Visceral Adipose Tissue Impairs Insulin Secretion and Insulin Sensitivity But Not Energy Expenditure in Obesity

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In obesity, a central pattern of fat distribution is mostly associated with hyperinsulinemia, insulin resistance, and hyperlipemia, thus promoting the development of non–insulin-dependent diabetes mellitus and cardiovascular disease. In addition, in obesity, changes in energy expenditure are hypothesized to be involved in the development or maintenance of excessive body fat storage. In this study, abdominal fat distribution by computed tomographic (CT) scan was used to study the relation between the visceral fat depot, insulin secretion, and insulin sensitivity in a group of obese subjects with normal glucose tolerance (n = 26; body mass index [BMI], 39 ± 1 kg/m^2) and a group of normal-weight control subjects (n = 9; BMI, 23 ± 1 kg/m^2). The minimal model method was used to assess insulin sensitivity, S_I, and first-phase (Φ1) and second-phase (Φ2) β-cell sensitivity from plasma glucose, insulin, and C-peptide concentrations measured during an intravenous glucose tolerance test ([IVGTT] 0.33 g/kg body weight). Moreover, we evaluated the relationships between these parameters and the resting metabolic rate (RMR) and glucose-induced thermogenesis (GIT) measured by indirect calorimetry. The data show the following: (1) in obese subjects, Φ1 is greater but not statistically different from the value in control subjects (252 ± 41 *v* 157 ± 25 dimensionless 10^9); (2) Φ2 is significantly higher in obese subjects (27 ± 4 *v* 14 ± 2 $min^{-1} \times 10^9$, $P < .05$), with a positive correlation between the amount of visceral adipose tissue (VAT) and Φ2 ($r = .49$, $P < .05$); (3) S_I is decreased in the obese group (2.8 ± 0.3 *v* 9.7 ± 1.6 $10^{-4} \cdot min^{-1}/(\mu U \cdot mL^{-1})$, $P < .0001$), with a negative correlation of S_I with the adiposity index BMI ($r = -.67$, $P < .0001$) and VAT ($r = -.56$, $P < .05$); (4) RMR, expressed in absolute terms, was significantly increased in obese versus lean subjects (5.9 ± 0.2 *v* 4.6 ± 0.3 kJ/min, $P < .01$), whereas when RMR was adjusted for fat-free mass (FFM), the difference between the two groups disappeared (0.09 ± 0.003 *v* 0.09 ± 0.002 kJ/min · kg FFM). We did not observe any difference in GIT between lean and obese subjects. Moreover, GIT was significantly correlated with FFM ($r = .69$, $P < .005$), but not with BMI. The amount of VAT did not correlate with RMR or GIT. In conclusion, these results suggest that in obese subjects with normal glucose tolerance, insulin sensitivity is impaired and the β-cell hyperresponse to glucose is mainly due to an enhanced second-phase β-cell secretion. The degree of visceral fat deposition seems to affect insulin secretion and worsens insulin sensitivity, but does not influence energy expenditure.

OBESITY can be defined as a syndrome characterized by an increase in body fat stores, its generation depending on an imbalance between energy intake and energy expenditure. Excessive body fat storage and particularly preferential fat deposition in the abdominal area was demonstrated to predispose the subject to metabolic disorders such as diabetes mellitus, hyperlipemia, and cardiovascular diseases.[1] In addition, hyperinsulinemia, insulin resistance, and hyperlipemia are distinctive features of the obesity syndrome. However, the impact of the visceral fat depot on β-cell secretion and insulin action is not well defined yet, and it is not clear whether the abdominal fat depot is a determinant or only a precipitating factor. A few studies have shown a negative correlation between insulin action, measured by euglycemic clamp or by steady-state plasma glucose techniques,[2] and body adiposity, estimated from the body mass index (BMI) and skinfold thicknesses.[3] However, a large variability in insulin action data was often observed in overweight and also in normal-weight subjects.[3] This could be accounted for by differences in percent body fat or body muscle. In particular, changes in skeletal muscular fiber composition were described in subjects with abdominal obesity.[4,5]

The relationship between the fat depot and insulin secretion also needs to be better elucidated, since conflicting results have been reported. Bonadonna et al[6] observed increased first- and second-phase insulin secretion in obese individuals during a hyperglycemic clamp. Walton et al[7] showed in a group of non-obese volunteers with normal glucose tolerance that both the BMI (an adiposity index) and subscapular to triceps ratio (a fat distribution index) were associated with an elevated second-phase but not first-phase plasma insulin response.

The possibility that a defect in energy metabolism underlies human obesity has received much attention, but thus far conflicting results have been obtained.[8-11] These discrepancies mostly derive from the differences in methods investigating energy expenditure and the expression of the results. These observations may be at least partly explained by differences in the phenotype of human obesities (ie, body composition *v* fat mass distribution). At present, it is clear that relationships between the resting metabolic rate (RMR) and the amount of lean and fat mass exist, but the impact of fat mass distribution on energy expenditure is still controversial.[12-15]

In the present study, we evaluated the role of abdominal adipose tissue, particularly the visceral depot, in insulin secretion and insulin action in a group of nondiabetic obese subjects. We used the minimal model approach to determine insulin sensitivity and first- and second-phase β-cell sensitivity from intravenous glucose tolerance test (IVGTT) data and computed tomographic (CT) scan at the L4 level to assess body fat distribution. In addition, we studied the relationships between

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the body composition, visceral abdominal fat depot, and energy expenditure.

SUBJECTS AND METHODS

Subjects

Two groups of subjects were studied: 26 obese and nine healthy volunteers. Their characteristics are shown in Table 1.

All the women admitted to the study were in the follicular phase of the menstrual cycle. None of the subjects had clinical or laboratory evidence of cardiac, hepatic, renal, or endocrine disease or were taking any medication. Patients with obesity secondary to endocrine diseases and obese subjects with diabetes mellitus or reduced glucose tolerance were excluded from the study. All subjects were weight-stable at the time of study, with no greater than a 2-kg weight loss or gain over the 6 months before the study.

The subjects were instructed to consume at least 200 to 300 g/d of carbohydrate over the 3 days before the study. Before participation in the study, each subject provided written informed voluntary consent.

Body Composition

Bioelectric impedance was used to measure body fat and fat-free mass (FFM), obtained by the total conductive volume of the body for each individual. It is based on the greater electrolyte content of FFM and its greater conductivity of electricity when compared with adipose tissue or bone, and on the geometric relationships between impedance and the volume of the conductor from Ohm's law. The measurements were taken on the right side of the body for the arm and leg using a BIA 101 impedance analyzer (RJL System, Detroit, MI), following the procedures of Lukaski et al.[16,17] This device uses a four-electrode arrangement that measures the resistance and reactance of a conductor (in ohms) to an injected alternating electric current of 800 μA at 50 kHz, as described by Chumlea et al.[18]

Fat Distribution

Waist and hip circumferences were used to determine the waist to hip ratio. In particular, circumferences were measured with a 1-cm–wide metal measuring tape, considering the waist as the minimum circumference measured between the xyphoid process and the umbilicus, and the hip as the most outward-extending points on the great trochanters.

Abdominal fat distribution was determined by axial CT scan (Siemens Somaton DRH, Germany) according to the method used by Sjostrom et al.[19] Total (TAT), visceral (VAT), and subcutaneous (SAT) adipose tissue were evaluated by single scanning at the L4 level. Subject centering was obtained by a lateral tomogram at the L4 level. Measures of the areas were obtained using a computer software package as described by Borkan et al.[20] In each scan, the perimeter of the body was outlined with a light-pen cursor and measured. Tissues with attenuation values between −190 and −30 Hounsfield units were defined as fat.

Table 1. Subject Characteristics (mean ± SEM)

Variable	Controls (n = 9)	Obese (n = 26)
General characteristics		
Sex (M/F)	3/6	8/18
Age (yr)	37 ± 4	34 ± 3
Height (cm)	171 ± 2	167 ± 2
Weight (kg)	65 ± 3	110 ± 4*
BMI (kg/m)	23 ± 1	39 ± 1*
Body composition		
Fat mass		
(kg)	18 ± 3	44 ± 2*
%	24 ± 2	40 ± 1*
FFM	46 ± 5	65 ± 2*
(kg)	71 ± 2	60 ± 1*

NOTE. Statistical analysis was made by ANOVA.
*$P < .01$ *v* control.

Experimental Protocol

Oral glucose tolerance test and energy expenditure. All subjects were given a 75-g oral glucose load after a 12-hour overnight fast. They were placed in a semirecumbent position, and an indwelling venous cannula was inserted into an antecubital vein. This catheter was kept patent by slow infusion of isotonic saline solution and was used to obtain all blood specimens. Blood samples for determination of plasma glucose, insulin, C-peptide, and free fatty acids (FFA) were drawn at 30-minute intervals for 3 hours.

At the same times, O_2- and CO_2-exchange measurements were performed by computed open-circuit continuous indirect calorimetry by ventilated hood (MMC HORIZON System; Sensor Medics, Anaheim, CA). O_2 consumption and CO_2 production were used to compute energy expenditure as expressed by the RMR, using Weir's formula ($[(1.1 \times RQ) + 3.9] \times \dot{V}o_2 \times 4.18$). After a rest period of 15 minutes, RMR was measured continuously for 30 minutes. After measurement of RMR, the subjects ingested the glucose load within 5 minutes (75 g glucose dissolved in 250 mL water). O_2 consumption and CO_2 production were recorded for 3 hours after the load. The cumulative postprandial increase above the RMR over 3 hours was defined as glucose-induced thermogenesis (GIT). The energy expenditure data in basal conditions were expressed as kilojoules per minute and then adjusted for FFM (kJ/min · kg FFM). GIT was calculated as the incremental area after the glucose load with respect to baseline RMR, and expressed as kilojoules per 3 hours.

IVGTT. An indwelling venous cannula was inserted into an antecubital vein. This catheter was kept patent by slow infusion of isotonic saline solution and was used to obtain all blood samples. A second venous cannula was inserted for glucose injection (0.33 g/kg body weight in 2 minutes) in the contralateral arm. To define glucose, insulin, and C-peptide levels, blood samples were taken at −13, −8, −3, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210, 240, 270, and 300 minutes. Heparinized samples were centrifuged under refrigeration and stored at −20°C until assay.

Minimal Model Analysis

Kinetics analysis of IVGTT data was performed using the minimal models of glucose disappearance,[21] C-peptide secretion, and kinetics.[22]

The minimal model of glucose disappearance[21] accounts for the effect of insulin and glucose concentrations on glucose disappearance during the test. In particular, it provides the parameter, S_I (10^4 min/(μU/mL)), the insulin sensitivity index, which measures the ability of insulin to enhance glucose disappearance and inhibit hepatic glucose production.

The second model[22] describes β-cell C-peptide secretion (equimolar with insulin) and its kinetics in the body. Two indices are provided by the model, first-phase ($\Phi 1$, dimensionless 10^9) and second-phase ($\Phi 2$, $min^{-1} \times 10^9$) β-cell responsivity to glucose. $\Phi 1$ measures the total amount of C-peptide secreted immediately after the glucose injection normalized to the distribution volume (mass · vol^{-1}) divided by the maximal increment of plasma glucose concentration (mass · vol^{-1}). Therefore, it is a ratio between concentrations, and its expression is dimensionless. $\Phi 2$ is the mean increase above basal of the second-phase secretion rate of C-peptide normalized to the distribution volume (mass · $vol^{-1} \cdot t^{-1}$) over the mean glucose stimulus (mass · vol^{-1}), and its final expression is in minutes. Parameters of whole-body C-peptide kinetics have been individualized following the method proposed by Toffolo et al.[22]

The two models were numerically identified using nonlinear least-squares estimation procedures.[23] Measurement errors were assumed to

be independent, gaussian with zero mean, and with a coefficient of variation of 2% and 6% for glucose and C-peptide, respectively.

Analytical Procedures

Plasma glucose level was measured by the glucose oxidase method (Glucose GOD-PERID; Boehringer, Mannheim, Germany). FFA were assayed enzymatically using the NEFA QUICK BMY Kit (Boehringer Mannheim Yamanouki, Tokyo, Japan). Immunoreactive insulin and C-peptide levels were measured in duplicate by radioimmunoassay using commercial kits (respectively: INSIK-5, Sorin, Saluggia, Italy, and C-PEPTIDE 125, Stillwater, MN).

Calculations and Statistics

All data were expressed as the mean ± SEM. Statistical comparisons were performed using the one-way between-group ANOVA, and multivariate analysis of variance when multiple dependent variables were selected (STATISTICA for WINDOWS, Release 4.0; STATSOFT, Tulsa, OK). Areas under the concentration curves were calculated by summing each trapezoidal region during the test; GIT was calculated as incremental areas after the glucose load above the basal RMR and expressed as Kilojoules per 3 hours, summing each trapezoidal region formed with a base at zero. Linear regression analysis was performed by standard techniques.

RESULTS

Subject characteristics are presented in Table 1. The obese subjects have a BMI of 39 ± 1 kg/m^2 (mean ± SEM).

Body Composition

Measures of bioelectric impedance showed increased fat mass both in absolute (kilograms) and percent values, in obese versus control subjects (Table 1).

FFM in absolute (kilograms) and percent values was greater in obese compared with control subjects (Table 1). Moreover, comparing sex, FFM in obese men (78 ± 2 kg, $P < .01$) was greater than in obese women (64 ± 2 kg) when expressed in absolute terms (kilograms), but when expressed as a percent of body weight, it did not show a significant increase (males *v* females, 62.6 ± 2.1% *v* 59.2 ± 1.2%). FFM in absolute terms was 60 ± 6 kg in lean men and 40 ± 5 kg in lean women ($P < .05$), and as a percent of body weight it was 84 ± 3% versus 73 ± 2% (males *v* females, $P < .01$).

Fat Distribution

In the obese population, the waist to hip ratio was 0.93 ± 0.03 (range, 0.82 to 1.03) without significant sex differences. TAT obtained by CT scan was 719 ± 43 cm^2 in the obese group, without significant differences between men (795 ± 73 cm^2) and women (687 ± 52 cm^2) (Table 2). SAT was 519 ± 37 cm^2 in the obese group, with values in men at 561 ± 79 cm^2 and in women 501 ± 41 cm^2 (Table 2). VAT was 205 ± 21 cm^2 in the obese group, without significant differences between men (235 ± 56 cm^2) and women (191 ± 20 cm^2) (Table 2).

The VAT/SAT ratio was 0.44 ± 0.07 in the obese group, and no significant difference between men (0.44 ± 0.1) and women (0.44 ± 0.07) was observed (Table 2).

In the obese subjects, a positive correlation between BMI and TAT ($r = .86$, $P < .0001$) and between TAT and VAT ($r = .47$, $P < .05$) was found. No significant correlation between VAT and BMI was present.

Table 2. Abdominal Fat Distribution Evaluated by CT Scan in Male and Female Obese Subjects

Adipose Area (cm^2)	Male	Female	All
TAT	795 ± 73	687 ± 52	719 ± 43
SAT	561 ± 79	501 ± 41	519 ± 37
VAT	235 ± 56	191 ± 20	205 ± 21
VAT/SAT	0.44 ± 0.10	0.44 ± 0.07	0.44 ± 0.07

NOTE. Values are expressed as the mean ± SEM.

OGTT

In the basal state glucose level, no difference was present between obese and control subjects (4.3 ± 0.1 *v* 4.3 ± 0.2 mmol/L), whereas glycemic area after the glucose load was significantly higher in obese than in control subjects (1,247 ± 49 *v* 971 ± 51 mmol/L · 180 min, $P < .005$). None of the subjects were affected by reduced glucose tolerance, according to the criteria of the National Diabetes Data Group.[24]

Basal FFA plasma levels were significantly higher in obese than in control subjects (747 ± 45 *v* 434 ± 35 μmol/L, $P < .001$). FFA decreased after the glucose load in both groups.

Basal plasma insulin and C-peptide concentrations were significantly higher in obese subjects than in controls (respectively, 158 ± 22 *v* 57 ± 7 pmol/L, $P < .01$, and 960 ± 99 *v* 430 ± 66 pmol/L, $P < .01$). Insulin and C-peptide areas after the glucose load were significantly higher in the obese (respectively, 115 ± 49 *v* 49 ± 5 nmol/L · 180 min, $P < .005$, and 553 ± 52 *v* 286 ± 61 nmol/L · 180 min, $P < .05$) than in control subjects.

IVGTT and Minimal Model Analysis

Basal glucose levels did not differ between the obese and control subjects, nor did the glucose area under the curve (obese *v* control, 1,567 ± 38 *v* 1,603 ± 83 mmol/L · 300 min). Basal insulin and C-peptide concentrations were higher in the obese than in control subjects; insulin and C-peptide areas under the curve were markedly elevated in the obese (respectively, 77 ± 8 nmol/L · 300 min and 438 ± 50 nmol/L · 300 min) versus the control subjects (respectively, 29 ± 3 nmol/L · 300 min, $P < .001$, and 211 ± 20 nmol/L · 300 min, $P < .01$).

The minimal model analysis of IVGTT data showed a higher but not significantly different $\Phi 1$ (252 ± 41 *v* 157 ± 25 dimensionless 10^9) and a significantly higher $\Phi 2$ (27 ± 4 *v* 14 ± 2 $min^{-1} \cdot 10^9$, $P < .05$) in obese compared with normal subjects (Fig 1).

S_I was significantly lower in the obese than in control subjects (2.8 ± 0.3 *v* 9.7 ± 1.6 $10^{-4} \cdot min^{-1}/[\mu U \cdot mL^{-1}]$, $P < .0001$; Fig 1).

Differences were not noted between men and women of the two groups.

Energy Expenditure

The preload (RMR) and post-load (GIT) energy expenditures for the two groups are presented in Fig 2. Expressed in absolute terms, the RMR in obese subjects was significantly higher than in controls (5.9 ± 0.2 *v* 4.6 ± 0.3 kJ/min, $P < .01$), but the data per unit FFM were similar in the two groups (obese *v* control, 0.09 ± 0.003 *v* 0.09 ± 0.002 kJ/min · kg FFM). No significant

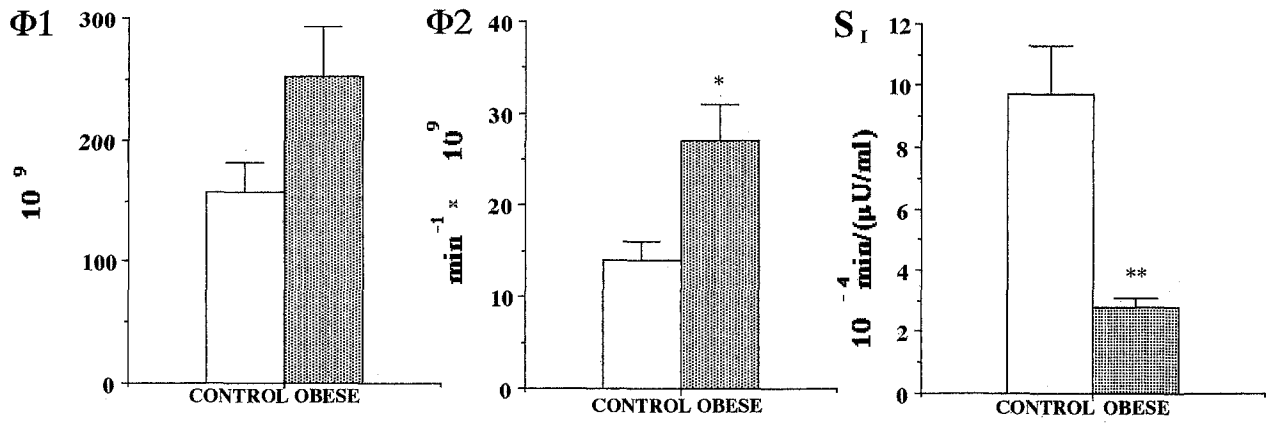

Fig 1. First-phase (Φ1) and second-phase (Φ2) β-cell sensitivity and insulin sensitivity (S_I) in control (n = 9) and obese (n = 26) subjects (mean ± SEM). *$P < .05$, control *v* obese; **$P < .0001$, control *v* obese.

difference in GIT was observed between control and obese subjects (147 ± 17 *v* 142 ± 17 ΔkJ/3 h).

Visceral Adiposity and Insulin Secretion

In obese subjects, VAT was correlated positively with the insulin area during OGTT ($r = .55$, $P < .05$) and with Φ2 ($r = .49$, $P < .05$), but no relationship was noted with Φ1.

Insulin area during the OGTT directly correlated with BMI in obese subjects ($r = .51$, $P < .05$), but no correlation was observed in control subjects.

B-cell sensitivity to glucose, as expressed by Φ1 and Φ2, did not appear to be correlated with BMI in both groups.

Visceral Adiposity and Insulin Sensitivity

In the obese patients, a negative correlation between VAT and S_I was found ($r = -.56$, $P < .05$). Also, TAT, but not SAT, showed a negative relationship with S_I ($r = -.54$, $P < .05$). VAT was correlated positively with glycemic area during the OGTT ($r = .51$, $P < .05$).

Basal plasma FFA showed a positive relation with BMI ($r = .72$, $P < .001$). A positive correlation was also obtained between plasma FFA and TAT ($r = .54$, $P < .05$) and between FFA and VAT ($r = .53$, $P < .05$) in the obese subjects. Moreover, a negative correlation was found between FFA and S_I ($r = -.65$, $P < .05$) in the obese patients.

A negative correlation between S_I and BMI was evident in obese subjects ($r = -.55$, $P < .05$), but this relationship was not found in control subjects.

Glycemic and insulinemic areas during the OGTT were directly related to S_I (respectively: $r = .58$, $P < .05$ and $r = .80$, $P < .0001$). Moreover, Φ2, but not Φ1, was negatively correlated with S_I ($r = -.61$, $P < .005$). This relation was observed in both groups of lean and obese subjects. Moreover Φ2, but not Φ1, was negatively correlated with S_I ($r = -.67$, $P < .01$) in the obese subjects, whereas in the control subjects, neither Φ2 nor Φ1 were correlated with S_I.

Visceral Adiposity and Energy Expenditure

RMR, in absolute terms, was related to BMI in both groups ($r = .55$, $P < .005$). Moreover, a positive correlation between FFM and RMR was shown ($r = .69$, $P < .0001$), and this relation was obtained in both groups of lean and obese subjects. GIT was also positively correlated with FFM ($r = .69$, $P < .005$). In obese subjects, no correlations were found between RMR, GIT, and parameters of body fat distribution.

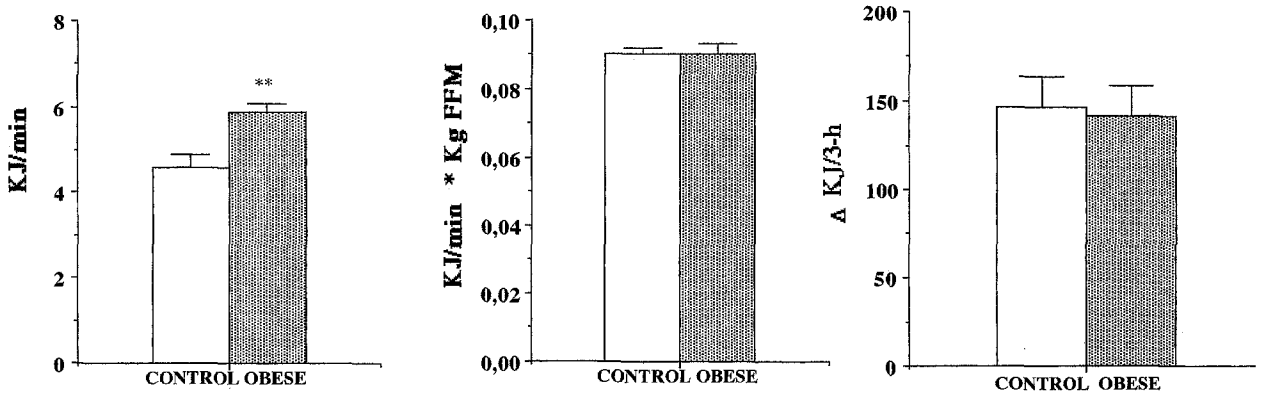

Fig 2. RMR, expressed in absolute terms (kJ/min) and corrected by FFM (kJ/min · kg FFM), and GIT, measured by indirect calorimetry during OGTT in control (n = 9) and obese (n = 26) subjects (mean ± SEM). GIT is expressed as incremental areas after the glucose load considering zero the basal RMR value and expressed as ΔkJ/3 h. **$P < .01$, control *v* obese.

DISCUSSION

The aim of our investigation was to examine the impact of abdominal fat content measured by CT scan on insulin secretion, insulin sensitivity, and energy expenditure in a group of obese patients with normal glucose tolerance. Our results show that visceral fat content influences both insulin secretion and insulin sensitivity in obese subjects without affecting RMR and GIT.

We measured abdominal fat content using a CT scan, which offers a better and direct characterization of subcutaneous and visceral fat distribution[21] than the currently used simple anthropometric measurements. Skinfold thickness and waist to hip ratio may be poorer quantitative measures to evaluate different adipose tissue pools than more direct methods, such as CT scan or nuclear magnetic resonance.[25] In particular, such techniques are important to estimate how much the splanchnic fat depot is a major factor in determining the development of endocrine-metabolic disturbances in obesity.[1]

β-Cell Secretion Kinetics and Insulin Sensitivity in Obesity

All our obese patients showed increased basal insulin levels and a hyperresponse of the β cell to both the oral and intravenous glucose load. The minimal model analysis of β-cell secretory kinetics during IVGTT showed a greater first-phase β-cell sensitivity in obese subjects. However, it was not statistically different from that of the lean subjects, probably because of the wide range of variability of Φ1 among obese subjects. Moreover, we observed a significantly higher Φ2 in the obese compared with control subjects.

The reported data on insulin secretion in obesity are often controversial, describing no difference in the dynamic sensitivities to glucose of first- and second-phase insulin secretion as studied by the C-peptide minimal model[26] or, on the contrary, an increase in first- and second-phase insulin secretion as assessed by hyperglycemic clamp.[6]

The lack of a significant difference in first-phase insulin secretion between obese and control subjects supports previous reports in which the early-phase insulin response to intravenous glucose or glucagon injection appears not to be affected by obesity.[27] However, progressive impairment in the first-phase β-cell response to glucose was evident with increasing severity of glucose intolerance; it has been reported that the first phase is clearly delayed in obese subjects with non–insulin-dependent diabetes mellitus.[27] We did not observe any correlation between the degree of insulin resistance (S_I), estimated using the minimal model, and first-phase β-cell sensitivity to glucose (Φ1).

Our results also confirm the presence of a significant reduction in insulin sensitivity in the obese population. In our obese subjects, the defective insulin action is not actually associated with impaired glucose tolerance. This means that the increased β-cell secretion is adequate to maintain glucose homeostasis. The increase in second-phase insulin secretion may be interpreted as a compensatory response to the reduced insulin sensitivity. This hypothesis is supported by a significant inverse correlation between S_I and Φ2.

Role of Adipose Tissue in β-Cell Secretory Kinetics and Insulin Sensitivity

In our study, the increase of visceral fat deposition (VAT) appears associated with the elevated insulin response area after both the oral and intravenous glucose load. Moreover, in the obese subjects, a positive correlation between the amount of VAT and the increase of second-phase β-cell sensitivity (Φ2) was observed. Similar results were also obtained by Walton et al,[7] who examined the relationship between fat distribution and insulin secretion in a group of individuals within the normal range of body weight. They reported that an increased centrality of fat distribution, measured by skinfold thicknesses, was associated with an elevated second-phase pancreatic insulin release. This observation turned out to be much more interesting for the lack of a correlation between insulin secretory pattern and adiposity index. Similarly, in the obese subjects, we did not observe any correlation between BMI and the insulin secretory indices (Φ1 and Φ2). Therefore, it seems likely that fat mass distribution rather than the degree of obesity plays a crucial role in developing the endocrine-metabolic features of this syndrome.

In our experiment, the degree of obesity, expressed by BMI, is associated with a decreased insulin sensitivity. These results are in agreement with previous reports, in which a negative correlation between the percent body fat, estimated by skinfold thicknesses, and insulin action during euglycemic clamp was noted.[3] On the other hand, Bogardus et al[28] showed that the degree of obesity was not linearly related to insulin action, since a significant decline in the action was evident with obesity increasing to 30% fatness and a further increase of body fat did not change insulin action. Furthermore, Campbell et al[29,30] found that insulin sensitivity was proportionally reduced to the degree of obesity above a threshold of 120% of ideal body weight in nondiabetic subjects. The same group reported that with increasing BMI, the insulin sensitivity of both hepatic and peripheral tissues declines also in patients with type II diabetes.[31]

In our obese subjects, the amount of visceral fat is associated with a decreased insulin sensitivity. In accord with our results, previous reports showed that an increased centrality of fat distribution[7] or intraabdominal fat[32] were associated with decreased insulin sensitivity in healthy subjects. However, Pedersen et al[33] observed that although total body fat content is an important predictor of reduced tissue sensitivity to insulin in non-obese subjects, body fat distribution becomes the main factor determining defective insulin action in obese subjects. Several studies have been performed to investigate the influence of fat distribution independently of obesity on glucose metabolism. These reports used mainly the waist to hip ratio to characterize the upper- or lower-body fat distribution, and concluded that central obesity worsened insulin sensitivity.[1,34] We have to consider that the waist to hip ratio may be a relatively poor index of central obesity,[25] and therefore studies by CT scan or nuclear magnetic resonance should better define the role of visceral fat in metabolic alterations. In this case, the distinction between superficial and deeply localized adipose tissue appears to be crucial.

The lipolytic activity of adipocytes from the visceral region is enhanced, and this may account for the importance of visceral

adiposity in affecting both insulin secretion and carbohydrate metabolism[1]: the increase in FFA flux from the splanchnic bed to the liver influences insulin clearance, increasing posthepatic insulin delivery[1] and plasma FFA levels and the peripheral FFA oxidation rate. This may contribute to the impairment in glucose utilization through the so-called Randle's cycle.[34] As a matter of fact, we observed elevated basal FFA levels in the obese subjects, which are positively correlated with the total amount of abdominal fat and with the visceral fat. Moreover, a negative correlation was found between FFA and the S_I.

Along the path from obesity to diabetes, an increased FFA release from adipose tissue and their peripheral oxidation may represent the very early phenomenon in developing insulin resistance and impaired glucose tolerance.[34]

Impact of Body Composition and Fat Distribution on Energy Expenditure

It has been shown that the RMR mostly depends on the size of the lean body mass.[35] Considering that obese subjects not only have an increased fat mass but also an enlarged lean body mass, this particular body composition contributes to a higher total absolute energy expenditure in obese versus lean control subjects.

In our study, we confirm previous observations[35] indicating the presence of higher RMR, expressed in absolute terms, in the obese group compared with the control group. Moreover, a positive correlation between RMR and FFM was observed. When RMR was adjusted for FFM, the difference in basal energy expenditure between the two groups disappeared.

A positive correlation between RMR and the degree of obesity, as estimated using the BMI, was also evident in our population. On the other hand, we did not observe any correlation between RMR and VAT, suggesting a lack of influence of the abdominal fat content on basal energy expenditure, as confirmed by a previous observation.[36]

In the present study, we did not find any difference in GIT between the lean and obese group and no relationship between GIT and BMI. This fact confirms the findings of some,[11,38-41,46] but it does not agree with studies by others, who observed a lower thermic response to glucose in obese subjects.[42-44] This may happen because of methodologic differences in evaluating postprandial thermogenesis, as well as the different way of expressing the results. Postprandial thermogenesis is the result of many processes, such as the energy cost of processing the substrates through the gastrointestinal tract, their metabolic utilization, and other factors (ie, meal size and composition, body composition, age, gender, and time of measurements). All these factors may influence the GIT, modifying the results.[44]

We found a direct positive relation between the amount of FFM and GIT, suggesting that the metabolically active component of the body must be seen not only as a major determinant of RMR, but also to influence the thermic response to ingested food, as recently confirmed by Van Gaal et al.[45]

The thermic effect of food seems to be directly related to the heat loss across the abdominal wall: by increasing the thickness of adipose tissue in the abdominal wall, heat leakage decreases proportionally.[46] Therefore, subjects characterized by upper-body obesity, as determined by a high waist to hip ratio, might display a decreased postprandial thermogenesis. Studying the possible relation of the abdominal fat depot with the thermic response to glucose, we did not observe any correlation between VAT and GIT. This observation agrees with the findings of Buemann et al,[47] who concluded that body fat distribution had no effect on 24-hour energy expenditure. However, in another study, increased visceral fat accumulation was associated with increased diet-induced thermogenesis in response to a mixed meal in obese women, but not in men.[15] On the contrary, Tataranni et al[48] found a negative correlation between the thermic effect of food and the degree of upper-body obesity in obese women only. We suggest that discrepancies between the different reports probably refer to the fact that the waist to hip ratio measures the fat localized at the abdominal level, but the waist circumference does not discriminate between the amount of fat surrounding the abdominal wall and fat inside the abdomen. Probably the thermic shield–reducing heat leakage must be identified in the superficial fat. We do not possess any data to confirm this hypothesis that further support the need to better define fat distribution at the abdominal level, using quantitative approaches as CT scan.

In summary, our results show that in obese subjects with normal glucose tolerance, an exaggerated second-phase insulin secretion accounts for most of the glucose-induced hyperinsulinemia, arising to compensate defective insulin sensitivity. Our findings clearly show that an increased adiposity at the visceral level results in a deterioration of the metabolic picture by increasing insulin secretion and decreasing insulin sensitivity. We found that the increase in visceral fat content does not imply changes in RMR and GIT in obese subjects.

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