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ASSESSMENT OF ATHEROMATOUS PLAQUE BY MULTISLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY IN PATIENT WITH ZERO CALCIUM SCORE

By

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ABSTRACT

Background: Zero calcium score (CS) is associated with low risk for mortality but not low risk for acute coronary disease developments. Soft plaque is vulnerable to fissuring and rupture.

Objective: To evaluate the frequency of coronary atheromatous plaque in patients with zero CS and the associated risk factors.

Patients and methods: This was a cross-sectional, retrospective study with 235 consecutive individuals with zero CS at Islam Cardiac Center from August 2019 to August 2020. A significance level of 5% was adopted.

Results: The frequency of atheromatous plaque in coronary arteries in 235 patients with zero CS was 26.81% (63 individuals). In the subgroup of atheromatous plaque with zero CS, mean age was 58±28 years, 40 (63.5%) were females, 29 (46.03%) hypertensive, 33 (52.38%) diabetics, 31 (49.2%) dyslipidemias, 12(19.05% had family history of premature coronary artery diseases (CAD), 20 (31.75%) smokers and body mass index (BMI) was 27.64±1.5. Fifteen patients (23.8%) had obstructive plaques (> 50%).

Conclusions: The frequency of atheromatous plaques with zero CS was high. So, absence of calcification does not exclude the presence of plaques, one fourth of them were obstructive, especially with aged individuals.

Keywords: Cardiovascular Diseases, Plaque, Atheromatous, Coronary Artery Disease, Calcium Score; Risk Factors.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality all over the world. Many investigations used for diagnosis and risk stratification of CAD patients that determine the plan for management of those patients *(Knuuti et al., 2019).*

In the era of advanced technology with plenty of available investigation tools, the patients walk in a dilemma of medical care. In cardiology practice, the big challenge is to choose the appropriate tool for the target patient especially those with subclinical CAD *(Mampuya, 2012).*

Coronary computed tomography angiography (CCTA) is a non-invasive anatomical tool with high diagnostic capability in detecting atheromatous plaques (either obstructive or non-obstructive) compared to the gold standard invasive coronary angiography.

CCTA can determine the extent of plaque calcification through calcium scoring (CS) which is a rapid simple screening test that may add also information of atheroma composition. Also, it can be estimated using single photon emission tomography (SPECT) machines during myocardial perfusion study *(Gabriel et al., 2018).*

Coronary calcification, assessed by CS is used for risk stratification of cardiac patient but those with zero CS still own the chance to have an atherosclerotic plaque, those plaques without calcification but lipid core and fibrous cap is vulnerable one with possibility of plaque fissuring and rupture and acute coronary syndrome development. Severe coronary atherosclerosis with multiple obstructive plaques may be present in coronary vessels with zero calcium score. So, zero CS is not a good negative test especially in those having atheromatous plaques *(Stefanadis et al., 2017).*

The aim of this work was to evaluate the frequency of coronary atheromatous plaque in patients with zero CS and the associated risk factors.

PATIENTS AND METHODS

This study was a cross-sectional retrospective study carried out from August 2019 to August 2020. Patients were consecutively selected and all subjected to CCTA by referral from their physicians for diagnostic imaging in Islamic Cardiac Center, Al-Azhar University.

History of cardiovascular risk factors were collected from each participant before the test in a special form. Patients with zero calcium score and intermediate risk for coronary artery disease according to Diamond and Forrester method were included in the study *(Lavenburg et al., 2019).*

Patients were excluded if they underwent percutaneous or surgical myocardial revascularization, previous history of acute coronary syndrome, previous stroke or peripheral vascular disease, atrial fibrillation or frequent extra systole, decompensated heart failure, renal impairment and inadequate breath holding.

CS and CCTA of coronary arteries were performed using a 160-slice scanner of Aquilion Prime 160™ (Toshiba™ Medical Systems Corporation, Otawara, Japan). The patients were on ivabradine 5 mg twice daily for at least 3 days before the test. Heart rates of all patients were determined 1 h before examinations. If heart rate was ≥ 65 bpm, the patient was orally administered 50 mg of oral beta blocker atenolol except those with contraindications to beta-blockers. A 0.5 mg sublingual dose of nitroglycerin was administered just before the scan. In each patient 60 mL of iodinated contrast followed by 50 mL of saline solution was injected. Contrast material administration was controlled by test bolus in the ascending aorta. The scan delay was 12 s. Images were reconstructed immediately after completing the scan to identify motion-free coronary artery artifacts. The reconstructed CT image data were transferred to a computer workstation for post-processing, including axial, multiplanar reformat, maximum intensity projection. In all individuals, irrespective of the image quality, every arterial segment was scored in an intent-to-diagnose fashion.

CS analysis was carried out with non-contrast CT using a longitudinal scan coverage from the level of the tracheal bifurcation to the superior border of cardiac silhouette, this including the whole diaphragm to evaluate the whole cardiac area.

The study was done in two phases: 1st CS was done by the Agatston score. Coronary calcification was defined by the presence of a lesion, its area greater than 1 mm2, and with the peak intensity equal to or greater than 130 Hounsfield Units (HU). The software automatically identify this and mark it with colors *(Gabriel et al., 2018).*

In the second phase, CCTA was done if calcium score is zero. Field of view (FOV) construction, voltage 120 kv and 400 miliamperes. 60 mL iodinated contrast media was administered intravenously through large bore cannula to patients still positioned on the table followed by 50 of saline.

Images were reconstructed immediately after completing the scan to identify motion-free coronary artery artifacts. The reconstructed CT image data were transferred to a computer workstation for post processing. In all individuals, irrespective of the image quality, every arterial segment was scored in an intent-to-diagnose fashion *(Kim et al., 2015).*

The presence of atheromatous soft plaque was examined only in vessels with a luminal diameter larger than 2 mm, divided into 16 segments. The segment involvement score (SIS) was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16) *(Gabriel et al., 2018).*

Statistical analysis:

Quantitative variables were described as mean and standard deviation. Qualitative data were expressed as frequency and parentage. Normality of the sample were ssessed by Kolmogorov-Smirnov test. According to data normality, the Student’s t-test was used for independent groups. The chi-square test was used for categorical variables. The data were analyzed statistically using IBM-SPSS-22 (Statistical Package for the Social Sciences version 22). The test was considered significant if the probability (p-value) was less than 0.05.

RESULTS

In the period of the study, 235 patients had Zero Calcium score. Age of patients was 56.87±10.22 years, 66% were female, 47.7% hypertensive, 51.9% diabetics, 48.9% dyslipidemias, 35.7% smokers, and 22.6% family history of premature CAD with BMI was 27.59±1.56 **(Table 1)**.

Table (1): Clinical characters of the studied population

Variables	Number
Age (years)	56.87±10.22
Female sex (%)	155 (66%)
Hypertension (%)	112 (47.7%)
Diabetes mellitus (%)	122 (51.9%)
Dyslipidemia (%)	115 (48.9%)
Family history of CAD (%)	53 (22.6%)
Smoking (%)	84 (35.7%)
Body mass index (kg/m^2)	27.59±1.56

CAD: coronary artery disease.

Atheromatous plaques were present in 63 patients (26.81%). The mean age of them was 58.28±10.05 years, 63.5% were females, 46.03% hypertensive, 52.38% diabetics, 49.2% dyslipidemias, 31.75% were smokers, 19.05% had history of family history of premature coronary artery disease and BMI was 27.64±1.5. No significant difference between those with plaques and without plaques regarding risk factors part from significant old age in patients with zero CS and atheromatous plaques. Presence of obstructive lesions more than 50% of the vessel lumen present in 23.8% (15/63) of cases with atheromatous plaques (6.4% of total population with zero calcium score). The distribution of obstructive plaques were 10 patients had one segment, 2 patients had two segments and 3 patients had more than two segments stenosis. While non-obstructive lesions in 76.2% (48/63) of patients, distributed as the following: a- in one segment 19 patients, b- two segments in 21 patients and c- more than two segments in 8 patients **(Table 2)**.

Table (2): Clinical characters of patients according to atheromatous plaques presence

Groups / Parameters	Atheromatous plaques (n=63)	Zero Calcium score without plaques (n=172)	P value
Age (years)	**58.28±10.05**	52.90±11.10	0.001
Female sex (%)	**40 (63.5%)**	**115 (66.86%)**	>0.05
Hypertension (%)	**29 (46.03%)**	**83(48.26%)**	>0.05
Diabetes mellitus (%)	**33(52.38%)**	**89(51.74%)**	>0.05
Dyslipidemia (%)	**31(49.2%)**	**84(48.84%)**	>0.05
Family history of CAD (%)	**12 (19.05%)**	**41(23.84%)**	>0.05
Smoking (%)	**20 (31.75%)**	**64(37.21%)**	>0.05
Body mass index (kg/m^2)	27.64±1.50	27.44±1.71	>0.05

The most affected segments in the distribution were of the left anterior descending artery (32/63), while the least affected vessel is the left circumflex in 11 segments only, and no left main reported affection. Two cases were presented in **Figure (1& 2)**.

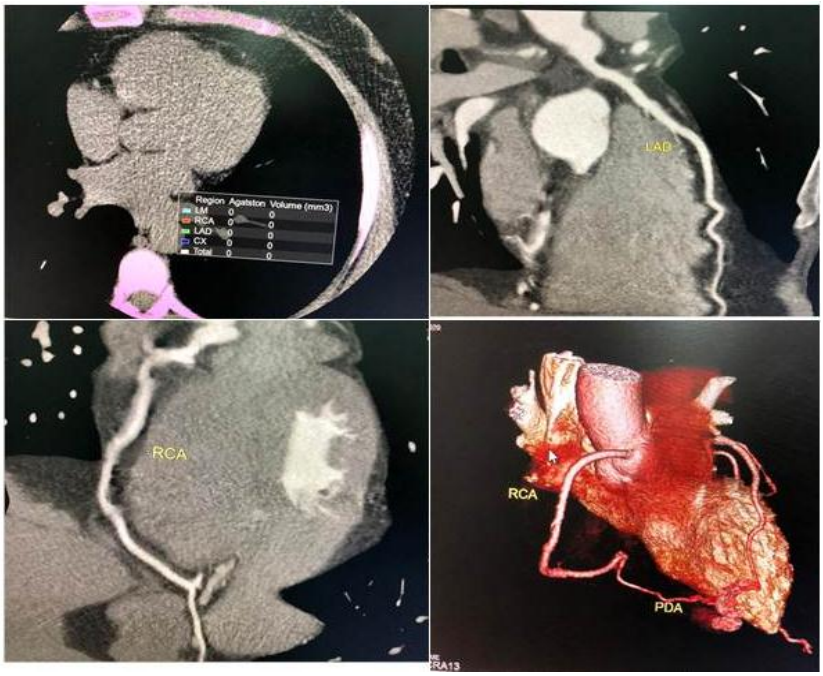

Figure (1): Calcium score zero in a patient with non-obstructive atheromatous soft plaque in distal LAD and proximal RCA.

Figure (2): Calcium score zero in a patient with an obstructive atheromatous soft plaque in mid LAD.

In comparing lipid profile between those with atheromatous plaques and without plaques, no significant difference between both groups although slight elevation in those with plaques **(Table 3)**.

Table (3): Lipid profile of patients according to atheromatous plaques presence.

Groups / Parameters	Atheromatous plaques (n=63)	Zero Calcium score without plaques (n=172)	P value
TC (mg %)	219.61±36.82	213.35±46.56	>0.05
LDL (mg %)	163.64±39.80	152.48±37.94	<0.05
HDL (mg %)	39.94±10.26	42.03±10.19	>0.05
TG (mg %)	172.84±30.46	165.60±24.73	>0.05
Risk ratio	4.41±1.62	3.94±1.58	<0.05

DISCUSSION

With the growing development of modern technology in the last decade, the role of CCTA is increasing and the role of CS in preventive cardiology is expanding *(Piepoli et al., 2016).* Lack of calcification of coronary tree associated with low vascular aging compared to the same coronary state with calcification and zero CS was reported to have warranty against mortality in western and Asian trials varied between 5 to 15 years *(Pechlivanis et al., 2020).* Zero calcium score does not mean no atherosclerosis, instead it can be used as risk stratification method. Atherosclerosis process is ended by calcification which is protective to the plaque, before calcification atherosclerosis process occur with vulnerable plaque prone to fissuring and development of acute coronary syndrome as proved by autopsy studied and optical coherence tomography (OCT) and intravascular ultrasound study (IVUS) *(Merghani et al., 2017).* Also, zero calcium study is not stationary process with follow up revealed increase of calcification and increased risk *(Shen et al., 2020).*

The main finding of this study was the significant presence of atheromatous plaques (26.81%) of those patients with zero calcium score. One fourth of them (6.4%) were obstructive (equal or more than 50% stenosis). No significant difference of risk factor predict the atheromatous plaque presence except old age and slight elevation of low density lipoprotein cholesterol (LDL-C) which are predictors of atheroma development.

When follow the previous studies, there is lack of agreement about the prevalence with wide range due to lack of fixing variables like symptoms, risk factors and indication of the test. This made some unavoidable bias. *Gabriel et al. (2018)* found the plaque were 9.3% but they choose obstructive coronary plaque (≥ 50% reduction of luminal diameter) in 4 different centers with different machines. *Moradi and Varasteh (2016)* stated that 4.1% of patients with zero CS had atheromatous plaque at CCTA.

Villines et al. (2011) in the CONFIRM study found that 13% for plaques showed less than 50% obstruction and 3.5% showed greater than 50% obstruction. Also, *Kim et al. (2015)* in their multicentric cohort study (a CORE64 sub-study) confirmed that 19% of zero CS patients had stenosis ≥50% but when followed they found that 13% of them required revascularization. So, zero

calcium score does not exclude the need for revascularization later on.

On the other hand, when choose the candidates presented with acute chest pain present in the emergency departments the prevalence may reach up to 39% in patients with zero calcium score *(Pursnani et al., 2015)*, although these samples is different from outpatient services of stable chest pain either typical or atypical.

In this study, the variables of predisposition to plaque were aging and LDL level which was different from literature studies as the samples were heterogeneous in between different studies with many ethnic and risk factor variations. So, trials found alcohol intake is a predictor which was fortunately not present in our study populations due to our Islamic and social issues.

Previous studies on obesity had suggested its protective role for CAD (obesity paradox) that not appear in our study, but this could be explained by not use abdominal obesity with accompanied subcutaneous fat in concern rather than BMI *(Parsa and Jahanshahi, 2015)*. Inclusion of asymptomatic individuals may change the percentage of atheromatous plaque.

The data on risk factors apart from lipid profile were obtained by questionnaires from the patients and abdominal obesity not taken into concern. Also, no study of the effect of long standing statin on atheromatous plaques calcifications and complications.

CONCLUSION

The prevalence of atheromatous plaques is high in patients with zero calcium score, and one fourth of them obstruct more than half of luminal diameter. Absence of coronary calcification does not rule out coronary atherosclerosis especially in old age and high LDL levels. Instead, it made them vulnerable to complications and primary prevention using statins in them may have a role.

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تقييم اللويحة الدهنية للشرايين التاجية بواسطة التصوير المقطعي متعدد الشرائح في مرضى درجة الكالسيوم الصفرية

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خلفية البحث: درجة الكالسيوم الصفرية مرتبطة بمخاطر وفاة منخفضة ولكن ليس الخطر منخفضًا لتطورات مرض الشريان التاجي الحاد فاللويحة الدهنية تكون أكثر عرضة للتشقق والتمزق.

الهدف من البحث: تقييم تواتر اللويحة الدهنية فى الشرايين التاجية عند المرضى ذوى درجة الكالسيوم صفر و علاقة ذلك بعوامل الخطورة.

المرضى وطرق البحث: تم فحص كل المرضى المترددين على المركز الإسلامى للقلب بجامعة الأزهر لعمل التصوير المقطعي للشرايين التاجية متعدد الشرائح ودراسة وجود لويحات دهنية في مرضى درجة الكالسيوم الصفرية فى الفترة من أغسطس 2019 إلى أغسطس 2020 ووجد 235 فردًا متتاليًا تنطبق عليهم هذه الشروط.

نتائج البحث: كان تواتر اللويحة الدهنية في الشرايين التاجية في 235 مريضًا من ذوى درجة الكالسيوم الصفرية بما يمثل26.81٪ (ربعهم من ذوى التضيق الشديد للشرايين التاجية) وكان متوسط العمر 58 ± 28 عاماً، 63.5 ٪ من الإناث، 46.03 ٪ يعانون من ارتفاع ضغط الدم، 52.38 ٪يعانون من مرضى السكرى، 49.2 ٪ يعانون من ارتفاع الدهون بالدم، 19.05٪ كان لدبهم تاريخ عائلي لأمراض الشرايين التاجية المبكرة، وكان 31.75 ٪ من المدخنين ووجد أن مؤشر كتلة الجسم كان 27.64 ± 1.5.

الإستنتاج: كان تواتر اللويحات الدهنية للشرايين التاجية مع درجة الكالسيوم الصفرية مرتفعًا. لذا فإن عدم وجود التكلس لا يستبعد وجود لويحات فى الشرايين التاجية خاصة مع كبار السن.