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Coronary plaques and pericardial fat volume assessment in patients with metabolic syndrome being evaluated for suspected coronary artery disease

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Abstract

The relationship between increased pericardial fat volume (PFV) and coronary plaque characteristics in patients with metabolic syndrome (MetS) is unclear. We aimed to assess PFV and coronary plaque characteristics, including type, stenosis severity, and presence of multiple plaques, among patients with MetS being evaluated for suspected coronary artery disease (CAD). This retrospective study included patients with suspected CAD who underwent computed tomography coronary angiography to exclude the presence of occlusive CAD. MetS diagnosis was based on the American Association of Clinical Endocrinologists criteria. The study included 811 individuals with suspected CAD who underwent MDCT examinations: 127 were in the MetS group, 71 were in the diabetes mellitus (DM) group, and 613 were in the control group (neither DM nor MetS). PFV was higher in the MetS group compared to the DM and the control groups (p=0.003). The MetS group had a higher prevalence of multiple (p<0.001) and mixed coronary plaques (p<0.001) compared to other groups. Increased age [odds ratio (OR) confidence interval (CI)=1.1(1-1.2), p=0.039] and PFV [OR (CI)=1 (1-1.2), p=0.027] showed an independent association with multiple plaque presence, while PFV was an independent predictor of mixed plaque presence [OR (CI)=1.1 (1-1.2), p=0.008]. In conclusion, patients with MetS had larger PFV and a higher prevalence of mixed and multiple coronary plaques than patients without MetS. PFV showed an independent and significant association with mixed and multiple coronary plaques among patients with MetS.

Key words: metabolic syndrome, pericardial fat, coronary atherosclerosis, plaque, angiography.

Introduction

Metabolic syndrome(MetS) is a cluster of interrelated comorbidities or factors that are associated with an elevated risk of coronary artery disease (CAD). In the literature, the primary components of MetS include obesity, dyslipidemia (elevated triglycerides or low high-density lipoproteins (HDL)), hypertension, and dysregulated glucose homeostasis [1]. Central obesity, which is associated with increased ectopic fat accumulation, is thought to be an early stage of metabolic dysfunction linked to the secretion of a variety of bioactive molecules or factors known as adipocytokines, such as leptin or plasminogen activator inhibitors, which are associated with thrombogenic vascular disorders [1,2]. In contrast, adiponectin, an adipocytokine with anti-inflammatory properties that protect against metabolic dysregulation and atherosclerotic vascular disorder, is compromised and dysfunctional in persons with visceral fat accumulation, possibly related to MetS [1,3]. Previous studies have reported a significant association between MetS and a higher incidence of high-risk coronary atherosclerosis and adverse cardiovascular events [4,5]. Also, patients with MetS have a higher coronary plaque burden and vulnerability, and this leads to poor prognosis [6].

The assessment of pericardial fat volume(PFV) has received extensive attention in recent years owing to its anatomic proximity to coronary vessels and myocardium. Furthermore, increased pericardial fat deposition has been proposed to be a transducer of systemic metabolic disorders and a systemic inflammatory state caused by obesity or metabolic dysregulation in the heart and coronary vessels [7,8]. Through an imbalance in the secretion of adiponectin and leptin, increased PFV may have a detrimental effect that leads to the formation and progression of coronary atherosclerosis under certain unhealthy conditions like obesity or diabetes mellitus, both of which are key components of MetS [9]. Despite extensive research on PFV over the last decade, the exact pathophysiological role of pericardial fat deposition in coronary atherosclerosis development and progression and metabolic syndrome is still unclear and remains inconsistent in the literature. Besides, more information on the relationship between PFV and coronary atherosclerosis burden in patients with MetS may allow for early detection of subclinical coronary atherosclerosis and implementation of proper preventive measures, such as weight loss or reduction of pericardial fat deposition [10].

The main aim of this study was to assess PFV and coronary plaque characteristics, including type, stenosis severity, and presence of multiple plaques among patients with MetS being evaluated for suspected CAD.

Materials and Methods

This retrospective study included symptomatic patients with suspected CAD who, between January 2013 and January 2024, underwent a 64-slice multi-detector computed tomography (MDCT) angiography examination at the Cardiology Center at Al-Sader Teaching Hospital to exclude the presence of occlusive CAD. At the time of MDCT examination, clinical data for each patient was obtained, including age, sex, a positive family history of premature CAD, current smoking, hypertension, and body weight and height measurements to compute body mass index (BMI). Diabetes mellitus (DM) was defined as fasting blood glucose levels ≥ 126 mg/dL or glycated hemoglobin (HbA1c) levels ≥ 6.5% or the use of diabetes-lowering drugs or insulin. MetS was diagnosed using the American Association of Clinical Endocrinologists (AACE)criteria, which included impaired fasting glucose or impaired glucose tolerance plus two or more of the following: BMI≥ 25 kg/m^2, dyslipidemia (triglycerides ≥150 mg/dl and/or HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women), blood pressure ≥ 130/85 mmHg or antihypertension use. [1,11] The enrolled patients provided verbal informed consent. Our medical college board approved this study.

MDCT scan protocol

A 64-slice CT coronary angiography scanner (Aquilon 64, v. 4.51 ER 010; Toshiba Medical Systems, Tochigi, Japan) was used for the coronary vessel examination. Pericardial fat volume was defined as any fat tissue inside the pericardial sac, which was evaluated using the contrast-enhanced phase in three dimensions. A three-dimensional image of the heart was created by manually tracing the pericardium layer. The entire fat tissue whose CT density ranged from – 250 to – 20 HU within the pericardium was measured using three-dimensional workstation statistical analysis to calculate PFV. The measurement of PFV is displayed in *Supplementary Figure 1*. For coronary plaque assessment, a plaque was defined as a structure of > 1 mm within and/or adjacent to the coronary artery lumen. Based on visual assessment, plaques were categorized into calcified plaque (> 70% calcification), mixed (containing both < 70% calcification and non-calcified (soft) components in a single plaque), and non-calcified(soft) plaque (without any calcification) (*Supplementary Figures 2-4*). The coronary plaque was regarded as single or multiple (≥ 2 plaques in one or more coronary arteries in the same patient). Occlusive coronary plaque was defined as a mean lumen diameter reduction of > 50% in a single vessel [7].

Two independent radiologists, each with more than five years of experience in MDCT coronary angiography interpretation, analyzed all of the MDCT data.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or as numbers (%), as appropriate. Student t-test was used to compare continuous variables distribution between study groups, whereas categorical variables were compared using the Chi-square test. A binary regression analysis was used to measure the odds ratio and 95% confidence interval [OR(CI)] for the association of PFV and classical coronary risk factors, including age, hypertension, smoking, family history of premature CAD, and BMI with mixed coronary plaque and multiple coronary plaques presence. P values less than 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

The study included 811 patients with suspected CAD who underwent MDCT exams to exclude the presence of occlusive CAD; 127 were in the MetS group,71 were in the DM group, and 613 were in the control group (neither DM nor MetS).

There was no significant difference in male sex(P=0.132), family history of premature CAD (P=0.052), and dyslipidemia(P>0.05) between the study groups. The age (58±8 years versus 56±8 years for DM and 53±11 years for the control group, P<0.001) and BMI(29±5 versus 26±6 for DM and 27±5 for the control group, P<0.001) of the MetS group were significantly higher than that of the DM and control group. The MetS group had a higher smoking prevalence than the other groups (P=0.006). PFV was higher in the MetS group (140±70 cm^3) compared to the DM group (119±65 cm^3) and the control group (113±60 cm^3) (P=0.003). The MetS group had a higher prevalence of multiple (P<0.001) and mixed coronary plaques (P<0.001) compared to other groups. Conversely, the DM group had a higher prevalence of calcified plaque (P<0001). No significant statistical difference was observed in the distribution of coronary plaque with ≥50% stenosis between groups. The clinical and MDCT characteristics of the enrolled patients are shown in Table 1

PFV and coronary plaque characteristics among MetS patients

PFV was significantly associated with mixed plaque (P<0.001) and multiple plaque presence (P=0.029), as shown in Figures 1 and 2. There was no significant association between PV and calcified or non-calcified plaque, as seen in Figure 1.

Regression analysis was performed to assess the association of PFV with multiple and mixed plaque presence among patients with MetS, after adjustment for classical coronary risk factors. Increased age [OR(CI)=1.1(1-1.2), P=0.039] and PFV [OR(CI)=1(1-1.2), P=0.027] showed an independent association with multiple plaque presence, while PFV was an independent predictor of mixed plaque presence[OR(CI)=1.1(1-1.2), P=0.008], as in Table 2.

There was no significant association between PFV and plaque stenosis severity, as shown in Figure 3.

Discussion and Conclusions

The prevalence of MetS varies in the literature. It depends on the baseline demographics (age, sex, and ethnicity) of the population under study as well as the criteria applied in various definitions [1]. The AACE criterion had the best specificity but the lowest MetS prevalence, with a frequency lower than 25% of the studied population [2,11]. Regardless of the criteria applied, MetS is highly prevalent and continues to rise across the world, most likely as a result of the obesity epidemic [1,2]. Age, sex, ethnicity, symptomatic versus asymptomatic individuals, and modality used to assess the coronary plaque in the study population all influence the association between MetS and cardiovascular plaques, which is inconsistent across the literature [2].

A cross-sectional observational study of 148 carotid artery plaques in asymptomatic patients using duplex ultrasound found that MetS was not associated with carotid artery plaque stenosis severity or thin fibrous plaque type [12]. Also, a sub-analysis of n PROSPECT trial showed no significant association between MetS and the presence of non-calcified components coronary plaques [13].

On the other hand, several clinical investigations have reported a significant association between MetS and mixed or non-calcified plaque development and progression, which is consistent with our findings [14-16]. Patients may be at high risk for adverse cardiovascular outcomes due to a substantial association of MetS with mixed coronary plaque presence. This is because the vulnerable plaque, which is significantly associated with high inflammatory burden and instability, may trigger plaque rupture and cause acute coronary syndrome [14,15].

In the present study, patients with MetS had high values of PFV, which also showed an independent and significant association with both multiple and mixed coronary plaques.

In our previous study, higher PFV values showed a significant and independent association beyond classical cardiovascular risk factors with mixed coronary plaque development among 198 patients with DM, suggesting the potential contribution of increased PFV in the early phase of the coronary atherosclerosis process [7].

High visceral fat deposition, including pericardial fat deposition, is known to be associated with MetS, and MetS is postulated to be a systemic expression of visceral fat dysfunction [17]. It has been reported that cardiac fat deposition, as a metabolically active tissue that is rich in anti-and pro-inflammatory adipokines and cytokines, is associated with increased local and systemic inflammation, oxidative stress, metabolic dysfunction, and changes in the lipid and inflammatory components of coronary plaques leading to destabilization of these plaques and accelerated atherosclerosis [9]. Furthermore, as PFV is more prominent in patients with mixed coronary plaque, it is connected with both plaque vulnerability and total plaque burden [7,9,18]. Hence, increased cardiac fat accumulation may contribute to the early development of coronary atherosclerosis and can predict the risk of adverse cardiac events before the deposition of calcium in the coronary atherosclerotic plaques, as previously observed in clinical reports [9,19]. In contrast to increased PFV, it is worth noting that reduction of pericardial fat deposition over time may lead to significant independent improvement in myocardial function and parameters, as well as, the reversal of MetS diagnosis and early reversible stages of coronary atherosclerosis that precede mature plaque calcification [3,20]. Overall, the results of the present study indicate that PFV may be a helpful imaging biomarker for predicting early reversible stages of coronary atherosclerosis, as well as for detecting high risk plaque and its subsequent consequences in patients with MetS. Prospective follow-up studies are required to confirm the results and determine the potential effect of PFV reduction on coronary atherosclerosis development and progression in patients with MetS.

There are several limitations in the present study. First, as this is a single-center retrospective study, it is not possible to establish a causal association between the MetS group's coronary plaque features and higher PFV values. Second, our study population consisted of symptomatic patients with suspected CAD, which may limit the generalizability of our results. The analyses on non-calcified plaque may have lacked statistical power as a small group of patients with MetS had non-calcified plaques.

In conclusion, patients with MetS had larger PFV and a higher prevalence of mixed and multiple coronary plaques than patients without MetS. PFV showed an independent and significant association with mixed and multiple coronary plaques among patients with MetS. Prospective studies are required to validate the results and determine the potential effect of PFV reduction on coronary plaque development and progression in patients with MetS.

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Online supplementary material:
Supplementary Figure 1. Multi-detector computed tomography image of epicardial fat volume measurement (green colored area) in the coronal section of the heart.
Supplementary Figure 2. Multi-detector computed tomography image of the left anterior descending artery with calcified plaque.
Supplementary Figure 3. Multi-detector computed tomography image of the left anterior descending artery with mixed plaque.
Supplementary Figure 4. Multi-detector computed tomography image of the left anterior descending artery with non-calcified (soft) plaque.

Table 1. Distribution of baseline clinical characteristics according to metabolic syndrome, diabetes mellitus, or control group (neither condition).

	Control (n=613)	Diabetes (n=71)	MetS (n=127)	p
Age(years), mean±SD	53±11	56±8	58±8	<0.001
BMI, mean±SD	27±5	26±6	29±5	<0.001
Male sex, n(%)	312(51%)	43(61%)	58(46%)	0.132
Blood pressure ≥130/85 mm Hg, n(%)	307(50%)	13(18%)	122(96%)	<0.001
Family history, n(%)	126(21%)	23(32%)	31(24%)	0.052
Elevated Triglyceride, n(%)	164(27%)	27(38%)	40(31%)	0.098
Low HDL, n(%)	143(23%)	22(31%)	39(31%)	0.108
Smoking, n(%)	131(21%)	27(38%)	32(52%)	0.006
PFV(cm^3), mean±SD	113±60	119±65	140±70	0.003
Coronary plaque presence, (n%)	268(44%)	44(62%)	78(61%)	0.001
Plaque with ≥50% stenosis, (n%)	95(15%)	12(17%)	17(13%)	0.377
Multiple plaque presence, n(%)	91(15%)	25(35%)	64(50%)	<0.001
Coronary plaque types				
Calcified, n(%)	185(30%)	32(45%)	51(40%)	<0.001
Mixed, n(%)	47(8%)	7(10%)	22(17%)	<0.001
Non-calcified, n(%)	36(6%)	5(7%)	11(9%)	0.050

Table 2. Regression analysis.

Multiple plaque presence		
Predictor	OR(CI)	P value
Age	1.1(1-1.2)	0.039
PFV	1(1-1.2)	0.027
Mixed plaque presence		
Predictor	OR(CI)	P value
PFV	1.1 (1-1.2)	0.008

Only predictors with P<0.05 are shown in the table.

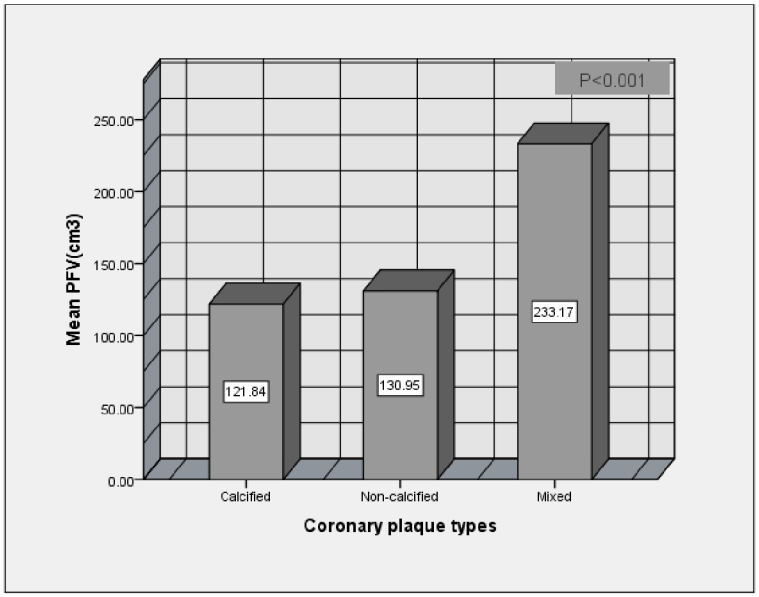

Figure 1. Relationship between PFV and coronary plaque types in patients with MetS.

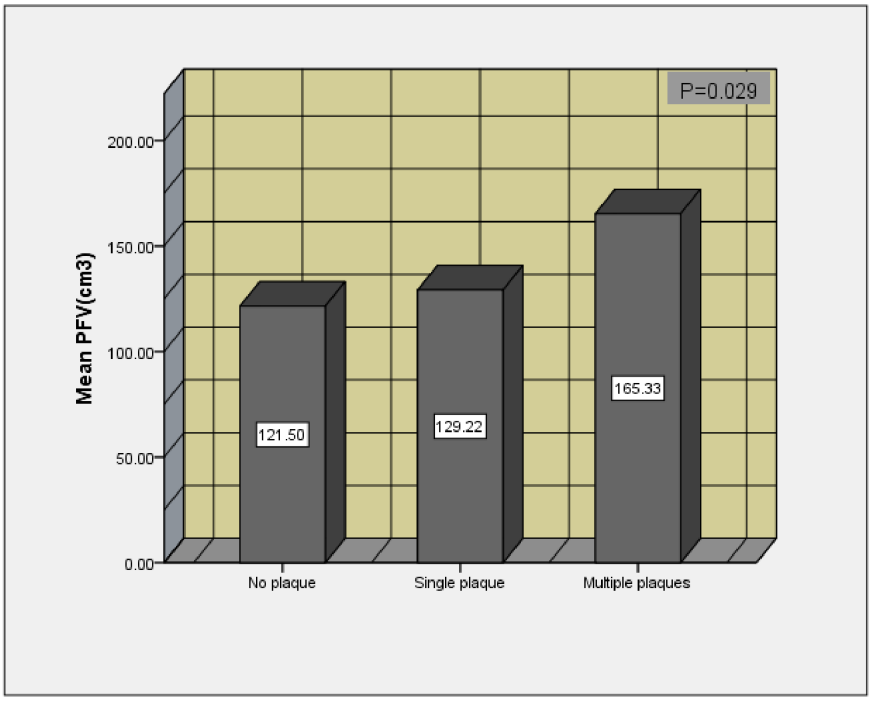

Figure 2. Relationship of PFV with single and multiple coronary plaque presence in patients with MetS.

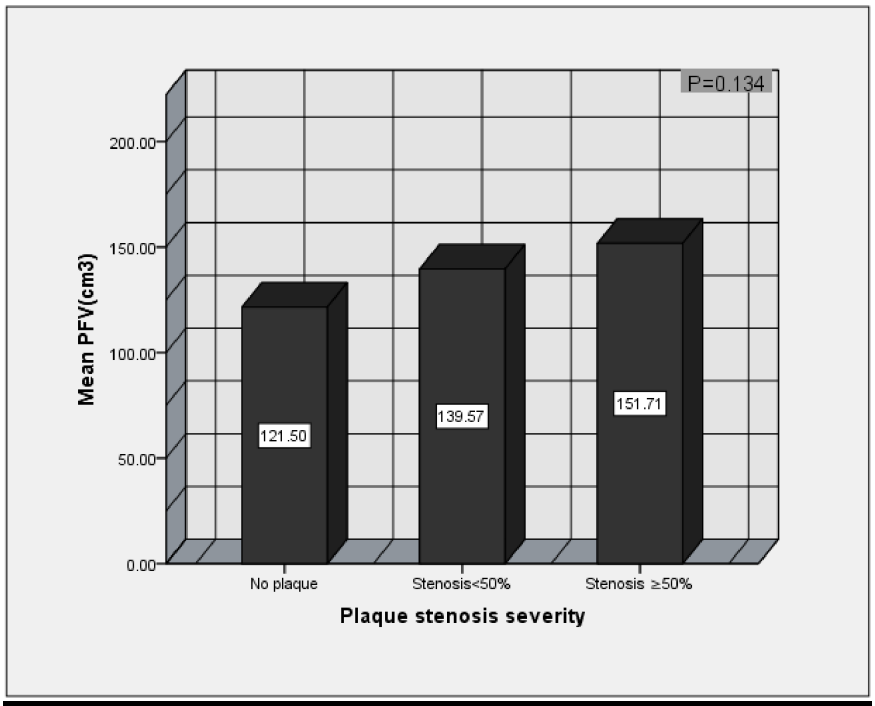

Figure 3. Relationship between PFV and coronary plaque stenosis severity in patients with MetS.