Role of Deep Abdominal Fat in the Association Between Regional Adipose Tissue Distribution and Glucose Tolerance in Obese Women

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Computed tomography (CT) was used to study the association between adipose tissue localization and glucose tolerance in a sample of 52 premenopausal obese women aged 35.7 ± 5.5 yr (mean ± SD) and with a body fat of 45.9 ± 5.5%. Body-fat mass and the body mass index (BMI) were significantly correlated with plasma glucose, insulin, and connecting peptide (C-peptide) areas after glucose (75 g) ingestion ($.40 \leq r \leq .51$, $P < .01$). Trunk-fat accumulation and the size of fat cells in the abdomen displayed highly significant correlations with postglucose insulin levels. The C-peptide area was also positively correlated with abdominal fat cell size ($r = .76$, $P < .01$) and was more closely associated with the sum of trunk skin folds ($r = .59$, $P < .001$) than with the extremity skin folds ($r = .29$, $P < .05$). Subcutaneous and deep–abdominal-fat areas measured by CT displayed comparable associations with the plasma insulin area ($r = .44$ and $.49$, respectively; $P < .001$) but marked differences in the associations with glucose tolerance. Indeed, subcutaneous abdominal fat was not significantly correlated with the glucose area, whereas deep abdominal fat showed a significant correlation ($r = .57$, $P < .001$) with the glucose area. Midthigh fat deposition measured by CT was not, however, correlated with plasma glucose, insulin, or C-peptide areas. Partial correlation analyses indicated that the effect of accumulation of deep abdominal fat on glucose tolerance was independent from total adiposity and that no association was observed between total adiposity and glucose tolerance after control for accumulation of deep abdominal fat. These results emphasize the importance of deep abdominal fat as an independent correlate of glucose tolerance in obese women. *Diabetes* 38:304–309, 1989

C-peptide	1 nM = 0.33 ng/ml	Insulin	1 pM = 0.139 μU/ml
Glucose	1 mM = 18 mg/dl		

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Received for publication 4 May 1988 and accepted in revised form 13 September 1988.

Many studies have shown that the regional distribution of adipose tissue is an important variable to consider in the association between obesity and disturbances in glucose homeostasis (1–6). Indeed, results from Kissebah and co-workers (2,6) and from Evans and co-workers (5,7) clearly indicate that upper-body obesity is associated with reduced glucose tolerance, hyperinsulinemia, and insulin resistance and that this effect of body-fat distribution is additive to and independent from the effect of obesity itself. Recent results from Peiris et al. (8) suggest that obesity is associated with insulin hypersecretion, whereas upper-body fat accumulation is associated with reduced hepatic insulin extraction and diminished insulin clearance (9).

In these studies, however, the proportion of upper-body fat was measured with the waist-to-hip circumferences ratio (WHR). Whereas this anthropometric variable provides a useful estimation of the proportion of abdominal or upper-body fat (6,10,11), it does not distinguish between accumulations of deep abdominal fat and subcutaneous abdominal fat. Computed tomography (CT) is a technology that allows the measurement of the amount of subcutaneous and deep fat at any site of the body (12,13), and results obtained with this technique have suggested that deep abdominal fat may be more closely associated with aberrations in glucose metabolism than subcutaneous fat (14,15).

The aim of this study was to investigate the associations between total body fat, body-fat distribution measured by anthropometric variables as well as by CT, and glucose metabolism in a sample of premenopausal obese women. Our results demonstrate the importance of deep abdominal fat and the negligible effect of thigh fat in the association between body-fat distribution and glucose metabolism.

MATERIALS AND METHODS

Subjects. Fifty-two premenopausal obese women gave written informed consent to participate to this study, which was approved by the Medical Ethics Committee of Laval Uni-

versity. Participants were subjected to a full physical examination by a physician, which included medical history. Women with cardiovascular disease, diabetes, or other endocrine disorders were excluded. Twelve women had plasma glucose values >140 but <200 mg/dl 2 h after an oral glucose tolerance test (OGTT) and were diagnosed as having impaired glucose tolerance following the classification of the National Diabetes Data Group (16). Measurements were performed while the subjects were in the early follicular phase of their menstrual cycle and in an apparent weight-stable period.

CT. CT was performed on a Siemens Somatom DRH scanner (Erlangen, FRG) with the methodology described by Sjöström et al. (12). The scanning was performed with 125 kV and a slice thickness of 8 mm. Briefly, the subjects were examined in the supine position with their arms stretched above their heads. Three CT scans were performed with a radiograph of the skeleton to determine the position of the scans: lower chest (Th8–Th9), abdomen (L4–L5), and midthigh. The position of each scan was measured at the nearest millimeter. Total and deep-fat areas at each scan were calculated by delineating the area with a graph pen and then computing the adipose tissue surfaces with an attenuation range of −30 to −190 HU (12,13). Deep–abdominal-fat area was measured by drawing a line within the muscle wall delineating the abdominal cavity. Subcutaneous-fat area was calculated by subtracting the amount of deep abdominal fat from the total fat area. The distance between the three scans was also measured to calculate the total adipose tissue volume from lower chest to midthigh. Although this adipose tissue volume does not represent the total adipose tissue volume, this volume has been shown to display a high correlation with body-density–derived fat mass (17).

Measurement of total body fat. Body density was measured by hydrostatic weighing (18) as previously described (19). The mean of six valid measurements was used to calculate the percentage of body fat from body density with the equation of Siri (20). Fat mass was obtained by multiplying the percentage of body fat by body weight. Pulmonary residual volume was measured with the helium-dilution method of Meneely and Kaltreider (21). Waist and hip circumferences as well as subcutaneous skin-fold thicknesses were measured by the procedures of the Airlie conference (22).

Abdominal and femoral fat cell sizes. To study the potential associations between abdominal and femoral adipose cell sizes and glucose metabolism, subjects were solicited for adipose tissue biopsies, and 17 women consented to undergo this procedure. In these subjects, adipose tissue was surgically obtained under local anesthesia from the abdominal (lateral to the umbilicus) and the femoral (anterior midthigh) fat deposits. About 500 mg of adipose tissue was obtained from each site. Fat cells were isolated by collagenase digestion (23), and mean fat cell size was determined with the use of a microscope equipped with a graduated ocular as previously described (24). The density of triolein was used to transform adipose cell volume into fat cell weight (19).

Glucose tolerance and plasma determinations. A 75-g oral glucose tolerance test was performed in the morning after an overnight fast. Blood samples were collected through a venous catheter from an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the determination of plasma glucose, insulin, and connecting peptide (C-peptide) concentrations. Plasma glucose was enzymatically measured (25), whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation (26). C-peptide was measured by a modification of the method of Heding (27), with the M-1221 antiserum, obtained from Novo (Bagsvaerd, Denmark), and polyethylene glycol precipitation (26). The postglucose plasma glucose, insulin, and C-peptide total areas under the curve were determined with the trapezoid method.

Statistical analyses. Associations between variables were quantified with the Pearson product-moment correlation coefficient. Partial correlation analyses were also performed to study the independent effects of total adiposity and of adipose tissue distribution on plasma glucose, insulin, and C-peptide concentrations. Finally, two subgroups of 10 obese women each with the highest and the lowest values of accumulation of deep abdominal fat were compared, and differences between subgroups were tested for significance with Student's *t* test.

TABLE 1
Correlation coefficients between body-density–derived fat mass and fat-free mass, anthropometric measures of body-fat distribution, and metabolic indices

	Fasting			Oral glucose tolerance test (areas)		
	Glucose	Insulin	C-peptide	Glucose	Insulin	C-peptide
Age	0.18	−0.11	0.05	0.16	0.02	0.27
Body mass index	0.65*	0.72*	0.59*	0.41†	0.51*	0.40†
Fat mass	0.64*	0.72*	0.61*	0.41†	0.47‡	0.42†
Fat-free mass	0.29§	0.45‡	0.28§	0.15	0.19	0.04
Skin folds						
Trunk	0.46‡	0.74*	0.68*	0.31§	0.67*	0.59*
Extremities	0.32§	0.48‡	0.46‡	0.13	0.26	0.29§
Trunk:extremities	0.16	0.35†	0.30§	0.20	0.50‡	0.41†
WHR	0.49‡	0.41†	0.36†	0.44‡	0.25	0.34†
Fat cell weight						
Abdominal	0.15	0.41	0.68†	−0.12	0.70†	0.76‡
Femoral	0.14	0.49§	0.43	−0.45	0.39	0.34

The plasma glucose, insulin, and C-peptide areas represent the total areas under the curve of their concentrations during the oral glucose tolerance test. WHR, waist-to-hip circumferences ratio.
*$P < .0001$, †$P < .01$, ‡$P < .001$, §$P < .05$.

TABLE 2
Correlations between adipose tissue (AT) volume and abdominal AT areas measured by computed tomography and metabolic variables

	Fasting			Oral glucose tolerance test (areas)		
	Glucose	Insulin	C-peptide	Glucose	Insulin	C-peptide
AT volume from lower chest to midthigh	0.61*	0.74*	0.62*	0.37†	0.52*	0.40†
Abdominal scan AT areas						
Deep	0.57*	0.59*	0.62*	0.57*	0.49‡	0.52
Subcutaneous	0.47‡	0.66*	0.50‡	0.16	0.44‡	0.29§
Deep/total	0.29§	0.17	0.31§	0.53*	0.25	0.41†

*$P < .0001$, †$P < .01$, ‡$P < .001$, §$P < .05$.

RESULTS

Subjects had a body mass index (BMI) of 34.2 ± 4.9 (mean ± SD) and a body fat of 45.9 ± 5.5%. Subjects' adiposity ranged from moderately (32.1% body fat) to massively (58.3% body fat) obese. All women were premenopausal, with ages ranging from 22.8 to 49.5 yr.

Correlations between age, body-density–derivated fat mass and fat-free mass, anthropometric measures of regional adipose tissue distribution, as well as abdominal and femoral fat cell weight and the metabolic profile, are shown in Table 1. Due to the homogeneity of the sample for age (women were all in the premenopausal stage), there was no significant correlation between age and metabolic variables. Body-fat mass was, however, significantly correlated with fasting and postglucose plasma glucose, insulin, and C-peptide concentrations ($.41 \leq r \leq .72$, $P < .01$ or $P < .001$). The proportion of subcutaneous trunk fat, as reflected by the trunk-to-extremity skin-fold ratio, was not significantly correlated with plasma glucose concentration in the fasting state or with the glucose area during the OGTT but was positively correlated with insulin and C-peptide areas. The proportion of abdominal fat, as estimated by the WHR, was positively correlated with the plasma glucose area ($r = .44$, $P < .01$) but not with the plasma insulin area during the OGTT. The WHR was also significantly correlated with the C-peptide area ($r = .34$, $P < .01$).

Whereas femoral fat cell size was only significantly correlated with fasting insulin levels and not correlated with insulin, glucose, or C-peptide areas, abdominal fat cell size was positively correlated with fasting C-peptide levels as well as with plasma insulin ($r = .70$, $P < .005$) and C-peptide ($r = .76$, $P < .001$) areas during the OGTT.

The total adipose tissue volume calculated from lower chest to midthigh was significantly correlated with the metabolic profile, the magnitude of the coefficients being close to the correlations observed for body-density–derived fat mass (Table 2). The deep and subcutaneous measures of adipose tissue areas at the abdominal region (L4–L5 scan) revealed, however, heterogeneous associations with metabolic indices. Indeed, whereas deep–abdominal-fat area was positively correlated with the plasma glucose area ($r = .57$, $P < .0001$), subcutaneous abdominal fat was not correlated with glucose area. The insulin area displayed comparable associations with deep and subcutaneous abdominal fat. Finally, the ratio of deep to total abdominal fat did not display a higher correlation with the metabolic profile than the absolute amount of deep abdominal fat.

Correlations for the CT measurements obtained for the

TABLE 3
Characteristics of subgroups of obese women with low and high accumulations of deep abdominal fat

	Low accumulation ($n = 10$)	High accumulation ($n = 10$)
Age (yr)	36.0 ± 4.0	36.1 ± 2.8
Body fat (%)	47.0 ± 6.4	49.8 ± 3.2
Adipose tissue area		
Abdominal		
Subcutaneous (cm^2)	551.8 ± 94.7	615.3 ± 141.0
Deep (cm^2)*	107.0 ± 33.4	186.7 ± 36.9
Deep/total*	0.16 ± 0.04	0.24 ± 0.05
Midthigh (cm^2)	517.5 ± 93.4	527.9 ± 94.9
Fasting		
Glucose (mg/dl)	89.0 ± 12.8	103.5 ± 10.6†
Insulin (μU/ml)	12.8 ± 8.3	21.0 ± 8.0‡
C-peptide (ng/ml)	2.9 ± 1.2	4.0 ± 1.1‡
Oral glucose tolerance test		
Glucose [$(mg \cdot dl^{-1} \cdot 180\ min^{-1}) \times 10^{-3}$]	20.5 ± 3.9	25.2 ± 3.4†
Insulin [$(\mu U \cdot ml^{-1} \cdot 180\ min^{-1}) \times 10^{-3}$]	11.4 ± 6.7	16.9 ± 5.5§
C-peptide [$(ng \cdot ml^{-1} \cdot 180\ min^{-1}) \times 10^{-3}$]	1.4 ± 0.5	1.8 ± 0.3‡

Values are means ± SD.
*Because subjects were assigned to these subgroups on the basis of the amount of deep abdominal fat, no statistical test was performed to measure group differences in accumulation of deep abdominal fat.
†$P < .01$, ‡$P < .05$, §$P = .06$.

lower chest and the midthigh scans were also computed (results not shown). In contrast to the L4–L5 scan, the deep-fat area at lower chest was not significantly correlated with glucose area. Subcutaneous-fat area at lower chest was, however, significantly correlated with fasting and postglucose plasma glucose, insulin, and C-peptide levels. The correlation between lower-chest subcutaneous area and glucose area was, however, due to the rather strong association observed between subcutaneous-fat area at lower chest and the deep–abdominal-fat area (r = .63, P < .0001). Indeed, partial correlation analyses indicated that after control for accumulation of deep abdominal fat, there was no significant association between lower-chest subcutaneous-fat area and glucose tolerance. On the other hand, there was still a significant association between intra-abdominal fat and glucose area after control for accumulation of subcutaneous fat at lower chest (r = .38, P < .01). Adipose tissue surfaces measured at the midthigh level were not significantly correlated with glucose, insulin, or C-peptide areas.

Because accumulation of deep abdominal fat (deep fat at L4–L5) appeared to be important in the determination of glucose tolerance, we further studied its effect by comparing the metabolic profile of women with low and high levels of deep abdominal fat (Table 3). These two subgroups of women did not differ in age or in percentage of body fat. These women also displayed comparable levels of subcutaneous abdominal and midthigh fat deposition. The subgroup of obese women with high accumulation of deep abdominal fat had almost twice as much deep abdominal fat than women with low levels of deep abdominal fat. Women with high deposition of deep abdominal fat also displayed significantly higher fasting plasma glucose, insulin, and C-peptide levels, as well as higher glucose and C-peptide areas, compared with the group of women with little deep abdominal fat. The difference between the two groups for the insulin area was close to statistical significance (P = .06).

Plasma glucose levels were significantly higher in the fasting state as well as 15, 30, 45, 60, and 90 min after glucose ingestion in women with high levels of deep abdominal fat compared with women with low accumulation of deep abdominal fat (Fig. 1). Whereas women with high levels of deep abdominal fat displayed significantly higher fasting plasma insulin and C-peptide levels in comparison with women with low abdominal fat, the postglucose levels were only significantly different at 60 and 90 min for insulin and at 60 min for C-peptide.

To further study the independent effects of accumulation of total body fat and of deep abdominal fat on glucose metabolism, partial correlation analyses were performed. After control for deep abdominal fat, body-fat mass was not significantly correlated with plasma glucose (r = .00), insulin (r = .14), or C-peptide (r = .05) areas. After control for total body fat, deep abdominal fat was, however, significantly associated with glucose area (r = .30, P < .01).

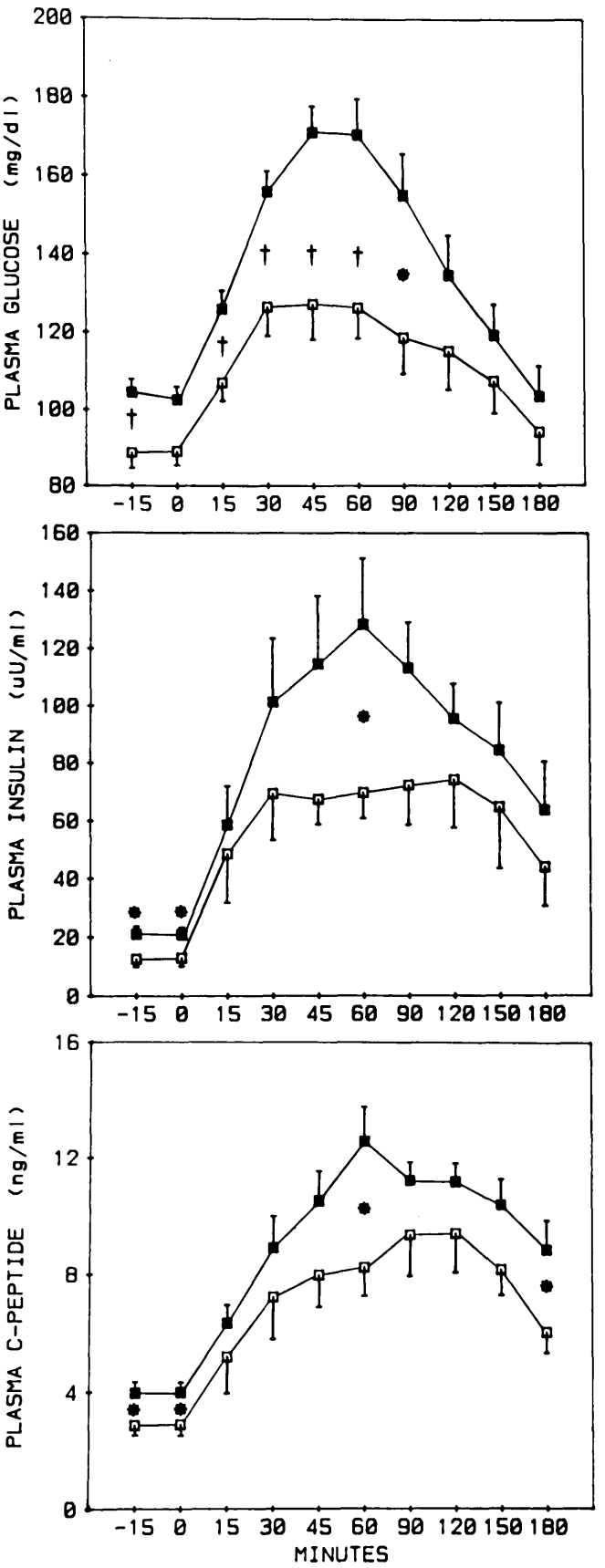

FIG. 1. Plasma glucose, insulin, and C-peptide concentrations in fasting state (−15 and 0 min) and during OGTT in obese women with high (■) or low (□) levels of deep abdominal fat (n = 10 subjects/group). *P < .05, †P < .01.

DISCUSSION

The results of this study indicate that, in a sample of premenopausal obese women selected for neither glucose metabolism nor for body-fat distribution, the absolute amount of body fat located in the deep abdominal region is an im-

portant variable to consider in the disturbance of glucose metabolism associated with obesity and body-fat distribution. Indeed, the level of deep abdominal fat was the body-fat distribution variable that displayed the highest association with the glucose area under the curve for the plasma glucose concentration during the OGTT. These results suggest that deep abdominal fat is an important correlate of the metabolic disturbances associated with body-fat distribution. After control for total adipose tissue mass, accumulation of deep abdominal fat remained significantly associated with glucose tolerance. Furthermore, obese women with low levels of deep abdominal fat did not display glucose intolerance, and high levels of deep abdominal fat were required to observe the aberrations in glucose metabolism associated with the high adipose tissue mass. These results are concordant with those of Sparrow et al. (14), who reported in a sample of 41 men that the amount of deep abdominal fat determined by CT was a significant correlate of plasma glucose levels measured 2 h after oral glucose administration. In a sample of 15 men and 31 women that included 12 diabetic subjects, Fujioka et al. (15) reported that the proportion of visceral fat measured by CT was correlated with the plasma glucose area under the curve after an OGTT. However, these two studies have used the BMI, which is a crude estimate of the amount of total body fat. In this study, body-fat mass was measured with the underwater weighing technique, and results indicate that deep abdominal fat is a more important correlate than the level of obesity itself. In addition, only the study of Fujioka et al. (15) reported plasma insulin levels, and their sample included diabetic subjects >50 yr old who had exhausted β-cell activity. In this study, none of the subjects was diabetic, and they were all <50 yr of age. We believe that plasma insulin and C-peptide levels measured in such a homogeneous sample may better reflect the adaptation of the pancreas to obesity and abdominal fat accumulation in young obese women, without the concomitant effect of age.

Our results also indicate that, in contrast to glucose tolerance, levels of plasma insulin and C-peptide areas are not correlated with the accumulation of deep abdominal fat after control for total body fat. Rather, it appears that the level of subcutaneous trunk fat as well as the extent of the abdominal fat cell hypertrophy are two important correlates of pancreatic insulin secretion. These observations are concordant with the results of Peiris et al. (8), who reported that increasing adiposity per se is associated with a higher pancreatic insulin secretion, whereas upper-body (abdominal) obesity is more closely associated with a reduced hepatic extraction of insulin. This phenomenon is probably responsible for the decreased metabolic clearance of insulin associated with abdominal obesity (9). Results of this study are compatible with the notion that accumulation of subcutaneous trunk fat, associated with the hypertrophy of subcutaneous abdominal adipocytes, is related to high pancreatic insulin secretion.

The mechanism for the association between the amount of deep abdominal fat and glucose tolerance is also not known. However, the high lipolytic activity of omental fat cells (28), their documented resistance to the antilipolytic action of insulin (29), and their proximity to the liver through the portal circulation are considered important factors of a hypothetical model proposed for the association between accumulation of visceral abdominal fat and insulin resistance (6,10,11).

It is, however, important to further emphasize that the association between deep abdominal fat and glucose tolerance as well as the relation of subcutaneous abdominal fat cells' hypertrophy to pancreatic insulin secretion may not necessarily reflect cause-effect relationships and that one or many additional factors may be involved. In this regard, the research of Kissebah et al. (6) has clearly shown that a high androgenic activity was associated with both an increased proportion of abdominal fat and a decreased insulin sensitivity (6,30). However, after control for sex hormone levels, they found that there was still a significant association between body-fat distribution and aberrations in glucose metabolism (6).

In summary, this study emphasizes the importance of deep abdominal fat as an independent correlate of glucose tolerance in premenopausal obese women. In addition, increased levels of subcutaneous trunk fat, associated with subcutaneous fat cell hypertrophy, are related to insulin hypersecretion.

ACKNOWLEDGMENTS

We are grateful to the subjects for their excellent collaboration, as well as to Judith Maheux, Claude Leblanc, Henri Bessette, Marie-Christine Pouliot, and Pierre Samson of the Physical Activity Sciences Laboratory for support in the data collection. We also thank Yolande Montreuil, Rachel Duchesne, Marie Martin, and Suzanne Brulotte for excellent assistance.

This study was supported by the Quebec Heart Foundation, The Canadian Fitness and Lifestyle Research Institute, the Natural Sciences and Engineering Research Council (NSERC) of Canada, and by the Fonds de la recherche en santé du Québec (FRSQ).

J.-P.D. is the recipient of an FRSQ research scholarship. M.F. is the recipient of an NSERC fellowship.

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