Association between the visceral adiposity index and the coronary artery calcification score and atherosclerotic plaque morphology

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ABSTRACT

Background: The relationship between the visceral adipose index (VAI), a surrogate marker of visceral adipose tissue dysfunction, and coronary atherosclerotic plaque (CAP) morphology remains unclear.

Aims: This study aimed to investigate the relationships between the VAI and the coronary artery calcification (CAC) score and CAP morphology in asymptomatic patients.

Methods: We retrospectively assessed 782 patients between January 2012 and January 2020. CAC scores were determined at the threshold of 130 Hounsfield units according to the Agatston technique using 64-slice computed tomography. Patients were assigned to groups with no plaque (NP), fatty plaque (FP), calcified plaque (CP), and mixed plaque (MP).

Results: The median VAI levels were significantly different in each group (NP: 1.2 vs. FP: 1.7 vs. CP: 2.3 vs. MP: 2.8; P <0.001). An increased VAI level was an independent predictor of the CAC score. The threshold value of the VAI exhibited a gradual increase in predicting CAP morphology. VAI threshold values were >1.6 for the FP group (vs. the NP group), >2.1 for the CP group (vs. the FP group), and >2.6 for the MP group (vs. the CP group).

Conclusion: High VAI levels independently predict an increased CAC score and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in asymptomatic patients and offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and diagnosing CAP morphology in patients with suspected coronary artery disease.

Key words: atherosclerosis, coronary artery calcium score, coronary artery disease, visceral adiposity index

INTRODUCTION

Atherosclerosis is an inflammatory process that begins as fatty streaks on the arterial wall and continues with the progression of plaque and complex lesions into the arterial lumen. Plaque rupture is associated with acute cardiovascular events such as thrombosis, myocardial infarction, and stroke [1]. This causes a significant global carotid atherosclerosis burden that increases with age [2]. Therefore, there is a need to identify inexpensive, accessible, and practical tools for preventing and managing carotid atherosclerosis and reducing the disease burden.

Coronary artery calcification (CAC), which is an important indicator of coronary atherosclerotic plaque (CAP) burden, is a pathognomonic finding of atherosclerosis and cardiovascular events [3]. Coronary artery calcification scores improve risk stratification when they are added to coronary computed tomography (CT) angiography results or the Framingham Risk Score [4]. Furthermore, CAC scores and CAP morphology are essential indicators of cardiovascular events and outcomes [5]. Visceral adipose tissue (VAT) plays a vital role in the development and morphology of CAP [6]. It can exacerbate the inflammatory response, trigger insulin resistance, and accelerate atherosclerosis [7]. However, imaging modalities such as multi-slice CT that allow for evaluation of CAP burden and morphology

WHAT'S NEW?

The findings of this study show that the visceral adipose index (VAI) as a surrogate for visceral adipose tissue dysfunction is associated with the coronary artery calcification (CAC) score and coronary atherosclerotic plaque (CAP) morphology. Increased VAI levels were found to be independent predictors of increased CAC scores and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in asymptomatic patients and offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and CAP morphology in patients with suspected coronary artery disease.

and VAT are costly, carry radiation risks, and are not accessible in some hospitals [8].

Increasing evidence indicates that VAT is associated with atherogenic dyslipidemia, characterized by decreased high-density lipoprotein cholesterol (HDL-C) and increased triglycerides [9]. The visceral adiposity index (VAI), derived from anthropometric and atherogenic parameters, is a simple proxy for visceral fat function confirmed by abdominal magnetic resonance imaging findings [10]. In addition, the VAI has been suggested as an important predictor of atherosclerosis [11]. Limited studies have reported a positive association between VAI levels and CAC scores [12–14], consistent with VAT studies [8, 15]. The VAI can be a powerful tool in the assessment of CAP burden. However, the relationship between the VAI and plaque morphology remains unclear. Therefore, this study was undertaken to investigate the relationships between the VAI and the CAC score and CAP morphology in asymptomatic patients.

METHODS

Patient selection

A total of 4 126 patients with suspected coronary artery disease (CAD) who were referred for multi-detector CT coronary angiography from a cardiac center between January 2012 and January 2020 were assessed retrospectively. The study was designed in compliance with the revised Declaration of Helsinki (2013, Brazil), followed all relevant ethics protocols, and was approved by the local ethics committee (no: E1-22-3009). The need for informed consent was waived by the local ethics committee due to the study's retrospective design.

A previous study reported a positive correlation between VAI and CAC scores ($r = 0.242$; $P < 0.001$) in asymptomatic patients who underwent cardiac CT [13]. Based on the correlation coefficient between VAI and CAC scores in this study, the sample size was calculated as a minimum of 175 patients using two-sided testing, 5% alpha error probability, and 90% power with G*Power v3.1 software [16]. The sample size formula was as follows: $N = ([Z_\alpha + Z_\beta] / C)^2 + 3$ [17], where the standard normal deviation for $\alpha = Z_\alpha = 1.96$, the standard normal deviation for $\beta = Z\beta = 1.28$, and the correlation coefficient (C) for small correlation=0.244 [18]. C was calculated as follows: $C = 0.5 \times \ln[(1 + r) / (1 - r)] = 0.244$, where $r = 0.242$.

Inclusion criteria were asymptomatic patients with cardiovascular risk profiles based on conventional risk factors such as smoking, hypertension, diabetes mellitus, and dyslipidemia. Exclusion criteria were a history of CAD, acute coronary syndrome, heart failure, rheumatic diseases, asthma, pulmonary embolism, inflammatory disease, acute and chronic kidney disease, peripheral artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, liver disease, and cancer. After the exclusion process, 782 patients were included in the study. The indication for CT in asymptomatic patients was based on evaluation of the CAC score for cardiovascular risk assessment [19]. The 10-year cardiovascular disease risk score was calculated using the Systematic Coronary Risk Estimation (SCORE) system (http://www.heartscore.org), which includes age, sex, smoking, systolic blood pressure, and lipid levels. Patients with diabetes mellitus are not included in the SCORE system because they have very high cardiovascular risk [19].

All patients' demographic, laboratory, and coronary angiography data were obtained from the hospital's electronic information system and patient files. Blood pressure of >140/90 mm Hg in repeated measurements or the use of antihypertensive drugs was defined as hypertension and a fasting plasma glucose level of ≥126 mg/dl or the use of antidiabetic drugs was defined as diabetes mellitus. Dyslipidemia was defined as current use of lipid-lowering agents or a triglyceride level of >150 mg/dl, low-density lipoprotein cholesterol (LDL-C) level of >100 mg/dl, and low HDL-C (<40 mg/dl for men, <50 mg/dl for women) [20].

Laboratory measurements

Blood samples of all patients were taken in the morning after patients had fasted before coronary angiography. Complete blood counts and lipid panels were measured using a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Thus, the levels of hemoglobin (photometrically), platelet count (impedance method), high-sensitivity C-reactive protein (hs-CRP) (immunoturbidimetric method), triglycerides and total cholesterol (enzymatic colorimetric method), and HDL-C (homogeneous enzymatic colorimetric method) were determined. LDL-C levels were calculated using the Friedewald formula.

The VAI was calculated with a sex-specific equation that included measurements of body mass index (BMI) and waist circumference where lipid levels were in mmol/l [10].

For Males:

$$VAI = \frac{\text{Waist circumference}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{Triglycerides}}{1.03} \times \frac{1.31}{\text{HDL} - \text{C}}$$

For Females:

$$VAI = \frac{\text{Waist circumference}}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{Triglycerides}}{0.81} \times \frac{1.52}{\text{HDL} - \text{C}}$$

Coronary artery calcification assessment

An oral beta-blocker agent (40 mg propranolol) was given to patients with heart rates of >75 beats/min 1 hour before the procedure. All images were acquired by 64 multi-slice CT (Toshiba Aquilion system, Tokyo, Japan) with a rotation time of 400 mm and a 1 mm reconstruction device able to descend to 0.5 sections. An automatic dose modulation system was used in the examinations and hearts were scanned in a craniocaudal direction from the carina to the apex. Imaging was performed by electrocardiogram (ECG) gating with 120 peak kilovoltage, 300 milliampere seconds, 3 mm section thickness, and 200–270 mm field of view (FOV) . All images were transferred to a workstation for CAC scoring and evaluated with a Toshiba Aqua 4.1 instrument (Otawara, Japan). CAC scores were calculated considering the 130 Hounsfield units threshold according to the Agatston technique [21]. The CAC score was categorized as zero, minimal (1–10), mild (11–100), moderate (101–400), or severe (>400) [22]. The classification of CAP was based on a previously reported modified American Heart Association classification. Accordingly, the coronary system was separated into 16 distinct segments based on original axial images, thin slices, maximum intensity projections, and cross-sectional reconstructions orthogonal to the long axis of each coronary segment (0.75 mm in thickness) [23]. One coronary plaque per segment was selected upon determining the number and significance of atherosclerotic coronary segments for all patients. CAP in each segment was classified as (1) zero-plaque or none (NP); (2) calcified plaque (CP) (higher CT intensity than the contrast-enhanced coronary lumen); (3) non-calcified plaque (non-CP) (lower CT intensity than the contrast-enhanced coronary lumen); or (4) mixed plaque (MP) (plaque containing calcified and non-calcified components). According to the presence of plaque, the patients were assigned to two groups – those with and without atherosclerosis.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, US). The normality distribution of numerical data was evaluated with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean with standard deviation (SD), and non-normally distributed variables were presented as median with quartiles (IQR). For comparisons between groups, Student's t-test, Mann-Whitney U test, one-way analysis of variance (ANOVA; post-hoc: Bonferroni test), or Kruskal-Wallis H test (post-hoc: Dunn's test) was used according to normality distributions. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with the χ^2 and Fisher's exact tests. Bonferroni adjustment was used in post-hoc analyses of the R × C contingency table. Spearman correlation analysis was used for the relationship between CAC scores and VAI levels. Linear regression analysis with the backward method was used for independent predictors of CAP burden and logarithmic transformation was applied to numerical variables that did not show normal distribution before analysis. Logistic regression analysis with the backward Wald method was performed to identify any possible independent predictors of atherosclerosis and plaque morphology. Medications were not included in the regression model because of the high collinearity between medication and comorbid conditions in the regression analyses. To evaluate the diagnostic performance of the VAI, the area under the curve (AUC) was calculated in the receiver operating characteristic (ROC) curve analysis and the cut-off values were determined according to the Youden index method. *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 782 patients were analyzed in the study, including 281 (35.9%) females and 501 males (64.1%) at mean (SD) age of 51.7 (7.2) years. The median CAC score was 0 (range = 0-3759), and 9% (n = 70) of the patients had minimal CAC scores, 15.1% (n = 118) had mild CAC scores, 8.2% (n = 64) had moderate CAC scores, and 3.3% (n = 26) had severe CAC scores. CAP was not detected in most of the patients (64.5%). The rates of patients with NP were 49.9% (n = 390), 14.6% for only fatty plaque (FP) (n = 114), 17% for only CP (n = 135), and 18.3% for MP (n = 143). Accordingly, the prevalence of atherosclerosis was 50.1% (n = 392). The mean age (52.8 vs. 50.4 years; *P* <0.001), ratios of female sex (51% vs. 20.8%; *P* <0.001), smoking (48.5% vs. 36.9%; *P* <0.001), diabetes mellitus (32.7% vs. 22.3%; *P* = 0.001), hypertension (52.0% vs. 40.0%; *P* = 0.001), and median VAI levels (2.3 vs. 1.2; *P* < 0.001) were higher in patients with atherosclerosis compared to those without. Distributions of demographic and clinical findings according to the presence of atherosclerosis are shown in Table 1.

The mean age was similar in the FP and NP groups and lower in those groups compared to other morphology groups. The mean age was also similar in the CP and MP groups. The proportion of female patients was lower in the NP group and higher in the MP group (NP: 20.8% vs. Only FP: 36.8% vs. Only CP: 49.6% vs. MP: 63.6%; *P* <0.001). The rate of smoking was lower in the NP group while it was similar in other morphology groups (NP: 36.9% vs. Only FP: 47.4% vs. Only CP: 48.1% vs. MP: 49.1%; *P* = 0.01). The rate of diabetes mellitus did not differ significantly in the only CP and MP groups, while it was higher compared to the other groups (NP: 22.3% vs. Only FP: 25.4% vs. Only CP: 37.8% vs. MP: 33.6%; *P* = 0.002). The hypertension rate was

Table 1. Distribution of demographic and laboratory findings

Variables	All population (n = 782)	Atherosclerosis		*P*-value
		No (n = 390)	Yes (n = 392)	
Age, years	51.7 (7.2)	50.4 (6.5)	52.8 (7.5)	<0.001
Female sex, n (%)	281 (35.9)	81 (20.8)	200 (51.0)	<0.001
BMI, kg/m^2	26.2 (3.4)	25.8 (3.5)	26.5 (3.4)	0.004
WC, cm	95.4 (7.7)	93.4 (7.9)	97.1 (6.9)	<0.001
Active smoking, n (%)	334 (42.7)	144 (36.9)	190 (48.5)	<0.001
Diabetes mellitus, n (%)	215 (27.5)	87 (22.3)	128 (32.7)	0.001
Hypertension, n (%)	360 (46.0)	156 (40.0)	204 (52.0)	0.001
Dyslipidemia, n (%)	424 (54.2)	159 (40.8)	257 (65.6)	<0.001
Laboratory findings				
Hemoglobin, g/dl	13.5 (1.4)	13.4 (1.3)	13.6 (1.5)	0.06
Neutrophil count, ×10^3/µl	3.9 (3.3–5.0)	3.6 (3.0–4.4)	4.4 (3.6–5.4)	<0.001
Platelet count, ×10^3/µl	257.1 (61.0)	257.6 (59.5)	256.5 (62.6)	0.80
Lymphocyte count, ×10^3/µl	2.6 (0.7)	2.7 (0.7)	2.5 (0.7)	<0.001
Monocyte count, ×10^3/µl	0.6 (0.2)	0.5 (0.1)	0.7 (0.2)	<0.001
HDL-cholesterol, mmol/l	1.3 (0.3)	1.4 (0.3)	1.2 (0.3)	<0.001
LDL-cholesterol, mmol/l	3.4 (1.0)	3.3 (0.9)	3.5 (1.1)	0.005
Triglycerides, mmol/l	1.5 (1.1–1.9)	1.3 (0.9–1.6)	1.7 (1.3–2.4)	<0.001
Hs-CRP, mg/l	0.8 (0.3–1.1)	0.3 (0.1–0.5)	0.8 (0.4–1.3)	<0.001
VAI	1.5 (1.2–2.2)	1.2 (0.9–1.5)	2.3 (1.7–3.2)	<0.001
Medications, n (%)				
Statins	407 (52.0)	157 (40.3)	250 (63.8)	<0.001
Acetylsalicylic acid	127 (16.2)	55 (14.1)	72 (18.4)	0.11
Beta-blockers	120 (15.3)	52 (13.3)	68 (17.3)	0.12
ACEi/ARBs	353 (45.1)	153 (39.2)	200 (51.0)	0.001
Metformin	183 (23.4)	83 (21.3)	100 (25.5)	0.16
DPP4i	122 (15.6)	53 (13.6)	69 (17.6)	0.12
Sulfonylurea	114 (14.7)	44 (11.3)	56 (14.3)	0.21
SGLT-2i	93 (11.9)	43 (11.0)	52 (13.3)	0.34
Insulin	140 (17.9)	61 (15.6)	79 (20.2)	0.10

Numerical variables were shown as mean (SD) or median (interquartile range [IQR]). Categorical variables were shown as number (%)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; β, regression coefficients; BMI, body mass index; CACS, coronary artery calcium score; CAP, coronary atherosclerotic plaque; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; HDL, high-density lipoprotein, hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SE, standard error; SGLT2i, sodium-glucose transport protein 2 inhibitors; VAI, visceral adiposity index; WC, waist circumference

higher in the MP group while it did not differ significantly between the other groups (NP: 40.0% vs. Only FP: 47.4% vs. Only CP: 45.2% vs. MP: 62.2%; $P = 0.001$). The median CAC score was higher in the MP group than in the CP group (MP: 50 vs. Only CP: 25; $P < 0.001$). Except for hemoglobin and platelet count, laboratory parameters showed significant differences in CAP morphology. The median VAI levels were significantly different in each group (NP: 1.2 vs. FP: 1.7 vs. CP: 2.3 vs. MP: 2.8; $P < 0.001$) (Figure 1, Table 2).

There were positive correlations between VAI levels and CAC scores in the whole population (r = 0.576; $P < 0.001$), male patients (r = 0.562; $P < 0.001$), female patients (r = 0.543; $P < 0.001$) (Supplementary material, *Table S1*), the only CP group (r = 0.478; $P < 0.001$), and the MP group (r = 0.512; $P < 0.001$). Based on categorized CAC scores, VAI levels were increased from the normal group to the severe group (Figure 1). Increased VAI levels were independent predictors of CAC scores (Table 3). Accordingly, it was determined that a 1-unit increase in log (VAI) level increased the CAC score by 1.83-fold independently of other risk factors.

Multivariable logistic regression models to predict the presence of atherosclerosis and CAP morphology are presented in Supplementary material, *Tables S2–S5*. Increased VAI levels were independent predictors of the presence of atherosclerosis in the whole population (vs. NP group) (odds ratio [OR], 20.72; $P < 0.001$), the only FP group (vs. NP group) (OR, 6.25; $P < 0.001$), the only CP group (vs. only FP group) (OR, 2.98; $P < 0.001$), and the MP group (vs. only CP group) (OR, 2.01; $P < 0.001$) (Table 4).

The threshold value of VAI for predicting the presence of atherosclerosis (vs. NP group) was > 1.6 (AUC, 0.898; sensitivity, 83.1%; specificity, 90.9%) (Figure 2A, Table 4). The threshold value exhibited a gradual increase in predicting CAP morphology (Table 4). Accordingly, the threshold value of the VAI was >1.6 for the only FP group (vs. NP group) (AUC, 0.825; sensitivity, 69.8%; specificity, 87.6%) (Figure 2B), > 2.1 for the only CP group (vs. only FP group) (AUC, 0.764; sensitivity, 63.8%; specificity, 85.1%) (Figure 2C), and > 2.6 for the MP group (vs. only CP group) (AUC, 0.712; sensitivity, 65.6%; specificity, 63.4%) (Figure 2D).

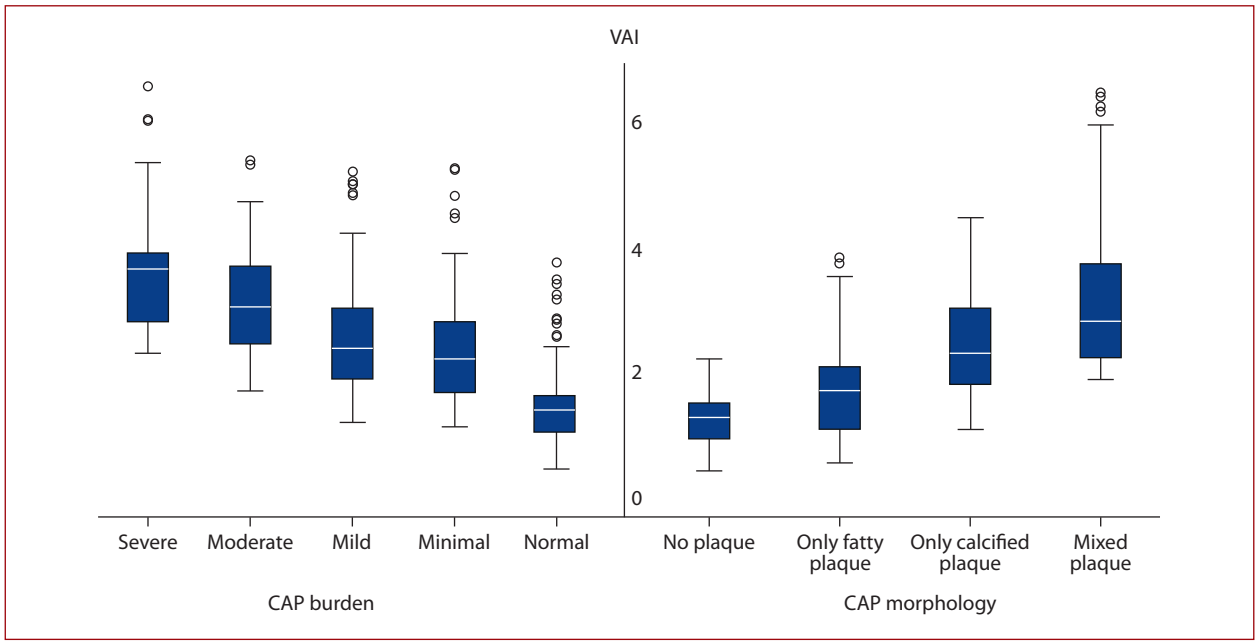

Figure 1. Box and whisker plots of VAI distribution by categorized CAC score and CAP morphology. Data are presented as median (interquartile range [IQR]). Outliers are shown in circles

Abbreviations: CAC, coronary artery calcification; CAP, coronary atherosclerotic plaque

Table 2. Factors associated with CAP morphology

Variables	No plaque (n = 390)	CAP morphology			*P*-value
		Only fatty plaque (n = 114)	Only calcified plaque (n = 135)	Mixed plaque (n = 143)	
Age, years	50.4 (6.5)	50.8 (7.4)	53.3 (7.0)[a, b]	54.0 (7.3)[a, b]	<0.001
Female sex, n (%)	81 (20.8)	42 (36.8)[a, c, d]	67 (49.6)[a, b, d]	91 (63.6)[a–c]	<0.001
BMI, kg/m^2	25.8 (3.5)[b, c, d]	26.3 (2.9)	26.4 (3.3)	26.9 (3.6)	0.002
WC, cm	93.4 (7.9)[b, c, d]	98.2 (4.5)	96.3 (7.2)	96.8 (8.1)	<0.001
Active smoking, n (%)	144 (36.9)[b, c, d]	54 (47.4)	65 (48.1)	71 (49.1)	0.01
Diabetes mellitus, n (%)	87 (22.3)	29 (25.4)	51 (37.8)[a, b]	48 (33.6)[a, b]	0.002
Hypertension, n (%)	156 (40.0)	54 (47.4)	61 (45.2)	89 (62.2)[a–c]	<0.001
Dyslipidemia, n (%)	159 (40.8)	59 (51.8)[a, c, d]	88 (65.2)[a, b, d]	110 (76.9)[a–c]	<0.001
Laboratory findings					
Hemoglobin, g/dl	13.4 (1.3)	13.5 (1.5)	13.6 (1.5)	13.7 (1.6)	0.16
Neutrophil count, ×10^3/µl	3.6 (3.0–4.4)	4.2 (3.5–5.1)[a, c, d]	4.6 (3.7–5.9)[a, b]	4.6 (3.8–5.7)[a, b]	<0.001
Platelet count, ×10^3/µl	257.6 (59.5)	256.6 (63.1)	255.9 (59.3)	257 (65.7)	0.99
Lymphocyte count, ×10^3/µl	2.7 (0.7)	2.6 (0.7)	2.4 (0.8)[a, b]	2.4 (0.7)[a, b]	<0.001
Monocyte count, ×10^3/µl	0.5 (0.1)	0.6 (0.2)	0.7 (0.2)[a, b]	0.7 (0.2)[a, b]	<0.001
HDL-cholesterol, mmol/l	1.4 (0.3)	1.2 (0.3)[a, d]	1.2 (0.2)[a, d]	1.0 (0.2)[a–c]	<0.001
LDL-cholesterol, mmol/l	3.3 (0.9)	3.5 (0.9)[a, d]	3.5 (1.1)[a, d]	3.8 (1.0)[a–c]	0.03
Triglycerides, mmol/l	1.3 (0.9–1.6)	1.3 (0.9–1.8)	1.7 (1.4–2.4)[a, b, d]	2.2 (1.6–2.7)[a–c]	<0.001
Hs-CRP, mg/l	0.3 (0.1–0.5)	0.6 (0.3–1.1)[a, c, d]	1.0 (0.8–1.7)[a, b, d]	1.8 (1.6–2.4)[a–c]	<0.001
VAI	1.2 (0.9–1.5)	1.7 (1.1–2.1)[a, c, d]	2.3 (1.8–3.0)[a, b, d]	2.8 (2.1–3.8)[a–c]	<0.001
Medication, n (%)					
Statins	157 (40.3)	55 (48.2)	86 (63.7)[a, b, d]	109 (76.2)[a, b, c]	<0.001
Acetylsalicylic acid	55 (14.1)	19 (16.7)	25 (18.5)	28 (19.6)	0.36
Beta-blockers	52 (13.3)	18 (15.8)	23 (17.0)	27 (18.9)	0.38
ACEi/ARBs	153 (39.2)	51 (44.7)	60 (44.4)	89 (62.2)[a, b, c]	<0.001
Metformin	83 (21.3)	22 (19.3)	37 (27.4)	41 (28.7)	0.14
DPP4i	53 (13.6)	18 (15.8)	24 (17.8)	27 (18.9)	0.41
Sulfonylurea	44 (11.3)	14 (12.3)	20 (14.8)	22 (15.4)	0.51
SGLT-2i	43 (11.0)	14 (12.3)	18 (13.3)	20 (14.0)	0.75
Insulin	61 (15.6)	21 (18.4)	27 (20.2)	31 (21.7)	0.35

Numerical variables were shown as mean (SD) or median (interquartile range [IQR]). Categorical variables were shown as number (%)
[a]*P* <0.05 vs. no plaque group. [b]*P* <0.05 vs. Only fatty plaque group. [c]*P* <0.05 vs. Only calcified plaque group. [d]*P* <0.05 vs. Mixed plaque group

Abbreviations: see Table 1

Table 3. Independent predictors of CAP burden

Variables	Univariable regression				Multivariable regression			
	β	95% CI		*P*-value	β	95% CI		*P*-value
		Lower	Upper			Lower	Upper	
Age, years	0.03	0.02	0.04	<0.001	0.03	0.02	0.03	<0.001
Female sex	0.55	0.43	0.68	<0.001	–	–	–	–
BMI	0.02	0.00	0.04	0.04	–	–	–	–
WC	0.02	0.01	0.02	<0.001	–	–	–	–
Active smoking	0.15	0.03	0.28	0.02	0.12	0.02	0.22	0.04
Diabetes mellitus	0.29	0.15	0.43	<0.001	0.13	0.02	0.24	0.02
Hypertension	0.28	0.15	0.40	<0.001	–	–	–	–
Dyslipidemia	0.44	0.32	0.56	<0.001	–	–	–	–
Hemoglobin	0.04	0.00	0.09	0.08	–	–	–	–
Neutrophil count	1.74	1.31	2.17	<0.001	–	–	–	–
Platelet count	0.01	–0.01	0.02	0.92	–	–	–	–
Lymphocyte count	0.08	–0.01	0.17	0.08	–	–	–	–
Monocyte count	0.02	0.01	0.02	<0.001	0.01	0.01	0.02	<0.001
HDL-cholesterol	–0.98	–1.19	–0.78	<0.001	–	–	–	–
LDL-cholesterol	0.05	0.02	0.08	0.02	–	–	–	–
Triglycerides	2.18	1.87	2.49	<0.001	–	–	–	–
Hs-CRP	2.24	1.62	2.86	<0.001	–	–	–	–
VAI	2.32	2.12	2.53	<0.001	1.83	1.61	2.05	<0.001
					Adjusted R^2 = 0.479; *P* <0.001			

Before linear regression analysis, logarithmic transformation was applied to CAC score, neutrophil, triglyceride, hs-CRP and VAI variables

Abbreviations: see Table 1

Table 4. Predictive value of VAI in atherosclerosis and CAP morphology

VAI	OR	95% CI		*P*-value	ROC curve analysis			
		Lower	Upper		AUC	Sensitivity	Specificity	Threshold value
Atherosclerosis								
Crude	26.56	16.09	43.84	<0.001	0.898	83.1%	90.9%	>1.6
Multivariable	20.72	12.03	35.68	<0.001				
Only FP (vs. NP)								
Crude	7.88	4.60	13.51	<0.001	0.825	69.8%	87.6%	>1.6
Multivariable	6.25	3.39	11.53	<0.001				
Only CP (vs. Only FP)								
Crude	3.16	2.14	4.66	<0.001	0.764	63.8%	85.1%	> 2.1
Multivariable	2.98	1.97	4.52	<0.001				
Mixed plaque (vs. Only CP)								
Crude	2.05	1.55	2.71	<0.001	0.712	65.6%	63.4%	>2.6
Multivariable	2.01	1.50	2.69	<0.001				

Abbreviations: AUC, area under the curve; CI, confidence interval; CP, calcified plaque; FP, fatty plaque; NP, non-plaque; OR, odds ratio; ROC, receiver operating characteristic; VAI, visceral adiposity index

The CAC score was 0 for 411 (95.4%) patients with VAI levels below 1.6. No CAP was detected in 358 of these patients. The remaining 53 patients had only FP. Accordingly, for 358 patients who had VAI levels of 1.6 and below, constituting 45.8% of the population, the CAC score was 0 and CAP was negative.

DISCUSSION

This study of asymptomatic patients without known CAD has demonstrated that high VAI levels, reflecting VAT dysfunction, were significantly associated with higher CAC scores and the presence of CAP. Moreover, this association was independent of the effects of other cardiovascular risk factors. This work has also provided new findings confirming that the VAI as a surrogate for VAT dysfunction is associated with CAP morphology. Thresholds of the VAI in distinguishing the presence and morphology of CAP offer different implications that may allow using it as a potential screening tool for the risk stratification of patients with suspected CAD.

High BMI or obesity plays a vital role in the development or acceleration of atherosclerosis by mediating some mechanisms such as abnormal lipid profiles, insulin resistance, and systemic inflammation. However, there is also evidence that obesity does not show a linear relationship with cardiovascular events after disease onset or that it presents

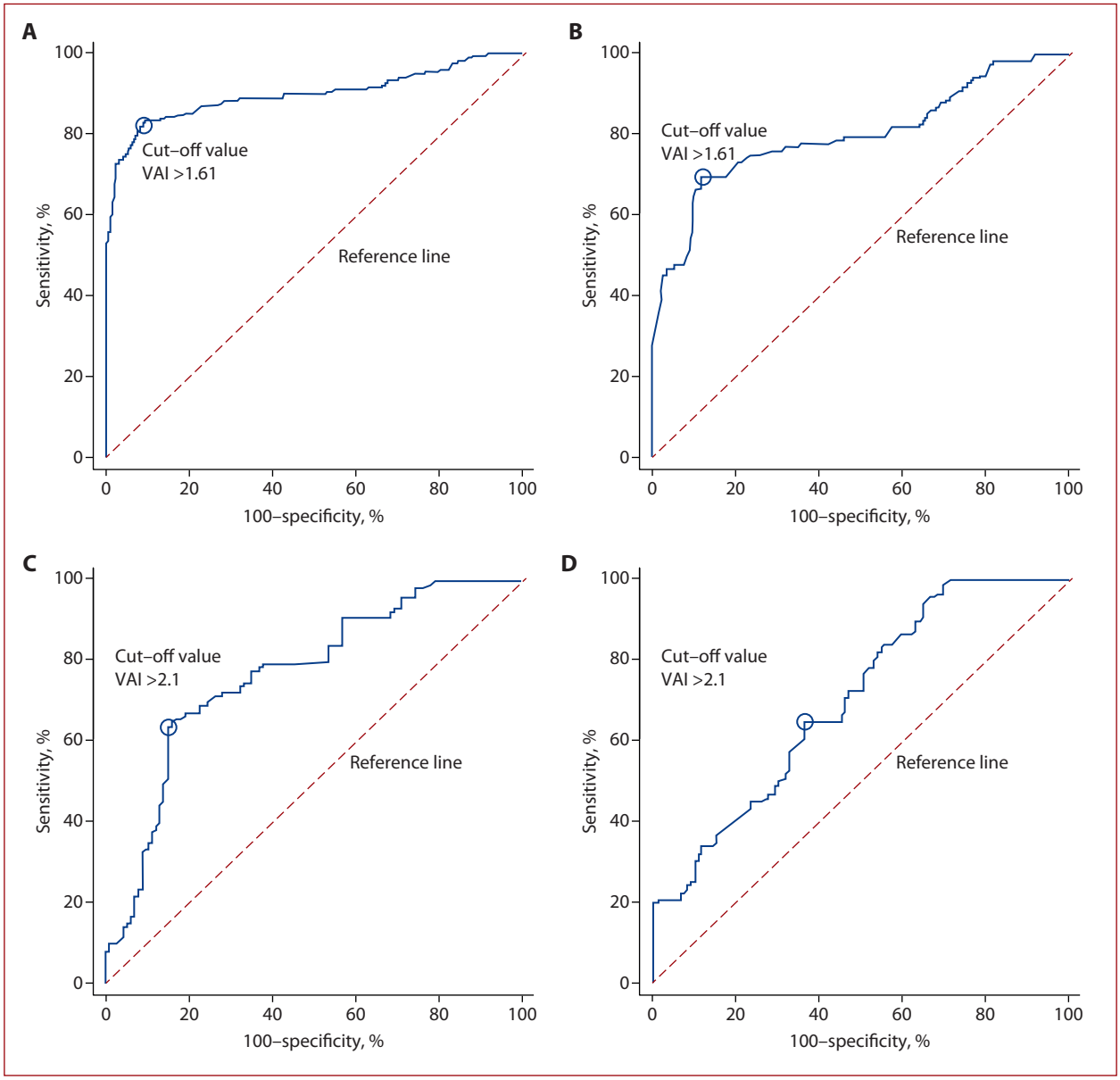

Figure 2. Diagnostic performance assessment of VAI in predicting presence and morphology of CAP. **A.** Presence of atherosclerosis vs. non-CAP. **B.** Only fatty plaque vs. non-CAP. **C.** Only calcified plaque vs. Only fatty plaque. **D.** Mixed plaque vs. Only calcified plaque

Abbreviations: VAI, visceral adipose index; other — see Figure 1

a potential protective effect in coexistence with cardiovascular disease [24]. These contradictions cause the so-called obesity paradox. Furthermore, an increased BMI level is associated with increased risk of atherosclerosis while not all patients who develop atherosclerosis are obese [25]. However, increasing evidence indicates that VAT is responsible for mechanisms mediated by obesity [26]. The VAI is an important surrogate marker of VAT and includes several parameters associated with VAT dysfunction. Furthermore, it has been reported that the VAI is a better predictor of cardiovascular events than its components [21, 27].

In asymptomatic patients with suspected CAD, the presence of atherosclerosis was associated with higher VAI and hs-CRP levels, and these were correlated with increased CAC scores. CAC, found in coronary arteries before the development of clinically significant narrowness, is an essential predictor of subclinical atherosclerosis [3]. Our results are consistent with previous studies that reported positive correlations between VAI levels and CAC scores [12–14]. This may be because, in addition to the effects of high triglycerides and low HDL-C in the development of atherosclerosis, VAT dysfunction can accelerate atherosclerosis by affecting adipokine production, insulin sensitivity, and inflammatory responses including nuclear factor kappa B activation and cytokine expression [7]. These mechanisms are also closely related to the progression of atherosclerotic lesions in addition to macrophage accumulation and play essential roles in plaque morphology [28]. Therefore, the VAI acts as a potential marker for CAD. A 1-unit increase in the VAI raised the probability of

atherosclerosis by 20.7-fold, independently of other risk factors, and a threshold value of >1.6 detected atherosclerosis with high diagnostic performance.

A cohort study of Chinese patients without increased carotid intima-media thickness and carotid plaque reported that increased VAI levels were an independent predictor of increased risk of carotid plaque [29]. To our knowledge, this is the first study to examine the relationship between the VAI and CAP morphology. The highest VAI levels were observed in the MP group, followed by the CP and FP groups. Furthermore, the VAI was found to be a common predictor of CAP morphology regardless of the patient's age, sex, and comorbid conditions, and it exhibited superior diagnostic performance. A retrospective study reported that higher VAT area tertiles were associated with a higher prevalence of CP in patients without diabetes mellitus. In contrast, there was no difference between tertiles among patients with diabetes mellitus. This difference was associated with a hypothesis that oxidative stress resulting from advanced glycation end products and hyperglycemia in patients with diabetes might significantly affect CAP morphology, thereby reducing the effect of VAT area [30]. Several studies have suggested that an increase in epicardial adipose tissue (EAT) is associated with MP and non-CP [31, 32]. EAT as part of VAT was shown to be an independent predictor of CAP burden [33]. Another study reported an increased prevalence of non-CP in patients with high EAT volume [34]. A study evaluating 565 consecutive patients with proven or suspected CAD showed that high VAT levels were associated with non-CP in men and CP in women. However, it was reported that VAT levels were more strongly associated with non-CP in the whole population [6]. Although the current literature offers conflicting results for EAT and VAT in CAP morphology, our results are partially consistent with those of previous VAT studies.

VAI levels were associated with CAP burden regardless of sex. In addition, it was positively correlated with the CAC score in cases of both MP and CP. Patients with MP also had higher CAC, hs-CRP, and triglycerides levels and lower HDL levels compared to patients with CP. Extensive VAT or its dysfunction may result in worse lipid profiles due to its atherogenic effects [9]. A recent study reported that low HDL-C levels were important predictors of the napkin-ring sign for high-risk coronary plaque despite statin therapy [35]. This is consistent with the lower HDL-C levels observed in MP or only CP patients with higher rates of statin use. In the formation of FP, macrophages consume cholesterol and turn into foam cells. This initiates an inflammatory response. In the later stages of atherosclerosis, the plaque becomes rich in calcium and can accumulate more dead foam cells and other debris, exacerbating the inflammatory response [28].

The VAI was an independent predictor of all CAP morphologies. Furthermore, the VAI yielded gradually increasing thresholds for distinguishing among CAP morphologies. More importantly, in the case of a CAC score of 0, it was found that the VAI discriminated between CAP being normal or non-CP. The prevalence of non-CP in asymptomatic patients has been reported to be between 4% and 38% while approximately 1% of patients with CAC scores of 0 were diagnosed with acute coronary syndrome [36–38]. The prevalence of FP was 14.6%, and a 1-unit increase in the VAI raised the probability of FP by 6.25-fold independently of traditional risk factors. The current findings have indicated that the majority of patients with VAI levels below the threshold of 1.6 should not be subjected to radiation exposure or unnecessary angiography. In asymptomatic cases, gradually increasing VAI threshold values may play a role in patients' risk stratification and treatment strategies such as lifestyle modification and pharmacological interventions. However, VAI levels may differ by ethnicity [39]. Therefore, the role of the VAI in plaque morphology warrants further investigation.

Limitations of the study

This study has some significant limitations. First, it had a single-center retrospective design. Second, patients were not separated by ethnicity. In addition, the distribution of CV risk factors such as smoking may differ in different populations [40]. Third, the VAT and EAT levels of the patients were not evaluated; considering the limited studies in the relevant literature, these parameters could be more descriptive in CAP morphology. Fourth, adipocytokine and pro-inflammatory cytokine levels were not measured. These parameters could better reflect the inflammatory milieu. Another significant limitation is the exclusion of patients with a history of CAD. This study does not fully reflect the CAD cohort as it investigated asymptomatic patients. Finally, calcium volume was not measured. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) registries suggest that calcium volume may be a superior parameter compared to Agatston CAC [4, 41].

CONCLUSIONS

In asymptomatic patients, high VAI levels independently predict increased CAC score and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in patients with suspected CAD, and it offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and CAP morphology in patients with suspected CAD.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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