Original Article

Coronary atherosclerosis evaluation among Iranian patients with zero coronary calcium score in computed tomography coronary angiography

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Abstract

Background: Coronary artery calcification (CAC) is a specific indicator of and a sensitive marker for the atherosclerotic disease process. However, calcium scoring may miss noncalcified plaques with clinical importance. The present study aimed to identify the presence and extent of coronary plaques in computed tomography coronary angiography (CTCA) in patients with a zero CAC score and the secondary endpoint was to evaluate the association between coronary risk factors and the presence of noncalcified plaques.

Materials and Methods: In a retrospective descriptive-analytic study, a total of 2000 consecutive patients who undergone CTCA between September 2012 and September 2014 at Alzahra Hospital in Isfahan, Iran were analyzed. Three hundred and eighty-five patients with a zero calcium score were included in the study. The demographic information and coronary artery disease (CAD), risk factors including diabetes mellitus (DM), hypertension, hyperlipidemia, smoking, and family history of CAD, were obtained from the questionnaire. Furthermore, the presence of plaques and extent of stenosis were evaluated in patients with zero CAC score.

Results: Of the 385 patients with a zero calcium score, 16 (4.2%) had atherosclerotic plaques. Among them, 6 (1.6%) had significant (>50%) coronary stenosis, and 10 (2.6%) had no significant (<50%) coronary stenosis. Hyperlipidemia, DM, and smoking were significantly associated with obstructive CAD. Furthermore, in patients with zero calcium score, DM, hyperlipidemia, and smoking had odds ratios of 5.9, 14, and 32.5 for the development of coronary artery plaques, respectively.

Conclusion: Although, CAC scoring is a noninvasive and valuable method to evaluate CAD; but zero CAC score does not absolutely exclude the CAD, especially in the presence of risk factors such as diabetes, hyperlipidemia, and smoking.

Key Words: Calcium score, coronary computed tomography angiography, noncalcified plaque

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INTRODUCTION

During the last century, cardiovascular events have grown rapidly from a relatively minor disease to a leading cause of morbidity and mortality. Cardiovascular events cause 50% of mortalities in developed countries and 25% of mortality in developing countries, nowadays.[1,2]

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Although, risk factors of cardiovascular disease were over ruled and controlled, and consequently mortalities of cardiovascular diseases were significantly declined over the last 50 years, it has been revealed that the process of declining is slowed down by emerging of several risk factors such as obesity and impaired lifestyle.[3,4]

Older age, family history of heart disease and race are considered as conventional risk factors of developing coronary artery disease (CAD). The risk of developing CAD increases with age, and includes age >45 years in males and >55 years in females. A family history of early heart disease is also a risk factor, including heart disease of father or brother diagnosed before age 55 years and mother or sister diagnosed before age of 65. Ethnic-specific differences in cardiovascular risk factors and variations in cardiovascular mortality worldwide have been revealed in a large study. Furthermore, hypertension (HTN), diabetes mellitus (DM), obesity, smoking, lack of physical activity, and mental stress are considered as modifiable risk factors of developing CAD.[5-7]

Recently, computed tomographic angiography (CTA) of coronary arteries has been recognized as a reliable imaging modality to exclude CAD, noninvasively. On the other hand, CT is currently the imaging modality of choice to find and measure the calcified plaques of coronary arteries, aortic valve and aorta plaques. Furthermore, although invasive coronary angiography remains the standard tool for detecting CAD, the use of coronary calcification scoring by multi-detector CTA has been recently argued as a noninvasive method for evaluation of coronary atherosclerosis.[8]

Coronary artery calcification (CAC) is a well-established marker of the total burden of coronary atherosclerosis. Atherosclerotic calcification is a well-organized, active process similar to bone formation that is thought to appear only when other aspects of atherosclerosis are also present. Although, calcification occurs more frequently in progressive plaques, it may also occur in small amounts in earlier lesions. Studies have revealed that plaques with microscopic evidence of mineralization are larger and are associated with larger coronary arteries. However, the relationship between arterial calcification and the probability of plaque rupture is less known.[9-11]

Large prospective studies have revealed that higher CAC scores are associated with increased risk of CAD-related events and considering CAC score as a CAD risk factor could improve cardiovascular risk stratification. Furthermore, autopsy results have shown that there is a correlation between calcification of coronary arteries and the severity of the stenosis.[12] Meanwhile, it has been shown in some studies that cardiovascular events could occur in patients with even zero CAC score, and surprisingly some studies showed that the prevalence of atherosclerotic plaques in patients with zero calcium score is high.[13]

Considering the aforementioned evidences (controversial results of different studies about prevalence of plaques in patients with zero calcium score), controversial results of different studies about risk factors that are associated with plaque in patients with zero calcium score, and paucity of similar studies in Iran, we conducted this study to help elucidating the relationship between CAD and CAC scoring in Iranian population.

MATERIALS AND METHODS

In a retrospective descriptive-analytic study, a total of 2000 consecutive patients who undergone CT coronary angiography (CTCA) between September 2012 and September 2014 at Alzahra Hospital in Isfahan, Iran were recruited into the study. All participants provided written informed consent. Exclusion criteria included the history of myocardial infarction, history of coronary bypass or percutaneous coronary intervention, renal failure, hyper/hypoparathyroidism, and contrast hypersensitivity.

Calcium score was calculated and finally 385 patients with a zero calcium score were selected for subsequent analysis.

The demographic information and coronary risk factors (DM, smoking, family history of heart disease, HTN, and hyperlipidemia) were obtained from the questionnaire.

Coronary CTA (CCTA) was performed using a 64-slice CT scanner (GE, lightspeed, VCT, General Electrics, USA). Noncontrasted cardiac CT was performed in a longitudinal scan field from tracheal carina down to the diaphragm. The corresponding images for calcium scoring were reconstructed with a slice width of 2.5–3 mm and slice interval of 1.25–1.5 mm. Collimation, 2 × 32 × 0.6 mm; section acquisition, 64 × 0.6 mm; pitch, 0.2; gantry rotation time, 350 msec; tube voltage, 120 kV; and tube current up to 600 mAs. current-time product, 600 mAs. Calcium score based on the Agatston algorithm was defined as the presence of a lesion with an area >1 mm^2, and peak intensity >130 HU, which was automatically identified and marked with color by the software. The presence of coronary plaques and extent of stenosis were evaluated in the patients with zero calcium score.

Image analysis was performed by an experienced radiologist in cardiovascular imaging. Coronary plaques were reported as present or absent. The stenosis extent was calculated by dividing the diameter of the narrowest part of the lumen by the diameter of a nearby lumen of the same segment. The plaques were detected using CTCA were categorized into two groups: Nonsignificant (<50%), and significant (>50%).

All data are expressed as the mean ± standard deviation. Statistical analysis of continuous variables was performed using Student's *t*-test and of dichotomous variables using Chi-square test. P <0.05 were considered significant. Multivariate analysis was also performed using multiple logistic regression analyses to determine associations with the presence of plaques in patients with zero calcium score. All analyzes were performed using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 2000 consecutive patients who undergone CTCA in our hospital between September 2012 and September 2014 were recruited into the study. All the patients were referred by a clinical physician to rule out CAD. CTCA revealed zero calcium score in 385 cases.

Of the 385 cases with a zero CAC score 188 (48.8%) were male and 197 (51.2%) were female. The mean age of males and females were 51.1 ± 11.4 and 54 ± 12 years, respectively. The patients' demographic and baseline data are depicted in Table 1.

In patients with zero CAC, 16 (4/2%) had coronary plaque. Of the cases with noncalcified plaques, 6 (1.6%) had significant coronary artery stenosis (narrowing of more than 50% of the lumen), and 10 (2.6%) had nonsignificant coronary disease (narrowing of <50% of the lumen).

Among the patients, 58 (15/1%) had DM, 120 (31/2%) had HTN, 111 (28/8%) had hyperlipidemia, 121 patients (31/4%) had positive family history of CAD and 29 (7/5%) were smokers.

The prevalence of DM, hyperlipidemia, and smoking was significantly higher in the patients with plaque in comparison with those without a plaque in univariate analysis [Table 1].

Using multivariate logistic regression test with the conditional backward method on the previous data, we showed that DM, hyperlipidemia, and smoking are significantly associated with CAD. DM, hyperlipidemia, and smoking had odds ratios of 5.9, 14, and 32.5 for the development of coronary artery plaques, respectively (predictors of plaque formation are presented in Table 2).

The prevalence of the presence of DM was significantly higher in the patients with significant plaque compared with the patient with nonsignificant plaque (P = 0.035). Other risk factors were not significantly different between the two groups (P > 0.05).

In 10 cases with nonsignificant stenosis, proximal of left anterior descending (LAD) artery was involved in 3 cases and mid-segment of LAD in 2 cases. Furthermore, 3 plaques were located in proximal of the right coronary artery (RCA), and 2 plaques were located in the proximal of left circumflex (LCX) artery.

In 6 cases with significant stenosis, 2 plaques were located in the proximal of LAD, 1 plaque were in the

Table 1: Demographic features and prevalence of cardiovascular risk factors of the patients with or without plaque

Risk factors	Risk factors status	With coronary plaque *n* (%)	Without coronary plaque *n* (%)	*P*
Diabetes mellitus	Negative	9 (56.3)	318 (86.2)	0.001
	Positive	7 (43.8)	51 (13.8)	
Hypertension	Negative	11 (68.8)	254 (68.8)	0.99
	Positive	5 (31.2)	115 (31.2)	
Hyperlipidemia	Negative	4 (25)	270 (73.2)	<0.001
	Positive	12 (75)	99 (26.8)	
Family history of heart disease	Negative	13 (81.3)	251 (68)	0.41
	Positive	3 (18.8)	118 (32)	
Smoking	Negative	11 (68.8)	345 (93.5)	<0.001
	Positive	5 (31.3)	24 (6.5)	
Age	<50	5 (31.3)	165 (44.7)	0.29
	≤50	11 (68.8)	204 (55.3)	
Sex	Male	10 (62.5)	178 (48.2)	0.26
	Female	6 (37.5)	191 (51.8)	

Table 2: Predictors of the presence of noncalcified plaques using multivariate regression analysis

Risk factors	OR	*P*	95% CI	
			Lower limit	Upper limit
DM	5.991	0.008	1.601	22.422
Hyperlipidemia	14.080	0.001	2.910	68.123
Family history of heart disease	0.279	0.114	0.057	1.361
Smoking	32.570	<0.001	5.786	183.343
Age	1.041	0.094	0.993	1.091

OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus mid-segment of LAD, 2 plaques in the proximal of RCA, and 1 plaque in the proximal of LCX.

DISCUSSION

The arrival of electron beam CT in the 1980s provided good temporal resolution to study the coronary arteries.[14] Although, it could not measure the degree of coronary stenosis, it did allow reliable identification of CAC.[15] CAC occurs almost exclusively as a consequence of atherosclerosis and so can be a sensitive marker of the atherosclerotic processes. Calcification does not necessarily concentrate at the site of the maximal stenosis, so cannot be used to diagnose obstructive coronary disease. However, the total amount of calcification can be a valuable marker of the total plaque burden. This burden can be quantified using Agatston score.

Different studies have shown the prognostic importance of coronary artery calcium. In a study of over 25,000 patients, a calcium score of 0 conferred a very low event rate, with a 12-year survival of 99.4%.[16] A meta-analysis of six studies revealed that an increasing CAC score means incremental increases in the relative risk of myocardial infarction or cardiac death at 3–5 years compared to a zero score.[17] CAC scoring is most useful in asymptomatic patients at intermediate risk of disease. The National Institute for Health and Clinical Excellence have suggested that the patients with suspected cardiac chest pain without confirmed CAD in whom the estimated likelihood of CAD is 10–29% (low-to-intermediate risk) should be offered CAC scoring. If the CAC is 0, other causes of chest pain should be considered. If the CAC is 1–400, then 64-slice CTCA should be offered. If the CAC score is >400, invasive angiography should be offered if clinically appropriate.[18,19]

One series has shown that 4% of symptomatic patients with a zero CAC score had significant stenosis at coronary angiography.[20] Other rates reported in literature are as following: 6.5% by Cheng *et al*., 10% by Choi *et al*., 12% by Sosnowski *et al*., and 20% by Ergün *et al*.[21] While, according to Meyer *et al*., study which was conducted on a group of Caucasian patients, the presence of coronary artery stenosis in individuals with zero calcium score is less likely and was calculated as 4 out of 1000.[22] In Almasi *et al*., study performed in Tehran, Iran; 12.1% of the patients with zero CAC score had coronary plaques.[8]

In our study, the prevalence of coronary plaques was 4.2%. This result is approximately consistent with frequencies that reported in previous studies. However, a study reported a frequency of 51% for atherosclerotic plaques in patients with zero CAC score.[13] The differences may be due to ethnical differences of the studies population. The difference of our results with the Almasi *et al*., a study that performed in Iran, could be explained by sample selection difference between two studies. In Almasi *et al*., study, the samples were recruited from patients who were a candidate for invasive coronary angiography that had a higher probability of CAD in comparison with our study patients who were a candidate for CTCA.

Using multivariate logistic regression test, we showed that DM, hyperlipidemia, and smoking are significantly associated with coronary plaques. Predictors of developing atherosclerotic plaques in patients with a zero CAC score have been evaluated in several studies. Büyükterz *et al*., and Rivera *et al*. showed that male gender, DM, and smoking are significant risk factors of developing noncalcified plaques. DM and smoking were reported to be significant risks in studies by Budoff *et al*. and Blaha *et al*. Ueda *et al*. reported DM and hypercholesterolemia as risk factors. Nikolaou *et al*. showed that diabetes, HTN, smoking, and obesity are significant risk factors.[21]

Our study was associated with some limitations that should be mentioned here; first, coronary risk stratification was not performed in participants before inclusion to the study and secondly, information about cardiovascular risk factors was obtained using questionnaire that is not a reliable method. Small sample size and retrospective design of the study are an additional limitation of our study; thus, conducting prospective studies with larger sample size on Iranian population is recommended. On the other hand, noncalcified plaques are more difficult to visualize by radiologists probably due to their low CT numbers. Studies have shown that 64-slice CCTA have a sensitivity ranged from 82% to 95%, and specificity from 95% to 97% for detection of plaques with >50% stenosis in >1.5 mm vessels. However, a sensitivity of about 35–50% have been reported for noncalcified plaques with <50% occlusion.[23] Therefore, using CTCA for detection of plaques is an inevitable limitation of our study.

CONCLUSION

The results of this study reveal that the zero calcium score is accompanied by the low probability of CADs, but does not absolutely exclude the existence of noncalcified plaques. Therefore, performing CTCA in referred patients who are under suspicion for CAD, in the presence of risk factors such as DM, hyperlipidemia, and smoking, even with zero CAC scoring, could prevent adverse cardiovascular events.

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Conflicts of interest

There are no conflicts of interest.

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