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Association between monocyte to HDL cholesterol ratio and mitral annulus calcification

Monosit HDL-kolesterol oranı ile mitral annülüs kalsifikasyonu arasındaki ilişki

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Abstract

Aim: Mitral annulus calcification (MAC) is characterized by degenerative calcification of the mitral valve annulus, MAC and atherosclerosis are similar in regard to risk factors and pathogenesis. Monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) is an inflammatory marker that is associated with several atherosclerotic diseases. We aimed to show the association of MHR levels with the presence of MAC.

Methods: This retrospective cohort study was conducted with MAC (+) patients who admitted to our echocardiography laboratory which constituted the study group (n=200) and MAC (-) patients which constituted the control group. Demographic features like age and sex, presence of hypertension and diabetes mellitus were similar between groups. Laboratory and echocardiographic parameters were recorded and evaluated for statistical analysis.

Results: When groups were compared according to echocardiographic parameters; left atrial diameter, pulmonary artery systolic pressure (PASP) were found to be positively correlated with the presence of MAC (r=0.271, p<0.001; r=0.329, p<0.001, respectively). MHR was significantly higher in study group {15.3 (11.9-20.6) vs. 10.8 (8.6-16.9) p<0.001}. In correlation analysis, MHR value was found to be positively correlated with presence of MAC (r=0.273; p <0.001).

Conclusion: We found that the presence of MAC was associated with higher MHR, and MHR was significantly correlated with MAC.

Keywords: Mitral annulus calcification, Monocyte, HDL

Öz

Amaç: Mitral annülüs kalsifikasyonu (MAK) mitral kapak annülüsünün dejeneratif kalsifikasyonu ile karakterizedir, MAK ve ateroskleroz risk faktörleri ve patogenez bakımından benzer özellikler taşır. Monosit sayısının yüksek dansiteli lipoproteine (HDL) oranı (MHO) birçok aterosklerotik hastalıkla ilişkili bir inflamatuvar belirteçtir. Biz MAK varlığı ile MHO derecesinin ilişkisini ortaya koymayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışma ekokardiyografi laboratuvarımıza başvurmuş 245 [MAK(+) 200 çalışma grubu hastası, MAK(-) 45 kontrol grubu hastası] ile yapılmıştır. Grupların demografik özellikleri; yaş, hipertansiyon ve diyabetes mellitus varlığı açısından benzerdi. Tümünün laboratuvar ve ekokardiyografik parametreleri değerlendirildi.

Bulgular: Gruplar ekokardiyografik veriler olan sol atriyum çapı, pulmoner arter sistolik basıncı (PASB) açısından karşılaştırıldığında MAK varlığı ile pozitif yönde ilişkili saptandı(sırasıyla, r=0,271, p<0,001; r=0,329, p<0,001). Monosit HDL kolesterol oranı, MAK (+) grupta MAK (-) gruba göre istatistiksel olarak anlamlı derecede yüksekti {15,3 (11,9-20,6) vs. 10,8 (8,6-16,9) p<0,001}. Korelasyon analizine göre Monosit HDL oranı MAK varlığıyla anlamlı olarak ilişkili saptandı (r=0,273; p<0,001).

Sonuç: Sonuçlarımız MAK bulunan hastalarda MHO'nun anlamlı derecede yüksek olduğunu ve MAK ile MHO'nun anlamlı derecede korele olduğunu ortaya koymuştur.

Anahtar kelimeler: Mitral annülüs kalsifikasyonu, Monosit, HDL

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Introduction

Mitral annulus calcification (MAC) is characterized by degenerative calcification of the mitral valve annulus [1,2]. Many studies have shown a strong association between MAC and cardiovascular risk factors [3,4]. MAC was considered a passive, degenerative, age-related process, but it can also result from an atherosclerotic process [5]. On the basis of pathological features seen in specimens of patients with MAC, it was suggested that MAC and atherosclerosis are different forms of the same disease [6]. The association of MAC with atherosclerotic diseases such as coronary artery disease and carotid disease has been shown in previous studies [7,8]. There is a close association of atherosclerosis and systemic inflammation, growing evidence also regarding the association between MAC and inflammation [9,10].

Monocytes play a major role both in the initiation and progression of atherosclerosis HDL prevents monocyte recruitment into the arterial wall via a decrease in the expression of adhesion molecules and thus inhibiting adhesion of monocytes to endothelium [11]. Recently It had been shown that high monocyte count and low high density lipoprotein (HDL) levels are associated with inflammation [12,13] and it has been reported that the monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) is a new prognostic marker in several cardiovascular diseases [14].

Given that both MAC and MHR are associated with cardiovascular risk factors and both are chronical inflammatory processes we hypothesized the possibility of association between presence of MAC and higher MHR levels.

Materials and methods

After approval of the local ethics committee, we started a retrospective cohort study.

Sample size

The sample size was calculated via the G* Power package program in post Hoc analysis, and the study was completed with 200 patients as study group and 45 patients as control group. The power of the study was calculated as 95% with the effect size of 0.60 at significance level of 0.05.

Study population

Between January 2017 and September 2018, a total of 200 consecutive MAC (+) patients who were admitted to our echocardiography laboratory were enrolled to study group. Age and sex-matched control group was composed of 45 MAC (-) patients who were admitted to our echocardiography laboratory due to suspicion of heart disease or other causes. All patients' demographic features and laboratory and echocardiographic parameters were evaluated retrospectively from our hospital data base.

Patients with severe valvular heart disease, coronary artery disease, history of rheumatoid fever, prosthetic valves, heart failure, malignancy, renal or hepatic dysfunction, acute or chronic infection or inflammatory condition, hematologic diseases including anemia or with chronic obstructive pulmonary disease were excluded.

Hypertension was defined as the documentation of systolic blood pressure≥ 140 mmHg and/or a diastolic blood pressure of ≥90 mmHg in at least two measurements, or the active use of any antihypertensive agent. Diabetes mellitus was defined as fasting plasma glucose levels more than 126 mg/dL or glucose level over 200 mg/dL at any measurement or active use of antidiabetic medications.

Transthoracic echocardiographic examination was performed using the Philips Epic 5 (Philips Healthcare, Andover, Massachusetts) instrument with a 1-5 MHz transducer. Standard parasternal long and short-axis views, and apical 2 and 4-chamber views were obtained for all patients. Left ventricular (LV) and left atrial (LA) diameter were measured from the M-mode images in parasternal long axis view [15]. Peak tricuspid regurgitant velocities were recorded by the continuous wave Doppler technique and a modified Bernoulli equation was used to estimate systolic pulmonary artery pressure (PASP). The modified Simpson's method was used for calculating the LV ejection fraction using the apical 4-chamber views [15].

MAC was defined as the presence of an echodense tracing, visualized throughout the systole and diastole, distinguishable from the posterior mitral leaflet and located anterior and parallel to the posterior LV wall and an intense echocardiographic structure at the junction of the atrioventricular groove and the posterior or anterior mitral leaflet on the parasternal long-axis, apical 4-chamber or 2-chamber, or parasternal short-axis 2D echocardiography views, ≥ 2 mm wide (when measured from the leading anterior to the trailing posterior edge at its greatest width) [16].

Samples of peripheral venous blood were drawn from the antecubital vein in the morning, after 12 h of fasting, and immediately studied at the laboratory without any time delay. Blood samples were taken into standardized tubes containing dipotassium ethylene dinitro tetraacetic acid (EDTA) for complete blood count (CBC). Coulter Counter LH Series (Beckman Coulter Inc., Hialeah, Florida, USA) was used for CBC analysis. Plasma levels of triglyceride, high-density lipoprotein, low-density lipoprotein, glucose, and creatinine were evaluated using an automated chemistry analyzer (Aeroset, Abbott, Holliston, MN, USA) using commercially available kits (Abbott, USA). Monocyte count was calculated using data obtained from the CBC differential analysis (using an automated blood cell counter). The reference value for monocyte in our laboratory is 0.2–1.2 × 103/dL and for HDL-C is 40–60 mg/dL. HDL-C levels were measured using a Beckman Coulter AU680 (Beckman Coulter Inc, CA, USA).

Statistical analysis

The statistical analyses were performed using SPSS Version 23 software (Armonk, NY, USA: IBM Corp). Categorical data are presented as numbers and percentages; Kolmogorov Smirnov test was performed in order to test normality for numerical variables. Continuous variables are presented as mean ± standard deviation when normally distributed and median and interquartile ranges (IQR) otherwise. Student's T test was performed in order to analyze significance of means; Mann Whitney U test was performed in order to analyze significance of differences of medians between two independent groups. Association between two continuous variables was measured by Pearson or Spearman correlation

coefficient as appropriate. A p value of <0.05 was considered statistically significant.

Results

Demographic features, presence of hypertension and diabetes mellitus were similar between groups. Demographic and echocardiographic features of the study groups have been represented in Table 1.

When groups were compared according to echocardiographic parameters, Left ventricular ejection fraction (LVEF) of study group was 60 (55-60) and control group was 60 (60-65) was lower and left ventricular end diastolic diameter (LVEDD) were higher in the study group (p=0.044 and p=0.006 respectively). But all of these parameters were in normal ranges according to guidelines. Left atrium diameter {40 (36-43) vs 36 (34-39), p<0.001} and pulmonary artery systolic pressure (PASP) was significantly higher in study group than control group {27 (20-30) vs 35 (28-40), p<0.001} (Table 1).

Table 1: Baseline characteristics and echocardiographic parameters of the groups

Parameters	Control group MAC (-) (n=45)	Study group MAC (+) (n=200)	p
Male, n (%)	21 (46.7%)	72 (36%)	0.123 [a]
Age, years	71.3	72.7	0.351 [b]
Hypertension, n (%)	32 (71.1%)	151 (75.5%)	0.331 [a]
Diabetes Mellitus, n (%)	20 (44.4)	100 (50)	0.306 [a]
LVEF , %	60 (60-65)	60 (55-60)	0.044 [c]
LVEDD, mm	44 (41-47)	46 (43-49)	0.006 [c]
LA diameter, mm	36 (34-39)	40 (36-43)	<0.001 [c]
Ascending aorta diameter, mm	35 (33-36)	35 (33-38)	0.295 [c]
PASP, mmHg	27 (20-30)	35 (28-40)	<0.001 [c]

a: Pearson chi-square, b: Student's T test, c: Mann Whitney-U test, LVEF: Left ventricle ejection fraction, LVEDD:Left ventricle end diastolic diameter, LA:left atrium, PASP: Pulmonary artery systolic pressure

Laboratory results of the groups have been represented in Table 2. Lipoprotein levels of the groups were different; patients in the study group have more dyslipidemic properties. Serum fasting glucose levels were higher in the study group {101 (89.5-119.5) vs. 115 (95.7-161.2), p=0.009} According to blood cell counts, monocyte values were higher in the study group {0.6 (0.5-0.78) vs. 0.5 (0.4-0.65), p=0.003}. Also monocyte to HDL cholesterol ratio was higher in the study group than control group {15.3 (11.9-20.6) vs. 10.8 (8.6-16.9) p<0.001}.

Table 2: Laboratory parameters of the groups

Parameters	Control group MAC (-) (n=45)	Study group MAC (+) (n=200)	p
Total cholesterol mg/dl	202.5±68	177.5±44	0.264 [a]
LDL-C mg/dl	136±28	127.2±36	0.106 [a]
HDL-C mg/dl	47.2±11.2	42.6±11.0	0.018 [a]
Triglyceride mg/dl	126 (96-186.7)	138.5 (99-215)	0.881 [b]
Glucose mg/dl	101 (89.5-119.5)	115 (95.7-161.2)	0.009 [b]
BUN mg/dl	39 (33-43.7)	45.5 (32-64)	0.193 [b]
Creatinine mg/dl	0.9 (0.8-1.02)	1.0 (0.8-1.22)	0.175 [b]
Albumin g/dl	4.1 (3.95-4.4)	3.9 (3.4-4.2)	0.001 [b]
Calcium mg/dl	9.5 (9.3-9.85)	9.3 (8.8-9.7)	0.004 [b]
Phosphorus mg/dl	3.3 (3.1-3.75)	3.6 (3.2-4.1)	0.022 [b]
Hemoglobin g/dl	13.6 (12.2-14.4)	12.7 (11.1-13.8)	0.003 [b]
RDW (%)	14.1±1.6	15.1±2.1	0.210 [a]
White blood cells 10^9/l	7.3 (6.2-8.8)	7.6 (6.3-9.3)	0.689 [b]
Neutrophils 10^9 /l	4.3 (3.5-5.8)	4.9 (3.8-6.0)	0.230 [b]
Lymphocytes 10^9 /l	2.1 (1.6-2.5)	1.8 (1.4-2.3)	0.093 [b]
Monocytes 10^9/l	0.5 (0.4-0.65)	0.6 (0.5-0.78)	0.003 [b]
Monocytes to HDL-C ratio	10.8 (8.6-16.9)	15.3 (11.9-20.6)	<0.001 [b]
Platelets 10^9/l	250 (195.5-296)	229 (193-281)	0.229 [b]
Mean platelet volume fL	8.4 (7.6-9.5)	8.6 (7.9-9.2)	0.501 [b]

Data are given as mean ±SD, median (interquartile range), a: Student's T test, b: Mann Whitney U test, BUN: Blood urea nitrogen, LDL-C: Low-density lipoprotein cholesterol, HDL-C, High-density lipoprotein cholesterol, RDW: Red cell distribution width

In correlation analysis MHR was found correlated with presence of MAC (r=0.273; p<0.001) Also serum albumin level was negatively correlated with left atrial diameter (r=-0.248, p=0.001), PASP were found to be positively correlated with presence of MAC (r=0.271, p<0.001; r=0.329, p<0.001, respectively) (Table 3). There was a positive correlation between PASP and LA diameter (r=0.465, p<0.001).

Table 3: Correlation between MAC and laboratory parameters

	r	p
Monocytes to HDL-cholesterol ratio	0.273	<0.001
Serum albumin	-0.248	0.001
LA diameter	0.271	<0.001
PASP	0.329	<0.001

r: Spearman-rho correlation coefficient, LA: left atrium, PASP: Pulmonary artery systolic pressure

Discussion

This present work demonstrates that MHR is significantly associated with the presence of MAC when compared with elderly individuals who have similar comorbidities and similar demographic characteristics. In some previous studies the demographic characteristics and risk factors of the control group were different, MAC (+) patients were more hypertensive and older than control group [17]. In our work, study and control groups were similar according to hypertension, age and presence of diabetes mellitus. Our study is the first to address the relationship between the MHR level and the presence of mitral annular calcification. We also found that dyslipidemia and impaired fasting glucose is also independently related with the presence of MAC.

In the main pathophysiology of MAC, calcium and phosphorus metabolism was thought to be in relation with this process [18]. In our study, median calcium level of MAC (+) group was lower and median phosphorus level was higher than control group but all these levels were in normal ranges. In our MAC (+) group left atrial diameter and SPAB were significantly higher than control group; this finding suggests that MAC may be associated with diastolic dysfunction.

MAC is known to be in close relationship with cardiovascular risk factors and many atherosclerotic diseases [3,19]. Correlation between MAC and carotid artery atherosclerosis, coronary and peripheral artery disease and aortic atheroma were demonstrated [7,20,21].

MAC is also considered to be a form of atherosclerosis, similar risk factors with atherosclerotic diseases and pathologic findings in MAC supports this idea [7].

Atherosclerosis is a chronic inflammatory disease characterized by strong immunological activity [22]. In the previous literature there were some data demonstrating the relationship between inflammation and MAC. A few studies demonstrated that inflammatory mediators increase in patients with calcification of valves [9, 23]. Varol et al. [10] reported the correlation between the neutrophil to lymphocyte ratio and MAC, which is an indirect inflammatory marker. Yayla et al. [17] reported the close association of ongoing inflammation as shown by the platelet lymphocyte ratio, another novel inflammatory marker, with the presence of MAC.

Monocyte activation is considered to be strongly associated with almost all aspects of chronic inflammation and cardiovascular diseases [24,25]. As a result of some stimuli, circulating monocytes become macrophages. Monocytes and macrophages can trigger an inflammatory cascade involving the production of cytokines [26]. On the other hand, high-density

lipoprotein cholesterol (HDL-C) molecules affect these pro-inflammatory and pro-oxidant effects of monocytes by inhibiting the migration-activation of monocytes and the proliferation-differentiation of the progenitor cells of monocytes [27-29].

Monocytes show pro-inflammatory and pro-oxidant effects, but HDL-C shows the opposite effects. Hence, it is logical to combine these parameters as a ratio and this ratio can be used as an indicator of oxidative stress and inflammation. The ratio of monocyte to HDL has recently emerged as a new cardiovascular prognostic marker. The association of MHR and cardiovascular diseases has been examined in a few studies. Kanbay et al. [30] reported that MHR is associated with worse cardiovascular outcomes in patients with chronic kidney disease.

In another study, in patients with acute ST-segment elevation myocardial infarction (STEMI), MHR values at admission were independently correlated with in-hospital adverse cardiovascular events and stent thrombosis and mortality [31]. In two different studies MHR values were found to be in relation with in-stent restenosis [32,33]; also MHR was found to be correlated with presence and severity of ectasia [13].

Limitations

There are some limitations in our study. First, this was a retrospective analysis of patients with MAC, focusing on the association of laboratory and echocardiographic parameters with the presence of MAC in a random time limit. Though we demonstrated a relationship with MHR and MAC, this observational finding may not establish a causal relationship. Although we excluded patients with coronary artery disease from study, data of atherosclerosis at other locations (carotid, aorta, etc.) were unavailable.

Conclusion

We have shown that MHR was significantly higher in patients with MAC when compared with controls with similar features, MHR was correlated with the presence of MAC. We also found that left atrial diameter and PASP was significantly higher in patients with MAC when compared with controls. All these findings reveal the importance of MHR in demonstrating inflammation, which is an important step in development of many cardiovascular diseases. Our results showing high MHR ratio in MAC (+) individuals support the idea that inflammation plays a role in MAC pathophysiology. The difference of MHR values of groups appears to be mainly tended to originate from monocyte counts. The difference between groups according to monocyte levels was more pronounced than the difference in HDL levels. This result can be interpreted as a finding supporting the place of inflammation in the pathophysiology of MAC. Further prospective studies are needed to establish the pathophysiological and clinical significance of increased MHR in patients with MAC.

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