Visceral Adiposity Index Is Associated with Insulin Sensitivity and Adipocytokine Levels in Newly Diagnosed Acromegalic Patients

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Context: The visceral adiposity index (VAI) has proved to be a marker of visceral adipose dysfunction, strongly associated with insulin sensitivity in both the general and specific populations of patients at metabolic risk.

Objective: The objective of the study was to test VAI as a useful tool to assess early metabolic risk in acromegaly.

Patients: Twenty-four newly diagnosed acromegalic patients (11 women and 13 men, aged 54.9 ± 13.6 yr) were grouped into those with normal (group A, n = 13, 54.2%) and those with high VAI (group B, n = 11, 45.8%).

Outcome Measures: Glucose, hemoglobin A1c, nadir and area under the curve (AUC) of GH (AUC_{GH}) during the oral glucose tolerance test, $AUC_{Cpeptide}$ during a mixed-meal tolerance test, M value during euglycemic-hyperinsulinemic clamp, oral dispositional index (DIo), each component of the metabolic syndrome, leptin, adiponectin, TNF-α, and IL-6.

Results: The VAI value was positively correlated with the age of patients ($\rho = 0.408$; $P = 0.048$), tumor volume ($\rho = 0.638$; $P = 0.001$), basal GH ($\rho = 0.622$; $P = 0.001$), nadir GH ($\rho = 0.534$; $P = 0.007$), AUC_{GH} ($\rho = 0.603$; $P = 0.002$), IGF-I ($\rho = 0.618$; $P = 0.001$), TNF-α ($\rho = 0.512$; $P = 0.010$), and $AUC_{Cpeptide}$ ($\rho = 0.715$; $p<0.001$) and negatively with adiponectin ($\rho = -0.766$; $P < 0.001$), M value ($\rho = -0.818$; $P < 0.001$), and DIo ($\rho = -0.512$; $P = 0.011$). Patients with high VAI showed significantly higher basal GH levels ($P = 0.018$), AUC_{GH} ($P = 0.047$), IGF-I ($P = 0.047$), $AUC_{Cpeptide}$ ($P = 0.018$), lower M value ($P < 0.001$), DIo ($P = 0.006$), and adiponectin levels ($P < 0.001$), despite the absence of a significantly higher prevalence in the overt metabolic syndrome and glucose tolerance abnormalities. AUC_{GH} proved to be the main independent factor influencing VAI.

Conclusions: In acromegaly, VAI appears to be associated with disease activity, adiponectin levels, and insulin sensitivity and secretion and is influenced independently by GH levels. VAI could therefore be used as an easy and useful new tool in daily clinical practice for the assessment of early metabolic risk associated with active acromegaly. **(*J Clin Endocrinol Metab* 97: 2907–2915, 2012)**

Growth hormone (GH) is a counterregulatory hormone that antagonizes the hepatic and peripheral metabolic effects of insulin, involving the stimulation of gluconeogenesis and lipolysis, which results in increased blood glucose and free fatty acid levels (FFA) (1, 2). GH mainly exerts its lipolytic effect in adipose tissue, by increasing adipose tissue hormone-sensitive lipase activity and resulting in an alteration in adipose tissue distribution

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Abbreviations: AUC, Area under the curve; BMI, body mass index; CV, coefficient of variation; DBP, diastolic blood pressure; DIo, oral disposition index; FFA, free fatty acids; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; MMTT, mixed-meal tolerance test; MRI, magnetic resonance imaging; MS, metabolic syndrome; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; ULN, upper limit of the normal; VAI, visceral adiposity index; WC, waist circumference.

and increased FFA flux from adipose to peripheral tissues (3). In acromegaly, the lipolytic and insulin-antagonistic effects of GH may alter adipose tissue distribution. Increasing GH/IGF-I levels are associated with a smaller proportion of total adipose tissue, and a negative correlation between insulin sensitivity and sc, im, and total adipose tissue was detected (4). Recently, we proposed a sex-specific mathematical index, the visceral adiposity index (VAI), based on simple anthropometric and metabolic parameters, as a surrogate marker of adipose tissue function and distribution independently correlated with cardiometabolic risk in the general population (5). VAI showed a strong association with both insulin sensitivity (evaluated with a euglycemic-hyperinsulinemic clamp) and visceral adipose tissue [measured with magnetic resonance imaging (MRI)] (5). Furthermore, circulating concentrations of inflammatory adipocytokines are recognized to be the most important factor in causing and maintaining insulin resistance (IR) as well as a rise in FFA levels (6). In our hypothesis, insulin sensitivity, lipolytic activity, and adipocytokine production, which play a main role in the genesis of cardiovascular sequelae in the general population (7–9), may be indirectly represented by VAI. The aim of this study was to test VAI as a useful new tool to assess early metabolic risk in patients with active acromegaly and to evaluate its association with adipocytokine levels and insulin sensitivity and secretion parameters.

Patients and Methods

For the purpose of the study, we enrolled 24 patients (13 males and 11 females; aged 54.9 ± 13.6 yr, range 33–78 yr) with active newly diagnosed acromegaly, who presented at the Endocrinology Section of the University of Palermo from January 1, 2004, to December 31, 2011. Patients with mixed GH/prolactin-secreting adenoma, previously treated with acromegaly therapy (surgery, somatostatin analogs, dopamine agonist, or pegvisomant) or with deficiency of one or more anterior pituitary hormones were excluded from this study. Activity of disease at the time of the study was confirmed by plasma mean GH profile, elevated age- and gender-corrected plasma IGF-I levels, and nonsuppressible GH after an oral glucose tolerance test (OGTT) (10). In all patients, MRI scan revealed the presence of a pituitary tumor. Tumor volume was calculated in line with the Di Chiro and Nelson formula (volume = height × length × width × π/6) and was expressed as cubic millimeters. The mean duration of the disease was established by patient interview, patient clinical pictures, and onset of osteoarticular symptoms. At the time of hospitalization, all patients signed a consent form for the scientific use of their data after a full explanation of the purpose of the study. This study was approved by the Institutional Review Board of the Faculty of Medicine, University of Palermo, and the identity of the participants remained anonymous during database analysis.

Study design

Body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in all patients. WC was measured at the midpoint between the lower rib and the iliac crest. After an overnight fast, lipid profile [total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol and triglycerides (TG)], hemoglobin A1c (HbA1c), mean fasting plasma GH (at least three blood samples at 30-min intervals), and IGF-I levels were measured. To normalize IGF-I for age in individual patients, we calculated the ratio between the IGF-I level and the upper limit of the normal (ULN) range for age (normal ≤ 1), and the data are presented as IGF-I ULN. OGTT was performed by measuring plasma blood glucose, insulin, and GH levels every 30 min for 2 h after a 75-g oral glucose load, and the area under the curve (AUC) of GH (AUC_{GH}) was calculated. Insulin sensitivity was tested with the euglycemic-hyperinsulinemic clamp (11). The clamp was performed under standard conditions, *i.e.* infusion of an insulin priming of 160 mU/m^2 body surface for the first 4 min of the test, followed by 40 mU/m^2 for the remaining 116 min; the rate of peripheral glucose utilization (M value) was calculated by dividing the glucose amount infused during the last 40 min by body weight measured in kilograms (milligrams per kilogram per minute). Under the steady-state conditions of euglycemia, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue sensitivity to exogenous insulin. β-Cell function was accurately and directly determined by measuring serum C-peptide levels before and after the standard mixed-meal tolerance test (MMTT) (12). A liquid meal (6 mg/kg up to a maximum of 360 ml) of Ensure Plus (25 g protein, 80.8 g carbohydrate, 20.6 g fat) was given after a 12- to 14-h overnight fast. Blood was drawn every 30 min for 120 min during the MMTT for the determination of glucose and C-peptide levels, and the AUC of C-peptide ($AUC_{Cpeptide}$) was calculated. In addition, β-cell function relative to insulin sensitivity, assessed by oral disposition index (DIo) (13), was evaluated.

To avoid significant gaps in time between the various tests, we routinely applied to all subjects our internal protocol of management of newly diagnosed acromegalic patients, which performs the OGTT during first access (baseline). If the diagnosis of acromegaly is confirmed, we plan the euglycemic-hyperinsulinemic clamp 1 wk after the baseline and the MMTT 2 wk after the baseline. VAI was calculated as described (5), using the following formulas differentiated according to sex, where TG levels are expressed in millimoles per liter and HDL is HDL-cholesterol levels expressed in millimoles per liter: for males, VAI = [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL); for females, VAI = [WC/36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL).

According to specific age-stratified cutoff points of VAI identifying patients with presumed visceral adipose dysfunction and cardiometabolic risk (14), we divided the patients into two groups: those with normal (group A, 13 patients) and those with high VAI (group B, 11 patients). The appropriate cutoff points of VAI used were the following: 2.52 for subjects under 30 yr, 2.23 for those aged between 30 and 42 yr, 1.92 between 42 and 52 yr, 1.93 between 52 and 66 yr, and 2.00 for subjects over 66 yr. In addition, to obtain better evaluation of adipose function, in all patients we measured serum levels of four circulating adipocytokines: leptin, adiponectin, IL-6, and TNF-α. All samples (for glycemia, HbA1c, lipid profile, insulin, C-peptide, GH, and

IGF-I) were immediately analyzed after the tests were performed in each individual after an overnight fast. Serum samples to be used for the adipocytokine determinations were kept frozen at −20 C until assayed at the end of the study.

Patients with a previous diagnosis of diabetes mellitus, already treated, were excluded from this study to avoid the impact of the treatment on metabolic parameters and because of their inability to perform the OGTT. At the time of the study, patients diagnosed after the OGTT as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) were treated with a controlled diet only after the completion of the study design to avoid the impact of strict adherence to diet on the results of the study and to evaluate the main role of GH on metabolic parameters. No patients with previous diagnosis of IFG or IGT recruited in the study were already receiving dietary or pharmacological treatment.

Among the patients affected by increased blood pressure, those with a previous diagnosis of hypertension (70%) received pharmacological treatment with sartans (58%) or angiotensin-converting-enzyme inhibitors (42%). The patients diagnosed as having systolic or diastolic hypertension for the first time at the time of the diagnosis of acromegaly did not receive any specific treatment until the end of the study design period (2 wk), during which they underwent intensive blood pressure control.

Among the dyslipidemic patients, those with a previous diagnosis (43%) had never received specific treatment. We first diagnosed dyslipidemia in four patients who had never received any dietary or pharmacological treatment until the end of the study protocol to avoid the impact of the treatment on metabolic parameters.

Hormone and biochemical assays

All biochemical data were collected after overnight fasting. Glycemia, HbA1c, and lipid levels were measured in our centralized accredited laboratory with standard methods. During the entire study period, GH samples from all subjects were run in the same immunoradiometric assay (Radium, Pomezia, Italy). The sensitivity of the assays was 0.05 μg/liter. The average intra- and interassay coefficients of variation (CV) were 4.5 and 7.9%, respectively. Serum IGF-I was measured using immunoradiometric assays (Diagnostic System Laboratories Inc., Webster, TX). The normal ranges (for age) were 180–625 and 151–530 (≤20), 118–475 and 118–450 (21–30), 102–400 and 100–390 (31–40), 100–306 and 96–228 (41–50), 95–270 and 90–250 (51–60), 88–250 and 82–200 (61–70), and 78–200 and 68–188 (≥70) μg/liter for men and women, respectively. The sensitivity of the assay was 0.8 μg/liter. The intra- and interassay CV were 3.4, 3.0, and 1.5% and 8.2, 1.5, and 3.7% for low, medium, and high points on the standard curve, respectively.

Serum insulin was measured by ELISA (DRG Instruments GmbH, Marburg, Germany). The sensitivity of the method was 1 IU/ml. The normal insulin range was 5–19 IU/ml. Serum C-peptide was measured by ELISA (DRG Instruments). The sensitivity of the method was 0.064 ng/ml. The intra- and interassay CV were 5.1–6.7% and 8.3–9.9%, respectively. The assays for the assessment of IGF-I, insulin, and C-peptide were constant during the entire period of the study. Circulating leptin and adiponectin were measured using ELISA kits from SPI bio (Montigny le Bretonneux, France). For leptin, the limit of sensitivity was 0.5 ng/ml, and the intra- and interassay CV were 3.0–7.5 and 3.2–9.2% at leptin levels of 3.5–25.5 and 5.4–25.1 ng/ml, respectively. For adiponectin, the limit of sensitivity was 0.7 μg/ml, and the intra- and interassay CV were 6.4–7.0 and 7.3–8.2% at adiponectin levels of 7.1–21.1 and 5.2–17.7 μg/ml, respectively. TNF-α was measured by ELISA (Amersham human TNF-α, Biotrak Easy ELISA; GE Healthcare, Piscataway, NJ). The sensitivity of the method was 2.5 pg/ml. The overall intra- and interassay CV were 6.0 and 9.3%, respectively. IL-6 was measured by ELISA (human IL-6 ultrasensitive; Invitrogen, Camarillo, CA). The sensitivity of the method was less than 104 fg/ml. The intra- and interassay CV were 4.7–8.3 and 6.7–10%, respectively.

Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± SD or as median and interquartile range for continuous variables; rates and proportions were calculated for categorical data. The normality of distribution of the quantitative variables was assessed by means of the Kolmogorov-Smirnov test). The differences between the two groups of patients (with normal or high VAI) were evaluated with the Mann-Whitney *U* test. Simple univariate correlations among continuous variables without normal distribution were determined by Spearman's test, the nonparametric equivalent for Pearson's test. To evaluate the independent variables influencing the VAI in all acromegalic patients, a linear regression model was performed. A P value <0.05 was considered statistically significant.

Results

The clinical and biochemical features of patients are shown in Table 1.

In the entire cohort of patients, the mean VAI value was 1.9 ± 0.8. Thirteen patients (54.2%) were classified as having normal VAI (group A), whereas 11 (45.8%) had high VAI (group B). No age, gender, or BMI difference was found between the two groups. Group B showed significantly higher basal GH [3.2 (3.10–3.6) *vs.* 3.3 (1.20–9.70) μg/liter; $P = 0.018$], AUC_{GH} [3700 (525–4230) *vs.* 763 (345–997); $P = 0.047$], and IGF-I ULN levels [2.40 (1.40–3.50) *vs.* 1.61 (1.03–2.16); $P = 0.047$] than group A, whereas no difference was found in nadir GH, tumor size, and duration of disease. Group B also showed a higher prevalence of family history for diabetes (10 *vs.* 4%; $P = 0.005$) (Table 2).

Using the National Cholesterol Education Program Adult Treatment Panel III criteria (15), in the whole cohort of patients, the metabolic syndrome (MS) was found in six patients (25%). Specifically, 17 patients (70.8%) had systolic hypertension, 13 (54.2%) had diastolic hypertension, seven (29.2%) were affected by hypertriglyceridemia, 10 (41.7%) showed increased WC, and seven (29.2%) had low HDL-cholesterol levels (Table 1). No difference in MS as a whole and in each of its components was reported between the two

TABLE 1. Clinical and biochemical features of all acromegalic patients

	Mean ± SD or [n (%)]
Age (yr)	54.9 ± 13.6
BMI (kg/m^2)	27.9 ± 1.6
Gender	
Males	13 (54.2)
Females	11 (45.8)
Family history for diabetes	14 (58.3)
Duration of disease (months)	58 ± 27.2
Tumor volume (mm^3)	1310 ± 660
Basal GH (μg/liter)	13.8 ± 14.6
Nadir GH (μg/liter)	13.2 ± 13.9
AUC_{GH}	1779 ± 1806
IGF-I (ULN)	2 ± 0.8
MS	6 (25)
Increased WC	10 (41.7)
Hypertriglyceridemia	7 (29.2)
Low HDL-cholesterol	7 (29.2)
Increased SBP or specific treatment	17 (70.8)
Increased DBP or specific treatment	13 (54.2)
Normal glucose tolerance	6 (25)
IFG	11 (45.8)
IGT	7 (29.2)
IFG + IGT	
Diabetes mellitus	
Fasting glucose (mmol/liter)	5.8 ± 0.6
Fasting insulin (UI/ml)	19.1 ± 16.7
M value (clamp)	2.69 ± 0.88
$AUC_{Cpeptide}$ (MMTT)	491 ± 251
DIo	1.05 ± 0.94
HbA1c (%)	5.7 ± 0.4
VAI	1.9 ± 0.8
Leptin (ng/ml)	8.15 ± 8.52
Adiponectin (μg/ml)	8.78 ± 4.56
TNF-α (ng/ml)	2.10 ± 1.40
IL-6 (pg/ml)	1.63 ± 0.59

groups, with the exception of the prevalence of systolic hypertension, which was significantly higher in group B (11 *vs.* 6%; $P = 0.006$) (Table 2).

Six of 24 patients (25%) were classified as having normal glucose tolerance, 11 (45.8%) IFG, and seven (29.2%) IGT. No patient had overt diabetes mellitus, according to the medical guidelines of the American Association of Clinical Endocrinologists (16) (Table 1). No difference in each category of glucose tolerance was found between the two groups, with the exception of a significantly higher prevalence of IGT in group B ($P = 0.001$). No difference between the two groups of patients was found in fasting glucose and HbA1c levels. The patients of group B showed higher $AUC_{Cpeptide}$ [769 (331–821) *vs.* 351 (279–421); $P = 0.018$] and lower M value [1.65 (1.42–2.70) *vs.* 3.30 (3.14–4); $P < 0.001$], DIo [0.39 (0.29–0.56) *vs.* 1.43 (0.44–2.50); $P = 0.006$], and adiponectin [4 (3.40–7.20) *vs.* 10.50 (9.10–15.95) μg/ml; $P < 0.001$] than those of group A, whereas no difference was found in leptin, TNF-α, and IL-6 levels (Figs. 1 and 2).

The differences in the clinical and biochemical features between group A and group B are shown in Table 2.

In univariate analysis, VAI was found to be directly correlated with age of patients ($\rho = 0.408$; $P = 0.048$), tumor volume ($\rho = 0.638$; $P = 0.001$), basal GH ($\rho = 0.622$; $P = 0.001$), nadir of GH ($\rho = 0.534$; $P = 0.007$) and AUC_{GH} ($\rho = 0.603$; $P = 0.002$) during OGTT, IGF-I ULN ($\rho = 0.618$; $P = 0.001$), and $AUC_{Cpeptide}$ ($\rho = 0.715$; <0.001) and inversely correlated with M value ($\rho = -0.818$; $P < 0.001$) and DIo ($\rho = -0.512$; $P = 0.011$). In addition, a strongly significant inverse correlation was found between VAI and adiponectin ($\rho = -0.766$; $P < 0.001$), whereas a significant direct correlation was found between VAI and TNF-α levels ($\rho = 0.512$; $P = 0.010$). No correlation was found with leptin and IL-6 (Table 3). In multivariate analysis, AUC_{GH} (B 0.677; $P = 0.001$) and the family history for diabetes (B 0.386; $P = 0.010$) were the only variables independently associated with VAI (Table 4).

Discussion

We analyzed the visceral adipose function, insulin sensitivity and secretion indexes, and adipocytokine levels in a group of newly diagnosed acromegalic patients. Our data show that VAI is independently influenced by GH levels. Patients with high VAI show decreased insulin sensitivity and seem to be less able to compensate the status of IR through an adequate increased insulin secretion. In our hypothesis, the lipotoxicity secondary to the lipolytic action of GH may be clinically expressed by VAI. In fact, in acromegaly, a lipotoxic condition has been described. Freda *et al.* (4) showed increased im adipose tissue despite a reduction in visceral and sc adipose tissue in 24 adults with active acromegaly compared with healthy subjects, and this finding might be associated with GH-induced IR. Our data showed a strong association between VAI and the rate of peripheral glucose utilization (M value) as in the general population (5). Furthermore, higher VAI showed a strong independent association with both cardiovascular and cerebrovascular events and better predictive capacity for the onset of diabetes events than its individual components (WC, BMI, TG, and HDL) (5, 17). This index has already been studied in specific populations of patients; in those with genotype 1 chronic hepatitis C and in those with nonalcoholic fatty liver disease, visceral adipose dysfunction identified by a higher VAI score proved to be independently associated with both steatosis and necroinflammatory activity, and fibrosis (18, 19) in women with polycystic ovary syndrome, VAI has proved to be an easy and useful tool for the assessment of cardio-

TABLE 2. Clinical and biochemical features of patients grouped according to VAI into those with normal (group A) or high VAI (group B)

	Acromegalic patients with normal VAI (group A) n = 13 (54.2%)	Acromegalic patients with high VAI (group B), n = 11 (45.8%)	*P*
Age (yr)	57 (46.50–69)	50 (45–62)	0.392
BMI (kg/m^2)	27.8 (26–29.10)	28 (27–30)	0.331
Gender [n (%)]			0.217
Males	9 (69.2)	4 (36.4)	
Females	4 (30.8)	7 (63.6)	
Family history for diabetes [n (%)]	4 (30.8)	10 (90.9)	0.005
Duration of disease (months)	64 (26–76)	62 (15–90)	0.820
Tumor volume (mm^3)	1200 (600–1425)	1800 (500–2400)	0.082
Basal GH (μg/liter)	3.3 (1.20–9.70)	32 (3.10–36)	0.018
Nadir GH (μg/liter)	5.50 (2–8.80)	19 (2.10–35)	0.082
AUC_{GH}	763 (345–997)	3700 (525–4230)	0.047
IGF-I (ULN)	1.61 (1.03–2.16)	2.40 (1.40–3.50)	0.047
MS [n (%)]	3 (23.1)	3 (27.3)	1
Increased WC [n (%)]	4 (30.8)	6 (54.5)	0.408
Hypertriglyceridemia [n (%)]	3 (23.1)	4 (36.4)	0.659
Low HDL-cholesterol [n (%)]	3 (23.1)	4 (36.4)	0.659
Increased SBP or specific treatment [n (%)]	6 (46.2)	11 (100)	0.006
Increased DBP or specific treatment [n (%)]	8 (61.5)	5 (45.5)	0.431
Normal glucose tolerance [n (%)]	5 (38.5)	1 (9.1)	0.166
IFG [n (%)]	8 (61.5)	3 (27.3)	0.123
IGT [n (%)]	0	7 (63.6)	0.001
IFG + IGT	0	0	
Diabetes mellitus	0	0	
Fasting glucose (mmol/liter)	6.16 (5.58–6.49)	5.94 (4.72–6.33)	0.082
M value (clamp)	3.30 (3.14–4)	1.65 (1.42–2.70)	<0.001
$AUC_{Cpeptide}$ (MMTT)	351 (279–421)	769 (331–821)	0.018
DIo	1.43 (0.44–2.50)	0.39 (0.29–0.56)	0.006
HbA1c (%)	5.8 (5.45–5.90)	5.70 (5.10–6.70)	0.392
Leptin (ng/ml)	4.80 (2.80–18.45)	6.10 (2.40–9.60)	0.865
Adiponectin (μg/ml)	10.50 (9.10–15.95)	4 (3.40–7.20)	<0.001
TNF-α (ng/ml)	1.30 (1.05–3.05)	3.30 (1.10–4)	0.082
IL-6 (pg/ml)	1.72 (1.35–2.07)	1.48 (1.06–1.80)	0.252

Unless indicated otherwise, results are shown as median (interquartile range).

metabolic risk associated with the oligomenorrheic phenotype (20).

In our cohort of patients, VAI proved to be strongly correlated with both GH and IGF-I levels and also with tumor volume. As expected, patient age seems to be an additional factor correlated with VAI, and these data seem to be in agreement with those of Fieffe *et al.* (21), who showed that age and BMI are significant risk factors of type 2 diabetics.

In this view, older patients and those with higher hormonal levels have more severe visceral adipose dysfunction. Interestingly, the prevalence of high VAI in our acromegalic patients was about twice that of the general population (45.8 *vs.* 22.78%) (14). Surprisingly, no difference in MS as a whole and in each of its components, except for systolic hypertension, was reported between the two groups of patients. A possible explanation might lie in the fact that the early stages of metabolic alterations are not highlighted by the classic criteria, whereas VAI seems to be able to show early signs of metabolic risk in patients without overt MS, because the variables are treated as continuous variables and not as dichotomous.

Regarding the increased systolic blood pressure in the group of patients with high VAI, these patients also showed higher GH and IGF-I levels and had a lower degree of insulin sensitivity. In our hypothesis, both the higher insulin levels, known to be associated with increased blood pressure levels in the general population, and higher GH levels, in concert with IGF-I, could have a main impact for the pathogenesis of sodium retention in acromegaly (22, 23).

Although patients with high VAI were less insulin sensitive, no significant difference in the glucose tolerance categories, except for IGT, was reported between the two groups of patients. This finding supports the hypothesis that VAI shows the early signs of metabolic risk in patients, although a significant reduction in glucose tolerance has not yet occurred. The majority of studies assessed the insulin secretion rate by measurement of insulin levels during OGTT, even though endogenous insulin secretion

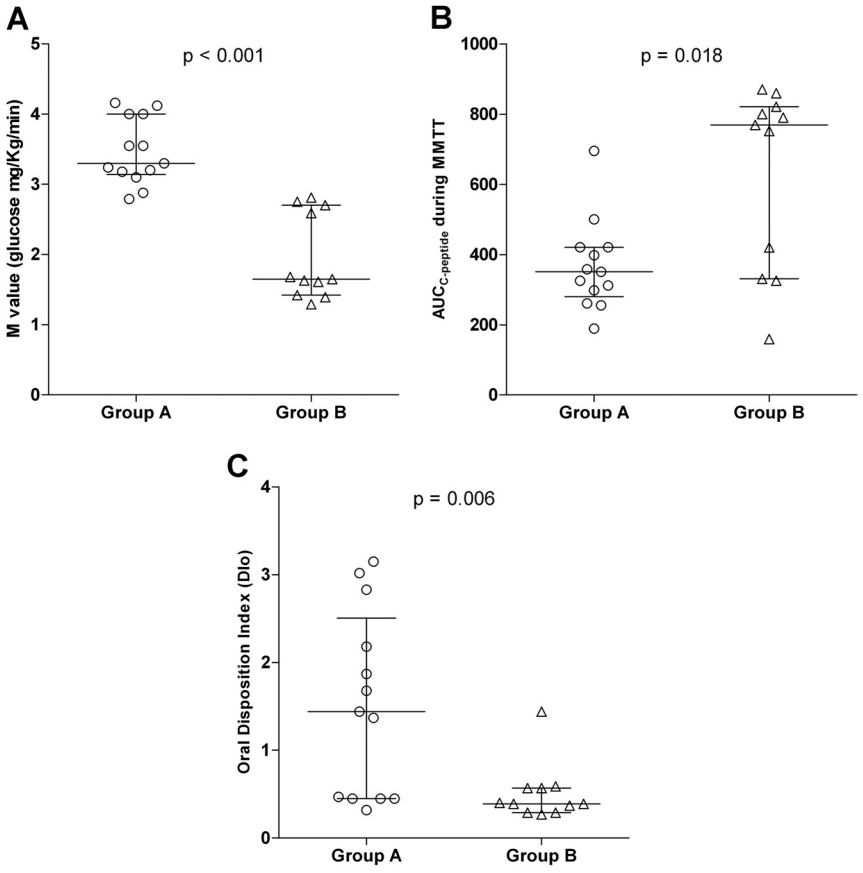

FIG. 1. Insulin-sensitivity and insulin-secretion indexes in acromegalic patients in relation to VAI. A, M value during euglycemic-hyperinsulinemic clamp in patients with normal and high VAI; B, $AUC_{C\text{-}peptide}$ during MMTT in patients with normal and high VAI; C, DIo in patients with normal and high VAI.

is assessed more efficiently by the measurement of C-peptide, which is cosecreted with insulin in a one-to-one molar ratio but, unlike insulin, undergoes poor first-pass clearance by the liver. Measurement of C-peptide provides a sensitive, well-accepted, and clinically validated assessment of β-cell function (24), and the gold standard measure of insulin secretion, represented by the measurement of the C-peptide during MMTT (12), has very rarely been used to assess insulin secretion in acromegaly (25).

The higher $AUC_{Cpeptide}$ in patients with high VAI might represent a compensatory mechanism to avoid clear glucose tolerance worsening. For a better evaluation of the ability of β-cells to adequately compensate the insulin resistance through increased insulin secretion, we also calculated DIo, which has been shown to predict the development of diabetes in adults (13). Patients with high VAI, despite higher $AUC_{Cpeptide}$, showed lower DIo, demonstrating inadequate insulin secretion relative to insulin sensitivity degree.

Our group recently also showed that active acromegaly is strongly associated with visceral adiposity dysfunction, and both somatostatin analogs and surgical therapies are able to improve it, as demonstrated by the significant VAI decrease after 12 months of therapy (26). However, this study was limited by the lack of data on adipocytokine assessment and evaluation of insulin sensitivity through the gold standard hyperinsulinemic-euglycemic clamp, because insulin sensitivity has been examined using these methods in only a minority of studies and in smaller cohorts of patients (27–30). We therefore analyzed cytokine (leptin and adiponectin) and proinflammatory (TNF-α and IL-6) activity to establish whether adipose function plays a main role in determining metabolic alterations in acromegalic patients and whether this can be adequately expressed by VAI. In this regard, data regarding adipocytokine levels in active acromegaly available in the literature are controversial, and the evaluation of a possible relationship between GH levels, adipose function, and insulin sensitivity has been poorly investigated.

In our study, patients with high VAI had lower adiponectin levels and consequently less protection against both IR and cardiometabolic risk (31–33). A few years ago, a correlation between leptin levels and BMI in acromegalic patients was found but with controversial data (34, 35). In our opinion, the leptin levels in our study did not show any significant correlation with VAI because leptin should be considered as an indirect index of overall adipose tissue, secreted by adipocytes in proportion to total adipocyte tissue mass, without a correlation with the quality of fat (36). In fact, a correlation between leptin levels and sc and total adipose tissue has been reported by other authors but without any correlation with GH and IGF-I levels (4).

A condition of hypoadiponectinemia in acromegaly was demonstrated (37), although Ronchi *et al.* (38) did not show any significant correlation between adiponectin and insulin sensitivity and resistance indexes. This is probably because insulin homeostasis was assessed by authors using homeostasis model assessment of IR index and quantitative insulin sensitivity check index and not the gold standard clamp (39).

In our patients, as expected, we found a positive correlation between TNF-α and VAI, suggesting a role of TNF-α as proinflammatory activity in visceral adipose dysfunction and IR, as already reported in the general

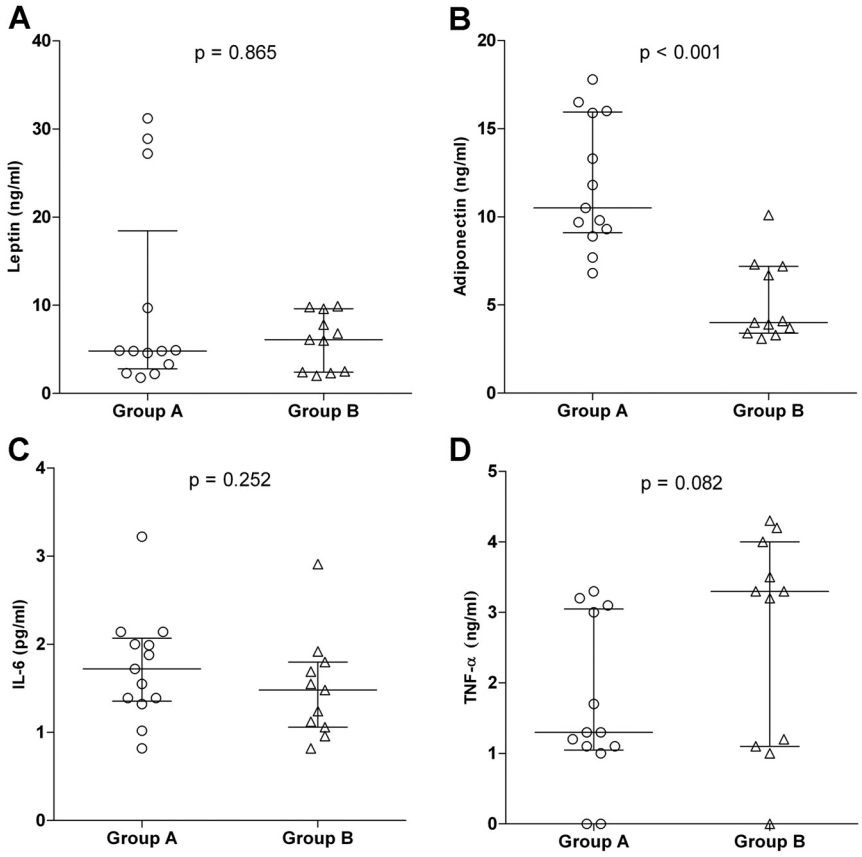

FIG. 2. Adipocytokine levels in acromegalic patients in relation to VAI. A, Leptin levels in patients with normal and high VAI; B, adiponectin levels in patients with normal and high VAI; C, IL-6 levels in patients with normal and high VAI; D, TNF-α levels in patients with normal and high VAI.

population (40). In our study, we did not find any significant correlation between IL-6 and all parameters evaluated. This datum is not surprising, because although a great deal of evidence implicates IL-6 in the development of IR, there is some conflicting evidence in the literature (41). The contribution of visceral adipose tissue to circulating levels of IL-6 seems modest (42), and the existing data in the literature about the role of IL-6 in acromegaly are extremely few (43).

A weakness of our study could be the limitation of the range of recruited acromegalic patients to a subgroup of patients with lower cardiovascular risk than a totally unselected group of acromegalic patients would have, because in our cohort, we did not have overt diabetic patients, although the data about VAI on acromegalic patients with different degrees of glucose abnormalities, including overt diabetes mellitus, are available in our previous paper (24).

Another limitation of our study is probably the lack of direct data on body composition, because MRI and computed tomography, to date considered the gold standard for the quantitative evaluation of visceral and sc adipose tissue (44), was not performed, because these two methods are extremely expensive and too complicated for use in routine practice.

We believe that it is important to clarify that the application of VAI as a marker of cardiometabolic risk could have some limitations, mainly relating to the presence of variables in the model that may change over time in relation to lifestyle and/or pharmacological treatment. Therefore, we suggest using VAI as an indicator of altered adipose function associated with cardiometabolic risk but without a predictive future role. Prospective large-scale studies aiming to consider the possible predictive value of VAI regarding cardiovascular risk must necessarily take into account its variation over time.

In conclusion, in active acromegaly, VAI, directly and independently influenced by GH levels and family history

TABLE 3. Correlation (univariate analysis) between VAI and disease parameters and insulin sensitivity and secretion indexes

Independent variables	Dependent variable: VAI	
	ρ	*P*
Age	0.408	0.048
Duration of disease	−0.328	0.118
Tumor volume	0.638	0.001
Basal GH	0.622	0.001
AUC_{GH}	0.603	0.002
GH nadir	0.534	0.007
IGF-I ULN	0.618	0.001
M value (clamp)	−0.818	<0.001
$AUC_{Cpeptide}$ (MMTT)	0.715	<0.001
DIo	−0.512	0.011
Leptin	0.257	0.225
Adiponectin	−0.766	<0.001
TNF-α	0.512	0.010
IL-6	−0.040	0.853

TABLE 4. Independent variables influencing VAI at multivariate analysis (multiple linear regression)

Independent variables	Dependent variable: VAI		
	β	SE	*P*
Age	0.165	0.010	0.238
AUC_{GH}	0.677	0	0.001
IGF-I ULN	0.024	0.160	0.904
Family history for diabetes[a]	0.386	0.190	0.010

[a] Categorical variable coded to binary (dummy) variables: no family history = 0; family history = 1.

for diabetes, may reflect a condition of cardiometabolic risk, characterized by altered production of adipocytokines, IR, and inadequate insulin secretion. Therefore, the routine use of this simple tool can show a degree of early cardiometabolic risk even in cases in which the overt MS and glucose abnormalities have not yet appeared.

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References

1. **Giustina A, Veldhuis JD** 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717–797
2. **Clemmons DR** 2002 Roles of insulin-like growth factor-I and growth hormone in mediating insulin resistance in acromegaly. Pituitary 5:181–183
3. **Szego CM, White** 1948 A The influence of purified growth hormone on fasting metabolism. J Clin Endocrinol Metab 8:594
4. **Freda PU, Shen W, Heymsfield SB, Reyes-Vidal CM, Geer EB, Bruce JN, Gallagher D** 2008 Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with growth hormone and insulin-like growth factor I excess due to acromegaly. J Clin Endocrinol Metab 93:2334–2343
5. **Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A; For the AlkaMeSy Study Group** 2010 Visceral Adiposity Index (VAI): A Reliable Indicator Of Visceral Fat Function Associated With Cardiometabolic Risk. Diabetes Care 33:920–922
6. **Boden G** 1997 Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes 46:3–10
7. **Mathieu P, Pibarot P, Larose E, Poirier P, Marette A, Després JP** 2008 Visceral obesity and the heart. Int J Biochem Cell Biol 40:821–836
8. **Taksali SE, Caprio S, Dziura J, Dufour S, Calí AM, Goodman TR, Papademetris X, Burgert TS, Pierpont BM, Savoye M, Shaw M, Seyal AA, Weiss R** 2008 High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 57:367–371
9. **Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH** 2000 Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. Am J Physiol Endocrinol Metab 278:E941–E948
10. **Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S. Acromegaly Consensus Group** 2010 A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95:3141–3148
11. **DeFronzo RA, Tobin JD, Andres R** 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–E223
12. **Greenbaum CJ, Mandrup-Poulsen T, McGee PF, Battelino T, Haastert B, Ludvigsson J, Pozzilli P, Lachin JM, Kolb H; Type 1 Diabetes Trial Net Research Group; European C-Peptide Trial Study Group** 2008 Mixed-meal tolerance test versus glucagon stimulation test for the assessment of β-cell function in therapeutic trials in type 1 diabetes. Diabetes Care 31:1966–1971
13. **Utzschneider KM, Prigeon RL, Faulenbach MV, Tong J, Carr DB, Boyko EJ, Leonetti DL, McNeely MJ, Fujimoto WY, Kahn SE** 2009 Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care 32:335–341
14. **Amato MC, Giordano C, Pitrone M, Galluzzo A** 2011 A Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis 10:183
15. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults** 2001 Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497
16. **Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, Hellman R, Jellinger PS, Jovanovic LG, Levy P, Mechanick JI, Zangeneh F; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force** 2007 American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 1(Suppl 1)3:1–68
17. **Bozorgmanesh M, Hadaegh F, Azizi F** 2011 Predictive performance of the visceral adiposity index for a visceral adiposity-related risk: type 2 diabetes. Lipids Health Dis 10:88
18. **Petta S, Amato M, Cabibi D, Cammà C, Di Marco V, Giordano C, Galluzzo A, Craxì A** 2010 Visceral adiposity index is associated with histological findings and high viral load in patients with chronic hepatitis C due to genotype 1. Hepatology 52:1543–1552
19. **Petta S, Amato MC, Di Marco V, Cammà C, Pizzolanti G, Barcellona MR, Cabibi D, Galluzzo A, Sinagra D, Giordano C, Craxì A** 2012 Visceral adiposity index is associated with significant fibrosis in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 35:238–247
20. **Amato MC, Verghi M, Galluzzo A, Giordano C** 2011 The oligomenorrhoic phenotypes of polycystic ovary syndrome are characterized by a high visceral adiposity index: a likely condition of cardiometabolic risk. Hum Reprod 26:1486–1494
21. **Fieffe S, Morange I, Petrossians P, Chanson P, Rohmer V, Cortet C, Borson-Chazot F, Brue T, Delemer B; French Acromegaly Registry** 2011 Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. Eur J Endocrinol 164:877–884
22. **Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M, Doucet A, Chanson P, Lombès M** 2008 Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. Endocrinology 149:3294–3305
23. **Horita S, Seki G, Yamada H, Suzuki M, Koike K, Fujita T** 2011 Insulin resistance, obesity, hypertension, and renal sodium transport. Int J Hypertens 2011:391762
24. **Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, Steffes MW** 2004 C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. Diabetes 53:250–264
25. **Parkinson C, Drake WM, Roberts ME, Meeran K, Besser GM, Trainer PJ** 2002 A comparison of the effects of pegvisomant and octreotide on glucose, insulin, gastrin, cholecystokinin, and pancreatic polypeptide responses to oral glucose and a standard mixed meal. J Clin Endocrinol Metab 87:1797–1804
26. **Giordano C, Ciresi A, Amato MC, Pivonello R, Auriemma RS, Grasso LF, Galluzzo A, Colao A** 25 November 2011 Clinical and metabolic effects of first-line treatment with somatostatin analogs or surgery in acromegaly: a retrospective and comparative study. Pituitary 10.1007/s11102-011-0365-5
27. **Higham CE, Rowles S, Russell-Jones D, Umpleby AM, Trainer PJ** 2009 Pegvisomant improves insulin sensitivity and reduces over-

night free fatty acid concentrations in patients with acromegaly. J Clin Endocrinol Metab 94:2459–2463
28. **Ertorer ME, Bakiner O, Anaforoglu I, Bozkirli E, Tutuncu NB, Demirag NG** 2007 Lanreotide autogel and insulin sensitivity markers: report of 5 acromegalic patients and literature review. Neuro Endocrinol Lett 28:727–733
29. **Lindberg-Larsen R, Møller N, Schmitz O, Nielsen S, Andersen M, Orskov H, Jørgensen JO** 2007 The impact of pegvisomant treatment on substrate metabolism and insulin sensitivity in patients with acromegaly. J Clin Endocrinol Metab 92:1724–1728
30. **Baldelli R, Battista C, Leonetti F, Ghiggi MR, Ribaudo MC, Paoloni A, D'Amico E, Ferretti E, Baratta R, Liuzzi A, Trischitta V, Tamburrano G** 2003 Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. Clin Endocrinol (Oxf) 59: 492–499
31. **Matsuzawa Y, Funahashi T, Kihara S, Shimomura I** 2004 Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 24: 29–33
32. **Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y** 2001 Circulating concentrations of the adipocyte protein adiponectin and decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 50:1126–1133
33. **Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA** 2001 Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86:1930–1935
34. **Damjanović SS, Petakov MS, Raicević S, Micić D, Marinković J, Dieguez C, Casanueva FF, Popović VJ** 2000 Serum leptin levels in patients with acromegaly before and after correction of hypersomatotropism by trans-sphenoidal surgery. J Clin Endocrinol Metab 85:147–154
35. **Tan KC, Tso AW, Lam KS** 2001 Effect of Sandostatin LAR on serum leptin levels in patients with acromegaly. Clin Endocrinol (Oxf) 54:31–35
36. **Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, Caro JF** 1996 Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334:292–295
37. **Lam KS, Xu A, Tan KC, Wong LC, Tiu SC, Tam S** 2004 Serum adiponectin is reduced in acromegaly and normalized after correction of growth hormone excess. J Clin Endocrinol Metab 89:5448–5453
38. **Ronchi CL, Corbetta S, Cappiello V, Morpurgo PS, Giavoli C, Beck-Peccoz P, Arosio M, Spada A** 2004 Circulating adiponectin levels and cardiovascular risk factors in acromegalic patients. Eur J Endocrinol 150:663–669
39. **Lorenzo C, Haffner SM, Stancáková A, Laakso M** 2010 Relation of direct and surrogate measures of insulin resistance to cardiovascular risk factors in nondiabetic finnish offspring of type 2 diabetic individuals J Clin Endocrinol Metab 95:5082–5090
40. **Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB** 1995 The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest 95:2111–2119
41. **Steensberg A, Fischer CP, Sacchetti M, Keller C, Osada T, Schjerling P, van Hall G, Febbraio MA, Pedersen BK** 2003 Acute interleukin-6 administration does not impair muscle glucose uptake or whole-body glucose disposal in healthy humans. J Physiol 548:631–638
42. **Tarantino G, Lobello R, Scopacasa F, Contaldo F, Pasanisi F, Cirillo M, De Caterina M, Conca P, Terracciano D, Gennarelli N, Ariello M, Mazzarella C, Grimaldi E, Macchia V** 2007 The contribution of omental adipose tissue to adipokine concentrations in patients with the metabolic syndrome. Clin Invest Med 30:E192–E199
43. **Bolanowski M, Daroszewski J, Zatonska K, Arkowska A** 2006 Circulating cytokines in relation to bone mineral density changes in patients with acromegaly. Neuro Endocrinol Lett 27:183–188
44. **Després JP** 2006 Is visceral obesity the cause of the metabolic syndrome? Ann Med 38:52–63