ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Relationship Between Mitral Annular Calcification and CRP/albumin Ratio

Mitral Anüler Kalsifikasyon ile CRP/albümin Oranı Arasındaki Ilişkinin Değerlendirilmesi

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ABSTRACT

Aim: *The relationship between mitral annular calcification (MAC) and atherosclerotic diseases is known. The CRP/albumin ratio (CAR) is one of the indicators of inflammation of the atherosclerotic process. We aim to examine the relationship between MAC and CAR values.*

Material and Method: *The study included 197 patients with MAC and a control group of 200 retrospectively between January 2021 and December 2021. We analyzed the relationship between CAR and MAC according to the hospital records, including laboratory findings, echocardiography reports, and patient characteristics.*

Results: *We found higher CAR values in patients with MAC compared to the control group (p<0.001). In addition, CAR was predictive for MAC determined by regression analysis (OR: 52.37, 95% CI: 7.37–372.06, p<0.001).*

Conclusion: *CRP/albumin ratio values, essential indicators of inflammation, were higher in the patient population with MAC. This finding may reveal that inflammation is also effective in the pathogenesis of MAC.*

Key words: *CRP/albumin ratio; inflammation; valvular calcification*

ÖZET

Amaç: *Mitral anüler kalsifikasyon (MAK) ile aterosklerotik hastalıklar arasındaki ilişki bilinmektedir. CRP/albümin oranı (CAO), aterosklerotik sürecin iltihaplanmasının göstergelerinden biridir. Amacımız MAK ve CAO değerleri arasındaki ilişkiyi incelemektir.*

Materyal ve Metot: *Ocak 2021 ile Aralık 2021 tarihleri arasında geriye dönük olarak 197 MAK'li hasta ve 200 kişilik bir kontrol grubu çalışmaya alındı. CRP/albümin oranı ve MAK arasındaki ilişkiyi laboratuvar bulguları, ekokardiyografi raporları ve hastaların demografik özelliklerini içeren hastane kayıtlarına göre analiz ettik.*

Bulgular: *Kontrol grubuna göre MAK'li hastalarda daha yüksek CAO değerleri bulduk (p<0,001). Ayrıca, CAO, yapılan regresyon analizine göre MAK için öngördürücüydü (OR: 52,37, %95 GA: 7,37–372,06, p<0,001).*

Sonuç: *Enflamasyonun önemli göstergelerinden olan CAO değerleri, MAK'li hasta popülasyonunda daha yüksekti. Bu bulgu, enflamasyonun MAK patogenezinde de etkili olduğunu ortaya koyabilir.*

Anahtar kelimeler: *CRP/albümin oranı; enflamasyon; kapak kalsifikasyonu*

Introduction

Mitral annular calcification (MAC) describes a chronic calcium deposition that occurs in the fibrous portion of the mitral valve and is usually localized to the posterior annulus. In this process, the role of endothelial damage leading to lipid accumulation and the formation of calcium deposits is emphasized[1,2]. A close relationship with atherosclerotic heart disease risk factors such as hyperlipidemia, obesity, type II diabetes and hypertension has been demonstrated[3,4]. While it was formerly thought to be a passive process caused by calcium deposition that increases with age, later research has pointed out a role for lipoproteins and chronic inflammation similar to that in atherosclerosis[5–7].

On the other hand, the ratio of rapidly rising C-reactive protein (CRP) in inflammation and albumin, which is a negative acute phase reactant, is known as one of the predictive parameters of inflammation in the atherosclerotic process, as shown in previous studies[8–10].

Studies examining the relationship of MAC with inflammation revealed conflicting results[11–13]. To answer questions in this regard, we designed this study examining the relationship between MAC and CRP/albumin ratio (CAR).

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Material and Methods

Study Population

In this retrospective study, we concluded 197 patients with MAC and 200 age and sex matched patients without MAC who admitted to our cardiology outpatient clinic between January 2021 and December 2021. Our inclusion criteria were as follows: age between 18–100, proper echocardiography report which marks if the patient has MAC. Patients with any known acute or chronic inflammatory disease, active infection, medication including steroids, severe heart valve disease, history of acute rheumatic fever, prosthetic valve, decompensated heart failure, malignancy, kidney or liver dysfunction, hematological disease, and chronic obstructive pulmonary disease were excluded from the study. The study was approved from the Institutional Ethics Committee and conducted in accordance with the Helsinki declaration.

Clinical and Laboratory Data

Clinical and demographic data were obtained from hospital medical records. Hypertension and diabetes were defined as stated by the guidelines[14,15]. Laboratory parameters including CRP and albumin were recorded in the blood samples given by the patients after 8 hours of fasting.

Echocardiography

A complete transthoracic echocardiogram was performed by the same cardiologist using a 3.5 MHz transducer and VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway). Mitral annulus calcification was defined as a highly dense echocardiographic structure with highly reflective features localized at the junction of the atrioventricular groove and the anterior or posterior leaflet of the mitral valve in the parasternal long or short axis, apical four– or two-chamber views[16].

Statistical Analysis

Since there was no data investigating the relationship between CAR and MAC, pre-analysis was performed with 15 patients with MAC and without MAC. When the sample size was calculated based on 95% power by statistical method, it was planned to include 200 patients with MAC and 200 patients without MAC by performing a power analysis.

Statistical analyzes were performed using the SPSS 20.0 (Statistical Package for Windows, Chicago, Illinois, USA) program. Kolmogorov-Smirnov test was used to examine the normal distribution of the data. Among the numerical variables, those with normal distribution (parametric) were expressed as mean, standard deviation, those that did not exhibit normal distribution (non-parametric) were expressed as median, median value (with interquartile range) and categorical variables as percentages. Student-t test or Mann-Whitney U-test was used for numerical variables, and chi-square test was used for analysis of categorical variables. Parameters predicting the presence of mitral annulus calcification were evaluated with multivariate logistic regression analysis.

Results

Baseline characteristics and laboratory parameters of the study groups are shown in Table 1. Mean age of control group and MAC group were 71.5±8.5 and 70.8±8.7 (p=0.39). There was no difference between the groups in terms of age, gender, comorbidities, smoking status and laboratory parameters except CRP, albumin, and CAR values. The CRP, albumin and CAR values of the MAC group were significantly higher than the control group [0.95 (0.50–2.13) vs. 0.67 (0.49–1.04), respectively, (p<0.001)].

Univariate and multivariate logistic regression analysis revealed a positive and independent relationship between CAR and MAC (OR: 52.37, 95% CI: 7.37–372.06, p<0.001) (Table 2). C-reactive protein was found to be an independent predictor for MAC.

Discussion

In this study, we showed that CAR levels were significantly associated with MAC and were also predictive of MAC. These findings are the first to show that inflammation is closely related to MAC besides other factors as mentioned earlier[3,4].

Studies examining the relationship between mitral annular calcification and inflammation have produced conflicting results. In a study examining the relationship between epicardial fat thickness and MAC, it was stated that adipose tissue may contribute to the formation of MAC through inflammatory cytokines[17]. In another study examining the relationship of inflammatory cytokines (C-reactive protein, intercellular

Table 1. *Baseline characteristic and laboratory parameters of patients*

	Control (n: 200)	MAC (n: 197)	P value
Age	71.5±8.5	70.8±8.7	0.39
Gender (Male)	69 (34.5%)	53 (26.9%)	0.81
Hypertension, n (%)	129 (64.5)	113 (57.3)	0.151
Diabetes Mellitus, n (%)	57 (28.5)	58 (29.4)	0.741
Smoking, n (%)	32 (16)	40 (20.3)	0.242
EF	56.2±7.0	56.9±5.5	0.295
Hemoglobin, g/dl	12.5±1.7	12.8±1.6	0.122
Glucose, mg/dl	122.4±52.2	119.7±50.9	0.601
Platelet, $10^3/mm^3$	293±101	290±91	0.783
WBC, $10^3/mm^3$	7.7±2.4	7.4±1.6	0.284
Albumin, mg/dl	4.4±0.3	4.3±3.7	0.004
Creatinin, mg/dl	0.83±0.19	0.85±0.18	0.141
Total cholesterol, mg/dl	200.4±40.1	208.4±34.6	0.474
HDL – cholesterol, mg/dl	42.2±11.5	43.2±11.1	0.200
LDL – cholesterol, mg/dl	120.7±25.2	123.6±24.7	0.177
Trigliseride, mg/dl	135 (95–85)	125 (91–184)	0.196
CRP	3.0 (2.1–4.8)	4.2 (2.2–9.4)	<0.001
CRP/Albumin ratio	0.67 (0.49–1.04)	0.95 (0.50–2.13)	<0.001

EF: Ejection Fraction; WBC: White Blood Cell; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CRP: C-reactive Protein.

Table 2. *Univariate and multivariate regression analyses for Mitral Annuler Calcification*

Univariate regression analyses	OR	p
Age	0.990 (0.968–1.013)	0.390
Gender	0.699 (0.455–1.073)	0.102
Hypertension	0.740 (0.494–1.110)	0.145
Hemoglobin	1.094 (0.976–1.227)	0.123
CRP/Albumin	52.37 (7.37 – 372.06)	<0.001

CRP: C-reactive Protein.

adhesion molecule-1, interleukin-6, and monocyte chemoattractant protein-1) with valve calcification, increased values of these cytokines were found in patients with valve calcification[13]. They concluded that this close relationship was due to shared risk factors of both entities. Also, in a study of HIV-infected patients, infection was shown to be a predictor of mitral and aortic valve calcification[11]. However, unlike our study, they showed no association between inflammatory biomarkers and valve calcification. We would like to underline that the CRP/albumin ratio was not used in this study. In a genome-wide association study, two loci near the proinflammatory IL1F9 gene were found to be associated with MAC, although they were not replicated constantly[18]. In prospective study with 27 years follow-up period, examining the long-term consequences of exposure to atherosclerotic risk factors, CRP levels were shown to be associated with mitral annular calcification, similar to our study[19]. In a cross-sectional study, red blood cell distribution width (RDW) was found to be higher in patients with MAC, and it was stated that this could be an indicator of ongoing inflammation[20]. In contrast, a study in hemodialysis patients showed that valve calcification is a non-inflammatory process and is mostly associated with hyperparathyroidism[21].

Recent studies have shown that CAR was a more accurate sign of inflammation in atherosclerotic process than CRP or albumin alone[8,9,22]. Studies showing how high CRP and low albumin levels play a role in the atherosclerotic process at the cellular level reveal the importance of CAR[23–27]. Our study is important in that it shows that CAR values, which are indirect indicators of the atherosclerotic process, and the presence of MAC are closely related.

The limitations of our study should be mentioned. First, due to the retrospective and cross-sectional nature of the study, it is not possible to establish a causal relationship between MAC and CAR values. Prospective and follow-up studies are needed. It should also be noted that the presence of MAC is a finding that can be missed in routine echocardiography reports. But this may have prevented possible bias. In addition, we remind that all echocardiography reports were reviewed within the specified date range and all eligible patients were included in the study. In addition, the fact that echo parameters are limited to only ejection fraction and mitral annular calcification presence can be seen as another limitation of the study. Reliability of patient information is another limitation of our study, as whether patients have an inflammatory disease or not is defined only based on hospital registry data.

Conclusion

In conclusion, in this study, CAR values were found to be significantly higher in the patient group with MAC than in the control group. Therefore, it draws attention to the importance of inflammation, which is still a controversial issue in the pathogenesis of MAC. Future studies are needed to test the accuracy of this data with a larger patient population, a prospective design, and different markers of inflammation.

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