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Relation of serum immunoglobulin E level with coronary artery disease and SYNTAX score

Serum immunglobulin E seviyesi ile koroner arter hastalığı ve SYNTAX skoru arasındaki ilişki

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Abstract

Aim: Inflammation has a significant role in the pathogenesis of atherosclerosis and allergic inflammation has also an important impact on atherosclerosis progression. In this study, we investigated whether the serum IgE levels are associated with coronary artery disease (CAD) and SYNTAX score as a parameter for severity of the disease.

Methods: A total of 171 patients who were planned coronary angiography were recruited consecutively into this study. The patients who had a diagnosis of asthma, autoimmune diseases, allergic dermatitis, history of allergic diseases, parasitic infections, malignancy, severe renal failure (estimated glomerular filtration rate <30 mL/min), chronic hepatic disease, rheumatic and valvular heart diseases were excluded from the study. The patients were divided into two groups according to the presence of CAD as called CAD and non-CAD groups. CAD was diagnosed according to the presence of more than 50% stenosis at least in one main coronary artery. Two expert cardiologists who were blinded to the patients' clinical and laboratory data reviewed the coronary angiography and evaluated the coronary atherosclerotic lesion severity independently. The SYNTAX score is calculated using the algorithm on the baseline diagnostic angiogram. Serum samples for determining total serum levels of IgE were collected from the patients were at the admission just prior to coronary angiography.

Results: Based on the coronary angiography, 88 patients (51.5%) were in the non-CAD and 83 patients (48.5%) were in the CAD group. CAD patients tend to be older (61.9±11.6 years vs 56.7±9.7years, p=0.002) and male (67.5% vs.47.7%, p=0.009) with a higher prevalence of hypertension (80.7% vs 63.6%, p=0.013), and hyperlipidemia (63.9% vs 28.4%, p<0.001) compared to non-CAD patients. The serum IgE levels were significantly higher in the CAD group than those in the non-CAD group (99.05 IU/ml (51-192) vs. 24.25 IU/ml (13.8-55), p<0.001). By multivariate logistic regression analysis, serum IgE levels were found as an independent predictor for CAD (OR 1.003; 95% CI 1.000–1.005; p=0.041). In addition, there was a positive moderate correlation between SYNTAX score and Ig E levels (r:0,483, p<0.001).

Conclusion: In this trial, we showed that the serum IgE levels are positively associated with the presence of CAD even after adjusting for traditional cardiovascular risk factors. Furthermore, serum IgE levels are correlated with the SYNTAX score and the complexity of coronary artery disease.

Key words : Immunoglobulin E, coronary artery diseae, atherosclerosis, SYNTAX score, allergic inflammation

Öz

Amaç: İnflamasyon aterosklerozun patogenezinde önemli bir role sahiptir. Alerjik inflamasyonun da aterosklerozun ilerlemesinde önemli bir etkisi mevcuttur. Çalışmamızda IgE düzeyi ile koroner arter hastalığı (KAH) arasında ilişki olup olmadığına baktık. Ayrıca ek olarak IgE ile KAH ciddiyetini gösteren SYNTAX skoru arasındaki ilişkiyi de değerlendirdik.

Metot: Çalışmaya ardışık olarak 171 tane koroner angiografi planlanan hasta alındı. Astım, oto immun hastalık, alerjik dermatit, alerji öyküsü, parazit infestasyonu, kanser, ciddi böbrek yetmezliği (glomeriüler filtrasyon hızı <30 ml/min), kronik karaciğer hastalığı, romatizmal kalp hastalığı, kalp kapak hastalığı olanlar dışlandı. Hastalar KAH varlığına göre olan ve olmayan diye iki gruba ayrıldı. En az bir ana koroner arterde %50 ve üzeri darlık KAH olarak değerlendirildi. Hastaların klinik ve laboratuvar sonuçlarından bağımsız olarak 2 kardiyoloji uzmanı tarafından KAH ciddiyeti SYNTAX skoru algoritmasına göre değerlendirildi. IgE düzeylerine ilk başvuruda, koroner angiografi öncesinde alınan venöz kan tahlillerinde bakıldı.

Sonuçlar: Koroner angiografi sonuçlarına göre 88 hasta (%51,5) KAH olan ve 83 hasta (%48,5) ise KAH olmayan olarak değerlendirildi. KAH olan grupta olmayan gruba göre yaş ortalaması daha yüksek (61,9±11,6 yıl vs 56,7±9,7 yıl, p:0,002), erkek cinsiyet daha fazla (67,5% vs.47,7%, p:0,009), hipertansiyon (80,7% vs 63,6%, p:0,013) ve hiperlipidemi (63,9% vs 28,4%, p<0,001) prevelansları daha fazla idi. Serum IgE düzeyleri KAH olan grupta olmayan gruba göre (99,05 IU/ml (51-192) vs. 24,25 IU/ml (13,8-55), p<0.001) daha yüksek idi. Çoklu logistik regresyon analizine göre IgE düzeyleri KAH için bağımsız bir faktör olarak bulundu (OR 1,003; 95% CI 1,000–1,005; p=0,041). Ek olarak, serum IgE düzeyleri ile SYNTAX skoru arasında orta derecede pozitif bir korelasyon tespit edildi (r:0,483, p<0,001).

Sonuç: Çalışmamızda geleneksel risk faktörleri düzenlendikten sonra, serum IgE düzeylerinin KAH varlığı açısından bağımsız pozitif bir faktör olduğu gösterildi. KAH ciddiyetini gösteren SYNTAX skoru ile serum IgE düzeyleri arasında orta derecede pozitif bir korelasyon tespit edildi.

Anahtar Kelimeler: Immunoglobulin E, koroner arter hastalığı, aterosklerozis, SYNTAX skoru, alerjik inflamasyon

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Introduction

Atherosclerosis is an inflammatory disease associated with multiple risk factors and a complex pathophysiology. Inflammation has a significant role on pathogenesis of atherosclerosis, initiation and progression of coronary plaque formation [1-2]. In addition, inflammation is associated with coronary plaque instability, stent thrombosis and in stent restenosis after stent implantation [3-4]. Although main classic inflammatory process is mediated by macrophages, neuthrophils and Th-1 lymphocytes, allergic inflammation also has an important impact on atherosclerosis progression. Immunoglobulin E (IgE) is a key component of response to allergens/antigens in atopic diseases and systemic anaphylaxis [5]. Biological activity of Ig E occurs via binding to Fc receptors which are present at the surface of mast cells (MCs), basophils, and monocytes. Mast cell accumulation has been shown in the coronary atheromatous lesions, especially at the actual sites of coronary plaque erosion or rupture; therefore, mast cell activation has been accepted as one of the mechanisms related to allergic inflammation with atherosclerotic disease progression [6]. On the recent studies, the relation between IgE level and atherosclerosis has been investigated and elevated Ig E levels were detected in the patients with coronary artery disease. Guo et al. [7] showed the relation between increased total serum IgE levels and coronary artery disease (CAD) and severity of CAD independently of traditional cardiovascular risk factors. Also some studies have evaluated the association between elevated Ig E and coronary artery plaque instabilization, and they observed higher mast cells and IgE levels within coronary artery walls in cardiac deaths from coronary artery thrombosis [5]. However, the relationship between total serum IgE levels and the SYNTAX score remains unclear.

In this study, we invastigated whether the serum IgE levels are associated with CAD and SYNTAX score.

Material and methods

A total of 171 patients who were planned coronary angiography between November 2019 and October 2020 on Fatih Medical Park Hospital were recruited consecutively into this study. The patients who had a diagnosis of asthma, autoimmune diseases, allergic dermatitis, history of allergic diseases, parasites infection, malignancy, severe renal failure (estimated glomerular filtration rate <30 mL/min), chronic hepatic disease, rheumatic and valvular heart diseases were excluded from study. Also, patients admitted to hospital with decompansated heart failure or shock were also excluded from the study. This study was approved by the ethics committee of Bahcesehir University (12/18/2019 and 2019-19/04) and conducted according to the principles described in the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Coronary angiography and image interpretation

Coronary angiography was performed with standart radial or femoral approach with an angiography unit (Axiom Artis, Siemens). CAD was diagnosed according to the presence of more than 50% stenosis at least in one main coronary arter. Two expert cardiologists who were blinded to the patients' clinical and laboratory data reviewed the coronary angiography and evaluated the coronary atherosclerotic lesion severity independently. SYNTAX score was calculated using the SYNTAX score algorithm on the baseline diagnostic angiogram [8].

Blood samples and definitions

Hypertension and diabetes were diagnosed according to the current guidelines [9-10]. Blood for determining total serum levels of IgE was collected from the patients at the admission just prior to coronary angiography. After an overnight fast for 12 hours, peripheral venous blood was drawn from all the patients to examine complete blood count and biochemical analysis.

Variables

Demographic data (age, sex, body mass index), clinical features (coexisting diseases, drug usage and laboratory analysis including white blood cell count (WBC) (K/uL), hemoglobin (gr/dL), hematocit (%), platelet count (K/uL), mean corpuscular volüme (MCV) (fl), neutrophil, lymphocyte and eosinophil counts (K/uL), low density lipoprotein-cholesterol (LDL-c) (mg/dL) and creatinine were evaluated and recorded.

Statistical analysis

Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov or Shapiro–Wilk's test) to determine whether or not they were normally distributed. Continuous variables with parametric distribution were expressed as mean ± standard deviation and with non-parametric distribution were expressed as median and interquartile range. Parametric continuous variables were analyzed using the Student T test and non parametric contionuous varaibles were analyzed with Mann-Whitney U test. Categorical data were expressed as frequencies and their differences were analysed using the Chi-squared test. Immunglobulin E levels and SYNTAX score results that were anormally distributed, and correlation coefficients and their significance were calculated using the Spearman test. A multiple logistic regression model was used to identify independent predictors of the for the coroner artery disease. Age, gender, hypertension, diabetes mellitus, dyslipidemia, baseline creatinine level, baseline neutrophil count and acetylsalicylic acid (ASA) usage were included in multiple logistic regression analysis. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, Illinois, USA). Statistical significance was taken as $p < 0.05$.

Results

Based on the coronary angiography, 88 patients (51.5%) were in the non-CAD and 83 patients (48.5%) were in the CAD group. The median SYNTAX score of the patients was 8 (IQR 5-14). The baseline clinical characteristics of the patients in the CAD and non-CAD groups are summarized in Table 1. CAD patients tend to be older (61.9±11.6 years vs 56.7±9.7 years, p=0.002) and male (67.5% vs.47.7%, p=0.009) with a higher prevalence of hypertension (80.7% vs 63.6%, p=0.013) and hyperlipidemia (63.9% vs 28.4%, p<0.001) compared to non-CAD patients. The number of patients on regular antithrombotic and antihyperlipidemic treatments were higher on the CAD group. The serum IgE levels were significantly higher in the CAD group than those in the non-CAD group (99.05 IU/ml (IQR 51-192) vs. 24.25 IU/ml (IQR 13.8-55), p<0.001). The CAD patients also had higher creatinine (0.84 mg/dl (IQR 0.78-1) vs. 0.81 mg/dl (IQR 0.69-0.92), p=0.007) and neuthrophil count (5.3 ±1.9 K/uL vs. 4.5 ±1.6 K/uL) when compared to non-CAD patients (Table 2). By multivariate logistic regression analysis, serum IgE levels were found as an independent predictor for CAD (OR 1.003; 95% CI 1.000–1.005; p=0.041) after adjusting for age, gender, diabetes, hypertension, hyperlipidemia, ASA usage, serum creatinine and neuthrophil counts (Table 3). In

addition, there was a positive moderate correlation between SYNTAX score and Ig E levels (r=0.483, p<0.001) (Figure 1).

Table 1: Demographic and baseline clinical characteristics of the non-cardiac disease (non-CAD) group and cardiac disease (CAD) group.

Variable		non-CAD group (n=88)	CAD group (n=83)	p
Age (years) [β]		56.7±9.7	61.9±11.6	0.002
Male sex [¥]		42 (47.7)	56 (67.5)	0.009
BMI (kg/m^2) [β]		29.5±5.5	29.8±7.8	0.841
Hypertension [¥]		56 (63.6)	67 (80.7)	0.013
Hyperlipidemia [¥]		25 (28.4)	53 (63.9)	<0.001
Diabetes mellitus [¥]		21 (23.9)	28 (33.7)	0.154
Chronic kidney disease [¥]		2 (2.3)	3 (3.6)	0.603
Atrial fibrillation [¥]		5 (5.8)	6 (7.4)	0.678
Drugs [¥]	ASA	34 (38.6)	49 (60.5)	0.005
	Beta-bloker	40 (45.5)	49 (60.5)	0.06
	Statin	14 (15.9)	37 (45.7)	<0.001
	ACE	18 (20.5)	17 (21.0)	0.932
	ARB	14 (15.9)	17 (21.0)	0.394
	CCB	22 (26.1)	26 (32.1)	0.152
	Oral AD	17 (19.3)	23 (28.4)	0.165
	Insulin	3 (3.4)	6 (7.4)	0.248

[β]: mean±standard deviation, [¥]: n (%). BMI: Body mass index, ASA: acetyl salicylic acid, ACE: Angioconverting enzyme, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, AD: antidiabetics.

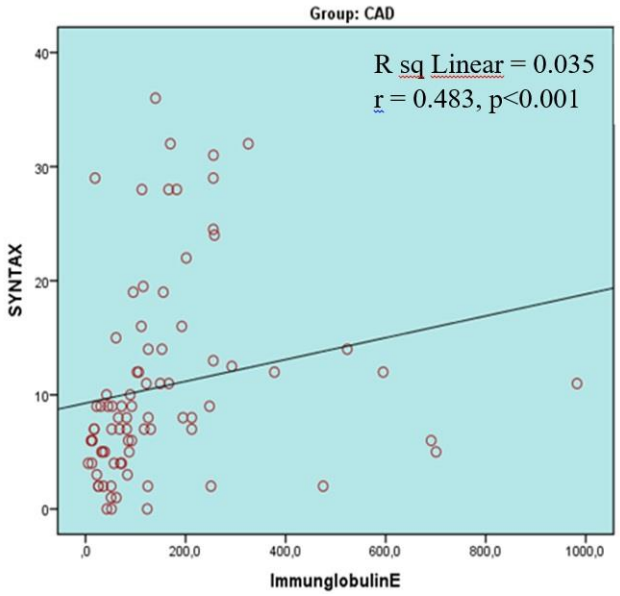


Figure 1: IgE and SYNTAX score correlation curve.

Table 2: Laboratory values of the non-cardiac disease (CAD) group and cardiac disease (CAD) groups.

Variables	non-CAD group (n=88)	CAD group (n=83)	p
WBC (K/uL) [β]	7.6±2.1	8.2±2.3	0.076
HGB (gr/dL) [β]	13.6±1.8	14±1.7	0.106
HCT (%) [β]	41.2±3.8	41.9±4.6	0.283
PLT (K/uL) [β]	260.2±65.8	252.3±61.9	0.365
MCV (fl) [β]	86.1 (81.1-89.3)	85.4 (82.1-88.5)	0.883
NEU (K/uL) [β]	4.5±1.6	5.3±1.9	0.003
Lymphocyte (K/uL) [β]	2.4±0.9	2.1±0.7	0.076
Eosinophil (K/uL) [µ]	0.16 (0.9-0.25)	0.16 (0.11-0.26)	0.686
LDL-c (mg/dL) [β]	129.6±41.7	138.6±49.6	0.204
Creatinine (mg/dL) [µ]	0.81 (0.69-0.92)	0.84 (0.78-1)	0.007
IgE (IU/ml) [µ]	24.25 (13.8-55)	99.05 (51-192)	<0.001

[β]: mean±standard deviation, [µ]: median (interquartile range).
HGB: hemoglobin, HTC: hematocrit, MCV: mean corpuscular volume, WBC: White blood cell, NEU: Neutrophil, LDL-c: Low density lipoprotein cholesterol, IgE: Immunglobulin E.

Table 3 : Independent predictors of coronary artery disease.

Variable	OR (95% Confidence Interval)	p
Age	1.057 (1.016 – 1.10)	0.006
Sex	2.330 (1.018 – 5.336)	0.045
Hypertension	1.016 (0.368- 2.809)	0.975
Diabetes mellitus	0.886 (0.373- 2.104)	0.784
Dyslipidemia	4.366 (1.813 – 10.512)	0.001
Baseline creatinine	0.638 (0.171 – 2.374)	0.502
Baseline neutrophil	1.304 (1.050- 1.619)	0.017
ASA usage	0.802 (0.369- 1.742)	0.802
IgE levels	1.003 (1.000 – 1.005)	0.041

OR: Odds ratio, ASA: acetyl salicylic acid

Discussion

In this study, we demonstrated a significant association between total serum IgE levels and CAD. Also, we found a positive correlation between SYNTAX score and IgE. In the previous study, the relation between SYNTAX score and serum tryptase level was demostrated [11]. But according to our knowlodge, this is the first study that evaluates the relationship with Ig E and SYNTAX score. Monocytes/macrophages, neutrophils, and T cells, mediated classic inflammatory responses have been found to be involved in the process of atherogenesis. In addition to that, many studies demonstrated that cellular mediators of allergic inflammation also may play a role in coronary artery plaque formation and progression [5]. Ig E has significant role in formation of allergic inflammation via activating mast cells by binding to its high-affinity receptor FcεR1 [5]. Previous studies demonstrated that number of mast cells increase with disease progression in atherosclerotic plaques and activated mast cells have a pro-atherogenic role in the pathogenesis of CAD [12]. Also, mast cells may play a role in

coronary plaque instability via causing intraplaque hemorrage [13]. Furthermore, IgE can interact with other types of immune cells, such as monocytes and their derivatives, macrophages, which then facilitate the pathogenesis of atherosclerosis by allergy-related mechanisms [14]. In these ways, Ig E may contribute the pathogenesis of CAD. There are numerous investigations have suggested the existence of possible links between atopy/allergic inflammation, high serum IgE, coronary artery atherosclerosis development, and acute coronary syndromes.

Firstly, Criqui et al. [15] investigated the association of serum IgE levels with myocardial infarction, stroke, and noninvasively diagnosed large-vessel peripheral arterial disease. They found a relation between IgE and cardiovascular disease in men but not in women. Szczeklik et al. [16] demonstrated increased IgE levels in the patients that admitted on hospitals with acute myocardial infarction levels. Similarly, in the recent studies had results confirms Szczeklik's results [16] in patients with myocardial infarction and unstable angina pectoris. In our study, we also found that the patients with coronary artery disease have higher serum Ig E levels compared to individuals with normal coronary arteries.

In terms of the relation between severity and Ig E, Guo et al. [7] evaluated the association with Gensini score and Ig E level, and they found a significant linear relation between Gensini score and the serum IgE level. Tryptase, a neutral protease selectively concentrated in the secretory granules of human mast cells, is released by mast cells and it has been used as a marker of mast-cell activation. Morici et al. [17] assessed the association between serum tryptase and the occurrence of major cardiovascular and cerebrovascular events (MACCE) at 2-year follow-up in patients admitted with acute coronary syndrome (ACS). In this trial, showed a significant correlation between serum tryptase level and MACCE and also there was a positive correlation between SYNTAX score and MACCE. However, in this study, no significant correlations between tryptase and SYNTAX score were found.

According to our knowledge, there is not any trial that evaluated the relation between IgE level and SYNTAX score. Our aim in this study to evaluate this relation and we found a statistically significant relation between SYNTAX score and serum Ig E level. So, according to this result Ig E may predict severity and complexity of coronary artery disease.

The main limitations of this study were small number of study population and the SYNTAX score of this study population was low. So, we couldn't divided the study population into groups according to SYNTX score.

In conclusion, in this trial we showed that the serum IgE levels are positively associated with the presence CAD even after adjusting for traditional cardiovascular risk factors. Furthermore, serum IgE levels are correlated with SYNTAX score and complexity of coronary artery disease.

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