The relationship between cortisol and IGF-I influences metabolic alteration in pediatric overweight and obesity

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Abstract

Background/objective: Data on metabolic impairments in Cushing's syndrome and GH deficiency all suggest that the relationship between cortisol and GH/IGF-I axis in obesity may have a role in the related diseases. However, studies focusing only on one of these hormones are often controversial in paediatrics. We aimed to explore the simultaneous relationship between cortisol and IGF-I with the metabolic alterations in paediatric obesity.

Subjects/methods: Retrospective cross-sectional study in a tertiary care center. We recruited 876 (441 males and 435 females) overweight and obese children and adolescents. A complete clinical and biochemical evaluation including OGTT was performed. Cortisol and IGF-I SDS were divided in quartiles and then crossed to explore the reciprocal influence of high/high, low/low, and high/low levels of each one on the metabolic alterations of obesity.

Results: Subjects in the higher quartiles of IGF-I-SDS and cortisol had an increased risk of hypertension, hypercholesterolemia, high levels of triglycerides, and reduced HDL cholesterol. Diversely, lower IGF-I-SDS quartiles were associated with higher blood glucose, insulin, insulin resistance, and reduced insulin sensitivity levels with the rise of cortisol quartiles.

Conclusions: We observed that apart from glucose metabolism that is associated with low IGF-I and high cortisol levels, the other parameters known to be associated with increased cardiovascular risk were related to high levels of both IGF-I and cortisol, even if within normal range. Cortisol and IGF-I play a complex role in the comorbidities of obesity, and the evaluation of both variables could clarify some of the discordant results.

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Introduction

Obesity is associated with a complex derangement of the endocrine regulation due to compensatory mechanisms. Many of them can have a role in the development of persistent metabolic alterations, resulting in the metabolic unhealthy obese phenotype.

Several studies have shown that abdominal obesity, hypertension, high triglycerides, and low HDL cholesterol levels are associated with functional hypercortisolism

(1, 2, 3), suggesting that a pharmacological inhibition of cortisol could be a valid option to avoid these kinds of complications (4, 5). We also recently demonstrated in children that ACTH and cortisol are differently associated with the risk of comorbidities in children and adolescents (6).

Moreover, obesity is associated with functional alterations of GH/IGF-I axis in obese subjects, a reduction

of GH levels has been detected both at baseline and in dynamic tests and weight loss rescues normal values (7). Although GH secretion is blunted, the dysregulation of the IGF-I system in obesity is uncertain, since IGF-I is detected as low, normal, or elevated, also in the paediatric age (8, 9, 10, 11). Population studies in adults show that IGF-I secretion is dependent on BMI with an inverse U-shaped curve and higher levels between a BMI of 30–35 kg/m², representing a critical metabolic and nutrient-sensing regulator (12). Furthermore, the interaction with several comorbidities is complex with direct or curvilinear associations (13), also influencing mortality (14).

The regulation of IGF-I in obesity is complex and many factors have a role, such as hypothalamic neuropeptides, ghrelin, insulin, circulating free fatty acids, and cortisol (11). Among the several players involved, both chronically raised cortisol levels and relative hypoadrenalism are associated with an impaired GH secretion, suggesting a dual dose-dependent effect (15). On the other hand, GH and IGF-I influence 1 β -hydroxysteroid dehydrogenase 1 activity in many organs, including adipose tissue and pancreas (5).

This evidence and data on metabolic impairments present in Cushing's syndrome and GH deficiency suggest that the relationship between cortisol and GH/IGF-I axis in obesity may have a role in the associated health diseases. Based on this hypothesis, the aim of this study is to explore the relationship between IGF-I and cortisol by crossing their quartiles with the metabolic alterations in paediatric obesity.

Methods

Study design and population

This was a cross sectional study. Data of 900 subjects, referred to the Paediatric Endocrine Service of our hospital for overweight and obesity, were collected from January 2005 to December 2016. Eligibility criteria were a general healthy status and overweight or obesity. Subjects with prior engagement in diet programs were excluded from the study. Other exclusion criteria were diagnosis of diabetes, high blood pressure (BP), use of drugs influencing glucose or lipid metabolism, endocrine or genetic obesity, prematurity, distress during blood sampling, and problematic phlebotomy (more than 5 min). The protocol was conducted in accordance with the declaration of Helsinki and approved by the Local Inter-Hospital Ethic Committee (Maggiore Hospital Ethical Committee,

n. 95/12). All parents gave prior informed consent, and careful explanations were provided to each patient.

Clinical measurements and biochemical analysis

Waist circumference, blood pressure levels, fasting and post-oral glucose tolerance test, glucose levels, insulin resistance, lipid profile, and liver enzymes were all considered as cardiometabolic risk factors.

Pubertal stages were determined by a physical examination, using the criteria of Marshall and Tanner (1, 2, 3, 4, 5, 16). Height was measured three times to the nearest 0.1 cm using the Harpenden stadiometer, and body weight with light clothing was assessed to the nearest 0.1 kg using a manual weighing scale. BMI was calculated as body weight divided by squared height (kg/m²). BMI deviation score (BMI z-score) was calculated by L, M, S method (17). All data were classified according to IOTF criteria (17). Waist circumference was measured in the area between the ribs and the iliac crest at the lowest horizontal circumference, while hip circumference at the level of the imaginary horizontal circumference passing through the femoral trochanters, in standing position, at the end of a normal breath. Both were recorded to the nearest 0.1 cm. Waist/height ratio was calculated as well.

Systolic BP (SBP) and diastolic BP (DBP), classified according to the American Paediatric Society's Guidelines (18), were measured three times at the right arm with participants seated quietly for at least 5 min using a standard digital oscillometric sphygmomanometer.

Blood samples were collected after 12 h of fasting in order to assess cortisol, insulin-like growth factor-I (IGF-I), alanine- (ALT), aspartate-aminotransferase (AST), glucose, insulin, total cholesterol, HDL cholesterol, and triglycerides. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald formula. Obese subjects also underwent an oral glucose tolerance test (OGTT; 1.75 g of glucose solution per kg, maximum 75 g). Plasma samples were immediately processed and stored at –80°C. All participants were evaluated for signs suggestive of Cushing's syndrome, according to the Endocrine Society's Guidelines (19). In case of positive screening, a 1 mg overnight dexamethasone suppression test and urinary free cortisol measurement were performed.

Cortisol levels (μ g/dL) were measured by LIAISON Analyzer with the SPALT principle (Solid Phase Antigen Linked Technique). Inter- and intra-assay coefficients of variation were 3.5 and 3.2% respectively with an analytical sensitivity of 0.16 μ g/dL.

Serum IGF-I values were measured by LIAISON Analyzer with a chemo-luminescence (CLIA) method and an analytical sensitivity less than 3 ng/mL. IGF-I s.d. score (IGF-I SDS) was calculated. Other analytical methods on ALT, AST, glucose, insulin, total cholesterol, HDL-cholesterol, and triglycerides were previously published (20, 21).

Definitions

Hypertension was defined ≥ 95 th percentile for sex and age, as suggested by National High Blood Pressure Education Program Working Group of American Academy of Pediatrics (18).

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes were defined according to American Diabetes Association (22). Using OGTT parameters, HOMA-IR, the Quantitative Insulin-sensitivity Check Index (QUICKI), and insulin sensitivity obtained from the Matsuda Index (ISI) were calculated. Formulas have been previously reported (23).

Statistical analysis

All data are expressed as mean $\pm$ s.d., absolute values, or percentages. Skewed variables were logarithmically transformed. Student *t*-test was used to investigate sex differences. IGF-I SDS and cortisol levels were categorised into quartiles. The ANOVA was used to evaluate the association among continuous clinical and metabolic variables (BMI, BMI Z-score, weight and waist circumference, SBP, DBP, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose levels, glucose levels at 120 min after the OGTT, fasting insulin, HOMA-IR, QUICKI, ISI index, AST, and ALT), cortisol, and IGF-I SDS quartiles. The ANOVA was also adjusted by confounding factors (Model 2: sex, age, Tanner stage, BMI, and waist circumference; Model 3: Model 2 + HOMA-IR). Among each IGF-I SDS quartile, logistic regression has been performed in order to calculate the association between cortisol quartiles and the odd ratio (OR, 95% IC) of each cardiovascular risk factor (hypertension, IFG, IGT, LDL-cholesterol > 75 th percentile, HDL cholesterol ≤ 10 th percentile, and triglycerides ≥ 90 th percentile). Cortisol quartiles were analysed as independent variables with the first quartile as reference. The analysis was adjusted for the same covariates used in the previous Model 3. Statistical significance was set up for $P < 0.05$. Samples ranging from 20 to 202 individuals have been estimated enough to demonstrate a difference of 20% in predicted prevalence of metabolic alterations across quartiles with 90% power and a significance level of

95% basing on our previous data. Because the prevalence of glucose alterations is relatively low in paediatric obesity, a reduction of 20% in HOMA-IR with a s.d. of 1.8 has been considered (6). Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS Inc.).

Results

Population

The final dataset included 876 patients (441 males and 435 females). Twenty-four children were excluded because they did not satisfy inclusion criteria (18 with a difficult blood sampling, 3 with hypothyroidism, and 3 with signs of infections at blood count cells). Clinical, biochemical, and hormonal characteristics of the population, stratified for sex, are reported in Table 1. Among them, 405 (46.1%) subjects were prepubertal and 471 (53.8%) were pubertal. Moreover, 215 (24.5%) subjects were overweight and 661 (75.5%) obese (271 of them were severely obese), according to the IOTF criteria, without a sex imbalance. Most of the population presented visceral obesity, in particular 841 (96%) subjects had a waist circumference ≥ 90 th percentile. Of the total cohort, 522 (59.6%) subjects had hypertension and 77 (8.8%) IFG or IGT. Nobody had type 2 diabetes. Levels of triglycerides ≥ 90 th percentile and HDL ≤ 10 th percentile were more frequent in boys.

Cortisol levels were lower than 5 $\mu\text{g/dL}$ in 65 subjects, and 40 of them repeated the measurement with normal values, whereas the other 25 subjects underwent the dynamic test with a normal response (24). Nobody had IGF-I levels and a phenotype suggestive for GH deficiency.

Associations among cortisol, IGF-I SDS quartiles, and cardio-metabolic parameters

Patients have been divided into IGF-I SDS and cortisol quartiles. Each quartile included 219 subjects. Then, we crossed quartiles in order to evaluate the influence of both quartiles on the cardiovascular and metabolic risk factors. Subjects have been classified into 16 groups based on the IGF-I SDS and cortisol quartiles, as shown in Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article).

BMI, BMI Z-score, weight, and waist circumference were similar in all cortisol and IGF-I SDS quartiles. In Models 1 and 2, age was positively correlated with the rise of cortisol quartiles of subjects in I and II quartiles of IGF-I SDS (I quartile $P < 0.05$; II quartile $P < 0.01$).

Table 1 Biochemical and clinical characteristics of subjects.

	All (n = 876)	M (n = 441)	F (n = 435)
Age	10.6 ± 3.2	10.6 ± 2.9	10.7 ± 3.4
Prepubertal	405 (46.1%)	246* (55.8%)	159* (36.6%)
Pubertal	471 (53.8%)	195* (44.2%)	276* (63.4%)
BMI Z-score (kg/m ²)	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.6
BMI (kg/m ²)	27.0 ± 4.7	27.1 ± 4.4	26.9 ± 5.0
Waist circumference (cm)	88.1 ± 13.6	88.8 ± 13.0	87.4 ± 14.2
SBP (mmHg)	124.8 ± 16.2	125.9 ± 16.4	123.7 ± 15.91
DBP (mmHg)	79.7 ± 11.1	80.6 ± 10.9	78.9 ± 11.2
SBP/DBP >95°	522 (59.6%)	270 (61.2%)	252 (57.9%)
Total cholesterol (mg/dL)	145.1 ± 26.8	144.0 ± 26.5	146.2 ± 27.1
HDL (mg/dL)	43.2 ± 9.8	42.9 ± 9.3	43.5 ± 10.2
TG (mg/dL)	75.3 ± 42.7	72.8 ± 39.5	77.8 ± 45.7
LDL (mg/dL)	86.7 ± 22.6	86.4 ± 22.5	87.0 ± 22.8
Glc0' (mg/dL)	86.5 ± 8.8	87.5 ± 9.0	85.4 ± 8.3
Glc120' (mg/dL)	108.9 ± 18.9	110.2 ± 18.4	107.6 ± 19.3
Insulin0' (μUI/mL)	14.3 ± 9.8	13.4 ± 8.5	15.3 ± 10.9
HOMA-IR	3.2 ± 2.4	3.0 ± 2.2	3.3 ± 2.5
ISI	4.33 ± 3.92	4.40 ± 3.41	4.27 ± 5.34
QUICKI	0.34 ± 0.06	0.34 ± 0.04	0.34 ± 0.05
AST (IU/L)	24.2 ± 7.8	25.4 ± 8.3	22.9 ± 7.2
ALT (IU/L)	23.8 ± 13.3	25.9 ± 16.0	21.6 ± 9.2
Cortisol (μg/dL)	11.3 ± 5.2	11.3 ± 5.0	11.3 ± 5.5
IGF-1 (ng/mL)	268.5 ± 121.4	237.8 ± 113.3	299.6 ± 121.5
IGF-1 SDS	0.15 ± 0.61	0.01 ± 0.58	0.30 ± 0.61

Significant differences between males and females: * $P < 0.001$, ** $P < 0.003$. All data are expressed as mean ± s.d., absolute values, or percentages.

ALT, alanine amino transferase; AST, aspartate amino transferase; DBP, diastolic blood pressure; glc0', fasting plasma glucose, glc120', blood glucose after 120 min of oral glucose tolerance test; HDL, High density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; IGF-1 SDS, insulin-like growth factor-1 s.d. score; Ins0', fasting insulin; ISI, insulin sensitivity index; LDL, low density lipoprotein; QUICKI, quantitative insulin sensitivity index; SBP, systolic blood pressure; TG, triglycerides.

SBP increased with cortisol quartiles in all the IGF-I SDS quartiles in all the models (Model 3: I IGF-I SDS quartile: $P < 0.02$; II IGF-I SDS quartile: $P < 0.02$; III quartile: $P < 0.01$; IV quartile: $P < 0.02$). Diversely, DBP did not vary at the increase of cortisol quartiles, independently from IGF-I SDS quartiles and model.

Total cholesterol was positively associated with cortisol into high levels of IGF-I SDS in all the models (IV quartile, Model 3: $P < 0.01$). The same trend was observed in the II quartile of IGF-I SDS only in Model 2 ($P = 0.056$).

HDL cholesterol level did not change with the increase of IGF-I SDS and cortisol quartiles in the crude model, while assuming significance and increasing with the rise of cortisol quartiles in IV IGF-I SDS quartile in Models 2 ($P < 0.02$) and 3 ($P < 0.02$).

LDL cholesterol was positively correlated with cortisol quartiles in IV IGF-I SDS quartile in Models 1 and 2 ($P < 0.02$), diversely by Model 3.

Triglycerides increased with cortisol quartiles in I and IV IGF-I SDS quartile ($P < 0.01$) in both Models 1 and 2. On the other hand, by using Model 3, the significance was maintained only in IV IGF-I SDS quartile ($P < 0.01$) (Fig. 1).

Figure 1

Triglycerides (mean ± s.d.) in the I (A: $P < 0.01$ in Model 2; B: $P < 0.01$, C: $P < 0.02$, and D: $P < 0.01$ in Model 1), II, III, and IV IGF-I SDS quartile (A: $P < 0.01$ in Model 3; B: $P < 0.05$, and C: $P < 0.02$ in Model 1).

Fasting glucose levels increased according to the increase of cortisol quartiles in I IGF-I SDS quartile ($P < 0.05$) and in IV IGF-I SDS quartile ($P < 0.02$) in Model 1. In Models 2 and 3, this significance was lost, while that in II IGF-I SDS quartile was obtained ($P < 0.03$). Regarding glucose levels at 120 min after the OGTT, there was no significance in any IGF-I SDS quartile.

Fasting insulin was positively correlated with cortisol in I IGF-I SDS quartile ($P < 0.03$) in the crude model but this was lost when covariates were inserted. Diversely, insulin resistance at fasting, expressed as HOMA-IR, and insulin sensitivity at fasting, expressed as QUICKI, increased and decreased, respectively, with the increase of cortisol quartiles in I IGF-I SDS quartile in all models (HOMA-IR: $P < 0.04$; QUICKI: $P < 0.05$) (Fig. 2). Similarly, ISI index decreased with the increase of cortisol quartiles in I quartile of IGF-I-SDS (Model 1: $P < 0.04$).

AST values increased with the increase of cortisol in I ($P < 0.05$) and III IGF-I SDS quartile in all the models (Models 1 and 2: $P < 0.008$; Model 3: $P < 0.01$), meanwhile ALT values increased with the rise of cortisol quartiles only in IV IGF-I SDS (Models 1 and 2: $P < 0.03$; Model 3: $P < 0.04$).

Associations among cortisol, IGF-I SDS quartiles, and metabolic alterations

Subjects included in the III IGF-I SDS quartile had a high risk of hypertension in III (OR: 2.665, CI 95% 1.029–6.900,

$P < 0.04$) and IV cortisol quartile (OR: 2.700, CI 95% 1.069–6.819, $P < 0.03$).

The risk of high levels of total cholesterol increased within III and IV cortisol quartiles in subjects in II, III, and IV IGF-I SDS quartiles (Table 2).

Subjects included in the IV IGF-I SDS quartile had a higher risk of having HDL cholesterol ≤ 10 th percentile when cortisol levels were in III (OR: 4.048, CI 95% 1.560–10.505, $P < 0.004$) and IV quartile (OR: 1.238, CI 95% 1.005–3.031, $P < 0.05$).

The risk of having triglycerides ≥ 90 th percentile increased in the IV cortisol quartile (OR: 3.291, CI 95% 1.117–9.698, $P < 0.03$) in the I IGF-I SDS quartile.

No significance was detected for IFG or IGT presence.

Discussion

Obesity is strongly associated with several comorbidities, including modification of hypothalamic-pituitary-adrenal (HPA) and GH/IGF-I axis. The development of cardiovascular diseases begins in paediatric age; therefore, the aim of the present study was to verify the presence of a possible association between cortisol, IGF-I values, and obesity-related complications in overweight and obese patients.

The data herein presented showed an association between different metabolic parameters, cortisol, and IGF-I SDS. Although our results establish the usual cardiovascular and metabolic cluster, they differ from previous results in some variables between the lowest and the highest level of IGF-I. These differences can be due to a different evaluation of the complex metabolic relationship between HPA and GH/IGF-1 axis.

First, despite an expected association based on literature (25, 26, 27), in our study, weight, BMI, BMI Z-score, and waist circumference did not vary in correspondence of an increase in cortisol and IGF-I SDS. However, discordant findings could partly derive from different inclusion criteria. Studies that reported associations of cortisol or IGF-I values with BMI and waist circumference included a normal-weight group of subjects, although often limited in dimension (25), or obese subjects belonging to a specific ethnic background (28). Other studies found an association only when daily urinary cortisol, urinary steroid metabolites or IGF-I binding proteins (27, 29) or more precise measures of fat mass were considered (3). Furthermore, during the paediatric age, HPA and GH/IGF-I axis regulation can be influenced by other factors, including obesity comorbidities.

Figure 2

HOMA Index (mean $\pm$ S.D.) in the I (A: $P < 0.05$ in the Model 2; B: $P < 0.02$ in Model 1), II, III, and IV IGF-1 SDS quartile.

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Table 2 Logistic regression of LDL cholesterol ≥ 75 per centile in quartiles of cortisol ($\mu\text{g/dL}$) and IGF-1 SDS quartiles.

	LDL ≥75 Percentile				
	Cortisol quartiles				
	I	II	III	IV	
I IGF1-SDS					$\chi^2 = 2.915$; $P = ns$
OR (95% CI)	1.000	0.642 (0.563–2.534)	1.041 (0.277–3.913)	1.823 (0.503–6.609)	
P-value		ns	ns	ns	
II IGF1-SDS					$\chi^2 = 9.633$; $P < 0.02$
OR (95% CI)	1.000	1.347 (0.371–4.887)	4.042 (1.280–12.771)	4.177 (1.38–15.336)	
P-value		ns	<0.01	<0.03	
III IGF1-SDS					$\chi^2 = 5.432$; $P = ns$
OR (95% CI)	1.000	2.597 (0.690–9.781)	1.781 (0.410–7.738)	4.096 (1.167–14.382)	
P-value		ns	ns	0.02	
IV IGF1-SDS					$\chi^2 = 8.127$; $P = ns$
OR (95% CI)	1.000	1.431 (0.454–4.507)	2.911 (1.164–8.791)	1.879 (0.562–6.285)	
P-value		ns	<0.05	ns	

Values in boldface represent significant results. Cortisol values were subdivided into quartiles as follows: I: $\leq 7.3 \mu\text{g/dL}$, II: $7.4\text{--}10.2 \mu\text{g/dL}$, III: $10.3\text{--}14.4 \mu\text{g/dL}$, and IV: $> 14.4 \mu\text{g/dL}$. The values of IGF-1 SDS were divided into quartiles as follows: I: ≤ -0.242 , II: $0.243\text{--}0.078$, III: $0.0079\text{--}0.045$, and IV: > 0.045 . The variables used in Model 3 were: gender, age, Tanner stage, BMI Log, HOMA, and waist circumference.

We introduced several factors to explain, at least partially, how metabolic parameters, cortisol, and IGF-I interact. We demonstrated that SBP increases significantly, when cortisol increases in all the IGF-I SDS quartiles as well as the risk of hypertension exists in the III IGF-I SDS quartile for the highest levels of cortisol. IGF-I levels have been associated to the risk of hypertension both in condition of GH or IGF-I deficiency and acromegaly (30, 31). Three mechanisms could have a major role: (i.) the lack of the stimulation of the production of nitric oxide, increasing vasodilation, and reducing platelet activation for the low levels of IGF-I (32), (ii.) the stimulation of stiffening and vasoconstriction of vessel muscle cells and progression of atherosclerotic disease (33, 34), and (iii.) the augmented sodium retention with the increase of circulating volume (35) for the high levels. In literature, some discordant results are present. Similar (31), higher (36, 37), or lower (38) IGF-I levels have been shown in hypertensive patients compared to normotensive ones. Recently, a Dutch study reported a U-shaped association between IGF-I levels and cardiovascular risk factors (39), partly in accordance with our results. Apart from IGF-I levels, we clearly showed that high SBP levels and risk of hypertension is present when cortisol levels are in the highest range of the normal values, suggesting that cortisol plays a decisive role in hypertension. Various mechanisms contribute to blood pressure increase: among the main ones, there is mineralocorticoid activity of cortisol. In hypercortisolism, renin-angiotensin-aldosterone system is altered, secondary to both central and peripheral over-expression of angiotensin II receptors (40). Moreover, cortisol induces a reduction in nitric oxide

synthesis, inhibiting activity of nitric oxide synthase (41), against what IGF-I usually causes. Moreover, other studies in obese children identified correlation between increased SBP and cortisol (6, 28, 42). As a result, some contrasting data in literature on IGF-I could be relative to the cortisol balance.

With regard to lipid profile, total cholesterol, LDL-, HDL-cholesterol, and triglycerides increased with the rise in cortisol levels with high IGF-1. This has been confirmed also in the logistic regression analysis, where an increased risk of hypercholesterolemia and hypertriglyceridemia with cortisol values $\geq 10.2 \mu\text{g/dL}$ (III and IV quartile) was highlighted. This result agrees with literature data: activation of HPA axis can promote alteration of lipid profile in both adults (43) and children (6) due to complex mechanisms, involving the recycling of lipids, acting on the liver and adipose tissue (44, 45). Triglycerides level is the only variable that increased also in patients with low levels of IGF-I with the rise of cortisol. Low levels of IGF-I have a burden on cardiac and metabolic risk factors, increasing over production of triglycerides also in paediatric obesity (46).

An intriguing association is that on HDL-cholesterol. We showed that HDL-cholesterol increased with the rise of cortisol levels with high IGF-I, but subjects in the IV IGF-I SDS quartile had, however, an increased risk of HDL-cholesterol ≤ 10 th percentile when cortisol levels were high. Two different physiological mechanisms could be hypothesized. Considering the role of IGF-I, a positive association between IGF-I and HDL-cholesterol values was found in several studies, including one in obese adolescents (47). The exact mechanism underlying the

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relationship between IGF-I and HDL cholesterol in obesity is not fully clarified: the main reason may be that IGF-I inhibits the hepatic expression of the class B1 scavenger receptor on the surface of the hepatocytes, causing a reduction in the hepatic intake of HDL cholesterol and an increase in its circulating levels (48). Furthermore, by considering cortisol, it has been highlighted that the adrenal gland uses cholesterol contained in HDL and not the one contained in LDL to synthesize steroid hormones (49, 50). Indeed, patients with low levels of HDL had a low response to the ACTH test, suggesting that a condition of partial adrenal insufficiency should be related to a reduction of HDL cholesterol (51). On the other hand, subjects in the IV IGF-I SDS quartile with highest cortisol levels had an increased risk of HDL cholesterol ≤ 10 th percentile when cortisol levels were high. We cannot exclude that, in the context of obesity, the state of low-grade inflammation associated with cortisol as well as hyper-nutrition is able to stimulate a pro-atherogenic lipid profile even in the paediatric age (52, 53). However, also a statistical bias could be hypothesized, linked to the sample size, although it resulted enough for all the cardiometabolic alterations considered or to the lack of a control group of normal-weight children.

Regarding glucose metabolism, diversely by other factors discussed until now, we showed that fasting glucose and insulin resistance augmented and in correspondence of that, QUICKI and ISI decreased with high cortisol levels in the I IGF-I SDS quartile. This result could be linked to the failure of insulin-like activity of IGF-I when its levels are low, resulting in an altered glycaemic and insulin status. Indeed, IGF-I can stimulate the use of glucose by activating GLUT4 and inhibiting gluconeogenesis, all insulin-like effects that improve insulin sensitivity (54). The absence of an association between fasting glucose and insulin resistance, with the increase of cortisol quartiles in IV of IGF-I SDS quartile, could be an attempt to overcome a condition of subtle hyperglycaemia and hyperinsulinemia resulting from obesity. This would be through by stimulating IGF-I secretion and exploiting its hypoglycaemic effects (27). Diversely, the lack of an association with altered glucose levels as IFG or IGT might be secondary to underpowered sample size, being that these conditions a rare event in Caucasian paediatric obese children (6, 55).

Lastly, AST and ALT showed a direct association both with cortisol and IGF-I SDS, especially in III and IV quartiles. ALT represents the most specific hepatocyte damage marker, even in paediatric age (56), and liver steatosis is the most common cause for overweight and

obese children and adolescents ranging up to 34% (56, 57) and being associated with a lipid profile characterized by hypertriglyceridemia and increased non-HDL cholesterol (58). This has been confirmed by our results. However, it has not been possible to perform abdominal ultrasound or liver biopsy to all enrolled children. Due to this absence of data, the increase of AST and ALT with the liver steatosis remains a hypothesis in this population. Although obesity is strongly associated with hepatic steatosis, an excess of adipose tissue is not the only cause for liver steatosis development. Indeed, patients with lipodystrophy show a marked insulin resistance and easily develop hepatic steatosis and type 2 diabetes, suggesting that it is not the obesity that causes the pathology, making lipolytic activity dysfunction the main factor (59). In our study, this could be justified by the lipolytic effect linked to functional hypercortisolemia associated with higher IGF-I levels suggestive of hyper-nutrition.

This study has several limitations. First, we did not recruit healthy normal-weight children. We tried to overcome this point by investigating a huge cohort composed of overweight, obese, and severely obese children and adolescents in the hypothesis that trends of comorbidities, cortisol, and IGF-I levels were associated with the progressive increase of weight scores. However, we cannot exclude that a control group with and without subtle metabolic alterations could modify some of our findings. Further studies including also healthy children are mandatory to confirm our suggestions. Second, we limited the used quartile-based categories to evaluate the relationship between cortisol/IGF-I and metabolic alterations. While this approach is largely used and generally produces valid results (60, 61, 62), other options (e.g. flexible modelling of the interaction of continuous variables) are available as well and could produce different results.

Third, the role of hyper-nutrition or unbalanced nutrition on the relationship among IGF-I, cortisol, and cardiometabolic parameters is a hypothesis in our study but also an exciting issue. Recent findings suggest that the adherence to a Mediterranean diet, mainly protein and milk intake are associated with the functionality of the GH/IGF-I axis and the cardiometabolic profile in adult obesity (63, 64). Moreover, skipping breakfast, and then reducing milk intake, has been associated with a worse metabolic profile also in paediatric obesity (65). Other foods have been associated with inflammation and may modulate the HPA axis (66). In the view of the role of nutrients as metabolic sensors, a complete picture of food habits is required in further studies.

In conclusion, this study aimed to establish the association between cortisol, GH/IGF-I axis, and metabolic complications in overweight and obese children and adolescents. We observed that some of the parameters known to be associated with increased cardiovascular risk were related to high levels of IGF-I and cortisol, even if within normal range. We showed that subjects with high IGF-I and cortisol had an increased risk of hypertension, hypercholesterolemia, high levels of triglycerides, and reduced HDL cholesterol. Diversely, lower IGF-I levels were associated with higher blood glucose, insulin, insulin resistance, and reduced insulin sensitivity levels with the rise of cortisol. These data suggest that cortisol and IGF-I play a complex role in the comorbidities of obesity. The evaluation of both variables could clarify some of the discordant results shown in literature on the role of IGF-I.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0792>.

Declaration of interest

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

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