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Research Article

Convergence between Severity of Coronary Artery Disease and Mitral Annular Calcification

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1. Abstract

1.1. Background: There is a well-established link between coronary artery calcium (CAC) score on computed tomography and the severity of coronary atherosclerosis. Cardiovascular events and mitral valve dysfunction are related to mitral annular calcification (MAC).

1.2. Objectives: This study aimed to detect the relationship between MAC detected by TTE and coronary calcium score (CCS) and the relation between MAC and extent of coronary artery disease (CAD) by computed tomography (CT).

1.3. Methods: This prospective cross-sectional study comprised 100 patients with symptoms of intermediate likelihood stable CAD and indicated for coronary CT angiography according to ESC guideline. Study participants were categorized into three main groups where Group I included: 50 patients without mitral annular calcification (control group). Group II: included 50 patients with mitral annular calcification. Then the participants of group II were sub-grouped into IIa group which included patients with mild MAC and group IIb which included patients with moderate to severe MAC.

1.4. Results: There was significant difference between 3 studied groups in ischemic heart disease (IHD) detected by electrocardiogram, calcium score, type of atherosclerotic CAD. In addition, MAC score is a good predicator for obstructive CAD (AUC =0.830, 95% CI =0.636 - 0.946, p value <0.001), with 100% sensitivity and 61.54% specificity. Coronary artery calcium (CAC) score is a good predicator for obstructive CAD (AUC =0.775, 95% CI =0.574 -0.912, p value =0.009), with 100% sensitivity and 61.54% specificity. Multivariate logistic regression showed that MAC was a good predictor for the presence of CAD (p =0.008).

1.5. Conclusions: We discovered a strong connection between MAC and CAC and higher CAD burden. These data demonstrate that the existence of MAC is an indication of atherosclerosis instead of simply a degenerative alteration in the mitral valve.

2. Keywords: Mitral Annular Calcification; Coronary Calcium Score; Coronary Artery Disease; Atherosclerosis

3. Introduction

Fibrous degenerative calcification of the mitral valve support ring over a long period of time, known as mitral annular calcium (MAC), is common in females and the geriatrics [1]. MAC has been proposed as a sign of widespread atherosclerosis and as a tool for identifying coronary artery disease [2]. MAC risk factors have been studied in a number of epidemiological studies. Age, smoking, obesity, and serum phosphate were found to be similar factors for calcific aortic valve disease. Significant differences have also been discovered, with MAC indicating a predominance of women and a greater relation to chronic kidney illness and mineral metabolism deregulation. Although a relation to low bone mineral density (BMD) has been hypothesized, it has yet to be established. Despite several studies into risk factors for incidence of MAC and prevalence, there have been no research on risk factors that influence disease activity to yet [3]. It has not been adequately researched if there is a link between the presence of MAC and CAC on a CT. There is a considerable positive link between severe MAC and CAC in both males and females, according to the limited research that was conducted. Mild MAC, on the other hand, has not showed the same link [4]. CAC seems to have a pattern comparable to coronary heart disease in terms of prevalence, with substantial increase in prevalence with age and significantly higher prevalence in males than in females [5]. Traditional coronary risk factors have been linked to coronary calcium. According to research, MAC is a circulatory system expression of widespread atherosclerosis [6]. Atherosclerosis is linked to deposits of calcium in the circulatory system. 2-dimensional transthoracic echocardiography (TTE), similar Computed Tomography (CT), may identify cardiac deposits of calcium and is a low-cost, noninvasive,

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portable, and nonradioactive technology. Coronary computed tomography is used to assess the coronary arteries calcium score and the semi quantitative scores of valvular calcium to determine an individual's risk of coronary artery disease [7]. A relation between MAC and calcifications in the cardiovascular system as measured by several modalities such as CT, echocardiography, and traditional chest x-ray film, as well as cardiovascular disease (CVD) risk factors, has also been proposed [8]. According to current research, cardiovascular calcification is a significant indicator of CAD presence [9]. The goal of this study was to detect the relation between MAC detected by TTE and CCS and the relation between MAC and extent of coronary artery disease by CT.

4. Patients and Methods

This prospective cross-sectional study comprised 100 patients presented with symptoms of intermediate likelihood stable CAD and indicated for coronary CT angiography according to ESC guideline who were recruited from the outpatient clinic of the Cardiology Department, Faculty of Medicine, Al-Azhar University, Egypt, between February 2021 to October 2021. All procedures involving human volunteers in this investigation were carried out in conformity with ethical guidelines of Al-Azhar University's ethical committee and its later modifications or similar ethical standards and an informed written consent were taken after informing the patients about the procedure. The exclusion criteria were age less than 30 years and more than 60 years, dialysis, balloon angioplasty, heart valve replacement, history of coronary bypass surgery, defibrillator implantation, pacemaker, or any other cardiac surgery, hyperparathyroidism, poor Echo-window, congenital heart disease with Rh heart disease, aortic valve stenosis, Rh valve disease, rhythm other than sinus, and contraindications for multi-slice computed tomography such as pregnancy, known allergy to iodinated contrast agent, and renal insufficiency. Study participants were categorized into two main groups where Group 1 included: 50 patients without MAC. Group 2: included 50 patients with MAC. Then the participants of group 2 were sub-grouped into IIa group which included patients with MAC and group IIb which included patients with moderate to severe mitral annular calcification. All patients included in this study were subjected to complete demographic and medical history such as hypertension, diabetes mellitus, tobacco use, CAD family history, and hypercholesterolemia. Full physical examination included general and cardiac examination. Routine Laboratory assessment such as (renal function test, parathormone level, serum calcium level, serum low density), lipid profile, echocardiography, ionized Ca, parathormone level, free T4 were also performed as well as twelve lead electrocardiograms (ECG) for detection of lipoprotein rate and rhythm and ischemic ECG. A strong echo-producing structure at the confluence of the atrioventricular groove and posterior mitral leaflet was included in the TTE criteria for MAC. MAC was categorized from mild to severe, considering its thickness and length. MAC was characterized as intense echocardiography producing structure situated at the mitral section of the atrioventricular section and posterior mitral leaflets in the parasternal long axis view. MAC is measured in millimeters from the leading anterior to the trailing posterior edge and quantified as mild < 4 mm, moderate to severe > 4mm considering its thickness. MAC - (0-3) Score: (0)- Normal echogenicity. (1)- Mild calcification (thickness <2 mm and length <5mm). (2)- Moderate calcification (thickness ≥2 mm and length ≥5mm). (3)- Severe calcification (Shadowing). Cardiac computed tomography (CT): Due to a suspicion of CAD, all patients underwent a cardiac CT scan, which included calcium scoring and coronary CT-angiography (CTA). The CT scans were done using a 160-slice CT scanner (Toshiba - Japan). Prior to data collection, Propranolol was gradually given orally to achieve a heart rate of ≤ 70 beats per minute.1. The Agatston score was measured on a dedicated workstation. 2.Prospectively ECG-triggered axial acquisition mode was used to perform coronary CTA in patients with a regular heart rate. 3.CAC score was calculated. 4. CAD was studied in the form of presence or absence of coronary artery disease (>70%CAD). a. Localization of arterial affection. b. Number of vessels affected. Patients with mitral valve stenosis, prosthetic valves, rheumatic valvular disease, a history of MI, PIC, CABG.

4.1. Statistical Analysis

Collected data were statistically analyzed using SPSS. The median and range were used to represent non-parametric data, whereas the mean and standard deviation were used to represent quantitative parametric data (SD). Qualitative data was expressed as frequency and percentage. Data were handled using ANOVA, independent sample t test, Mann-Whitney U test and Chi-square tests for statistical analysis. The independent variables in patients with MAC and CAD were determined using multivariate logistic regression analyses. P value ≤ 0.05 was considered statistically significant.

5. Results

All patient's characteristics were insignificantly different among the three groups (Table 1).

IHD detected by electrocardiogram was significantly different among the three groups (Table 2).

Calcium score was significantly different among the three groups; worse with moderated to severe than mild MAC and in mild than control (P<0.001) (Table 3).

Regarding the type of atherosclerotic CAD among the studied groups, there was a significant difference in number of obstructive CAD among the studied groups. (p <0.001) (Table 4).

CAC score is a good predicator for obstructive CAD (AUC =0.775, 95% CI =0.574 -0.912, p value =0.009). with 100% sensitivity and 61.54% specificity (Figure 1).

MAC score is a good predicator for obstructive CAD (AUC =0.830, 95% CI =0.636 - 0.946, p value <0.001). with 100% sensitivity and 61.54% specificity (Figure 2).

MAC is a good predictor for the presence of CAD. (p =0.008) (Table 5).

Table 1: Patient's characteristics among the three groups.

		Control (n = 50)	Mild (n = 21)	Moderate to severe (n = 29)	P value
Age (years)	**Mean ± SD**	51.18 ± 8.97	49.29 ± 9.16	51.28 ± 6.94	0.651
	Range	30 – 75	30 – 60	35 - 60	
Weight (kg)	**Mean ± SD**	86.92 ± 10.28	86.95 ± 11.89	81.52 ± 11.00	0.082
	Range	66 – 110	68 – 108	60 - 99	
Sex	**Male**	40 (80.00%)	15 (71.43%)	16 (55.17%)	0.064
	Female	10 (20.00%)	6 (28.57%)	13 (44.83%)	
Smoking		21 (42.0%)	9 (42.86%)	6 (20.69%)	0.125
Family history		3 (6.0%)	1 (4.76%)	2 (6.9%)	0.952
Hypertension		26 (52.00%)	8 (38.10%)	11 (37.93%)	0.372
DM		22 (44.0%)	6 (28.57%)	13 (44.83%)	0.427
Hypercholesterolemia		25 (50.0%)	12 (57.14%)	11 (37.93%)	0.375
Hypertriglyceridemia		18 (36.00%)	6 (28.57%)	7 (24.14%)	0.527

Data are presented as mean ± SD or number (%)

Table 2: Electrocardiogram among the three groups.

		Control (n = 50)	**Mild (n = 21)**	**Moderate to severe (n = 29)**	**P value**
ECG	**Normal**	38 (76.0%)	10 (47.62%)	14 (48.28%)	**0.016***
	IHD	12 (24.0%)	11 (52.38%)	15 (51.72%)	

Data are presented as number (%) IHD: IHD

Table 3: Calcium score among the three groups.

		Control (n = 50)	Mild (n = 21)	Moderate to severe (n = 29)	P value
Calcium score	**Normal**	38 (76.0%)	0 (0.0%)	0 (0.0%)	**<0.001***
	Mild	10 (20.0%)	2 (9.52%)	6 (20.69%)	
	Moderate	2 (4.0%)	19 (90.48%)	9 (31.03%)	
	Severe	0 (0.0%)	0 (0.0%)	14 (48.28%)	
Median (IQR)		6.5 (4-10)	247 (198-327)	298 (199-613)	

Data are presented as number (%)

Table 4: Details of distribution atherosclerotic.

		Control (n = 50)	Mild (n = 21)	Moderate to severe (n = 29)	P value
Atherosclerotic CAD	**Non-obstructive**	8(16%)	2(9.52%)	3(10.34%)	**0.002***
	Obstructive	0	4 (19.05%)	10 (34.48%)	
Sites of obstructive CAD	**LAD**	0	3 (14.28%)	5(17.24%)	0.768
	RCA	0	1 (4.76%)	3 (10.34%)	
	LCX	0	0	1(3.45%)	
	LM	0	0	1(3.45%)	

Data are presented as number (%) LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, LM: left main artery, *: significant as p value <0.05.

Table 5: multivariate logistic regression of various variables for prediction of CAD

	Odds ratio	**95% CI**	**P value**
MAC	4.45	1.483-13.387	**0.008***
Age	0.981	0.927-1.037	0.503
Male Sex	1.418	0.494-4.073	0.516
Hypertension	0.561	0.213-1.477	0.242

MAC: Mitral annular calcification

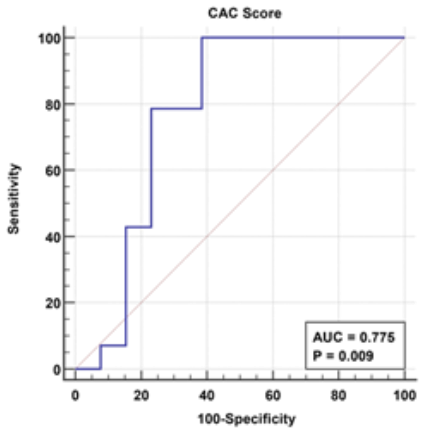

Figure 1: ROC curve CAC score for prediction of obstructive CAD

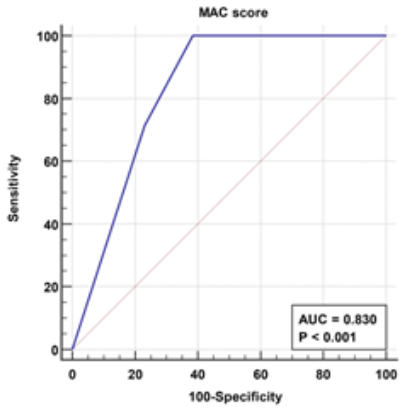

Figure 2: ROC curve MAC score for prediction of obstructive CAD

6. Discussion

CVD, particularly IHD, is the major cause of death and lost healthy years in the United States. Further, CVD is also the leading cause of death worldwide, with developing countries bearing more than 60% of the global burden [10]. Nevertheless, MAC was considered to be a passive, age-related degenerative process, mounting data now suggests that it is a highly controlled process with distinct characteristics that are comparable to both medial and atherosclerotic cardiovascular calcification [1]. The patient with CT-detected CAC has crossed the line from having CVD risk factors to having identified subclinical coronary artery disease. Stress causes a variety of physiological changes that may be linked to cardiovascular disease [11]. Our results showing that there was no statistically significant difference amongst the three studied groups according to smoking, family history, hypertension, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia. However, Dai et al. [12] reported that one of the most critical risk factors for the development of this disease is family history. Further, Timón et al. [13] noted that diabetes, especially type 2 diabetes, is a risk factor for CAD. The risk of CAD has been found to be greater in diabetic patients than in non-diabetic ones. Diabetes has been linked to hyperlipidemia, which is defined by low HDL cholesterol levels as well high triglyceride levels. Also, Hajar et al. [14] showed that extensive epidemiological research has identified the risk factors for the development of CAD, which include smoking, diabetes, hyperlipidemia, and hypertension. Our results showing that there was a highly significant difference between the three studied groups in terms of IHD (IHD). Birkhoelzer et al. [15] found that the CMAC echocardiographic prevalence was 0.64% of patients with MAC and 0.068% of the general population. Echocardiography is used to detect MAC in patients less than 65 years may be an independent predictor of substantial CAD, TVD and the incidence of left main illness was considerably higher. WHO [16] reported that IHD is still the main reason of death in countries of all socioeconomic levels. Rates vary per country and are declining in the majority of them, showing significant potential for improvement. Future progress may be hindered by rising hypertension in some developing nations and, more importantly, global obesity growth. IHD is the major reason of death worldwide, accounting for < 9 million deaths in 2016. In our study, calcium score was significantly different among the three groups; worse with moderated to severe than mild MAC and in mild than control (P<0.001). Along with our study Budoff et al. [17] noted that Any CAC seen on CT increases the likelihood of clinical coronary heart disease and ASCVD, which encompasses cerebrovascular as stroke and coronary heart disease as acute myocardial infarction. On the other hand Mahmoud et al. [18] demonstrated that regarding left main CAD, no statistically significant difference was detected among patients with ordinary aortic and mitral valve and patients with aortic valve sclerosis (AVS) and/or MAC. Further, [11] noted that the CAC score is a direct indicator of the quantity of the present calcified atheroma, and it is closely linked with total coronary atheroma, which encompasses both measured and unmeasured non calcified plaque. In our study, MAC score is a good predicator for obstructive CAD (AUC =0.830, 95% CI =0.636 - 0.946, p value <0.001). with 100% sensitivity and 61.54% specificity. CAC score is a good predicator for obstructive CAD (AUC =0.775, 95% CI =0.574 -0.912, p value =0.009). with 100% sensitivity and 61.54% specificity. Similarly, Ahmed et al. [19] found that regarding presence or absence of any obstructive/non obstructive CAD; MAC score was a good predictor (AUC =0.581, 45% sensitivity and 43% specificity (95% CI = 0.419-0.619)) as well CAC score ((AUC = 0.763, 82% sensitivity and 80% specificity (95% CI = 0.814-0.913)). In line with our findings, Yerramasu et al, [20], found that regarding CAC, the sensitivity, specificity, negative predictive value, and positive predictive value of CAC ≥ 1 for detection of obstructive CAD were 96, 53, 32, and 98%, respectively. As a result, obstructive CAD could be excluded reliably by the absence of coronary calcification. In our study, MAC is a good predictor for the presence of CAD. (p =0.008). In agreement with our results, Atar et al. [21] found on multivariate analysis that MAC (p = 0.02) was an independent predictor of the presence of significant CAD. Furthermore, Acartürk et al [22]. highlighted that multivariate analysis revealed that MAC was an independent predictor of severe CAD (p = 0.02), therefore patients with MAC should be evaluated for the existence of severe CAD and, as a result,

for diagnostic and therapeutic measures aimed at improving their prognosis.

7. Conclusions

The extent of calcification around annulus of the mitral valve appears to be an important element in the pathophysiology of CMAC and CAC. Therapeutic efforts to slow the progression of MAC could target annular calcification, further data is needed to better recognize risk factors, disease implications, the progression from MAC to CMAC, and the time of proposed treatments such as reduction of risk factor, medicinal therapeutics or surgical management.

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