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Gender disparity impact on the vascular calcification and pericardial fat volume in patients with suspected coronary artery disease

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SOUHRN

Kontext: V literatuře zatím neexistuje shoda ohledně vlivu pohlaví na korelaci mezi kalcifikací koronárních tepen (coronary artery calcification, CAC) na jedné straně a kalcifikací aortálního kořene (aortic root calcification, ARC) a objemem perikardiálního tuku (pericardial fat volume, PFV) na straně druhé.
Cíl: Zjistit vliv pohlaví na korelaci CAC s ARC a PFV u iráckých pacientů s podezřením na ischemickou chorobu srdeční diagnostikovanou metodou multidetektorové CT (MDCT).
Metody: V období mezi lednem a prosincem roku 2014 bylo v Iráku do studie zařazeno celkem 130 po sobě jdoucích pacientů se středně vysokou předtestovou pravděpodobností, na základě vyšetření metodou MDCT, přítomnosti ischemické choroby srdeční. Z uvedeného počtu bylo 111 pacientů shledáno vhodnými pro zařazení do studie. Pacienti byli rozděleni do skupin mužů (n = 54) a žen (n = 57).
Výsledky: U mužů nebyla významná korelace mezi PFV s hodnotami CAC a ARC nalezena. CAC významně korelovala s ARC (r = 0,392; *p* = 0,003). Korelace mezi CAC a ARC přetrvávala i po adjustaci na PFV, věk a kardiální rizikové faktory (*p* = 0,01; CI = 0,067–0,492). U žen hodnota PFV významně korelovala s hodnotou CAC (r = 0,413; *p* = 0,001); tato korelace přetrvávala i po multivariační regresní adjustaci na ARC, věk a kardiální rizikové faktory (*p* = 0,016; CI = 0,067–0,612), přičemž nebyla zjištěna žádná významná korelace mezi PFV a ARC. Korelace hodnoty ARC s CAC nebo s PFV nebyla statisticky významná. Hodnota ARC vykázala významnou spojitost s mužským pohlavím (*p* = 0,04), přičemž rozdíl v PFV a CAC mezi oběma skupinami hodnocenými ve studii nedosáhl statistické významnosti.
Závěr: Hodnota PFV významně korelovala s CAC u žen, zatímco u mužů byla zjištěna významná korelace mezi ARC a CAC.

ABSTRACT

Background: There is no consensus in the literature on the influence of gender on the correlations between coronary artery calcification (CAC) with aortic root calcification (ARC) and pericardial fat volume (PFV).
Objective: To investigate the impact of gender on the correlations between PFV, CAC and ARC in Iraqi patients with suspected coronary artery disease (CAD) assessed by multi-detector CT (MDCT).

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Methods: One hundred thirty consecutive Iraqi patients with intermediate pretest probability of ischemic heart disease who underwent MDCT examination for assessment of CAD were recruited between January and December 2014. Of these, 111 patients were found to be eligible and were enrolled in the study. Patients were divided into male group (n = 54) and female group (n = 57).

Results: In male patients, PFV showed no significant correlation with CAC and ARC. CAC showed a significant correlation with ARC (r = 0.392, *p* = 0.003). The correlation between CAC and ARC persisted even after adjustment for PFV, age and cardiac risk factors (*p* = 0.01, CI = 0.067–0.492). In female patients, PFV showed a significant correlation with CAC (r = 0.413, *p* = 0.001) and this correlation persisted even after multivariate regression adjustment for ARC, age and cardiac risk factors (*p* = 0.016 , CI = 0.067–0.612) while there were no significant correlation between PFV and ARC. ARC showed no significant correlation with CAC and PFV. ARC showed a significant association with male gender (*p* = 0.04) while there were no significant difference in PFV and CAC between the two groups of study.

Conclusion: PFV was significantly associated with CAC in female while ARC showed a significant association with CAC in male.

Introduction

Gender disparity plays an important role in cardiovascular disease prevalence and burden with significant gender related differences reported in cardiovascular clinical presentation mortality, morbidity and risk factors profiles [1].

Coronary artery calcification (CAC) is a reported imaging marker of subclinical atherosclerosis and has incremental prognostic values beyond those of traditional cardiac risk scores for cardiovascular disease (CVD) prognosis and it may help in reclassification of patients at increased risk [2,3].

Pericardial fat is an adipose tissue surrounding the heart, with anatomic proximity to the epicardial coronary arteries. In recent years, pericardial fat volume (PFV) has been proposed as an imaging biomarker of increased cardiovascular risk [4,5].

To the best of the authors' knowledge, there is little information regarding the association between aortic root calcification (ARC) and coronary atherosclerosis markers and calcification, because the evaluation of the aortic root or thoracic aorta calcification is not a standard part of the routine cardiovascular workup.

The main aim of this study was to investigate the impact of gender disparity on the correlations of PFV, CAC and ARC in patients with intermediate test probability of coronary artery disease (CAD) assessed by multi-detector CT (MDCT).

Materials and methods

This cross-sectional study was carried out at the Cardiology Center at Al-Sader Teaching Hospital. Informed consent was obtained from all individual participants included in the study. The study was approved by our institution. One hundred thirty consecutive Iraqi patients with intermediate pretest probability of ischemic heart disease based on their age, sex and cardiac symptoms and who underwent 64-slice MDCT angiography for assessment of CAD were recruited between January and December 2014. Of these, 111 patients were found to be eligible and were enrolled in the study.

Nineteen patients were excluded because of a poor examination technique or motion artifact (n = 8), aortic root anomalies or dissection (n = 2), difficulty in accurate pericardial fat volume calculation or segmentation of fat (n = 6), or data were missing (n = 3).

For analytical purposes, patients were divided into two groups according to their gender: male group (n = 54 [49%]) and female group (n = 57 [51%]).

Using standard physician-based questionnaires, a history of conventional cardiac risk factors for CAD was obtained from each patient at the time of coronary MDCT angiography examination including a positive family history of premature CAD (occurring before the age of 55 years in men and before 65 years in women), current smoking history (more than 10 cigarettes per day in the last year), a history of hypertension or use of anti-hypertension medications, hyperlipidemia was defined as total cholesterol $\geq$ 200 mg/dl or triglyceride levels $\geq$150 mg/dl or use of lipid lowering drugs, a history of diabetes mellitus or use of insulin or diabetic lowering drugs and obesity with a body mass index $\geq$ 30. Patients with two or more cardiac risk factors were considered to have multiple risk factors.

CT scan protocol

CT coronary angiography was performed with a 64-slice scanner (Aquilon 64, v. 4.51 ER 010; Toshiba Medical Systems, Tochigi, Japan). Before multi-slice CT angiography was performed, a non-contrast CT was acquired to measure the calcium score according to the Agatston for total heart calcium (summed across all lesions identified within coronary arteries) using a sequence scan with a slice thickness of 3 mm [6].

Coronary calcification area was defined as at least three contiguous voxels with a CT density > 130 Hounsfield units. When the patient's heart rate was more than 65 bpm, a β-blocker (metoprolol; 20–60 mg orally) was administered before the scan. A bolus of 80 ml contrast medium (Omnipaque; 350 mg/ml iodine) was injected intravenously at a rate 5 ml/s, followed by 30 ml of normal saline. The scan was obtained from the aortic arch to the level of the diaphragm during a single breath hold. Using retrospective ECG-gating and ECG-dependent tube current modulation, the following parameters were performed: collimation, width 32.5 cm × 32.5 cm; slice thickness: 0.5 mm; rotation time: 0.35 s; tube voltage: 120 kV; maximum effective tube current: 890 mA and table feed: 0.3 mm/rotation at 75% of R-R cardiac cycle. Examination time took ~10 s. CT images were reconstructed using a smooth kernel (B25f) with a slice thickness of 0.5 mm (increment of 0.3 mm). CT data sets were transferred to a dedicated workstation (Vitrea 2 Workstation; Vital Image, Plymouth, MN, USA) for image analysis.

The aortic root was defined as the part of the aorta lying within 3 cm from the caudal aspect of the aortic annulus containing sinuses of Valsalva and the sinotubular junction. The total calcium score of the aortic root was calculated using Agatston method according to this definition. Areas in the aortic root with an attenuation > 130 Hounsfield units and an area > 1 mm^2 were considered to be calcified lesions. All MDCT images were assessed by two independent radiologists with more than 5 years' experience in coronary MDCT angiography interpretation.

PFV was defined as any fatty tissue located within the pericardial sac and measured three-dimensionally with the contrast-enhanced phase. PFV was measured three-dimensionally with the contrast-enhanced phase. The layer of the pericardium was manually traced and a three-dimensional image of the heart was constructed. Then the PFV was quantified by calculating the total volume of the tissue whose CT density ranged from –250 to –20 HU within the pericardium by using three D workstation statistical analysis.

Statistical analysis

Data are presented as mean ± standard deviation or as numbers with percentages, as appropriate. Categorical data are expressed as frequencies and group comparisons were performed using Pearson's chi-square test. Continuous variables are presented as mean ± standard deviation and were compared using the Student's t-test or analysis of variance, as appropriate. Correlations between PFV, ARC and CAC were examined using Pearson's correlation analysis. Multiple logistic regression was used to analyze the correlations of CAC with PFV and ARC. A P-value of less than 0.05 was considered statistically significant. SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Male group

Composed of 54 (49%) patients, age 54 ± 10 years. PFV mean and median were 119.8 ± 79 cm^3 and 107 cm^3 respectively and range from 10 to 375 cm^3. ARC (calcium score above zero) prevalence was 30%. CAC (calcium score above zero) prevalence was 39%. Patient characteristics are summarized in Table 1.

PFV showed no significant correlation with CAC, ARC and age of patients ($p > 0.05$). CAC showed a significant correlation with ARC (r = 0.392, $p = 0.003$; Fig. 1) and patient's age (r = 0.363, $p = 0.007$). The correlation between CAC and ARC persisted even after adjustment for PFV, age and cardiac risk factors ($p = 0.01$, CI = 0.067–0.492) while the correlation between age and CAC becomes non-significant after being adjusted to cardiac risk factors, ARC and PFV ($p = 0,158$, CI = 1.09–6.50).

ARC showed a significant association with patient's age (r = 0.303, $p = 0.02$) but this correlation attenuated and became non-significant after multivariate regression adjustment for cardiac risk factors, CAC and PFV ($p = 0.146$, CI = –1.28–8.38).

Female group

Composed of 57 (51%) patients (age 54.7 ± 9 years). PFV mean and median were 102.2 ± 74 cm^3 and 78 cm^3 respectively and range from 7 to 367 cm^3. ARC (calcium score above zero) prevalence was 28%. CAC (calcium score above zero) prevalence was 30%. PFV showed a significant correlation with CAC (r = 0.413, $p = 0.001$; Fig. 2) and this correlation persisted even after multivariate regression adjustment for ARC, age and cardiac risk factors ($p = 0.016$, CI = 0.067–0.612) while there was no significant correlation between PFV with ARC and age of patients ($p > 0.05$). ARC showed no significant correlation with CAC and PFV ($p > 0.05$).

Table 1 – Patients' characteristics.			
Parameter	Male (n = 54)	Female (n = 57)	p value
Age	54 ± 10 years	54.7 ± 9.6 years	0.7
Cardiac risk factors			
Hypertension	17 (31%)	34 (60%)	0.003
Smoking	13 (24%)	16 (28%)	0.6
Hyperlipidemia	8 (15%)	11 (19%)	0.5
Diabetes	6 (11%)	2 (3.5%)	0.1
Family history	5 (9%)	6 (10%)	0.8
Obesity	9 (17%)	19 (33%)	0.04
Multiple	14 (26%)	17 (30%)	0.6
CAC			
Mean	80 ± 146	38 ± 91	0.07
ARC			
Mean	65.5 ± 178	14.8 ± 48	0.04
PFV			
Mean	119 ± 79 cm^3	102 ± 74 cm^3	0.2

ARC – aortic root calcification; CAC – coronary artery calcification; PFV – pericardial fat volume.
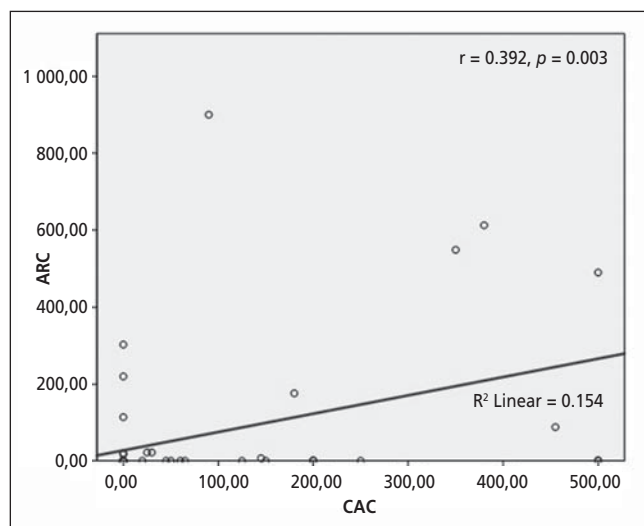
Fig. 1 – A significant correlation was observed between ARC and CAC in male patients. ARC – aortic root calcification; CAC – coronary artery calcification.
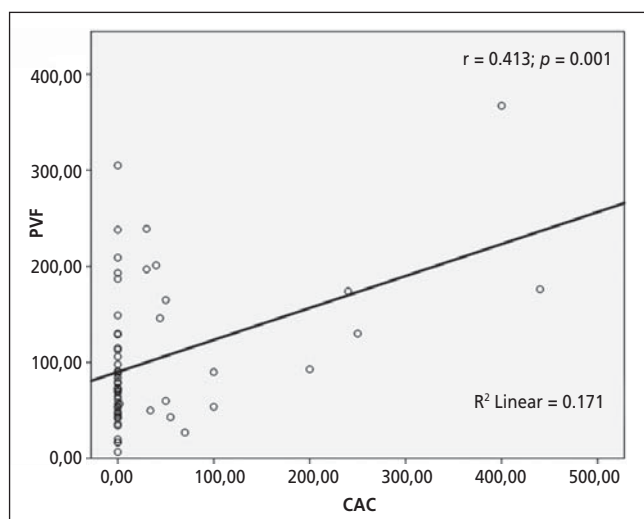

Fig. 2 – A significant correlation was observed between PFV and CAC in female patients. CAC – coronary artery calcification; PFV – pericardial fat volume.

Regarding the distribution of cardiac risk factors among male and female groups, hypertension and obesity were more prevalent in females compared to males (p = 0.003 and 0.04 respectively).

Comparison between male and female groups regarding CAC, PFV and ARC difference showed a significant association of ARC with male gender (p = 0.04) while there was no significant difference in PFV and CAC between the two groups of study.

Discussion

In our study, PFV was significantly correlated with CAC in female patients while ARC showed a significant correlation with CAC in male patients.

There were no significant gender related differences in the prevalence of CAC and PFV except for ARC which was more prevalent in male patients.

The gender gap in cardiovascular disease clinical presentation, risk factors profiles, morbidity and mortality has been reported with multiple potential factors that could be attributed for this gap [1,7].

According to the results of autopsy in 83 patients who died from acute coronary syndrome, gender gap appears to be related to factors peculiar to women although both male and female patients present the same overall plaque burden [7].

So, it is of paramount importance to search for a sensitive imaging biomarker of cardiovascular atherosclerosis risk in both male and female patients.

There is no consensus in the literature on the influence of gender on the pericardial fat deposits.

However, Rosito et al. suggest that cardiac fat is more associated with risk factors in females than in males [8].

Gender related differences have been reported in the pathophysiology of major risk factors, including hypertension, obesity and vascular atherosclerosis. Framingham Heart Study reported that visceral adipose tissue was significantly associated with blood pressure, impaired fasting glucose and metabolic syndrome and these relations between visceral adipose and risk factors were consistently stronger in women than in men [9].

This might help explain the higher prevalence of hypertension and obesity in female patients compared to the male patients in our study.

A more profound fat redistribution has been reported to occur in female than in male rats particularly with increasing age and this might help explain the potential role of adipose tissue in coronary atherosclerosis in postmenopausal women [10].

Interestingly, cardiac fat amount measured by transthoracic echocardiography was the only independent inverse predictor of coronary flow reserve, as opposed to conventional risk factors for atherosclerosis in women complaining of chest pain suggesting the importance of cardiac fat as an easy diagnostic marker for risk stratification of women with chest pain [11].

It has been reported that body mass index (BMI) and waist circumference have limited sensitivity and specificity in correlation with cardiovascular risk and may not be representative of visceral adipose burden [12,13].

In the last decade, increased pericardial fat thickness measured by using echocardiography or PFV by using CT/MRI correlates well with visceral adiposity and metabolic syndrome, and hence is associated with CAD risk and extent [13].

There is a significant gender difference in calcification pattern and coronary heart disease presentation and males younger than 60 years tended to have a unique pattern of coronary calcification and earlier presentation compared to females of similar age [14].

Interestingly, it has been reported that females have a greater microvascular and endothelial dysfunction relative to males and pericardial fat is associated with early endothelial dysfunction that may precede coronary calcification and the development of mature atherosclerotic changes whereas the coronary calcium score could represent a stable phase of atherosclerosis [4].

These gender related differences in CAC pattern and endothelial dysfunction could be the explanation for the lack of association between CAC and PFV in male patients.

The potential role of ARC over measured conventional risk factors and CAC in identifying asymptomatic patients before clinical cardiac events remains to be determined as aortic calcification may presage the development of symptomatic coronary artery disease particularly in patients with hyperlipidemia [2,15].

Thoracic aortic calcium score has been shown to be independently associated with age ≥ 65 years and male sex, and abdominal aortic calcium score was shown to be independently associated with age ≥ 65 years in 315 patients assessed by positron-emission tomography / computed tomography [16].

In addition, Takasu et al. found a higher prevalence of ascending aortic calcification in male patients aged 55 years and older [17].

Our previous study reported that ARC significantly correlated with CAC, coronary calcified plaques and number of coronary stenotic vessels measured using the volumetric and Agatston scoring methods [2].

There were several limitations in this study. First, the study was a single center investigation, and the population was not randomly selected, as it involved only patients with intermediate pretest probability of ischemic heart disease based on physician referral. There is, therefore, the possibility of selection bias. Second, our algorithm for quantifying PFV was not completely automatic and still required user interaction. Third, a causal relationship between ARC, CAC and PFV cannot be established because of the cross-sectional nature of our study.

Further studies using increased population sizes and with follow-ups are needed to investigate the role of and gender related difference of ARC and PFV as an imaging marker with prognostic significance in identifying patients with advanced coronary disease, and also to report on the effect of intensive therapeutic strategies on PFV and ARC.

Conclusion

A significant impact of gender disparity on the correlations between CAC with ARC and PFV was reported in this study. The findings highlight the importance of PFV in coronary atherosclerosis development in female gender and the significant correlation of ARC with coronary atherosclerosis in male gender.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical statement
I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare, that informed consent requirements do not apply to this manuscript.

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