

Hypertriglyceridemic Waist Phenotype Predicts Increased Visceral Fat in Subjects With Type 2 Diabetes

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OBJECTIVE— Greater accumulation of visceral fat is strongly linked to risk of cardiovascular disease. However, elevated waist circumference by itself does not always identify individuals with increased visceral fat.

RESEARCH DESIGN AND METHODS— We examined 375 subjects with type 2 diabetes from the CHICAGO cohort for presence of hypertriglyceridemic waist phenotype (waist circumference >90 cm in men or >85 cm in women, in conjunction with a plasma triglyceride concentration of ≥ 177 mg/dl) to determine its usefulness for identifying subjects with increased amounts of visceral fat. We divided subjects into three groups: group 1 (low waist circumference and low triglycerides; waist circumference ≤ 90 cm in men or ≤ 85 cm in women and triglyceride <177 mg/dl, $n = 18$), group 2 (high waist circumference and low triglycerides; waist circumference >90 cm in men or >85 cm in women and triglycerides <177 mg/dl, $n = 230$), and group 3 (high waist circumference and high triglycerides; waist circumference >90 cm in men or >85 cm in women and triglycerides ≥ 177 mg/dl, $n = 127$).

RESULTS— Subjects in group 3 had significantly higher visceral fat ($P < 0.0001$), A1C ($P < 0.01$), and coronary artery calcium ($P < 0.05$) compared with group 2, despite similar age, BMI, and waist circumference. The relationship of the phenotype to atherosclerosis, however, was attenuated by adjustment for HDL cholesterol, triglyceride-rich lipoprotein cholesterol, apolipoprotein B, or LDL particle number.

CONCLUSIONS— The presence of hypertriglyceridemic waist phenotype in subjects with type 2 diabetes identifies a subset with greater degree of visceral adiposity. This subset also has greater degree of subclinical atherosclerosis that may be related to the proatherogenic lipoprotein changes.

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Despite the strong association of obesity, especially abdominal obesity, to metabolic and cardiovascular disease, not all obese individuals carry the same metabolic and cardiovascular risk (1,2). The metabolic syndrome (a cluster of metabolic abnormalities that include glucose intolerance, central obesity, dys-

lipidemia, and hypertension) has been used to identify individuals at high risk for type 2 diabetes and cardiovascular disease (3,4). A hypertriglyceridemic waist phenotype defined as an elevated waist circumference (>90 cm in men or >85 cm in women) along with an elevated plasma triglyceride concentration (de-

finied as a level ≥ 177 mg/dl) has been proposed and shown to be a stronger marker of cardiovascular risk and a better predictor of cardiovascular disease than the metabolic syndrome in nondiabetic subjects (5,6). Deposition of visceral fat may be most closely linked to the metabolic and cardiovascular risk associated with both the metabolic syndrome and the hypertriglyceridemic waist phenotype (6).

The CHICAGO cohort is a well-characterized group of men and women with type 2 diabetes who had measurements of abdominal fat depots by computed tomography (CT) and coronary artery calcium (CAC) by electron-beam tomography (7–9). We evaluated the prevalence of hypertriglyceridemic waist phenotype in this cohort and report its usefulness for identifying subjects with diabetes who have higher levels of visceral fat. We further examined the metabolic and cardiovascular impact of this phenotype in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects for the current analysis were non-Hispanic white ($n = 246$) and non-Hispanic black participants ($n = 129$) in the CHICAGO trial, a prospective study of the effects of pioglitazone compared with glimepiride on carotid intima-media thickness in subjects with type 2 diabetes recruited from 28 clinical sites in Chicago (7–9). The details of the study have been previously reported (7–9). Data included in this report were obtained prior to randomization to treatment groups. All subjects were asymptomatic for coronary artery disease at baseline. The study was approved by central and local institutional review board committees, and all participants provided written informed consent. All subjects underwent measurements of height, weight, and waist and hip circumference by a trained nurse at the baseline visit. Waist circumference was measured at the level of umbilicus to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by the square of height in meters.

Subjects underwent an abdominal CT scan for determination of visceral adipose

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tissue (VAT) and subcutaneous adipose tissue (SAT), as previously described (9). Fasting blood samples were obtained at the baseline visit for measurements of A1C, lipid panel, and LDL particle number by previously described techniques (7,8). Triglyceride-rich lipoprotein (TRL) cholesterol was calculated by subtracting the directly measured values for LDL and HDL cholesterol from total cholesterol. Non-HDL cholesterol was calculated by subtracting the directly measured values for HDL cholesterol from total cholesterol. CAC was determined using previously described techniques (8).

Statistical methods

The cohort was divided into three phenotypes based on criteria for hypertriglyceridemic waist: group 1 included subjects with waist circumference ≤ 90 cm in men or ≤ 85 cm in women and triglyceride levels < 177 mg/dl, group 2 included subjects with waist circumference > 90 cm in men or > 85 cm in women and triglyceride levels < 177 mg/dl, and group 3 (hypertriglyceridemic waist) included subjects with waist circumference > 90 cm in men or > 85 cm in women and triglyceride levels ≥ 177 mg/dl (5). There was only one subject who had an elevated triglyceride level and low waist circumference. Analyses were performed with inclusion of that subject in group 2 (since he had intermediate phenotype) but were also repeated after exclusion of that subject, which did not impact any of our results.

Log transformation of the data was performed when necessary to achieve homogeneity of variance. Age, BMI, and waist circumference were compared using ANCOVA with Bonferonni post hoc analysis to evaluate the differences among the three groups. Categorical variables among the three groups were compared using χ^2 analysis. Differences in LDL, HDL, and TRL cholesterol and VAT, SAT, total abdominal fat (TAT), A1C, and CAC scores were examined using general linear model with Bonferonni analysis to compare the differences among the three groups. These analyses were also adjusted for age, BMI, sex, diabetes treatment, years of smoking, insulin use, duration of diabetes, and use of statins. Analyses for VAT, SAT, and TAT were also performed separately for each sex. Since racial differences in VAT have been reported, with blacks having lower amount of VAT compared with whites (10), we examined the impact of race on the usefulness of the

Table 1—Baseline characteristics of study participants based on hypertriglyceridemic waist phenotypes

	Group 1	Group 2	Group 3
n	18	230	127
Age (years)	67 \pm 10*	61 \pm 8	60 \pm 7
BMI (kg/m ²)	24.7 \pm 2.8	33.0 \pm 4.9†	32.5 \pm 4.6†
Waist circumference (cm)	81.4 \pm 5.0	109.1 \pm 12.0†	108.6 \pm 10.9‡
Duration of type 2 diabetes (months)	121 \pm 159	94 \pm 83	86 \pm 79
A1C (%)	7.0 \pm 0.8	7.3 \pm 0.9	7.6 \pm 1.1‡
Sex (%)			
Men	39	61	65
Women	61	39	35
Smoking (%)			
Current	17	15	15
Former	50	48	54
Never	33	37	31
Diabetes therapy (%)			
None	11	12	21§
Sulfonylurea	17	16	15
Metformin	28	25	36§
Sulfonylurea and metformin	22	34	25§
Insulin	22	13	3§
Statin use (%)			
On statin	50	53	60
No statin	50	47	40

Data are means \pm SD or percent. Group 1 (low waist circumference and low triglycerides; waist circumference ≤ 90 cm in men or ≤ 85 cm in women and triglycerides < 177 mg/dl); group 2 (high waist circumference and low triglycerides; waist circumference > 90 cm in men or > 85 cm in women and triglycerides < 177 mg/dl, $n = 230$); and group 3 (high waist circumference and high triglycerides; waist circumference > 90 cm in men or > 85 cm in women and triglyceride ≥ 177 mg/dl, $n = 127$). * $P < 0.05$ vs. groups 2 and 3; † $P < 0.0001$ vs. group 1; ‡ $P < 0.01$ vs. groups 1 and 2; § $P < 0.01$ vs. group 2.

hypertriglyceridemic waist phenotype for identifying subjects with increased visceral fat. To do this, we examined the relationship between the phenotype and abdominal fat distribution separately for each race and performed a test of heterogeneity for the relation between race and hypertriglyceridemic waist phenotype and body fat distribution. The analyses for the relationship between body distribution and CAC score were further adjusted for A1C, HDL cholesterol, TRL cholesterol, non-HDL cholesterol, apolipoprotein (apo) B, and LDL particle number. Analyses were performed using the 11.0 PC package of SPSS statistical software (SPSS, Chicago, IL). A $P \leq 0.05$ was considered significant.

RESULTS— The cohort was divided into three groups based on the criteria for hypertriglyceridemic waist (5). The baseline characteristics of the three groups are summarized on Table 1. The mean age for group 1 was 67 years, for group 2 was 61 years, and for group 3 was 60 years. Subjects in group 1 were older compared with subjects in groups 2 and 3 ($P = 0.002$).

The average BMI for group 1 was 24.7 ± 2.8 kg/m², for group 2 was 33.0 ± 4.9 kg/m², and for group 3 was 32.5 ± 4.6 kg/m². The average waist circumference for group 1 was 81.4 ± 5.0 cm, for group 2 was 109.1 ± 12.0 cm, and for group 3 was 108.6 ± 10.9 cm. Subjects in group 1 were leaner ($P < 0.0001$) and had lower waist circumference ($P < 0.0001$) compared with subjects in groups 2 and 3. There were no differences in age, BMI, or waist circumference between subjects in groups 2 and 3.

Thirty-nine percent of subjects in group 1 were men compared with 61% in group 2 and 65% in group 3, but these differences were not statistically significant (Table 1). There were no differences in smoking status, duration of diabetes, or statin use among the three groups (Table 1). There were differences in diabetes therapy among the three groups, with a higher percentage of subjects in group 3 not taking any diabetes medication (21%) compared with group 1 (11%) and group 2 (12%). Furthermore, fewer subjects in group 3 were taking insulin (3%) compared with group 1 (22%) and with group

Table 2—Comparison of lipid profile based on hypertriglyceridemic phenotype

Group	Triglycerides (mg/dl)	LDL cholesterol (mg/dl)	HDL cholesterol (mg/dl)	TRL cholesterol (mg/dl)	Non-HDL cholesterol (mg/dl)	ApoB (mg/dl)
1 (n = 18)	114 ± 381	109 ± 156	61 ± 58	19 ± 17	129 ± 34	80 ± 30
2 (n = 230)	117 ± 111	110 ± 45	51 ± 17*	19 ± 17	130 ± 30	80 ± 30
3 (n = 127)	270 ± 185†	119 ± 75	42 ± 23†	40 ± 23†	159 ± 45‡	100 ± 30‡

Data are means ± SD. Group 1 (low waist circumference and low triglyceride; waist circumference ≤90 cm in men or ≤85 cm in women and triglycerides <177 mg/dl); group 2 (high waist circumference and low triglyceride; waist circumference >90 cm in men or >85 cm in women and triglycerides <177 mg/dl, n = 230); and group 3 (high waist circumference and high triglyceride; waist circumference >90 cm in men or >85 cm in women and triglycerides ≥177 mg/dl, n = 127). Analysis is adjusted for age, BMI, sex, diabetes treatment, years of smoking, insulin use, duration of diabetes, and use of statins. TRL cholesterol was calculated by subtracting the directly measured values for LDL and HDL cholesterol from total cholesterol. Non-HDL cholesterol was calculated by subtracting the directly measured values for HDL cholesterol from total cholesterol. *P < 0.01 vs. group 1; †P < 0.0001 vs. groups 1 and 2; ‡P < 0.01 vs. groups 1 and 2.

2 (13%), and more subjects in group 3 were taking metformin-only therapy (36%) compared with groups 1 (28%) and 2 (25%).

Differences in lipid profile are demonstrated in Table 2. Level of TRL cholesterol was higher in group 3 compared with group 1 (P < 0.0001) and group 2 (P < 0.0001) (Table 2). Level of non-HDL cholesterol and apoB were higher in group 3 compared with group 1 (P = 0.001 for both non-HDL and apoB) and group 2 (P < 0.0001 for both non-HDL and apoB) (Table 2). There were no differences in LDL cholesterol levels among the three groups (Table 2). HDL cholesterol levels were higher in group 1 compared with group 2 (P = 0.01) and group 3 (P < 0.0001). HDL cholesterol levels were also significantly higher in group 2 compared with group 3 (P < 0.0001) (Table 2). LDL particle number was higher in group 3 (1,709 ± 563) compared with group 2 (1,369 ± 500; P < 0.0001) and with group 1 (1,254 ± 450; P = 0.001) (data not shown).

Table 3 summarizes the differences in body fat distribution among the three groups. Subjects in group 1 had significantly lower TAT and VAT compared with subjects in both groups 2 and 3 (P < 0.0001 for all comparisons), while SAT did not differ among the three groups in adjusted analyses. Despite similar BMI and waist circumference in groups 2 and 3 (Table 1), subjects in group 2 had significantly lower VAT (P < 0.0001) compared with those in group 3 (Table 3). These differences in VAT and TAT among groups persisted after adjustment for A1C, apoB levels, LDL particle number, HDL cholesterol, TRL cholesterol, and non-HDL cholesterol. Furthermore, similar results were obtained if each sex was examined separately. Since the racial makeup of groups 2 and 3 were different in our sample (42% of group 2 are black vs. 16% of group 3) and race has been reported to influence abdominal fat distribution (10), we examined the differences in VAT among groups separately for each race. For whites and blacks exam-

Table 3—Body fat distributions based on hypertriglyceridemic waist phenotypes

Group	TAT (cm ³)		VAT (cm ³)		SAT (cm ³)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
1 (n = 18)	173 ± 47	292 ± 780	62 ± 24	95 ± 54	112 ± 36	204 ± 62
2 (n = 230)	330 ± 101	316 ± 85*	128 ± 57	117 ± 60*	205 ± 84	204 ± 71
3 (n = 127)	337 ± 85	340 ± 94*	149 ± 51	150 ± 67†	194 ± 61	195 ± 73

Data are means ± SD and adjusted means ± SD with P value only reported for adjusted means. Group 1 (low waist circumference and low triglyceride; waist circumference ≤90 cm in men or ≤85 cm in women and triglycerides <177 mg/dl); group 2 (high waist circumference and low triglyceride; waist circumference >90 cm in men or >85 cm in women and triglycerides <177 mg/dl, n = 230); and group 3 (high waist circumference and high triglyceride; waist circumference >90 cm in men or >85 cm in women and triglycerides ≥177 mg/dl, n = 127). Analyses for TAT, VAT, and SAT are adjusted for age, BMI, sex, diabetes treatment, years of smoking, insulin use, duration of diabetes, and use of statins. *P < 0.0001 vs. group 1; †P < 0.0001 vs. groups 1 and 2.

ined separately, subjects in group 3 had greater amounts of visceral fat compared with those in group 2, even after adjustment for age, BMI, smoking years, duration of diabetes, sex, and statin use (similar to findings for the combined group). Furthermore, tests of heterogeneity were not significant for the interaction between race, hypertriglyceridemic waist, and visceral fat. These results indicate that the hypertriglyceridemic waist phenotype can be useful for identifying both white and black subjects with increased visceral fat.

Subjects in group 3 had the highest A1C level (7.6 ± 1.1) compared with group 2 (7.3 ± 0.9; P < 0.01) and group 1 (7.0 ± 0.8; P < 0.01), after adjustment for age, BMI, diabetes therapy, insulin use, duration of diabetes, years of smoking, and statin use. CAC scores were higher in group 3 (255 ± 77) compared with group 2 (218 ± 48) (P < 0.03), after adjustments for age, BMI, diabetes therapy, insulin use, duration of diabetes, years of smoking, and statin use. There was no difference in CAC between group 1 (202 ± 168) and the other two groups, which is most likely related to the small sample size. The difference in CAC scores between groups 2 and 3 remained significant after addition of A1C to the model (P < 0.05, data not shown). However, differences in CAC scores between groups 2 and 3 were no longer present after further adjustment for HDL cholesterol (P = 0.1), TRL cholesterol (P = 0.6), non-HDL cholesterol (P = 0.2), apoB levels (P = 0.2), or LDL particle number (P = 0.3) (data not shown). HDL cholesterol was a predictor of CAC in a model adjusted for age, BMI, diabetes therapy, insulin use, duration of diabetes, years of smoking, and statin use. However, its predictive value was lost after addition of hypertriglyceridemic waist phenotype or TRL cholesterol to the model. TRL cholesterol was a strong independent predictor of CAC even after addition of hypertriglyceridemic waist phenotype and HDL cholesterol to the model (P = 0.004, data not shown).

CONCLUSIONS— In this study, we found that in a large well-characterized cohort of obese subjects with type 2 diabetes, the presence of elevated triglycerides, along with an elevated waist circumference (both defined as proposed for the hypertriglyceridemic waist phenotype in nondiabetic subjects) (5,6), identifies a subgroup with higher amount of

visceral fat. The relationship remained after adjustment for multiple factors including age, sex, BMI, duration of diabetes, years of smoking, diabetes therapy, insulin, A1C, and statin use.

The existence of benign obesity or overweight and obese individuals who are metabolically healthy is well recognized (1,2). A recent study indicates that among the National Health and Nutrition Examination Survey cohort, 51% of overweight and 32% of the obese adults are metabolically healthy. Furthermore, in this study, waist circumference was not different between the two obese subgroups (metabolically healthy versus those with metabolic abnormalities) (1). The relation of waist circumference to abdominal adiposity is complicated as this measurement correlates well with the amount of total abdominal fat but cannot distinguish between subcutaneous and visceral adiposity. Numerous epidemiologic, as well as physiologic, studies have suggested that visceral fat is more strongly associated with metabolic risk factors as well as cardiovascular disease than subcutaneous abdominal fat (6,11). For instance, individuals matched for subcutaneous abdominal fat, but with different degrees of visceral fat, have been shown to have markedly different levels of insulin resistance and glucose tolerance (12). Surgical removal of abdominal subcutaneous fat in obese subjects did not result in metabolic improvements or beneficial changes in cardiovascular risk factors (13). Conversely, removal of visceral fat has led to metabolic improvements (14). Adipose tissue has been shown to secrete a number of inflammatory mediators (15), and visceral adipose tissue has been shown to secrete higher quantities of these inflammatory cytokines (15,16). Hence, visceral fat may be the distinguishing factor separating metabolically healthy obese individuals from obese individuals who are not metabolically healthy.

Several investigators, including us, have demonstrated that an increase in the size of visceral fat depot is associated with metabolic syndrome, inflammation, dyslipidemia, and coronary artery disease (17–20). Measurement of visceral fat depot requires imaging techniques such as CT or magnetic resonance imaging that are not practical screening tools for the general population due to cost and radiation exposure. The concept of a hypertriglyceridemic waist has been proposed by Despres and colleagues (5,6) for identifying viscerally obese individuals at risk for

cardiovascular disease. This group advocates that a fasting plasma triglyceride level of ≥ 177 mg/dl in conjunction with abdominal obesity (waist circumference >90 cm in men and >85 cm in women) is a better predictor of metabolic and cardiovascular risk than the metabolic syndrome (5,6). In a study by another group of investigators (21), among the National Cholesterol Education Program (NCEP) criteria for metabolic syndrome, waist circumference and triglyceride levels best correlated to visceral adiposity and insulin resistance. The results of the current study confirm that simultaneous measurement of fasting triglycerides and waist circumference is a useful approach for identifying subjects with the greatest amount of visceral fat even among obese subjects with type 2 diabetes.

CAC measured by electron-beam tomography is a measure of total coronary atherosclerosis that has been validated by coronary angiogram (22). The amount of CAC has been shown to correlate well with the amount of atherosclerotic plaque in patients with type 2 diabetes (23). In large prospective studies, CAC has been found to be a significant predictor of cardiovascular disease in symptomatic and asymptomatic subjects (24). In the current study, we demonstrate that subjects with greater degree of visceral adiposity based on hypertriglyceridemic waist, independent of many factors including glycemic control, had the highest CAC score. The difference in CAC between groups 2 and 3 was significant but perhaps not as large as might be expected given the more profound metabolic abnormalities in the latter group (Table 2). This could be related to an overall higher prevalence of CAC in type 2 diabetes compared with nondiabetic subjects (25). Nonetheless, subjects in group 3 had significantly higher amount of CAC compared with those in group 2, though both groups had similar BMI and waist circumference. However, the relationship between the hypertriglyceridemic phenotype and CAC was not present after adjustments for HDL cholesterol, non-HDL cholesterol, TRL cholesterol, LDL particle number, or apoB. In a previous study of the CHICAGO cohort (8), our group has reported that visceral adipose tissue predicted CAC but not after adjustment for TRL cholesterol. Due to the cross-sectional nature of this study, we are not able to make any conclusions regarding the causal nature of the associations observed.

In this study, A1C was highest in the subset with hypertriglyceridemic waist (group 3). These differences were present even after adjustment for a number of confounders including age, sex, BMI, diabetes therapy, duration of diabetes, years of smoking, and use of insulin and statins. A higher percentage of subjects with hypertriglyceridemic waist phenotype were treated with metformin, and fewer were treated with either insulin or sulfonylurea compared with those with lower triglyceride levels and elevated waist circumference. The reasons for these differences in therapy are not clear; however, all of the analyses in our report were adjusted for diabetes therapy and insulin use.

In summary, our results indicate that even in the presence of type 2 diabetes, an elevated waist circumference, by itself, does not identify subjects with the highest accumulation of visceral fat. Addition of fasting triglyceride levels to waist circumference is a simple and inexpensive method for clinicians to identify those with greatest amount of visceral fat and thus greatest metabolic and cardiovascular risk. In diabetes, the association of the hypertriglyceridemic waist phenotype with coronary atherosclerosis may be related to the proatherogenic lipoprotein changes associated with the phenotype.

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