Impact of Body Mass Index on Vascular Calcification and Pericardial Fat Volume Among Patients with Suspected Coronary Artery Disease

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ABSTRACT: Objectives: This study aimed to assess the effect of body mass index (BMI) on the relationship between pericardial fat volume (PFV), aortic root calcification (ARC) and coronary artery calcification (CAC) among patients with suspected coronary artery disease (CAD). Methods: This cross-sectional study took place between January and December 2014 at the Kufa University Teaching Hospital, Najaf, Iraq. A total of 130 consecutive patients with an intermediate pretest probability of ischaemic heart disease who underwent 64-slice multidetector computed tomography (CT) angiography during the study period were recruited. Of these, 111 were included in the study and divided into groups according to BMI. Imaging markers were measured on CT angiography. Results: A total of 28 patients were obese, while 42 and 41 were overweight and normal weight, respectively. The median PFV, CAC and ARC were 109 cm^3 (interquartile range [IQR]: 52–176 cm^3), 0 Agatston score (IQR: 0–52 Agatston score) and 0 Agatston score (IQR: 0–15 Agatston score), respectively, in the normal weight group in comparison to 79 cm^3 (IQR: 43–138 cm^3), 0 Agatston score (IQR: 0–54 Agatston score) and 0 Agatston score (IQR: 0–0 Agatston score), respectively, in the obese group. Significant correlations were observed between PFV and CAC (r^2 = 0.22; P = 0.002) and ARC and CAC (r^2 = 0.37; P < 0.001) in the normal weight group. However, no significant correlations were observed for obese and overweight patients. Conclusion: These findings indicate that BMI may not be an accurate tool for measuring adiposity or assessing subclinical coronary atherosclerosis in patients with suspected CAD.

Keywords: Body Mass Index; Obesity; Pericardium; Coronary Vessels; Vascular Calcification; Atherosclerosis; Coronary Angiography.
Over the last few decades, the global prevalence of obesity has increased dramatically; this is concerning due to the crucial role that obesity plays in metabolic disorders and in increasing the risk of cardiovascular disease. Several non-invasive measurement-based techniques have been used to define obesity, including body mass index (BMI), waist circumference, waist-to-hip ratio and abdominal wall thickness. However, there is as yet no optimal method for accurately assessing the burden and distribution of adipose tissue believed to be involved in coronary and vascular atherosclerosis.

As a marker of subclinical coronary atherosclerosis, coronary artery calcification (CAC) has an incremental prognostic role which differs to traditional cardiac risk factors and is associated with a higher cardiovascular burden and improved coronary risk stratification. Research has shown that CAC is a more effective predictor of cardiovascular events and assessment of atherosclerosis burden. However, little is known regarding the relation of aortic root calcification (ARC) to coronary atherosclerosis and obesity. Pericardial fat is a local fat deposit that covers 80% of the surface of the heart, with a close anatomical proximity to the epicardial coronary arteries; pericardial fat volume (PFV) is an emerging imaging marker that has been reported to be involved in coronary atherosclerosis. The main aim of this study was to assess the impact of BMI on emerging radiological markers of coronary atherosclerosis (CAC, ARC and PFV) in patients with suspected coronary artery disease (CAD).

Methods

This cross-sectional study was carried out between January and December 2014 at the Cardiology Center of the Kufa University Teaching Hospital, Najaf, Iraq. A total of 130 consecutive Iraqi patients with suspected CAD based on age, gender and the presence of cardiac symptoms who had undergone 64-slice multi-detector computed tomography (MDCT) angiography for assessment of CAD during the study period were recruited. The exclusion criteria for a MDCT examination included haemodynamic instability, a history of cardiac surgery, iodine-based contrast allergies, renal failure (creatinine levels of ≥1.5 mg/dL), atrial fibrillation or other unstable heart rhythms, an inability to perform breath-holding, the presence of intracardiac devices (e.g. pacemakers), pregnancy or contraindications for the use of β-blockers. Of those recruited, 19 patients were subsequently disqualified due to poor imaging technique or motion artifacts (n = 8), aortic root anomalies or dissections (n = 2), difficulties in accurate PFV calculation or segmentation of fat (n = 6) or missing data (n = 3). A total of 111 patients were hence included in the study and divided into obese (BMI of ≥30 kg/m²), overweight (BMI of 25–29.9 kg/m²) or normal weight (BMI of <25 kg/m²) groups.

Non-contrast multidetector computed tomography (CT) was performed on all patients with suspected CAD using a sequence scan with a slice thickness of 3 mm. Total heart calcium levels were measured according to the Agatston method. Thereafter, 64-slice CT coronary angiography was performed (Aquilion™ 64, Version 4.51 ER 010, Toshiba Medical Systems Corp., Otawara, Japan) according to previously defined methods. The scan was obtained from the aortic arch to the level of the diaphragm during a single breath-hold. Retrospective electrocardiograph (ECG)-gating and ECG-dependent tube current modulation was performed using defined parameters. Following this, CT images were reconstructed using a smooth kernel (B25f) with a slice thickness of 0.5 mm (increment of 0.3 mm) and data sets were transferred to a VitreaWorkstation™ (Vital Images Inc., Minnetonka, Minnesota, USA) for image analysis.
A minimum of three contiguous voxels with a CT density of >130 Hounsfield units (HU) was considered to define the CAC area. Coronary artery stenosis severity was classified visually according to mean lumen diameter as normal, non-obstructed (reduction of <50%) or obstructive (reduction of ≥50% in a single vessel) by comparing the narrowest segment of the lumen diameter with the more proximal or distal normal segment in two orthogonal projections.  

The part of the aorta lying within 3 cm of the caudal aspect of the aortic annulus containing the sinuses of Valsalva and the sinotubular junction was defined as the aortic root. According to this definition, total ARC was measured using the Agatston method [Figure 1]. Areas in the aortic root with an attenuation of >130 HU and an area of >1 mm² were considered to be calcified lesions. Any adipose tissue located within the pericardial sac was considered to denote pericardial fat; this was measured three-dimensionally with a contrast-enhanced phase [Figure 2]. The pericardial layer was manually traced and a three-dimensional (3D) image of the heart constructed. The PFV was then estimated using a 3D workstation by measuring the total volume of pericardial tissue with a CT density between -250 and -20 HU. All MDCT data sets were evaluated by two independent radiologists with more than five years of experience in MDCT angiography data analysis. Significant differences between ARC, CAC and PFV markers among the BMI groups were analysed. Subsequently, the relationships between ARC, CAC and PFV in each group was analysed.

The presence of conventional cardiac risk factors for CAD was obtained from each patient at the time of the coronary MDCT angiography examination during clinical history-taking. Conventional cardiac risk factors included the following: positive family history of early CAD occurring before 55 years of age in men and 65 years of age in women; current smoking status and history defined as more than 10 cigarettes per day in the last year; history of hypertension or use of anti-hypertension medications; hyperlipidaemia (total cholesterol ≥200 mg/dL, triglyceride levels ≥150 mg/dL or use of lipid-lowering drugs); history of diabetes mellitus or use of antidiabetic or insulin-lowering drugs; and obesity (BMI of ≥30 kg/m²). Patients with two or more of these risk factors apart from obesity were considered to have multiple CAD risk factors.

Data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 13.0 (IBM Corp., Chicago, Illinois, USA). Results were presented as interquartile ranges (IQRs) or percentages, as appropriate. Categorical data were expressed as frequencies and group comparisons were performed using Pearson’s Chi-squared test. Continuous variables were presented as median values and IQRs and were compared using the Student’s t-test, analysis of variance or non-parametric Mann-Whitney U test, as appropriate. Correlations between PFV, ARC and CAC were examined using Pearson’s correlation coefficient or Spearman’s rank correlation for nonparametric data. A multiple regression analysis was used to analyse correlations between the dependent variables (CAC, PFV and ARC) and the independent variable (BMI) after multivariate adjustment for age, gender, hypertension, smoking, diabetes, family history of premature CAD and hyperlipidaemia. A P value of <0.050 was considered statistically significant.

This study was approved by the ethical committee of the Faculty of Medicine, University of Kufa. Informed consent was obtained from all patients included in the study.
Results

Of the 111 patients included in the study, 54 were male (49%). The mean age of the total sample was 54.2 ± 10.3 years. According to BMI category, 28 patients were obese (25%), 42 were overweight (38%) and 41 were of normal weight (37%), with mean ages of 51.3 ± 9.5 years, 56.8 ± 10.3 years and 54.7 ± 10.2 years, respectively. Median PFV (109 cm$^3$; IQR: 52–176 cm$^3$) and ARC (0 Agatston score; IQR: 0–15 Agatston score) values were highest in the normal weight group and lowest in the obese group, respectively. In comparison, median CAC values were highest in the obese group and lowest in the normal weight group (0 Agatston score; IQR: 0–54 Agatston score versus 0 Agatston score; IQR: 0–52 Agatston score). In the overweight group, the median PFV, ARC and CAC scores were 87 cm$^3$ (IQR: 69–130 cm$^3$), 0 Agatston score (IQR: 0–2 Agatston score) and 0 Agatston score (IQR: 0–53 Agatston score), respectively. Differences in PFV, CAC and ARC scores among the patient groups were not statistically significant ($P = 0.419, 0.871$ and 0.631, respectively).

Additionally, there was no significant difference in the distribution of obstructive coronary stenosis among the groups ($P = 0.121$). The presence of CAD risk factors was also similar among the groups, except that there were more patients with multiple risk factors in the normal weight group compared to the obese and overweight groups ($P = 0.032$) [Table 1].

For the obese patients, no significant correlations were observed between PFV and CAC ($r^2 = 0.01; P = 0.167$), obstructive coronary artery stenosis ($r^2 <0.01; P = 0.338$) or ARC ($r^2 = 0.02; P = 0.266$). Also, ARC showed no significant correlation with CAC ($r^2 = 0.04; P = 0.541$) or obstructive coronary stenosis ($r^2 = 0.04; P = 0.335$). In the overweight group, no significant correlation was observed between PFV and CAC ($r^2 = 0.03; P = 0.521$), obstructive coronary stenosis ($r^2 <0.01; P = 0.611$) or ARC ($r^2 = 0.01; P = 0.745$); additionally, ARC showed no significant correlation with CAC ($r^2 = 0.03; P = 0.244$) or obstructive coronary stenosis ($r^2 = 0.02; P = 0.322$). In the normal weight group, a significant correlation was observed between PFV and CAC ($r^2 = 0.22; P = 0.002$) and obstructive coronary stenosis ($r^2 = 0.18; P = 0.004$).

Table 1: Demographic and imaging characteristics and presence of risks factors among patients with suspected coronary artery disease (N = 111)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese group (n = 28)</th>
<th>Overweight group (n = 42)</th>
<th>Normal weight group (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>51.3 ± 9.5</td>
<td>56.8 ± 10.3</td>
<td>54.7 ± 10.2</td>
<td>0.217</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (32)</td>
<td>23 (55)</td>
<td>22 (54)</td>
<td>0.156</td>
</tr>
<tr>
<td>Female</td>
<td>19 (68)</td>
<td>19 (45)</td>
<td>19 (46)</td>
<td>0.138</td>
</tr>
<tr>
<td>CAD risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (43)</td>
<td>16 (38)</td>
<td>23 (56)</td>
<td>0.211</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (21)</td>
<td>10 (24)</td>
<td>13 (32)</td>
<td>0.510</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>5 (18)</td>
<td>6 (14)</td>
<td>6 (15)</td>
<td>0.982</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (7)</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td>0.954</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
<td>5 (18)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>0.150</td>
</tr>
<tr>
<td>Multiple*</td>
<td>4 (14)</td>
<td>10 (24)</td>
<td>17 (41)</td>
<td>0.032</td>
</tr>
<tr>
<td>Imaging marker scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median CAC score (IQR) in Agatston</td>
<td>0 (0–54)</td>
<td>0 (0–53)</td>
<td>0 (0–52)</td>
<td>0.832</td>
</tr>
<tr>
<td>Median ARC score (IQR) in Agatston</td>
<td>0 (0–0)</td>
<td>0 (0–2)</td>
<td>0 (0–15)</td>
<td>0.632</td>
</tr>
<tr>
<td>Median PFV (IQR) in cm$^3$</td>
<td>79 (43–138)</td>
<td>87 (69–130)</td>
<td>109 (52–176)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

SD = standard deviation; CAD = coronary artery disease; CAC = coronary artery calcification; IQR = interquartile range; ARC = aortic root calcification; PFV = pericardial fat volume.

*Presence of two or more risk factors in the same patient. †Luminal stenosis ≥50%.
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although there was no significant correlation between PFV and ARC ($r^2 = 0.04; P = 0.113$). The correlations between PFV and CAC ($P = 0.003$; confidence interval [CI] = 0.218–1.012) and between PFC and obstructive coronary stenosis ($P = 0.03$; CI = 6.441–137.517) persisted after multivariate adjustment for age, gender, ARC and conventional CAD risk factors. Furthermore, ARC showed a significant correlation with CAC ($r^2 = 0.37; P < 0.001$) and obstructive coronary stenosis ($r^2 = 0.23; P = 0.001$); these correlations persisted after multivariate adjustment for age, gender, PFV and conventional CAD risk factors ($P < 0.001$; CI = 0.342–0.870 and $P = 0.003$; CI = 6.742–29.445, respectively).

Multiple regression analysis was performed to assess the relationship of BMI with CAC, ARC and PFV in the sample after adjustment for age, gender and conventional CAD risk factors [Table 2]. No significant correlation was observed between BMI and any of these markers, including PFV [Figure 3].

Discussion

The use of BMI as a method for identifying obesity has several limitations. For example, BMI calculations do not usually take into consideration age, gender, bone structure, muscle mass or the time relationship between obesity and the clinical outcome being measured.7 Furthermore, BMI measurements do not differentiate between body weight due to muscle mass and weight due to adipose mass; the latter is now considered a key factor involved in various metabolic and cardiovascular disorders.1 Moreover, the relationship between BMI and percentage of adipose tissue is not linear and differs between men and women.7 In recent years, the results of several studies have suggested that obesity as determined by BMI is not necessarily equivalent to poor metabolic health or adverse cardiovascular outcomes; these findings have led to the generation of a new term—metabolically healthy obesity—which refers to obese subjects who satisfy the current definition of obesity without being metabolically unhealthy.11–13 Interestingly, ‘U’- or ‘J’-shaped associations between BMI and cardiovascular outcomes or mortality have been identified, in which obese patients show better outcomes in terms of cardiovascular morbidity and total mortality compared to patients of a normal weight.1,13 This inverse relationship between BMI and morbidity or mortality rates has been referred to as the “obesity paradox”.1,13 In a meta-analysis of data from 89 studies including 1,300,794 patients, Wang et al. reported a ‘J’-shaped relationship between prognosis

Table 2: Multiple regression analysis of imaging markers with body mass index and risk factors among patients with suspected coronary artery disease (N = 111)

<table>
<thead>
<tr>
<th>CAD risk factor</th>
<th>ARC</th>
<th>PFV</th>
<th>CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RC</td>
<td>SE</td>
<td>P value</td>
</tr>
<tr>
<td>BMI</td>
<td>0.59</td>
<td>0.9</td>
<td>0.521</td>
</tr>
<tr>
<td>HTN</td>
<td>18.82</td>
<td>27.1</td>
<td>0.434</td>
</tr>
<tr>
<td>Smoking</td>
<td>21.45</td>
<td>30.0</td>
<td>0.453</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.14</td>
<td>12.1</td>
<td>0.853</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>21.54</td>
<td>33.4</td>
<td>0.514</td>
</tr>
<tr>
<td>Family history</td>
<td>11.62</td>
<td>43.5</td>
<td>0.723</td>
</tr>
<tr>
<td>Age</td>
<td>2.83</td>
<td>1.1</td>
<td>0.012</td>
</tr>
<tr>
<td>Male gender</td>
<td>53.31</td>
<td>25.6</td>
<td>0.031</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; ARC = aortic root calcification; PFV = pericardial fat volume; CAC = coronary artery calcification; RC = regression coefficient; SE = standard error; BMI = body mass index; HTN = hypertension.

Figure 3: Non-significant correlation between body mass index and pericardial fat volume among patients with suspected coronary artery disease (N = 111). PFV = pericardial fat volume; BMI = body mass index.
and BMI in patients with CAD. Thus, the use of BMI as a measure of obesity may lead to bias in assessing relationships between obesity and cardiovascular health and outcomes.

An inconsistent and complex relationship between obesity and vascular calcification has been described in the literature. Several studies have suggested that obesity is associated with increased CAC and calcification of the aorta; however, these studies were performed in relatively young populations or among individuals without known CAD or clinically significant coronary disease. On the other hand, an inverse relationship between vascular calcification and reduced bone density among the elderly has been suggested in more recent studies, whereby low BMI was independently associated with decreased bone mineral density which, in turn, was associated with increased vascular calcification. Rhee et al. compared CAC scores assessed by MDCT among 24,000 participants with different metabolic health and obesity statuses; CAC levels were similar for both non-obese but metabolically unhealthy individuals and metabolically unhealthy obese paticipants. This finding suggests that metabolic health is more closely associated with CAC than obesity via a complex pathway. Recently, after studying the CT scans of 276 participants scoring multiple arteries, including the coronary arteries and aorta, Takx et al. reported the systemic nature of cardiovascular calcifications, with a weak link between BMI and cardiovascular calcifications among different arterial beds.

With regards to the relationship between PFV, vascular calcification and obesity, considerable evidence supports the vital role of pericardial fat accumulation in the coronary atherosclerosis process via the secretion of hormones and cytokines that modulate coronary artery haemostasis. The concept of normal weight obesity—defined as a normal BMI and excess body fat percentage—has been recently reported as an important risk factor for cardiovascular disease and metabolic dysregulation; higher amounts of visceral fat even with a normal BMI carry an elevated cardiovascular risk. Kim et al. reported that patients with normal weight obesity have a higher subclinical atherosclerosis incidence than normal weight lean patients due to a higher amount of visceral fat, regardless of other clinical risk factors for atherosclerosis.

A recent systematic review and meta-analysis of 38 studies examining the relationship between epicardial fat and generalised obesity, central or visceral adipose tissue and the components of metabolic syndrome found a highly significant correlation between epicardial fat and BMI. Two CT-based studies found that increased cardiac fat was associated with CAD in non-obese patients and with metabolic syndrome regardless of BMI status. Additionally, a magnetic resonance imaging-based study reported that cardiac fat deposits were associated with a worse cardiometabolic profile in non-obese persons. Nevertheless, it is important to note that there is significant heterogeneity between echocardiography-based and CT-based studies in the assessment of cardiac fat deposits, whereby the volumetric quantification of cardiac fat using MDCT is highly reproducible compared to more simple measurements of thickness and area using echocardiography. Two-dimensional echocardiographic measurements may not be accurate enough to assess the 3D-distribution of pericardial fat deposits. Moreover, the differences in anatomical description (pericardial versus epicardial fat) and discrepancies and ambiguities in the definition and nomenclature of fat deposits around the heart can attenuate the strength of reported associations between cardiac fat deposits and obesity.

In the present study, significant correlations were observed between ARC and PFV with CAC in the normal weight group, while ARC, CAC and PFV showed no significant correlations in the overweight and obese groups. The assessment of different markers of coronary atherosclerosis through an automated (CAC and ARC) or semi-automated (PFV) scoring system using MDCT was a strength of the current study. However, there were several limitations. First, the patients were not randomly selected and only those patients with suspected CAD from a single centre were included, potentially resulting in selection bias which may limit generalisation of the results. Second, the sample size was relatively small. Third, causal relationships between PFV, ARC and CAC could not be inferred due to the cross-sectional design of the study. Fourth, the progression of CAC and ARC was not assessed; hence, obesity may have been associated with arterial calcification progression. Finally, a high BMI at the time of the MDCT examination may not necessarily reflect long-term obesity.

**Conclusion**

In the present study, PFV and ARC showed a significant correlation with subclinical coronary atherosclerosis (CAC and obstructive coronary stenosis) in normal weight patients. However, no significant correlations were observed for obese and overweight patients. These results suggest that BMI may not be an accurate tool for the measurement of adipose tissue or the assessment of arterial calcification burden among patients with suspected CAD.
CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No funding was received for this study.

References


