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Distribution of Subcutaneous Fat Predicts Insulin Action in Obesity in Sex-specific Manner

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Abstract

The pattern of adipose tissue (AT) distribution is an important predictor of metabolic risk. The aim of this study was to analyze the association of peripheral (insulin-mediated glucose disposal—M) and hepatic (suppression of endogenous glucose production—EGP) insulin action with abdominal (subcutaneous abdominal AT—SAAT, intraabdominal AT—IAAT) and thigh AT depots in obese individuals. Fifty-seven Pima Indians with normal glucose tolerance underwent magnetic resonance imaging (MRI) and euglycemic-hyperinsulinemic clamp. M was negatively related to intraperitoneal IAAT ($P = 0.02$) and deep SAAT ($P = 0.03$). Suppression of EGP was negatively related to total ($P < 0.05$) or deep SAAT ($P < 0.05$ and $P = 0.01$, respectively), and total or intraperitoneal IAAT ($P = 0.009$ and $P = 0.002$, respectively). A significant interaction with sex was found in the association between superficial SAAT and M, so that in women, but not men, M negatively correlated with superficial SAAT ($P = 0.02$). In stepwise regression analysis, both M ($r^2 = 0.09$) and EGP suppression ($r^2 = 0.17$) were associated only with intraperitoneal IAAT in the whole group. In the sex-specific analysis (because of the significant interaction), lower M was associated with higher deep SAAT ($r^2 = 0.15$) in combination with lower superficial SAAT ($r^2 = 0.09$) in men, and with higher superficial SAAT ($r^2 = 0.29$) in combination with lower thigh subcutaneous AT ($r^2 = 0.16$) in women. Although intraperitoneal IAAT and deep SAAT were major predictors of peripheral and hepatic insulin action in obese Pima Indians, the largest variance in M rate was explained in a sex-specific manner by relative size of subcutaneous AT depots.

INTRODUCTION

Obesity is considered an important risk factor for insulin resistance; however, many obese individuals are still relatively insulin sensitive (1,2). Excess accumulation of adipose tissue (AT) in the upper part of the body, particularly when it is accumulated in the intraabdominal area, is associated with insulin resistance, glucose intolerance, and type 2 diabetes mellitus (3–8). However, peripheral insulin action is associated also with subcutaneous abdominal AT (SAAT) (2,9,10). Adding to the complexity, different layers within intraabdominal AT (IAAT) and SAAT may have distinct anatomic and metabolic characteristics (i.e., deep layer of SAAT, which is located between the abdominal wall and the fascia superficialis and contains adipocytes with high lipolytic activity (11), as well as the intraperitoneal portion of IAAT

which drains into portal circulation) and thus may be more metabolically detrimental than other abdominal AT depots (2,12–14). In addition, gluteofemoral AT has been identified as a “sink” for circulatory fatty acids, thereby being protective against insulin resistance (15).

Pima Indians of Arizona have a high prevalence of obesity and type 2 diabetes mellitus (16). Prospectively, both obesity and decreased insulin-mediated glucose disposal (M) predict type 2 diabetes mellitus in Pima Indians with normal glucose tolerance (17). A previous study in Pima Indians with a wide range of adiposity showed that SAAT, but not IAAT, was a significant predictor of M after adjustment for percentage of body fat (BF) (10). However, the small sample size ($n = 20$) prevented evaluation of the relative contribution of different AT depots to insulin action in Pima Indians.

In this study we hypothesized that anatomical subdivisions of classic abdominal AT depots and addition of thigh AT may improve the predictive role of AT distribution on insulin action in obese Pima Indians with normal glucose tolerance.

METHODS AND PROCEDURES

The Subjects in this study were at least half Pima (or closely related Tohono O’Odham) Indians from the Gila River Indian Community. All subjects were between 18 and 45 years of age, obese (percentage of BF ≥ 25 for males, ≥ 30 for females), with normal plasma fasting and 2-h glucose concentration values according to a 75-g oral glucose tolerance test (World Health Organization 1999 criteria; <110 and <140 mg/dl, respectively), and nonsmokers at the time of the study. Acute and chronic diseases were excluded on the basis of medical history, physical examination, and routine laboratory tests. Subjects who had evidence of serious medical conditions (including autoimmune, cerebrovascular, and ischemic heart disease) or were taking any medications were excluded. The protocol was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases, and all subjects provided written informed consent before participation. To minimize changes in glucose and adipose metabolism resulting from ovarian hormonal effects, the female subjects were studied during the follicular phase (days 0 through 14) of the menstrual cycle.

All subjects were admitted for 10–14 days to the National Institutes of Health Clinical Research Unit in Phoenix, Arizona, and were placed on a weight-maintaining diet (containing 50% of calories as carbohydrates, 30% as fat, and 20% as protein) for 2–3 days before clinical testing. At least 3 days after admission, and after a 12-h overnight fast, subjects underwent a 2-h 75-g OGTT to exclude impaired glucose tolerance or diabetes. Body composition was measured by dual-energy X-ray absorptiometry using a total body scanner (DPX-L; Lunar Radiation, Madison, WI) as described previously (18).

Adipose tissue distribution at the abdomen and the thigh was measured by magnetic resonance imaging (MRI) on a General Electric 1.5 T Sigma scanner (General Electric, Milwaukee, WI). Images were acquired using a spin lattice longitudinal relaxation time-weighted spin echo pulse sequence with a repetition time of 700 ms and a minimum full (14–35 ms) echo time. A sagittal localizing scan was used to center transverse sections on the level of the bifurcation of the aorta (~4th–5th lumbar interspace) and midthigh. A series of transverse 7-mm sections were scanned with a gap of 2 mm to prevent signal crossover from adjacent sections. Slices with a resolution of 256×256 were analyzed using image analysis software (ImageJ, Bethesda, MD). A histogram of pixel intensity in the region of interest was displayed, and the intensity corresponding to the nadir between the lean and fat peaks was used as a cutpoint. Three slices were analyzed in each subject, and the average value for each region of interest was used for further analyses. Abdominal AT compartments were defined as proposed previously (19): (i) IAAT as the sum of the pixels in the area defined by internal boundaries of the abdominal

muscle wall; (ii) SAAT as the sum of the pixels located outside of the outermost boundaries of the muscle wall. IAAT was further subdivided into intraperitoneal and retroperitoneal; in case the demarcation line was not visible (majority of scans), it was defined arbitrarily by drawing a straight line across the anterior border of L4–L5 and the psoas muscles, continuing on a tangent toward the posterior borders of ascending and descending colon, and extending to the abdominal wall. SAAT was further subdivided into superficial and deep areas by identifying fascia that demarcates these two depots. SAAT was also divided into anterior and posterior compartments by drawing a perpendicular line along the anterior edge of the vertebral bodies (13). At the thigh, subcutaneous and internal AT were separated by manual tracings around the fascia lata surrounding skeletal muscle. Bone marrow AT was excluded.

Insulin action was assessed at physiological insulin concentrations during hyperinsulinemic-euglycemic glucose clamp (20). Briefly, after overnight fast a primed (30 μ Ci) continuous (0.3 μ Ci/min) 3-[3 H] glucose infusion was started to determine endogenous glucose production (EGP). At least 2 h after starting the isotope infusion, a primed continuous intravenous insulin infusion was administered for 100 min at a constant rate of 40 mU/m²/min. Average systemic insulin concentration during last 40 min of clamp was 53 mU/l (range 49–63). Blood samples for measurement of 3-[3 H] glucose specific activity were collected at the end of the basal period and every 10 min during the final 40 min of insulin infusion. Under basal (i.e., fasting) conditions, EGP was calculated as the 3-[3 H] glucose infusion rate divided by the steady-state plasma 3-[3 H] glucose specific activity. The rate of total insulin-stimulated glucose disposal was calculated for the last 40 min of the insulin infusion and was corrected for the rate of EGP calculated from Steele's equation (21). The degree of hepatic insulin sensitivity was calculated as the ratio of absolute differences (clamp minus fasting) in EGP and plasma insulin concentrations. Individual variation in plasma glucose and insulin concentrations during the clamp was taken into account in the calculation of the M (20,22). All measurements derived from the clamp were normalized to estimated metabolic body size (or fat-free mass + 17.7 kg) to account for the fact that the intercept of the relationship between fat-free mass and resting metabolic rate is not zero (23).

Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin concentrations by an automated immunoassay (Access; Beckman Instruments).

Statistical analyses were performed using the software of the SAS Institute (Cary, NC). Normality of the data was tested by the Shapiro–Wilk test. The values for non-normally distributed variables were logarithmically transformed before analyses to approximate normal distributions. If normal distribution was not achieved by logarithmic transformation, nonparametric tests were used. The Student's *t*-test or Wilcoxon–Mann–Whitney test was used for sex comparison. Pearson (*r*) or Spearman (*p*) correlation was used to test for correlation between the variables. The effect of confounders was accounted for by partial correlation or by general linear regression analysis, which was also used to test for interaction terms with sex. Stepwise linear regression analysis was used to determine which of the AT depots had the largest effect on peripheral and hepatic insulin action. Significant outliers (calculated by extreme studentized deviate method) were not included in the regression models. *P* values <0.05 were considered to be statistically significant.

RESULTS

Anthropometric and metabolic characteristics of the subjects and comparisons between the sexes are shown in Table 1. Women had higher BF, superficial SAAT in the abdomen, subcutaneous AT in the thigh, and basal EGP compared to men.

Figure 1 depicts the distribution of values for different abdominal AT depots across the group and shows their relationship with age. After adjustment for sex in the partial correlation, age was negatively associated with all subcutaneous abdominal depots, whereas IAAT and its subdepots were positively associated with age. No significant correlation was found between age and AT depots in the thigh (Figure 1) or BF ($\rho = -0.16$, $P = 0.2$).

After adjustment for age and sex in the partial correlation, all thigh and SAAT depots were positively correlated with BF and were highly correlated among themselves. The IAAT depots were also correlated among themselves, and total IAAT correlated with BF and all subcutaneous depots. However, intraperitoneal IAAT was not correlated with superficial SAAT or any of the measures of thigh AT. Retroperitoneal IAAT was not correlated with either BF or internal thigh AT (Table 2).

Fasting plasma insulin concentration ($r = 0.43$, $P = 0.001$), but not M ($\rho = -0.20$, $P = 0.1$), fasting EGP ($r = -0.06$, $P = 0.7$), or suppression of EGP ($r = -0.24$, $P = 0.07$) were associated with BF. Fasting plasma insulin levels were positively related to SAAT depots (total, superficial, and deep SAAT shown in Figure 2; anterior and posterior SAAT, $r = 0.45$ and $r = 0.44$, $P = 0.0006$ and $P = 0.0007$, respectively) as well as to total and intraperitoneal IAAT (Figure 2). M was negatively related to deep SAAT and to intraperitoneal IAAT and showed borderline inverse association with total SAAT (Figure 3). The interaction term sex $\times$ superficial SAAT indicated a sex difference in the relationship of fasting plasma insulin concentration and M with superficial SAAT. In fact, higher fasting plasma insulin (Figure 2) and lower M (Figure 3) were associated with higher superficial SAAT in women but not in men ($P > 0.3$). Fasting EGP was not associated with any of the abdominal or thigh AT depots (data not shown). The degree of EGP suppression was negatively associated with total and deep SAAT, and total or intraperitoneal IAAT (Figure 4). No significant associations were found between AT depots in the thigh and fasting plasma insulin levels or peripheral or hepatic insulin action (data not shown).

In the stepwise linear regression analysis including all measured AT depots adjusted for age and sex in the initial step, intraperitoneal IAAT explained the largest variance in both peripheral ($r^2 = 0.09$, $P = 0.02$) and hepatic insulin action ($r^2 = 0.17$, $P = 0.002$) in the whole group. Because of the significant interaction term between sex and superficial SAAT, the stepwise linear regression analysis was performed also in each sex separately. Lower M was explained by increased deep SAAT ($r^2 = 0.15$) and decreased superficial SAAT ($r^2 = 0.09$) in men, and by increased superficial SAAT ($r^2 = 0.29$) and decreased subcutaneous thigh fat ($r^2 = 0.16$) in women. Increased intraperitoneal IAAT was the only determinant of reduced hepatic insulin action in both men ($r^2 = 0.16$, $P = 0.02$) and women ($r^2 = 0.18$, $P = 0.05$) in the stepwise linear regression analysis.

DISCUSSION

In this study increased intraperitoneal and deep subcutaneous abdominal fat were significant predictors of impaired peripheral and hepatic insulin action in obese Pima Indians with normal glucose regulation. In women, increased fasting plasma insulin levels and reduced peripheral insulin sensitivity were also associated with enlarged superficial SAAT depot. Although intraperitoneal fat explained the largest variance in both peripheral and hepatic insulin sensitivity in the whole group, in the sex separate analysis the largest variance in peripheral insulin action was explained by more deep and less superficial subcutaneous abdominal fat in men, and by more superficial subcutaneous abdominal fat and less subcutaneous thigh fat in women.

The etiological role of an increased accumulation of fat in the upper body in the pathogenesis of metabolic and cardiovascular complications of obesity has been recognized for a long time (3,24). The development of computed tomography and MRI has allowed quantification of different AT compartments in the body (25–27). Several studies have found that insulin action was negatively related to the size of the IAAT (4,5,8,28). As intraabdominal adipocytes are more sensitive to lipolytic stimuli compared to subcutaneous fat cells *in vitro* (29,30) and fatty acid overload significantly impairs insulin action (31), it has been suggested that increased visceral fat decreases insulin action via increased delivery of fatty acids in insulin-sensitive tissues (12). Isotope dilution studies confirmed that fatty acid uptake in the liver and in the periphery was positively related to visceral AT area and that the relative contribution of lipolysis from the visceral compartment to the systemic fatty acid pool was higher in obese compared to lean individuals (32). Fatty acids of intraabdominal origin, however, represent only a minor fraction of fatty acids utilized by the liver and skeletal muscle (32). Thus, additional mechanisms were proposed to explain the detrimental effect of increased intraabdominal fat accumulation on hepatic and peripheral insulin action compared to the subcutaneous depot including differences in endocrine function such as secretion of leptin (33), adiponectin (34), or interleukin-6 (35).

In support of the “portal theory” (12), the intraperitoneal depot which is drained into portal circulation, but not the retroperitoneal depot which is drained into systemic circulation, was a significant determinant of hepatic insulin action in our study. Similar to the report by Abate *et al.* (2), the intraperitoneal but not the retroperitoneal fat was associated also with reduced peripheral insulin action. This may be related to higher lipolytic sensitivity of intraperitoneal adipocytes compared to adipocytes from the retroperitoneal depot (36). Other studies found that both retro- and intraperitoneal fat were negative determinants of glucose uptake in obese men and women (7,8). These studies, however, did not account for possible incomplete suppression of EGP.

In several study groups (2,9), including Pima Indians (10), SAAT was associated with peripheral insulin action at least as strongly as intraabdominal fat. Although less sensitive to lipolytic stimuli than visceral adipocytes, subcutaneous abdominal adipocytes have higher overall rates of basal lipolysis compared to intraabdominal adipocytes (29,30,37) and supply the majority of fatty acids utilized in the liver and skeletal muscle (32). In our study, SAAT was a borderline predictor of peripheral and a significant predictor of hepatic insulin action. In the whole group, these relationships were explained by deep SAAT, which may contain adipocytes with relatively higher lipolytic activity compared to superficial SAAT (11). This is consistent with some studies (13,14) but different from other reports (7,8). As mentioned earlier, glucose disposal might have been underestimated in the later two studies by not taking into account EGP. Furthermore, fascia superficialis was visible in all scans in our study; thus, we were able to measure the actual area of the superficial and deep AT in contrast to these two studies where it was assessed arbitrarily as the anterior and posterior SAAT (7,8). As in those studies, if SAAT was arbitrarily defined as anterior or posterior, insulin action was not associated with either depot.

In agreement with other studies (38,14), women had more superficial SAAT and similar amount of deep SAAT compared to men, and superficial SAAT was also a better predictor of fasting plasma insulin levels compared to deep SAAT. Here we show that increased superficial SAAT in women predicted lower peripheral but not hepatic insulin action. Whether it reflects different metabolic characteristic of adipocytes in the superficial depot is not clear. In fact, the *in vitro* study showing higher lipolytic response in adipocytes from the deep SAAT was performed on AT samples from predominantly (seven of eight) men (11). To our knowledge, no comparison of adipocytes from the two subcutaneous abdominal fat layers has yet been reported in women.

It has been suggested that lower-body fat is protective against insulin resistance by buffering the flux of fatty acids in the circulation in the postprandial period (15). Although subcutaneous AT in the thigh was not associated with insulin action, stepwise linear regression analysis showed that after adjustment for superficial SAAT increased amount of subcutaneous thigh fat was a positive determinant of peripheral insulin action in women. In contrast, glucose disposal rate in men was positively associated with superficial SAAT after adjustment for deep SAAT. Altogether these data indicate that increased accumulation of fat in superficial SAAT in men and in subcutaneous thigh fat in women may counteract obesity-related impairment of peripheral insulin action.

The cross-sectional and observational design of our study does not permit interpretation of the direction of the relationships. As reviewed elsewhere (39), insulin promotes fat storage by stimulating both adipogenesis and lipogenesis, and inhibiting lipolysis. We cannot exclude that increased accumulation of fat in abdominal depots may in part reflect hyperinsulinemia as the compensatory response to insulin resistance. Also, it must be noted that hepatic insulin sensitivity in >40% of the study group with complete suppression of EGP depends on fasting EGP, which was not related to any of the AT depots. Moreover, EGP during the clamp and consequently rates of glucose disposal might have been further underestimated due to dilution effect of unlabeled glucose when using a constant isotope infusion (40). Multicollinearity between different AT depots entered in the stepwise regression model is another potential limitation making difficult to dissect out the depot which explains the largest variance in insulin action. However, the depots chosen by the stepwise modeling were similar in strength of association to those in the univariate analysis.

In conclusion, increased intraperitoneal and deep subcutaneous abdominal fat accumulation was a negative predictor of insulin effect on both glucose disposal and EGP in obese Pima Indians with normal glucose tolerance. Because peripheral insulin action was negatively related to superficial SAAT in women but not in men, and because it was not related to total or retroperitoneal AT in either sex, anatomic subdivision of SAAT and visceral abdominal AT provides additional important information about metabolic risk related to obesity in this population.

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Figure 1.

Spearman correlation (partial sex, regression lines, and 95% confidence interval) between age and the abdominal and thigh adipose tissue depots. Symbols: closed circles, men; open circles, women. *Correlation coefficients without significant outliers (indicated by arrows). sc., subcutaneous.

Figure 2.

Pearson correlation between abdominal (abd.) adipose tissue (AT) depots (adjusted for age and sex) and fasting plasma insulin concentration. Symbols: closed circles, men, open circles, women. *Sex interaction term $P = 0.03$. Regression lines and 95% confidence interval are shown only for significant relationships (indicated in bold). Dashed line represents regression line for women. sc., subcutaneous.

Figure 3.

Spearman correlation between abdominal (abd.) adipose tissue (AT) depots (adjusted for age and sex) and insulin-mediated glucose disposal rate. Symbols: closed circles, men; open circles, women. *Sex interaction term $P = 0.04$. Regression lines and 95% confidence interval are shown only for significant relationships (indicated in bold). Dashed line represents regression line for women. EMBS, estimated metabolic body size; sc., subcutaneous.

Figure 4.

Pearson correlation between abdominal (abd.) adipose tissue (AT) depots (adjusted for age and sex) and insulin-mediated inhibition of endogenous glucose production. Symbols: closed circles, men, open circles, women. Regression lines and 95% confidence interval are shown only for significant relationships (indicated in bold).

Table 1
Anthropometric and metabolic characteristics of the study population

	All (n = 57)	Men (n = 35)	Women (n = 22)
Age (years)	25 (21, 34)	25 (23, 34)	24 (20, 34)
Body fat (%)	35 (6)	32 (4)	40 (4) [‡]
Subcutaneous abd. AT (cm ²)	587 (467, 693)	554 (153)	643 (533, 727)
Superficial	236 (89)	192 (64)	294 (257, 339) [‡]
Deep	350 (114)	362 (113)	332 (115)
Anterior	193 (159, 252)	192 (69)	218 (189, 254)
Posterior	377 (93)	361 (90)	402 (93)
Intraabdominal AT (cm ²)	121 (42)	129 (42)	110 (39)
Intraperitoneal	77 (33)	83 (33)	68 (31)
Retroperitoneal	43 (34, 50)	44 (37, 50)	42 (16)
Subcutaneous thigh AT (cm ²)	150 (59)	128 (50)	185 (55) [‡]
Internal thigh AT (cm ²)	37 (14)	32 (22, 47)	38 (12)
Fasting glucose (mg/dl)	90 (8)	90 (8)	90 (8)
2-h glucose (mg/dl)	114 (94, 127)	114 (94, 127)	112 (17)
Fasting insulin (mU/l)	10 (7, 13)	10 (7, 12)	12 (5)
M (mg/kg _{EMBS} ·min)	2.6 (2.3, 3.1)	2.7 (2.3, 3.1)	2.7 (0.7)
EGP-fasting (mg/kg _{EMBS} ·min)	1.7 (0.3)	1.6 (0.3)	1.8 (1.6, 1.9) [*]
EGP-insulin (mg/kg _{EMBS} ·min)	0.3 (0, 0.6)	0.1 (0, 0.6)	0.4 (0.3)

Data are means (s.d.) for normally distributed variables or median (25th, 75th percentile) for non-normally distributed variables.

AT, adipose tissue; EMBS, estimated metabolic body size; EGP, endogenous glucose production; M, insulin-mediated glucose disposal.

^{*} $P < 0.05$

[‡] $P < 0.001$

[‡] $P < 0.0001$, sex comparison by Student's *t*-test or Wilcoxon–Mann–Whitney test.

Table 2
Spearman correlation (partial age and sex) between percentage of body fat and abdominal and thigh AT depots

	Body fat	Subcutaneous abdominal AT				Intraabdominal AT			Thigh AT	
		Total	Superf.	Deep	Ant.	Post.	Total	Intrap.	Retrop.	Total
SAAT	0.68 ^{\$}	—								
Superficial	0.61 ^{\$}	0.75 ^{\$}	—							
Deep	0.56 ^{\$}	0.92 ^{\$}	0.52 ^{\$}	—						
Anterior	0.63 ^{\$}	0.92 ^{\$}	0.75 ^{\$}	0.84 ^{\$}	—					
Posterior	0.68 ^{\$}	0.92 ^{\$}	0.65 ^{\$}	0.88 ^{\$}	0.76 ^{\$}	—				
IAAT	0.36 [†]	0.57 ^{\$}	0.36 [†]	0.54 ^{\$}	0.53 ^{\$}	0.51 ^{\$}	—			
Intrapertitoneal	0.31 [*]	0.51 ^{\$}	0.24	0.54 ^{\$}	0.49 [†]	0.47 [†]	0.91 ^{\$}	—		
Retropertitoneal	0.20	0.34 [*]	0.33 [*]	0.27 [*]	0.28 [*]	0.28 [*]	0.62 ^{\$}	0.27 [*]	—	
Thigh AT	0.69 ^{\$}	0.66 ^{\$}	0.56 ^{\$}	0.61 ^{\$}	0.61 ^{\$}	0.72 ^{\$}	0.36 [†]	0.26	0.29 [*]	—
Subcutaneous	0.66 ^{\$}	0.56 ^{\$}	0.51 ^{\$}	0.52 ^{\$}	0.51 ^{\$}	0.62 ^{\$}	0.30 [*]	0.16	0.31 [*]	0.95 ^{\$}
Internal	0.30 [*]	0.38 [†]	0.26	0.38 [†]	0.36 [†]	0.47 [†]	0.19	0.26	−0.02	0.49 [†]

Ant., anterior; AT, adipose tissue; IAAT, Intraabdominal AT; Intrap., intraperitoneal; Post., posterior; Retrop., retroperitoneal; SAAT, Subcutaneous abdominal AT; Subc., subcutaneous; Superf., superficial.

* $P < 0.05$

[†] $P < 0.01$

[‡] $P < 0.001$

^{\$} $P < 0.0001$.