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Cardiovascular Risk Factors Associated with Mitral Annular Calcification in a Non-Rheumatic Population

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ABSTRACT

Mitral Annular Calcification (MAC), cardiovascular disease marker was common in non-rheumatic populations but was frequently disregarded in clinical evaluations. **Objective:** To MAC and to assess effect of these factors on cardiac function in non-rheumatic adult population. **Methods:** From September 2022 to August 2023, we conducted this cross-sectional study at Cardiac Center, Pakistan institute of medical sciences Islamabad that included 182 adults aged 50 years and older. We evaluated the patient's clinical history, demographic data and echocardiographic and laboratory results. The association between the presence of MAC and cardiovascular risk factors (age, hypertension, diabetes, dyslipidemia, smoking, obesity and chronic renal disease) was analyzed using logistic regression. Echocardiographic data were used to provide insight into cardiac function. **Results:** The prevalence of MAC was substantially correlated with hypertension (OR = 2.30), diabetes (OR = 2.00), dyslipidemia (OR = 1.75) and obesity (OR = 1.07). Also, smoking demonstrated a significant correlation with MAC. In comparison to those without MAC, individuals with MAC exhibited substantially lower ejection fractions, increased left atrial diameters and impaired diastolic function, as indicated by cardiac function assessments. **Conclusions:** In non-rheumatic population, MAC was significantly associated with conventional cardiovascular risk factors, particularly hypertension and diabetes.

INTRODUCTION

In the chronic degenerative condition, Mitral Annular Calcification (MAC), calcium deposits in the fibrous base of the mitral valve leaflets characterize the disorder, mostly impacting non-rheumatic elderly population [1]. Imaging tools such as echocardiography can accidentally detect MAC, but now we know it's more of a warning sign of cardiovascular disease and death than a benign aberration [2]. Knowing what causes MAC in people who don't have rheumatoid arthritis is important since it could lead to better understanding of cardiovascular disease in general and how to treat it [3]. A complicated interaction of mechanical stress, lipid infiltration, and chronic inflammation characterizes the pathogenesis of MAC, much to the processes seen in atherosclerosis [4, 5]. Because of these similarities, scientists are looking for shared cardiovascular risk factors that could put people at risk for MAC. For instance, calcium deposition could be hastened when the mechanical strain on the mitral valve annulus rises from hypertension [6]. In a similar line, the calcification process and dyslipidemia, a disorder marked by either low high density lipoprotein (HDL) or greater low density lipoprotein (LDL) cholesterol levels, have been linked to oxidative alteration of lipids, which sets off inflammatory pathways [7, 8]. Advanced glycation end-products, encouraged by diabetes mellitus, help to produce increased inflammation and fibrosis inside the

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cardiac structure, so aggravating hyperglycemia and hence raising the risk. One other important risk factor, smoking aggravates calcific deposition by causing both systemic inflammation and oxidative stress [9, 10]. Furthermore, very important is Chronic Kidney Disease (CKD); the disturbance of calcium and phosphate balance in CKD usually results in arterial and valvular calcifications, therefore acting as the major risk factor for MAC [11]. Age and gender also have important influence; women and older persons have higher frequency. Consistent with noted rises in cardiovascular and osteoporotic risks among older women, this demographic pattern suggested that post-menopausal hormonal changes may distress calcium metabolism [12, 13]. Furthermore, new studies on genetic predispositions and biomarkers linked with MAC, such inflammatory cytokines and genetic polymorphisms, are ongoing [14]. In general, it is essential to comprehend MAC risk factors for non-rheumatic population in order to not only foresee the likelihood of developing this condition but also to situate it within the broader context of cardiovascular risk management [15].

The aim of this study was to find and evaluate cardiovascular risk factors for mitral annular calcification in the population free of rheumatoid arthritis and to determine their respective roles of these elements in the initiation of this condition.

METHODS

This cross-sectional study, spanning September 2022 to August 2023, took place in Pakistan Institute of Medical Sciences in Islamabad. All patients provided informed consent prior to their participation in the study. Without rheumatoid arthritis, researchers set out to investigate for cardiovascular risk factors linked to mitral annular calcification. The minimal necessary sample size for this study 182 participants was found by using of power analysis with 95% CI and 80% power with expected prevalence rates for MAC were 10% [16]. This study selected adults (50 and above) without rheumatoid arthritis from stratified random selection process as the representative sample. Originally stratified based on gender and age, population was then controlled for probable confounds by other factors. Volunteers were selected at random to provide sufficient representation of every stratum. The study excluded those having history of rheumatic heart disease, past heart valve surgery or any notable valvular abnormalities. Structured interviews and medical record reviews were implemented to accumulate comprehensive demographic and clinical data. Age, sex, smoking status, body mass index (BMI), history of hypertension, diabetes, dyslipidemia and chronic kidney disease were among the variables that were collected. Echocardiographic examinations were conducted by the cardiologists who were unaware of the clinical data of the participants, utilizing echocardiography machine (GE Vivid E95). The presence and extent of MAC were evaluated and documented. The echocardiographers implemented a particular protocol to quantify the girth of mitral annulus and to identify calcification points. In order to evaluate the levels of fasting glucose, total cholesterol, HDL, LDL cholesterol and triglycerides, blood samples were obtained following 12-hour fast. Serum creatinine levels were assessed to assess renal function and CKD-EPI equation was employed to estimate GFR. Data analysis were conducted using 25.0 version of SPSS software Descriptive statistics—which comprised frequencies and percentages summed demographic and clinical traits of the study participants. Chi-square tests examined categorical variables; independent sample t-tests assessed continuous variables across groups. Presenting findings of the regression analysis as odds ratios with 95% CIs and p-value less than 0.05 established statistical significance. Approved by the Institutional Review Board, Reference No F.3-1/2023(ERRB)/Chairman of Pakistan Institute of Medical Sciences, Islamabad, this study was carried out in compliance with ethical standards described in Declaration of Helsinki. All individuals gave written informed permission. Mitral Annular Calcification (MAC) is the buildup of calcium deposits around the mitral valve, which can impair valve function and lead to conditions like mitral regurgitation or stenosis (Figure 1).

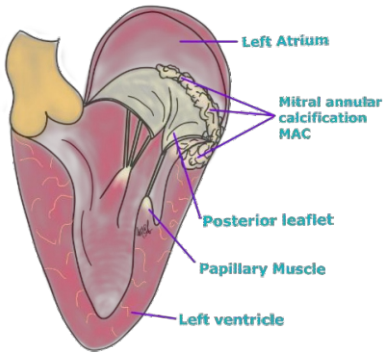

Figure 1: Mitral Annular Calcification (Source: https://www.mitraltherapies.com/mac)

RESULTS

The findings of our cross-sectional study, offered thorough examination of the cardiovascular risk factors, linked to mitral annular calcification in a non-rheumatic population. Demographic characteristics, clinical history, laboratory markers and echocardiographic parameters were evaluated in sample of 182 participants. In order to identify independent predictors of MAC and investigate potential interactions among various risk factors, multivariate logistic regression was implemented. The results demonstrated substantial correlations and provided unique perspective on the intricate relationship between systemic health conditions and development of MAC. They emphasized both modifiable and non-modifiable risk factors that contributed to the prevalence of MAC in the elderly population. The comparison between patients with

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and without MAC reveals several statistically significant differences. Patients with MAC were significantly older, with the mean age of 67.5 ± 8.9 years compared to 62.1 ± 10.2 years in those without MAC (p = 0.003). While the sex distribution was relatively balanced across both groups, with no significant difference in the proportion of males and females (p = 0.672), other health factors show notable differences. Patients with MAC have a higher mean BMI (29.4 ± 4.8 kg/m^2) compared to those without MAC (27.2 ± 5.5 kg/m^2), with a significant p-value of 0.015. Additionally, smoking status was more prevalent in MAC group (23.9%) compared to those without MAC (14.4%), with a p-value of 0.033. Hypertension was significantly more common in the MAC group (72.8% vs. 47.8%, p = 0.001), as was diabetes (51.1% vs. 27.8%, p = 0.001) and dyslipidemia (54.3% vs. 34.4%, p = 0.002). Chronic kidney disease also appears to be more prevalent in the MAC group (20.7% vs. 10%, p = 0.026). These findings suggested that patients with MAC tend to be older and have a higher prevalence of several cardiovascular risk factors compared to those without MAC (Table 1).

Table 1: Baseline Characteristics of Study Participants (n=364)

Variable	Total Mean ± SD / N (%)	With MAC Mean ± SD / N (%)	Without MAC Mean ± SD / N (%)	Chi-Square	p-value
Age (Years)	64.8 ± 9.7	67.5 ± 8.9	62.1 ± 10.2	8.76	0.003*
Male (%)	89 (48.9%)	46 (50%)	43 (47.8%)	0.18	0.672
Female (%)	93 (51.1%)	46 (50%)	47 (52.2%)		
Body Mass Index (Kg/m^2)	28.3 ± 5.2	29.4 ± 4.8	27.2 ± 5.5	5.87	0.015*
Smokers	35 (19.2%)	22 (23.9%)	13 (14.4%)	4.56	0.033*
Hypertension	110 (60.4%)	67 (72.8%)	43 (47.8%)	13.29	0.001*
Diabetes	72 (39.6%)	47 (51.1%)	25 (27.8%)	11.82	0.001*
Dyslipidemia	81 (44.5%)	50 (54.3%)	31 (34.4%)	9.56	0.002*
Chronic Kidney Disease	28 (15.4%)	19 (20.7%)	9 (10%)	4.98	0.026*

The analysis revealed that several factors were significantly associated with MAC. Each additional year of age increased the odds of having MAC by 6% (p<0.01). A higher BMI was also associated with increased odds of MAC, with each unit increase in BMI raising the odds by 8% (p<0.05). Hypertension more than doubled the odds of having MAC (OR: 2.29), while diabetes also significantly raised the odds by 2.03 (p<0.05). Dyslipidemia was found to increase the odds by 80% and chronic kidney disease was associated with the twofold increase in the odds of MAC (p<0.05). However, male sex and smoking status were not significantly associated with MAC, as indicated by their p-values of 0.432 and 0.116, respectively (Table 2).

Table 2: Logistic Regression Analysis of Risk Factors for Mitral Annular Calcification

Variables	Odds Ratio	95% CI	p-Value
Age (Per Year Increase)	1.06	1.03 - 1.09	0.001*
Male Sex	1.22	0.74 - 2.01	0.432
Body Mass Index	1.08	1.02 - 1.14	0.007*
Smoking Status	1.65	0.88 - 3.10	0.116
Hypertension	2.29	1.35 - 3.87	0.001*
Diabetes	2.03	1.23 - 3.36	0.006*
Dyslipidemia	1.80	1.09 - 2.96	0.022*
Chronic Kidney Disease	2.10	1.01 - 4.36	0.046*

The analysis of age groups revealed a significant association between age and presence of MAC (p<0.01), indicating that MAC was more common in older age groups. In the 50-59 years group, 26.1% of participants had MAC, while in the 60-69 years group, this percentage increased to 51.4%. Among participants aged 70-79 years, 75% were found to have MAC, making it the group with the highest prevalence. Interestingly, the prevalence dropped slightly to 53.8% in participants aged 80 years and older. Chi-Square test prevailed the likelihood of having MAC increases with age, particularly in those aged 70-79 years (Table 3). The analysis showed significant differences in laboratory markers between the MAC and non-MAC groups. Fasting glucose, total cholesterol, LDL cholesterol, and triglycerides were all significantly higher in the MAC group (p < 0.005), while HDL cholesterol was significantly lower in the MAC group. These results suggest that elevated glucose, cholesterol, and triglyceride levels, along with lower HDL, were associated with the presence of MAC (Table 3).

Table 3: Prevalence of Mitral Annular Calcification by Age Group

Age Groups	Total Participants	With MAC	MAC (%)	Chi-Square	p-value
50-59 Years	46	12	26.1	15.24	0.001*
60-69 Years	70	36	51.4		
70-79 Years	40	30	75.0		
80+ Years	26	14	53.8		

Chi-square test

Table 4 showed the correlation between Mitral Annular Calcification (MAC) and various laboratory markers, highlighting potential associations with cardiovascular risk factors (Table 4).

Table 4: Correlation of Mitral Annular Calcification with Laboratory Markers

Laboratory Marker	Mean Level in MAC Group	Mean Level in Non-MAC Group	T-Test	p-value
Fasting Glucose (mg/dL)	126.3	98.7	6.78	<0.001
Total Cholesterol (mg/dL)	205.5	187.9	3.92	0.001
LDL Cholesterol (mg/dL)	131.2	119.8	2.88	0.005
HDL Cholesterol (mg/dL)	40.2	45.1	-3.10	0.003
Triglycerides (mg/dL)	184.6	150.3	4.22	<0.001

The analysis of cardiac parameters showed significant differences between MAC and non-MAC groups. The ejection fraction was found to be significantly lower in MAC (58.9%) than non-MAC group (62.3%) (p<0.01). The left atrial diameter was significantly larger in the MAC group (38.4 mm) than in the non-MAC group (34.7 mm). Additionally, the mitral valve E/A ratio was significantly lower in the MAC group (0.9) compared to the non-MAC group (1.2) (p<0.01), indicating that patients with MAC had impaired diastolic function (Table 5).

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Table 5: Impact of Mitral Annular Calcification on Cardiac Function

Laboratory Marker	Mean Value in MAC Group	Mean Value in Non-MAC Group	T-Test	p-value
Ejection Fraction (%)	58.9	62.3	-3.55	0.001
Left Atrial Diameter (mm)	38.4	34.7	4.29	<0.001
Mitral Valve E/A Ratio	0.9	1.2	-5.62	<0.001

independent sample t test

Several noteworthy main and interaction effects linked to MAC were uncovered in the investigation. The odds increased by 5% for every year of age, indicating that age bear significant influence. An additional risk factor for MAC was a high BMI, with a 7% increase for every unit increase. The likelihood of MAC in hypertensive adults increased by 10% each year as they got older, according to an interaction effect and hypertension itself greatly raised the risks (OR: 2.30). The odds of MAC were twofold in people with diabetes and their risks were much higher for men due to an interaction effect ($p<0.05$). Dyslipidemia considerably raised the risks and an interaction with age revealed a 3% increase in odds per year ($p<0.05$), however smoking did not exhibit a significant interaction impact with BMI ($p=0.085$) (Table 6).

Table 6: Multivariate Analysis of Risk Factors and Interactions for Mitral Annular Calcification

Variables	Main Effects (Odds Ratio)	Interaction Effects	95% CI	p-value
Age (Per Year)	1.05	-	1.02 - 1.08	0.002
Male Sex	1.15	-	0.70 - 1.89	0.580
Body Mass Index	1.07	-	1.01 - 1.13	0.015
Hypertension	2.30	Age * Hypertension	1.50 - 3.50	<0.001
		1.10 per Year Increase	1.05 - 1.15	0.001
Diabetes	2.00	Diabetes * Sex	1.20 - 3.30	0.007
		1.50 if male	1.10 - 2.00	0.020
Smoking	1.60	Smoking * BMI	0.90 - 2.80	0.120
		1.05 per BMI unit	0.99 - 1.11	0.085
Dyslipidemia	1.75	Dyslipidemia * Age	1.00 - 2.50	0.048
		1.03 per year increase	1.00 - 1.06	0.040

independent sample t test

DISCUSSION

Current results were consistent with a research that established the correlation between presence of MAC and age, hypertension, diabetes, dyslipidemia, smoking and obesity, underscoring the multifactorial nature of this condition. In line with previous studies, our investigation confirmed that the incidence of MAC increases with age. Diel R *et al.*, in 2018 found that the likelihood of acquiring MAC rose somewhat with passing years. This finding was in line with other research suggesting that MAC was mostly an age-related degenerative process [17]. It was known that oxidative stress and systemic inflammation contribute to the calcification of cardiac tissues [18], which may explain the age-related increase. Hypertension was found to be a strong predictor of MAC in our investigation, outweighing other risk variables by a significant margin. This association was more pronounced in the elderly, suggesting that chronic hypertension may hasten mitral annulus calcification. These results were in line with those of Singh S *et al.*, in 2017, who discovered that persistently high blood pressure can cause structural changes in the heart, which could put people at risk for Myocardial Infarction (MAC) [19]. Additionally, MAC was substantially related with diabetes, especially in men. The presence of advanced glycation end-products, which play a role in calcification, was likely fostered by the chronic hyperglycemic environment [20, 21]. Differences in hormone levels, diabetes control strategies, and fat distribution patterns between the sexes were possible causes of the gender gap [22]. Dyslipidemia may have a role in atherosclerotic processes similar to those seen in valvular calcification, according to previous studies [23]. According to our findings, dyslipidemia was significantly linked to MAC. The interaction impact between age and dyslipidemia that our study found further emphasizes the significance of aggressive lipid control as part of preventive interventions for MAC in older populations. There was a correlation between smoking status, particularly being a current smoker, and the risk of MAC. Cigarette smoke induces inflammatory and oxidative activities, which may speed up the calcific processes within the mitral valve structure [24]. Curiously, it appears that there was a correlation between smoking and Body Mass Index (BMI), suggesting that smokers who were overweight may be at a higher risk. This highlights the need for specific initiatives to address this population. Obesity, as assessed by Body Mass Index (BMI), was another strong predictor of MAC. Chronic inflammation and elevated cardiac workload may play a role in the complex link between obesity and MAC [25]. In addition, there was a high correlation found between CKD and MAC, which was in line with the notion that CKD was linked to calcium-phosphate metabolism abnormalities, which in turn increase the risk of vascular and valvular calcifications [26]. From a clinical perspective, our findings about the impact of MAC on heart function were especially significant. Left atrial diameters were bigger, mitral valve E/A ratios were compromised, and ejection percentages were lowered in participants with MAC. Untreated cardiac dysfunction or heart failure could be a consequence of MAC, according to these echocardiographic findings. This lines up with what Kato Y *et al.*, in 2023 found, which was that valve calcification was associated with negative cardiac outcomes like reduced systolic and diastolic function [26]. Although our study shed light on the causes and effects of MAC, future studies should use longitudinal designs to better understand the correlations between risk variables and the progression of the disease.

CONCLUSIONS

Age, hypertension, diabetes, dyslipidemia, obesity and smoking were found to be significant predictors of mitral

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annular calcification in a non-rheumatic population, according to this study. It appears that hypertension and diabetes were major contributors to the development of MAC, since these two disorders showed the largest connections. Studies on diastolic function, left atrial diameter, and ejection fraction also showed that MAC significantly affects cardiac function. In light of these findings, it was clear that early intervention and control of cardiovascular risk factors were crucial for MAC prevention in order to lessen the likelihood of the condition's onset and the cardiac problems it might cause.

Authors Contribution

Conceptualization: MUR
Methodology: MF, AA[1], AR
Formal analysis: MI
Writing, review and editing: AA[2]

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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