Prevalence of noncalcified plaques and coronary artery stenosis in patients with coronary calcium scores of zero

Saud M. Al-Muhaidb[a], Abdul Mohsen M. Aljebreen[a], Zamel A. AlZamel[a,b] and Ahmed Fathala[a]

Objectives **A higher coronary artery calcium score (CACS) is associated with increased coronary artery plaque burden resulting in increased cardiovascular risk. Conversely, the absence of calcium indicates a low risk of cardiovascular events. However, coronary plaque calcification is a late manifestation of atherosclerosis; earlier stages of atherosclerosis present noncalcified plaques (NCPs) A recent study demonstrated that the absence of coronary artery calcification deposit does not preclude obstructive stenosis or the need for revascularization in patients with a high suspicion of coronary artery disease (CAD). Our study aimed to investigate the prevalence of NCP and the severity of coronary artery stenosis in symptomatic patients in our local population who were referred for coronary artery computed tomography angiogram (CCTA) with 0 CACS.**

Methods **A total of 299 patients who had undergone CACS and CCTA, and had scored zero for coronary artery calcium. Patients included had clinically appropriate indications, mainly chest pain with variable severity with no history of CAD. The presence of CAD risk factors, such as diabetes, hypertension, and smoking, was obtained from reviewing patient charts. The CCTA analysis was performed to evaluate for coronary artery stenosis and the presence of NCP. The severity of stenosis was quantified by visual estimation and divided into 0% stenosis, 1–25% stenosis, 26–50% stenosis, and more than 50% stenosis.**

Results **The prevalence of NCP was 6.4% (19 of the 299). Among the 19 patients with NCP, 52.6% had no identified coronary artery stenosis, 26.3% had less than 25%, and 21% had stenosis between 25 and 50%. None had stenosis greater than 50%. There was a strong association between male sex (*P*=0.001), smoking (*P*=0.0.004), hypertension, and NCP (*P*=0.042), but no association was found between NCP and age or diabetes**

Conclusions **In patients with a high clinical suspicion of CAD, the absence of coronary artery calcification does not rule out CAD; up to 6.4% of these patients have early CAD as evidenced by NCP detected by CCTA, and none have more than 50% stenosis, However, future prognostic and long-term follow-up studies are needed to determine prognostic value of NCP in patients with 0 CACS. *Coron Artery Dis* 32: 179–183 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.**

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[a]Department of Radiology, Cardiothoracic Imaging and Nuclear Medicine Section, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia and [b]Chest disease hospital, Al Sabah Medical Specialized area Al shuwaikh, Kuwait

Correspondence to Ahmed Fathala, MD, Department of Radiology, Cardiovascular Imaging and Nuclear Medicine Section, King Faisal Specialist Hospital and Research Center, MBC#28, PO Box 3354, Riyadh, Saudi Arabia
Tel: +966552532402; fax: +966144224841; e-mail ahm35799@hotmail.com

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Introduction

Assessment of coronary artery calcification with electron-beam computerized tomography or multidetector computed tomography (CT) is performed to evaluate atherosclerotic disease [1,2]. The coronary artery calcium score (CACS) predicts cardiovascular events independently of standard coronary artery disease (CAD) risk factors [3–5]. A higher CACS is associated with increased coronary artery plaque burden resulting in increased cardiovascular risk. Conversely, the absence of calcium indicates a low risk of cardiovascular events [6,7]. However, coronary plaque calcification is a late manifestation of atherosclerosis [8]; earlier stages of atherosclerosis present noncalcified plaques (NCPs) and plaques with a mixed composition containing extracellular lipid and fibrous tissue [9,10]. Such plaques are also prone to rupture and thrombosis causing acute coronary syndrome [11,12]. A recent study demonstrated that the absence of coronary artery calcification deposit does not preclude obstructive stenosis or the need for revascularization in patients with a high suspicion of CAD [13]. Our study aimed to investigate the frequency of NCP and the severity of coronary artery stenosis in symptomatic patients in our local population who were referred for coronary artery computed tomography angiogram (CCTA) and who scored zero for coronary artery calcium.

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Methods

Study population

Between January 2017 and February 2019, 299 patients were selected for our study population who had undergone CACS and CCTA, and had scored zero for coronary artery calcium. Patients included had clinically appropriate indications, mainly chest pain with variable severity. To rule out obstructive CAD, patients with a history of coronary artery bypass grafting, percutaneous coronary intervention, or positive stress tests were excluded, as were patients with inadequate image quality. The presence of CAD risk factors, such as diabetes, hypertension, and smoking, was obtained from reviewing patient charts. Hypertension was defined as the use of antihypertensive medication or known but untreated hypertension. Diabetes mellitus was defined as fasting blood glucose of more than 126 mg/dL (7.0 mmol/L) or the use of hypoglycemic medications. Current smokers and those who quit smoking less than 30 days before examination were included as smokers; the rest were characterized as nonsmokers. Other CAD risk factors, such as family history or hypercholesterolemia were not included because these factors were not available in many patients' charts. The study was conducted in accordance with hospital research ethics; as it was a retrospective clinical study using anonymized data, it did not require specific ethics approval.

Coronary computed tomography angiogram and detection of noncalcified plaques

Coronary CTA results were collected retrospectively using ECG-gated or prospectively ECG triggered protocols from either of two scanners; Siemens Healthcare, Erlangen, Germany or GE Healthcare, Waukesha, Washington, USA. The image analysis was performed on a cardiac workstation (Advantage Window, GE Healthcare) by two independent, experienced cardiac radiologists; in case of discord, the final interrelation was reported by consensus. The CTA analysis was performed per coronary artery segments using the protocol of the Society of Cardiovascular Computed Tomography [14]; for each coronary segment, the reader deemed the image quality adequate to evaluate for coronary artery stenosis and the presence of NCP. Subjects with nonevaluable segments were excluded from the study. The severity of stenosis was quantified by visual estimation and divided into 0% stenosis, 1–25% stenosis, 26–50% stenosis, and more than 50% stenosis. NCP was defined as any discernible structure that could be assigned to the coronary artery wall, with a CT number below the contrast-enhanced coronary lumen but above the surrounding connective tissue and that could be identified in at least two independent planes [15].

Statistical analysis

Data were analyzed using SPSS software, version 16 (IBM Corporation, Armonk, New York, USA). Simple descriptive analysis in the form of means and SDs was used for quantitative data. Qualitative data were described in numbers and percent distribution. A comparison was done using the chi-square test for categorical variables. Association with risk factor was expressed using odds ratio and a 95% confidence index. The level of significance was set at $P < 0.05$.

Results

Population demographics and coronary artery disease risk factors

The study population consisted of 299 individuals with typical and atypical chest pain and high clinical suspicion of CAD. Of the total study population, 174 (58.2%) were female and 125 (41.8%) were male. The mean age was 52.8 ± 10 years; ages were grouped into under 50 years and over 50 years. Only 6% of the study population were smokers; 51.2% were hypertensive, and 43.5% were diabetics, as shown in Table 1.

Frequency and distribution of noncalcified plaque and coronary artery stenosis

The prevalence of NCP was 6.4% (19 of the 299). The coronary artery with the highest NCP was the left main coronary artery (47%), followed by the left anterior descending artery (36.8%), right coronary artery (10.5%), and the percentage for multiple coronary arteries was only 5.3%. Among the 19 patients with NCP, 52.6% had no identified coronary artery stenosis, 26.3% had less than 25%, and 21% had stenosis between 25 and 50%. None had stenosis greater than 50% (Table 2).

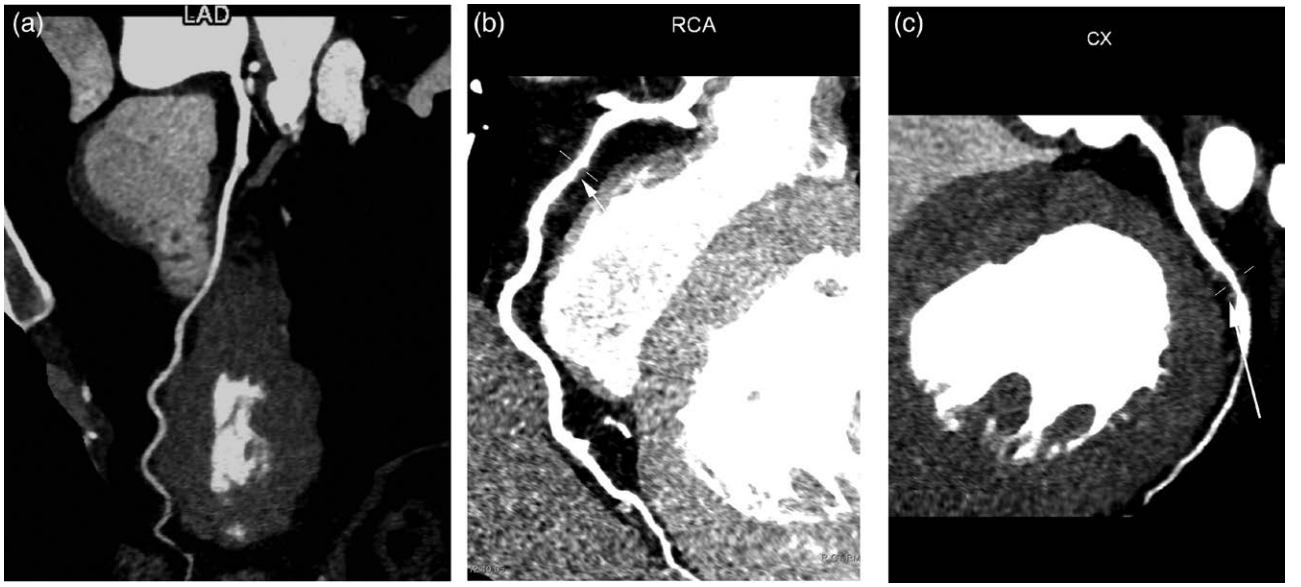
Demographics of patients with and without noncalcified plaques

Fifteen of the 125 male patients (12.0%) had NCP, while only 4 of 174 female patients (2.3%) did. This tendency of NCP to be higher in males is statistically significant ($P = 0.001$). Of the 18 smokers, 4 had NCP (22.2%), compared to only 15 of the 266 nonsmokers (5.3%) had NCP; the positive correlation between smoking and NCP is significant ($P = 0.004$). There was a strong association between hypertension and NCP ($P = 0.042$), but no association was found between NCP and age ($P = 0.237$) or diabetes ($P = 0.725$) (Table 3).

Discussion

We found the prevalence of NCP in patients with undefined chest pain syndrome with zero CACS to be 6.4% in our cohort. Most of these patients had mild (under 50%) stenosis. Detection of these plaques noninvasively by CCTA would probably improve the CAD risk stratification of these patients with zero CACS, and more importantly, it indicates that patients with zero CACS do have early CAD. This relatively high prevalence of NCP is partly due to the high sensitivity of CCTA for plaque detection. The prevalence of subclinical coronary atherosclerosis in the general population is unknown but is likely higher than the prevalence of NCP [16]. To our knowledge, this is the first study in the literature to

Fig. 1



Three multiplanar reformatting images from coronary computed tomography angiography of three different patients with (a) no stenosis, (b) less than 25% stenosis, and (c) 25–50% stenosis. LAD; left anterior descending artery, RCA; right coronary artery, LCX; left circumflex artery.

Table 1 Patient characteristics, total study population (*N*) 299

	Number	Percent
Sex		
Female	174	58.2%
Male	125	41.8%
Age/years, means±SD	52.8±10	
Age <50 years	100	33.4%
Age >50 years	199	66.6%
Smoking		
Yes	18	6%
No	281	94%
Hypertension		
Yes	153	51.2%
No	146	48.8%
Diabetes		2 (1.5%)
Yes	130	43.5%
No	169	56.5%

Table 2 Frequency and coronary artery distribution and stenosis of noncalcific plaques (*N*) 299

Noncalcific plaques	Number	Percent
Present	19	6.4%
Absent	280	93.6%
Coronary artery distribution of the noncalcific plaques		
LAD	7	36.8%
RCA	2	10.5%
LM	9	47.4%
Multiple sites	1	5.3%
Coronary artery stenosis in patients with noncalcific plaques, *N*=19 patients		
Normal (no stenosis)	10	52.6%
Less than 25%	5	26.3%
25–50% Stenosis	4	21.1%
More than 50%	0	0%

LAD, left anterior descending artery; LM, left main; RCA, right coronary artery.

evaluate the presence of NCP in our local population. There are few similar studies that investigate the prevalence and prognosis of NCP in different patient populations with different demographics. Cheng *et al.* found that the incidence of NCP in patients without coronary artery calcification was 2.7% and a 0.5% incidence of significant stenosis [17]. The prevalence of NCP varies widely from one study to another; for example, another study reported that up to 51% of patients with zero CACS have NCP; 3.7% of those patients had moderate stenosis and 1.5% had severe stenosis [16]. In contrast, another study reported that NCP was detected in 29.8% of symptomatic patients [18]. In addition to the prevalence of NCP in patients with zero CACS, in this study, we looked at the demographic differences of patients with and without NCP. NCP is more common in males, in patients with hypertension, and active smokers, but there was no association between NCP and age or the presence of diabetes, therefore, patients with risk factors such as male sex, smoking, and hypertension may benefit from CCTA to discover NCP. If present, these patients would likely benefit from aggressive risk factor modification

The prognosis of NCP in individuals with zero CACS has been investigated in prior studies. Motoyama *et al.* reported that NCP is a risk factor for future acute coronary syndrome in patients with known or suspected CAD [19]. Another study found that NCP was an independent predictor with incremental prognostic value for acute coronary syndrome [20].

In addition, CCTA can identify imaging correlation of pathologically determine vulnerable plaques, such as thin-cap fibroatheroma and necrotic core. Studies using

Table 3 Demographics of patients with and without plaques, total study population (*N*) 299

		Plaques		
		No (n=280)	Yes (n=19)	P value
Sex				
Female	*N*	170 (97.7%)	4 (2.3%)	0.001
Male	*N*	110 (88.0%)	15 (12.0%)	
Age				
<50 years	*N*	96 (96.0%)	4 (4.0%)	0.237
≥50 years	*N*	184 (92.5%)	15 (7.5%)	
Hypertension				
No	*N*	141 (96.6%)	5 (3.4%)	0.042
Yes	*N*	139 (90.8%)	14 (9.2%)	
Diabetes				
No	*N*	159 (94.1%)	10 (5.9%)	0.725
Yes	*N*	121 (93.1%)	9 (6.9%)	
Smoking status				
No	*N*	266 (94.7%)	15 (5.3%)	0.004
Yes	*N*	14 (77.8%)	4 (22.2%)	

CCTA have demonstrated as association between four major plaque characteristics and future of acute coronary syndrome: positive remodeling, low attenuation plaque, spotty calcification, and napkin ring sign [21,22]. Studies have shown that CCTA has an excellent accuracy to detect plaques compared with the gold standard intervenes ultrasound, with an area under the curve for receiver operating characteristic analysis of 0.94, a sensitivity of 90%, and specificity of 92% [23].

Our study has several limitations. We did not include asymptomatic patients but only symptomatic patients with a high clinical suspicion of CAD, so the prevalence of NCP in asymptomatic patients cannot be determined based on our data. The possible benefit of detection of NCP by CCTA should be weighed against the potential hazard of radiation delivered by CCTA. CCTA probably underestimates the extent of plaque burden; if intravascular ultrasound had been performed on these patients, an even greater degree of NCP may have been detected. Finally, we did not conduct long-term follow-up on the patients with NCP detected by CCTA to investigate the impact of NCP on cardiovascular events.

In summary, in patients with a high clinical suspicion of CAD, the absence of coronary artery calcification does not rule out CAD; up to 6.4% of these patients have early CAD as evidenced by NCP detected by CCTA, and almost 50% of those patients have less than 50% stenosis. The presence of NCP is more prevalent in male patients, patients with hypertension, and active smokers. Although the CACS does add prognostic value to standard CAD risk factors, direct imaging of coronary artery wall by CCTA may be helpful in certain groups of patients to identify NCP and guide therapy. Whether the presence of NCP in patient with 0 CACS indicates increased cardiovascular event risk, and whether the detection of NCP beyond coronary calcification add any benefit in CAD risk stratification remain to be answered by future prognostic and long-term follow-up studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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