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ORIGINAL ARTICLE

Resistin, visfatin, leptin and omentin are differently related to hormonal and metabolic parameters in growth hormone-deficient children

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Abstract
Purpose The effect of growth hormone (GH) on adipose tissue and the role of adipokines in modulating metabolism are documented, but with discordant data. Our aim was to evaluate the impact of GH treatment on a series of selected adipokines known to have a metabolic role and poorly investigated in this setting.
Methods This is a prospective study. Thirty-one prepubertal children (25 M, 6 F; aged 8.5 ± 1.6 years) with isolated GH deficiency treated with GH for at least 12 months and 30 matched controls were evaluated. Auxological and metabolic parameters, insulin sensitivity indexes, leptin, soluble leptin receptor, adiponectin, visfatin, resistin, omentin, adipocyte fatty acid-binding protein and retinol-binding protein-4 were evaluated before and after 12 months of treatment.
Results At baseline, no significant difference in metabolic parameters was found between GHD children and controls, except for higher LDL cholesterol ($p = 0.004$) in the first group. At multivariate analysis, LDL cholesterol was independently associated with resistin (B 0.531; $p = 0.002$), while IGF-I was the only variable independently associated with visfatin (B 0.688; $p < 0.001$). After 12 months, a significant increase in fasting insulin ($p = 0.008$), Homa-IR ($p = 0.007$) and visfatin ($p < 0.001$) was found, with a concomitant decrease in LDL cholesterol ($p = 0.015$), QUICKI ($p = 0.001$), ISI Matsuda ($p = 0.006$), leptin ($p = 0.015$) and omentin ($p = 0.003$)]. At multivariate analysis, BMI was the only variable independently associated with leptin (B 0.485; $p = 0.040$).
Conclusions GH treatment modifies adipokine secretion and the perturbation of some adipokine levels could contribute to the clinical and metabolic changes observed during the follow-up.

Keywords Growth hormone · Children · Adipokines · Insulin sensitivity

Introduction

Growth hormone (GH) during childhood, in addition to promote linear growth, plays a key metabolic role and adipose tissue is known to be an important target for GH action [1]. Adipocytes secrete hormones known as adipokines, many of which regulate metabolism and influence insulin sensitivity and secretion [2]. Untreated GH deficiency (GHD) in children, as well as in adults, is associated with abnormalities in body composition, in addition to a cluster of cardiometabolic risk factors such as increased peripheral inflammatory markers and impairment in glucose and lipid metabolism, and GH treatment seems to exert beneficial effects on most of these alterations [3–5].

Given the known effect of GH on adipose tissue and the role of adipokines in modulating metabolism and insulin homeostasis, many studies have evaluated the effect of GHD and GH treatment on the circulating levels of the most common adipokines, such as leptin and adiponectin. A negative impact on these adipokine levels has been reported in untreated GHD children, with a partial improvement during GH treatment, but with very discordant data across the studies. GHD seems to be associated with elevated leptin levels which most likely reflect an increased fat mass in these

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patients [6] and a direct effect of GH on leptin production and metabolism is hypothesized [7] although this effect is not confirmed by all studies [8]. Conversely, adiponectin seems to be unaffected in untreated GHD, and GH treatment has been shown to have discordant effect on its levels [9, 10]. Similarly, the relationship between the modifications of adipokine levels and the metabolic changes that occur in GHD children has not been unequivocally demonstrated [11, 12]. Given the discrepancies of the existing data about the role of the most investigated adipokines, our aim was to analyze in children affected by GHD how GH replacement modifies a series of new selected adipokines, known to have a metabolic role and poorly investigated in this setting, and the relationship of these modifications with the metabolic changes.

Materials and methods

We prospectively studied 31 prepubertal children (25 M, 6 F; mean age 8.5 ± 1.6 years; range 5.3–10.3) with isolated GHD consecutively admitted to the Section of Endocrinology of the University of Palermo during the years 2013–2014, treated with GH for at least 12 months and never investigated before in other clinical studies. Thirty prepubertal healthy subjects, matched for sex (22 M, 8 F), age (mean age 8.9 ± 1.6 years; range 4.6–10.6) and BMI were recruited among children referred for assessment of short stature as a control group at baseline. All children, even the older ones, were in the first stage of sexual development to avoid any interference of the onset of puberty with insulin sensitivity and body composition and maintained the prepubertal hormonal status during the observation period. For the same reasons, we excluded children affected by multiple pituitary hormone deficiency or receiving other hormonal replacement treatment, to exclusively evaluate the effects of GH. The diagnosis of GHD was established by the clinical, auxological and biochemical criteria of the GH Research Society [13].

As auxological data, we considered height and growth velocity 1 year before the diagnosis. Clinical and auxological criteria included height more than 2 standard deviations (SDS) below the mean and a growth velocity over 1 year more than 1 SDS below the mean for age, or a decrease in height SDS of more than 0.5 over 1 year or, without severe short stature, a growth velocity more than 2 SDS below the mean over 1 year or, finally, height more than 1.5 SDS below the midparental height.

As a radiological criterion, we considered a bone age delay, estimated from an X-ray of the left wrist and hand and evaluated according to the methods of Greulich and Pyle, of at least 1 year with respect to the chronological age [14]. Biochemically, GHD was demonstrated by failure of GH to respond to an arginine and glucagon stimulation test, performed on two different days, with GH peaks below 7 μg/l. Neuroimaging, with magnetic resonance imaging of the hypothalamic-pituitary region, in line with our protocol, was performed in children with signs pointing to multiple pituitary hormone deficiency or indicative of an intracranial lesion and in children with more severe GHD, like those with height more than 3 SDS below the mean, GH peak ≤ 3 μg/l or IGF-I levels below 2 SDS (No. 18 children). Among them, three patients showed a pituitary hypoplasia and 2 a partial empty sella. The patients received GH once daily at bedtime with a pen injection system. During the entire follow-up, insulin-like growth factor (IGF)-I levels allowed us to determine the GH dose. Specifically, the target was IGF-I levels between 0.5 and 1.5 SDS. The initial daily dose of GH was 0.025 mg/Kg, increased to 0.028 mg/Kg from month 6 to 12.

Study protocol

In all patients, after the diagnosis of GHD was made, the auxological and metabolic evaluation was performed at baseline and after 12 months of GH treatment, while in the control subjects these evaluations were performed only at baseline.

In addition to the measurement of body height, body mass index (BMI) and waist circumference (WC), in all children a blood sample was drawn after an overnight fast for the measurement of IGF-I, fasting glucose, fasting insulin, Hemoglobin A1c (HbA1c) and lipid profile [total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol]. This sample also served as the baseline sample for an oral glucose tolerance test (OGTT). Blood samples were collected every 30 min for 2 h for glucose and insulin measurements.

Height, growth velocity, BMI and IGF-I were expressed as SDS due to the wide age range of patients.

As surrogate estimates of insulin sensitivity, we used the homeostasis model assessment estimate of insulin resistance (Homa-IR) [15], the quantitative insulin sensitivity check index (QUICKI) [16] and the insulin sensitivity index (ISI), a composite index derived from the OGTT and validated by Matsuda and DeFronzo [17].

To evaluate the adipose function, in all children we measured the serum levels of leptin, soluble leptin receptor (sOB-R), adiponectin, visfatin, resistin, omentin, adipocyte fatty acid-binding protein (AFABP) and retinol-binding protein-4 (RBP4) after an overnight fast.

The institutional Ethics Committee of the University of Palermo approved this study. At the time of hospitalization, an informed consent for the scientific use of the data was obtained from both the participants and their parents.

Hormone and biochemical assays

All biochemical data were collected after overnight fasting. Glycaemia and lipids were measured by standard methods (Modular P800, Roche, Milan). HbA1c levels were determined by HPLC (Bio-Rad Laboratories, Milan, Italy). Serum insulin was measured by ELISA (DRG Instruments GmbH, Germany). The sensitivity of the method was 1 IU/ml. The normal insulin range (IU/ml) was 5–19. GH levels were measured by ELISA assay using commercially available kits (hGH SENSITIVE ELISA Mediagnost E022, Germany). The sensitivity yields 0.0115 µg/l, with intra- and inter-assay coefficients of variation (CV) 3.7–7.9 and 3.1–5.9 %, respectively. The 2nd International Standard NIBSC Code 98/574 was used as standard material. Serum IGF-I was assayed in the same laboratory with ELISA assay (OCTEIA IGF-I kit, IDS Inc., Fountain Hills, AZ, USA). The sensitivity of the method was 1.9 µg/l. The inter- and intra-assay CV values were 7–7.1 and 2.3–3.5 %, respectively, at IGF-I levels of 90.7–186 and 66.7–120.9 µg/l, respectively. The normal ranges (males and females combined) of total IGF-I levels (µg/l) were the following: 12–108 (0–1 years); 13–100 (1–3 years); 26–280 (3–6 years); 85–230 (6–9 years); 98–404 (9–12 years); 142–525 (12–15 years); 146–415 (15–20 years). Values were expressed as SDS according to the normative data provided by the manufacturer. Human leptin (ng/ml), sOB-R (ng/ml), adiponectin (µg/ml), resistin (ng/ml), visfatin (ng/ml), RBP4 (µg/ml), AFABP (ng/ml) and omentin-1 (ng/ml) were assayed using an ELISA sandwich enzyme immuno-assay (BioVendor, Heidelberg, Germany).

Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± SDS or as median values ± interquartile range (IR) for continuous variables, when appropriate (i.e. for the variables without normal distribution). Normality of distribution for quantitative variables was assessed with the Kolmogorov–Smirnov test. The differences between groups were evaluated with the *t* test when with normal distribution or with the Mann–Whitney test (nonparametric test) when without normal distribution. Pearson's correlation was performed among continuous variables with normal distribution; correlations among continuous variables without normal distribution were determined using the Spearman's test (nonparametric equivalent for Pearson test). To identify the independent variables which influence the adipokine levels, a linear regression model was performed. A p value <0.05 was considered statistically significant.

Results

Clinical and hormonal parameters

The clinical and hormonal features of control subjects and of GHD children at diagnosis and after 12 months of GH treatment are shown in Table 1.

No significant difference in height, BMI SDS and WC SDS between GHD children at baseline and control subjects was found. As expected, GHD children at baseline showed significantly lower growth velocity (−2.7 ± 0.3 vs. −1.5 ± 0.2 SDS; $p < 0.001$), IGF-I [−2.31 (−3.67 to −0.95) vs. 1.47 (−1.19–2.11) SDS; $p < 0.001$)] and GH peak after both arginine (4.3 ± 1.1 vs. 10.9 ± 2.6 µg/l; $p < 0.004$) and glucagon test (5.5 ± 1.1 vs. 16.2 ± 3.7 µg/l; $p < 0.001$) than controls.

In GHD children after 12 months, we observed a significant increase in growth (height: −1.6 ± 0.6 vs. −2 ± 0.7 SDS; $p < 0.001$; growth velocity: 1.3 ± 0.4 vs. −2.7 ± 0.3 SDS; $p < 0.001$), with a concomitant significant increase in IGF-I [0.54 (0.07–1.15) vs. −2.31 (−3.67 to −0.95) SDS; $p < 0.001$)] and a decrease in BMI [− 0.80 (−2.64–1.25) vs. −0.39 (−2.26–1.81) SDS; $p = 0.047$)], without significant change in WC SDS (Table 1).

Metabolic parameters

No significant difference was found in fasting glucose (4.6 ± 0.6 vs. 4.4 ± 0.2 mmol/l; $p = 0.206$), fasting insulin [(2.4 (0.5–15.1) vs. 2.4 (0.8–6.6) IU/ml; $p = 0.735$)], HbA1c (5.2 ± 0.3 vs. 5.2 ± 0.3 %; $p = 0.961$) and insulin sensitivity indexes between GHD children at baseline and control subjects. GHD children showed higher LDL cholesterol (2.4 ± 0.6 vs. 1.9 ± 0.1 mmol/l; $p = 0.004$) than controls, without any difference in triglycerides, total and HDL cholesterol (Table 1).

After 12 months of GH treatment, a significant increase in fasting insulin [6 (1.5–17.4) vs. 2.4 (0.5–15.1) IU/ml; $p = 0.008$)], and Homa-IR [1.3 (0.2–5.4) vs. 0.5 (0.1–4.2); $p = 0.007$)] was documented, with a concomitant decrease in LDL cholesterol (2.1 ± 0.6 vs. 2.4 ± 0.6 mmol/l; $p = 0.015$), QUICKI (0.36 ± 0.05 vs. 0.44 ± 0.08; $p = 0.001$) and ISI Matsuda [7.1 (2.6–22) vs. 17.2 (6.2–37.7); $p = 0.006$)]. No significant change was observed in fasting glucose, HbA1c, triglycerides, total and HDL cholesterol (Table 1).

Adipokine levels

Serum adipokine levels of control subjects, GHD children at baseline and after 12 months of GH treatment are shown in Table 2.

Table 1 Clinical and biochemical features of control subjects and GHD children at diagnosis (baseline) and after 12 months of GH treatment

	Control group (*N. 30*)	GHD at baseline (*N. 31*)	GHD at 12 months (*N. 31*)	*p*	*p**
Gender Males Females	19 (79) 5 (21)	25 (81) 6 (19)	25 (81) 6 (19)	0.892	–
	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	8.9 ± 1.6	8.5 ± 1.6	9.5 ± 1.6	0.312	–
Height (SDS)	−1.8 ± 0.8	−2.0 ± 0.7	−1.6 ± 0.6	0.277	<0.001
Growth velocity (SDS)	−1.5 ± 0.2	−2.7 ± 0.3	1.3 ± 0.4	<0.001	<0.001
BMI (SDS)	−0.91 (−1.43–0.19)	−0.39 (−2.26–1.81)	−0.80 (−2.64–1.25)	0.308	0.047
WC (SDS)	0 (−1.22–0.67)	−0.22 (−1.72–1.44)	−0.01 (−1.89–1.58)	0.551	0.550
IGF-I (SDS)	1.47 (−1.19–2.11)	−2.31 (−3.67 to −0.95)	0.54 (0.07–1.15)	<0.001	<0.001
GH peak after arginine test (μg/l)	10.9 ± 2.6	4.3 ± 1.1	–	0.004	–
GH peak after glucagon test (μg/l)	16.2 ± 3.7	5.5 ± 1.1	–	<0.001	–
Glucose metabolism					
Fasting glucose (mmol/l)	4.4 ± 0.2	4.6 ± 0.6	4.7 ± 0.5	0.206	0.329
HbA1c (%)	5.1 ± 0.3	5.2 ± 0.3	5.2 ± 0.2	0.961	0.516
Fasting insulin (IU/ml)	2.4 (0.8–6.6)	2.4 (0.5–15.1)	6 (1.5–17.4)	0.735	0.008
Insulin sensitivity indexes					
Homa-IR	0.4 (0.1–1.3)	0.5 (0.1–4.2)	1.3 (0.2–5.4)	0.554	0.007
QUICKI	0.45 ± 0.06	0.44 ± 0.08	0.36 ± 0.05	0.578	0.001
ISI Matsuda	14.8 (5.9–38.4)	17.2 (6.2–37.7)	7.1 (2.6–22)	0.855	0.006
Lipid metabolism					
Total cholesterol (mmol/l)	4.3 ± 0.4	4.3 ± 0.7	4.1 ± 0.6	0.905	0.187
HDL cholesterol (mmol/l)	1.8 ± 0.4	1.6 ± 0.2	1.7 ± 0.2	0.170	0.470
LDL cholesterol (mmol/l)	1.9 ± 0.1	2.4 ± 0.6	2.1 ± 0.6	0.004	0.015
Triglycerides (mmol/l)	1.6 ± 0.3	1.4 ± 0.4	1.6 ± 0.6	0.088	0.157

Data are presented as rates and proportions for the categorical data and as mean ± standard deviation (SDS) or median ± interquartile range (IR) for the continuous variables, when appropriate

p Difference between control group and GHD subjects at baseline

* *p* Difference between GHD subjects at baseline and GHD subjects at 12 months of GH treatment

Table 2 Serum adipokine levels of control subjects and GHD children at diagnosis (baseline) and after 12 months of GH treatment

	Control group (*N. 30*) Mean ± SD	GHD at baseline (*N. 31*) Mean ± SD	GHD at 12 months (*N. 31*) Mean ± SD	*p*	*p**
Leptin (ng/ml)	1.5 (0.9–6.6)	1.5 (0.1–11.2)	1 (0.01–7.4)	0.980	0.015
Leptin receptor (sOB-R) (ng/ml)	26.2 (4.6–40)	21.4 (7.5–49)	20 (10.8–48.3)	0.721	0.189
Leptin/sOB-R ratio	0.05 (0.02–0.6)	0.05 (0–0.6)	0.05 (0–0.5)	0.316	0.891
Adiponectin (μg/ml)	14.35 ± 3.84	13.14 ± 4.72	13.37 ± 5.09	0.310	0.716
Resistin (ng/ml)	3 (1–4.3)	3.7 (1.4–7.8)	4.5 (2.4–20.1)	0.007	0.075
Visfatin (ng/ml)	2.9 (0.1–15.1)	0.4 (0–10.1)	3.4 (0–14.6)	0.011	<0.001
RBP4 (μg/ml)	18.17 ± 7.73	17.92 ± 6.23	17.10 ± 5.61	0.492	0.539
AFABP (ng/ml)	12.20 ± 4.40	13.77 ± 8.36	14.72 ± 8.57	0.939	0.483
Omentin (ng/ml)	334 (20.9–450)	304 (214–427)	283 (168–395)	0.221	0.003

Data are presented as mean ± standard deviation (SDS) or median ± interquartile range (IR), when appropriate

RBP4 retinol-binding protein-4, *AFABP* adipocyte fatty acid-binding protein

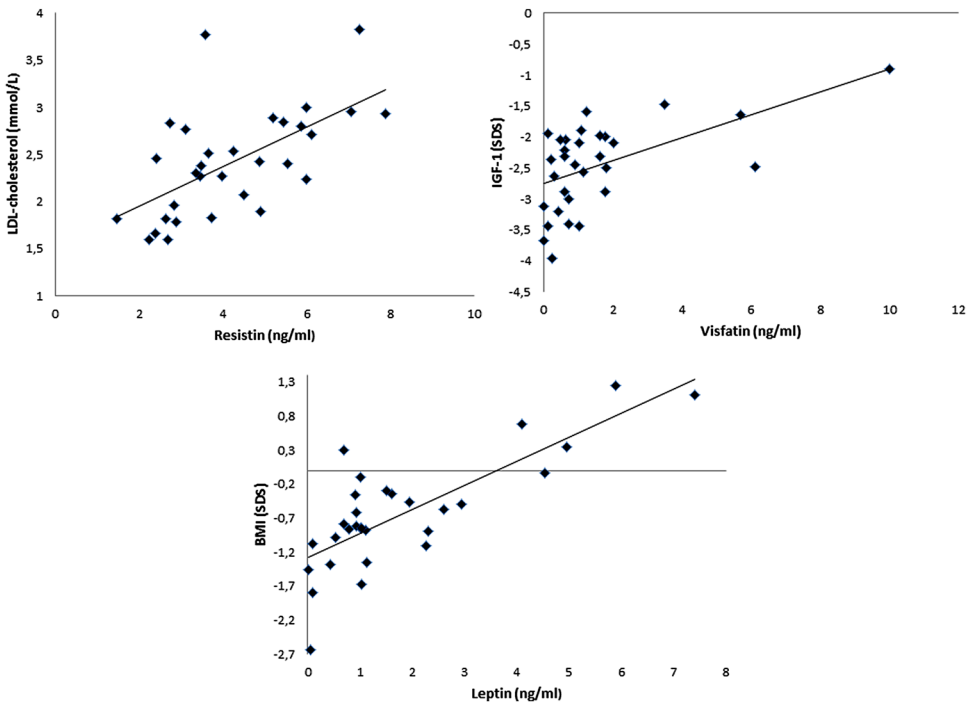

Fig. 1 Independent variables influencing resistin, visfatin and leptin levels at multivariate analysis

At baseline GHD children showed significantly higher resistin [3.7 (1.4–7.8) vs. 3 (1–4.3) ng/ml; $p = 0.007$)] and lower visfatin [0.4 (0–10.1) vs. 2.9 (0.1–15.1) ng/ml; $p = 0.011$)] than controls, without significant difference in other adipokine levels.

At univariate analysis, resistin was found to be directly correlated with BMI (rho 0.318; $p = 0.018$) and LDL cholesterol (rho 0.535; $p < 0.001$) and multivariate analysis confirmed the independent correlation between resistin and LDL cholesterol (B 0.531; $p = 0.002$) (Fig. 1).

Conversely, visfatin was found to have a significant inverse correlation with fasting glucose (rho −0.334; $p = 0.019$) and a direct correlation with IGF-I (rho 0.394; $p = 0.021$) and total cholesterol (rho 0.325; $p = 0.027$). IGF-I (B 0.688; $p < 0.001$) was the only variable independently associated with visfatin at multivariate analysis (Fig. 1).

Adiponectin was directly correlated with ISI Matsuda (rho 0.341; $p = 0.045$) and QUICKI (rho 0.443; $p = 0.005$) and negatively with fasting insulin (rho −0.419; $p = 0.008$) and Homa-IR (rho −0.443; $p = 0.005$), but none of these

variables was independently correlated with adiponectin at multivariate analysis. No significant correlation with metabolic parameters was found for the other adipokines evaluated (data not shown).

After 12 months of treatment, we found a significant decrease in leptin [1 (0.01–7.4) vs. 1.5 (0.1–11.2) ng/ml; $p = 0.015$)] and omentin levels [283 (168–395) vs. 304 (214–427) ng/ml; $p = 0.003$)], with a concomitant increase in visfatin (3.4 (0–14.6) vs. 0.4 (0–10.1) ng/ml; $p < 0.001$). A trend in increase in resistin, although not statistically significant, was found [4.5 (2.4–20.1) vs. 3.7 (1.4–7.8) ng/ml; $p = 0.075$)], while no significant change was found in sOB-R, adiponectin, resistin, AFABP and RBP4 (Table 2).

At univariate analysis, leptin levels at 12 months were found to be directly correlated with BMI (rho 0.683; $p < 0.001$), WC (rho 0.670; $p < 0.001$), fasting insulin (rho 0.449; $p = 0.013$), Homa-IR (rho 0.591; $p = 0.001$) and inversely correlated with QUICKI (rho −0.432; $p = 0.017$). At multivariate analysis, BMI (B 0.485; $p = 0.040$) was the only variable independently associated with leptin (Fig. 1).

Visfatin at 12 months was found to be correlated with IGF-I (rho 0.572; $p = 0.002$), while omentin was negatively correlated with fasting insulin (rho −0.484; $p = 0.007$) and Homa-IR (rho −0.582 $p = 0.001$) and positively with ISI Matsuda (rho 0.648; $p = 0.017$). At multivariate analysis, none of the variables was independently associated with omentin. No significant correlation with metabolic parameters was found for the other adipokines evaluated (data not shown).

Discussion

Overall, our results suggest that GH treatment exerts its metabolic effects in different ways. If on the one hand GH favorably affects adipose metabolism, as demonstrated by the improvement in lipid profile, reduction in leptin and increase in visfatin levels, on the other it acts by negatively altering the insulin sensitivity.

In our study, GHD children at diagnosis showed a worse metabolic panel, characterized by an unfavorable lipid profile and higher resistin levels. Several studies report an improvement in lipid profile after GH treatment [4], and our study also confirms this. Moreover, in our study, LDL cholesterol independently correlates with resistin levels, which are higher in GHD children than controls. Indeed, a possible mediator of the GH-modulated insulin sensitivity may be resistin, which has been shown to be linked to obesity and insulin resistance [18]. Higher resistin levels in untreated GHD children than controls have already been documented [19], while the effect of GH treatment is controversial. Our data are in agreement with some studies that have documented that GH treatment does not seem able to strongly modify resistin levels in GHD adults [10, 20], although we found a trend to an increase in resistin levels after 12 months, though not statistically significant. Partially in line with our results, Nozue et al. [21] demonstrated a rise in resistin after short-term GH therapy in GHD children, while López-Siguero et al. [12] showed a decline in resistin at 6 months of GH treatment and these data are in line with those of Meazza et al. [19] who showed a decrease in resistin levels. However, despite the lack of a statistically significant change, the trend to an increase in resistin in our patients during GH treatment is concomitant with a significant reduction in insulin sensitivity, as demonstrated by the decline in QUICKI and ISI Matsuda, in line with previous studies. We already demonstrated through euglycemic hyperinsulinemic clamp a decrease in insulin sensitivity in GHD children after GH treatment, even without evident changes in glucose tolerance [22] as well as a trend toward reduced insulin sensitivity with a compensatory hyperinsulinemic response or increased insulin levels, but with normal glucose levels, after GH treatment have been demonstrated [23]. In our opinion, the lack of changes in resistin levels, despite the increase in insulin resistance indexes, can be explained by the other significant changes that occur during GH treatment and that may impact the metabolic balance, such as the beneficial effects of GH on body composition and leptin levels. In our study, despite the lack of difference in leptin, sOB-R, BMI and WC between GHD children at baseline and controls, we found a significant decrease in leptin after GH treatment with an independent correlation with BMI, as demonstrated by other studies [24]. Notably, in this study, visfatin has proved to be the only adipokine to directly correlate with IGF-I levels. Visfatin is thought to have insulin-mimetic effects in various tissues [25] and it seems to be affected by weight loss, as demonstrated by Petelin et al. [26] in overweight subjects. Li et al. [27] showed higher visfatin levels in adults with GHD than controls, but to date data on visfatin during GH treatment are not available. We found lower visfatin in GHD children than controls at baseline and a rise in its levels after GH treatment, concomitantly with the increase in IGF-I. These data are partially in agreement with our previous data. Indeed, in acromegalic patients, we recently showed a correlation between visfatin, insulin sensitivity and IGF-1 levels, concluding that visfatin in acromegaly could be considered a useful index of disease activity [28]. Therefore, the increase in visfatin in GHD children could represent a favorable metabolic effect of GH treatment, correlated with the IGF-I increase and independent of the deterioration in insulin sensitivity. Conversely, we found no difference in AFABP and RBP4 levels, parameters known to be related with metabolic syndrome, cardiovascular risk factors and insulin resistance [29, 30], between GHD children and controls, and

no significant change during GH treatment. These findings could be in line with some clinical studies which failed to show a relationship with metabolic parameters [31].

As regards adiponectin levels in GHD patients, the existing data are quite controversial. Adiponectin seems to be unaffected in untreated GHD [20], and GH treatment seems to have discordant effects on adiponectin, increasing it [12] or leaving it unchanged or slightly modifying it [10, 11]. We found a significant correlation between adiponectin and insulin sensitivity indexes at baseline, in line with other studies [32]. However, our data also confirm the unchanged adiponectin levels after GH treatment.

Finally, although no significant difference was found at baseline between GHD and controls, we surprisingly found a significant reduction in omentin levels after 12 months of treatment. It has been determined that omentin enhances insulin-stimulated glucose uptake in adipose tissue and many studies have shown that omentin is negatively correlated with BMI and fat mass, insulin resistance and metabolic syndrome [33, 34]. Our data are partially in agreement with these findings. Indeed, a negative correlation between omentin and insulin resistance indexes was found after GH treatment, although it was not confirmed at multivariate analysis.

In conclusion, if this study is quite confirmatory for many of the parameters investigated, such as insulin sensitivity and leptin levels, we showed for the first time the behavior of new selected adipokines, known to have a metabolic role and never investigated before in this setting, and their correlation with some metabolic and hormonal parameters. The action of GH could modify adipokine secretion, and the perturbation of some adipokine levels correlates with metabolic impairment. If resistin and omentin resulted differently correlated with some metabolic parameters, respectively, at baseline and after GH treatment, conversely visfatin proved to be strongly correlated with the hormonal target in GHD subjects (as IGF-I), and leptin with body mass. In addition, during GH treatment, the favorable metabolic effects seem to be represented by a decrease in leptin and an increase in visfatin, while the negative effects seem to be represented by a decrease in omentin.

The main limitation of this study may be related to the small size of the population studied and to the short-term follow-up. In our opinion, these factors could be responsible for the lack of statistical significance in the evaluation of some adipokines. To better understand whether all the above-mentioned adipokines may represent a metabolic biomarker useful to identify the progression toward metabolic abnormalities associated with GH treatment in GHD children, we believe that these data must be validated in additional larger prospective studies with longer follow-up, where patients are randomized to different GH doses.

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Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent for the scientific use of the data was obtained from both the participants included in the study and their parents.

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