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ORIGINAL ARTICLE

Visceral fat amount is associated with carotid atherosclerosis even in type 2 diabetic men with a normal waist circumference

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Objective: Our objective was to investigate whether determination of the quantity of visceral fat has an additional benefit in assessing atherosclerotic burden in men with type 2 diabetes compared with the traditional measurement of waist circumference (WC) alone.

Methods: This was an observational study performed in 368 men with type 2 diabetes, consecutively enrolled in Diabetes Clinics. Common carotid artery far-wall intima-media thickness (IMT), WC and visceral fat thickness (VFT), as measured by ultrasonography, were measured for each subject. Abdominal and visceral obesity were defined as a WC >90 cm and a VFT $\geqslant 47.6$ mm, respectively.

Results: Among subjects with abdominal obesity ($n=174$), 35 subjects did not have visceral obesity. In contrast, among the subjects without abdominal obesity ($n=194$), 88 patients had visceral obesity. Despite no differences in age, glucose control, lipid profile and treatment modalities, there was a significant difference in carotid IMT based on VFT strata, but not WC strata. The subjects without abdominal obesity, but who had visceral obesity, had a higher carotid IMT compared with subjects with abdominal obesity, but without visceral obesity (maximal, 0.94 ± 0.35 vs 0.78 ± 0.17 mm; and average, 0.74 ± 0.19 vs 0.64 ± 0.14 mm, respectively, $P<0.001$).

Conclusions: Subjects having visceral obesity, regardless of a normal WC, showed a higher carotid IMT compared with those with increased WC, but less visceral fat. In addition to WC, a direct estimation for visceral fat may provide an additional role in assessing atherosclerotic burden in men with type 2 diabetes.

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Introduction

Obesity has been associated with a broad spectrum of cardiometabolic disturbances, including hypertension, dyslipidemia, glucose intolerance and even cardiovascular disease (CVD).[1] In particular, visceral obesity compared with overall obesity might play a major role in the development of metabolic syndrome, CVD, or both.[2] Therefore, estimating visceral fat accumulation is important to identify individuals at high risk for CVD.

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The simplest and most widely used method of assessing visceral fat accumulation is measuring the waist circumference.[3] Although waist circumference is recognized as an independent and powerful risk factor for CVD,[4,5] there might be substantial variations in the visceral fat amount among persons with a similar waist circumference because waist circumference itself performs poorly in discriminating between visceral and subcutaneous fat.[6] Therefore, it is possible that subjects with a normal waist circumference may be more prone to metabolic syndrome or CVD if they have centrally located body fat.

The aim of this study was to investigate whether measurement of the quantity of visceral fat by ultrasonography may have an additional role in assessing atherosclerotic burden in men with type 2 diabetes compared with a measure of waist circumference alone. Our hypothesis was that the quantity of visceral fat, as measured by ultrasonography, is significantly associated with carotid intima-media thickness (IMT) independent of established cardiovascular risk factors and waist circumference in men with type 2 diabetes.

Methods

Subjects

Three-hundred sixty-eight consecutive men with type 2 diabetes participated in this study. Exclusion criteria included the following: endocrinopathies other than diabetes, type 1 diabetes mellitus, abnormal renal function, a history of treatment with thiazolidinediones or insulin in the past 6 months, use of anti-obesity drugs or corticosteroids and weight loss >3 kg during the past 3 months. All participants signed consent forms, and the Institutional Review Board of Pochon CHA University approved this study.

Body weight and height were measured in all participants, when they were wearing light clothing and not wearing shoes. The waist circumference was measured at the midpoint between the lateral iliac crest and the lowest rib. All the participants underwent measurement of fasting plasma glucose, HbA1c, insulin, total cholesterol, HDL-cholesterol and triglyceride after a 12-h fasting period. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) equation (fasting plasma glucose [mmol l^{-1}] × fasting serum insulin [$\mu\text{U ml}^{-1}$]/22.5).

Ultrasonographic measurement of visceral fat thickness, subcutaneous fat thickness and carotid IMT

Ultrasonography was performed using a Prosound α10 (Aloka, Tokyo, Japan), as described by Suzuki *et al.*[7] Transverse scanning was performed to measure visceral fat thickness (VFT) using a 3.5 MHz probe and to measure subcutaneous fat thickness (SFT) using a 10.0 MHz probe, 1 cm above the umbilicus. The VFT was defined as the distance between the anterior wall of the aorta and the internal face of the rectus abdominis muscle perpendicular to the aorta, and the SFT was defined as the thickness of the fat tissue between the skin-fat interface and the linea alba. The intra- and inter-observational reproducibility of the ultrasonographic estimations was 1.2–1.9 and 1.5–2.5% for VFT, and 1.8–3.0 and 3.8–5.0% for SFT, respectively.

The bilateral common carotid arteries were scanned using a high-resolution ultrasonographic system (Prosound α10; Aloka, Japan) with a 10.0 MHz linear transducer. Scanning was performed at the far wall of the mid and distal common carotid artery by a lateral longitudinal projection. The IMT was defined as the distance between the media-adventitia interface and the lumen-intima interface, and was measured in the 20 mm proximal to the origin of the carotid bulb using the IMT measurement software, Intimascope (Media Cross Co., Tokyo, Japan).[8] Average IMT was the mean value of 99 computer-based points in the region, and maximal IMT was the IMT value at a maximal point of the region. The same investigator performed all the ultrasonographic procedures used to estimate the abdominal adiposity and the IMT.

Abdominal obesity was defined as waist circumference >90 cm, which is an Asian criterion for abdominal obesity.[9] Visceral obesity, an excess accumulation of visceral fat, was defined as a VFT ⩾47.6 mm. In our previous study,[10] this value for VFT was chosen as the discriminator value to predict the presence or absence of metabolic syndrome in Korean participants.

Statistical analysis

Continuous variables were reported as the mean ± s.d., and categorical factors were reported as percentages. The intergroup comparisons were performed using ANOVA followed by Scheffe's *post hoc* test to adjust for multiple comparisons. In particular, the comparison between IMT in the different groups was made using analysis of covariance model that included age and BMI as the covariate. The comparison in the prevalence of CVD and treatment modalities were performed using a χ^2-test. Multiple regression analysis was used to assess the independent association between the carotid IMT and VFT adjusting for various risk factors. $P<0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 11.0; SPSS Inc., Chicago, IL, USA).

Results

The participants were classified into four groups by the respective criteria of the waist circumference and VFT (Table 1). BMI and waist circumference were higher in those with abdominal obesity regardless of whether they had visceral obesity or not. Among participants with abdominal obesity ($n=174$), 35 of them (20.1%) did not have visceral obesity. In contrast, among the participants without abdominal obesity ($n=194$), 88 patients (45.4%) had visceral obesity. Age, duration of diabetes, smoking status, the prevalence of CVD, blood pressure, treatment modalities, glucose control and lipid profiles were not significantly different among the groups, except that the triglyceride levels and HOMA-IR increased with VFT, but not waist circumference (Table 1). The participants without abdominal obesity, but with visceral obesity, showed higher VFT compared to those with abdominal obesity, but without visceral obesity (60.0 ± 9.8 vs 44.1 ± 10.7 mm, $P<0.001$), even though participants without abdominal obesity, but with visceral obesity, had a significantly lower waist circumference (85.6 ± 3.8 vs 92.4 ± 2.3 cm, $P<0.001$; Table 1). In spite of having a higher VFT, the participants without abdominal obesity, but with visceral obesity, had a lower SFT compared to those with abdominal obesity, but without

Table 1 Clinical characteristics of the subjects according to waist circumference and visceral fat thickness

	Waist ⩽ 90 cm		*Waist > 90 cm*	
	VFT < 47.6 mm	*VFT ⩾ 47.6 mm*	*VFT < 47.6 mm*	*VFT ⩾ 47.6 mm*
N	106	88	35	139
Age (years)	46.8 ± 8.5	47.8 ± 8.2	45.9 ± 11.5	47.5 ± 10.1
Duration of diabetes (years)	6.4 ± 4.5	5.3 ± 3.7	4.8 ± 3.9	5.1 ± 4.7
BMI (kg/m^2)	22.4 ± 2.3	24.2 ± 1.5*	26.5 ± 2.0*,**	28.0 ± 2.6*,**
Current smoker (%)	15.8	14.3	16.7	15.5
Prevalence of CVD (%)	7.8	15.9	12.1	16.5
Waist circumference (cm)	82.4 ± 4.2	85.6 ± 3.8*	92.4 ± 2.3*,**	96.9 ± 4.7*,**,***
SFT (mm)	17.9 ± 6.5	17.9 ± 4.9	26.3 ± 7.9*,**	21.5 ± 8.1*,**
VFT (mm)	36.8 ± 8.0	60.0 ± 9.8*	44.1 ± 10.7*,**	72.8 ± 12.8*,**,***
Systolic blood pressure (mm Hg)	127 ± 14	132 ± 15	132 ± 14	136 ± 17
Diastolic blood pressure (mm Hg)	82 ± 10	84 ± 13	82 ± 10	86 ± 12
Oral hypoglycemic agent (%)				
Sulfonylurea	31.1	10.2	24.2	10.1
Metformin	35.8	51.1	42.9	59.7
Sulfonylurea+Metformin	33.1	48.7	32.9	30.2
Statin (%)	17.9	23.9	17.1	25.2
Antihypertensive agent (%)	33.0	55.7	40.0	56.8
Glucose (mmol l^{-1})	8.08 ± 2.57	7.35 ± 1.57	7.72 ± 2.18	8.17 ± 2.19
HbA1c (%)	7.8 ± 1.9	7.2 ± 1.6	7.3 ± 1.6	7.9 ± 2.0
Total cholesterol (mmol l^{-1})	4.60 ± 0.97	4.61 ± 0.95	4.68 ± 0.68	4.98 ± 0.95
HDL-cholesterol (mmol l^{-1})	1.23 ± 0.25	1.10 ± 0.20	1.20 ± 0.21	1.05 ± 0.23
Triglyceride (mmol l^{-1})	1.75 ± 1.02	2.37 ± 1.37	2.20 ± 1.12	2.90 ± 1.68*
LDL-cholesterol (mmol l^{-1})	2.66 ± 0.75	2.56 ± 0.65	2.51 ± 0.64	2.67 ± 0.80
HOMA-IR	1.98 ± 1.71	2.45 ± 1.55	2.37 ± 1.31	3.65 ± 2.19*,***

Abbreviations: CVD, cardiovascular disease; SFT, subcutaneous fat thickness; VFT visceral fat thickness. Data are the means ± s.d. or N (or %). *$P < 0.05$ vs waist ⩽90 cm and VFT <47.6 mm; **$P < 0.05$ vs waist ⩽90 cm and VFT ⩾47.6 mm; ***$P < 0.05$ vs waist >90 cm and VFT <47.6 mm.

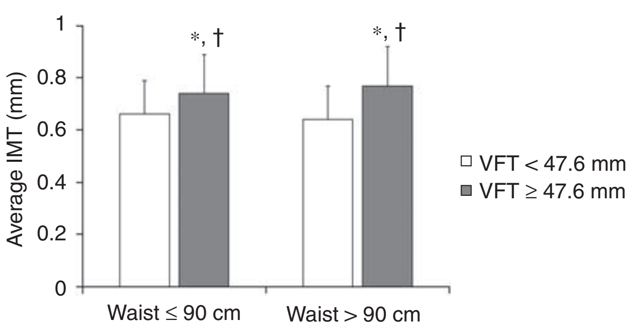

Figure 1 Average intima-media thickness (IMT) according to waist circumference and visceral fat thickness (VFT). *$P < 0.001$ vs waist ⩽90 cm and VFT <47.6 mm; †$P < 0.01$ vs waist >90 cm and VFT <47.6 mm.

visceral obesity (17.9 ± 4.9 vs 26.3 ± 7.9 mm, $P < 0.001$; Table 1).

Figure 1 shows the average carotid IMT in the four groups, stratified by waist circumference and VFT. There was a significant difference in average IMT between groups classified by VFT within the same waist circumference strata. On the contrary, the average IMT did not differ by the waist circumference within the same VFT strata. Participants without abdominal obesity, but with visceral obesity, had significantly increased maximal (0.94 ± 0.35 vs 0.78 ± 0.17 mm, $P < 0.001$) and average (0.74 ± 0.19 vs 0.64 ± 0.14 mm, $P < 0.001$) carotid IMT compared with participants with abdominal obesity, but without visceral obesity. These results remained similar even after adjustment for age and BMI using analysis of covariance model.

Using the average IMT as the dependent variable in multiple regression analysis, age, VFT and systolic blood pressure were independent factors associated with carotid IMT (Table 2). However, waist circumference, HOMA-IR and LDL-cholesterol did not contribute independently to the increased carotid IMT in this model.

Discussion

Whether visceral fat is a causal factor or simply a marker of the cardiometabolic profile remains controversial. Many epidemiologic studies have shown increased visceral fat accumulation to be an independent risk factor for type 2 diabetes mellitus and cardiovascular risk conditions or future events, such as coronary artery disease, stroke and hypertension.[1,11–13] In fact, several anthropometric indices for estimating the abdominal fat distribution, such as waist-to-hip ratio, waist circumference and recently, waist-to-height ratio,[5,14] have been regarded as important markers of cardiovascular risk. However, the waist-to-hip ratio may

Table 2 Multiple regression analysis for independent factors associated with carotid average intima-media thickness

Variables	*Standardized β*	P-*value*
Age	0.333	<0.001
Waist circumference	0.030	0.725
Visceral fat thickness	0.261	0.001
Systolic blood pressure	0.161	0.011
HOMA-IR	0.025	0.547
LDL-cholesterol	0.089	0.142

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.

mask the accumulation of abdominal fat, if the hip circumference is also increased.[15] The waist circumference, which is strongly associated with visceral adiposity, is the preferred measure in the clinical setting for identifying those at high risk for metabolic syndrome or CVD. However, waist circumference also has been criticized for not differentiating visceral fat from subcutaneous fat, and actually, an increased waist circumference may be the consequence of excess subcutaneous, not visceral, abdominal adiposity, a situation sometimes observed even in centrally obese patients with a normal risk-factor profile.[6]

This study emphasized that all people who are defined as not having abdominal obesity by waist circumference were not less susceptible to cardiovascular risk, because some individuals were more prone to visceral fat accumulation for a given waist circumference. In contrast, some individuals with increased waist circumference, but a lower quantity of visceral fat, might be overestimated as high-risk centrally obese patients, despite being actually at a low risk. Particularly striking were findings of more increased carotid IMT in participants with normal waist circumference, but high VFT than those with high waist circumference, but normal VFT. That is, the association between VFT and carotid IMT was independent of waist circumference, a simple measure of central obesity and waist circumference alone could not exactly assess the risk of visceral obesity. Recently, Lear *et al*. also reported in healthy volunteers that visceral adipose tissue area measured by computed tomography (CT) was independently associated with carotid atherosclerosis.[16] However, Lear *et al*. did not demonstrate why waist circumference could not reflect all of this risk. In contrast, we demonstrated more definitely why Asians show a greater propensity to develop diabetes and CVD at relatively low BMI or waist circumference values, and why previous reports on the association between anthropometric measures of abdominal obesity and atherosclerosis are conflicting.[17–20]

The standard method of quantifying the amount of visceral fat is CT,[21] such as the report by Lear *et al*.[16] However, exposure to ionizing radiation, high cost and low availability prevent the wide use of CT in clinical and epidemiologic studies. Ultrasonography is a widely available instrument to most clinical settings and could avoid the weaknesses of CT. Several studies report that the diverse indices using ultrasonography are a reliable way of quantifying the visceral fat depot.[7,22–26] We had previously reported that ultrasonographic VFT was strongly correlated with visceral adipose tissue area by CT and could be a reliable risk factor associated with CVD and metabolic syndrome.[10] Therefore, measuring directly visceral fat accumulation by ultrasonography may be simple but important for identifying truly high risk individuals to CVD.

An overlooked problem in measuring visceral fat using ultrasonography is the absence of a definite cutoff value to define visceral obesity. In our previous study,[10] a VFT of 47.6 mm in men was suggested as a cutoff for predicting the presence of metabolic syndrome, and this study defined visceral obesity by this cutoff value of VFT. Although this cutoff value was somewhat arbitrary, similar results were obtained even when the VFT cutoff (52.4 mm) corresponding to a visceral adipose tissue area of 100 cm^2 was selected to define visceral obesity (data not shown).

It has to be kept in mind that this study was a cross-sectional study and was performed only in men with type 2 diabetes. Our study showed an independent association of VFT with carotid IMT, but did not observe the future CVD events and mortality. Although a number of women participated in this study, we did not have enough women to analyze the effect of VFT to carotid IMT according to various groups and menopause status. However, the preliminary result in women showed a similar trend with those in men (data not shown). The relationship of total adiposity to visceral fat accumulation and to several metabolic diseases may vary among different populations. Several studies suggest that Asians are more prone to visceral fat accumulation for a given waist circumference than Caucasian.[27,28] Accordingly, our results may differ from those in other ethnic groups. To definitely validate the need for the additional measure of quantifying visceral fat accumulation, well-controlled, prospective studies are warranted.

In conclusion, a substantial proportion of diabetic men with normal waist circumference had visceral obesity. Such participants showed an increased IMT compared with those having increased waist circumference but less visceral fat. In addition to waist circumference, a direct estimation for visceral fat, such as VFT, may provide an additional role in identifying diabetic patients with an increased atherosclerotic burden.

Conflict of interest

We have no relevant financial conflicts of interest to disclose.

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