Diagnostic value of copeptin in acute myocardial infarction

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Abstract. – OBJECTIVE: The aim of this study was to investigate the effectiveness of copeptin in the early diagnosis of acute myocardial infarction (AMI), and to compare the diagnostic efficacy of copeptin with other cardiac markers.

PATIENTS AND METHODS: A total of 160 cases were enrolled in the study. All were over 18 years of age, and consisted of 54 non-ST elevation MI (NSTEMI), 54 ST segment elevation MI (STEMI), and 52 healthy subjects (controls). Serum troponin-I, CK-MB mass, copeptin and CRP levels were measured in each of the cases, and were compared between the three groups for statistical differences.

RESULTS: The copeptin levels in the STEMI (p < 0.001) and NSTEMI (p = 0.042) groups were found to be significantly higher than the control group. Spearman’s correlation analysis showed a significant positive correlation between the level of copeptin and the presence of AMI (r = 0.285, p < 0.001), CK-MB mass (r = 0.246, p = 0.002), and troponin-I (r = 0.199, p = 0.012). Sensitivity, specificity, and AUC values of the tests, according to ROC analysis performed for the diagnosis of AMI were: troponin-I > 0.1 ng/mL (71.0%, 100.0%, and 0.855); CK-MB mass > 3.59 ng/mL (77.8%, 92.3%, and 0.911); CRP > 6.37 mg/L (53.7%, 88.5%, and 0.769); and copeptin > 2.47 ng/mL (66.7%, 75.0%, and 0.676), respectively (p < 0.001).

CONCLUSIONS: Cardiac troponin remains the gold standard biomarker for the diagnostic evaluation of AMI. Copeptin can be used as a diagnostic marker in patients with suspected AMI in combination with other biomarkers, but, copeptin alone should not be considered as a single diagnostic marker in patients with suspected AMI.

Key Words: Acute myocardial infarction, Diagnosis, Copeptin, Troponin-I, CK-MB, CRP.

Introduction

Acute myocardial infarction (AMI) is one of the most common complaints in emergency departments (EDs). Recently, many potential biomarkers have been studied for the early and appropriate diagnosis of AMI. Cardiac troponin I (cTnI) and troponin T are commonly used for determining the extent of cardiac muscle injury in AMI. However, studies for novel early diagnostic biomarkers continue. One such biomarker is copeptin, a 39-amino-acid peptide on the C-terminal portion of pro-arginine vasopressin that is synthesized and released along with arginine vasopressin. Recent works suggest that there is a strong relationship between elevated serum levels of copeptin and diseases, such as lower respiratory tract infection, sepsis, stroke, and acute pancreatitis. It has been reported that copeptin levels in patients with AMI are higher than that of controls. There are also studies suggesting that the use of copeptin as a non-specific marker, together with troponins, may exclude the diagnosis of AMI, with a negative predictive value ranging from 97% to 100% in patients presented to EDs with acute chest pain. However, currently, there are no studies on the use of copeptin to diagnose acute myocardial infarction in the Turkish population.

In this study, our aim was to determine the diagnostic value of copeptin in comparison with other commonly used markers, in Turkish AMI patients.

Patients and Methods

The study was approved by the local Ethics Committee. Patients were enrolled into the study after being admitted to the ED for AMI. A total of 108 patients, aged 18 years or over, and 52 healthy controls were included in the study. Patients were divided into two subgroups; Group I, with non ST-elevated MI (n = 54), and Group II, with ST-elevated MI (n = 54). Writ-
Results

Demographic details and laboratory findings of Groups I and II, and the healthy controls are given in Table I. The percentage of males in Groups I and II, and healthy controls were 57.7%, 61.1%, and 87.0%, respectively. In Group II, the rate of male gender was found to be significantly higher, when compared to Group I ($p = 0.002$), and healthy controls ($p = 0.001$). The mean age was found to be $60.1 \pm 11.1$, $59.5 \pm 9.6$, and $55.3 \pm 12.6$ years in Groups I and II, and healthy controls, respectively. The mean age of patients in Group I was found to be significantly higher than controls ($p = 0.040$).

When groups were compared according to BMI, Group I had a significantly higher mean value than Group II ($p = 0.012$). Similarly, smoking status was significantly different between the groups, with the highest percentage being in Group II (70.4%, $p < 0.05$). When the rate of HT history was analyzed, group II had the highest rate compared with group I, and healthy controls (57.4%, $p = 0.032$). Type II DM was most commonly seen in group I, and this finding was statistically significant when compared to the other groups (40.7%). The rate of hyperlipidemia was significantly higher in groups I and II, compared with healthy controls ($p < 0.001$). There were no significant differences for family history of CAD between the two patient groups, but the healthy controls were found to have slightly smaller rates of CAD in the family than group I ($p = 0.047$).

When laboratory findings of the participants were investigated, it was found that CK-MB levels were significantly different between all three groups. In Group II, CK-MB levels were 6-fold higher than that of Group I ($p < 0.001$). Similarly, cTnI levels were significantly different between groups. Group II showed the highest elevation of serum cTnI ($p < 0.001$). Serum levels of CRP in Groups I and II were significantly higher than healthy controls ($p < 0.001$).

Mean serum copeptin levels (ng/mL) were found to be 2.22 (2.18-2.35), 2.50 (2.34-2.72), and 2.94 (2.85-3.24) in healthy controls, group I, and group II, respectively. In group II, serum levels of copeptin were found to be significantly higher than that of group I and healthy controls ($p < 0.001$). Additionally, the copeptin levels in Group I were significantly higher than healthy controls ($p = 0.042$). Table I and Figure 1 represent the comparison of serum copeptin levels between the patient groups and healthy controls.
When Spearman's correlation analysis was performed, it revealed that copeptin levels positively correlated with the presence of AMI ($r = 0.285$, $p < 0.001$), serum CK-MB levels ($r = 0.246$, $p = 0.002$), and serum cTnI levels ($r = 0.199$, $p = 0.012$). However, we could not determine any correlation between copeptin levels and demographical findings of the patients involved. Table II summarizes the correlation of copeptin with laboratory findings, and the demographical characteristics. After ROC analysis, the AUC values for specificity and sensitivity were calculated. According to our results, copeptin and CRP values were found to be significantly lower than cTnI and CK-MB ($p < 0.001$). Our results also revealed that the diagnostic value of copeptin was lower than cTnI and CK-MB, but 13% higher than CRP. A comparison of the diagnostic values for biomarkers is provided in Figure 2.

ROC analysis was performed to evaluate the clinical use of copeptin in the differential diagnosis of ST-elevated MI and non-ST-elevated MI. It showed that copeptin, with a cut-off value of > 2.74 ng/mL, had 70.37% sensitivity and 64.81% specificity (AUC = 0.623, $p = 0.029$).

**Discussion**

Coronary artery disease (CAD) is the leading cause of death and disability in the world. The main risk factors for CAD are well described in the literature, and include male gender\(^6\), and in our study, the majority of AMI patients were male. Age is another independent risk factor for CAD, and although CAD mortality rates have declined over
the past four decades in western countries, it is still responsible for approximately 1/3 of all deaths in individuals over middle age\textsuperscript{7,8}. In our study, 91.7\% of individuals in the two patient groups were found to be aged 45 or above, supporting the fact that the risk of CAD increases as an individual gets older. Obesity is a serious health problem, with its incidence increasing worldwide\textsuperscript{9}. The relationship between high BMI and CAD has been reported previously\textsuperscript{8,10}. In our work, the patients with CAD also had BMI above the normal range.

Smoking is another factor that increases the risk of CAD. It is also known that a decrease in smoking leads to a decrease in mortality\textsuperscript{11}. Although in a meta-analysis, smoking was not found to be associated with CAD\textsuperscript{9}, there are studies that have reported that smoking, along with other risk factors, can predict the 10-year coronary event risk\textsuperscript{12-14}. In our study, smoking was significantly higher in the two patient groups when compared to the healthy controls.

Hypertension is a risk factor for cardiovascular disorder, both for hemodynamic reasons (hemorrhagic stroke and aortic dissection), and because of the acceleration of atherosclerosis\textsuperscript{15}. Additionally, two CAD risk factors, HT and DM, are associated with an increased risk of having an unrecognized MI. Indeed, the prevalence of both unrecognized and recognized MI are increased with severe HT, but the proportion of unrecognized MI is considerably higher in hypertensive people compared to normotensive subjects\textsuperscript{16}. Diabetes is usually associated with atherogenic dyslipidemia. Elevated concentrations of glucose in the blood enhances glycation, primarily of low-density lipoprotein (LDL) cholesterol, particles which become more susceptible to oxidation, are cytotoxic to the endothelium and promote the adhesion of blood platelets\textsuperscript{17}. According to our study, HT, DM, and hyperlipidemia are more common in the two patient groups compared to the healthy controls.

A family history of CAD is known to be one of four individual risk factors (age, gender, family history of CAD, and genetic markers)\textsuperscript{18}. However, some studies in the literature have reported that a family history of CAD does not predict the presence and/or extent of coronary artery calcification, which leads to CAD\textsuperscript{19,20}. Accordingly to our study, a family history of CAD was not significant in the patient groups, when compared to healthy controls.

The diagnosis of AMI is well-defined in the literature, and is based on the detection of a rise and fall in troponin, with at least one value greater than the 99\% percentile of the upper reference limit for the assay. It is also known that markers of myocardial necrosis, such as cardiac troponin and CK-MB are the gold standard in the detection of non-STEMI, and their use is recommended by current guidelines\textsuperscript{21}. In our study, we determined that CK-MB and cTnI levels were more elevated in group II, compared with group I and healthy controls. This finding is acceptable when we consider that the diagnosis of non-STEMI is based on elevated serum levels of myocardial injury markers.

### Table II. Results of Spearman’s correlation analysis between copeptin levels and demographical, and laboratory findings.

<table>
<thead>
<tr>
<th>Copeptin</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>0.115</td>
<td>0.149</td>
</tr>
<tr>
<td>Age</td>
<td>0.028</td>
<td>0.727</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.041</td>
<td>0.607</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.104</td>
<td>0.191</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.063</td>
<td>0.426</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>0.015</td>
<td>0.848</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.049</td>
<td>0.535</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>0.034</td>
<td>0.673</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.285</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>0.117</td>
<td>0.140</td>
</tr>
<tr>
<td>CK-MB mass</td>
<td>0.246</td>
<td>0.002</td>
</tr>
<tr>
<td>Troponin-I</td>
<td>0.199</td>
<td>0.012</td>
</tr>
</tbody>
</table>

BMI: Body-mass index, CHD: Coronary artery disease, CRP: C-reactive protein. Statistically significant values are presented in bold.
We found that serum CRP levels were higher in the two patient groups than the healthy controls. CRP is important because of its role as a marker of inflammation, which has an essential role in the development of atherosclerosis. Elevations in CRP have been shown to predict the presence of coronary disease among apparently healthy subjects, and to predict adverse events in the setting of AMI\textsuperscript{22,23}. However, contrarily, there are studies that report that CRP is not associated with the severity of CAD\textsuperscript{24,25}. High-sensitivity CRP is reported to exist in very small amounts in serum and fluids of healthy subjects (the normal serum concentration is approximately 3.5 mg/L), but in inflammatory reactions, the amount of hs-CRP suddenly increases by up to 3,000 times its normal concentration, within 6 to 48 hours. Serum levels of hs-CRP also increase in diseases such as bacterial infections, viral infections, rheumatic fever, acute myocardial infarction, cancers, rheumatoid arthritis, and tuberculosis. The amount of hs-CRP also increases after surgery, transferring large amounts of blood, vaccinations, and pulmonary embolism\textsuperscript{26}.

The main finding of our study is that copeptin levels in patients with CAD were significantly higher than in healthy subjects. Calmarza et al\textsuperscript{27} reported that copeptin represented an additional value in the differentiation between non-STEMI patients and non-NSTEMI patients, as well as between ACS patients and patients with stable angina with a cut-off value of 10 pmol/L. There are reports suggesting that copeptin, in combination with highly sensitive cTnI (hs-cTnI), could be used to rule out AMI\textsuperscript{28,29}. However, there are also studies reporting that copeptin has no additional value when compared to troponin in patients with CAD, and a direct release of copeptin from the human heart is not detectable in AMI\textsuperscript{30,31}. In a review on copeptin by Möckel et al\textsuperscript{3}, it was reported that copeptin-troponin rule-out should be applied only in patients at low to intermediate risk of ACS, who are generally fit to be discharged. They also concluded that in low to intermediate risk patients with suspected ACS, the combined testing of copeptin and troponin at presentation to rule out NSTEMI could be a promising strategy. In our study, copeptin levels in AMI patients were higher than in the healthy controls. Moreover, copeptin levels in STEMI patients were significantly higher than in non-STEMI patients. In a study of 478 patients by Thelin et al\textsuperscript{3}, the combination of hs-cTnI and copeptin was reported to demonstrate significantly higher sensitivity in identifying NSTE-ACS compared with a repeat hs-cTn. However, our results revealed that copeptin levels were more useful in the diagnosis of STEMI, even though it strongly correlated with both STEMI and non-STEMI. There are other reports that support our findings; for example, in some studies, copeptin elevation was found to be greater in patients with STEMI than in patients with NSTE-ACS\textsuperscript{32,33}.

In a study by Keller et al\textsuperscript{28}, the association between classical risk factors and median copeptin levels was investigated. Male gender, obesity, smokers, and diabetes in patients with chest pain, and patients with diabetes in unstable angina pectoris, were found to have significantly higher copeptin levels. Female patients presenting with AMI had lower copeptin levels compared with male patients. The authors explained this by the longer time interval between the onset of chest pain and admission of female patients. Furthermore, the prevalence of HT and hyperlipidemia tended to be related to copeptin levels, however, in our study, we could not determine any relationship between demographical features of the patients and copeptin levels.

The most important limitations of this report were the low number of patients, and the fact that it was a single center study. Nevertheless, this is the first study on the use of copeptin to diagnose acute myocardial infarction, in the Turkish patient population.

**Conclusions**

We observed that troponins remain the gold standard for the diagnosis of AMI. In this study, we could not determine adequate evidence that copeptin is superior to other markers, already widely used in patients with suspected AMI, admitted to EDs. However, in combination with troponins, copeptin may be used to rule out acute coronary syndrome. Further investigations into the early and appropriate diagnosis of AMI are needed.

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**Conflict of interest statement**

There is no potential financial and non-financial conflict of interest. Any part of this paper is not under consideration for publishing or published in any where else.
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