BMD) and delayed skeletal maturation, an increased percentage of body fat (%BF) with central fat deposition, and accompanying lean mass reduction [3–7].

Furthermore, long-standing GHD increases the risk of cardiovascular complications related to overweight or obesity, lipid disorders, insulin resistance, and alterations in adipokine profile and serum ghrelin levels. According to recent studies, GH/IGF1 may play a crucial role in regulating the secretion of adipokines and ghrelin [5–19]. However, the results are conflicting: some studies report increased serum leptin and adiponectin levels [13, 14, 20], while others found reduced leptin [15, 21] and no influence on adiponectin serum levels [15]. Ghrelin stimulates GH secretion, increases food intake, and generates weight gain [15, 22]. The primary metabolic effects are exerted by acylated ghrelin (AG), while plasma unacylated ghrelin (UAG) may inhibit ghrelin and be involved in critical endocrine processes [14, 23]. Ghrelin cor-

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relates negatively with body mass index (BMI), %BF, fasting insulin, and leptin values [12, 15]. The effects of ghrelin in treated GHD patients are contradictory. Some studies have reported no effect or a significant decrease in ghrelin levels [15, 24, 25]. In contrast, one study reported elevated ghrelin in non-treated GHD children and decreased ghrelin with children's age, suggesting the presence of GH-independent factors increasing ghrelin secretion [26].

Replacement therapy with recombinant human growth hormone (rhGH) was determined to modify body composition, decrease total body fat, improve lipid metabolism, and increase BMD in children with GHD, thus emphasising the crucial role of the GH/IGF1 axis in adult body composition and BMD outcomes and the need for continuing replacement treatment during the transition from paediatric to adult age, despite the closure of epiphyseal growth plates [27]. Whether the metabolic impact is due to body composition modifications or direct GH influence is unclear [5–16]. The rhGH treatment normalises BMD, reducing osteoporotic fracture risk by modifying bone formation and resorption markers from the start of therapy [4, 27, 28]. FGF23, mainly produced by osteocytes, regulates phosphorus metabolism and skeletal mineralisation. Studies have shown that GHD children have increased renal phosphorus reabsorption during replacement therapy, possibly due to FGF23 [2, 29].

This study aimed to evaluate the effects of rhGH replacement therapy on body composition and the relationship between the somatotropic axis and adipokines, ghrelin, and FGF23 in non-obese prepubertal children with GHD over a period of 12 months.

Material and methods

Subjects

This prospective, observational study consecutively sampled 42 non-obese prepubertal children (14 girls, 28 boys) diagnosed with idiopathic GHD at our Endocrinology Clinic. The local Ethics Committee approved the study, and informed consent was obtained before participation. The children had a mean age of 9.2 ± 2.6 years, with no significant differences between sexes ($t = 1.860$, $p = 0.070$). All subjects, after an initial evaluation of 7 days, started a 12-month course of GH replacement therapy (0.035 mg/kg/day) and were monitored at 6 and 12 months. The prepubertal status (Tanner stage I) was maintained during observation. The diagnosis of GHD was confirmed using the national GH treatment protocol and criteria [30]. This involves children with confirmed GHD, requiring a combination of auxological, biochemical, hormonal, and radiological assessments. Key criteria include height less than –2.5 SDS from the mean, or a significant height deficit over time or compared to genetic potential; bone age delayed by over 2 years; failure of 2 GH stimulation tests or one failed test plus low serum IGF1 and a maximum GH peak of 7 ng/mL in 2 GH provocation tests [30]. Other potential causes of short stature were ruled out. Magnetic resonance imaging was performed and showed normal hypophysis in all subjects. Exclusion criteria included pubertal onset, overweight or obese status (> 85th percentile) [31], and other metabolic disorders or diseases.

Blood sampling and biochemical analysis

During the initial visit, we recorded a detailed clinical history and the patient's age, sex, weight (kg), height (cm), BMI (weight/height^2), and bone age. After a 12-hour fast, morning blood samples were collected and frozen at –45°C for analysis. Patients were evaluated for various factors at baseline, 6 months, and 12 months during rhGH replacement therapy, including serum IGF1 levels, insulin-like growth factor-binding protein 3 (IGFBP3), AG and UAG, adiponectin, leptin, C-terminal FGF23, serum phosphorus, calcium, 25-OH-vitamin D, parathormone (PTH), glucose, glycosylated haemoglobin (HbA_{1c}), insulin, cholesterol, triglycerides, and insulin resistance (HOMA-IR).

The concentrations of IGFBP3 were determined quantitatively using a ligand-binding immunoassay (LIA, Reutlingen, Germany). Serum levels of AG, UAG, leptin, and adiponectin were measured using ELISA (BioVendor, Brno, Czech Republic). Serum C-terminal FGF23 levels were analysed using an ELISA kit (SEA746Hu, USCN Life Sciences, Wuhan, China) that measured both active and inactive FGF23 obtained after proteolytic cleavage of FGF23 in EDTA plasma centrifuged immediately after collection. Body composition was assessed using a Hologic QDR-4500 densitometer and total body dual-energy X-ray absorptiometry (DXA).

Statistical analysis

We used SPSS 24.0 to conduct a comparative study on monitored parameters. The results are presented as mean ± standard error of the mean (SEM), and ANOVA was used to compare 3 sets of values. Pearson correlation was used for normally distributed data, and Spearman's rank correlation was used for skewed data to evaluate variable changes. Significant correlations were analysed through multiple regression to identify independent connections between variables. A threshold of $p < 0.05$ was considered statistically significant.

Results

Descriptive

Figures 1–4 present the baseline, 6-month, and 12-month analytical data. All children experienced accelerated growth, with an average increase of ~8 cm/12 months in height (ΔSD height = 0.57 ± 0.24, ΔSD height velocity = 1.39 ± 1.53). Weight and BMI also exhibited steady and significant growth throughout the monitoring year, with ~4 kg and 0.6 units, respectively (as shown in Figure 1, upper panel, ΔSD BMI = 1.88 ± 0.43). Total body fat content and %BF decreased significantly over the study period, while lean mass increased steadily, with statistically significant differences among all 3 evaluations (Fig. 1, lower panel).

Leptin levels decreased significantly at 6 months (Fig. 2, upper panel), while AG and adiponectin increased dramatically at 6 and 12 months compared to baseline. UAG decreased at 6 months and then slightly increased but remained significantly lower than baseline (Fig. 2, lower panel). The AG/UAG ratio also varied considerably (Fig. 2, lower panel).

Total bone mineral density (BMD) and bone mineral content (BMC) significantly increased after 12 months of GH replacement therapy (Fig. 3, upper panel). However, the total calcium levels did not vary significantly during the monitored interval. All patients received supplementation with 25-(OH)-vitamin D and the increase in serum vitamin D was accompanied by an increase in serum phosphate levels and a substantial increase in plasma cFGF23 and IGF1 levels (as shown in Fig. 3, upper panel and lower panel, and Figure 1, middle panel).

Total and low-density lipoprotein (LDL) cholesterol significantly decreased after 12 months of GH replacement, while high-density lipoprotein (HDL) cholesterol and triglycerides did not show significant variations during the monitored interval (shown in Fig. 4, upper panel). All parameters of glucose metabolism, although registering significant variations, fell within the normal range at the intermediate and final assessment (shown in Fig. 4, lower panel). The correlations between changes in body composition, adipokines, ghrelin, and FGF23 during GH replacement therapy at 6 and 12 months.

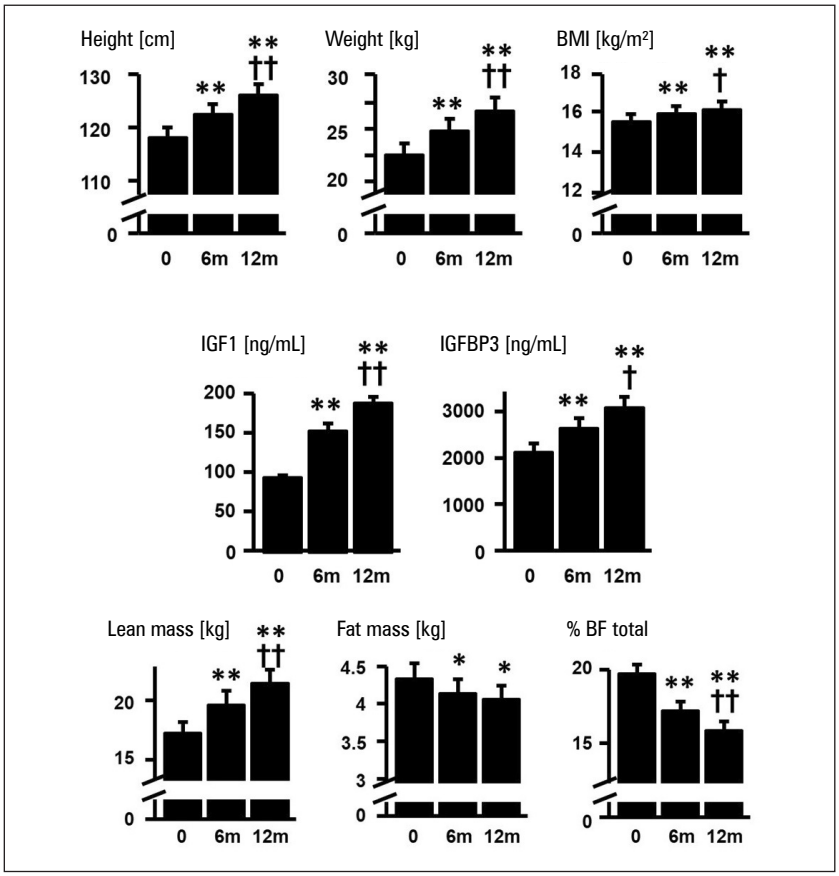

Figure 1. *The changes of anthropometric, body composition, and somatotropic axis parameters. BMI — body mass index; IGF1 — insulin-like growth factor 1; IFGBP3 — insulin-like growth factor-binding protein 3; %BF — percentage of body fat. Asterisks — compared to mean initial value. Daggers — compared to the mean value at 6 months. One symbol — p < 0.05. Two symbols — p < 0.01*

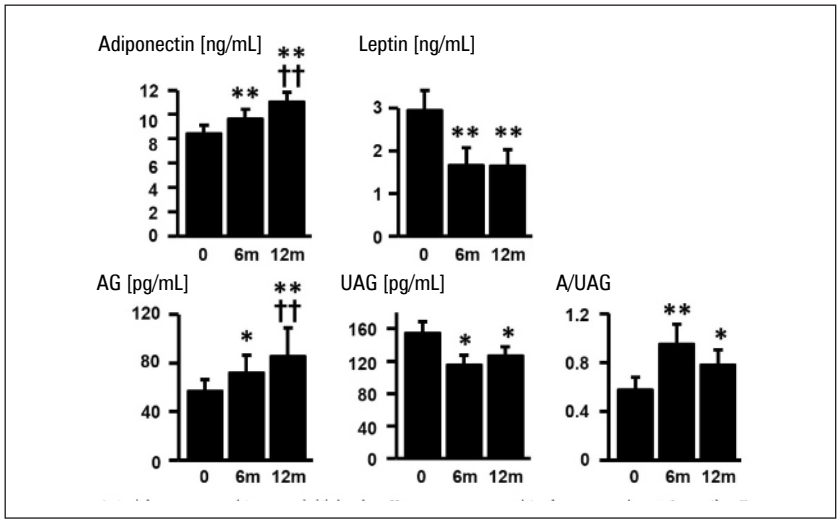

Figure 2. *The effects of recombinant human growth hormone (rhGH) replacement therapy on adiponectin, leptin, acylated ghrelin (AG), and unacylated ghrelin (UAG). Asterisks — compared to mean initial value. Daggers — compared to the mean value at 6 months. One symbol — $p < 0.05$. Two symbols — $p < 0.01$*

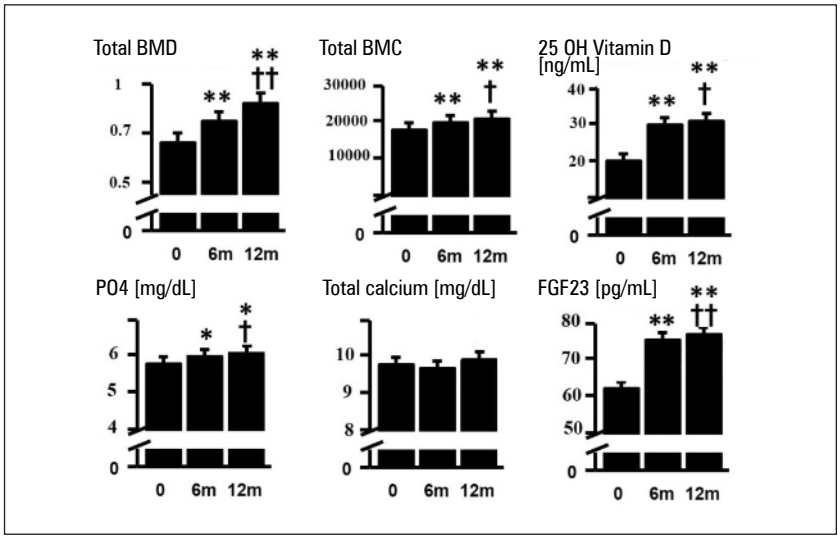

Figure 3. *The effects of recombinant human growth hormone (rhGH) replacement therapy on calcium-phosphorus metabolism, fibroblast growth factor 23 (FGF23), and bone mineral density (BMD). Asterisks — compared to mean initial value. Daggers — compared to the mean value at 6 months. One symbol — $p < 0.05$. Two symbols — $p < 0.01$*

After 12 months of therapy, we analysed the effect of GH therapy and body composition changes on adipokines, UAG, AG, and FGF23 levels by studying the dynamic correlations between variable variations (Δ = T12 – T0) (Tab. 1 and 2).

Changes in adiponectin and UAG were negatively correlated with SD BMI, probably due to GH therapy-induced changes in adipose tissue (Tab. 1). GH therapy significantly increased lumbar, neck, and total BMD and BMC, improving lumbar Z-score. FGF23 values correlated sporadically with body composition parameters at 6 and 12 months, while IGFBP3 showed significant direct proportionality with most parameters of body composition at all 3 time points (Tab. 2).

Regression models adjusted for insulin, cholesterol, and HOMA-IR showed significant correlations with Δleptin, Δadiponectin, and ΔUAG as the dependent variables. GH treatment independently influenced the variation of leptin and adiponectin but not ghrelin; also, the effect of trunk fat variation was added for changes in leptin. IGF1 variation at 12 months correlated only with lean mass variation, which was not

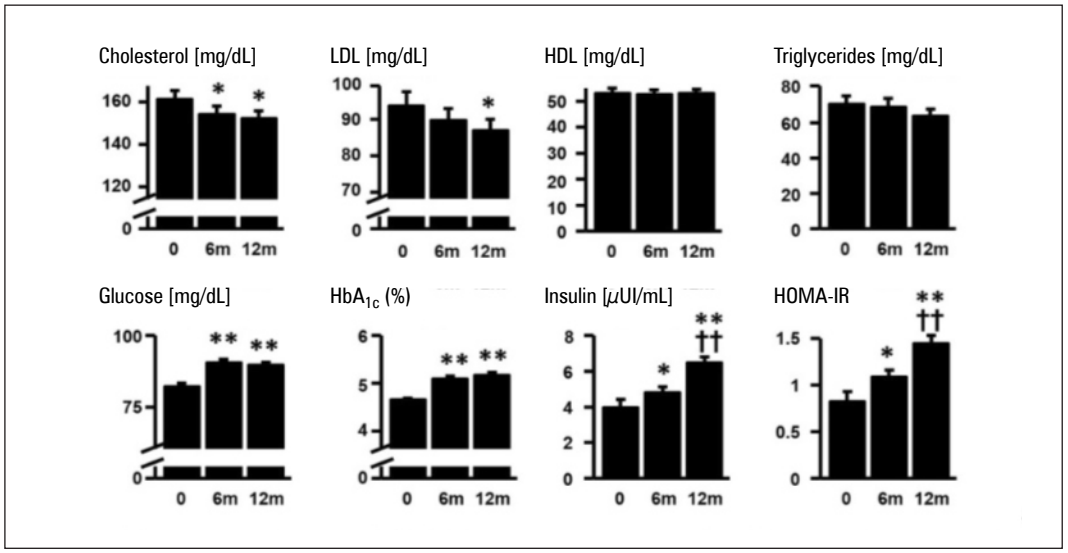

Figure 4. *The impact of recombinant human growth hormone (rhGH) replacement therapy on lipid and glucose metabolism. Asterisks — compared to mean initial value. Daggers — compared to the mean value at 6 months. One symbol — $p < 0.05$. Two symbols — $p < 0.01$. LDL — low-density lipoprotein; HDL — high-density lipoprotein; HbA_{1c} — glycosylated haemoglobin; HOMA-IR — homeostasis model assessment of insulin resistance*

Table 1. ***Correlations between changes in adipokines, ghrelin, insulin growth factor (IGF1) levels, and body composition parameters after 12 months of growth hormone (GH) therapy***

	ΔLeptin [ng/mL]	ΔAdiponectin [ng/mL]	ΔUAG [pg/mL]	ΔAG [pg/mL]	ΔIGF1 [ng/mL]	ΔSD_IGF1
ΔIGF1 [ng/mL]						
r	0.177	0.370*	0.220	–0.212	1	0.690*
p	0.262	0.016*	0.162	0.177	–	< 0.001*
ΔSD_IGF1 [ug/mL]						
r	0.384*	–0.007	0.078	–0.221	0.690*	1
p	0.012*	0.966	0.621	0.160	< 0.001*	–
ΔTotal fat [g]						
r	0.261	–0.136	–0.217	0.008	–0.043	0.244
p	0.096	0.391	0.168	0.958	0.786	0.120
ΔTrunk fat [g]						
r	0.554*	–0.165	0.001	–0.166	0.101	0.297
p	< 0.001*	0.297	0.994	0.294	0.525	0.056
ΔTotal lean [g]						
r	–0.087	0.289	0.316*	–0.121	0.319*	–0.211
p	0.586	0.063	0.041*	0.444	0.040*	0.090
ΔLegs–arms fat [g]						
r	–0.096	–0.169	–0.293	0.155	–0.103	0.180
p	0.545	0.285	0.059	0.325	0.516	0.569
ΔIGFBP3						
r	–0.226	0.012	0.049	–0.113	0.128	–0.032
p	0.150	0.941	0.760	0.477	0.419	0.842

Results are expressed as coefficients r and p; *significant correlations; UAG — unacylated ghrelin; AG — acylated ghrelin; IGFBP3 — insulin-like growth factor-binding protein 3; SD — standard deviation

Table 2. *Correlations between changes in fibroblast growth factor 23 (FGF23), insulin growth factor 1 (IGF1)/insulin-like growth factor-binding protein 3 (IFGBP3), and body composition*

	FGF23 [pg/mL]			IGF1 [ng/mL]			IGFBP3 [ug/mL]		
	Baseline	6 months	12 months	Baseline	6 months	12 months	Baseline	6 months	12 months
Height [cm]									
r	–0.077	0.214	0.328*	0.677*	0.613*	0.681*	0.615*	0.583*	0.546*
p	0.629	0.173	0.034*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
SDS Height									
r	–0.404*	–0.106	0.019	0.409*	0.563*	0.513*	0.505*	0.683*	0.646*
p	0.008*	0.503	0.905	0.005*	0.000*	0.000*	0.000*	0.002*	0.000*
BMI [kg/m^2]									
r	–0.057	0.156	0.216	0.429*	0.573*	0.516*	0.453*	0.471*	0.553*
p	0.722	0.323	0.169	0.005*	0.000*	0.000*	0.003*	0.002*	0.000*
ΔTotal fat [g]									
r	–0.208	0.092	–0.059	0.720*	0.462*	0.584*	0.609*	0.514*	0.487*
p	0.186	0.564	0.711	0.000*	0.002*	0.000*	0.000*	0.000*	0.001*
ΔTotal lean [g]									
r	–0.037	0.209	0.361*	0.555*	0.668*	0.637*	0.550*	0.555*	0.588*
p	0.817	0.185	0.019*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
BMC total [g]									
r	0.016	0.325*	0.193	0.546*	0.434*	0.520*	0.622*	0.504*	0.440*
p	0.922	0.036*	0.221	0.000*	0.004*	0.000*	0.000*	0.001*	0.004*
Z–Score lumbar									
r	–0.242	–0.201	–0.390*	–0.317*	–0.436*	–0.462*	–0.280	–0.139	–0.106
p	0.123	0.201	0.011*	0.041*	0.004*	0.002*	0.073	0.380	0.503
BMD total [g/cm^2]									
r	0.147	0.450*	0.266	0.259	0.522*	0.398*	0.208	0.250	0.204
p	0.353	0.003*	0.089	0.098	0.000*	0.009*	0.186	0.110	0.195
BMD lumbar [g/cm^2]									
r	0.066	0.271	0.364*	0.533*	0.562*	0.661*	0.432*	0.435*	0.518*
p	0.678	0.082	0.018*	0.000*	0.000*	0.000*	0.004*	0.004*	0.000*
BMD neck [g/cm^2]									
r	–0.103	0.178	0.298	0.182	0.419*	0.434*	0.214	0.331*	0.418*
p	0.517	0.258	0.055	0.249	0.006*	0.004*	0.174	0.032*	0.006*

Results are expressed as coefficient r and p; *significant correlations; BMI — body mass index; BMC— bone mineral content; BMD — bone mineral density; FGF23 — fibroblast growth factor 23; IGF1 — insulin-like growth factor 1; IFGBP3 — insulin-like growth factor-binding protein 3

significantly associated with any of the adipokines. Therefore, the effect of IGF1 increment on the variation of adipokines was independent of body composition parameters - lean or fat mass (Tab. 3). At 12 months, only lean mass variation correlated with IGF1 variation, independent of adipokines and body composition parameters (Tab. 1 and 3).

Regression models were used to find significant correlations between serum levels of FGF23 and various parameters, including age, sex, serum phosphate levels, 25 (OH) vitamin D, IGF1, and PTH. At 12 months, the most significant factors contributing to FGF23 variations were SDS IGF1, total fat, IGFBP3, total BMD, and BMI (Tab. 3). We examined the correlation between FGF23 serum levels and BMD/BMC evolution. We used a multiple regression model to predict total BMD/BMC values based on independent variables, including 25-OH-vitamin D, PTH, FGF23, calcium, and phosphorus. However, the FGF23 variable was statistically insignificant and did not significantly impact the dependent variable, except for a small contribution to total BMC (coefficient –2.321) (Tab. 3).

Discussion

In addition to promoting linear growth, GH has various metabolic effects, influencing body composition, muscle mass, adipose and osseous tissues, and lipid and glucose homeostasis. The GH/IGF1 axis positively affects bone formation through direct interaction with osteoblasts receptors and locally produced skeletal IGF1 [3, 4, 27, 28]. Research on FGF23 and phosphate homeostasis disorders has revealed a bone-kidney axis that regulates bone mineralisation, which is essential for proper growth. At the same time, achieving and maintaining normal peak bone mass during childhood and adolescence is crucial to prevent osteoporosis later in life. Normal linear growth depends on the integrity of the FGF23 axis, which is evident in hypophosphataemic rickets — a genetic disorder characterised by an excess FGF23, leading to impaired linear growth [32].

GH induces whole-body lipolysis, mainly in the fasting state, a physiological mechanism to provide energy from fat depots [8, 33–35]. GH therapy can gradually improve body composition and metabolic parameters in GHD children by reducing total fat mass and %BF while increasing total lean mass [36, 37]. Indeed, in our study, we observed a decrease in total fat mass and %BF and an increase in total lean mass in GHD children after GH therapy. We observed a significant increase in BMI, which differs from the findings of similar studies. The research conducted by Giavoli et al. [38] showed a marked decrease in BMI after 12 months of GH treatment, while other authors did not notice any significant change [5]. To exclude or limit the influence of puberty and obesity on body composition parameters, insulin action, and adipokines secretion [12–14], we only included pre-pubertal (Tanner stage 1) patients with an initial normal body weight (BMI < p85) [31]. The prevalent gain in lean mass among our non-obese patients might have contributed to increased BMI. Similarly to other research [5, 6, 37], our study confirms the positive effects of GH replacement therapy on lipid parameters in GHD children. Specifically, total cholesterol and LDL levels decreased significantly during the follow-up period.

It was previously believed that adipose tissue had no endocrine function. But it is now known to play a vital role in regulating metabolism and affect hormonal changes during puberty through adipokines produced by fat cells, such as leptin and adiponectin [11, 12, 34, 37]. When adipokine secretion is altered in patients with GHD, it can lead to changes in lipid and carbohydrate levels and fat tissue accumulation [13]. Treatment with daily rhGH administration can correct the somatotropic axis and normalise IGF1 levels, improving the metabolic profile and reducing cardiovascular risk by directly and/or indirectly affecting adipokines and ghrelin secretion [5, 13, 15]. In our study, levels of leptin and UAG decreased significantly after GH treatment, while adiponectin and AG values increased. This suggests a direct or indirect influence of rhGH therapy. Several studies have described similar variations in adiponectin and leptin levels [6, 20–23, 39]. However, some studies have reported no significant impact on adiponectin levels after initiating treatment or increased leptin concentrations in a small group of GHD children following treatment [5, 13].

Leptin is a type of adipokine positively linked to the total amount of fat in the body [20, 33, 35, 39]. During GH therapy, there is often a significant decrease in fat mass and percentage, and an increase in lean mass. Other studies [15–23, 39] reported that this can decrease leptin levels. Our study found that even though our patients had a normal weight at the start of treatment, there was a significant decrease in their fat mass, which may have contributed to the decrease in circulating leptin. Before treatment and during the 12-month follow-up, leptin was positively correlated with fat mass, with the strongest correlation being changes in trunk fat. However, it is also possible that somatotropic hormones directly affect leptin secretion independent of adipose tissue. In children and adults with GHD, the level of leptin increases as adipose tissue increases [20, 21, 39]. Our study also found that changes in IGF1 levels independently predicted changes in leptin levels, along with the expected correlation with fat mass.

GHD children typically exhibit higher BMI and %BF than the general population. This is often linked to decreased adiponectin concentrations [33], associated with an elevated risk of atherosclerosis [21]. While some studies have failed to detect significant differences in adiponectin levels between GHD subjects and control groups following GH therapy [14], other authors have observed increased adiponectin levels, particularly among females [25]. Such an increase may be considered a cardiovascular benefit of GH therapy, especially given its inverse relationship to risk factors such as blood glucose and triglycerides [20]. Our study found that changes in IGF1 levels were the only independent predictor of adiponectin variations, while variations in body composition components did not significantly influence adiponectin secretion. This suggests that the increase in adiponectin is related to direct GH effects rather than changes in body composition.

In our study, we found that rhGH therapy did not have a significant impact on ghrelin levels, according to our regression analysis. However, we did notice a decrease in UAG concentrations, which we believe is related to the increase in insulin following GH replace-

ment therapy [12]. While other studies have reported conflicting results, varying from a marked increase in AG levels to a decrease in total ghrelin or the absence of any significant variation [15, 14, 24, 25], none have investigated both forms of ghrelin simultaneously. Our research demonstrates that AG increases and UAG decreases in GHD children who undergo GH therapy. The mechanism underlying these opposing effects of rhGH on AG and UAG is not yet clear, as IGF1 did not correlate with the ghrelin modifications in our study. However, a direct stimulating effect of the therapeutic rise in IGF1 upon ghrelin secretion was previously described [41]. One possible explanation is that GH therapy has multiple metabolic consequences, which may explain the contradictory findings. Therefore, ghrelin acylation may be mainly increased during metabolic changes during GH therapy, such as increased insulin secretion, age, or BMI [12].

Only a few studies [2, 29, 42] have identified a connection between the GH/IGF1 and FGF23/Klotho axis. Our research is at the forefront of investigating the relationship between FGF23 and bone parameters in children with GHD. In our research, there is an increase in serum phosphate and phosphaturic FGF23 levels during GH therapy, probably due to a rise in renal phosphate tubular reabsorption. Similar findings have been reported in studies involving children and adults with GHD who underwent GH substitution therapy [42, 43]. Some may assume that the suppression of the FGF23 is the cause of the increase in serum phosphate levels in relation to the GH/IGF1 axis. However, our data and other studies [2, 29, 42] suggest that the rise in serum phosphate due to GH is not caused by suppressing the phosphaturic FGF23 system. Our findings align with 2 other studies. One solely examined plasma cFGF23 levels and found a comparable rise in cFGF23, suggesting GH's effect is not dosage dependent. The level of cFGF23 tended to increase, even after adjusting for age, gender, total calcium, and phosphorus [29]. This rise in FGF23 may be a side effect of GH therapy. Efthymiadou et al. [2] had a more comprehensive approach, measuring cFGF23, iFGF23, and klotho, but found similar results for FGF23 variations during GH treatment. Our research supports the findings of previous studies that there is a correlation between SDS height and IGF1 and a strong association between SDS height and FGF23 levels [2], which was observed in healthy children as well [1]. This highlights the importance of phosphate homeostasis for proper growth and mineralisation of the growth plate and emphasises the significance of an intact FGF23/klotho axis. Our findings suggest that the positive relationship between FGF23, height SDS, and IGF1 is probably due to the influence of FGF23 on linear growth. There may be a connection between FGF23 and body composition, particularly with BMD and BMC. This suggests that the FGF23 system may directly impact maintaining healthy bones.

Conclusion

GHD children experience metabolic abnormalities, which may be related to changes in body composition and altered levels of hormones such as leptin, adiponectin, ghrelin, and FGF23. Our research has shown that even normal-weight children with GHD experience a significant decrease in body fat after 12 months of treatment. This beneficial modification is accompanied by an increase in adiponectin and AG levels but a decrease in leptin and UAG levels and an improved BMD. These improvements can have a positive and long-term effect on the child's metabolism, and cardiovascular and bone health. Additionally, IGF1, in response to GH therapy, directly impacts leptin and adiponectin concentrations, independently of body composition. The relationship between FGF23 and height SDS and IGF1 suggests a potential role of FGF23 in linear growth through the regulation of phosphate homeostasis, essential for bone mineralisation. However, further research is required to identify the complex molecular mechanisms and metabolic pathways by which the GH/IGF1 axis influences and interacts with adipokine secretion, ghrelin, and FGF23.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, A.D.B.

Ethics statement

The local Ethics Committee approved this study, and informed consent was obtained before participation.

Author contributions

A.D.B. — investigation, patient selection, data collection, statistical analysis, literature review, writing (original draft preparation). S.C.B. — statistical analysis and interpretation, writing (review and editing). L.L. — conceptualization, study design, investigation, data collection, supervision. M.-C.U — conceptualization, study design, investigation, data collection, supervision. C.P. — conceptualization, patient selection, data collection, statistical analysis, writing (review and editing), supervision. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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