Relationship of Body Fat Distribution Pattern to Atherogenic Risk Factors in NIDDM
Preliminary Results

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Because recent knowledge indicates that the distribution of fat deposits in men may be a better predictor of cardiovascular disease than the degree of obesity alone, some risk factors for atherosclerosis were evaluated in 51 middle-aged men with non-insulin-dependent diabetes mellitus. Abdominal adiposity (waist/hip ratio, WHR) was related to parameters of metabolic control, lipid parameters, and known vascular complications in three different groups. In groups with abdominal obesity, mean annual hemoglobin A_1 was significantly ($P < .01$) higher than in patients without an abdominal fat distribution. Atherogenic index was significantly increased in the group with the highest WHR and high-density lipoprotein cholesterol (HDL-chol) levels were significantly decreased in both groups with upper-body fat distribution. The frequency of peripheral vascular disease, coronary ischemic heart disease, and hypertension was most prominent in diabetic subjects with an abdominal fat mass distribution. A highly significant ($P < .001$) correlation was present between WHR and HDL-chol and WHR and the total-cholesterol/HDL-chol ratio; this significant correlation remains after correction for body mass index. A similar correlation could be found between WHR and systolic and diastolic blood pressures. These results demonstrate an association of excess abdominal fat, even without manifest obesity, with worse diabetes metabolic control, cardiovascular complications, and blood lipid levels actually considered to play an important role in atherogenesis. *Diabetes Care* 11:103–106, 1988

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In the late 1950s, Vague (1) reported the relationship between upper-trunk android (male) obesity and the prevalence of diabetes mellitus or glucose intolerance. Kissebah et al. (2) reported different responses of glucose and insulin to an oral glucose load in obese subgroups with upper- and lower-body obesity; they found hyperinsulinemia to be a characteristic feature of upper-segment body mass distribution. A different metabolic behavior of fat cells of different regions was suggested. More recently, Larsson et al. (3) stressed that abdominal adipose tissue distribution is the best predictor of cardiovascular disease and death, independent of commonly used indices of obesity.

Because the site of fat accumulation is considered a predominant factor for the metabolic disorders of obesity, we evaluated differences in body fat distribution in relation to metabolic control, lipids, and cardiovascular complications among male subjects with non-insulin-dependent diabetes mellitus (NIDDM).

PATIENTS AND METHODS

Fifty-one male NIDDM patients, seen at our outpatient clinic over 4 consecutive mo, participated in this study. All were known to have had diabetes for at least 3 yr and were followed regularly at our clinic.

All patients showed a stable but excessive body weight despite repeated dietary advice; most were treated with sulfonylureas (mostly glyburide) and/or biguanides in the most obese group. All patients showed fasting C-peptide values >0.50 pM, which usually doubled after breakfast, confirming that they had NIDDM. No differences in therapy were present in the three subgroups, and insulin-treated patients were excluded.

Five patients were treated with antihypertensive medication, mainly hydralazine; the same criteria for definition of hypertension were used for these individuals. Patients under treatment who had blood pressures below diagnostic levels were classified as hypertensive.

Regional adiposity was reflected by the waist-to-hip circumference ratio (WHR); the waist circumference was measured at the level of the umbilicus and the hip circumference was measured at the iliac crest level, as described by Larsson et al. (3). Overt abdominal adiposity was considered to be WHR >1; WHR determinations were performed by the same investigator. Sitting blood pressure was recorded in identical circumstances. Obesity was defined as a body mass index (BMI; kg/m^2) >28 (4). Patients were divided into three subgroups according to their fat mass distribution: group 1, 20 nonobese diabetic subjects (WHR <1); group 2, 12 nonobese diabetic subjects with an excess of abdominal adipose tissue (WHR >1); and group 3, 19 obese diabetic subjects (WHR >1) with abdominal adiposity.

On the same day as the WHR determination, after an overnight fast, blood was taken from an antecubital vein for determinations of total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-chol). Diabetes metabolic control was reflected by the glycosylated hemoglobin (HbA_1) value, determined by the mean annual HbA_1 value of at least four determinations throughout the previous year.

Cholesterol and triglycerides were measured with a commercial kit (Boehringer, Mannheim, FRG) and the HDL-chol fraction according to the method described by Lopes-Virella et al. (5). HbA_1 was determined after separation and elimination of the reversible fraction on cation-exchange microcolumns (Boehringer). The diagnosis and presence of macrovascular complications was based on clinical hospital chart data and physical examination according to the following criteria. Hypertension was considered to be a systolic pressure >160 mmHg and/or a diastolic pressure >95 mmHg. The criteria for peripheral vascular disease were hospital admission with the diagnosis of stroke or admission for amputation surgery or gangrene treatment. The criteria for coronary heart disease were proved myocardial infarction and proved ischemic heart disease by coronary arteriography and/or significant ECG-tracing abnormalities confirming coronary heart disease.

Analysis of variance (ANOVA) was used to test for the equality of different means. When the original null hypothesis in the ANOVA was rejected, it was also important to know which means were different from the others; to group the means, a Newman-Keuls multiple-range test was used (6). Linear association between the several parameters was investigated by simple or multiple correlation where appropriate. Values are expressed as means ± SD.

RESULTS

As shown in Table 1, the mean ages in the three subgroups were not significantly different. Table 1 also shows mean BMI values and the mean WHR indicating the abdominal distribution of fat mass in groups 1 and 2. HbA_1 values (normal values from our laboratory 5–8%) were significantly ($P < .01$) lower (7.83 ± 1.25%) in the nonobese group 1 versus a mean of 9.34% in groups 2 and 3. Duration of diabetes from date of diagnosis was not significantly different in our three groups (8.3, 9.2, and 7.8 yr, respectively). Table 2 shows higher values for triglycerides and atherogenic index (total cholesterol/HDL-chol ratio) in groups with abdominal adiposity; HDL-chol values were significantly ($P < .05$ and $P < .01$, respectively) lower in these groups. The lowest HDL-chol value (34.6 ± 7.1 mg/dl) was obtained in the nonobese group with abdominal obesity ($P < .01$).

A significant ($r = -.49$; $P < .005$) negative correlation was found between the WHR and HDL-chol values, and a significant positive correlation was found between the WHR and the atherogenic index ($r = .48$; $P < .005$). When corrected for BMI, the partial correlation between WHR and HDL-chol was $r = -.53$ ($P < .001$), whereas a nonsignificant correlation of $r = .28$ was found between BMI and HDL-chol after adjustment for WHR values. After correction for BMI, a similar relationship was found with a partial correlation coefficient ($r = .52$) between WHR and atherogenic index ($r = -.34$ between BMI and atherogenic index after correction for WHR). A significant ($P < .001$) correlation was found between the WHR and systolic ($r = .55$) and diastolic ($r = .49$) blood pressures.

Table 3 shows the frequency of peripheral vascular disease (PVD), coronary heart disease, and hypertension in the three different groups. PVD was present in both

TABLE 1
Characteristics of three subgroups studied for body fat distribution

	Age (yr)	Body mass index (kg/m^2)	WHR (cm)	HbA_1 (%)
Group 1	55.7 ± 8.1	24.3 ± 1.9	0.93 ± 0.04	7.83 ± 1.25
Group 2	56.4 ± 4.9	25.7 ± 1.6	1.05 ± 0.04	9.36 ± 1.95
Group 3	56.8 ± 9.2	31.6 ± 2.4	1.03 ± 0.03	9.33 ± 2.30

Values are means ± SD. Group 1, nonobese, waist/hip ratio (WHR) <1; group 2, nonobese, WHR >1; group 3, obese, WHR >1. No significant difference was present for mean age, but HbA_1 was significantly ($P < .01$) elevated in the 2 groups with abdominal obesity (groups 2 and 3). Differences between or among bracketed values are not statistically significant (Newman-Keuls multiple-range test).

TABLE 2
Mean values for total and HDL cholesterol, triglycerides, and atherogenic index

	Cholesterol (mg/dl)	HDL cholesterol (mg/dl)	Triglycerides (mg/dl)	Atherogenic index
Group 1	221 ± 43	43.8 ± 8.6	114 ± 46	5.26 ± 1.64
Group 2	233 ± 39	34.6 ± 7.1	158 ± 59	6.96 ± 1.79
Group 3	211 ± 24	37.3 ± 8.7	187 ± 122	5.98 ± 1.66

Values are means ± SD. Group 1, nonobese, waist/hip ratio (WHR) <1; group 2, nonobese, WHR >1; group 3, obese, WHR >1. Differences between or among bracketed values are not statistically significant (Newman-Keuls multiple-range test). HDL, high-density lipoprotein.

groups with an excess of abdominal fat, 42 and 37% for groups 2 and 3, respectively, whereas nonobese group 1 subjects without excess abdominal fat showed only 10% macrovascular lesions. The prevalence of hypertension was more pronounced in groups with abdominal adiposity, 42 and 47% for groups 2 and 3, respectively. In the nonobese group without upper-trunk obesity, only 5% of patients were hypertensive.

DISCUSSION

Both obesity (7) and diabetes mellitus (8) are associated with a high frequency of metabolic alterations and an elevated risk for coronary heart disease and atherosclerosis. Secondary hyperlipidemia and hypertension could be one of a series of factors contributing to these vascular complications (9,10). In the 1950s, Vague (1) stressed the difference in prevalence of these risk factors between obese subjects with fat excess located in the upper or lower part of the body.

The prospective study of Larsson et al. (3) that indicated abdominal adiposity in middle-aged men might be a better predictor of cardiovascular disease prompted us to evaluate some atherosclerotic indices in a group of obese and nonobese NIDDM subjects. In this preliminary survey, only middle-aged male NIDDM subjects were evaluated because of the known sex differences in the effect of diabetes mellitus on lipid fractions (11) and the effect of race and sex on the obesity-related risk for hypertension (12).

Although Vague (1) has already reported the relation of upper-segment obesity and diabetes mellitus, our results are the first to show that metabolic deteriorations in diabetic subjects can be found independently of the degree of obesity as long as abdominal fat-mass excess is present. By use of the mean annual HbA_1 value, a valuable index could be obtained for the mean metabolic control over the last year.

The observation that serum triglycerides, HDL-chol concentration, and the total-cholesterol/HDL-chol ratio were associated with the WHR is in accordance with earlier work by Larsson et al. (3) and Evans et al. (13). This finding remained true after correction for BMI. The higher mean WHR is not only associated with worse diabetic metabolic control but also with the greatest frequency of macrovascular complications. Hyperinsulinism and relative diminished insulin sensitivity are probably contributing factors in the pathogenesis of high triglyceride and low HDL-chol levels (14).

Note also that body fat topography correlated with systolic and diastolic blood pressure. It is not an entirely new finding that blood pressure is higher in diabetic subjects with endogenous hypertriglyceridemia and a suspected hyperinsulinism (15). A striking finding in our study was the association of upper-trunk fat predominance with an increased prevalence of vascular and cardiac complications, regardless of the presence of obesity. This suggests that abdominal fat acts metabolically in a different way than lower-body fat.

There is growing evidence that differences in fat distribution can be predictive of differences in the prevalence of metabolic abnormalities. Despite its limitations, this preliminary study confirms the undesirable effect of an excess of abdominally located fat cells, even without manifest obesity, on diabetes metabolic control, lipid fractions, and cardiovascular complications. Further prospective long-term studies should elucidate the cellular origin of this phenomenon both in obesity and "diabesity."

TABLE 3
Frequency of peripheral vascular disease, coronary heart disease, and hypertension

	Peripheral vascular disease	Coronary heart disease	Hypertension
Group 1	2/20 (10)	6/20 (30)	1/20 (5)
Group 2	5/12 (42)	6/12 (50)	5/12 (42)
Group 3	7/19 (37)	9/19 (47)	9/19 (47)

Values are number of cases/number of subjects in each group, with percentages in parentheses. Group 1, nonobese, waist/hip ratio (WHR) <1; group 2, nonobese, WHR >1; group 3, obese, WHR >1.

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