Body Fatness and Fat Distribution as Predictors of Metabolic Abnormalities and Early Carotid Atherosclerosis

Rieko Takami, md[1]
Noriyuki Takeda, md[2]
Makoto Hayashi, md[1]
Akihiko Sasaki, md[2]
Shinichi Kawachi, md[2]
Koji Yoshino, md[2]
Kazuhisa Takami, md[2]
Kazuya Nakashima, md[2]
Akifumi Akai, md[1]
Noriyoshi Yamakita, md[1]
Keigo Yasuda, md[2]

OBJECTIVE — To test the hypothesis that intra-abdominal fat plays a primary role over general adiposity for metabolic abnormalities and atherosclerosis.

RESEARCH DESIGN AND METHODS — We cross-sectionally studied 849 Japanese men aged 50.3 ± 8.5 years (range 20–78) with BMI 23.5 ± 2.9 kg/m^2. Intimal-medial thickness (IMT) of the carotid artery was measured by ultrasound. General adiposity was assessed by BMI. Waist circumference and waist-to-hip ratio (WHR) were used as a surrogate measure for abdominal fat. Abdominal subcutaneous fat area (ASF) and intra-abdominal fat area (IAF) were measured by computed tomography. Correlations between these measures and carotid IMT were analyzed. The interaction of generalized adiposity (BMI) and IAF in relation to metabolic variables, such as glucose tolerance, insulin resistance, and serum lipids, was also evaluated.

RESULTS — BMI, waist circumference, WHR, ASF, and IAF were all correlated with carotid IMT. Adjustment for BMI eliminated the associations between IMT and waist circumference, ASF, and IAF. In contrast, WHR retained a significant correlation with IMT. BMI and IAF were associated with insulin resistance, glucose tolerance, HDL cholesterol, and blood pressure independently of each other. IAF was an independent correlate for serum triglyceride, but BMI was not.

CONCLUSIONS — The primary importance of IAF over general adiposity for carotid atherosclerosis was not confirmed. Caution is recommended when using WHR as a measure of abdominal fat. The roles of IAF for metabolic abnormalities may be more limited than conventionally thought. BMI and WHR are simple and better clinical predictors for carotid atherosclerosis versus IAF.

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Obesity is a growing problem in many countries, and its role in cardiovascular disease has drawn increasing attention (1). Since the early 1980s, a number of researchers have reported based on anthropometric measurements that abdominal distribution of fat is a significant risk factor for the development of diabetes, dyslipidemia, and cardiovascular disease (2–6). Soon thereafter, application of computed tomography and magnetic resonance imaging (MRI) enabled investigators to directly measure abdominal fat distribution and to precisely analyze the relationship between fat topography and metabolic abnormalities. Intra-abdominal fat has been proposed as the most important determinant of obesity-related metabolic abnormalities (7–9). Experimental evidence supporting this notion is that relatively increased lipolytic activity of omental fat cells and their direct portal-venous drainage causes the liver to be exposed to a high concentration of free fatty acids, which in turn results in hepatic insulin resistance and dyslipidemia (7). In addition, regional differences in adipocyte production of cytokines between subcutaneous and visceral fat depots have been reported (10). Despite increasing acceptance of this concept, direct evidence of the association between intra-abdominal fat and cardiovascular disease is very limited (11–13).

Measurement of intimal-medial thickness (IMT) of the carotid artery by *B*-mode ultrasonography is a noninvasive and easily applicable method to quantitate carotid atherosclerosis. IMT of the carotid artery has been shown to predict future incidence of cardiovascular disease (14–15). This study was designed to analyze the relationship of body fatness and abdominal fat distribution measured by direct methods to carotid IMT and to metabolic cardiovascular risk factors. Particular attention was placed on whether intra-abdominal fat has a stronger association with carotid IMT and metabolic risk factors than generalized adiposity.

RESEARCH DESIGN AND METHODS

Subjects and protocol

The study subjects were 849 Japanese men with a mean age of 50.3 ± 8.5 years (mean ± SD) (range 20–78) and a mean BMI of 23.5 ± 2.9 kg/m^2 (range 15.2–36.1). They entered the study after giving informed consent. They were recruited between 1996 and 1998 from participants of a human dry dock in Matsunami

From the [1]Department of Internal Medicine, Matsunami General Hospital, Kasamatsu, and the [2]Third Department of Internal Medicine, Gifu University School of Medicine, Gifu, Japan.

Address correspondence and reprint requests to Noriyuki Takeda, MD, Third Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500-8705, Japan. E-mail: ntkd@cc.gifu-u.ac.jp.

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Abbreviations: ADA, American Diabetes Association; ASF, abdominal subcuatenous fat area; AUC-IRI, area under the curve of immunoreactive insulin; AUC-PG, AUC of plasma glucose; CT, computed tomography; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IAF, intra-abdominal fat area; IGT, impaired glucose tolerance; IMT, intimal-medial thickness; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

General Hospital, which is situated in an urban area of Gifu, Japan. Human dry dock is a popular medical service available nationwide in Japan. Most of our study subjects were workers. They came to the dock in the morning and stayed there for 36 h until they finished all scheduled medical examinations at 4:00 P.M. on the following day. The study was approved by the ethics committee of Matsunami General Hospital and by the Gifu University School of Medicine.

The health checkup program included urinalysis, blood cell counts, blood chemistry, and a 75-g oral glucose tolerance test (OGTT). Electrocardiogram, chest X-ray, upper gastrointestinal series, and computer-assisted tomographic scanning of the abdomen were also included in the program. An OGTT was done after an overnight fast. Blood was drawn before and 1 and 2 h after a glucose ingestion. Plasma glucose and insulin (16) were measured by a glucose oxidase method and a double-antibody radioimmunoassay, respectively. Diabetes and impaired glucose tolerance (IGT) were judged by the new guidelines of the American Diabetes Association (ADA) for the diagnosis of diabetes (17). An area under the curve of plasma glucose (AUC-PG) and an area under the curve of immunoreactive insulin (AUC-IRI) for 75-g OGTT was calculated by a trapezoidal rule as an index of glucose metabolism.

Since we measured only fasting plasma insulin values in the initial phase of the study, 102 subjects were missing, and the number of subjects available for AUC-IRI was 751. A parameter based on a homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from a pair of values of fasting plasma glucose (FPG) (18). Serum total cholesterol (19), triglyceride (20), and HDL cholesterol (21) were measured by the methods described elsewhere.

Circumference of the waist (umbilical level) and hip (maximum of buttocks) were measured (n = 811, measurements were not done in 38 subjects) to the centimeter. The waist-to-hip ratio (WHR) circumference was calculated. Abdominal subcuatenous fat area (ASF) and intra-abdominal fat area (IAF) were measured by computed tomographic scans (22) with a Lemage SX-E (General Electric Yokogawa Medical System, Tokyo) at the level of the umbilicus. The window was set between −30 and −190 Hounsfield units. The range of interest for a measurement of IAF area was set by outlining the inside of the muscle layer of the abdominal wall. A single-slice computed tomography (CT) measurement of regional abdominal fat area was validated as an accurate estimate of abdominal adipose tissue volume (23).

Intimal-medial thickness (IMT) of the common carotid artery was measured by *B*-mode ultrasound using a Logiq 500 (General Electric Yokogawa Medical System) according to the method of Pignoli et al. (24) but slightly modified. A longitudinal two-dimensional ultrasound image of the common carotid artery was scanned by a 10-MHz linear array transducer while patients were in a supine position. The greatest IMT and those measured 1 cm upstream and downstream from the site of the greatest IMT were measured bilaterally. In total, six IMT values were obtained for each subject. An average of these measurements was calculated and used for statistical analyses. The measurement of IMT was performed by a single physician (R.T.) throughout the study, so as to avoid interobserver variation. Smoking status, diabetes history, and treatment were obtained by a self-administered questionnaire. Smoking status was expressed by the Brinkman index, which is calculated as number of cigarettes per day multiplied by years of smoking. Smoking status was missing in 49 subjects because of incompleteness of the answers.

Table 1—*Clinical and metabolic characteristics*

Variable	*n*	Mean	SD
IMT (mm)	849	0.70	0.13
Age (years)	849	50.28	8.43
Height (cm)	849	167.81	5.66
Weight (kg)	849	66.16	9.42
Waist (cm)	811	82.79	7.72
Hip (cm)	811	92.36	5.67
WHR	811	0.90	0.05
BMI (kg/m^2)	849	23.47	2.90
IAF (cm^2)	849	100.70	44.91
ASF (cm^2)	849	125.30	53.03
FPG (mmol/l)	849	5.63	0.97
AUC-PG (mmol/l · min)	849	901.23	272.35
HbA_{1c} (%)	849	5.30	0.71
Fasting immunoreactive insulin (pmol/l)	848	49.26	21.99
AUC-IRI (pmol/l · min)	751	25388	18042
HOMA-IR	848	1.81	0.97
Total cholesterol (mmol/l)	849	5.21	0.84
HDL cholesterol (mmol/l)	849	1.39	0.37
Triglyceride (mmol/l)	849	1.66	1.15
Systolic blood pressure (mmHg)	849	123.47	18.13
Diastolic blood pressure (mmHg)	849	78.77	11.96
Brinkman index	801	443.44	527.26

Waist, circumference of the waist; Hip, circumference of the hip maximum of buttocks. The Brinkman index is calculated as number of cigarettes per day multiplied by years of smoking.

Statistical methods

Data are expressed as means ± SD. Statistical analyses were performed with SAS version 6.12 for Windows (SAS Institute, Cary, NC). Relations between variables were evaluated by Spearman's rank-correlation test. For multivariate analysis, confounders of the association between two variables were included in regression models as covariates, and partial correlation coefficients were calculated.

RESULTS

Clinical characteristics of the subjects

As shown in Table 1, the mean BMI of 849 Japanese men was much lower than that of white and black men in the U.S. population age ≥20 years (25). The BMI of our subjects fairly well represents the average for Japanese men within this age

Table 2—*Correlations between carotid IMT and fat-related measures*

	IMT adjusted for age and smoking			IMT adjusted for age, smoking, and BMI	
Variable	*n*	*r*	*P*	*r*	*P*
BMI	801	0.138	0.0001	—	—
IAF	801	0.098	0.0058	0.010	0.7708
ASF	801	0.104	0.0034	−0.013	0.7049
Waist	766	0.126	0.0005	0.019	0.6073
Hip	766	0.047	0.1909	−0.080	0.0276
WHR	766	0.165	0.0001	0.106	0.0034

range (20–78 years) and accords with that obtained in recent population-based studies in Japan (26). Based on the new ADA guideline for diagnosis of diabetes (17), there were 581 (68.0%) subjects with normal glucose tolerance, 85 (10.0%) with impaired FPG, 163 (19.1%) with IGT, and 73 (8.5%) with type 2 diabetes. The prevalence of type 2 diabetes and IGT in the study population is similar to the reports from the community-based studies in Japan (26). The average IMT was 0.70 ± 0.13 mm. According to the guidelines of the National Cholesterol Education Program (NCEP) (27), hypercholesterolemia (≥5.18 mmol/l), hypertriglyceridemia (≥2.26 mmol/l), and low HDL cholesterolemia (≥0.9065 mmol/l) were found in 415 (48.6%), 164 (19.2%), and 49 (5.7%) of these subjects, respectively. Hypertension (diastolic blood pressure ≥90 mmHg, systolic blood pressure ≥140 mmHg) was found in 211 (24.7%) subjects.

Correlations of IMT with BMI, waist circumference, WHR, and CT-measured abdominal fat areas

The correlation coefficient between several measures of body habitus and the carotid IMT after adjustment for age and smoking status are shown in Table 2. Age itself was correlated positively with carotid IMT ($r = 0.302$). BMI, waist circumference, WHR, IAF, and ASF were all correlated positively with IMT. However, additional adjustment for BMI eliminated the association of IAF, ASF, and waist circumference with carotid IMT. In contrast, WHR retained a significant correlation with IMT. After controlling for IAF, BMI still retained a statistically significant correlation with carotid IMT ($r = 0.107$, $P = 0.0030$).

Correlations of BMI and IAF with metabolic variables as well as blood pressure

To examine the interaction between BMI and IAF in relation to metabolic variables and blood pressure, partial correlation coefficients were calculated after BMI and IAF were controlled for each other (Table 3). After adjustment for BMI, IAF was correlated positively with FPG and insulin, AUC-PG, AUC-IRI, HOMA-IR, total cholesterol, triglyceride, and systolic and diastolic blood pressure; it was negatively correlated with HDL cholesterol. When IAF was adjusted for, BMI was associated with all of these metabolic variables and blood pressure, except for triglyceride levels.

CONCLUSIONS — BMI, waist circumference, WHR, CT-measured IAF, and ASF were correlated with IMT of the common carotid artery after adjustment for age and smoking habit in Japanese men. These results are consistent with the notion that body adiposity is a risk factor for atherosclerosis. The main purpose of our study was to test the hypothesis that abdominal fat (especially intra-abdominal fat) plays a specific role over general fatness for atherosclerosis. We found that the association of waist circumference, IAF, and ASF with carotid IMT was eliminated after additional adjustment for BMI. In sharp contrast, WHR retained a statistically significant correlation even after adjustment for BMI.

Regarding the correlation between WHR and carotid IMT, our results accord excellently with those reported from the atherosclerosis risk in communities study (14). In this large-scale community-based study, it was demonstrated that both BMI

Table 3—*Partial correlations of metabolic variables with BMI and IAF after adjustment for each other*

	IAF				BMI			
	Adjusted for age		Adjusted for age and BMI		Adjusted for age		Adjusted for age and IAF	
Variable	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
FPG	0.232	0.0001	0.131	0.0001	0.862	0.0001	0.072	0.0355
AUC-PG	0.254	0.0001	0.150	0.0001	0.218	0.0001	0.071	0.0399
HbA_{1c}	0.059	0.0840	0.024	0.4876	0.063	0.0665	0.032	0.3529
Fasting immunoreactive insulin	0.552	0.0001	0.286	0.0001	0.571	0.0001	0.332	0.0001
AUC-IRI	0.445	0.0001	0.237	0.0001	0.433	0.0001	0.208	0.0001
HOMA-IR	0.549	0.0001	0.294	0.0001	0.556	0.0001	0.310	0.0001
Total cholesterol	0.194	0.0001	0.089	0.0099	0.196	0.0001	0.092	0.0071
HDL cholesterol	−0.326	0.0001	−0.143	0.0001	−0.343	0.0001	−0.181	0.0001
Triglyceride	0.435	0.0001	0.307	0.0001	0.330	0.0001	0.065	0.0595
Systolic blood pressure	0.265	0.0001	0.136	0.0001	0.252	0.0001	0.108	0.0016
Diastolic blood pressure	0.293	0.0001	0.167	0.0001	0.261	0.0001	0.095	0.0058

and WHR were associated with carotid IMT in black and white men. More importantly, WHR retained a significant correlation with carotid atherosclerosis after adjustment for BMI. The investigators of the study concluded that abdominal obesity is an important risk factor for atherogenesis. Discordance between WHR and CT-measured IAF in our study raises an intriguing problem. It is very clear that the correlation between WHR and carotid IMT after adjustment for BMI cannot be explained by intra-abdominal fat. It is more reasonable that there are other unknown factors that intervene between WHR and carotid IMT. Our results confirm clinical utility of WHR as a predictor of atherosclerosis. At the same time, they recommend caution in the interpretation of WHR as a surrogate measure for abdominal adiposity. Alternatively, since there are close correlations between fat-related measures, it can be argued that adjustment of these measures for each other is not adequate. If we adopt the latter view in a strict sense, the concept of abdominal obesity itself may need reevaluation because statistical adjustment for general adiposity has been a common investigational strategy for epidemiological and clinical studies in this field (5,6,14,28).

Whatever the explanation, our results do not support the hypothesis that abdominal fat (especially intra-abdominal fat) plays a specific role over general adiposity for carotid atherosclerosis.

The variance of carotid IMT, which was explained by the variables included in the study, was rather small (10–15%). There are several possible explanations. Because the associations between metabolic abnormalities and cardiovascular disease can be mediated not only by atherosclerosis but also by thrombosis and other mechanisms, the associations of these variables with carotid atherosclerosis may actually be weak. Alternatively, the measurement of carotid IMT and/or risk factors may not be precise enough. Such measurement errors may have resulted in the underestimation of the associations. Another possibility is that IMT is a complex trait, and many factors contribute to its determination. Finally, it is well known that cardiovascular disease is relatively uncommon among Japanese populations compared with Caucasian populations. Variations in carotid IMT and cardiovascular risk factors may be inherently low in our study subjects.

Over the past two decades, the notion that intra-abdominal fat is the most important determinant of obesity-related metabolic disorders has rapidly gained acceptance in the field of obesity research. The notion was based on a number of studies (28–33) that measured abdominal fat directly by CT scan or magnetic resonance imaging and demonstrated that glucose tolerance, insulin sensitivity, and serum lipids were closely associated with IAF. The most convincing evidence was that IAF was associated with these metabolic variables after adjustment for generalized adiposity, but generalized adiposity did not have such associations independently of IAF (20,30). This study offers an opportunity to re-examine these points using the same logic that was used in studies that involved a much smaller number of subjects. In analyses adjusted for age, BMI and IAF showed strong correlations with AUC-PG, AUC-IRI, HOMA-IR, HDL cholesterol, triglyceride, and blood pressure. In accordance with previous studies, IAF retained significant associations with all of these variables after adjustment for BMI. However, after adjustment for IAF, BMI also retained significant associations with all of the variables except for triglyceride. These results suggest that IAF may play a specific role in triglyceride metabolism. Nonetheless, specificity of IAF in terms of its relationship to metabolic variables is much more limited than conventionally thought.

We investigated Japanese men exclusively. Therefore, the results may not be applicable to women and other ethnic groups, especially to those characterized by an increased prevalence of obesity.

In conclusion, the present study did not confirm the primary role of IAF in carotid atherosclerosis. We recommend caution in the interpretation of the results obtained by using WHR as a measure of abdominal fat. More research is clearly needed to better understand the pathophysiology of IAF. Meanwhile, BMI and WHR are simple and better clinical predictors of early carotid atherosclerosis than CT-measured IAF.

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