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ORIGINAL ARTICLE

Alteration of the growth hormone axis, visceral fat dysfunction, and early cardiometabolic risk in adults: the role of the visceral adiposity index

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Abstract The aim of the study is to clarify the relationship between adipose tissue dysfunction, metabolic profile and growth hormone (GH)/insulin-like growth factor (IGF)-I secretion in healthy adult subjects. We investigated the metabolic profile in a cohort of 231 consecutive healthy subjects in relation to GH, IGF-I levels, and visceral adiposity index (VAI). Anthropometric measures, lipid profile, and glucose and insulin levels during oral glucose tolerance test, Homa-IR and ISI Matsuda, IGF-I and GH peak after GHRH plus Arginine test were analyzed. The subjects with high VAI showed lower GH peak (22.8 ± 11.1 vs. 42.2 ± 21.3 μg/L; $p = 0.049$) and lower IGF-I (presented as IGF-I under normal range, UNR) (0.54 ± 0.14 vs. 0.64 ± 0.12; $p = 0.005$) than group with normal VAI. ROC curve analysis identified the cut-off, able to detect subjects with high VAI, i.e., 31.8 μg/L for GH peak and 0.63 for IGF-1 UNR. The subjects with GH peak and IGF-I UNR under the cut-off showed significantly higher levels of VAI, systolic and diastolic blood pressure, glucose and insulin levels, Homa-IR, and lower ISI Matsuda, with a concomitant worse lipid profile (all $p < 0.001$). A strong relationship between GH axis, VAI and metabolic risk has been demonstrated. A percentage of apparently healthy subjects show a degree of visceral adipose dysfunction associated with GH and IGF-I levels that do not meet the criteria of overt GH deficiency (GHD). Long-term prospective studies could help to clarify and confirm whether a hypothetical condition of subclinical GHD could be taken into account as a new clinical entity.

Keywords Growth hormone · Visceral adiposity · Metabolic risk · GH deficiency

Introduction

Growth hormone deficiency (GHD) in adult life is well known to be associated with increased fat and reduced lean mass, altered cardiac structure and function, adverse lipid profile, glucose intolerance and insulin resistance, and increased cardiovascular morbidity and mortality [1–7]. On the other hand, there is robust evidence that obesity results in a secondary reduction in GH secretion and that substantial weight loss may restore spontaneous and stimulated GH secretion [8–13]. Body mass index (BMI) is negatively correlated with GH secretion [10, 11, 14] due both to reduced GH production and increased GH-clearance [12]. However, how obesity reduces GH secretion has not been clarified and there is an increasing evidence that free fatty acids (FFA) play a significant role [15, 16]. In clinically non-obese healthy adults, relative abdominal adiposity proved to be a major negative determinant of stimulated GH secretion [10]. Conversely, the existence of

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Table 1 Clinical and biochemical features of 231 subjects enrolled into the study

	Subjects (%)
Gender	
Men	118 (51.1)
Women	113 (48.9)
	Mean ± SD
Age (year)	44.2 ± 20.2
BMI (Kg/m^2)	28.2 ± 6.5
WC (cm)	89.3 ± 16.8
VAI	1.51 ± 0.81
Basal GH (μg/L)	0.31 ± 0.44
Nadir GH (μg/L)	0.13 ± 0.12
AUC_{GH} (μg/L)	32.5 ± 28.7
GH peak (μg/L)	38.6 ± 21.2
IGF1 (UNR)	0.62 ± 0.13
SDS IGF1	−0.02 ± 0.68
	Subjects (%)
Metabolic syndrome	24 (10.3)
High VAI	43 (18.6)
Increased WC	82 (35.5)
Hypertriglyceridemia	42 (18.2)
Low HDL cholesterol	33 (14.3)
Increased Systolic Blood Pressure or specific treatment	30 (13)
Increased Diastolic Blood Pressure or specific treatment	14 (6.1)
Impaired fasting glucose (IFG)	24 (10.4)
Impaired glucose tolerance (IGT)	12 (5.2)
IFG + IGT	26 (11.3)
Diabetes mellitus (DM)	22 (9.5)

BMI body mass index, *WC* waist circumference, *VAI* visceral adiposity index, *AUC* area under the curve, *UNR* under the average of the normal range for age, and *SDS* standard deviation score

changes of the insulin-like growth factor (IGF)-I axis in obesity is controversial. There are data showing decreased [14, 17, 18], normal [12, 19] or even elevated [20] IGF-I levels in adult obese patients.

Adiposity and the GH axis are reportedly tightly interrelated [21]; data, however, originated mostly in patients with hypothalamus-pituitary diseases, while in the general population, data are still limited. The visceral adiposity index (VAI), a gender-specific mathematical index based on simple anthropometric [BMI and waist circumference (WC)] and metabolic [triglycerides (TG) and HDL cholesterol (HDL)] parameters, has been proposed as a surrogate marker of adipose tissue function and distribution, independently correlated with insulin sensitivity and cardiometabolic risk in the general population [22]. VAI has shown to be a good marker of adipose tissue dysfunction in the general population [22–24] and in populations at metabolic risk such as women with PCOS [25], patients with non-alcoholic fatty liver disease [26], acromegaly [27, 28], prolactinoma [29] or diabetes mellitus [30, 31].

The current study is based on the hypothesis that fat distribution and/or function, represented by VAI, correlates with the GH axis. To clarify this association, we investigated the metabolic profile and the visceral adipose function in a cohort of consecutive healthy subjects in relation to GH levels after stimulus test.

Materials and methods

Patients

For the purpose of this study, at the section of Endocrinology University "Federico II" of Naples, between January 1st 2009 and December 31st 2011, GH secretion was evaluated after GHRH plus Arginine (GHRH+Arg) test [32] in 231 subjects, 118 men and 113 women, aged 44.2 ± 20.2 years, recruited consecutively among the medical and paramedical personnel of the Department and their relatives, and/or patients' relatives. The study was part of a large database started in 1997 to investigate the role of GH on the cardiovascular system, approved by the Ethical Committee of the "Federico II" University of Naples in 1997 (no.63/97). An informed consent has been obtained from each subject after full explanation of the purpose and nature of all procedures used.

Clinical and biochemical features of subjects enrolled into the study are shown in Table 1.

The exclusion criteria for entering this study were: (1) diagnosis of overt GH deficiency or GH excess (2) personal history of pituitary diseases as reported in interviews with individual subjects; (3) previous or current treatments with drugs known to interfere with glucose or lipid metabolism or to influence blood pressure; (4) previous treatment with corticosteroids for longer than 2 weeks; (5) previous or current treatment with estrogens or testosterone for longer than 12 weeks; (6) smoking of more than 15 cigarettes/day and alcohol abuse (more than 3 glasses of wine/day); (7) presence of previous diagnosis and already known diabetes mellitus or hypertension; 8) severe obesity. Of initial 296 patients, 65 were excluded since GH levels were assayed before beginning of use of modern GH assay, in line with international recommendations [33].

Study design

This is an analytical, retrospective study to analyze the relationship between the visceral adiposity and GH-IGF-I secretion in a sample representative of the general population. Anthropometric measurements were performed with

the subjects wearing only underwear without shoes. Standing height was measured to the nearest cm using a wall-mounted stadiometer. Body weight was determined to the nearest 50 g using a calibrated balance beam scale. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference (WC) was measured at the midpoint between the lower rib and the iliac crest. Systolic (SBP) and diastolic (DBP) blood pressure were measured in all patients. Patients were analyzed according to each criterion of the metabolic syndrome (MS) [34] and each category of glucose tolerance (GT) [35]. After an overnight fast, lipid profile (total, HDL and LDL cholesterol, and triglycerides) glucose and insulin levels, and IGF-I were measured. IGF-I levels were reported as standard deviation score (SDS) age- and gender-adjusted. In addition, we calculated the ratio of the observed serum IGF-I levels to the average of the normal range for age. The data were presented as IGF-I under normal range (IGF-I UNR) and we considered equal to 1, the perfectly average IGF-I value and <1 the IGF-I levels below the average. The GHRH + Arg test was performed as previously reported [36]. Arginine (arginine hydrochloride, Salf, Bergamo, Italy) was given at the dose of 0.5 g/Kg, up to a maximal dose of 30 g slowly infused from time 0 to 30 min, while GHRH (Geref, Serono, Rome, Italy and GHRH Ferring, Milan, Italy) was given at the dose of 1 μg/Kg as i.v. bolus at time 0. Blood samples were taken every 30 min from 0 up to 90 min. The highest GH levels measured from time 30 to 90 min during the test were taken for analysis as peak GH. The area under the curve (AUC) of GH (AUC_{GH}) was calculated.

The oral glucose tolerance test (oGTT) was performed by measuring plasma blood glucose and insulin every 30 min for 2 h after 75 g oral glucose load. The AUC of glucose (AUC_{GLU}) and insulin (AUC_{INS}) during 2 h-OGTT were calculated. Basal insulin resistance (IR) was assessed using homeostasis model assessment of the insulin resistance (Homa-IR) index [37], while the stimulated insulin sensitivity was measured using the insulin sensitivity index (ISI), a composite index derived from the OGTT and validated by Matsuda et al. [38].

As the surrogate of visceral fat function in all patients, we calculated VAI as described [22], using the following formulas differentiated according to sex, where TG is fasting triglycerides levels expressed in mmol/L and HDL is HDL cholesterol levels expressed in mmol/L:

$$\text{Males}: \text{VAI} = [\text{WC}/39.68 + (1.88 \times \text{BMI})] \times (\text{TG}/1.03) \times (1.31/\text{HDL}),$$

$$\text{Females}: \text{VAI} = [\text{WC}/36.58 + (1.89 \times \text{BMI})] \times (\text{TG}/0.81) \times (1.52/\text{HDL}).$$

According to specific age-stratified cut-off points of VAI identifying patients with presumed visceral adipose dysfunction and cardiometabolic risk, we grouped the entire cohort of patients into those with normal and high VAI. The appropriate cut-off points of VAI used were previously calculated in a general population as follows: 2.52 for subjects under 30 years, 2.23 for those aged between 30 and 42 years, 1.92 between 42 and 52 years, 1.93 between 52 and 66 years, and 2.00 for subjects over 66 years [23].

Hormone and biochemical assays

Glycemia and lipid levels were measured in centralized accredited laboratories with standard methods. 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. Serum GH was measured by CLIA using Liaison hGH kit of Diasorin. The hGH sensitivity is 0.052 μg/L, thus undetectable GH levels were arbitrarily considered 0.05 μg/L. The intra-assay CVs were 4.4, 1.6, and 2.0 % for the low, medium, and high points of the standard curve, respectively. The inter-assay CVs were 6.0, 7.7, and 6.8 % for the low, medium, and high points of the standard curve. The hGH values were evaluated against the World Health Organization Second International Standard reference reagent 98/574. Serum IGF-I was measured by CLIA after automatized extraction using Liaison IGF-I kit of DiaSorin. The IGF-I sensitivity is <3 μg/L. The intra-assay CVs were 4.3, 3.0, and 3.3 % for the low, medium, and high points of the standard curve, respectively. The inter-assay CVs were 4.4, 3.3, and 3.6 % for the low, medium, and high points of the standard curve. The IGF-I values were evaluated against 1st WHO International Standard for Insulin-like Growth Factor-I NIBSC 02/254.

Statistical methods

The Statistical Packages for Social Sciences SPSS version 17 and MedCalc version 11.3 were used for data analysis. Baseline characteristics were presented as mean ± standard deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative data was assessed by Kolmogorov–Smirnov test. Differences between groups were detected by unpaired Student's t test for continuous variables and by χ^2-test, and Fisher's exact test (when appropriate) for categorical variables. Differences in hormonal parameters (GH-IGF-1 axis) were calculated after being adjusted for age and for all

Table 2 Subjects features in relation to visceral adiposity index (VAI)

	Subjects with normal VAI No 188 (81.4 %) Mean ± SD	Subjects with high VAI No 43 (18.6 %) Mean ± SD	Univariate analysis *p*	Multivariate analysis* *p* OR (IC 95 %)
Age (years)	41.6 ± 19.8	55.8 ± 18.2	<0.001	
BMI (Kg/m^2)	27.6 ± 6.7	30.8 ± 5.1	0.003	
WC (cm)	86.4 ± 15.9	102.2 ± 14.5	<0.001	
Systolic blood pressure (mmHg)	124.6 ± 15.5	136.5 ± 10.6	0.009	
Diastolic blood pressure (mmHg)	79 ± 7.3	83 ± 4.3	0.054	
Total cholesterol levels (mmol/L)	4.95 ± 0.78	6.10 ± 0.74	<0.001	
HDL cholesterol levels (mmol/L)	1.48 ± 0.17	1.23 ± 0.11	<0.001	
LDL cholesterol levels (mmol/L)	2.91 ± 0.79	4.06 ± 0.74	<0.001	
Triglycerides levels (mmol/L)	1.21 ± 0.32	1.78 ± 0.25	<0.001	
Fasting glucose levels (mmol/L)	5.07 ± 0.20	6.06 ± 0.74	<0.001	
Fasting insulin levels (mmol/L)	9.42 ± 5.64	13.16 ± 6.06	<0.001	
$AUC_{glucose}$ (mmol/L)	967 ± 189	1108 ± 190	<0.001	
$AUC_{insulin}$ (mmol/L)	7597 ± 5209	9282 ± 6362	0.068	
Homa-IR	2.2 ± 1.5	3.5 ± 1.6	<0.001	
ISI Matsuda	5.9 ± 3.8	3.4 ± 1.8	<0.001	
Basal GH (μg/L)	0.35 ± 0.47	0.13 ± 0.21	0.005	0.076 0.28 (0.07–1.14)
AUC_{GH} (μg/L)	35.2 ± 29.6	20.6 ± 21.2	0.003	0.896 0.99 (0.98–1.05)
Nadir GH (μg/L)	0.14 ± 0.13	0.08 ± 0.07	0.003	0.621 0.29 (0–36.55)
GH peak (μg/L)	42.2 ± 21.3	22.8 ± 11.1	<0.001	0.049 0.96 (0.93–1)
IGF1 (UNR)	0.64 ± 0.12	0.54 ± 0.14	<0.001	0.005 0.01 (0–0.29)
SDS IGF1	0.05 ± 0.67	−0.03 ± 0.65	<0.001	0.017 0.54 (0.32–0.89)

* Values adjusted for age and for all metabolic parameters, excluding the collinear variables with VAI, resulted significantly different between the two groups ($p < 0.05$), using a logistic regression model

VAI visceral adiposity index, *BMI* body mass index, *WC* waist circumference, *AUC* area under the curve, *UNR* under the average of the normal range for age, and *SDS* standard deviation score

metabolic parameters, excluding the collinear variables with VAI, resulted significantly different between the two groups, using a logistic regression model. Receiver operating characteristic (ROC) analysis was used to assess the ability of GH peak, IGF-I UNR, Homa-IR, ISI Matsuda, total and LDL cholesterol, AUC_{GLU}, and AUC_{INS} to indicate increased VAI score. ROC curves indicate the probability of a true-positive result as a function of the probability of a false positive result for all possible threshold values of above selected parameters. ROC curve analysis was performed using the MedCalc software (version 11.3.0 for Windows), which uses calculation of the area under the curve (C-statistic) and 95 % confidence intervals by the technique of Hanley and McNeil. Statistical significance of the difference between C-statistic of GH peak and IGF-1 UNR and the other parameters (Homa-IR, ISI Matsuda, total cholesterol, AUC_{GLU}, and AUC_{INS}) separately was calculated by the method of Hanley and McNeil. A p value of <0.05 was considered statistically significant.

Results

The clinical and biochemical features of subjects are shown in Table 1. In the entire cohort of subjects, the mean GH peak after GHRH+Arg test was 38.6 ± 21.2 μg/L. None of the subjects had GH peak after GHRH+ARG below 9.1 μg/L, the currently accepted cut-off to diagnose adult GH deficiency [39], nor had GH peak between 9.1 and 16.5 μg/L, representing the 1st and the 3rd percentile of the general population according with Aimaretti et al. [32]. The mean IGF-I SDS was −0.02 ± 0.68, with a mean IGF-I UNR 0.62 ± 0.13.

Using the "National Cholesterol Education Program (NCEP-Adult Treatment Panel III, ATP III)" criteria [34], in the whole cohort of subjects, the overt complete MS was found in 24 subjects (10.3 %). Specifically, 30 (13 %) subjects had systolic hypertension, 14 had (6.1 %) diastolic hypertension, 42 (18.2 %) had hypertriglyceridemia, 82 (35.5 %) had increased WC, and 33 (14.3 %) had low HDL cholesterol levels (Table 1).

Twenty-four out of 231 subjects (25 %) were classified as having impaired fasting glucose (IFG), 12 (5.2 %) impaired glucose tolerance (IGT), 26 (11.3 %) IFG + IGT, and 22 (9.5 %) showed after OGTT a previously unknown overt diabetes mellitus (DM), according to the medical guidelines of the American Association of Clinical Endocrinologists [35].

In the entire cohort of subjects, the mean VAI was 1.51 ± 0.81. One hundred and eighty-eight subjects (81.4 %) were classified as having normal VAI, while 43 (18.6 %) had high VAI. The subjects with high VAI were older (55.8 ± 18.2 vs. 41.6 ± 19.8 years; $p < 0.001$) and with greater BMI (30.8 ± 5.1 vs. 27.6 ± 6.7 kg/m^2; $p = 0.003$) than those with lower VAI. In addition, subjects with high VAI showed a significant worse lipid and glucose profile than subjects with lower VAI, with a concomitant higher Homa-IR (3.5 ± 1.6 vs. 2.2 ± 1.5; $p < 0.001$) and lower ISI Matsuda (3.4 ± 1.8 vs. 5.9 ± 3.8; $p < 0.001$) (Table 2). No difference was found in basal GH (0.13 ± 0.21 vs. 0.35 ± 0.47 μg/L; $p = 0.076$), AUC_{GH} (20.6 ± 21.2 vs. 35.2 ± 29.6; $p = 0.896$), and nadir GH during OGTT (0.08 ± 0.07 vs. 0.14 ± 0.13 μg/L; $p = 0.621$) when hormonal values were adjusted for age and all significant metabolic variables using a logistic regression model. Conversely, group of subjects with high VAI showed lower GH peak after GHRH + Arg (22.8 ± 11.1 vs. 42.2 ± 21.3 μg/L; $p = 0.049$), IGF-I UNR (0.54 ± 0.14 vs. 0.64 ± 0.12; $p = 0.005$), and IGF-I SDS (−0.03 ± 0.65 vs. 0.05 ± 0.67; $p = 0.017$) than group with normal VAI (Table 2).

In order to identify the optimal cut-off point, able to detect subjects with high VAI, ROC curve analysis was performed for GH peak, IGF-I UNR, Homa-IR, ISI Matsuda, Total Cholesterol, LDL Cholesterol, $AUC_{glucose}$, and $AUC_{insulin}$ (Table 3). The C-statistics were then compared to verify the predictive values of the above-mentioned parameters. No significant differences were found between the C-Statistics of GH peak, IGF-I UNR and Homa-IR, ISI Matsuda, total cholesterol, $AUC_{glucose}$, and $AUC_{insulin}$ (Table 4).

GH peak and IGF-I UNR threshold levels, calculated by maximizing the combined specificity and sensitivity in the ROC curves, were 31.8 μg/L (sensitivity: 83.7 %; specificity: 63.8 %) and 0.63 (sensitivity: 79.1 %; specificity: 56.9 %), respectively (Table 3).

Considering the cut-off of 31.8 μg/L for GH peak and of 0.63 for IGF-I UNR, we grouped the subjects into those with at least a value higher than the above-mentioned cut-off (Group A, No 168; 72.7 %) and those with low values of both GH peak and IGF-I UNR (Group B, No 63; 27.3 %). The subjects with values under cut-off were older (51.4 ± 22.7 vs. 41.6 ± 18.6 years; $p = 0.001$) and with a higher prevalence of men than women ($p = 0.044$). In addition, the subjects with GH peak < 31.8 μg/L and IGF-I UNR < 0.63 showed significantly higher levels of VAI (2.12 ± 0.85 vs. 1.28 ± 0.67; $p < 0.001$), systolic (144.2 ± 11.5 vs. 122.6 ± 13.8 mm/Hg; $p < 0.001$) and diastolic blood pressure (86 ± 4.5 vs. 78.2 ± 6.9 mm/Hg; $p < 0.001$), Homa-IR (4 ± 1.9 *vs.* 1.9 ± 1.1; $p < 0.001$), fasting glucose (2.75 ± 0.34 vs. 2.33 ± 0.35 mmol/L; $p < 0.001$), $AUC_{glucose}$ (1103 ± 209 vs. 952 ± 176 mmol/L; $p < 0.001$), fasting insulin (15.12 ± 6.95 vs. 8.24 ± 4.11 mmol/L; $p < 0.001$), $AUC_{insulin}$ (10985 ± 6814 vs. 6757 ± 4361 mmol/L; $p < 0.001$), and lower ISI Matsuda (3 ± 1.6 vs. 6.4 ± 3.8; $p < 0.001$), with a concomitant worse lipid profile (Figs. 1, 2).

Discussion

We investigated the metabolic profile and the visceral adipose function, indirectly expressed by VAI, in a group of subjects without overt GH axis dysfunction in relation to GH and IGF-I levels, and their mutual relationship. Our data show a strong correlation between visceral adiposity and GH axis, highlighting how GH values quite higher than those recognized as diagnostics for overt GHD could be associated with a condition of visceral adiposity dysfunction and cardiometabolic risk.

Currently, the peak GH response less than 3.0 μg/L to an insulin tolerance test (ITT) is considered the gold standard for the biochemical diagnosis of severe adult GHD [40, 41], while Aimaretti et al. showed that the combined administration of arginine, which presumably reduces hypothalamic somatostatin secretion, and GHRH is safe and provides a strong stimulus to GH secretion and thus could be used as an alternative test of pituitary GHD,

Table 3 Area under ROC curves of selected metabolic parameters and related optimal cut-off point to detect subjects with high VAI

	Cut-off point	Sens. (%)	Spec. (%)	Area under ROC curve	SE	95 % CI	*p*
GH peak	<31.8	83.7	63.8	0.767	0.03	0.70–0.82	<0.001
IGF-1 UNR	<0.63	79.07	56.91	0.709	0.04	0.64–0.76	<0.001
Homa-IR	>2.7	72.09	74.47	0.758	0.04	0.69–0.81	<0.001
ISI Matsuda	<4.1	79.07	61.17	0.715	0.03	0.65–0.77	<0.001
Total cholesterol	>5.47	79.07	78.72	0.852	0.03	0.79–0.89	<0.001
LDL cholesterol	> 3.53	76.74	79.79	0.847	0.03	0.79–0.89	<0.001
$AUC_{glucose}$	>967.3	81.40	65.96	0.729	0.04	0.66–0.78	<0.001
$AUC_{insulin}$	>6570	65.12	64.89	0.609	0.04	0.54–0.67	0.027

Sens sensitivity, *Spec* specificity, *SE* standard error, *VAI* visceral adiposity index, *UNR* under the average of the normal range for age, and *AUC* area under the curve

Table 4 Pairwise comparison between C-statistic of GH peak–IGF-1 UNR and Homa-IR, ISI Matsuda, total cholesterol, $AUC_{glucose}$, and $AUC_{insulin}$

	Differences between C-statistics	SE	95 % CI	*p*
GH peak versus Homa-IR	0.008	0.03	−0.06 to 0.008	0.807
GH peak versus ISI Matsuda	0.052	0.03	−0.01 to 0.12	0.146
GH peak versus total cholesterol	0.084	0.04	0–0.17	0.056
GH peak versus $AUC_{glucose}$	0.038	0.04	– 0.04–0.12	0.191
GH peak versus $AUC_{insulin}$	0.158	0.05	0.05–0.26	0.063
IGF-1 UNR versus Homa-IR	0.049	0.05	−0.05 to 0.14	0.333
IGF-1 UNR versus ISI Matsuda	0.005	0.05	−0.09 to 0.10	0.912
IGF-1 UNR versus total cholesterol	0.142	0.05	0.04–0.24	0.064
IGF-1 UNR versus $AUC_{glucose}$	0.019	0.05	−0.08 to 0.12	0.714
IGF-1 UNR versus $AUC_{insulin}$	0.100	0.06	−0.01 to 0.22	0.101
GH peak versus IGF-1 UNR	0.057	0.04	−0.02 to 0.14	0.185

AUC area under the curve, *UNR* under the average of the normal range for age

C-statistic were 0.767 (95 % CI 0.70–0.82) for GH peak, 0.709 (95 % CI 0.64–0.76) for IGF-1 UNR, 0.758 (95 % CI 0.69–0.81) for Homa-IR, 0.715 (95 % CI 0.65–0.77) for ISI Matsuda, 0.852 (95 % CI 0.79–0.89) for total cholesterol, 0.847 (95 % CI 0.79–0.89) for LDL Cholesterol, 0.729 (95 % CI 0.66–0.78) for $AUC_{glucose}$, and 0.609 (95 % CI 0.54–0.67) for $AUC_{insulin}$

with a cut-off of 9.1 μg/L [32]. In addition, it would be reasonable to use different GH cut-off points according to BMI for the stimulus test. In fact, peak of GH has to be normalized for age and BMI as young, and lean people produce physiologically more GH under stimulation [21, 36, 42, 43]. Corneli et al. showed that the appropriate cut-off points for diagnosing GHD were 11.5 μg/L for those with a BMI less than 25 kg/m^2, 8.0 μg/L for a BMI of 25–30 kg/m^2, and 4.2 μg/L for those with a BMI greater than 30 kg/m^2 [44]. As stimulation test, the GHRH + ARG test was chosen in this study because of previous studies showing reliable comparison with ITT [32], reliable cut-off for the GHD diagnosis, as correlated with lipid, bone and cardiac status [45–47], and high reproducibility [48].

Conversely, it is a matter of fact that the analysis of IGF-I levels is not sufficient to diagnose GHD, though increased IGF-I levels are essential to diagnose GH excess. Reduced IGF-I levels are not required to diagnose GHD as many patients with clear-cut GHD might have normal IGF-I levels. The usefulness of an IGF-I estimation in the diagnosis of adult GHD is a matter of contention. Hoffman et al. found [49] that 70 % of IGF-I values in adult-onset GHD patients were within the range of normal subjects [49], while a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment, and therefore require GH stimulation testing [41].

Two previous studies have demonstrated that GH peak after GHRH + ARG [36] and GH nadir during OGTT [43] depend on age, BMI, and waist circumference so that appropriate diagnostic cut-off should consider these variables. The role of BMI has been clearly demonstrated to modify GH peak after GHRH + ARG in large series of hypopituitary patients by Corneli et al. [44], but BMI only partially reflect visceral adiposity. In fact, in a study including both WC and BMI as predictors of response [36], a stronger effect of the former on the latter has been demonstrated. Similarly WC, more than BMI, suppressed

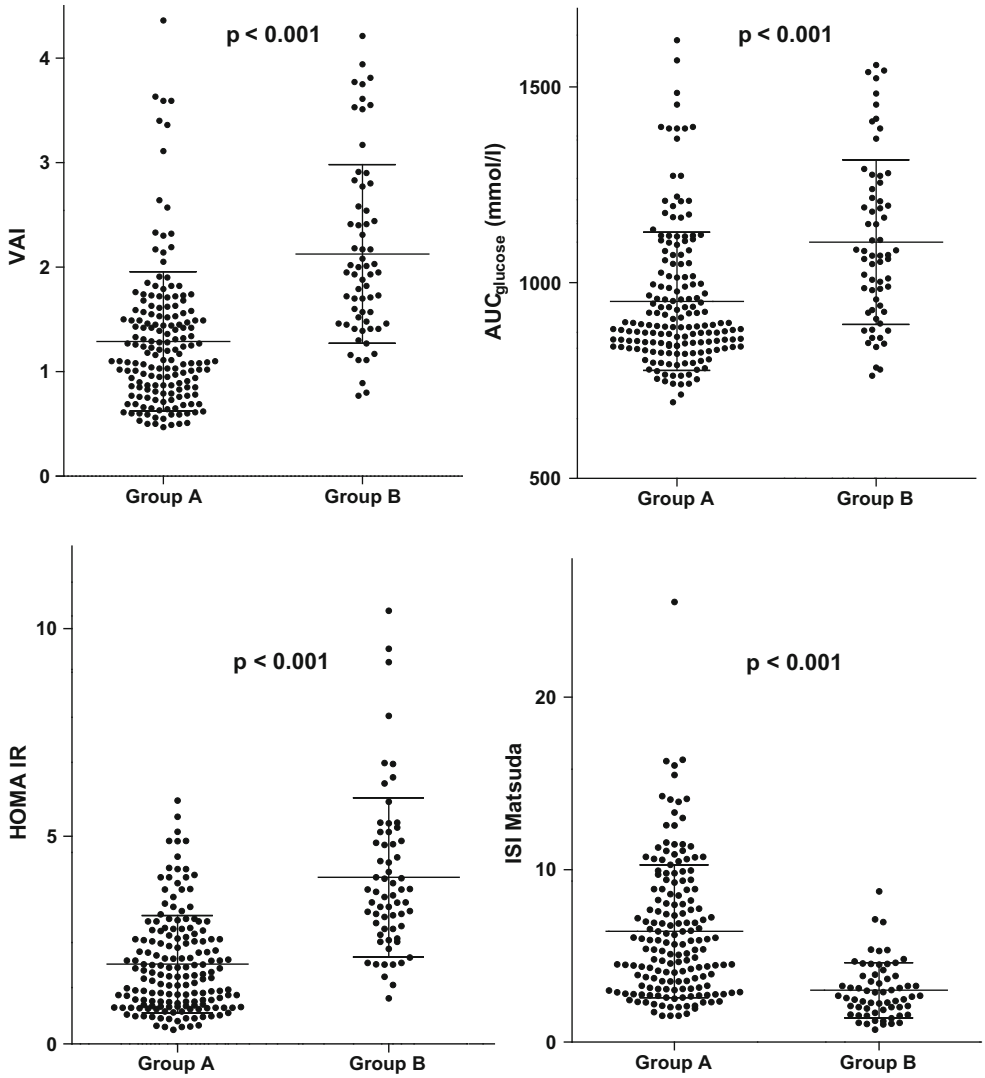

Fig. 1 Differences in visceral adiposity index (VAI), $AUC_{glucose}$, Homa-IR, and ISI Matsuda between subjects with GH peak lower than cut-off of 31.8 μg/L and IGF-1 UNR lower than cut-off of 0.63 (Group A), and those with at least a value higher than the above-mentioned cut-off (Group B)

GH nadir after OGTT [43]. Despite this evidence, cut-off peak GH and nadir GH after stimuli are still considered worldwide without an appropriate cut-off for WC.

Ideally, the possibility to use one single value representing at the same time BMI, WC, and lipid profile could be very useful, and in this light VAI might help in determining the best stratification of GH secretion in relation to cardiometabolic risk. In this study, we found that GH values, after GHRH-Arg test lower than 31.8 μg/L with IGF-I UNR lower than 0.6, are associated with a cardiometabolic risk status, represented by high VAI.

It is well known that overt GHD in adults has been associated with an adverse metabolic profile and abnormalities in body composition that may have an impact on cardiovascular risk. In fact, a clustering of cardiovascular clinical risk factors has been reported in GHD patients, including truncal adiposity and increased visceral fat, changes in body composition and insulin resistance, negative changes in lipid profiles and abnormal hemostatic factors, and an increased cardiovascular mortality [50–52].

In our cohort of subjects, we found a higher prevalence of subjects with high VAI than patients with overt MS. These findings are in line with previous data [22] and a possible explanation might lie in the fact that the early stages of metabolic alterations are not highlighted by the classic criteria of MS, whereas VAI seems to be able to show early signs of metabolic risk in patients without overt MS, since the variables are treated as continuous variables and not as dichotomous.

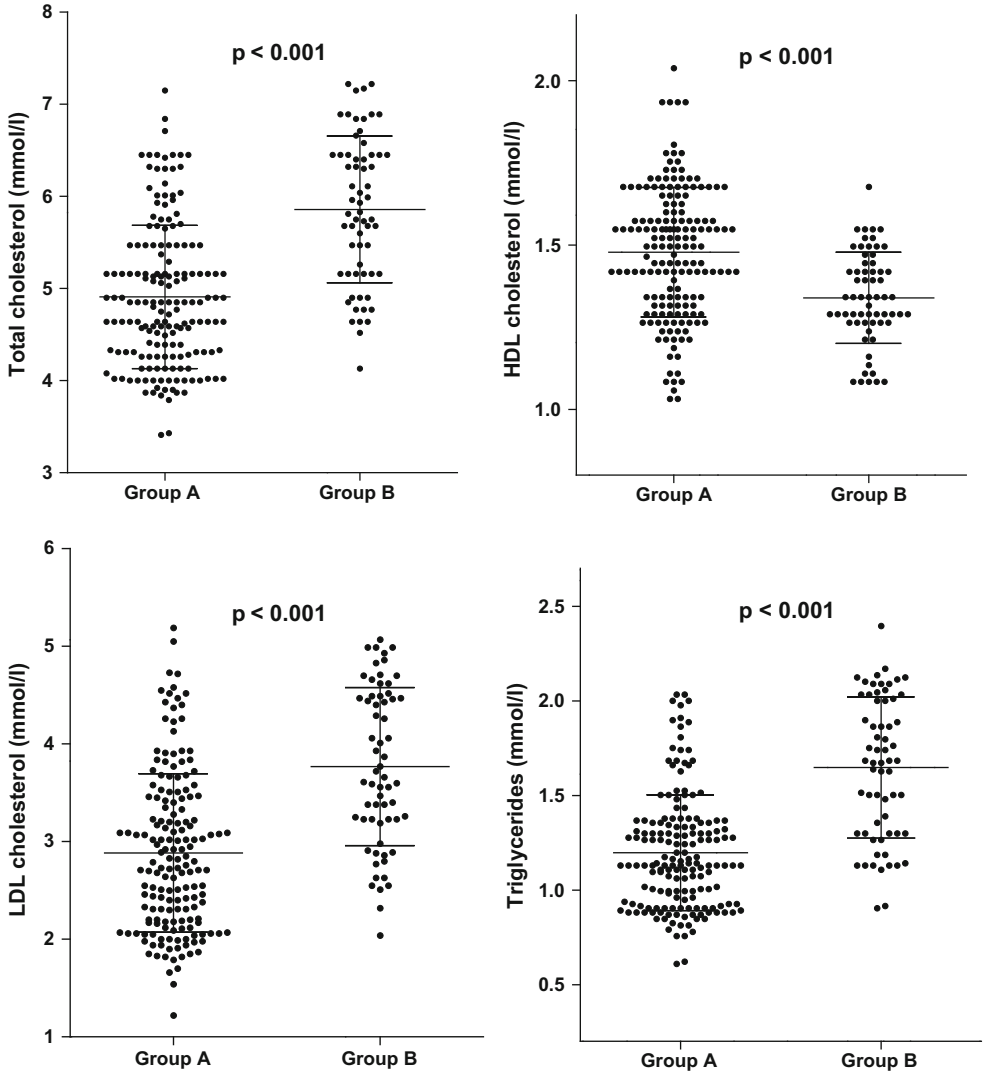

Fig. 2 Differences in lipid profile (total, HDL, LDL cholesterol, and triglyceride levels) between subjects with GH peak lower than cut-off of 31.8 μg/L and IGF-1 UNR lower than cut-off of 0.63 (Group A), and those with at least a value higher than the above-mentioned cut-off (Group B)

As expected, patients with high VAI were older, with higher BMI, and with worse lipid and glucose profile, and these data seem to be in agreement with those of Fieffe et al., which showed that age and BMI are significant risk factors of metabolic alterations and type 2 diabetes [53]. In addition, this group of subjects also showed lower peak of GH after GHRH–Arg test and lower IGF-I levels. In this view, the subjects with lower GH and IGF-I have more severe visceral adipose dysfunction. We found that the GH and IGF-I cut-off derived from ROC analysis resulted in higher values than those recognized as diagnostic for adult GHD. The cut-off found is associated with a better and satisfactory area under the ROC curve to detect with a good accuracy the subjects with high VAI. Then the parameters GH peak and IGF-I resulted as having a comparable good sensitivity and specificity to detect a condition of cardiometabolic risk to that of other metabolic parameters associated with this risk, as Homa-IR, ISI Matsuda, lipid profile, and AUC of glucose and insulin during OGTT. These data have been confirmed when we grouped the subjects in relation to GH and IGF-I levels below or beyond the above-mentioned cut-off. In fact, the 63 subjects who had both GH and IGF-I levels below the established cut-off, predominantly of male gender and older, showed higher VAI and a worse cardiometabolic profile, in terms of higher systolic and diastolic blood pressure, higher glucose and insulin levels, lower degree of insulin sensitivity, and worse lipid profile.

In our hypothesis, the existence of continuum of GH peak responses to stimulation test between the normal peak and those recognized as diagnostic for severe GHD could clarify these findings. If the overt adult GHD is associated with a well-known clinical syndrome characterized by altered body composition, reduced bone mineralization, unfavorable lipid profile, reduced cardiac performance, early atherosclerosis, and impaired quality of life [1, 7, 54], we demonstrated that some clinical feature of this syndrome may also be present with GH levels much higher than those used for the diagnosis of adult GHD, outlining a condition of subclinical GHD. In previous studies, performed both in children and adults, the condition of partial GHD, which are in between the severe GHD and the normal GH secretion, is associated with abnormal growth velocity, body composition, insulin sensitivity, and cardiometabolic risk [55–57]. Even if partial or subclinical GHD in adults is not recognized as a clinical entity [39], the current study supports initial findings that show metabolic alterations even in subjects with GH values that do not meet the diagnostic criteria for overt GHD. We found a well highest percentage of high VAI than MS in our population, supporting the finding that high VAI identifies an early condition of cardiometabolic risk, even without an overt MS. These data are of greater value if we consider that the study population is resident in southern Italy, where the prevalence of MS is higher than in other regions, but this could also be a limitation of the current study, given that the prevalence of IFG, IGT, DM, and overweight in our population was found to be slightly greater.

In conclusion, a strong relationship among GH axis, VAI and cardiometabolic risk has been demonstrated in this cohort of subjects. A percentage of 27.3 % of apparently healthy subjects show a degree of visceral adipose dysfunction associated with GH and IGF-I levels without overt GHD. Long-term prospective studies could help to clarify and confirm whether a hypothetical condition of subclinical GHD in adults could be taken into account as a new clinical entity.

Author statement The authors hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere. By signing this letter, each of us acknowledges that he or she participated sufficiently in the work to take public responsibility for its content. This work will not be submitted for publication elsewhere until the editorial board has decided whether to publish the article.

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