Investigation of the relationship between serum homocysteine levels and cardiac markers and biochemical parameters in ST-elevated myocardial infarction

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SUMMARY

Although electrocardiographic changes are used widespreadly to characterize patients presenting with myocardial infarction (MI), little is known about recent incidence rates, treatment, and outcomes of patients presenting for MI, which is also stratified by ST-segment elevation (STEMI). Homocysteine (Hcy) metabolism is essential in methionine availability, protein homeostasis, and DNA methylation. Therefore, it is necessary in post-genomic and epigenetic regulation mechanisms. As a result, impaired Hcy metabolism leading to high Hcy concentrations in blood plasma (hyperhomocysteinemia) is linked to the excessive free-radical production. The aim of this study is to evaluate the relationship between routinely-measured cardiac parameters, lipid profile, homocysteine and lipoprotein (a) levels in the diagnosis of STEMI. The study subjects comprised 100 patients diagnosed with STEMI and 100 healthy individuals. Homocysteine, lipoprotein (a), cardiac parameters and routine biochemical parameters were measured in serum obtained from blood samples taken from patients and healthy individuals.

The study indicates that in the patient group, leukocyte ($p< 0.01$), neutrophil ($p< 0.01$), CRP ($p< 0.01$), total cholesterol ($p< 0.01$), LDL-cholesterol ($p< 0, 01$) levels were found to be higher. Lymphocyte count, albumin ($p< 0.05$), uric acid ($p< 0.01$), and HDL-cholesterol ($p<0.01$) levels were found to be low. Again, CK ($p<0.01$), CK-MB ($p<0.01$), troponin ($p<0.01$), homocysteine ($p< 0.01$), and lipoprotein (a) ($p< 0.01$) levels were found to be higher in the patient group than in the control group. As a result, it can be concluded that the relationship between routinely-measured cardiac parameters, lipid profile, Homocysteine and lipoprotein (a) levels may be important in the diagnosis of STEMI, and the results obtained will make a base for further studies in this field.

Key words: Homocysteine – Lipoprotein (a) – Myocardial infarction – Heart diseases – Acute coronary syndrome

INTRODUCTION

Acute coronary syndrome (ACS), particularly myocardial infarction (MI), is associated with a systemic inflammatory response that can accel-

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erate coronary atherosclerotic processes, leading to plaque formation and increased risk of cardiovascular events (Aimo et al., 2021). ACS patients without ST elevation are divided into two groups: patients who do not have ST elevation, but have myocardial damage proven by elevation in damage markers [non-ST elevation myocardial infarction (NSTEMI)]; and patients with unstable angina (UA). The causes of UA and NSTEMI ACS are usually atherosclerotic diseases (Meriç, 2012). It has high mortality and morbidity rates worldwide (Sanchıs-Gomar et al., 2016). Therefore, cardiac biomarkers are important in providing specific, rapid results in diagnosing MI and non-cardiac cases (Yöntem et al., 2017).

In the past, cardiac biomarkers were only important for detecting acute myocardial infarction and monitoring myocardial necrosis. Biomarkers may be proteins or enzymes such as creatine kinase-myocardial band (CK-MB) and troponin, which occur due to myocardial ischemia or necrosis in the course of ACS. The use of cardiac biomarkers is essential for early diagnosis and risk assessment of ACS. Mediators that play a role in disease course may be potential treatment targets. Homocysteine metabolism is crucial for regulating methionine availability, protein homeostasis, and deoxyribonucleic acid (DNA) methylation, thus providing key pathways for post-genomic and epigenetic regulation mechanisms. As a result, impaired homocysteine metabolism and excessive free radical production, leading to high homocysteine concentrations in blood plasma (hyperhomocysteinemia), are associated with induced oxidative stress (Koklesova et al., 2019). Although a study reported that increased homocysteine levels increased the risk of coronary artery disease (CAD), research on the mechanism of homocysteine relationship with cardiovascular diseases is still continuing (Djurıc et al., 2018). Lipoprotein (a) is a molecule that is very similar to the low-density lipoprotein (LDL) molecule in structure, but differs from LDL due to the presence of apolipoprotein (a) linked to apo B100 via a disulfide bridge (Farzam And Senthılkumaran, 2022). This molecule, discovered by Berg in 1963, has been the subject of much debate, and it has been reported that it may play an essential role in the pathogenesis of atherosclerosis (Berg, 1963). This study aimed to investigate in individuals with ST-elevation myocardial infarction (STEMI) the relationship between some analytes, such as serum homocysteine and lipoprotein (a) levels, and cardiac and some biochemical parameters, and the importance of these parameters in diagnosing myocardial infarction.

MATERIALS AND METHODS

This study was conducted after the approval of Kafkas University, Faculty of Medicine Non-Interventional Clinical Research Ethics Committee dated 27/11/2019. Human Homocysteine (0.2-60 nmol/ml) was determined using an ELISA Kit (Bioassay Technology Laboratory), and lipoprotein (a) (0.23-15 ng/ml) with Human lipoprotein α, Lp-α ELISA Kit (Elabscience). In the study, 100 patients who were admitted to our University Health Research and Application Center and whose preliminary diagnosis of CAD was confirmed via angiographic evaluation (STEMI was diagnosed based on electrocardiogram (ECG) findings) and 100 healthy individuals matched with the patients were used as the control group. Troponin and cardiac biomarkers of the control group were found to be within normal limits, and there were no abnormal ECG findings. Similarly, individuals with heart failure, cardiomyopathy, pulmonary embolism, and substance abuse history were excluded from the study. Serum creatine kinase (CK), (38-174 UI/L) CK-MB, (0.6-208.7 ng/ml) total cholesterol, (201-239 mg/dl) LDL-cholesterol (LDL-C), (100-189,mg/dl) triglyceride, (150-199 mg/dl) High-density lipoprotein-cholosterol (HDL-C), (40-60 mg/dl) uric acid, (2.3-7.6 mg/dl) C-Reactive Protein (CRP), (0.1-96 mg/dl) albumin, (2.48-3.72 g/dl), and troponin I (0.2-8.0 ng/ml) were measured in the control and patient groups, and leukocytes, neutrophils, lymphocytes, and platelets were measured in the whole blood specimen. Blood samples, at the request of the relevant physician, from the patient and control groups were taken into hemogram tubes with Ethylenediaminetetraacetic acid (EDTA) for whole blood analyses, and into vacutainer containing gel for the reminder analytes, and the latter were centrifuged in a refrigerated centrifuge at 3,000 rpm for

15 minutes. The resulting sera were maintained at -80°C until the day of biochemical testing.

Biochemical measurements

For serum homocysteine and lipoprotein (a) analyses, ELISA (Enzyme-Linked Immuno Sorbent Assay) kits as mentioned above were used. A plate reader (Biotech) was used for the determination. The specimens of patients and controls were analyzed using a hemogram analyzer (ABX Pentra DX 120, Horiba Ltd, Japan), an electrochemiluminescence immunoassay analyzer (Cobas e601, Roche Diagnostics, Germany), and in a clinical chemistry analyzer (COBAS C 501, Roche Diagnostics, Germany). For the determination of total CK, CK-MB, total cholesterol, LDL-C, triglyceride, HDL-C, uric acid, CRP, albumin, and troponin I, and for leukocyte, neutrophil, lymphocyte, and platelet counting, commercial kits were used.

Ethics Committee Approval

This study was conducted after the approval of our University's, Faculty of Medicine Noninterventional Clinical Research Ethics Committee dated 27/11/2019.

Statistical analysis

The statistical analysis of the obtained data was performed using the SPSS 20.0 package program. Quantitative data are presented as standard error. In data analysis, the distribution of continuous variables was determined using the Kolmogorov-Smirnov normality test. The Mann-Whitney-U test was used to compare two independent groups of data that were found not to comply with normal distribution. The Spearman test was used in the correlation analysis. The p-value <0.05 was accepted as statistically significant.

RESULTS

The study was conducted with a total of 200 participants: 143 (71.5%) males and 57 (28.5%) females. The control group consisted of 65 males (65%) and 35 females (35%). The patient group included 78 (78%) males and 22 (22%) females. Pearson chi-square test was used to determine gender distribution between groups. A statistically significant difference was observed ($p<0.05$) (Fig. 1-A). The control group included 33 individuals with diabetes mellitus (DM), 43 individuals with hypertension, and 26 smokers, and the patient group covered 25 with diabetes mellitus (DM), 41 with hypertension, and 51 smokers. The presence of DM and hypertension between the groups was evaluated with the Pearson chi-square test, and no statistically significant difference was observed between the groups ($p>0.05$). Smoking was found to be statistically higher in the patient group ($p<0.001$) (Fig. 1-B).

Student t-test was applied to the complete blood count parameters of the control and patient groups. The leukocyte and neutrophil counts between the groups were statistically significantly higher in the patient group than in the control group ($p<0.001$). Lymphocyte counts were lower in the patient group ($p<0.01$) than in the control group. Although platelet counts were lower in the patient group compared to the control group, they were not statistically significant ($p>0.05$) (Fig. 2-A).

When the results of biochemical parameters of the control and patient groups were evaluated with the student t-test, it was observed that there were statistically significant increases in CRP, total cholesterol, and LDL-C levels between the groups ($p<0.001$, $p<0.01$, and $p<0.001$, respectively). On the other hand, statistically significant decreases were observed in serum albumin, uric acid, and HDL-C levels between the groups ($p<0.001$, $p<0.01$, and $p<0.001$, respectively). Triglyceride levels were found to be statistically insignificant and higher in the patient group than in the control group ($p>0.05$). Non-HDL-C levels were found to be lower in the patient group compared to the control group, although it was not statistically significant ($p>0.05$) (Fig. 2-B,C).

Statistically significant increases in cardiac markers (Troponin I, CK, CK-MB, lipoprotein (a), and homocysteine levels) were observed in the patient group compared with the control group ($p<0.001$) (Fig. 2-D, E). Spearman correlations between lipoprotein (a) and homocysteine levels and troponin levels in the patient group showed statistically significant positive relationships ($r = 0.609$, $p < 0.01$ for lipoprotein (a) vs. troponin, and $r = 0.593$, $p>0.01$ for Homocysteine vs. troponin

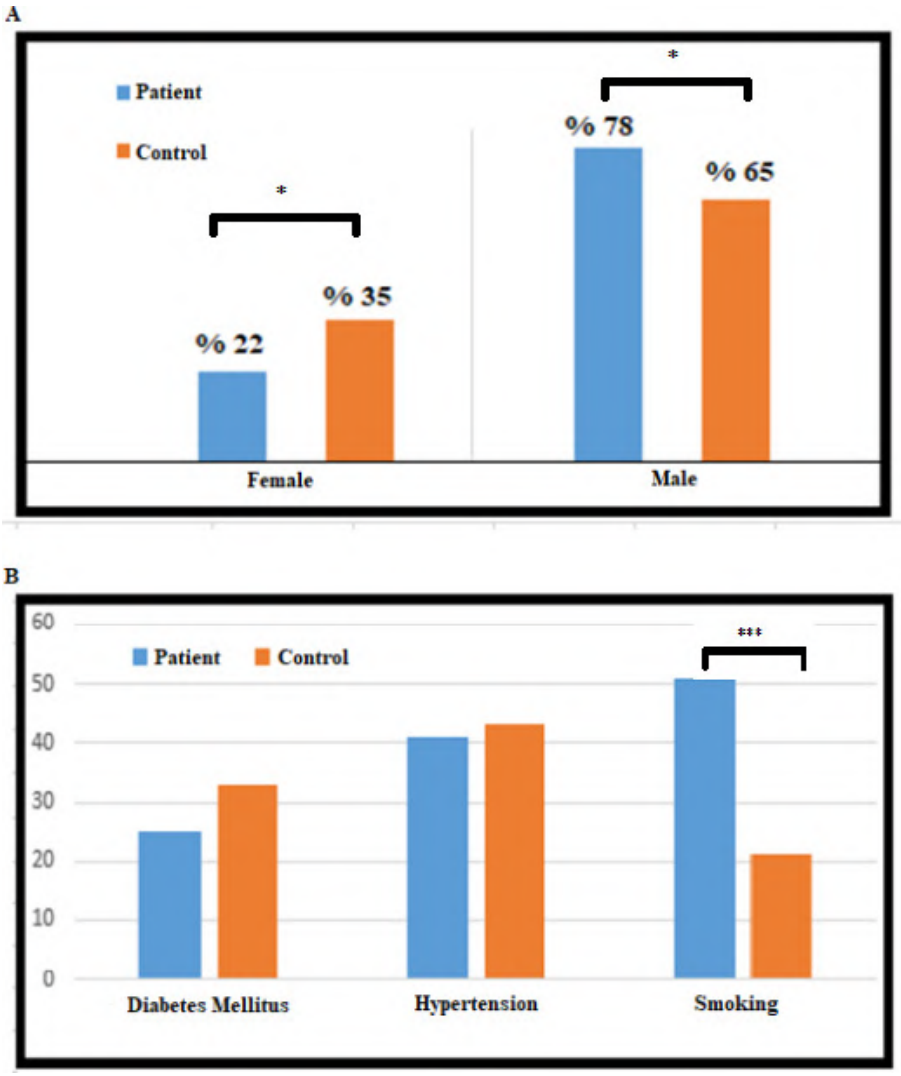

Fig. 1.- Comparison of gender distribution between groups and comparison of the presence of diabetes mellitus, hypertension and smoking according to groups. **A.** p<0.05; **B.** No statistically significant difference was observed between the groups in the presence of DM and hypertension (p>0.05). Smoking was found to be statistically higher in the patient group (p<0.001). Statistically significant: *: p<0.05, **: p<0.01, ***: p<0.001.

I, Fig. 3-A and B, respectively). Similarly, the correlations between cardiac parameters and troponin I levels exhibited statistically significant positive relationships in the patients: r =0.642, p<0.01 between troponin I and CK, r = 0.702, p<0.01 between troponin I and CK-MB, and r =0.232, p<0.01 between troponin I and LDL-C. Conversely, there was a statistically significant negative correlation between troponin I and HDL-C levels (r = - 0.344, p<0.01) (Table 1).

Table 1. Correlation coefficients between Lipoprotein (a), Homocysteine, LDL, HDL and Cardiac parameters and troponin I.

	CK-MB (ng/ml)	CK (UI/L)	Lipoprotein (a) (ng/ml)	Homocysteine (nmol/ml)	LDL (mg/dl)	HDL (mg/dl)
Troponin	,702**	,642**	,609**	,593**	,232**	-,344**
CK-MB		,854**	,513**	,520**	,265**	-,278**
CK			,517**	,557**	,267**	-,232**
Lipoprotein (a)				,477**	,241**	-,339**
Homocysteine					,209**	-,227**
LDL						-,168*

** Correlation is significant at p<0.01 level. * Correlation is significant at p<0.05 level.

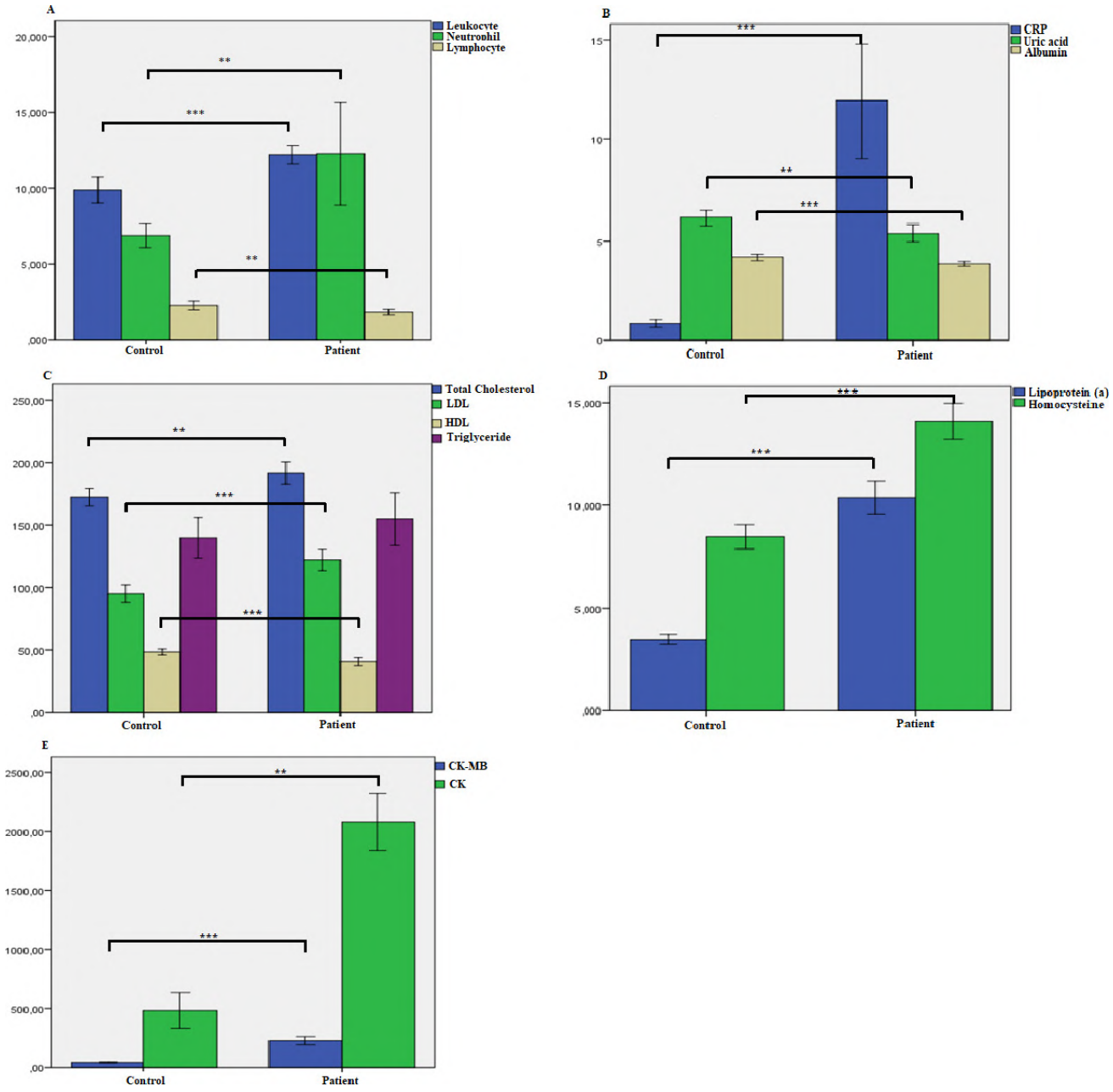

Fig. 2.- Comparison of complete blood count parameters ((Leukocyte (10*9/L), Neutrophil (10*9/L), Lymphocyte (10*9/L)) between groups, comparison of CRP (mg/d), uric acid (mg/dl) and albumin (g/dl) values between groups, comparison of lipid parameters ((Total Cholesterol (mg/dl), LDL (mg/dl), HDL (mg/dl), Triglyceride (mg/dl)) between groups, comparison of lipoprotein (a) (mg/dl) and homocysteine (nmol/ml) levels between groups, and comparison of CK (UI/L) and CK-MB (ng/ml) levels between groups. Statistically significant: *: p<0.05, **: p<0.01, ***: p<0.001.

DISCUSSION

Coronary Artery Disease (CAD) is defined as a cardiovascular disorder that occurs due to the occlusion of coronary arteries (Ross, 1999). When the endothelial function of the arterial wall is impaired, atherosclerosis begins due to the accumulation of lipoprotein droplets in the coronary vessels, and ultimately, CAD develops (Badimon et al., 2012). Clinical manifestations of CAD include stable angina, acute coronary syndromes (unstable angina, non-ST- elevation MI, and ST-elevation MI), heart failure, and sudden death (Kotecha and Rakhit, 2016).

Troponins (I and T), CK, and CK-MB are among the commonly used biochemical markers for diagnosing and following up myocardial infarction. In this study, CK, CK-MB, and troponin I levels were observed to be higher in the patient group than in

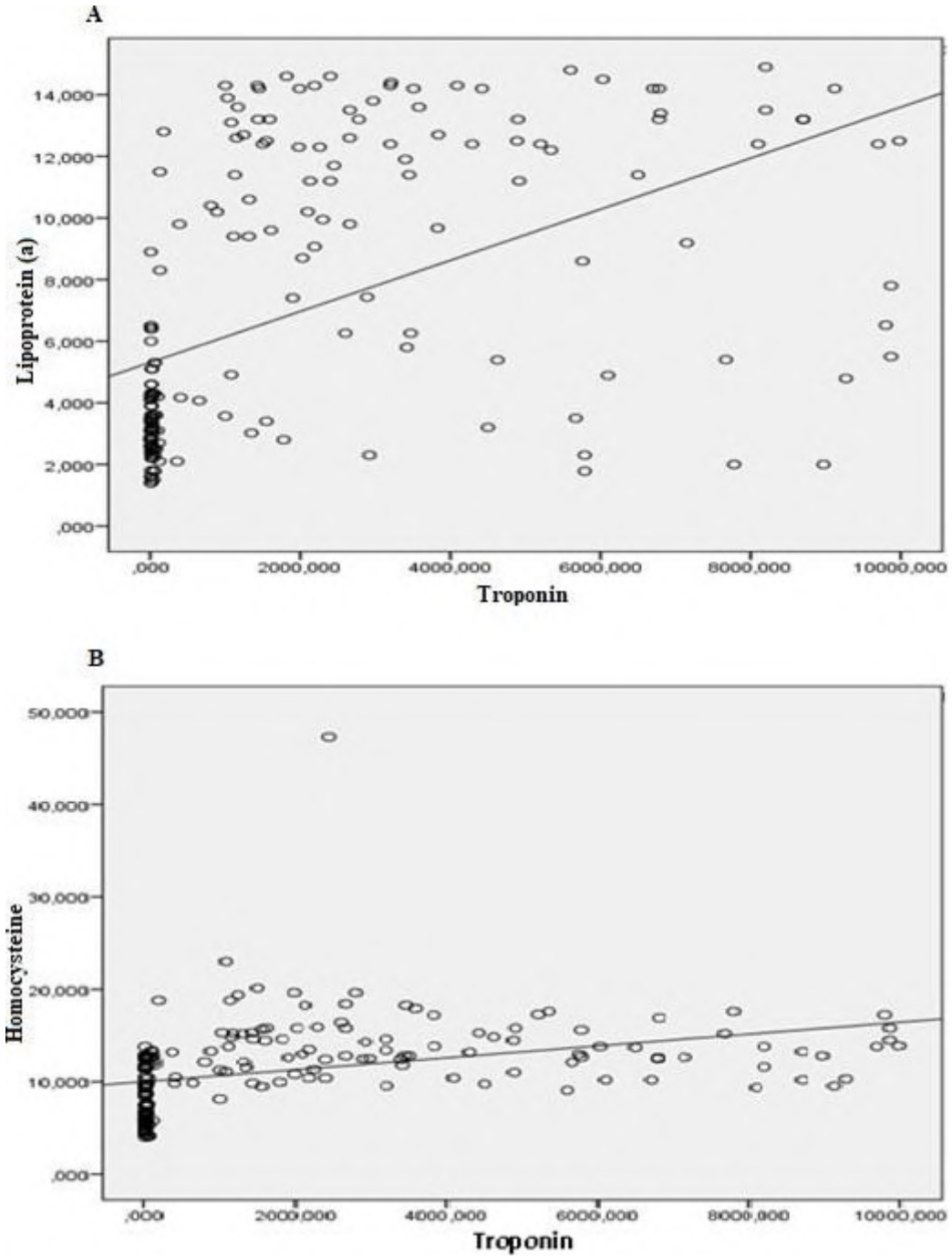

Fig. 3.- Correlation curve between Lipoprotein (a) (mg/dl) and troponin (ng/ml) levels and correlation curve between Homocysteine (nmol/ml) and troponin (ng/ml) levels.

the control group ($p<0.001$). It is known that cardiac cell membrane damage due to myocardial necrosis causes troponin release into the circulation. However, one should consider that cardiac troponin release may occur even in reversible cell damage without necrosis, making the interpretation of troponin results more complex (Park et al., 2017).

Several studies have been conducted on gender-based differences in acute coronary syndrome (Hochman et al., 1999; Milner et al., 1999; Pope et al., 2000). While STEMI is characterized by similar chest pain symptoms in both men and women, women, especially at a younger age, have fewer ST elevations (ST) on admission and more vaso-vegetative symptoms that may mask chest pain. The frequency of STEMI is more common in men than in women (Hochman et al., 1999; Milner et al., 1999; Pope et al., 2000). It is assumed that exposure to endogenous estrogens in women delays the manifestation of atherosclerotic disease. In this regard, the Women's Ischemia Syndrome Evaluation (WISE) study reported that young

women with endogenous estrogen deficiency have a more than sevenfold increase in the risk of CAD (Bairey et al., 2003). Our study determined that the proportion of men (78%) in the patient group was higher than that of women (22%), consistent with the literature. We support the idea that the lower frequency of STEMI in women compared to men may be because of the estrogen hormone in women (Sutton-Tyrrell et al., 1998). Epidemiological findings explaining the relationship between smoking and CAD have been supported by numerous studies over 30 years (Weintraub, 1990; Ceylan et al., 2011; Gallucci et al., 2020).

In our study, the smoking rate was found to be higher at $p<0.001$ in the patient group compared to the control group; the patients had impaired blood lipid profiles, which caused endothelial dysfunction and increased the risk of thrombosis (Ceylan et al., 2011). Several inflammatory biomarkers, such as CRP, may be useful in predicting the risk of coronary heart disease (CHD) (Roubille et al., 2018). CRP is a commonly used marker of inflammation (Puzianowska-Kuznicka et al., 2016). Although it is mainly produced in liver hepatocytes, CRP can also be released by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (Sproston and Ashworth, 2018). A study of 126 STEMI cases showed a positive association between CRP levels and cardiac failure. The study reported a negative relationship with left ventricular ejection fraction and concluded that CRP is a marker of the severity and complications of STEMI (Dedobbeleer at al., 2004). Another study conducted in 2008 determined that CRP levels increased in proportion to infarct size and could be used as a prognostic biomarker (Roubille et al., 2018). In our study, it was observed that the CRP levels of the patient group were statistically significantly higher than the control group. When all these studies are evaluated together with their results, one can conclude that inflammation is critically important in STEMI (Habib et al., 2011). It has been reported that high leukocyte count is a strong and independent predictor in determining the risk of CAD in patients of both genders with and without CHD, and that leukocytes and their subtypes (e.g., neutrophils, monocytes, lymphocytes, basophils, and eosinophils) are associated with the risk of CHD, peripheral artery disease, and stroke (Madjid and Fatemi, 2013). In this study, leukocyte and neutrophil counts were higher in the patient group than in the control group ($p<0.05$). Conversely, the lymphocyte count was found to be lower in the patients than in the controls ($p<0.05$). Our findings associated with leukocyte, neutrophil, and lymphocyte counts are consistent with the literature (Dragu et al., 2008; Nunez et al., 2011).

The latter suggested that low lymphocyte counts may be related to the development of CAD (Nunez et al., 2011). One can easily predict that the low lymphocyte count may be due to the development of atherosclerosis, a disease frequently observed in systemic inflammatory response. Hypoalbuminemia is evaluated as an independent prognostic biomarker for many cardiovascular diseases, such as CAD, heart failure, congenital heart disease, infective endocarditis, and stroke. Due to the anti-inflammatory, antioxidant, anticoagulant, antiplatelet aggregation activity and colloid osmotic effects of albumin, hypoalbuminemia can be considered as a risk factor for the development of CAD (Arques, 2018), which shows that our finding associated with serum albumin levels in the patient group is compatible with previous data. Lipoproteins are named according to the type of lipid and apolipoprotein they have. Through further hydrolysis of their triacylglycerol content, very-low-density lipoprotein (VLDL) remnants (namely, intermediate density lipoproteins, (IDLs)) are formed and are then transformed into LDL particles. LDL, which has the apolipoprotein component ApoB100, is considered the leading cholesterol carrier in the peripheral circulation. Its high levels in circulation are considered one of the major CHD risk factors (Shabana et al., 2020). If the cholesterol content of LDL particles is determined as LDL-C, one can estimate the LDL lipoprotein content of blood coarsely.

Consequently, high blood LDL-C means elevated LDL particles in circulation, which is considered the main atherogenic lipoprotein. Conversely, low HDL-C is thought to play a role in atherogenesis because of the antiatherogenic action of HDL particles in circulation (Lamarche et al., 1995; Goldbourt et al., 1997).

As a result, our findings associated with the patients' total cholesterol, LDL-C, and HDL- C levels are compatible with the studies mentioned above.

Uric acid, the last catabolic product of purine metabolism, is a strong antioxidant in human blood plasma and protects cells from damage by clearing reactive oxygen species. In addition, it has been speculated that the loss of albumin and urate oxidase may extend lifespan (Lee et al., 2013). It is well known that oxidative stress may play a role in the pathogenesis of atherosclerosis and CAD (Lefer and Granger, 2000). Uric acid at normal levels is the primary quantitative determinant of the total antioxidant capacity of plasma and is stated to play a role in preventing the formation of atherosclerosis (Cao And Prıor, 1998; Clermont et al., 2000; Pasalic et al., 2012). The present study proposed lower serum uric acid levels in the patient group ($p<0.01$), which is consistent with the effectiveness of oxidative stress in the development of CAD.

Lipoprotein (a) is an LDL-like particle that contains an apolipoprotein B100 molecule that is covalently linked to a very large glycoprotein, apolipoprotein (a), which is synthesized by the liver. Although the particle's physiological role and vascular effects remain unclear, in vitro and animal studies indicate that lipoprotein (a) promotes inflammation, foam cells, and thrombosis formation (Poon et al., 1997; Nielsen et al., 1998; Boffa et al., 2004). Many prospective epidemiological studies note that baseline lipoprotein (a) concentration is positively associated with the risk of coronary heart disease (Craig et al., 1998; Danesh et al., 2000; Bennet et al., 2008).

The higher lipoprotein (a) levels in the patient group ($p<0.001$) in this study is well supported by the previous studies reporting the association of CAD formation with increased lipoprotein (a), resulting in inflammation, foam cell and thrombosis formation (Hamasaki and Kotani, 2020).

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate in the biosynthesis of methionine and cysteine amino acids. Homocysteine is produced by demethylation of dietary methionine, which is abundant in animal protein. In 1969, McCully, in his study of an 8-year-old patient with homocystinuria who died of a stroke and an infant with a hereditary defect in cobalamin metabolism who died of cardiac arrest, suggested that elevated homocysteine levels caused premature atherosclerosis (McCully, 1969; Gauthier et al., 2003). Although intense criticism was initially made, scientific studies investigating the possible relationship between hyperhomocysteinemia and atherosclerotic vascular diseases gained momentum in the early 1970s. As a result, it was reported that homocysteine concentrations may be associated with stroke, coronary artery disease, peripheral vascular disease, and deep vein thrombosis (Gauthier et al., 2003). A study conducted in 2023 suggested that homocysteine may be an independent risk factor for STEMI (Ou et al.,2023). High homocysteine levels in the patient group ($p<0.001$) may lead to vascular endothelial dysfunction, atherosclerosis, and thrombosis, which is supported by the above-mentioned studies.

CONCLUSIONS

The study investigated the relation of high serum lipoprotein (a) and homocysteine levels to atherosclerosis in STEMI patients, and a statistically significant association was found between STEMI and lipoprotein (a) and Homocysteine. Similarly, high levels of leukocyte and neutrophil counts, CRP, total cholesterol, LDL-C, CK, CK-MB, and troponin I and the low levels of lymphocyte count, albumin, uric acid, and HDL-C levels in STEMI patients point the association mentioned above. These results indicate that lipoprotein (a) and homocysteine levels in addition to the measurements of cardiac biomarkers, lipid profiles, inflammatory markers, negative and positive acute phase reactants, and leukocyte parameters of complete blood count can also be considered as routinely-measured analytes in the diagnosis of cardiac events.

Can these two analytes, serum lipoprotein (a) and homocysteine levels be used as cardiac risk factors or as both cardiac risk factors and markers of cardiac damage? Patients diagnosed with STEMI have fewer identifiable risk factors compared to types of ACS.

Therefore, more sensitive prediction models different from traditional cardiovascular scoring

systems need to be investigated to identify high-risk patients. Troponin levels, a marker used in the diagnosis of STEMI, may also increase for other systemic reasons. Due to the reasons that cause secondary troponin elevation, high troponin levels do not always suggest the diagnosis of ACS. While the search for biomarkers that can be used in diagnosis, similar to troponin levels, is still ongoing, we conducted our study in response to the question of whether homocysteine and lipoprotein, which are known risk factors, can be used for diagnosis. As included in our findings, both markers were statistically significantly and moderately correlated with troponin.

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AUTHORS' CONTRIBUTIONS

Study concept and design: E.T. and E.T. Acquisition of data: E.T. Analysis and interpretation of data: E.T., and E.T., M.K. Drafting of the manuscript: E.T. and M.K Critical revision of the manuscript for important intellectual content: E.T., M.K. and E.T Statistical analysis: E.T.

ETHICAL APPROVAL

This study was conducted after the approval of our University, Faculty of Medicine Non-Interventional Clinical Research Ethics Committee dated 27/11/2019.

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