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Relationship between serum copper and TIMI flow grade in ST-elevation myocardial infarction

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Abstract

Coronary artery disease (CAD) involves a complex atherosclerotic process, and many factors play a role in this process. Although there are studies evaluating the development and severity of CAD with trace elements in the blood, there is no study evaluating coronary flow to our knowledge. This study aimed to evaluate the relationship between coronary flow and trace elements after percutaneous intervention in ST-elevation myocardial infarction (STEMI). This study included 126 consecutive patients who presented to the emergency department with STEMI between May 2023 and August 2023. Thrombolysis in myocardial infarction (TIMI) flow grades were calculated after primary percutaneous coronary intervention, and patients were categorized into two groups: low TIMI flow grade and normal TIMI flow grade. The diagnosis of STEMI was defined according to European acute coronary syndrome (ACS) guidelines. Demographic and clinical data were recorded. After coronary angiography, blood tests for trace elements were obtained in addition to routine laboratory parameters. All variables were compared between the two groups. There was no significant difference between low and normal TIMI flow grade groups regarding age and gender. Killip score (p=0.004) and tirofiban (p<0.001) use were higher in the low TIMI flow grade group. Serum copper, high-density lipoprotein, low-density lipoprotein, diabetes mellitus, hypertension, and platelet variables were included in binary logistic regression analysis; low serum copper (p=0.014, OR=1.023, Cl=1.005-1.042) was found to be a risk factor for low TIMI flow grade. Regarding the outcomes of this research, we found that serum copper levels are an important risk factor for low TIMI flow grade in STEMI.

Keywords: Copper, coronary artery disease, TIMI flow, no-reflow, trace elements

Introduction

Reperfusion of the ischemic myocardium quickly is the optimal way to treat ST-elevation myocardial infarction (STEMI). Reperfusion via primer percutaneous coronary intervention (PPCI) is now the favored technique and the current standard of care for STEMI. Nevertheless, in 12% to 32.8% of STEMI patients undergoing PPCI, the desired coronary blood flow is not achieved, a condition referred to as the no-reflow phenomenon [1]. The clinical relevance of inadequate reflow is evidenced by its association with heart failure, malignant arrhythmias, and increased mortality over the short- and long-term. No-reflow may be caused by distal embolization, vasospasm, microvascular damage, oxidative stress, and ischemia-reperfusion injury [2]. Despite this, the underlying factors behind the no-reflow phenomenon remain unclear.

Essential trace elements such as zinc and magnesium are involved in most of the metabolic events and enzymatic processes that ensure the function of cells. The lack of zinc and magnesium is thought to be associated with cardiovascular diseases. As the responsible mechanism, it is accepted that it plays a role in the anti-atherosclerotic process by reducing the expression of factors (TNF-alpha and IL-1) that play a role in the atherosclerosis

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mechanism and free oxygen radicals. These elements, which are associated with the development of atherosclerosis, have been shown to decrease coronary artery disease (CAD) [3]. However, studies evaluating the effect on the severity of CAD are limited. In addition, only some studies in the literature include a patient group specific to STEMI [4].

It has been shown that zinc levels in the blood decrease in myocardial infarction, congestive heart failure, and conduction system abnormalities, leading to adverse cardiac outcomes [5]. Previously, it was reported that zinc given after coronary reperfusion reduced arrhythmias and positively affected myocardial recovery. Although the mechanisms of cardiovascular diseases at the biochemical and cellular levels are known, the relationship of zinc with these processes has yet to be clarified. Several views are put forward. The decrease in zinc levels may affect CAD, which is positively correlated with age. A second opinion is that it can act as a protective factor against endothelial damage. The atherosclerotic process begins with endothelial damage. In this process, apoptosis develops in cells due to oxidized low-density lipids (LDL and inflammatory markers secreted from monocyte cells. It is thought to slow down this process by inhibiting the activation of nuclear factor-kB (NF-kB), which regulates adhesion molecules on adhesion surfaces and plays a protective role [5,6]. Magnesium (Mg+2) plays a role in regulating endothelial cell function and vascular smooth muscle tone. It is responsible for the pathogenesis of atherosclerosis, CAD, heart failure, hypertension, and cardiac arrhythmias [5].

The link between copper and CAD risk is complex and incomplete. Nevertheless, numerous biological pathways have been suggested to explain this link. Copper is vital in multiple enzymes necessary for antioxidant protection, such as Superoxide dismutases (SOD) and ceruloplasmin. SOD is an enzyme that changes superoxide radicals into hydrogen peroxide, whereas ceruloplasmin is an antioxidant protein that aids in eliminating free radicals [7]. When copper levels are insufficient, the functioning of these enzymes can be impeded, thus causing an increase in oxidative stress and inflammation, both of which are established risk factors for CAD. Due to the available information, low copper levels are associated with increased levels of oxidative stress and inflammation, which in turn is associated with an increased risk of CAD; in fact, low copper levels can lead to increased oxidative stress and inflammation by impairing the activity of antioxidant enzymes [8].

Within the scope of this research, we aimed to elucidate the relationship between the serum elements and thrombolysis in myocardial infarction (TIMI) flow grades in STEMI.

Material and Methods

This prospective, retrospective, and cross-sectional study included 126 consecutive patients admitted to the emergency department with STEMI between May 2023 and August 2023. The diagnosis of STEMI is defined according to the European Acute Coronary Syndrome (ACS) guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was granted from our institution on 18.07.2023 with protocol number 01, and informed consent has been obtained from all participants.

The presence of chest pain and consecutive ST-elevation in at least two leads on a 12-lead electrocardiogram (ECG) was considered STEMI. All patients received anti-platelet and anti-coagulant therapy at doses appropriate for ACS. Patients were taken to the catheterization laboratory within two hours, and PPCI was performed. After coronary angiography, thrombus burden and TIMI flow grades were evaluated. Simultaneous routine blood samples were taken. Patients with TIMI $\leq$2 flow grade after stent implantation were grouped as low TIMI flow grade, and those with TIMI -3 flow grade were categorized as normal TIMI flow grade. Patients were evaluated using a standardized questionnaire, including clinical history, physical examination, and laboratory tests. In addition, risk assessment of acute myocardial infarction (AMI) in the early period was performed according to the Killip classification applied in the coronary intensive care unit. Exclusion criteria were previous coronary artery bypass graft operation, cardiac valve operation, STEMI requiring cardiopulmonary resuscitation, known electrolyte imbalance, malignancy, sepsis, malabsorption, and alcoholism.

TIMI flow grades were defined as follows: Stage 0: complete atherosclerosis and distal vessels at occluded sites did not fill with forward flow; Stage 1: a small amount of contrast medium passes through the site of vessel occlusion, a small proportion of distal vessels open, and vessel filling is incomplete; Stage 2: Contrast medium can fill the distal coronary arteries, but the filling and emptying rate of contrast medium is significantly slower than that of normal coronary arteries; Stage 3: complete coronary reperfusion, complete filling or contrast emptying within three cardiac cycles.

Complete blood count parameters were performed using a Sysmex XT- 1800i (Sysmex, Kobe, Japan) automated hematology analyzer. NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), and SII (platelet*neutrophil count/lymphocyte count) were calculated as inflammation indicators. Glucose, aspartate transaminase, alanine transaminase, creatinine, total cholesterol, high-density lipids (HDL), LDL, triglycerides, sodium, potassium, chlorine, calcium, phosphate, creatinine kinase, CK-MB, magnesium, copper, zinc, iron, C-reactive protein (CRP), and troponin-I values were measured. CRP/albumin ratio (CAR) was calculated.

Statistical analysis

All data were analyzed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). According to coronary angiographic images, TIMI flow grades were categorized into two groups: low and normal TIMI flow grades. The Kolmogorov-Smirnov test

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assessed whether the data were normally distributed between the groups. Numerical variables were expressed as mean ± standard deviation, and categorical variables as number and percentage. Independent sample t-test or Mann-Whitney U test was used to compare the numerical data of the two groups. The chi-square test was used to compare categorical variables. The correlation of variables with the TIMI flow grade was analyzed. In addition, logistic regression analysis was used to find the factors affecting low TIMI flow grade. P<0.05 was considered statistically significant.

Results

According to coronary angiography images, 126 patients were divided into low TIMI flow grade and normal TIMI flow grade. No significant difference was found between low and normal TIMI flow grade groups regarding age and gender. Killip score (p=0.004) and tirofiban (p<0.001) use were higher in the group with low TIMI flow grade. Other clinical characteristics between the two groups are denoted in Table 1.

Table 1. A comparison of demographic and clinical characteristics between groups

	Low TIMI flow grade n=45	Normal TIMI flow grade n=81	P value
Age, year	63.71±11.60	63.50±14.51	0.931
Male, n%	29 (64.4)	42 (51.9)	0.172
BMI	29.83±4.84	29.21±4.28	0.460
DM, n%	20 (44.4)	40 (49.4)	0.595
HT, %	32 (71.1)	46 (56.8)	0.113
Smoking, n%	14 (31.1)	22 (27.2)	0.638
Culprit lesion			
LAD artery, n%	20 (44.4)	28 (34.6)	
RCA, n%	10 (22.2)	25 (30.9)	0.296
CX, n%	14 (31.1)	28 (34.6)	
Killip rating (3 or 4)	6 (13.3)	0 (0)	0.004
Tirofiban using, n%	19 (42.2)	5 (6.2)	<0.001
Known HF, n%	7 (15.6)	8 (9.9)	0.346
Known CAD, n%	7 (15.6)	8 (9.9)	0.346
Known CKD, n%	7 (15.6)	9 (11.)	0.473

BMI: body mass index, CAD: coronary artery disease, CKD: chronic kidney disease, DM: diabetes mellitus, CX: circumflex, HF: heart failure, HT: hypertension, LAD: left anterior descending, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction, p<0.05 are shown in bold

Laboratory values and inflammatory markers were compared between the two groups. Platelet (p=0.029), HDL (p=0.027), LDL (p=0.012), and serum copper (p=0.002) values differed between the two groups. HDL and LDL values were higher in the low TIMI flow grade group. There was no difference between the two groups in inflammatory markers (Table 2).

Factors affecting low TIMI flow grade were investigated. When serum copper, HDL, LDL, diabetes mellitus, hypertension, and platelet variables were included in binary logistic regression analysis, low serum copper (p=0.014, OR=1.023, Cl=1.005-1.042) was found as a risk factor for low TIMI flow grade (Table 3).

Table 2. Inflammatory markers and laboratory values between TIMI flow groups

	Low TIMI flow grade n=45	Normal TIMI grade n=81	P value
Hemoglobin, g/dL	13.54±1.70	13.18±1.38	0.194
Neutrophil, 103/µL	5.85±2.12	6.19±2.56	0.449
Lymphocyte, 103/µL	2.35±0.99	2.36±1.27	0.984
Platelet, 103/µL	242.91±54.22	269.08±77.55	0.029
Creatinine, mg/dL	1.02±0.28	1.03±0.22	0.818
Calcium, mg/dl	8.87±0.58	9.01±0.69	0.255
Copper, µg/dL	86.36±18.23	99.13±26.13	0.002
Zinc, µg/dL	83.76±26.61	76.24±27.49	0.139
Magnesium, mg/dL	1.90±0.26	1.93±0.73	0.757
Iron, µg/dL	124.55±25.31	115.37±29.38	0.805
Albumin, g/dl	4.02±0.40	4.11±0.55	0.363
Total protein, g/dL	6.30±1.14	6.55±1.14	0.242
Triglyceride, mg/dL	178.37±80.76	178.45±73.83	0.996
CRP, mg/L	6.69–11.17	8.83–15.55	0.217*
HDL, mg/dL	44.03±9.87	39.93±9.87	0.027
LDL, mg/dL	109.24±31.59	94.19±32.00	0.012
NLR	2.46–2.27	2.55–2.52	0.485*
SII	537.42–611.67	637. 56–884.88	0.208*
CAR	1.69–2.82	2.22–3.88	0.297*
PLR	98.35–74.31	123.38–92.23	0.112

CRP: C-reactive protein /albumin ratio, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: systemic immune inflammation index, p <0.05 are shown in bold, * Variables are expressed as median and interquartile range

Table 3. Factors affecting low TIMI flow grade

	B	OR	P	95% Cl	
				Lower	Upper
Copper	0.023	1.023	0.014	1.005	1.042
High-density lipoprotein	–0.028	0.973	0.231	0.930	1.018
Low-density lipoprotein	–0.011	0.989	0.128	0.976	1.003
Diabetes mellitus	0.076	1.079	0.856	0.475	2.450
Hypertension	–0.291	0.748	0.510	0.315	1.776
Platelet	0.005	1.005	0.131	0.999	1.011

Furthermore, the correlation between serum copper and CRP was highest (Figure 1).

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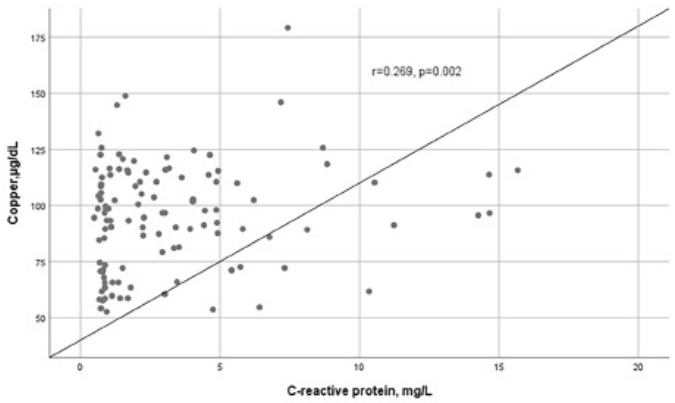

Figure 1. Graph showing the correlation between serum copper and C-reactive protein

Discussion

In some previous studies, it has been determined that trace elements can play a very important role in the vessels, causing various effects by damaging the vessel wall or protecting the vessel wall, changing the lipid profile. Trace elements are important components of some metalloenzymes responsible for maintaining myocardial integrity. Therefore, these trace elements are thought to be closely associated with the risk of heart disease. Studies reported that unstable serum trace element concentrations are detected in some patients diagnosed with AMI [9].

Essential trace elements are involved in most metabolic events and enzymatic processes that ensure the function of cells and are thought to be associated with cardiovascular diseases. Trace elements play a role in the anti-atherosclerotic process by reducing the expression of factors (TNF-alpha and IL-1) that play a role in the atherosclerosis mechanism and free oxygen radicals. These elements, which are associated with the development of atherosclerosis, have been shown to decrease coronary artery disease[10]. However, studies evaluating coronary flow in STEMI are limited. Almost no study has included a specific patient group for STEMI [11]. Their role in cardiomyopathies, arrhythmias, and coronary artery disease has been investigated. It has been shown that zinc levels in the blood decrease in myocardial infarction, congestive heart failure, and conduction system abnormalities, leading to adverse cardiac outcomes [12].

The atherosclerotic process begins with endothelial damage. In this process, apoptosis develops in cells due to oxidized LDL and inflammatory markers secreted from monocyte cells. It is thought to slow down this process by inhibiting the activation of nuclear factor-kB (NF-kB), which regulates adhesion molecules on adhesion surfaces and enables a protective role [13].

Trace elements play a role in regulating endothelial cell function and vascular smooth muscle tonus. They are responsible for the pathogenesis of atherosclerosis, coronary artery disease, heart failure, hypertension, and cardiac arrhythmias. Their deficiencies were associated with many cardiovascular adverse events, even mortality and morbidity. This has led to the requirement to examine the effect of this element in myocardial infarction [14]. In our study, factors affecting low TIMI flow grade were investigated. Low serum copper was found to be a risk factor for low TIMI flow grade. Furthermore, the correlation between copper and CRP was highest. We can say that copper has an effect on no-reflow in coronary arteries.

There is a significant relationship between excessive reactive oxygen species (ROS) production and the mechanism of MI [15]. As a result of ROS production, direct cell damage occurs, and cell necrosis develops. ROS also plays an important role in stimulating signal transfer in the ischemic area or adjacent myocardium to regulate inflammatory cytokines [16].

Copper and iron are essential trace elements in the body. They are effective in various metabolic activities such as neuroconductivity, transport, excretory processes, and functioning as cofactors. Copper is an important trace element associated with various metalloproteins. These studies have determined a significant relationship between increased copper concentrations and CAD risk [17].

Although it is not fully revealed how high serum copper concentration plays a role in the pathogenesis of atherosclerosis, a negative correlation between serum copper concentration and high-density lipoprotein levels has been denoted. Increased serum copper concentrations and decreased serum zinc concentrations were detected in patients with myocardial infarction. Studies show that serum copper levels may increase due to leakage from necrotic tissues after myocardial infarction, and serum zinc concentrations may decrease due to removal from the circulation to be used to repair damaged but not necrotic myocardial parts. Iron and copper, known as essential promoters of free radical formation, accelerate lipid peroxidation. Zinc, a biological antioxidant, also prevents lipid peroxidation and stabilizes membranes [18].

Previous studies elaborated that nutrient trace element content is also responsible. It is known that a diet low and absence of copper content increases the serum lipid level, weakens the heart functions, and prepares the ground for atherosclerosis. The association of zinc with cardiovascular disease risk is indirect rather than direct by antagonism with copper. The relationship between magnesium and atherosclerosis has yet to be made clear. However, when serum magnesium decreases, severe cardiac problems occur. In AMI, serum copper level increases, magnesium decreases, and zinc values show variable values following the acute phase [19]. Our study found no correlation between TIMI flow grades and zinc and magnesium levels. However, studies including high multivolume patient populations may elucidate the effect on coronary flow role.

Systemic inflammatory responses have an important role in the development and prognosis of CAD. Simple routine laboratory assays can determine the systemic inflammatory response. In this context, NLR, PLR, CAR, and SII markers have been used in recent years to predict coronary artery plaque vulnerability,

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CAD severity, and long-term adverse cardiac outcomes of CAD. Borghini et al. followed patients with CAD for five years [20]. They found that NLR, SII, and PLR were independent predictors of cardiac mortality. NLR has been demonstrated to play a role in primary and secondary cardiac protection. A novel index of SII, formerly used for cancer patients, was formulated that included platelets in addition to NLR. SII has been reported to be elevated in ACS, and its effect on cardiac mortality has been shown [21]. However, although these indices are closely associated with ACS, studies with TIMI flow grade are limited. In our study, inflammatory indices were not associated with low TIMI flow grade.

Inflammation is involved in all stages of atherosclerosis. CRP and albumin are also recognized as indicators of inflammation. CRP is an acute-phase protein synthesized in the liver and is elevated in inflammation. It has been reported to be used to show the extent of atherosclerosis of coronary arteries and as a prognostic marker in CAD. The reason for the relationship between CRP and CAD has not been fully elucidated. However, some hypotheses have been proposed. CRP activates the complement system, disrupts endothelial cell structure, and affects coronary arteries by negative fibrinolysis [22]. Low albumin levels have been associated with cardiovascular diseases [23]. It has been stated that albumin deficiency may play an active role in the pathogenesis of CAD by increasing blood viscosity, endothelial dysfunction, and platelet activation. CAR is an index obtained by dividing CRP and albumin by each other. It has been shown that this index may be superior to CRP and albumin alone in determining the presence and severity of CAD [24]. In our study, we thought markers may be associated with low TIMI flow grade in ACS. Although there was a correlation between CRP and low TIMI flow grade, we showed that it did not affect low TIMI flow grade after PPCI.

A time-dependent significant increase in serum copper in AMI was detected in acute and old infarction cases. However, they emphasized that the increase was higher in the acute period. This was attributed to elevated serum copper during AMI to increased ceruloplasmin activity, which acts as an acute phase reactant against acute tissue injury in the infarcted heart. Serum copper, potassium, and phosphor levels are good indicators of myocardial damage and infarct area [25]. In patients presenting with AMI, low serum copper may carry a risk of coronary artery slowing and thrombus after intervention (ballooning or stenting) of the culprit coronary artery. Earlier initiation of a glycoprotein (GP) IIb/IIIa receptor (tirofiban) inhibitor of intracoronary platelet aggregation or the ready availability of thrombus aspiration catheters would provide time to manage the development of no-reflow and reduce the time the patient's coronary artery remains occluded. There is a necessity to conduct further extensive experiments and observations to ascertain the exact part played by copper and other trace elements in ACS and no-reflow. In our study, copper was a marker of low TIMI flow grade. However, the effect of copper was relatively small at a low TIMI flow grade. Increasing the number of patients may increase this effect. In addition, the role of external copper dietary supplementation in patients with ACS may be elucidated by further studies.

Our study has some limitations. First, we can evaluate epicardial coronary arteries in ACS in coronary angiography. We cannot obtain information about the coronary microvascular circulation of the patients. Also, we do not have information about the previous coronary microvascular circulation of the patients because they have not undergone coronary angiography before. Second, the malnutrition status of the patients was not evaluated. Third, it was performed in a small population, including single-center, retrospective patients.

Conclusion

Regarding the outcomes of this research, we found that low serum copper levels were an important risk factor for low TIMI flow grade. Monitoring trace elements at the post-myocardial infarction state could leverage the clinician's decision-making.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was granted from our institution on 18.07.2023 with protocol number 01.

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