Is Visceral Fat Really a Coronary Risk Factor?

A Multi-Detector Computed Tomography Study

Yukiko SHIMAMOTO,¹ MD, Masato MIZUKOSHI,² MD, Akio KUROI,² MD, Toshio IMANISHI,² MD, Tatsuya TAKESHITA,³ MD, Masaki TERADA,¹ MD, and Takashi AKASAKA,² MD

SUMMARY

Metabolic syndrome (MS) is currently considered to be a risk factor for arteriosclerotic disease. The accumulation of visceral fat leads to arteriosclerotic disease after other risk factors have developed and either direct or mutual effects occur. The aim of this study was to verify whether visceral fat serves as an independent coronary risk factor. A total of 3157 patients who had undergone multi-detector computed tomography (MDCT) were analyzed via computed tomographic angiography and the measurement of their visceral fat area. Coronary arteries with > 70% stenosis were considered to be significant. The visceral fat area was measured at the umbilical level, and an area of 100 cm² or more was defined as visceral obesity. Coronary risk factors (ie, hypertension, dyslipidemia, diabetes mellitus, family history, and smoking) were obtained from the patient medical records. The patients were divided into two groups: a visceral obesity group, 1130 patients (137.0 ± 31.1 cm²) and a nonvisceral obesity group, 2027 patients (57.3 ± 25.8 cm²). A significant difference in the incidence of coronary stenosis between the two groups was observed. According to multivariable analysis, the factors affecting coronary stenosis were age, gender, dyslipidemia, diabetes mellitus, and the ratio of visceral to subcutaneous fat. Visceral obesity was not found to be an independent coronary risk factor. Visceral obesity demonstrated the predominant presence of coronary risk factors. (Int Heart J 2013; 54: 273-278)

Key words: Computed tomography, Obesity, Coronary artery disease

One risk of arteriosclerotic disease is metabolic syndrome (MS). MS, which is caused by a combination of the consumption of excess calories and a lack of exercise, is currently attracting a great deal of attention. Visceral fat is one of the important factors in the diagnostic criteria of MS.¹⁻⁶⁾ Accumulation of visceral fat is a serious effect and it can cause arteriosclerotic diseases as a result of coronary risk factors such as diabetes mellitus, dyslipidemia, and hypertension, and direct or mutual effects.⁷⁻¹³⁾ The criterion of visceral fat area (VFA) that causes obesity-related disorders is considered to be 100 cm², although several waist-circumference thresholds have been recommended in different populations and ethnic groups.^{1,14,15)}

It is recognized that visceral fat contributes to metabolic disorders by altering levels of adipocyte-derived cytokines.¹⁶⁻²⁰⁾ Accumulation of visceral fat lowers the concentration of adiponectin, which has antiatherogenic and antidiabetic effects in the blood.¹⁷⁾ A decrease in the secretion of adiponectin causes excessive secretion of cytokines and tumor necrosis factor α (TNF- α).¹⁸⁾ The blood concentration of plasminogen activator inhibitor type 1 (PAI-1), a fibrinolytic regulation factor, and the amount of visceral fat present are both positively correlated.¹⁹⁾ All of these factors are considered to affect the pathogenesis of arteriosclerosis. Therefore, it is believed that the accumulation of visceral fat affects blood vessels directly and causes arterio-

sclerotic changes. In the clinical field, the relationship between the level of adiponectin and MS has previously been established.²⁰⁾

VFA measured with computed tomography (CT) is a marker of visceral obesity. In addition, multi-detector computed tomography (MDCT) can detect coronary atherosclerosis.²¹⁾ The aim of this study was to evaluate adiposity (VFA, the subcutaneous fat area (SFA)) and coronary atherosclerosis with MDCT and to then verify whether the accumulation of visceral fat serves as an independent risk factor for coronary artery disease.

METHODS

Study population: The study population originally consisted of 4395 patients who were referred for coronary lesion assessment by MDCT at our clinic between November 2005 and June 2012. The majority of the indications for coronary CT angiography (CCTA) consisted of a history of chest pain, pre-operative examination, abnormal ECG, and follow-up of coronary artery disease. A total of 1238 patients with severe calcification due to difficulties in the diagnosis of the stenosis severity and history of CAD were excluded, so the final number of patients enrolled was 3157 patients (66.0 ± 11.3

From the ¹ Wakayama-Minami Radiology Clinic, Departments of ¹ Cardiovascular Medicine and ² Public Health, Wakayama Medical University, Wakayama, Japan.

Address for correspondence: Takashi Akasaka, MD, Department of Cardiovascular Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama, Wakayama, 641-8510, Japan.

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years, male/female 1811/1346). The clinical characteristics and medical history of coronary risk factors including hypertension, dyslipidemia, diabetes mellitus, family history, and smoking were assessed from the patient medical records. Japanese guidelines for each disease were followed, wherein hypertension is diagnosed at a systolic blood pressure of 140 mmHg or more and diastolic blood pressure of 90 mmHg or more. Dyslipidemia is considered to be present when the low density lipoprotein (LDL) cholesterol level is at or above 140 mg/dL, or the triglyceride level is at or above 150 mg/dL, or the high density lipoprotein (HDL) cholesterol level is at or below 40 mg/dL. Diabetes mellitus is considered to be present when levels are at or above 126 mg/dL for fasting blood sugar levels, or 200 mg/dL or more in an oral glucose tolerance test, or 200 mg/dL or more for casual blood glucose. The conditions of the patients were diagnosed by their family doctor, while smoking history and family history were self-reported.

This study complies with the provisions of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of our clinic. Written informed consent was obtained from all participants.

Acquisition and analysis of MDCT images: The 64-slice CT (Brilliance 64, Philips, Eindhoven, Netherlands) was performed with a collimation of 64×0.625 mm, beam pitch of 0.2, pixel size of 0.39×0.39 mm, rotation time of 420 ms, tube current of 330–500 mA, and voltage of 120 kV. For the contrast-enhanced scan, 45–80 mL (body weight kg $\times$ 1.0 mL) of contrast media (Iopamiron370[®], Bayer Schering Pharma, Berlin, Germany) was injected at 3–5 mL/s followed by 20 mL saline injection at the same flow rate. The start of the contrast-enhanced scan was adapted to bolus tracking. The raw data of the scans was reconstructed using algorithms optimized for retrospective ECG-gated multi-slice spiral reconstruction. The reconstructed image data of CT was transferred to a computer workstation for post-processing (Virtual Place Lexus, AZE Inc., Tokyo). All scans were performed for 10 seconds with the patient holding their breath. Patients received a beta-blocker if their heart rate was > 70 beats/minute.

The analysis of 64-MDCT image data was performed by two experienced readers (SY and AT). Quantitative measurements were performed under concordance of two observers. In CT angiography (CTA), coronary arteries with $> 70\%$ stricture were diagnosed as having significant stenosis.²²⁾ The diagnostic

performance of CTA diagnosis compared with coronary angiography at this clinic is as follows: sensitivity, 97%; specificity, 90%; and negative predictive value, 97%.

Measurement of VFA and SFA with MDCT: Visceral fat was prospectively measured at the time of coronary examination. Abdominal scans were conducted at the lumbar 4–5 levels and single 5 mm slices were imaged during breath hold. Fat areas in the images were determined at the umbilical level, using commercially-available software (Virtual Place, AZE Inc., Tokyo). The fat area was defined as the image with attenuation ranging from -130 HU to -80 HU. The intraperitoneal area with such attenuation was defined as VFA, and the extraperitoneal area with a similar attenuation between the skin and the muscle was defined as SFA. Furthermore, visceral obesity was identified when VFA was 100 cm^2 or more according to previous reports.^{11,12)}

Statistical analysis: PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. Continuous variables are expressed as the mean $\pm$ SD and categorical variables are presented as number (%) and were compared using the chi-square test or Fisher's exact test. Differences between the two groups were tested by the unpaired *t* test. Statistical comparisons between more than 3 groups were performed by one-way ANOVA and post hoc multiple comparisons were performed using the Bonferroni test. A multivariable logistic regression model was used to determine predictors of coronary stenosis. The odds ratio for the presence of coronary stenosis was also quantified. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics: The patient characteristics are shown in Table I. Visceral obesity was observed in 1130 subjects and there were more male and younger subjects in this group when compared to the group without visceral obesity. It was significant that the patients in the visceral obesity group had a slightly higher rate of coronary risk factors, including hypertension, dyslipidemia, diabetes mellitus, as well as a higher incidence of smoking. There was a significant difference in the incidence of coronary stenosis between the visceral obesity group and the nonvisceral obesity group. The incidence of coronary sten-

Table I. Patient Characteristics

	Visceral obesity (<i>n</i> = 1130)	Nonvisceral obesity (<i>n</i> = 2027)	<i>P</i>
Age, years	65.2 $\pm$ 10.4	66.4 $\pm$ 11.8	< 0.001
Male / Female	810 / 320	1001 / 1026	< 0.001
Coronary risk factor	877 (78)	1388 (68)	< 0.001
Hypertension	661 (58)	915 (45)	< 0.001
Dyslipidemia	438 (39)	632 (31)	< 0.001
Diabetes mellitus	320 (28)	352 (17)	< 0.001
Smoking	277 (26)	370 (18)	< 0.001
Family history	59 (5)	174 (9)	< 0.001
Visceral fat area, cm^2	137.0 $\pm$ 31.1	57.3 $\pm$ 25.8	< 0.001
Waist circumference, cm	97.0 $\pm$ 7.7	84.3 $\pm$ 8.2	< 0.001
Body mass index, kg/m^2	26.5 $\pm$ 3.3	22.6 $\pm$ 3.1	< 0.001
V/S	1.01 $\pm$ 0.4	0.59 $\pm$ 0.4	< 0.001
Coronary stenosis	363 (32)	493 (24)	< 0.001

Data are presented as mean $\pm$ SD or number (%). V/S indicates the ratio of visceral fat to subcutaneous fat.

osis correlated positively with the number of coronary risk factors (Figure 1A). Furthermore, the incidence of visceral obesity

Figure 1. Relationship between the number of coronary risk factors and the incidences of coronary stenosis and visceral obesity. Panel A shows that coronary stenosis was detected more frequently as the number of coronary risk factors increased. Panel B shows that visceral obesity was observed more frequently as the number of coronary risk factors increased. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

correlated positively with the number of coronary risk factors (Figure 1B). Age, male gender, visceral fat area, hypertension, dyslipidemia, diabetes mellitus, smoking, and the ratio of visceral to subcutaneous fat significantly affected the presence of coronary stenosis when assessed by univariate analysis. Factors whose level of significance in univariate analysis was $P < 0.05$ were selected for multivariate analysis. According to multivariable analysis, age, male gender, dyslipidemia, diabetes mellitus, and the ratio of visceral to subcutaneous fat were significantly correlated with the presence of coronary stenosis (Table II). Table III shows the odds of the number of coronary risk factors for the presence of coronary stenosis in each group. The risk for coronary stenosis increased in proportion to the increase in the number of coronary risk factors, whether or not the patients were diagnosed as having visceral obesity. A total of 892 patients without coronary risk factors were placed in the non-risk factor group. The patient characteristics of the non-risk factor group are shown in Table IVa. Visceral obesity was observed in 253 subjects, which featured more male patients when compared to the group without visceral obesity. There was a significant difference between the visceral obesity group and the nonvisceral obesity group in the incidence of coronary stenosis. There were more visceral obesity patients in the group with coronary stenosis compared with the group without coronary stenosis in the non-risk factor group (visceral obesity/nonvisceral obesity 73/116 versus 180/523. $P < 0.001$).

Multivariable analysis determined VFA was not significantly correlated with the presence of coronary stenosis (Table IVb). Since visceral fat was related to gender and age, we chose to examine fat distribution as well (Figure 2). While women have more total fat and subcutaneous fat, men have more visceral fat and a greater abdominal girth. For men, the amount of total fat peaks at between 50 and 54 years of age, and then the amounts of total fat, visceral fat, and subcutaneous fat tend to gradually decrease. In comparison, the amounts of total fat, visceral fat, and subcutaneous fat in women tend to

Table II. Univariate Analysis and Multivariate Analysis of Factors Affecting the Presence of Coronary Stenosis

	Univariate analysis				Multivariate analysis			
	SRC	P	Odds ratio	95%CI	SRC	P	Odds ratio	95%CI
Age, years	0.313	< 0.001	1.03	1.02–1.04	7.94	< 0.001	1.04	1.03–1.05
Gender	0.474	< 0.001	2.62	2.17–3.18	8.92	< 0.001	2.84	2.26–3.57
Visceral fat area	0.172	< 0.001	1.00	1.00–1.00	-0.63	0.53	1.00	1.00–1.00
Hypertension	0.140	0.002	1.32	0.98–1.40	0.957	0.34	1.10	0.91–1.33
Dyslipidemia	0.075	< 0.001	1.18	0.98–1.40	2.265	0.024	1.26	1.03–1.54
Diabetes mellitus	0.290	< 0.001	2.01	1.68–2.52	5.00	< 0.001	1.96	1.57–2.43
Smoking	0.103	0.016	1.30	1.05–1.61	0.023	0.981	1.00	0.79–1.27
V/S	0.348	< 0.001	2.21	1.82–2.39	2.08	0.037	1.33	1.02–1.74
Family history	0.073	0.128	0.67	0.40–1.12				
Waist	-0.007	0.869	1.0	0.99–1.01				

	Multivariate analysis (Male)				Multivariate analysis (Female)			
	SRC	P	Odds ratio	95%CI	SRC	P	Odds ratio	95%CI
Age, years	8.61	< 0.001	1.04	1.03–1.05	5.24	< 0.001	1.04	1.03–1.05
Visceral fat area	-0.02	0.82	1.00	1.00–1.00	-2.89	0.004	0.99	1.00–1.00
Hypertension	1.64	0.10	1.17	0.97–1.41	3.02	0.003	1.53	1.16–2.02
Dyslipidemia	4.87	< 0.001	1.66	1.36–2.04	2.71	0.007	1.44	1.11–1.87
Diabetes mellitus	6.70	< 0.001	2.06	1.67–2.55	4.21	< 0.001	1.96	1.43–2.68
Smoking	0.08	0.94	1.01	0.83–1.23	2.05	0.04	1.63	1.02–2.62
V/S	0.81	0.42	1.11	0.87–1.42	2.23	0.026	1.72	1.07–2.76

SRC indicates standard regression coefficient; CI, confidence interval; and V/S, the ratio of visceral fat to subcutaneous fat.

Table III. Number of Coronary Risks and the Presence of Coronary Stenosis

	<i>n</i>	Odds ratio	95%CI
No visceral obesity	2027		
0 risk factors	639	1.00	
1 risk factor	676	1.22	0.93–1.60
2 risk factors	494	1.73	1.31–2.29
3 risk factors	200	3.62	2.56–5.10
4–5 risk factors	18	2.87	1.09–7.56
Visceral obesity	1130		
0 risk factors	253	1.83	1.30–2.56
1 risk factor	307	1.62	1.17–2.23
2 risk factors	329	2.33	1.72–3.15
3 risk factors	201	2.92	2.06–4.13
4–5 risk factors	40	3.69	1.91–7.10

CI indicates confidence interval.

Table IVa. Patient Characteristics in Non-Risk Factor Group

	Visceral obesity (<i>n</i> = 253)	Nonvisceral obesity (<i>n</i> = 639)	<i>P</i>
Age, years	65.5 ± 12.9	65.1 ± 10.4	0.152
Male / Female	200 / 53	301 / 338	< 0.001
Visceral fat area, cm ²	135.7 ± 31.4	53.6 ± 26.4	< 0.001
Waist circumference, cm	96.9 ± 7.5	83.5 ± 8.4	< 0.001
Body mass index, kg/m ²	26.4 ± 3.3	22.3 ± 3.1	< 0.001
V/S	1.04 ± 0.42	0.55 ± 0.37	< 0.001
Coronary stenosis	73 (29)	116 (18)	< 0.001

Data are presented as mean ± SD or number (%). V/S indicates the ratio of visceral fat to subcutaneous fat.

Table IVb. Multivariate Analysis of Factors Affecting the Presence of Coronary Stenosis in Non-Risk Factor Group

	SRC	Multivariate analysis		
		<i>P</i>	Odds ratio	95%CI
Age, years	5.445	< 0.001	1.05	1.03–1.06
Gender	5.505	< 0.001	3.27	2.14–4.98
V/S	-0.935	0.350	0.79	0.48–1.30
Visceral fat area	2.713	0.067	1.01	1.00–1.01

	Multivariate analysis (Male)				Multivariate analysis (Female)			
	SRC	<i>P</i>	Odds ratio	95%CI	SRC	<i>P</i>	Odds ratio	95%CI
Age, years	7.145	< 0.001	1.05	1.04–1.07	3.965	< 0.001	1.04	1.02–1.07
V/S	-0.816	0.415	0.84	0.56–1.27	0.327	0.744	1.15	0.50–2.65
Visceral fat area	1.663	0.096	1.00	1.00–1.01	0.891	0.323	1.00	1.00–1.01

V/S indicates the ratio of visceral fat to subcutaneous fat.

increase after they reach menopausal age, and then begin to decrease after around 70 years of age.

DISCUSSION

This study shows that while the accumulation of visceral fat is not an independent coronary risk factor, it does significantly affect the presence of coronary stenosis when assessed using univariate analysis. Patients in the visceral obesity group had several other coronary risk factors, indicating that they had a high risk of developing coronary arterial lesions. Furthermore, visceral fat is a fundamental condition that leads to the development of arteriosclerosis when associated with other risk factors. When presenting the distribution map of fat by age and gender, it becomes obvious that disparity in gender and age is related to the amount of fat. The ratio of visceral to subcutaneous fat may serve as the index which rectifies the difference in the fat distribution according to age and gender. However, photography by CT confirms the need for an index such as simple waist circumference measurement in establishing visceral fat measurement. It is also thought that individuals with visceral obesity who are over 70 years of age have a high risk of developing coronary arterial lesions;^{12,13} however, the amount of visceral fat usually begins decreasing around this age.

Several studies have shown that the accumulation of visceral fat causes arteriosclerosis via various internal secretion factors.^{16,23,24} Decreased adiponectin secretion causes excessive secretion of the cytokine TNF- α and the subsequent inflammation of vessels.^{18,25,26} The blood concentration of PAI-1, a fibrinolytic factor, and the amount of visceral fat have a positive correlation,^{19,27,28} and these factors are considered to affect arteriosclerosis. It is believed that the accumulation of visceral fat causes lipid metabolism disorder, glucose intolerance, and high blood pressure, and that it affects arteriosclerosis through these humoral factors²³ as well. Visceral fat measured using MDCT has been reported to be involved in coronary artery disease.²⁹ However, lower levels of high-density lipoprotein-cholesterol may be the most useful marker for predicting coronary artery disease, independent of other metabolic markers, such as lower levels of adiponectin, VFA or present medication.³⁰ The hazard ratios for both types of mortality increased not only in individuals with MS, but also in non-overweight individuals with a constellation of risk factors when compared with non-overweight individuals with no risk factors.³¹ Furthermore, it has been reported that visceral adipose accumulation is associated with the presence of non-calcified plaque and plaque vulnerability, as detected by CCTA.³² It has been reported that a correlation good for CT value OK of plaque and non-calcified plaque was seen in CCTA,³³ and it has also been reported that low attenuation coronary plaques on MDCT can

* $P < 0.05$, ≤ 49 versus each age group; † $P < 0.05$, 50-54 versus each age group; ‡ $P < 0.05$, 55-59 versus each age group; § $P < 0.05$, 60-64 versus each age group; || $P < 0.05$, 65-69 versus each age group; ¶ $P < 0.05$, 70-74 versus each age group; # $P < 0.05$, 75-79 versus each age group

Figure 2. Comparison of fat distribution and incidence of visceral obesity according to age and gender. Each panel (A, B, C) shows the relationship of total fat, visceral fat, and subcutaneous fat to age and gender, respectively. Panel D shows the relationship of the incidence of visceral obesity to age and gender.

predict future acute coronary syndrome events.³⁴⁾ As such, we believe that it is necessary to also consider the relation with plaque quality as well. Thus, this report may be helpful in detecting high risk patients. On the other hand, although there have only been a few reports, coronary atherosclerosis was not found to be correlated with visceral fat.^{35,36)}

The present study shows that the accumulation of visceral fat is not an independent coronary risk factor. The accumulation of visceral fat is considered to be effective in determining high-risk patients as it reflects current lifestyle trends. Visceral obesity checkups are also important. For younger people, such checkups can help to reveal an unhealthy lifestyle and the presumption of early stages of coronary arterial lesions, while for people over 70 years of age, the checkups will be an indicator of existing coronary arterial lesions. It is thought that improving dietary habits and exercise can easily reduce the amount of visceral fat. Exercise is reported to be effective against other coronary risk factors such as high blood pressure and dyslipidemia. In ordinary examinations, focusing on reducing the amount of visceral fat and abdominal girth can ameliorate risk factors and prevent the development of cardiovascular disease.

Study limitations: Unfortunately, the present study may also have several limitations. First, the study subjects were all patients referred to the clinic specifically to be checked for coronary arterial lesions, thus there may be an underlying selection bias. Ideally, a new and similar study would be performed with an unselected population presenting no symptoms, although the indicated contrast injection and radiation by MDCT would

not be ethically prohibited for subjects without symptoms of ischemic heart disease. Second, and regrettably, this study did not include a comparison with an established group of MS subjects as there was no blood sampling data at the time of MDCT; therefore, there is not enough data related to glucose intolerance and hypertriglyceridemia to aid in diagnosing MS.

Conclusions: While visceral obesity was not shown to be an independent coronary risk factor, it did demonstrate the predominant presence of coronary risk factors. As such, it is reasonable to conclude that visceral obesity may be a cause of other coronary risk factors, which may eventually develop into coronary stenosis.

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