CLINICAL STUDY

Thigh intermuscular fat is inversely associated with spontaneous GH release in post-menopausal women with abdominal obesity

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Abstract

Context: The metabolic syndrome is characterized by an increased accumulation of visceral adipose tissue (VAT) and blunted GH secretion. There are, however, no data on the association between GH secretion and other fat depots (in liver and muscle).

Objective/design: The aim of this cross-sectional study, which included 20 post-menopausal women with abdominal obesity, was to determine the association between GH secretion and regional adipose tissue (AT) distribution. Twelve-hour GH profiles (2000–0800 h) were performed by blood sampling every 20 min. GH was analyzed using an ultra-sensitive assay followed by approximate entropy (ApEn) and deconvolution analysis.

Results: In simple regression analyses, both basal and pulsatile GH secretions correlated negatively with VAT and thigh intermuscular adipose tissue (IMAT), but not with hepatic fat content. There was no correlation between ApEn and the AT depots studied. In multiple regression analysis, pulsatile GH secretion correlated inversely with thigh IMAT (B -coefficient = -0.67 ; $P < 0.01$), whereas the correlation with VAT became non-significant. Furthermore, in multiple regression analysis, basal GH secretion correlated negatively with VAT (B -coefficient = -0.77 ; $P = 0.001$), but not significantly with thigh IMAT.

Conclusion: In post-menopausal women with abdominal obesity, pulsatile GH secretion demonstrated an independent, negative association with thigh IMAT, whereas basal GH secretion showed an independent, negative association with VAT. These findings suggest that the neuroendocrine association between fat mass and somatotrophic axis is depot-dependent. We have identified thigh IMAT to be important in this interplay.

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Introduction

Excess visceral adipose tissue (VAT) is a central feature of metabolic syndrome, which is associated with an increased risk of cardiovascular disease (CVD) (1) and diabetes mellitus type-2 (DM) (2). Increased visceral fat mass is also associated with blunted growth hormone (GH) secretion, and therefore a relative hyposomatotrophism is observed in viscerally obese subjects (3). Studies using highly sensitive GH assays, combined with deconvolution analysis and approximate entropy (ApEn) statistics, have provided new insights into the intricate regulation of GH release (4, 5). Using such a methodology, a study involving healthy subjects showed an inverse association between increased VAT and blunted GH secretion that was independent of age and gender (6). Assessment of body composition

using computed tomography (CT) or magnetic resonance imaging (MRI) has also contributed to the understanding of the impact of GH on regional fat distribution, both in acromegalic patients (7), who have reduced VAT and severe GH-deficient adults, who have increased VAT (8, 9). Fat infiltration of the liver and skeletal muscle is linked with insulin resistance and other metabolic perturbations characterizing metabolic syndrome, as in VAT (10, 11). An association between hepatic and/or muscle fat accumulation and GH secretion has, however, not been studied. We have examined the association between adipose tissue (AT) distribution (abdominal, hepatic and muscle fat depots) and the pattern of spontaneous GH secretion. Potential associations between GH secretion and metabolic risk factors were also studied.

Subjects and methods

Subjects

This was a cross-sectional study of 20 post-menopausal women with abdominal obesity. The criteria for inclusion were: age between 50 and 65 years, a body mass index of 25–35 kg/m², a serum insulin-like growth factor I (IGF-I) concentration between -1 and -2 s.d. scores, a waist:hip ratio of more than 0.85, and a sagittal diameter of more than 21.0 cm. All women were post-menopausal at least 1 year before the trial and had not received oestrogen replacement therapy in 6 months prior to the trial. The criteria for exclusion were overt DM, CVD, claudication intermit-tens, stroke, any malignancy, and other hormone treatment.

Study protocol Participants attended the outpatient clinic three times within a month, with at least 1 week between each visit. At the first visit, insulin sensitivity was assessed using a euglycaemic hyper-insulinaemic glucose clamp, after an overnight fast, as described previously (12). Body weight and CT measurements of body composition were also assessed during the first visit. At the second visit, participants were admitted to the clinic for a 12-h GH profile, with blood sampling every 20 min from 2000 to 0800 h. The patients were allowed to maintain their normal caffeine and/or tobacco consumption during the 12-h period. At the third visit, an oral glucose tolerance test (OGTT) was performed after an overnight fast. A standard dose of 75 g glucose was administered; plasma glucose was measured at baseline, 30, 60, 90 and 120 min. The criteria used to define normal and impaired glucose tolerance, and overt DM, were based on the Committee Report (1998) from the American Diabetes Association (13).

Ethical considerations

Informed consent was obtained from each patient before study entry. The study was approved by the Regional Ethical Review Board at the University of Gothenburg.

GH secretory status

The level of GH secretion was determined using deconvolution analysis, as described previously (14). A randomness score (ApEn ratio) was applied to quantify the pattern regularity of GH release (15). ApEn ratios approaching 1.0 denote greater secretory irregularity, whereas lower ApEn values imply greater regularity (16). The analysis was conducted blind to the time-series assignments.

Assessment of regional fat depots

Regional body fat was assessed using CT. Abdominal s.c. adipose tissue (SAT) and VAT in the fourth lumbar vertebra (L4) and SAT and intermuscular adipose tissue (IMAT) in the right thigh were measured. IMAT is the AT between the muscle bundles within the boundary of the muscle fascia. Tissue areas were quantified with the subject in a recumbent position with a General Electric High Speed Advantage CT system, version RP2 (GE Medical Systems, Milwaukee, WI, USA). Three scans were obtained from each participant. Scan 1 was obtained in the thigh region 1 cm below the gluteal fold, scan 2 at the L4 level, and scan 3 at the mid-liver level. In the case of scan 1, the tissue areas of the right leg are reported. The tissue areas were assessed as described previously (17). The effective radiation dose equivalent per examination was <0.8 mSv using a dose-reduction protocol (18).

The IMAT regions were manually corrected and distinguished by the operator when necessary. Attenuation of the liver and spleen was determined within three circular regions of interest located in the dorsal side of each organ. Attempts were made to avoid vessels, artifacts, and non-homogenous areas. Hepatic fat content was determined by measurement of liver attenuation (absolute values) and by the liver:spleen attenuation ratio. This ratio shows an inverse linear correlation with hepatic fat content, when determined using either histomorphometric (19) or biochemical methods (20). Cut-off values for the diagnosis of a fatty liver were considered to be a liver attenuation of ≤ 30 Hounsfield units (HU) or a liver:spleen ratio of <1 . We determined the mean muscle attenuation in HU in the right thigh. *In vivo* measurements using CT have shown that skeletal muscle attenuation is inversely associated with muscle lipid content (21).

Biochemical assays

All blood samples were centrifuged within 1 h of sampling and the serum was stored at -80°C until use. Plasma GH concentrations were analyzed using a highly sensitive chemiluminescence assay with a lower detectability limit of 0.002 $\mu\text{g/l}$ (at 2 s.d. above the assay blank) and 0.005 $\mu\text{g/l}$ (at 3 s.d. above the assay blank), as described (22).

The median intra- and inter-assay coefficients of variation (CV) values were $<7.5\%$. The serum concentration of IGF-I was determined by a hydro-chloric acid/ethanol extraction RIA using authentic IGF-I for labelling (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) with within-assay CV values of 2.2 and 4.2% at serum concentrations of 125 and 345 $\mu\text{g/l}$ respectively. The s.d. score for IGF-I was calculated from the predicted IGF-I values, adjusted for typical age and gender values obtained from the population. The IGF-binding protein I (IGFBP-I) was

determined by ELISA (Immunotech, Marseille, France). The GH-binding protein (GHBP) was also determined by ELISA and the sensitivity of the assay, as calculated for the mean $\pm$ 2 s.d., was 1.69 pmol/l. Intra-assay CV values were 5.6 and 3.2% at serum concentrations of 20.25 and 93.49 pmol/l respectively. Inter-assay CV values were 8.4 and 6.3%, at serum concentrations of 20 and 93.9 pmol/l respectively (Diagnostic Systems Laboratories, Inc., TX, USA). Serum insulin levels were determined by RIA (Pharmacia) and blood glucose was measured using the Gluco-quant method (Roche/Hitachi). HbA1c was determined by high-pressure liquid chromatography (Walters, Millipore AB, Waters, Sweden) and C-peptide levels were assessed using an immunoassay method (Dako Diagnostics Ltd, Dakopatt AB, Glostrup, Denmark). Free fatty acid (FFA) levels were determined using an enzymatic colorimetric method (NEFAC; Waco, Neuss, Germany). Oestradiol levels were determined by RIA (DiaSorin, Stillwater, MN, USA). Lipid parameters were determined by routine laboratory measurements as described (23).

Statistical analysis

All calculations were performed using STATISTICA for Macintosh, version 4.1 (StatSoft, Inc., Scandinavia, Uppsala, Sweden). All descriptive statistical results are presented as the mean $\pm$ s.e.m. All the variables were tested for normality using the Kolmogorov–Smirnov test. Variables with non-normal distribution were transformed logarithmically before analysis. The Pearson product–moment correlation coefficient was calculated to determine whether associations existed between any of the regional fat depots and any measure of basal or pulsatile GH secretion, and other metabolic variables. Two multiple regression models and forward stepwise

analysis were applied. The first model was used to determine which fat depots were predictors of GH secretion; the variables entered in the model were: pulsatile and log of basal GH secretion as dependent variables, and thigh IMAT, VAT, age, and GHBP as independent variables. The second model tested whether markers of insulin sensitivity and other metabolic factors might explain/contribute to the association between GH secretion and fat depots. Pulsatile and log of basal GH secretion were used as dependent variables and glucose disposal rate (GDR), fasting insulin, fasting glucose, IGFBP-I and triglycerides (TG), VAT, and thigh IMAT as independent variables. A two-tailed P value <0.05 was considered significant.

Results

All women had normal fasting glucose and HbA1c. One individual was diagnosed with glucose intolerance and another with type-2 DM by using OGTT. The patient with DM was excluded from all statistical analyses.

Association between GH secretion and regional fat depots

Basal and pulsatile GH secretions correlated negatively with VAT and thigh IMAT, using simple regression analysis, but not with mean thigh muscle attenuation or hepatic fat content (Table 1). The negative correlation between pulsatile GH secretion and thigh IMAT is shown in Fig. 1a and the negative correlation between log basal GH secretion and VAT in Fig. 1b. There was no correlation between ApEn and regional AT depots (Table 1).

Table 1 Correlation between fat depots and indices of GH secretion in postmenopausal women with abdominal obesity.

	Thigh SAT	Thigh IMAT	Mean muscle attenuation	Abdominal SAT	VAT	Liver attenuation
ApEn	0.3 $P<0.2$	0.3 $P<0.2$	0.1 $P<0.9$	0.3 $P<0.2$	0.2 $P<0.4$	0.1 $P<0.7$
Basal GH secretion rate * (μ g/l per min)	-0.2 $P<0.4$	-0.6 $P<0.01$	0.4 $P<0.06$	-0.5 $P<0.06$	-0.7 $P<0.001$	-0.0002 $P<0.9$
Half-life (minute)	-0.1 $P<0.7$	0.3 $P<0.2$	-0.4 $P<0.1$	-0.1 $P<0.6$	0.1 $P<0.8$	0.5 $P<0.07$
Number of peaks	0.1 $P<0.7$	0.2 $P<0.3$	0.2 $P<0.5$	0.2 $P<0.3$	0.1 $P<0.8$	0.2 $P<0.5$
Mean interval (minute)	0.004 $P<0.9$	-0.4 $P<0.1$	-0.1 $P<0.8$	-0.2 $P<0.4$	-0.1 $P<0.8$	0.1 $P<0.8$
Mean area (pulse mass)	-0.02 $P<0.9$	-0.7 $P<0.001$	0.4 $P<0.1$	-0.4 $P<0.1$	-0.5 $P<0.05$	-0.1 $P<0.6$
Basal GH secretion† (μ g/l per min $\times$ sampling duration)	-0.2 $P<0.4$	-0.6 $P<0.01$	0.4 $P<0.06$	-0.5 $P<0.06$	-0.7 $P<0.001$	-0.0004 $P<0.9$
Pulsatile GH secretion (number of peaks $\times$ mean area)	-0.02 $P<0.9$	-0.7 $P<0.002$	0.4 $P<0.1$	-0.3 $P<0.2$	-0.6 $P<0.02$	-0.04 $P<0.9$
Total secretion (basal + pulsatile GH secretion)	-0.04 $P<0.9$	-0.7 $P<0.002$	0.4 $P<0.1$	-0.4 $P<0.1$	-0.6 $P<0.01$	-0.03 $P<0.9$
%Pulsatile (pulsatile to total ratio $\times$ 100)	0.4 $P<0.1$	-0.5 $P<0.05$	0.2 $P<0.4$	0.1 $P<0.6$	-0.1 $P<0.6$	-0.2 $P<0.4$

Correlation analysis was based on the Pearson product–moment correlation coefficient. P values refer to *log basal secretion rate and †log session basal secretion. ApEn, approximate entropy; SAT, subcutaneous adipose tissue; IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue.

Figure 1 (a) Association between pulsatile growth hormone (GH) secretion (number of peaks $\times$ mean area) and thigh intermuscular adipose tissue (IMAT) (cm^2). Pearson's correlation coefficient: $r = -0.7$, $P < 0.002$. $N = 19$. (b) Association between log basal GH secretion ($\mu\text{g/l}$ per min $\times$ sampling duration) and visceral adipose tissue (VAT) (cm^2). Pearson's correlation coefficient: $r = -0.7$, $P = 0.001$. $N = 19$.

Associations among GH secretion, metabolic markers and fat depots

Using simple regression, log basal and pulsatile GH secretions correlated positively with GDR: both $r = 0.5$, $P < 0.05$; with IGFBP-I: $r = \text{both } 0.6$, $P < 0.01$; and negatively with insulin concentration, fasting glucose and TG: all $r = -0.5$, $P < 0.05$. ApEn showed a linear correlation with GHBP ($r = 0.5$, $P < 0.05$). Simple regression showed a positive correlation between GHBP and abdominal SAT ($r = 0.6$, $P < 0.01$), VAT ($r = 0.5$, $P = 0.04$) (Table 2), and thigh SAT ($r = 0.5$, $P < 0.05$) (data not shown), while no correlation was observed with liver attenuation or thigh IMAT (Table 2).

Associations between abdominal and thigh fat depots

VAT area correlated positively with thigh IMAT ($r = 0.7$, $P < 0.0001$) and inversely with thigh mean muscle attenuation ($r = -0.5$, $P < 0.04$). An inverse correlation was also found between mean thigh muscle attenuation and thigh IMAT ($r = -0.7$, $P < 0.002$).

GH secretion, fat depots and metabolic risk factors

When basal GH secretion was used as a dependent variable and VAT, thigh IMAT, age, and GHBP as independent variables in a forward stepwise regression analysis, a negative correlation was obtained with VAT ($B\text{-coefficient} = -0.77$, $P < 0.001$) but not with thigh IMAT. In the regression equation, VAT and age explained 57% of the variability of basal GH secretion ($R^2 = 0.57$, overall P value = 0.002). An inverse correlation with thigh IMAT was demonstrated ($B\text{-coefficient} = -0.67$, $P < 0.01$; $R^2 = 0.45$, overall P value = 0.002) using pulsatile GH secretion as dependent variable, whereas the relationship with VAT became non-significant. In the same multiple regression model, neither age nor GHBP showed any correlation with basal or pulsatile GH secretion. In the second multiple regression model (Table 3), using log basal GH secretion as dependent variable, VAT was the only independent predictor of basal

Table 2 Correlations between fat depots and metabolic indices in postmenopausal women with abdominal obesity.

	Thigh IMAT	Abdominal SAT	VAT	Liver attenuation	Muscle attenuation
GDR (mg/kg min)	-0.5 $P < 0.04$	-0.7 $P < 0.001$	-0.5 $P < 0.03$	0.7 $P < 0.002$	0.4 $P < 0.1$
Serum FFA (mmol/l)	0.4 $P < 0.1$	0.5 $P < 0.04$	0.6 $P < 0.02$	-0.6 $P < 0.02$	-0.6 $P < 0.02$
TG (mmol/l)	0.4 $P < 0.2$	0.1 $P < 0.7$	0.3 $P < 0.3$	-0.1 $P < 0.7$	-0.6 $P < 0.02$
Fasting glucose (mmol/l)	0.3 $P < 0.06$	0.2 $P < 0.001$	0.7 $P < 0.001$	0.3 $P < 0.7$	0.2 $P < 0.2$
2-h Glucose (mmol/l)	0.5 $P < 0.06$	0.7 $P < 0.001$	0.7 $P < 0.001$	-0.1 $P < 0.7$	-0.3 $P < 0.2$
Plasma insulin (mU/l)	0.8 $P < 0.001$	0.5 $P < 0.07$	0.8 $P < 0.001$	-0.2 $P < 0.5$	-0.4 $P < 0.09$
GHBP (pmol/l)	0.3 $P < 0.3$	0.6 $P < 0.01$	0.5 $P < 0.04$	-0.1 $P < 0.8$	0.001 $P < 1$

Correlation analysis was based on the Pearson product-moment correlation coefficient. GDR, glucose disposal rate; FFA, free fatty acids; TG, triglycerides; GHBP, growth hormone binding protein; SAT, subcutaneous adipose tissue; IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue.

Table 3 Associations among GH secretion, fat depots and metabolic indices.

Dependent variables in the equation	Independent variables in the equation	Simple regression* <i>r</i> ; <i>P</i> -value	Multiple regression† <i>B</i> ; <i>P</i> -value
(a) Log basal GH secretion	VAT	−0.7; <0.00	−0.53; 0.01
	IGFBP-I	0.6; <0.01	0.29; 0.13
	TG	−0.5; <0.05	−0.22; 0.2
(b) Pulsatile GH secretion	IMAT	−0.7; <0.01	−0.85; 0.01
	IGFBP-I	0.6; <0.01	0.40; 0.06
	F-insulin	−0.5; <0.05	0.29; 0.3
	F-glucose	−0.5; <0.05	−0.39; 0.1
	VAT	−0.6; <0.05	0.41; 0.2
	TG	−0.5; <0.05	−0.19; 0.3

*By Pearson product-moment correlation coefficient. †By multiple regression analysis, forward stepwise, second model. Number of cases = 18. The beta (*B*) coefficient shows the relative contribution of each independent variable. *P*-level for each variable: statistically significance <0.05. In the equation (a): *R*-square = 0.66; *P* = 0.002. In equation (b): *R*-square = 0.74; *P* = 0.01. *R*-square is a measure of how well the model fits the data. *P* is the overall *P*-value of each multiple regression equation. VAT, visceral adipose tissue; IGFBP-I, insulin-like growth factor binding protein-I; TG, triglycerides; IMAT, intermuscular adipose tissue.

GH secretion, while IGFBP-I, TG, GDR, fasting insulin, and fasting glucose lost significance. In the same model, using pulsatile GH secretion as the dependent variable, thigh IMAT was the only independent predictor of pulsatile GH secretion, whereas VAT and metabolic risk factors had no predictive value.

Discussion

The major findings of this study were: (i) an independent inverse relationship between blunted pulsatile GH secretion and thigh IMAT in post-menopausal women with abdominal obesity and (ii) VAT was predominantly associated with basal GH secretion, while no association was found between hepatic fat content and GH secretion. Twelve-hour night-time GH profiles with sampling every 20 min were used to appraise the GH secretory status. As a result, mean values reflect the secretion when maximal GH release occurs. The utility of night-time GH profiles for deconvolution and ApEn analysis has previously been validated with sampling every 10 min (4), whereas 24-h GH profiles with sampling every 20 min is well-established (15, 24). Even 24-h GH profiles with 30-min sampling intervals yield marked contrasts in GH secretory patterns between GH-deficient adults and healthy controls (25). Finally, using low-normal serum IGF-I concentrations as a criterion for including women in the trial could have influenced the results. Varying oestrogen was, however, not a confounding factor in this trial, as all women were in the menopausal stage and were not receiving oestrogen-replacement therapy.

An independent correlation was found between VAT and basal GH secretion rate. This is in line with previous findings that increased VAT is linked with blunted GH secretion (6, 26). One of the early studies suggested that abdominal adiposity was predominantly associated with a decreased GH secretory burst mass in older men (27), while a later study in healthy, pre-menopausal women found high VAT accumulation associated with both reduced basal and pulsatile GH secretions, and with a

loss of regularity of GH release (16). It is therefore clear that there is a negative association between the amount of VAT and GH secretion, seemingly independent of age and gender. From the present and previous data, it is possible that the relationship between VAT and basal GH secretion is stronger in women than in men. The mechanism for the relationship between VAT and blunted GH secretion has not yet been established, but increased serum levels of FFA in abdominal obesity may reduce GH secretion (28) as also indicated in our regression analysis. There is evidence that subjects with abdominal obesity have blunted lipolysis during fasting, which may be an effect of attenuated GH response during fasting (28). Therefore, abdominal obesity *per se* may contribute to augmented fat accumulation, possibly through a state of relative GH insufficiency (29, 30). It has also been suggested that insulin resistance induced by intra-abdominal fat accumulation may contribute to blunted GH secretion by suppression of serum IGFBP-I leading to increased free IGF-I levels (30). In this study, simple regression analysis showed inverse correlations between fasting insulin and both basal and pulsatile GH secretions, and positive correlations between IGFBP-I and both basal and pulsatile GH secretions support this mechanism. IMAT has been described using CT scans, or more recently MRI, as the accumulation of AT surrounding skeletal muscle bundles. The inverse relationship between pulsatile GH secretion and IMAT found in this study has not been described previously. However, there is evidence that basal and pulsatile GH secretions are regulated in a distinct manner (4). In rodents, data suggest that the pulsatile component of GH secretion is more important for body growth (31–33), whereas the basal component is more important for the lipolytic effect (34, 35). This may support our finding that thigh IMAT was more strongly related to the pulsatile component, whereas VAT is more strongly related to the basal component of GH secretion. Therefore, one could hypothesize that there are different mechanisms for the interaction between thigh IMAT and pulsatile GH secretion and the one

between VAT and basal GH secretion. Only abdominal fat depots correlated positively with GHBP concentration. GHBP levels may interfere with the GH analysis and could therefore be a confounding factor in the association between basal GH secretion and VAT. However, since GHBP had no predictive value in multiple regression analysis, it probably did not exert a major influence on the results.

In the multiple regression model, thigh IMAT and VAT were the strongest predictors of pulsatile and basal GH secretions, independent of age. Moreover, in the multiple regression analysis, we did not observe any association between fasting insulin concentration and GH secretion. This is in agreement with previous data indicating that blunted GH secretion is not associated with hyperinsulinaemia *per se* (36), and it is therefore most likely that mechanisms other than those related to insulin are involved in, or modulate the relationship between thigh IMAT and pulsatile GH secretion. IMAT, but not mean muscle attenuation, demonstrated a clear association with insulin sensitivity and GH secretion. The reason for these differences is unknown, but may be related to the method used to quantify the lipid content within the muscle. Although the method of measuring muscle attenuation has proved to have a low variability (<1%), it is not capable of differentiating between intra-myocellular lipids and lipids outside the myocyte. Moreover, factors such as variation in the protein content of muscle, skeletal muscle perfusion, and extracellular water may alter muscle attenuation (37). The muscle attenuation assessed using CT may, therefore, be a less specific measure of intra- rather than intermuscular fat content. Previous studies (4,16) have shown a positive association between VAT and ApEn ratio, suggesting a loss in regularity of GH secretion with increasing VAT. In women with polycystic ovary syndrome, a loss of regularity in the pattern of GH secretion is associated with VAT accumulation (38). Furthermore, in GH-deficient adults, IGF-I concentrations have been shown to correlate positively with ApEn ratios, suggesting that GHD patients with low IGF-I concentrations had a more regular pattern of GH release than those with more normal serum IGF-I levels (25). In the present study, we could not detect any correlation between ApEn and VAT. However, the selection of women with low-normal serum IGF-I concentrations together with the small range of VAT in this study could possibly explain this lack of correlation. The metabolic impact of IMAT has not been explored until recently. A relationship exists between thigh IMAT accumulation and insulin resistance in healthy individuals (37). Thigh IMAT is also associated with the abdominal fat accumulation seen in male and female elderly patients with type-2 DM (11). Furthermore, it has been proposed that, with increasing levels of adiposity, differences in regional AT distribution, with a greater IMAT accumulation in relation to VAT, could explain

differences in glucose intolerance and DM that are related to ethnicity (39). In this study, a multiple regression model showed that VAT and hepatic fat content were independent predictors of insulin resistance, whereas IMAT or muscle fat content were not. This is consistent with the hypothesis that the mechanism by which muscle metabolism causes insulin resistance is different from that induced by VAT (40). However, it does not exclude the possibility that impaired lipid oxidation in skeletal muscle is linked to both muscle fat accumulation and development of visceral adiposity (41). Further studies are needed to explore this issue to determine whether increased IMAT deposition is simply the result of more severe obesity or if it is associated specifically with intra-abdominal fat as suggested by our analysis, which showed women with increased thigh IMAT and abdominal fat displayed more marked disturbances in their metabolic profile.

In conclusion, in post-menopausal women with abdominal obesity, pulsatile GH secretion showed an independent, negative association with thigh IMAT, whereas basal GH secretion demonstrated an independent, negative association with VAT. There was no association between hepatic fat content and GH secretion. These findings suggest that the mechanisms modulating interactions between fat mass and the somatotrophic axis are depot-dependent. We have identified thigh IMAT to be of importance in this interplay.

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