Association between Abdominal Wall Fat Index on Ultrasonography and Carotid Atherosclerosis in Non-obese Men

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We tried to investigate whether accumulation of visceral fat, assessed by a simple but widely used ultrasonographic method, was associated with common carotid atherosclerosis in non-obese men ranging from 16 to 79 years old. The subjects were consecutive 297 male in-patients whose body mass index ranged from 18.5 kg/m² to 25 kg/m². An ultrasonographic evaluation using a 7.5 MHz linear type B-mode probe was performed by a specialist to determine the intima-media thickness (IMT) of the common carotid artery and the maximal thickness of peritoneal fat (Pmax) at the anterior surface of the liver and the minimal thickness of subcutaneous fat (Smin) of the abdomen. The Pmax/Smin ratio, which was termed the abdominal wall fat index (AFI), was then calculated. The mean age $\pm$ standard deviation in this series was 65 $\pm$ 13 (range, 15–79) years. Multiple regression analysis using IMT as an objective variable, adjusted by various risk factors as explanatory variables, showed that AFI [β , 0.0538; 95% confidence interval (CI), 0.0116–0.0960] was a significant independent contributing factor along with known risk factors such as age, smoking status, systolic blood pressure, HDL-cholesterol and LDL-cholesterol. We found that AFI was useful in evaluating disorders of metabolism and atherosclerosis in non-obese men. *J Atheroscler Thromb*, 2005; 12: 85–91.

Key words: Intima-media thickness, Risk factor, Common carotid artery, Visceral fat

Introduction

The distribution of body fat has been reported to be closely related to metabolic disorders. However, the degree of obesity is not necessarily correlated with the severity and frequency of such disorders. Ito *et al.* (1) reported that excess accumulation of fat mass, especially in the upper body, was related to dyslipidemia in normal-weight Japanese individuals. Moreover, intra-abdominal adiposity has been found to be associated with glucose intolerance, elevated triglyceride (TG), low HDL cholesterol (HDL-C) levels, and hypertension in both clinical

and population-based prospective cohort studies (2). Recently, Fujimoto *et al.* (4) reported that intra-abdominal visceral fat, as well as blood pressure and plasma glucose, are important independent risk factors for incident coronary heart disease in this population of diabetic and nondiabetic Japanese-American men. Measurement of such accumulation is therefore an important step in assessing risks of atherosclerosis. However, the alternative of computed tomography (CT) scanning (2–4) and magnetic resonance imaging (5) can offer a better estimation, but exposure to high radiation levels, cost and technical difficulty are major disadvantages. Alternative noninvasive methods to quantify regional adiposity have been used in clinical and epidemiological studies. The use of waist-to-hip ratio (WHR) or waist circumference (1), and abdominal fat deposition by ultrasonography (6, 7–9) as predictors of atherosclerotic risk have been reported.

Recently, we demonstrated that measuring the preperitoneal and subcutaneous fat thickness by ultrasonogra-

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phy could reflect body fat distribution more accurately, and was useful in evaluating disorders of metabolism, hypertension and atherosclerosis in non-obese as well as obese women (9). In obese men, several studies have showed that intra-abdominal visceral fat accumulation determined by CT scanning may be related to the appearance of these risk factors and contribute to the development of atherosclerosis (10–11). However, to our knowledge, few studies have focused on the measurement of preperitoneal and subcutaneous fat thickness by ultrasonography in non-obese men. Therefore, this study assessed the accumulation of visceral fat by ultrasonography and determined its relation to various risk factors for atherosclerosis as well as its association with common carotid atherosclerosis in non-obese men.

Materials and Methods

Subjects

The subjects were consecutive male in-patients in the Medical Department of Seiyō Municipal Nomura Hospital enrolled between September 1996 and August 2004. Men, aged from 15 to 79 years, with body mass index (BMI) from 18.5 to 25 kg/m² were screened for inclusion in the study. Patients with a history of upper abdominal surgery were excluded to avoid any possible effect on measurement of fat thickness. Informed consent for the procedure was obtained from each patient. The subjects were 297 men aged 65 ± 13 (range, 15–79) years.

Ultrasound image analysis

An ultrasonographic evaluation (Hitachi EUB-565) using a 7.5 MHz linear type B-mode probe was performed by a specialist to evaluate sclerotic lesions of the common carotid arteries and fat thickness on a day close to the day of blood biochemistry analysis (within 2 days). Patients were placed in supine position, and the bilateral carotid arteries were observed obliquely from the anterior and posterior directions. We measured the thickness of the intima-media complex (IMT) on the far wall of the bilateral common carotid artery about 10 mm proximal to the bifurcation of the carotid artery (as the image at that site is more clearly depicted compared with that of the near wall) (12, 13) as well as the wall thickness near the 10 mm point on the B-mode monitor, then used the mean value for analysis. To investigate the relation between IMT and various factors, all subjects were divided into three groups based on tertile of IMT.

Regarding the measurement of fat thickness, the subjects were placed in a supine position, the probe was held perpendicular to the skin at the epigastrium, and vertical scanning was performed along the abdominal median from the processus xiphoideus to the umbilicus to measure the maximal thickness of preperitoneal fat (Pmax) at the anterior surface of the liver and the mini-

mal thickness of the subcutaneous fat (Smin) of the abdomen. Then the Pmax/Smin ratio (abdominal wall fat index, AFI) was calculated (14).

Other various risk factors

We measured systolic (SBP) and diastolic blood pressure (DBP) in the right upper arm of patients in a seated posture using an automatic oscillometric blood pressure recorder (UA-766, AND Co. Ltd, Tokyo, Japan). Cigarette smoking was quantified based on daily consumption and duration of smoking. For blood biochemistry analyses, total cholesterol (T-C), TG and HDL-C, uric acid were measured under a fasting condition within 24 hours of admission. LDL cholesterol (LDL-C) level was calculated by the Friedewald formula. History of use of antihypertensive and antilipidemic drugs was also evaluated. The presence of diabetes mellitus was defined as a history of treatment for diabetes mellitus.

Criteria for the determination of atherosclerotic risk factors were as follows:

- Hypertension shown by administration of antihypertensive drugs.
- Diabetes mellitus revealed by the use of hypoglycemic drugs or insulin therapy, or case history.
- Hypertriglyceridemia shown by TG concentrations higher than 150 mg/dl.
- High LDL-C level shown by LDL-C concentrations higher than 140 mg/dl or the use of antilipidemic drugs.
- Low HDL-C level shown by HDL-C less than 40 mg/dl.

To investigate the relationships between AFI and the involvement of multiple atherosclerotic risk factors (metabolic syndrome + high LDL-C), we calculated the sum of the above risk factor scores giving one point for each of the five items if present (risk factor morbidity index).

Statistical analysis

Statistical analysis was performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, IL, USA). Differences among three groups divided based on IMT (IMT-1, 0.48–0.85 mm; IMT-2, 0.86–1.04 mm; IMT-3, 1.05–2.23 mm) were analyzed by one-way ANOVA or χ^2 -test. Correlations between various characteristics and IMT were made using Pearson's correlation test. The relation between IMT and risk factors including AFI were examined by stepwise multiple linear regression analysis. A value of $p < 0.05$ was considered significant.

Results

Table 1 shows the background characteristics of the three groups divided by IMT. Age ($p < 0.001$), smoking status ($p = 0.008$), SBP ($p < 0.001$), antihypertensive drug use ($p < 0.001$), T-C ($p = 0.001$), HDL-C ($p = 0.014$), LDL-C ($p < 0.001$), risk factor morbidity index ($p < 0.001$) and atherosclerotic disease ($p < 0.001$) were higher in the

Table 1. Characteristics of subjects by carotid intima-media thickness.

	IMT-1 (0.48–0.85)	IMT-2 (0.86–1.04)	IMT-3 (1.05–2.23)	
Characteristics	<i>n</i> = 105	<i>n</i> = 97	<i>n</i> = 95	<i>p</i> -value [§]
Age (years)	57 ± 16	68 ± 8	69 ± 7	< 0.001
Body mass index [†] (kg/m ²)	22 ± 2	22 ± 2	22 ± 2	0.094
Smoking status [‡]	23 ± 22	30 ± 24	33 ± 27	0.008
Systolic blood pressure (mmHg)	126 ± 19	136 ± 21	143 ± 23	< 0.001
Diastolic blood pressure (mmHg)	76 ± 12	78 ± 12	79 ± 12	0.132
Antihypertensive drug use, <i>N</i> (%)	22 (21.0)	47 (48.5)	49 (51.6)	< 0.001
Total cholesterol (mg/dl)	166 ± 44	164 ± 41	185 ± 44	0.001
Triglyceride (mg/dl)	104 ± 74	88 ± 45	106 ± 51	0.068
HDL-cholesterol (mg/dl)	52 ± 19	48 ± 20	44 ± 18	0.014
LDL-cholesterol (mg/dl)	93 ± 38	98 ± 35	120 ± 39	< 0.001
Antilipidemic drug use, <i>N</i> (%)	0	1 (1.0)	5 (4.2)	0.057
Uric acid (mg/dl)	5.4 ± 1.6	5.6 ± 1.7	5.8 ± 1.8	0.222
Diabetes mellitus, <i>N</i> (%)	25 (23.8)	23 (23.7)	28 (29.5)	0.575
Risk factor morbidity index	1.0 ± 1.0	1.2 ± 0.9	1.8 ± 1.0	< 0.001
Smin (mm)	8.5 ± 3.1	8.5 ± 3.3	8.3 ± 2.5	0.823
Pmax (mm)	7.6 ± 3.1	8.1 ± 3.4	8.4 ± 3.8	0.279
Abdominal wall fat index	0.95 ± 0.40	1.05 ± 0.57	1.09 ± 0.60	0.138
Atherosclerotic disease, <i>N</i> (%)	14 (13.3)	37 (38.1)	47 (49.5)	< 0.001
Ischemic stroke, <i>N</i> (%)	11 (10.5)	28 (28.9)	39 (41.1)	< 0.001
Ischemic heart disease, <i>N</i> (%)	4 (3.8)	10 (10.3)	11 (11.6)	0.102

Plus-minus values are means ± SD. [†]: Body mass index is the weight in kilograms divided by the square of the height in meters.

[‡]: Smoking status: daily consumption (packs) × duration of smoking (years). IMT: carotid intima-media thickness. Pmax: the maximal thickness of peritoneal fat at the anterior surface of the liver; Smin: the minimal thickness of subcutaneous fat of the abdomen. [§]: one-way ANOVA or χ^2 -test.

groups with higher IMT. There were no inter-group differences in BMI, DBP, TG, Antilipidemic drug use, uric acid, presence of diabetes mellitus, Smin, Pmax and AFI.

Table 2 shows a correlation coefficient between their background characteristics and IMT. Age ($p < 0.001$), smoking status ($p < 0.001$), SBP ($p < 0.001$), antihypertensive drug use ($p < 0.001$), T-C ($p = 0.009$), HDL-C ($p = 0.010$), LDL-C ($p < 0.001$) and antilipidemic drug use ($p = 0.038$), uric acid ($p = 0.020$) and AFI ($p = 0.016$) were significantly correlated with IMT.

Figure 1 shows a correlation between the AFI, Pmax, Smin, age, SBP and LDL-C and IMT. The correlation coefficient between the AFI, age, SBP and LDL-C, and IMT were significant. On the other hand, the correlation between the Pmax and Smin, and IMT were not significant.

Figure 2 shows the subjects' risk factor morbidity in-

dex in relation to the AFI. The risk factor morbidity index of the group with the highest AFI was significantly more than that of the group with the lowest AFI ($p = 0.007$).

Multiple regression analysis using IMT as an objective variable, adjusted by various risk factors as explanatory variables, showed that AFI [β , 0.0538; 95% confidence interval (CI), 0.0116–0.0960] was a significant independent contributing factor along with known risk factors such as age, smoking status, SBP, HDL-C and LDL-C (Table 3).

Discussion

The results of our investigation show that in a sample of men selected with regard to normal BMI, AFI which was the Pmax/Smin ratio, was a significant independent contributing factor to metabolic disorders, along with

Table 2. Correlation between various characteristics and carotid intima-media thickness.

Characteristics	Intima-media thickness correlation coefficient	p-value [§]
Age (years)	0.470	< 0.001
Body mass index [†] (kg/m ²)	0.052	0.374
Smoking status [‡]	0.258	< 0.001
Systolic blood pressure (mmHg)	0.313	< 0.001
Diastolic blood pressure (mmHg)	0.097	0.097
Antihypertensive drug use (Yes = 1, No = 0)	0.276	< 0.001
Total cholesterol (mg/dl)	0.151	0.009
Triglyceride (mg/dl)	0.035	0.552
HDL-cholesterol (mg/dl)	-0.149	0.010
LDL-cholesterol (mg/dl)	0.233	< 0.001
Antilipidemic drug use (Yes = 1, No = 0)	0.120	0.038
Uric acid (mg/dl)	0.135	0.020
Diabetes mellitus (Yes = 1, No = 0)	0.026	0.655
Abdominal wall fat index	0.140	0.016
Pmax	0.097	0.094
Smin	-0.044	0.454

[†]: Body mass index is the weight in kilograms divided by the square of the height in meters. [‡]: Smoking status: daily consumption (packs) × duration of smoking (years). An addictive model (Yes = 1, No = 1) were used for antihypertensive and antilipidemic drug use. Pmax: the maximal thickness of peritoneal fat at the anterior surface of the liver; Smin: the minimal thickness of subcutaneous fat of the abdomen. [§]: Pearson's correlation test.

known risk factors such as age, smoking status, systolic blood pressure, HDL-C and LDL-cholesterol. The investigation also showed that the maximal thickness of preperitoneal fat (Pmax) and the minimum thickness of subcutaneous fat (Smin) in the abdomen could be determined by ultrasonography, useful in evaluating carotid atherosclerosis.

Yamamoto *et al.* (15) reported that visceral fat accumulation (Pmax) assessed by ultrasonography may play a role in the progression of IMT in non-obese middle-aged men, but AFI was not correlated with IMT. However, in our study, IMT was associated with AFI rather than Pmax. We have already reported that ultrasonographically determined AFI in women is related to SBP, DBP, T-C and TG, and is an independent risk factor for IMT (9). In this study, AFI also showed good correlation with risk factor

scores (metabolic syndrome + high LDL-C) in non-obese men with a BMI from 18.5 to 25 kg/m² as well as women with a BMI over 22.0 kg/m² (9). Furthermore, AFI is a risk factor for coronary heart disease because the severity of coronary stenosis for both men and women was higher in the high-AFI groups than in the low-AFI groups (16). Abdominal wall fat index, which we chose as a tool for expressing the fat distribution in the abdomen, was strongly related to the atherosclerotic risk factor and carotid atherosclerosis in non-obese men.

Alternative non-invasive methods to quantify regional adiposity have been developed in screening and epidemiological studies, in consideration of exposure to radiation, and the great expense and low availability of CT. Therefore, the use of BMI (17), waist-to-hip circumference ratio (1), waist circumference (1–18), body composition dual-energy x-ray absorptiometry (19), waist/height ratio (20) and more recently abdominal fat deposition by ultrasonography are utilized as simple and common methods of measuring abdominal obesity (2, 6–9, 14, 15). Okada *et al.* (17) demonstrated that IMT was independently correlated with BMI, T-C, HDL-C, LDL-C and SBP in males and with BMI, T-C, TG, HDL-C, LDL-C, HbA1c, SBP, and DBP in females. Han *et al.* (18) reported that larger waist circumference increased cardiovascular risks in 2183 men and 2698 women aged 20–59 years selected at random from the civil registry of Amsterdam and Maastricht. However, Hsieh *et al.* (20) suggested that the weight/height ratio may be a better predictor of multiple coronary heart disease risk factors such as blood pressure, fasting plasma glucose, hemoglobin A_{1c}, TG, T-C and HDL-C than BMI or the waist/hip ratio. We used a simple, widely available ultrasound device to assess the maximal thickness of preperitoneal fat (Pmax) and the minimal thickness of subcutaneous fat (Smin). Pmax was significantly correlated with visceral fat measurement by CT at the umbilical level ($r = 0.70$, $p < 0.001$) and Smin, the subcutaneous fat area ($r = 0.83$, $p < 0.001$) (14). In the present study, AFI is positively correlated with the risk factor morbidity index. AFI is strongly associated with IMT adjusted for other atherosclerotic risk factors. These data suggest that AFI based on visceral fat accumulation in non-obese men may be an important predictor of IMT.

Body fat accumulation has been shown to be an important predictor of atherosclerosis, and the complexity of this relationship has been illustrated in recent studies in which regional adiposity on body was more closely associated with atherosclerosis incidence than was the magnitude of generalized obesity (1–11, 15, 16). Visceral obesity or visceral fat accumulation without obesity is closely associated with what Matsuzawa *et al.* (21) describes as “visceral fat syndrome”, or what Reaven (22) describes as “Syndrome X”, such metabolic and circulatory disorders as insulin resistance, glucose intolerance,

Fig. 1. Correlation between abdominal wall fat index (AFI), the maximal thickness of preperitoneal fat (Pmax) at the anterior surface of the liver, the minimal thickness of the subcutaneous fat of the abdomen (Smin), age, systolic blood pressure (SBP) and LDL-cholesterol (LDL-C), and carotid intima-media thickness (IMT).

hypertriglyceridemia, hypertension, decreased plasma concentration of HDL-C and increased plasma concentration of LDL-C. We also observed this finding in relation to visceral fat accumulation group by ultrasonography, which reinforces the role of AFI in the identification of people at high risk for carotid atherosclerosis.

Thus, the question is why increased visceral fat results in the progression of atherosclerosis. The function of adipocytes has been proven to differ according to location. Adipocytes of fat accumulated in the peritoneum

and other visceral locations are metabolically active and exhibit a higher rate of lipolysis by catecholamines or facilitation of lipid mobilization compared to cells obtained from subcutaneous adipose tissue (23, 24). It has been shown that visceral fat accumulation that is mainly composed of omental and mesenteric adipocytes is closely related to metabolism in the liver. Release of excessive free fatty acids into portal circulation causes overproduction of very low density lipoprotein (VLDL) that may result in hypertriglyceridemia and hypercholesterolemia

Fig. 2. Subject distribution and risk factor morbidity index in relation to the abdominal wall fat index (compared with the highest risk group by one-way ANOVA: $p = 0.026$). § : unpaired t -test. AFI: abdominal wall fat index.

(25). A reduction in insulin sensitivity of hepatocytes as well as disturbance of glucose metabolism may also be promoted. Recent advances in the biology of adipose tissue have demonstrated that adipose tissue is not an energy storage organ but secretes a variety of molecules which affect metabolism of the whole body (26, 27). This article found an effect of AFI on IMT after adjusting for other atherosclerotic risks. These metabolic disorders may result in promoting atherosclerosis over the long term.

In conclusion, we suggest that ultrasonographically determined AFI is a useful parameter for evaluating disorders in lipid metabolism and atherosclerosis in non-obese men.

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Table 3. Relation between conventional risk factors and carotid atherosclerosis as determined by multiple linear regression analysis.

Characteristics	beta (95% CI)	p-value
Age (years)	0.0070 (0.0052-0.0088)	< 0.001
Smoking status	0.0015 (0.0006-0.0025)	0.001
Systolic blood pressure (mmHg)	0.0022 (0.0011-0.0032)	< 0.001
HDL-cholesterol (mg/dl)	- 0.0013 (- 0.0025- - 0.0002)	0.025
LDL-Cholesterol (mg/dl)	0.0011 (0.0005-0.0016)	< 0.001
Abdominal wall fat index	0.0538 (0.0116-0.0960)	0.013

CI: confidence interval. Body mass index, diastolic blood pressure, antihypertensive drug use, total-cholesterol, triglyceride, antilipidemic drug use, uric acid and presence of diabetes mellitus were not included in final model by stepwise multiple linear regression analysis.

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