Circulation Reports
Circ Rep 2021; 3: 674–681
doi:10.1253/circrep.CR-21-0082

ORIGINAL ARTICLE
Obesity

Association Between Major Adverse Cardiovascular Events and the Ratio of Subcutaneous Fat Area to Visceral Fat Area in Patients Who Have Undergone Multidetector Row Computed Tomography

Yuuka Shibata, MD; Yuhei Shiga, MD, PhD; Yasunori Suematsu, MD, PhD;
Kohei Tashiro, MD, PhD; Yuto Kawahira, MD;
Kai Morita, MD; Takashi Kuwano, MD, PhD;
Makoto Sugihara, MD, PhD; Shin-ichiro Miura, MD, PhD

Background: Obesity is a critical cardiovascular risk factor that has been defined in terms of body mass index (BMI), abdominal circumference (AC), and fat area. In this study, we examined which markers of obesity are most closely associated with major adverse cardiovascular events (MACE).

Methods and Results: This prospective cohort study enrolled 529 consecutive patients who initially underwent coronary computed tomography angiography for screening of coronary atherosclerosis at Fukuoka University Hospital (FU-CCTA Registry) and either were clinically suspected of having coronary artery disease (CAD) or had at least 1 cardiovascular risk factor with a follow-up of up to 5 years. Measurements of subcutaneous fat area (SFA), visceral fat area (VFA), and AC were quantified using multidetector row computed tomography. The primary endpoint was MACE. SFA and the SFA to VFA ratio (SFA/VFA) were significantly lower in the MACE than non-MACE group. SFA, AC, BMI, and SFA/VFA were each independently associated with MACE. Receiver operating characteristic curve analysis revealed a greater area under the curve for SFA/VFA than for the other parameters. The cut-off level of SFA/VFA with the greatest sensitivity and specificity for the diagnosis of MACE was 1.45 (sensitivity 0.849, specificity 0.472).

Conclusions: Our results suggest that SFA/VFA may be a marker for evaluating the presence of MACE.

Key Words: Abdominal circumference; Body mass index; Major adverse cardiac events; Subcutaneous fat area; Visceral fat area

Because of changes in lifestyle and diet, the prevalence of obesity or overweight is increasing in both developed and developing countries.[1–3] Obesity has reached epidemic proportions, and both the incidence and prevalence of obesity continue to increase.[4,5] Obesity is strongly associated with reduced longevity, as well as with stroke, thrombosis, and the development of coronary artery disease (CAD).[6–8] Obesity is not only a chronic disease that seriously endangers people's health, but it is also an important risk factor for type 2 diabetes (DM),[9,10] hypertension (HTN),[11,12] and cardiovascular diseases.[13–15] The current definition of obesity defines it in terms of body mass index (BMI), a widely used surrogate for adiposity. However, BMI is influenced by parameters other than body fat, such as muscle mass and fluid status. Abdominal obesity, measured in terms of abdominal circumference (AC), has been suggested to be a better predictor of cardiovascular events, and this is supported by recent data. In Japan, obesity is defined as BMI ≥25 kg/m^2. Metabolic syndrome is defined according to modified guidelines as AC ≥85 cm in males and ≥90 cm in females or a visceral fat area (VFA) ≥100 cm^2 and the presence of ≥2 of the following: high blood pressure (systolic blood pressure [SBP] ≥130 mmHg, diastolic blood pressure [DBP] ≥85 mmHg, or taking antihypertensive medication), dyslipidemia (DL; triglyceride (TG) ≥150 mg/dL or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL) or high fasting glucose (fasting glucose ≥110 mg/dL or taking glucose-lowering medication).[16]

Received June 30, 2021; revised manuscript received August 4, 2021; accepted August 25, 2021; J-STAGE Advance Publication released online October 5, 2021 Time for primary review: 18 days

Department of Cardiology, Fukuoka University School of Medicine, Fukuoka (Y. Shibata, Y. Shiga, Y. Suematsu, K.T., Y.K., K.M., T.K., M.S., S.M.); Department of Cardiology, Fukuoka University Nishijin Hospital, Fukuoka (Y.K., S.M.), Japan

S.M. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Shin-ichiro Miura, MD, PhD and Yuhei Shiga, MD, PhD, Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: miuras@cis.fukuoka-u.ac.jp (S.M.); yuheis@fukuoka-u.ac.jp (Y. Shiga)

ISSN-2434-0790

Table 1. Patient Characteristics

	All patients (n=529)	Non-MACE group (n=496)	MACE group (n=33)	P value (non-MACE vs. MACE)
Age (years)	66±11	66±11	66±11	0.9
Male sex (%)	51	49	73	0.009
Family history[A] (%)	23	23	18	0.509
Smoking (%)	36	35	58	0.009
Hypertension (%)	69	68	79	0.194
SBP (mmHg)	136±19	135±19	139±24	0.249
DBP (mmHg)	77±13	77±12	78±15	0.625
Diabetes (%)	23	22	36	0.061
HbA1c (%)	6.0±1.1	6.0±1.1	6.2±1.0	0.271
FBG (mg/dL)	110±34	109±34	118±33	0.139
Dyslipidemia (%)	62	62	64	0.842
TG (mg/dL)	135±94	136±94	152±105	0.287
HDL-C (mg/dL)	55±15	55±15	52±16	0.259
LDL-C (mg/dL)	112±31	112±30	110±34	0.638
L/H ratio	2.2±0.8	2.2±0.8	2.3±1.1	0.348
Non HDL-C (mg/dL)	141±39	141±39	139±39	0.757
MetS (%)	36	36	46	0.249
CAD (%)	56	54	82	<0.002
VD	1.0±1.1	1.0±1.1	1.8±1.1	<0.0001
CACS (AU)	254±683	224±586	694±1,470	0.0001
Gensini Score (AU)	13±16	12±13	29±36	<0.0001

Continuous variables are expressed as mean±SD. [A]A family history of myocardial infarction, angina pectoris, or sudden death. AU, arbitrary units; CACS, coronary artery calcium score; CAD, coronary artery disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; L/H, LDL-C to HDL-C ratio; MACE, major adverse cardiac events; MetS, metabolic syndrome; non-HDL-C, total cholesterol minus HDL-C; SBP, systolic blood pressure; TG, triglyceride; VD, number of vessels with significant disease.

Adipocytes are considered to differentiate from mesenchymal stem cells to preadipocytes, and mature adipocytes can store excess energy as TG. Adipocytes can be classified according to size (small and large), adipose tissue can be classified according to color (white and brown), and fat location can be classified as visceral or subcutaneous (VF and SF, respectively). Many studies have shown that VF has a detrimental effect on metabolism and the risk of CAD.[17–19] Excess energy is considered to be converted into neutral fat and is initially stored in SF. The volume of SF is predetermined in each individual, and when the amount that can be allocated to SF is exceeded, the destination changes to VF.[20] The best tool for estimating SF and VF is multidetector row computed tomography (MDCT). MDCT has become more widely available in many general hospitals and enables the accurate, non-invasive assessment of coronary artery stenosis,[21] calcification,[22] and plaque imaging.[23]

Although BMI, AC, SF area (SFA), VFA, the ratio of SFA to VFA (SFA/VFA), and SFA+VFA are all considered markers of obesity, it is not known which markers are most closely associated with cardiovascular events. Therefore, in this study we investigated the associations between the presence of major adverse cardiovascular events (MACE) and BMI, AC, SFA, VFA, SFA/VFA, or SFA+VFA.

Methods

Study Subjects

In all, 529 subjects who were clinically suspected of having CAD or who had at least 1 cardiac risk factor (HTN, DL, DM and smoking) were enrolled in this study. All subjects underwent MDCT coronary angiography between April 2012 and June 2017. Patients with creatine >2.0 mg/dL or contrast-induced allergy did not undergo MDCT.

The procedures in this study were performed in accordance with the Declaration of Helsinki and the ethical standards of the Independent Review Board of Fukuoka University. The study protocol was approved by the Independent Review Board of Fukuoka University (IRB #09-10-02) and all subjects provided informed consent prior to taking part in the study.

Evaluation of Coronary Arteries Using MDCT

Coronary arteries were evaluated using MDCT:[24] 266 patients were scanned by 64-MDCT (Aquilion 64; TOSHIBA, Tokyo, Japan) and 263 patients were scanned by 320-MDCT (Aquilion ONE ViSION; TOSHIBA).

The region of interest was placed within the ascending aorta, and the scan was started when the computed tomography (CT) density reached 100 Hounsfield units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and diaphragm.

Overall, 15 coronary artery segments were assessed in all patients. Narrowing of the normal contrast-enhanced lumen to ≥50% that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant stenosis in CAD. In addition, in all patients, the atherosclerotic severity of CAD was assessed in terms of the Gensini score.[25,26]

Measurement of AC, SFA, VFA, SFA/VFA, and SFA+VFA

Scans were performed by MDCT and a Ziostation work-

Table 2. Medications Used

	All patients (n=529)	Non-MACE group (n=496)	MACE group (n=33)	P value (non-MACE vs. MACE)
ACEI/ARB (%)	40	39	58	0.032
CCB (%)	39	39	36	0.789
β-blocker (%)	11	11	0	0.139
Diuretic (%)	11	11	15	0.452
Statin (%)	36	36	39	0.668
Eicosapentaenoic acid (%)	3	3	3	0.903
Sulfonylurea (%)	10	1	24	0.009
α-glucosidase inhibitor (%)	3	3	3	0.951
Biguanide (%)	7	7	9	0.662
Thiazolidinedione (%)	2	2	3	0.827
DPP-4 inhibitor (%)	11	11	18	0.201
Insulin (%)	4	4	3	0.776

Continuous variables are expressed as the mean±SD. ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase-4; MACE, major adverse cardiac events.

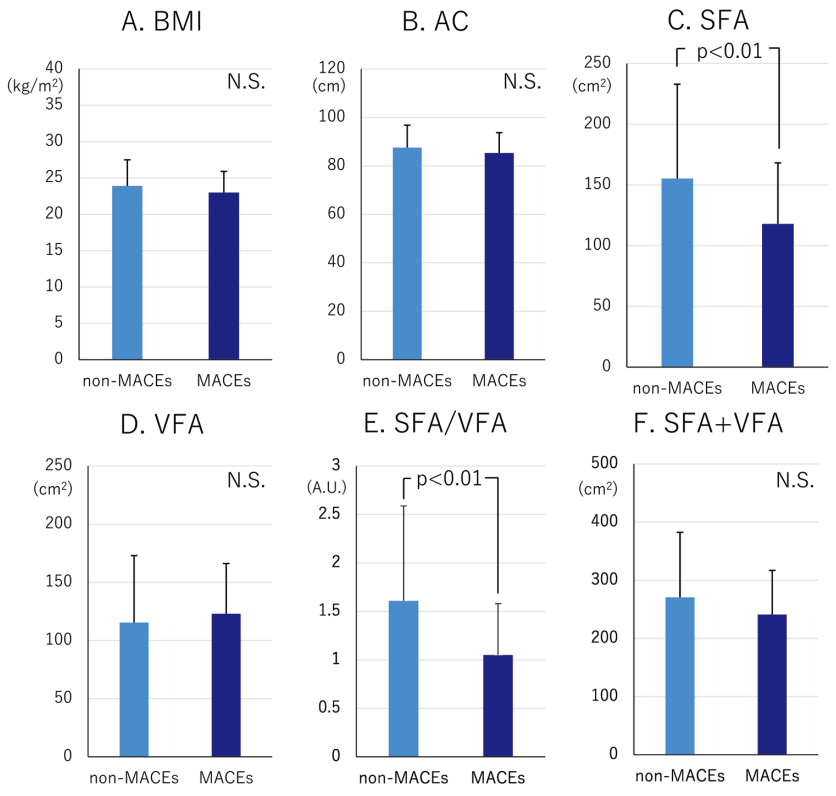

Figure 1. (**A**) Body mass index (BMI), (**B**) abdominal circumference (AC), (**C**) subcutaneous fat area (SFA), (**D**) visceral fat area (VFA), (**E**) SFA to VFA ratio (SFA/VFA) and (**F**) SFA+VFA in the major adverse cardiovascular events (MACE) and non-MACE groups. Data are the mean±SD. AU, arbitrary units.

station (Ziosoft, Tokyo, Japan). To measure AC, SFA, and VFA, scans were performed using only MDCT. These values were measured from CT cross-sectional scans at the level of the umbilicus with a Ziostation workstation. The pericardium was traced manually.

Evaluation of MACE

MACE were analyzed with a follow-up of up to 5 years. Clinical follow-up information was obtained from medical records and by telephone interviews. MACE were defined as cardiovascular death, acute myocardial infarction (MI), coronary revascularization, and ischemic stroke. For a diagnosis of MI, the patient had to have shown both evidence of ischemic electrocardiogram changes and elevation of cardiac enzymes. Coronary revascularization was performed if the lesion had significant luminal stenosis (>50% diameter stenosis) in the presence of angina symptoms and/or proven myocardial ischemia in the target vessel. Cardiovascular death was identified during the follow-up period. When patients had significant coronary stenosis as assessed by CCTA and received coronary intervention immediately after CCTA, the intervention was not included in

MACE as coronary revascularization.

Evaluation of Risk Factors for CAD

Information was collected for BMI, SBP, DBP, serum total cholesterol (TC), TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C) concentrations, the LDL-C to HDL-C ratio, non-HDL-C (calculated by subtracting HDL-C from TC), uric acid (UA), fasting glucose, HbA1c, smoking status (current vs. non-smokers), family history (MI, angina pectoris, or sudden death), and medication as risk factors in all patients.

BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was determined as the mean of 2 measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 min rest. All blood samples were drawn in the morning after the patients had fasted overnight. Data regarding a history of HTN, DL, DM, and a history of smoking were obtained from patients' medical records. Patients who had a current SBP/DBP ≥140/90 mmHg or who were receiving antihypertensive therapy were considered to have HTN. Patients with LDL-C ≥140 mg/dL, TG ≥150 mg/dL, and/or HDL-C <40 mg/dL or who were receiving lipid-lowering therapy were considered to have DL.[27] DM was defined using the American Diabetes Association criteria[28] or on the basis of patients taking glucose-lowering medication. Hyperuricemia was defined as a serum UA level ≥7.0 mg/dL or the administration of uric acid-lowering drugs.

Statistical Analysis

Statistical analyses were performed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA) and Excel 2016 (SSRI, Tokyo, Japan) at Fukuoka University (Fukuoka, Japan). Continuous variables are shown as the mean±SD. Categorical and continuous variables were compared between groups using Chi-squared analysis and t-tests, respectively. Multivariate logistic regression analysis was used to identify independent variables that were related to the presence or absence of MACE. Receiver operating characteristic (ROC) curve analysis was used to determine cut-off levels of BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA to distinguish between the presence and absence of MACE at the highest

Table 3. Predictors of the Presence of MACE

Variables	Regression coefficient	Standard error	χ^2	OR (95% CI)	P value
Predictors including BMI in the presence of MACE					
Age	−0.003	0.019	0.023	0.997 (0.962–1.034)	0.88
Male sex	0.712	0.474	2.316	2.057 (0.812–5.211)	0.128
Family history[A]	−0.208	0.480	0.187	0.813 (0.317–2.081)	0.665
Smoking	0.489	0.431	1.288	1.631 (0.701–3.794)	0.256
Hypertension	0.087	0.547	0.025	1.091 (0.373–3.189)	0.873
Diabetes	0.287	0.499	0.331	1.332 (0.501–3.545)	0.565
Dyslipidemia	0.034	0.398	0.007	1.035 (0.474–2.259)	0.932
BMI	−0.130	0.064	4.124	0.878 (0.775–0.996)	0.042
ACEI/ARB	0.772	0.448	2.965	2.163 (0.899–5.206)	0.085
SU	0.590	0.513	1.323	1.805 (0.660–4.938)	0.25
Predictors including AC in the presence of MACE					
Age	4.240	0.018	0.001	1.000 (0.965–1.037)	0.982
Male sex	0.698	0.471	2.200	2.010 (0.799–5.056)	0.138
Family history[A]	−0.194	0.480	0.164	0.823 (0.322–2.108)	0.686
Smoking	0.517	0.429	1.450	1.677 (0.723–3.888)	0.229
Hypertension	0.129	0.549	0.055	1.137 (0.388–3.335)	0.815
Diabetes	0.239	0.501	0.227	1.270 (0.476–3.387)	0.634
Dyslipidemia	0.048	0.400	0.015	1.049 (0.479–2.299)	0.904
AC	−0.045	0.022	4.132	0.956 (0.916–0.998)	0.042
ACEI/ARB	0.743	0.447	2.766	2.103 (0.876–5.050)	0.096
SU	0.650	0.518	1.578	1.916 (0.695–5.287)	0.209
Predictors including SFA in the presence of MACE					
Age	−0.002	0.019	0.010	0.998 (0.962–1.035)	0.92
Male sex	0.312	0.491	0.402	1.366 (0.521–3.579)	0.526
Family history[A]	−0.149	0.481	0.096	0.862 (0.336–2.211)	0.757
Smoking	0.473	0.428	1.221	1.605 (0.693–3.717)	0.269
Hypertension	0.108	0.548	0.039	1.114 (0.381–3.259)	0.844
Diabetes	0.171	0.500	0.117	1.186 (0.446–3.159)	0.732
Dyslipidemia	0.057	0.400	0.021	1.059 (0.483–2.321)	0.886
SFA	−0.007	0.003	5.007	0.993 (0.987–0.999)	0.025
ACEI/ARB	0.760	0.449	2.873	2.139 (0.888–5.153)	0.09
SU	0.664	0.517	1.645	1.942 (0.704–5.355)	0.12

(**Table 3** continued the next page.)

Variables	Regression coefficient	Standard error	χ^2	OR (95% CI)	P value
Predictors including VFA in the presence of MACE					
Age	0.005	0.018	0.089	1.005 (0.970–1.042)	0.765
Male sex	0.675	0.473	2.030	1.963 (0.776–4.965)	0.154
Family history[A]	–0.179	0.477	0.014	0.836 (0.328–2.133)	0.708
Smoking	0.539	0.428	1.586	1.715 (0.741–3.970)	0.208
Hypertension	0.027	0.544	0.002	1.027 (0.354–2.980)	0.961
Diabetes	0.149	0.491	0.093	1.161 (0.444–3.038)	0.761
Dyslipidemia	–0.077	0.407	0.036	0.926 (0.417–2.056)	0.85
VFA	–2.660	0.003	0.006	1.000 (0.993–1.006)	0.937
ACEI/ARB	0.674	0.445	2.296	1.962 (0.820–4.694)	0.13
SU	0.623	0.501	1.545	1.864 (0.698–4.976)	0.214
Predictors including SFA/VFA in the presence of MACE					
Age	0.004	0.018	0.049	1.004 (0.968–1.041)	0.825
Male sex	0.061	0.496	0.015	1.063 (0.402–2.811)	0.902
Family history[A]	–0.135	0.482	0.078	0.874 (0.340–2.247)	0.78
Smoking	0.499	0.424	1.386	1.647 (0.718–3.778)	0.239
Hypertension	–0.009	0.554	2.629	0.991 (0.334–2.937)	0.987
Diabetes	0.032	0.502	0.004	1.032 (0.386–2.758)	0.95
Dyslipidemia	–0.257	0.398	0.418	0.773 (0.354–1.687)	0.518
SFA/VFA	–0.969	0.367	6.980	0.379 (0.185–0.779)	0.008
ACEI/ARB	0.801	0.460	3.037	2.228 (0.905–5.486)	0.081
SU	0.654	0.515	1.612	1.923 (0.701–5.279)	0.204
Predictors including SFA+VFA in the presence of MACE					
Age	0.001	0.018	0.002	1.001 (0.965–1.037)	0.967
Male sex	0.568	0.476	1.428	1.765 (0.695–4.485)	0.232
Family history[A]	–0.174	0.478	0.132	0.841 (0.329–2.146)	0.717
Smoking	0.509	0.429	1.409	1.664 (0.718–3.86)	0.235
Hypertension	0.095	0.546	0.030	1.1 (0.377–3.209)	0.862
Diabetes	0.196	0.493	0.158	1.217 (0.463–3.2)	0.691
Dyslipidemia	0.049	0.405	0.015	1.051 (0.475–2.323)	0.903
SFA+VFA	0.002	0.002	2.110	0.997 (0.994–1.001)	0.146
ACEI/ARB	0.445	0.445	2.446	2.004 (0.838–4.79)	0.118
SU	0.507	0.507	1.618	1.906 (0.705–5.149)	0.203

[A]A family history of myocardial infarction, angina pectoris, or sudden death. AC, abdominal circumference; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; MACE, major adverse cardiac events; OR, odds ratio; SFA, subcutaneous fat area; SU, sulfonylurea; VFA, visceral fat area.

possible sensitivity and specificity levels. Two-sided $P<0.05$ was considered significant.

Results

Patient Characteristics

The characteristics of all 529 patients (268 [51%] males, 261 [49%] females) are presented in **Table 1**. The frequency of HTN, DM, and DL in the entire patient cohort was 69%, 23%, and 62%, respectively. The mean age of patients was 66±11 years. There were significant differences in patient characteristics between the MACE and non-MACE groups. Specifically, the percentage of males, smokers, and those with CAD were significantly higher in the MACE than non-MACE group; in addition, the number of vessels with significant disease, the coronary artery calcium score, and the Gensini score were significantly higher in the MACE group (**Table 1**).

Table 2 shows the medications used by all patients, as well as those in the MACE and non-MACE groups separately. Among the entire patient cohort, 40%, 39%, and 36% of patients were using angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB), calcium channel blockers, and statins, respectively. There were significant differences in medications used between the MACE and non-MACE groups, with the use of ARB/ACEI and sulfonylurea (SU) being significantly higher in the MACE group.

BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA in the MACE and Non-MACE Groups

Figure 1 shows BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA in the MACE and non-MACE groups. As can be seen from **Figure 1**, SFA and SFA/VFA were significantly lower in the MACE than non-MACE group.

Predictors of MACE, Including BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA

We used logistic regression analysis to investigate independent predictors of MACE in all patients (**Table 3**). We selected conventional coronary risk factors (age, sex, family history, smoking, HTN, DM, and DL), ACEI/ARB,

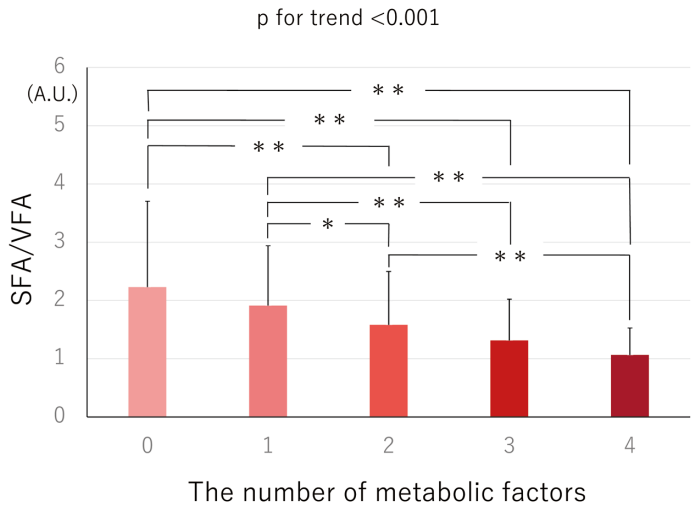

Figure 2. Association between the number of metabolic factors and the ratio of subcutaneous fat area to visceral fat area (SFA/VFA). The metabolic factors were: VFA ≥100 cm^2, fasting glucose ≥110 mg/dL, systolic blood pressure ≥135 mmHg and/or diastolic blood pressure ≥85 mmHg, and triglyceride ≥150 mg/dL and/or high-density lipoprotein-cholesterol <40 mg/dL. Data are the mean±SD. *P<0.05, **P<0.01. AU, arbitrary units.

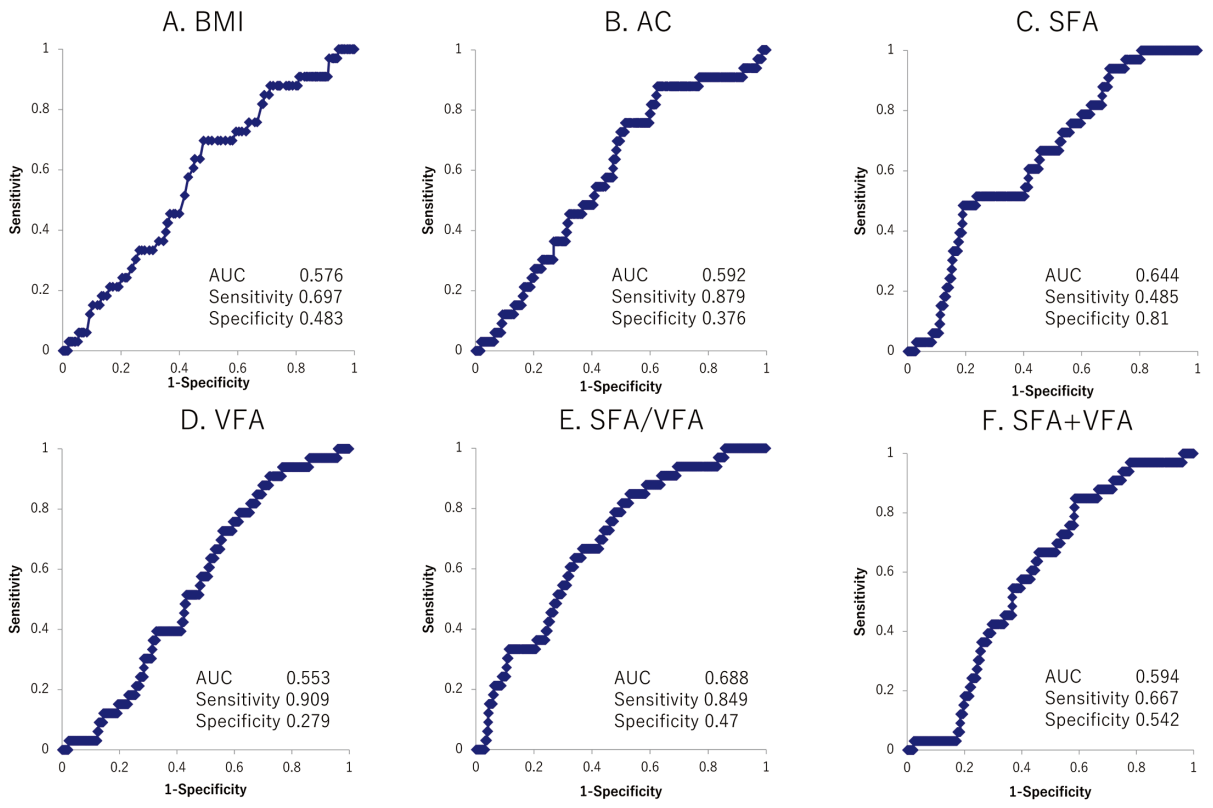

Figure 3. Cut-off values of (**A**) body mass index (BMI), (**B**) abdominal circumference (AC), (**C**) subcutaneous fat area (SFA), (**D**) visceral fat area (VFA), (**E**) SFA to VFA ratio (SFA/VFA), and (**F**) SFA+VFA for the presence of major adverse cardiovascular events. AUC, area under the curve.

SU, BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA as variables. As indicated in **Table 3**, the presence of MACE was independently associated with BMI (P=0.042), AC (P=0.042), SFA (P=0.025), and SFA/VFA (P=0.008), but not with VFA or SFA+VFA.

Correlation Between the Number of Metabolic Factors and SFA/VFA

Subjects were divided into 5 groups according to the number (0–4) of metabolic factors (VFA ≥100 cm^2, fasting glucose ≥110 mg/dL, SBP ≥135 mmHg and/or DBP ≥85 mmHg,

TG ≥150 and/or HDL-C <40 mg/dL) they were positive for. In this analysis, SFA/VFA decreased significantly as the number of metabolic factors present increased (**Figure 2**).

Cut-Off Values of BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA for MACE

Because BMI, AC, SFA, VFA, SFA/VFA, and SFA+VFA are associated with each other, we performed ROC curve analysis to determine which markers of obesity are most closely related to the presence of MACE (**Figure 3**). This analysis indicated that SFA/VFA may be a more useful marker than BMI, AC, VFA, SFA, and SFA+VFA because it had the highest area under the curve (AUC), although there were only small differences in AUC among the 6 factors. The cut-off level of SFA/VFA with the greatest sensitivity and specificity for the diagnosis of MACE was 1.45.

Discussion

The most important finding of the present study was that higher SFA/VFA is associated with a lower rate of MACE at the time of CCTA as screening for CAD. Higher SFA/VFA was more closely associated with a lower risk of MACE than higher BMI, AC, VFA, SFA, and SFA+VFA.

BMI is easy to determine and is the anthropometric measure most frequently used to investigate obesity. Conversely, the validity of BMI has been questioned. BMI does not reflect regional body fat distribution. In some studies, central obesity and abdominal fat were more closely associated with cardiometabolic risk factors[29] and chronic disease risk[30,31] than overall obesity. Therefore, using BMI could lead to an inaccurate assessment of fat.[32] Although AC is a representative indicator of central obesity, the AUC values for both BMI and AC were relatively low in the present study. In addition, the results of a meta-analysis suggest a near J-shaped association between AC and all-cause mortality.[33] Because SFA and VFA, which contribute to AC, are considered to be important indicators, SFA and/or VFA may be more important markers than AC.[34,35]

The volume of SF that can accumulate is predetermined and varies according to the individual. When this limit is exceeded, adipocytes will accumulate as VF. Adipocytes in visceral adipose tissue are enlarged and accumulate a large amount of neutral fat, but the amount that can be accumulated in VF varies according to the individual. When fat storage in subcutaneous tissue is limited and energy intake becomes excessive, it becomes impossible to cope with the growth and enlargement of VF, and the liver, pancreas, skeletal muscle, and cardiovascular system are affected. It is believed that ectopic fat deposition also progresses in organs.[20] It has been reported that VF and SF differ in the differentiation of adipocytes themselves and exhibit distinctly different metabolic kinetics. For example, it has been reported that VF has greater lipogenic ability than SF.[36] Thus, when patients have a higher SFA/VFA at the time of CCTA, their fat is mainly accumulated in SFA, rather than VFA. Patients with a higher SFA/VFA may have lower lipogenic ability, and the fat storage function in subcutaneous tissue may be maintained. VF and ectopic fat may accumulate further over time and atherosclerosis may progress. This may be one reason why patients with a higher SFA/VFA have a low prevalence of MACE.

In general, the periods in life during which SF increases dramatically are limited and are believed to be the neonatal period, infancy, adolescence, and pregnancy/childbirth in females.[37] Premenopausal women, who have high levels of estrogen, have sufficient reserve capacity to accumulate SF, so that VF is unlikely to accumulate. Conversely, in adult males over 30 years of age and in postmenopausal females who are deficient in estrogen, the reserve capacity to accumulate SF is limited. When the energy intake exceeds consumption due to overeating and a lack of exercise, surplus energy is available and fat becomes VF. It may also enlarge and accumulate as ectopic fat.[38] In the present study, the non-MACE and MACE groups were the same age, but the MACE group had a significantly higher percentage of males than the non-MACE group. Although plasma concentrations of estrogen, which is associated with SFA/VFA, were not measured in the present study, sex differences, such as in menopause and/or estrogen levels, may affect the presence of MACE.

Study Limitations

This study has several important limitations. First, the sample size was relatively small, which limited our ability to determine significance. Second, although MDCT is not a gold standard for the evaluation of CAD, recent studies have shown that both its sensitivity and specificity are approximately 95% of the sensitivity and specificity of invasive coronary angiography for the identification of significant coronary stenosis.[39] Third, we did not take into account changes in body weight or fat area during the follow-up period. A large-scale prospective study will be needed to address these issues.

Conclusions

Our results suggest that SFA/VFA may be a useful marker for the presence of MACE.

Acknowledgments

None.

Sources of Funding

This study did not receive any specific funding.

Disclosures

S.M. has received remuneration from Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., Boehringer Ingelheim, Otsuka Pharmaceutical Co., and Bayer Yakuhin, Ltd.; research funding from Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., Astellas Pharma Inc., and Bayer Yakuhin, Ltd.; scholarship funds from Alfresa Corporation, and is a member of *Circulation Reports*' Editorial Team. Y. Suematsu has received research funding from the Uehara Memorial Foundation. The remaining authors have no conflicts of interest to disclose.

IRM Information

This study as approved by the Ethics Committee of Fukuoka University Hospital (IRB #09-10-02).

Data Availability

The deidentified participant data will not be shared.

References

1. Weitz CA, Friedlaender FR, Van Horn A, Friedlaender JS. Modernization and the onset of overweight and obesity in Bougainville and Solomon Islands children: Cross-sectional and longitudinal comparisons between 1966 and 1986. *Am J Phys Anthropol* 2012; **149:** 435–446.
2. Bu S, Ruan D, Yang Z, Xing X, Zhao W, Wang N, et al. Sex-specific prevalence of diabetes and cardiovascular risk factors in

the middle-aged population of China: A subgroup analysis of the 2007–2008 China National Diabetes and Metabolic Disorders Study. *PLoS One* 2015; **10:** e0139039.
3. Dancause KN, Vilar M, Chan C, DeHuff C, Wilson M, Soloway LE, et al. Patterns of childhood and adolescent overweight and obesity during health transition in Vanuatu. *Public Health Nutr* 2012; **15:** 158–166.
4. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; **288:** 1723–1727.
5. Freedman DS, Khan LK, Serdula MK, Galuska DA, Dietz WH. Trends and correlates of class 3 obesity in the United States from 1990 through 2000. *JAMA* 2002; **288:** 1758–1761.
6. Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the pathophysiology of obesity-associated cardiovascular disease. *Circulation* 2002; **105:** 2923–2928.
7. Krauss RM, Winston M, Fletcher RN, Grundy SM. Obesity: Impact on cardiovascular disease. *Circulation* 1998; **98:** 1472–1476.
8. Visscher TL, Seidell JC. The public health impact of obesity. *Annu Rev Public Health* 2001; **22:** 355–375.
9. Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: A meta-analysis and systemic review. *Diabetes Metab Res Rev* 2011; **27:** 515–527.
10. Wang C, Li J, Xue H, Li Y, Huang J, Mai J, et al. Type 2 diabetes mellitus incidence in Chinese: Contributions of overweight and obesity. *Diabetes Res Clin Pract* 2015; **107:** 424–432.
11. Adair LS. Dramatic rise in overweight and obesity in adult Filipino women and risk of hypertension. *Obes Res* 2004; **12:** 1335–1341.
12. Anderson AK. Prevalence of anemia, overweight/obesity, and undiagnosed hypertension and diabetes among residents of selected communities in Ghana. *Int J Chronic Dis* 2017; **2017:** 7836019.
13. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014; **383:** 970–983.
14. Keys A. Overweight, obesity, coronary heart disease and mortality. *Nutr Rev* 1980; **38:** 297–307.
15. Patt MR, Yanek LR, Moy TF, Becker DM. Assessment of global coronary heart disease risk in overweight and obese African-American women. *Obes Res* 2003; **11:** 660–667.
16. 2005 Examination Committee of criteria for diagnosis of metabolic syndrome in Japan. Definition and criteria for diagnosis of metabolic syndrome. *J Jpn Soc Int Med* 2005; **94:** 794–809.
17. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: Association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007; **116:** 39–48.
18. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: The Framingham Heart Study. *Circulation* 2008; **117:** 605–613.
19. Kannel WB, Cupples LA, Ramaswami R, Stokes J 3rd, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. *J Clin Epidemiol* 1991; **44:** 183–190.
20. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. *J Clin Endocrinol Metab* 2005; **90:** 6300–6302.
21. Rumberger JA, Sheedy PF 3rd, Breen JF, Schwartz RS. Coronary calcium, as determined by electron beam computed tomography, and coronary disease on arteriogram. Effect of patient's sex on diagnosis. *Circulation* 1995; **91:** 1363–1367.
22. Nitta K, Akiba T, Suzuki K, Uchida K, Ogawa T, Majima K, et al. Assessment of coronary artery calcification in hemodialysis patients using multi-detector spiral CT scan. *Hypertens Res* 2004; **27:** 527–533.
23. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, et al. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol* 2004; **43:** 842–847.
24. Mitsutake R, Niimura H, Miura S, Zhang B, Iwata A, Nishikawa H, et al. Clinical significance of the coronary calcification score by multidetector row computed tomography for the evaluation of coronary stenosis in Japanese patients. *Circ J* 2006; **70:** 1122–1127.
25. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983; **51:** 606.
26. Sayın MR, Çetiner MA, Karabağ T, Doğan SM, Aydın M, Yavuz N. The relationship between the Gensini score and complete blood count parameters in coronary artery disease. *Koşuyolu Kalp Dergisi* 2012; **15:** 51–54.
27. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, et al. Goals of dyslipidemia management. *J Atheroscler Thromb* 2007; **14:** 209–212. doi:10.5551/jat.e554.
28. American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care* 2004; **27**(Suppl 1)**:** S11–S14.
29. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: Systematic review and meta-analysis. *Obes Rev* 2012; **13:** 275–286.
30. Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, et al. Assessing adiposity: A scientific statement from the American Heart Association. *Circulation* 2011; **124:** 1996–2019.
31. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. *Lancet* 2005; **366:** 1640–1649.
32. Després JP. Body fat distribution and risk of cardiovascular disease: An update. *Circulation* 2012; **126:** 1301–1313.
33. Jayedi A, Soltani S, Zargar SM, Khan TA, Shab-Bidar S. Central fatness and risk of all cause mortality: Systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ* 2020; **370:** m3324.
34. Okuno T, Koseki K, Nakanishi T, Ninomiya K, Tomii D, Tanaka T, et al. Prognostic impact of computed tomography-derived abdominal fat area on transcatheter aortic valve implantation. *Circ J* 2018; **82:** 3082–3089.
35. Sato F, Maeda N, Yamada T, Namazui H, Fukuda S, Natsukawa T, et al. Association of epicardial, visceral, and subcutaneous fat with cardiometabolic diseases. *Circ J* 2018; **82:** 502–508.
36. Jensen MD, Sarr MG, Dumesic DA, Southorn PA, Levine JA. Regional uptake of meal fatty acids in humans. *Am J Physiol Endocrinol Metab* 2003; **285:** E1282–E1288.
37. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. *Nature* 2008; **453:** 783–787.
38. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; **444:** 881–887.
39. Ropers D, Rixe J, Anders K, Küttner A, Baum U, Bautz W, et al. Usefulness of multidetector row computed tomography with 64- × 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. *Am J Cardiol* 2006; **97:** 343–348.