Original Articles

Does Intra-Abdominal Adipose Tissue in Black Men Determine Whether NIDDM Is Insulin-Resistant or Insulin-Sensitive?

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Insulin resistance in black Americans with non-insulin-dependent diabetes mellitus (NIDDM) is found in only 60% of those with a body mass index (BMI) of <30 kg/m^2, suggesting that NIDDM can occur independent of peripheral insulin resistance. When insulin resistance is present, it is not necessarily correlated with obesity. Numerous studies have shown that increased amounts of intra-abdominal adipose tissue are associated with various metabolic abnormalities. We therefore investigated whether the occurrence of insulin resistance in black NIDDM men could be explained by the pattern of body adipose tissue distribution rather than total adiposity. Twenty-two near-normoglycemic black men (fasting plasma glucose [mean ± SD] = 104 ± 10 mg/dl, HbA_{1c} = 4.6 ± 0.78%, age 48.9 ± 9.2 years, and BMI 26.5 ± 2.4 kg/m^2) were studied. The euglycemic insulin clamp with 1 mU · kg^{-1} · min^{-1} insulin infusion and D-[3-^{3}H]glucose was used to measure insulin action. Whole-body computed tomography with 22 scans was used to determine body composition. Total body adipose tissue was 19.6 ± 7.5 l, and the percentage of body fat was 27 ± 7. Glucose disposal ranged from 2.5 to 8.1 mg · kg^{-1} · min^{-1} (10 men were insulin-sensitive and 12 were insulin-resistant). There was a strong inverse correlation between glucose disposal and the proportion of total adipose tissue in the intra-abdominal region (r = −0.78, P < 0.001), while there was no correlation between glucose disposal and total muscle volume, BMI, total adipose tissue volume, or total subcutaneous adipose tissue volume. When insulin resistance is present, it is highly correlated with an increase in the proportion of intra-abdominal adipose tissue. The data raise the possibility that insulin resistance in black NIDDM men may be a consequence of increased intra-abdominal adipose tissue mass. *Diabetes* 44:141–146, 1995

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NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; CT, computed tomography; R_D, glucose disposal rate; HPLC, high-performance liquid chromatography; WHR, waist-to-hip ratio; kg-LBM, kilogram of lean body mass; HDL, high-density lipoprotein.

The role of insulin resistance in the pathogenesis of non-insulin-dependent diabetes mellitus (NIDDM) remains controversial. Some investigators claim that insulin resistance in muscle is the major underlying genetic abnormality (1–4) and that an additional defect in insulin secretion impairs the individual's ability to sustain a compensatory hyperinsulinemia. Others claim that the primary genetic defect is in the β-cell (5–7) and that insulin resistance is the result of an acquired abnormality, such as physical inactivity and/or obesity, which modulates the age of onset of clinical NIDDM.

Our studies in black NIDDM subjects suggest that NIDDM occurs independent of insulin resistance (8–11). Most of our NIDDM subjects who are at ideal body weight (body mass index [BMI] <24 kg/m^2) have normal insulin action as determined by using the euglycemic insulin clamp. Those who are clearly obese (BMI >28.5 kg/m^2) are insulin-resistant, while those with a BMI between 24 and 28.5 kg/m^2 are as likely to have normal insulin action as to be markedly insulin-resistant. The data can be explained by one of several hypotheses. There may be two genetically discrete forms of NIDDM: an insulin-resistant variant for which the primary abnormality is in muscle and an insulin-sensitive variant for which the primary abnormality is decreased insulin secretion from the β-cell. Another possibility is that insulin resistance is an acquired, not a primary, abnormality of muscle. Our data are not consistent with insulin resistance being acquired as a result of generalized obesity. Therefore, we sought to determine if insulin resistance in black NIDDM subjects could be explained by alterations in adipose tissue distribution and body composition. Using sensitive computed tomography (CT) techniques for measuring fat distribution, we studied 22 black, normal-weight or moderately obese NIDDM men. Our data indicate that in this population intra-abdominal adipose tissue mass is highly correlated with insulin resistance and could be a major determinant of insulin action.

RESEARCH DESIGN AND METHODS

Twenty-two near-normoglycemic black NIDDM men were selected for study (fasting plasma glucose [mean ± SD] = 104 ± 10 mg/dl and HbA_{1c} = 4.6 ± 0.8%) (Table 1). The duration of the diagnosis of diabetes ranged from 1 to 10 years. Seventeen subjects were on diabetic diet therapy only. Their glucose area during a standard 2-h oral glucose tolerance test is significantly greater than that of our published normal nondiabetic

TABLE 1
Characteristics of 22 NIDDM men

	Mean	Range
Age (years)	48.9 ± 9.2	35–64
BMI (kg/m^2)	26.5 ± 2.4	20.7–30.2
Height (cm)	174.6 ± 5.4	165–184
Weight (kg)	81.3 ± 9.4	60.7–95.0
WHR	0.93 ± 0.08	0.85–1.17
Total body fat (l)	19.2 ± 6.5	4.7–31.3
Percentage of body fat	27 ± 7	13–37
Fasting plasma glucose (mg/dl)	104 ± 10	86–120
Fasting plasma insulin (μU/ml)	11 ± 7	3–29

Data are means ± SD.

control subjects (23,402 ± 787 vs. 14,469 ± 610 mg · min^{-1} · dl^{-1}) (8). Four subjects were taking low doses of sulfonylureas, and one was taking insulin. The glucose disposal rates (R_D) of the five subjects taking pharmacological agents had been measured previously when diabetes was well controlled with diet therapy alone; R_D values were virtually identical when diabetes was well controlled with or without subjects receiving pharmacological agents. The use of subjects with NIDDM who are near-normoglycemic allows for the study of glucose metabolism unencumbered by hyperglycemia. Subjects had a constant body weight for at least 3–4 months before study. No patient had significant renal, hepatic, or cardiac disease, and none were using agents known to affect glucose metabolism. All subjects had consumed at least 150 g carbohydrate for 3 days before any study.

The study was approved by the Institutional Review Board of the State University of New York Health Science Center at Brooklyn. All patients gave written informed consent. The patients were studied in the Clinical Research Center at University Hospital at Brooklyn.

Body composition determined by axial CT. A General Electric Pace scanner (Milwaukee, WI) was used to calculate the total visceral, intra-abdominal, and subcutaneous adipose tissue volume and total muscle volume. Scanning was performed at 120 kV with a slice thickness of 5 mm with the subjects' arms stretched over their heads. Twenty-two scans were performed at the anatomic levels recommended by Sjostrom and colleagues (12). The area of all pixels with attenuation values between −190 and −30 HU for adipose tissue and between −30 and 120 HU for muscle were determined by the computer. Corrections for beam-hardening artifacts were done manually as necessary. The subcutaneous area of each scan was determined by circumscribing the area outside the body and halfway through the muscle wall of the trunk with the light pen. Intra-abdominal adipose tissue was measured from the proximal edge of the symphysis to the level of T8–T9. The retroperitoneum was included in the intra-abdominal region. The upper- and lower-body subcutaneous adipose tissue included the sum of subcutaneous adipose tissue above and below the caudal edge of the pubic symphysis. The truncal subcutaneous adipose tissue was the sum of subcutaneous adipose tissue between the caudal edge of the pubic symphysis and the caudal edge of the sternoclavicular joint.

Volume calculations. From the scout film, the distance between scans was determined to the nearest millimeter. From these distances and the various muscle and adipose tissue areas, the total volumes were calculated using the following formula: $V = \sum_{i=23}^{i} a_i (b_i + c_i) \div 2$, where a_i is the distance between scans and b_i and c_i are the areas of adipose (or muscle) tissue in two adjacent scans (12). Total adipose tissue was defined as the sum of visceral and subcutaneous adipose tissue. The fat-free mass was calculated by subtracting the total adipose tissue mass from the total body weight. Total adipose tissue mass was calculated as the total adipose tissue volume in liters multiplied by 0.92 (12). The lean body volume was calculated by subtracting the total adipose tissue volume from the total body volume and is used throughout this study as a surrogate for lean body mass.

Anthropometric measurements. The waist was measured as the narrowest circumference between the lower costal margin and the iliac crest in the standing position. The hip was the maximum circumference at the level of the femoral trochanters.

Insulin sensitivity. Insulin sensitivity was measured by using the euglycemic hyperinsulinemic clamp with a 1 mU · kg^{-1} · min^{-1} insulin and D-[3-^{3}H]glucose infusion (13,14) as previously described (9,15). Plasma glucose was clamped at fasting euglycemic levels with a coefficient of variance of 5%. D-[3-^{3}H]glucose was infused for 150 min before beginning the insulin infusion. The R_D is the sum of exogenously administered glucose and hepatic glucose production and was measured during the last hour of the 2-h insulin infusion. The isotopic determination of glucose kinetics sometimes resulted in an underestimation of the R_D, as evidenced by negative values for hepatic glucose production (16,17). When this occurred, hepatic glucose production was considered to be completely suppressed and the R_D was assumed to be the steady-state glucose infusion rate.

TABLE 2
Correlation between insulin action and various components of body composition

Glucose disposal mg · kg-LBM^{-1} · min^{-1} correlation with	r*	P value
Total intra-abdominal adipose tissue volume	−0.61	<0.01
Intra-abdominal AT/Total AT	−0.78	<0.001
Intra-abdominal AT/SubQ AT	−0.74	<0.001
Total muscle volume	−0.09	NS
Subcutaneous AT volume	−0.17	NS
Total AT volume	−0.32	NS
Percentage of AT	−0.35	NS
WHR	−0.48	<0.05
Waist circumference	−0.42	<0.05

r is Pearson's correlation coefficient. AT, adipose tissue.

Analytical method. Plasma glucose was measured by a glucose oxidase method with a Beckman glucose analyzer (Beckman, Fullerton, CA). Plasma insulin was measured with a double-antibody radioimmunoassay technique having a lower limit of detection of 2.5 ng/ml by using a kit purchased from Incstar (Stillwater, MN). Specific activity of D-[3-^{3}H]glucose was determined for plasma samples deproteinized with barium hydroxide and zinc sulfate. HbA_{1c} was determined by an automated high-performance liquid chromatography (HPLC) technique with a normal range of ≤4.9%. Fasting serum lipids were measured enzymatically as previously described (15).

Materials. Human insulin was supplied by Lilly (Indianapolis, IN). D-[3-^{3}H]glucose (13.5 Ci/mmol) was purchased from Du Pont-NEN (Boston, MA) and had been chromatographed to 98% purity by HPLC.

Statistical analysis. Group means were compared by using Student's t test. Linear regressions were calculated by using Pearson's correlation coefficient and by using multiple regressions. Data are expressed as means ± SD. The two-sample Z test for equality of correlation was used to test for differences in correlation coefficients in dependent samples (18).

RESULTS

Patient characteristics. The characteristics of the 22 men are shown in Table 1. They were from normal-weight to moderately obese with a BMI (mean ± SD) of 26.5 ± 2.4 and a range of 20.7 to 30.2 kg/m^2. Total body adipose tissue volume (sum of the visceral and subcutaneous adipose tissue) was 19.2 ± 6.5 l (range 4.7 to 31.3 l), and percentage of adipose tissue (total adipose tissue volume divided by total body volume) was 27 ± 7% (range 13–37%). The fasting plasma insulin ranged from 3 to 29 μU/ml. The fasting plasma glucose was not >120 mg/dl in any subject.

Insulin action. Glucose disposal ranged from 2.5 to 8.1 mg · kg^{-1} · min^{-1} in response to a physiological insulin infusion of 1 mU · kg^{-1} · min^{-1}, with plasma glucose levels being maintained at euglycemic fasting levels of 104 ± 10 mg/dl. Ten subjects with normal insulin sensitivity and 10 subjects with insulin resistance had R_D values of 7.1 ± 0.5 and 3.3 ± 0.6 mg · kg^{-1} · min^{-1}, respectively ($P < 0.001$); plasma insulin concentrations (mean ± SE) during the insulin infusion were 96 ± 6 and 101 ± 8 μU/ml (NS). Insulin resistance was defined as an R_D <5.5 mg · kg^{-1} · min^{-1}, 2 SDs below the mean glucose disposal of our nondiabetic population (19). Because glucose disposal is a function of lean body mass, we

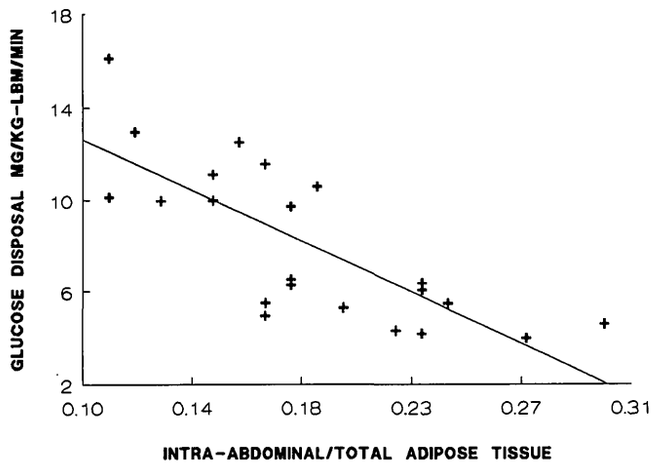

FIG. 1. Intra-abdominal-to-total adipose tissue versus glucose disposal. Correlation of the proportion of intra-abdominal to total adipose tissue and insulin-mediated glucose disposal (per kg-LBM) during an insulin infusion of 1 mU · kg^{-1} · min^{-1} ($r = -0.78$, $P < 0.001$).

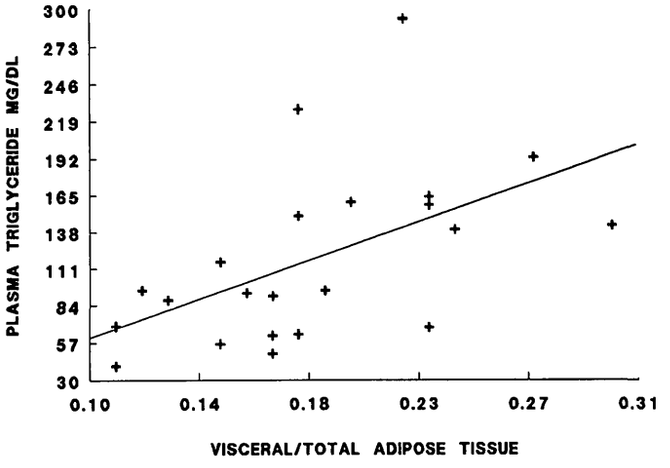

FIG. 3. Visceral-to-total adipose tissue versus plasma triglyceride. Correlation of plasma triglyceride levels and intra-abdominal:total adipose tissue ($r = 0.55$, $P < 0.01$).

have expressed it in these terms. Glucose disposal per kilogram of lean body mass (kg-LBM) ranged from 4.0 to 16.11 mg · kg-LBM^{-1} · min^{-1}, and this parameter is used in the subsequent data analyses.

Body composition. Similar to the wide range of glucose disposal, there was also a wide range of intra-abdominal and subcutaneous adipose tissue. Intra-abdominal adipose tissue ranged from 0.5 to 8.5 l. The total subcutaneous adipose tissue ranged from 4.1 to 27.3 l. The fat free mass ranged from 56.8 to 75.2 kg, lean body volume ranged from 30.5 to 61.3 l, and the total muscle volume ranged from 29.4 to 43.3 l.

Table 2 and Figs. 1 and 2 demonstrate the correlations between glucose disposal and total adipose tissue as well as the various adipose tissue compartments. There was a highly significant inverse correlation between the proportion of the total adipose tissue located in the intra-abdominal compartment and insulin-mediated glucose disposal (per kg-LBM) ($r = -0.78$, $P < 0.001$) (Fig. 1). In addition, the absolute intra-abdominal adipose tissue volume and glucose disposal per kg-LBM were also highly inversely correlated ($r = -0.61$, $P < 0.01$). These correlations contrasted with the lack of relationship between insulin-mediated glucose disposal and BMI ($r = -0.30$, NS) (Fig. 2). Neither the percentage of body fat nor the total adipose tissue volume showed a correlation with insulin-mediated glucose disposal per kg-LBM ($r = -0.35$ and 0.32, respectively). Multiple regression analysis showed that glucose disposal was significantly inversely related to the proportion of adipose tissue that is intra-abdominal and not to total body fat, percentage of fat, or BMI. The stepwise multiple regression yielded only one significant variable (intra-abdominal/total adipose tissue), which accounted for ~61% of the variance of glucose disposal ($r = -0.78$). The probability of observing this by chance was $P < 0.00005$ with a power of 0.999. The addition of BMI, total body fat, and percentage of fat, not previously entered into the multiple regression equation because of lack of significance, increased the variance accounted for by only an additional 2%.

Further analysis showed that the correlation coefficient between glucose disposal per kg-LBM and intra-abdominal/total adipose tissue ($r = -0.78$) was significantly ($P < 0.02$) greater than the correlation between glucose disposal and either percentage of body fat ($r = -0.35$) or total body fat ($r = -0.32$). These analyses all demonstrate that insulin-mediated glucose disposal was highly inversely correlated with intra-abdominal adipose tissue and not with total adiposity.

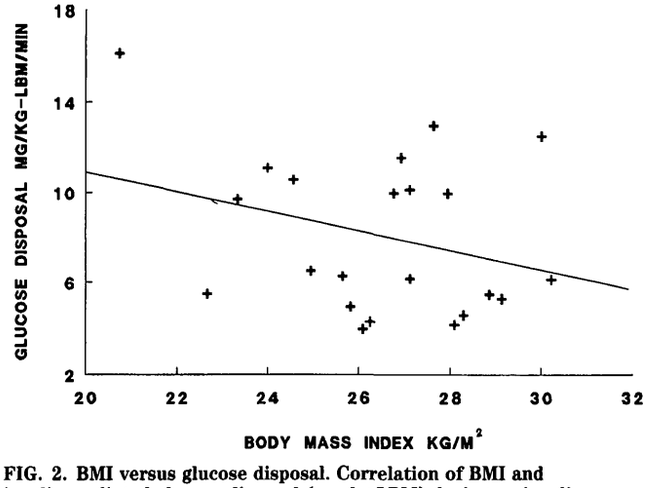

FIG. 2. BMI versus glucose disposal. Correlation of BMI and insulin-mediated glucose disposal (per kg-LBM) during an insulin infusion of 1 mU · kg^{-1} · min^{-1} ($r = -0.30$, NS).

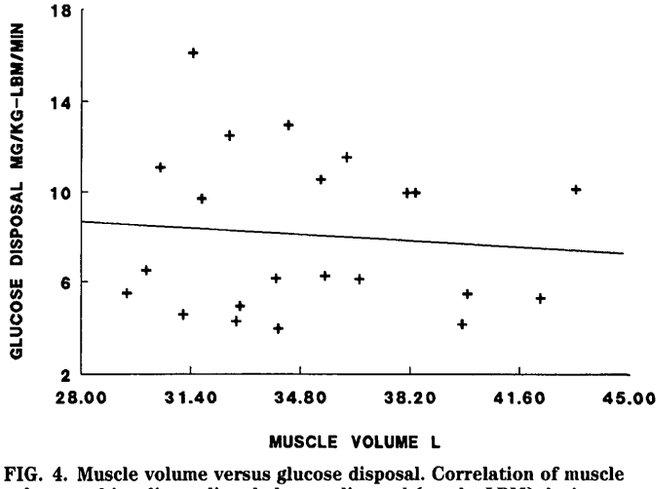

FIG. 4. Muscle volume versus glucose disposal. Correlation of muscle volume and insulin-mediated glucose disposal (per kg-LBM) during an insulin infusion of 1 mU · kg^{-1} · min^{-1} ($r = -0.09$, NS).

TABLE 3
Relationship between different methods of expressing glucose disposal and adipose tissue distribution

Method of expressing glucose disposal	Intra-abdominal/total adipose volume	WHR
mg · kg body wt^{-1} · min^{-1}	−0.81*	−0.49†
mg · kg fat-free $mass^{-1}$ · min^{-1}	−0.77*	−0.46‡
mg · 1 muscle vol^{-1} · min^{-1}	−0.75*	−0.47‡
mg · kg-LBM^{-1} · min^{-1}	−0.78*	−0.48‡

* $P < 0.001$. † $P < 0.01$. ‡ $P < 0.05$.

The anthropometric measures of waist-to-hip ratio (WHR) and waist girth were also inversely correlated with insulin-mediated glucose disposal ($r = -0.48$ and $r = -0.42$, $P < 0.05$). The WHR and waist circumference were correlated with the total intra-abdominal adipose tissue volume ($r = 0.50$, $P < 0.05$; and $r = 0.79$, $P < 0.001$).

The intra-abdominal adipose tissue volume and proportional intra-abdominal adipose tissue were each correlated with serum triglyceride level ($r = 0.55$, $P < 0.01$) (Fig. 3), but not with high-density lipoprotein (HDL) cholesterol levels ($r = -0.35$, $P > 0.10$). Fasting plasma insulin correlated positively with serum triglycerides and negatively with HDL cholesterol levels ($r = 0.63$ and -0.64, respectively, $P < 0.01$), while glucose disposal correlated inversely with serum triglycerides and positively with HDL cholesterol levels ($r = -0.59$, $P < 0.01$ and $r = 0.52$, $P < 0.05$, respectively).

There was no relationship between glucose disposal per kg-LBM and total subcutaneous adipose tissue volume ($r = -0.17$, NS), as shown in Table 2; nor was there any relationship between glucose disposal and upper body, lower body, or truncal subcutaneous adipose tissue volumes ($r = -0.30$, $r = -0.13$, and $r = -0.30$ [NS], respectively). Furthermore, there were no significant relationships between glucose tolerance and either glucose disposal or measures of body composition. Because most insulin-mediated glucose disposal occurs in muscle tissue, we analyzed the relationship between insulin-mediated glucose disposal and muscle volume. Figure 4 shows that no significant relationship exists ($r = -0.09$, NS). Regardless of how glucose disposal is expressed, in terms of lean body volume, body weight, fat free mass, or muscle volume, it is highly inversely correlated with the proportion of intra-abdominal adipose tissue (Table 3). Thus, our data show that it is the intra-abdominal adipose tissue and not subcutaneous adipose tissue or muscle volume that correlates most highly with insulin-mediated glucose disposal in black NIDDM men.

Our data can also be analyzed as if they represent two discrete groups, insulin-sensitive and insulin-resistant, rather than a single continuous group. Although the groups do not differ in age, BMI, total fat volume, or percentage of body fat (Table 4), they do differ in intra-abdominal adipose tissue measures, either in absolute terms or as a proportion of total adipose tissue. The groups also do not differ in subcutaneous adipose tissue or muscle volume, but do show marked differences in lipid profiles. The so-called metabolic disease cluster is seen in patients with increased intra-abdominal adipose tissue and insulin resistance.

DISCUSSION

The concept that insulin resistance is a primary genetic disorder of insulin action in muscle arose from numerous studies purporting that lean NIDDM subjects and their normoglycemic relatives are all resistant to insulin action, regardless of the technique used to measure it (2–4,20). These early studies failed to define whether the patients were truly normal weight (BMI ≤25 kg/m^2 for men and ≤23 kg/m^2 for women), had a normal distribution of adipose tissue, or were normotensive. Despite the shortcomings of those studies, many investigators have pursued and continue to pursue a primary abnormality of insulin action in muscle as the major defect in NIDDM (21,22).

Several early studies in nondiabetic subjects showed that there is a relationship between body fat and insulin-mediated glucose disposal. Bogardus et al. (23) found an inverse correlation between insulin-mediated glucose disposal and percentage of body fat ($r = -0.35$) in nondiabetic Caucasian men. Yki-Jarvinen and Koivisto (24) reported an inverse correlation ($r = -0.7$) between insulin-mediated glucose

TABLE 4
Differences among insulin-sensitive and insulin-resistant NIDDM men

	Insulin-sensitive NIDDM	Insulin-resistant NIDDM	*P* value
n	10	12	
Age (years)	45.7 ± 8.7	51.6 ± 9.0	NS
BMI (kg/m^2)	25.9 ± 2.7	26.93 ± 2.1	NS
Glucose disposal (mg·kg body wt^{-1}·min^{-1})	7.07 ± 0.5	3.32 ± 0.6	0.0001
Glucose disposal (mg·kg-LBM^{-1}·min^{-1})	11.5 ± 2.0	5.3 ± 0.9	0.0001
Fasting plasma insulin (μU/ml)	6 ± 3	14 ± 7	0.002
Total fat volume	17.0 ± 7.0	21.0 ± 5.7	NS
Percentage of body fat	24.2 ± 6.8	28.7 ± 5.5	NS
Total intra-abdominal AT volume	2.49 ± 2.3	4.71 ± 1.85	0.003
Total SubQ AT volume	14.24 ± 6.04	15.86 ± 3.92	NS
Total muscle volume	35.21 ± 4.0	34.90 ± 4.09	NS
Intra-abdominal/total AT ratio	0.15 ± 0.03	0.22 ± 0.04	0.0001
Total visceral/total SubQ ratio	0.19 ± 0.04	0.32 ± 0.08	0.0001
Upper body SubQ AT volume	8.74 ± 3.9	10.88 ± 3.18	NS
Lower body SubQ AT volume	5.5 ± 2.3	5.0 ± 1.1	NS
Total cholesterol (mg/dl)	170 ± 30	200 ± 28	0.02
Triglyceride (md/dl)	78 ± 23	153 ± 67	0.003
HDL cholesterol (mg/dl)	50 ± 14	38 ± 6	0.03
LDL cholesterol (md/dl)	106 ± 24	131 ± 28	0.04

Data are means ± SD; all volumes are in liters. AT, adipose tissue; LDL, low-density lipoprotein.

disposal and percentage of body fat as estimated by skin-fold thickness measurements in 23 normal-weight nondiabetic men. Campbell and Gerich (25) found that insulin-mediated glucose disposal is impaired only beyond a BMI of 26.8 kg/m^2. We found an inverse correlation of -0.45 ($P < 0.05$) between insulin-mediated glucose disposal, when expressed similarly per kg body wt, and percentage of body fat determined by axial CT.

Our data are also consistent with recent reports that have focused on adipose tissue distribution and its relationship to glucose metabolism, insulin action, and NIDDM (25–35). Methods to assess intra-abdominal adipose tissue mass have ranged from simple measures, such as the WHR, to such sophisticated techniques as magnetic resonance imaging and axial CT. Lean Japanese-American NIDDM subjects have more intra-abdominal adiposity than control subjects (26). Increased intra-abdominal adipose tissue in Japanese-Americans (CT) and increased WHR in Swedish men and Mexican-Americans are predictive of the development of NIDDM (27–29). Nondiabetic individuals with increased intra-abdominal adipose tissue have a greater plasma glucose and insulin rise after the administration of oral glucose (30–34).

A relationship between obesity and the presence of insulin resistance in NIDDM individuals has been suggested in several recent studies. Arner et al. (35) found normal insulin sensitivity in lean men and insulin resistance in obese men with NIDDM. By using WHR as an index of intra-abdominal obesity, they found no difference between the sensitive and the resistant NIDDM subjects and concluded that obesity, per se, was responsible for the insulin resistance. Kelley et al. (36) found that lean NIDDM men and lean control subjects who did not differ in BMI, percentage of fat, or WHR had similar, normal insulin-mediated overall and leg R_D values. Kohrt et al. (37) measured WHR, waist circumference, and total adiposity in a group of lean insulin-sensitive normal subjects and subjects with impaired and diabetic glucose tolerance. They found a correlation between insulin-mediated glucose disposal and waist circumference in men and between insulin-mediated glucose disposal and WHR in women. None of these studies presented data on actual adipose tissue distribution nor did they compare insulin-sensitive and insulin-resistant subsets having comparable BMIs.

Our data showing the separate associations of intra-abdominal adipose tissue and serum triglyceride levels in NIDDM subjects confirm data in other populations (31,38–40). The relationship between HDL cholesterol and glucose disposal did not reach statistical significance.

In conclusion, we have previously demonstrated that 60% of black NIDDM subjects with BMI < 30 kg/m^2 are insulin-resistant (9). Here we demonstrate that, when insulin resistance is present, the degree of insulin resistance is highly correlated with an increase in intra-abdominal adipose tissue. This suggests the following hypotheses: *1*) insulin resistance in NIDDM is an acquired abnormality secondary to an increase in intra-abdominal adipose tissue; and *2*) NIDDM consists of two discrete disorders: one in which insulin resistance is a primary disorder and causes selective increases in intra-abdominal adipose tissue and another in which insulin action is normal, the only primary defect being deficient β-cell insulin secretion. Studies are needed to test which of these hypotheses is correct.

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