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Higher beta-2 microglobulin levels may predict the coronary slow flow phenomenon

Yüksek beta-2 mikroglobulin düzeyleri koroner yavaş akım fenomeni için öngördürücü olabilir

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ABSTRACT

Aim: To examine the association between plasma levels of β-2 microglobulin (β-2M), a protein previously associated with atherosclerosis, and the presence of coronary slow flow phenomenon (CSFP).
Material and Methods: 124 subjects who admitted to cardiology outpatient clinic with chest pain and directed to coronary angiography were investigated. Sixty-six of them had healthy coronary arteries and the others coronary slow flow. Venous blood samples were obtained to determine β-2M levels. TIMI frame count (TFC) was used to assess the classification of slow flow.
Results: Patients with coronary slow flow had higher levels of β-2M levels than healthy controls (2042.0 ± 660.2 and 1692.7 ± 403.4 ng / mL respectively) and the difference was statistically significant (p<0.001). β-2M levels were positively correlated with TFC (r=0.262, p= 0.003). Although groups were different in terms of β-2M, LDL and total cholesterol, Receiver operating characteristic (ROC) curve analysis demonstrated stronger predictive value of β-2M compared to LDL or total cholesterol in predicting the presence of CSF in our study population (area under curve [AUC] 0.748, 0.632 and 0.581; p<0.001, p=0.025 and p= 0.061 respectively).
Conclusion: High serum β-2M levels can be used as a biomarker to evaluate the slow flow.

Key words: beta-2 microglobulin, coronary slow flow

ÖZ

Amaç: Bu yazının amacı, daha önce ateroskleroz ile ilişkili olduğu saptanan bir protein olan β-2 mikroglobulin (β-2M) plazma seviyeleri ile koroner yavaş akım varlığı arasındaki ilişkiyi incelemektir.
Gereç ve Yöntemler: Göğüs ağrısı ile kardiyoloji polikliniğine başvuran ve koroner anjiyografiye yönlendirilen 124 olgu incelendi. 66'sında normal koroner arterler, diğerlerinde koroner yavaş akım vardı. β-2M seviyesini belirlemek için venöz kan örneklerinden elde edilen plazma numuneleri toplandı. Yavaş akım sınıflandırmasını değerlendirmek için TIMI kare sayısı (TFC) kullanıldı.
Bulgular: Koroner yavaş akımlı hastalarda beta-2 mikroglobulin düzeyleri sağlıklı kontrollere göre (sırasıyla 2042.0 ± 660.2 ve 1692.7 ± 403.4 ng / mL) daha yüksekti ve fark istatistiksel olarak anlamlıydı (p < 0.001). β-2M düzeyleri TFC ile pozitif korelasyon gösterdi (r= 0.262, p = 0,003). Gruplar β-2M, LDL ve total kolesterol açısından farklılık gösterse de, işlem karakteristik eğrisi (ROC) analizi, çalışma popülasyonumuzda koroner yavaş akım varlığını tahmin etmede LDL ve total kolesterole kıyasla β-2M'nin daha güçlü öngörücü değerini göstermiştir (ROC eğrisinin altında kalan alan [AUC] 0.632, 0.581 ve 0.748; p=0.025, p=0.061 ve p<0.001 sırasıyla).
Sonuç: Yüksek serum beta-2 mikroglobulin düzeyleri yavaş akım varlığını değerlendirmek için bir biyobelirteç olarak kullanılabilir.

Anahtar kelimeler: beta-2 mikroglobulin, koroner yavaş akım

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INTRODUCTION

The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by delayed distal vessel opacification in the absence of significant epicardial coronary disease. This phenomenon has clinical importance because it may be the cause of angina at rest or during exercise. In patients with CSFP, hospitalization and diagnostic catheterization rate is high due to chest pain, however the prognosis is as good as that of the normal population [1]. Although some underlying etiologies such as abnormally high microvascular resistance and widespread atherosclerosis of coronary arteries have been proposed, the exact pathophysiological mechanism of this phenomenon remains unclear. It is thought to be a form of microvascular circulation defect and a precursor of an occlusive epicardial artery disease [2].

There have been many studies in which the relationship between serum biomarkers and the presence and severity of CSFP was investigated. Considering that one of the underlying important mechanisms is endothelial dysfunction, beta-2 microglobulin (β-2M) levels, which have been found to be high in those with endothelial dysfunction recently and which are considered to be predominant in pathologies such as coronary artery disease and diabetic nephropathy, are unknown in CSFP [3-4]. Ballew et al. found that β-2M would provide better cardiovascular risk prediction than serum creatinine in chronic kidney disease [5]. In another study, Amighi and his colleagues determined that β-2M was independently associated with adverse cardiovascular outcome in asymptomatic carotid atherosclerosis [6].

In this study, we examined the association between coronary slow flow and plasma β-2M levels

MATERIAL AND METHODS

Study population

The cohort study, performed between January 2019 and September 2019, consisted of 58 patients with coronary slow flow and 66 patients with normal coronary arteries displayed with angiography. Normal coronary angiography was described as coronary epicardial vessels without any lesions including plaque and slow flow as epicardial vessels with the TFC levels above the determined limits, and without any other lesions. Chronic or acute renal disease, viral infections, history of any cancer type, multiple myeloma, hemodynamic factors that can decrease coronary flow such as hypotension or bradi-tachyarrhythmias, were exclusion criteria. The study protocol was approved by the Ethics Committee of Çukurova University Medicine School and performed in accordance with the Declaration of Helsinki.

Laboratory analysis

Laboratory analysis included routine complete blood count, kidney and liver function tests, lipid profile, C reactive protein (CRP) and sedimentation rate. 12 hours fasting venous blood samples were obtained and serum lipid levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol and triglycerides (TG) were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA) using commercial kits (Abbott). LDL was measured with direct method and CRP concentration was measured by the nephelometric method. These routine tests were done before angiography. From patients with slow flow, beta-2 microglobulin levels were studied after angiography. Serum β-2M levels were examined using flow cytometry method.

Calculation of TIMI Frame Count

The time required for a coronary artery to reach a specified point distally from the beginning of filling was calculated as a cine-frame and named the TIMI frame count (TFC), which is used to standardize slow flow. The distal point is the distal bifurcation of the left anterior descending artery (LAD), the distal bifurcation of the longest branch for the circumflex artery (Cx), the first lateral branch of the posterolateral artery (PL) for the right coronary artery (RCA). The measurements showed that LAD was 1.7 times longer than RCA and Cx, and the calculated LAD frame number was divided by 1.7 and corrected. The slow and normal coronary flow pattern limits reported in the literature for each coronary artery were 36.2 ± 2.6 squares for LAD, 22.2 ± 4.1 squares for Cx and

20.4 ± 3 squares for RCA [7].

Statistical analysis

All statistical analysis were performed with an SPSS 17 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables characterized by normal distribution were expressed as mean ± standard deviation (mean ± SD) and categorical variables as numbers and percentages. Comparisons of the continuous variables between groups were performed using the independent samples t-test and categorical variables with chi-square test as appropriate and correlations between variables using the Pearson product-moment correlation analyses. A two-tailed p value of less than 0.05 was considered as significant. A receiver operating characteristic (ROC) curve was constructed to determine the diagnostic accuracy of variables. The optimal cut-off of β-2M as well as the sensitivity and specificity of the test was calculated using the Youden index.

RESULTS

The control group with normal coronary arteries consisted of 31 males and 35 females, whereas the coronary slow flow group comprises 32 males and 26 females. The mean age of control group was 51± 8 years while it was 52 ± 7 years in the coronary slow flow group. The demographic characteristics of groups and laboratory tests are expressed in Table 1.

Inflammation markers such as sedimentation rate and CRP were similar (p=0.370 and 0.249) and there was no difference between whole blood counts between the groups. Coronary slow flow patients had higher levels of total cholesterol and LDL levels from controls and it was statistically significant (p<0.01).

The coronary angiography results showed that 30 patients (51%) had SCFP in LAD, 5 patients (9%) in Cx, 6 patients (10%) in RCA and 17 patients (30%) in two or more vessels. β-2M levels were higher at RCA slow flow than LAD or Cx. Mean β-2M levels were 2431.0 ± 885.6 ng/ mL for RCA, 2067.1 ± 692.7 ng/ mL for LAD and 2140.3 ±808.1 ng/ mL for Cx and the difference between subgroups was statistically significant (p= 0.001). Mean TIMI frame count of coronary slow flow patients was 31.24 ± 4.00 and 27.32 ± 2.99 for controls (p<0.001) (Figure A). β-2M was positively correlated with TFC (r= 0.262, p= 0.003) (Figure B). In subgroup analysis, non-RCA and RCA groups were differed in terms of TFC, but there was not any difference for other epicardial arteries (p= 0.013 for RCA, p=0.672 for LAD and p=0.812 for Cx).

Table 1-Demographic characteristics and laboratory results of groups, and statistical analysis

Variables	Control group (n=66)	Slow flow group (n=58)	p value
Female n, (%)	35 (53)	26 (45)	0.506
Age, years	51 ± 8	52 ± 7	0.193
Triglycerides (mg/dL)	201.5 ± 15.2	224.3 ± 19.4	0.472
HDL (mg/dL)	41.4 ± 8.1	42.4 ± 7.9	0.482
LDL (mg/dL)	121.1 ± 27.2	139.8 ± 33.0	0.002*
T.Cholesterol (mg/dL)	192.6 ± 45.9	214.3 ± 44.4	0.004*
Creatinine (mg/dL)	0.65 ± 0.13	0.67 ± 0.12	0.480
ALT (U/L)	19.9 ± 10.4	21.3 ± 10.4	0.445
WBC (x 103/mL)	8.1 ± 2.1	7.8 ± 1.6	0.451
HGB (mg/dL)	13.5 ± 1.6	13.7 ± 1.6	0.393
PLT (x 103/mL)	242.6 ± 52.8	257.3 ± 65.6	0.159
CRP (mg/L)	3.9 ± 4.8	5.1 ± 5.6	0.249
Sedimentation (mm/s)	9.4 ± 6.4	10.7 ± 8.8	0.370
Beta-2 microglobulin (ng/mL)	1692.7 ± 403.4	2042.0 ± 660.2	<0.001*

HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transaminase, WBC: white blood count, HGB: hemoglobin, PLT: platelets, CRP: c- reactive protein, * statistically significant

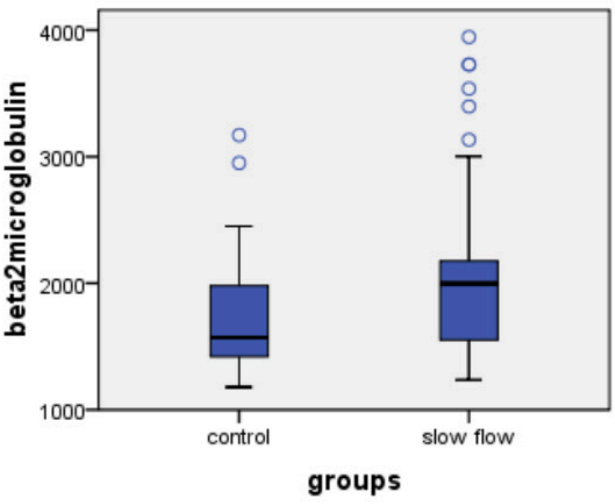


Figure A- Beta-2 microglobulin levels of groups

The coronary slow flow was positively correlated with LDL, total cholesterol and β-2M levels (p=0.002, r=0.295 ; p=0.009, r=0.233 and p<0.001, r=0.310 respectively). The correlation between coronary slow flow and β-2M was higher.

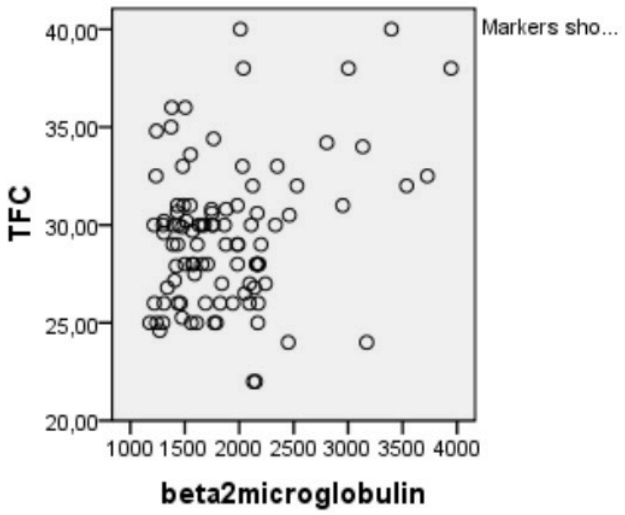
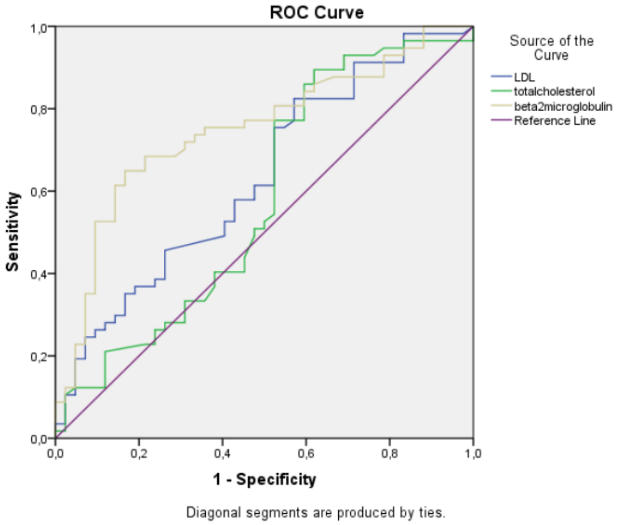


Figure B- Correlation between Beta-2 microglobulin and TFC

ROC curve analysis showed β-2M level moderately predicted diagnosis of CSFP with an area under the curve (AUC) of 0.748. The optimal cut-off value of β-2M for predicting CSF was 1551 ng/mL (75% sensitivity and 66% specificity, 95% CI: 0.650-0.846, p<0.001) (Figure C).



Variables	Area Under the Curve	95 % CI	p value
Beta-2 microglobulin	0.748	0.650-0.846	<0.001
LDL	0.632	0.522-0.743	0.025
Total cholesterol	0.581	0.462-0.700	0.061

Figure C- ROC plot for beta-2 microglobulin, LDL and total cholesterol

DISCUSSION

The coronary slow flow is the slow progression of contrast agent in the coronary bed, although there are normal or near-normal coronary arteries angiographically. Though the pathophysiology is not clear, microvascular disease is thought to be at the forefront. Patients with CSF may admit to the outpatient clinic with atypical chest pain, exercise angina, unstable angina pectoris, non-Q MI and Q wave MI [8]. The left anterior descending (LAD) artery is most often involved, followed by RCA and the Cx [9]. In our study, distribution of slow flow was similar to these results.

Some studies have reported male gender as a predictor of the coronary slow flow phenomenon, while others have found no relation between sex and slow flow [10]. 55% of the study population was male but there was no relation established between sex and CSFP in this paper. Although previous observational studies have concluded that these patients have good prognosis, Zhu et al. revealed that an age above 50 and dyslipidemia are associated with adverse outcome in patients with CSF [11]. The mean age of the CSF group was 53 and the groups differed in terms of LDL and total cholesterol levels in our study.

The coronary slow flow phenomenon is accepted as a spectrum of coronary artery disease and coronary artery endothelial dysfunction. The mechanism for the association between β-2M and coronary artery disease remains unclear, but the relationship between β-2M and immunity and inflammation disorders suggests that β-2M may play a role in vascular inflammation [12]. Several biomarkers such as omentin -1, endocan, adropin and sLOX-1 have been shown to be related to the presence and severity of coronary artery slow flow [13-14-15-16]. Lovren et al. stated that adropin levels were found to be lower in patients with coronary slow flow and negatively correlated with mean TFC. They claimed that adropin is expressed in coronary artery endothelial cells and it plays a potential endothelial protective role [16]. To the contrary of adropin, results of our study showed that increased β-2M levels may be a predictive biomarker for the coronary slow flow.

β-2M is a low-molecular-weight protein released by activated T and B lymphocytes. The estimated

half-life time is short (2 h) [17]. β-2M has been shown to increase in several inflammatory and hematologic disorders, such as systemic lupus erythematosus, acquired immunodeficiency syndrome, multiple myeloma, lymphoma and leukemia [18-19-20]. To our knowledge, β-2M in the coronary slow flow has not been evaluated. Our study is the first to investigate the relationship between β-2M and the coronary slow flow.

Serum beta-2 microglobulin is a well-established prognostic factor in multiple myeloma and follicular lymphoma [21]. Univariate analysis of prognostic factors revealed that poor performance status [Eastern Cooperative Oncology Group Performance scale (ECOG PS) ≥2] and elevated serum β-2M (≥1.8 g/mL) were significantly associated with shorter overall survival. Serum β-2M levels were significantly predictive of poor prognosis according to univariate analysis. Most studies defined a cut-off level of serum β-2M level between 2.0 to 3.5 and analysis showed 1.8 as the best cut-off level to establish a significant survival benefit [22]. Although the mechanism underlying the negative prognostic impact of elevated serum β-2M is unclear, a widely accepted hypothesis is that it is related to high tumor burden [23]. This data supports the role of inflammation and beta 2 microglobulin.

In our study, β-2M levels were higher in patients with the coronary slow flow than controls and β-2M was positively correlated with serum LDL and total cholesterol. β-2M had the most considerable effect on the coronary slow flow phenomenon. Furthermore, patients with the coronary slow flow in RCA had higher levels of β-2M and also higher TFC levels than others.

As a result, β-2M may reflect the prevalence of the coronary slow flow phenomenon and there was a weak correlation between β-2M levels and the severity of disease. β-2M could be a potential indicator of the CSFP.

Our study had some limitations namely that it was a single center study and had no follow-up period. Additionally, the study population was small and the groups differed in terms of LDL cholesterol that leads to endothelial dysfunction and microvascular disease. Finally, there was no designated treatment protocol.

CONCLUSION

We demonstrated that elevated serum β-2M levels were independently associated with the presence of angiographically proven coronary slow flow phenomenon, and a weak correlation between the severity of the disease and β-2M. Further studies are needed to support the usability of β-2M as a biomarker for the coronary slow flow.

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