# The relationship between copeptin and some of the biomarkers in Iraqi myocardial infarction patients

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## Abstract

Myocardial infarction (MI) is a leading cause of death and morbidity globally, accounting for up to 40% of all deaths. Atherosclerotic inflammation is a key element in the creation of coronary plaque as well as the progression of the plaque to an unstable condition, which leads to MI. In the present paper, we attempted to measure whether there is any association of copeptin (CPP) with FSG, lipid profile, $Ca^{+2}$, $Fe^{+2}$, $Cu^{+2}$, cTnT, and CPK-MB in Iraqi MI patients. This study included 54 MI patients from Al-Ramadi and Al-Fallujah teaching hospitals, as well as 30 healthy people who served as controls. ELISA was used to determine the level of CPP in the blood, while FSG, TG, T.Cho, HDL, CPK (MB), and cTn-T, $Cu^{+2}$, $Fe^{+2}$, and $Ca^{+2}$ by enzymatic colorimetric methods. Serum level of CPP was higher in MI patients than in healthy people (P< 0.000l), CPP has an important positive correlation with FSG , TG, VLDL, $Cu^{+2}$, CPK.MB and cTn-T with P<0.01, the area under receiver operating characteristic (AUROC) of FSG was (0.9451), CPP (0.8596), T.Cho (0.5225), TG (0.8639), HDL (0.788), LDL (0.804), VLDL (0.8889), $Ca^{+2}$ (0.7948), $Fe^{+2}$ (0.6951), $Cu^{+2}$ (0.6963), CPK (MB) (0.9948), cTn-T(1). Serum CPP level can be used as a tool for diagnosing MI disease. Also, FSG, CPK (MB), and cTn-T may be good biomarkers in the diagnosis of MI disease.

## Keywords

Myocardial Infraction • Copeptin • Troponin-T • FSG

## Introduction

Myocardial infarction (MI) is described as the death of myocardial cells as a result of prolonged ischemia, diminished cellular glycogen, relaxed myofibrils, and sarcolemmal disruption. The earliest ultrastructural alterations appear 10 to 15 minutes after ischemia begins. MI due to prolonged ischemia is known as myocardial necrosis; myocardial necrosis injury can, however, be found in conditions following non-ischemic myocardial injury, including heart failure, myocarditis, arrhythmias, renal failure, pulmonary embolism, and other very simple percutaneous or surgical treatments.

Copeptin (CPP) is stored as AVP in the same neurosecretory granules, leading to co-secretion when plasma osmolality and volume depletion are increased and rapid suppression when plasma osmolality is increased Intake of fluid (load or infusion of oral water. CPP levels have been shown to be substantially higher in women than in men; after as little as a quart of water, there is a drop in blood pressure. CPP can have prognostic value not only in the short term but also in recognizing patients who are at higher long-term risk, elevated concentrations of CPP in the Elderly Patients with heart failure symptoms were related after a heart attack, there's a greater

likelihood of dying from any cause. Serum CPP has recently been tested among male Iraqi with chronic kidney disease. Unlike cTn, copeptin release is non-specific and can be induced by a variety of acute clinical situations such as acute heart failure, pulmonary embolism, and sepsis. However, Stallone et al. discovered that there is a strong link between high copeptin levels and mortality, which can be explained by age and comorbidities [1].

The key explanation for the cTn test was that myocardial necrosis causes membrane destruction, which causes troponin to be released and detected in the bloodstream. The amount of cTn in the cytosolic pool is equivalent to that of CK-MB; however, per gram of cTn in the myocardium, it is 13 to 15 times higher than CK-MB due to a large amount of cardiac troponin in the contractile device. We can see why troponin is more responsive than CK-MB because cTn levels increase in the peripheral blood, while CK-MB normal levels are less than 1 gram, after inflammation, ischemia, toxic injury, or infarction have caused myocardial damage.

Calcium is considered to be essential in the pathophysiology of a variety of diseases, and this is particularly true when it comes to the cardiovascular system and the diseases that it causes; calcium affects blood pressure since it is involved in the process of

vasoconstriction, calcium ions are also an important component of electrical conduction in the heart. In 2019, a study was conducted by Insulin resistance, hyperinsulinemia, and vascular calcification are common in diabetic individuals, which not only increase atherosclerosis but also speed the development of stable plaques into unstable plaques or plaque rupture, resulting in blood clotting and adverse coronary artery events. Iron is needed for the human body to function properly; as a result, it is a part of several proteins and is a central micronutrient in metabolism and enzymes that play a role in biological processes, including transport and storage of oxygen [2].

Researchers discovered that Iron deficiency had been shown to impair the contraction of human heart muscle cells by decreasing their mitochondrial function and energy production, which reduces the ability of the heart to function, leading to coronary artery disease and myocardial infarction in the population.

The main goal of this study was to determine the serum level of CPP in MI patients and controls to explore the correlation between CPP with a number of biochemical variables in Iraqi MI patients.

## Materials and Methods

This data contains fifty-four patients with MI, and 30 HCs were recorded in the study, age range within 45-70 year randomly chosen from Al-Anbar Governorate those attending in Ramadi teaching hospital and Al-Fallujah teaching hospital between September 2020 to December 2020.

Rejection principles for MI patients were empty of severe diseases or contagion at time of study also those with known illness [3].

Rejection principles for HCs were chosen Among those who were healthy control and did not have diabetes, hypertension, and ischemic heart disease, the rest had no history of smoking or drinking alcohol, they also did not have severe disease or infection at the time of sampling, HCs were not specific to any prescribed drugs or dietary restrictions and other diseases were excluded, they apparently seem healthy. Blood samples from MI patients and HCs were obtained early in the morning (8-10:30 am) after fasting for 12 hours overnight [4].

The Anthropometric measurement (AMs) were performed for all participants in the study BMI was calculated by dividing weight (kg) by height squared (m2). Measurement waist circumference (WC) and hip circumference (HC),, and the waist to hip circumference ratio were calculated as the WC divided by the HC. All biochemical parameters were measured by enzymatic methods and with commercial kits (Spain, Linear), and the level of CPP was measured by Elisa kit (BT LAB China).

## Statistics

GraphPad Prism 7.04 was used to conduct statistical analyses of our findings (GraphPad Software, La Jolla, CA, USA). The consequences are called the mean, standard error of the mean (SEM), and standard deviation (SD). A t-test was used to confirm the statistical significance of the differences between subjects with and without MI, two-tailed Pearson correlations were used to test bivariate associations, and the investigation's accuracy was determined using

The area under the ROC curve. The significance level was set at P 0.05 [5].

## Results

Table (1) shows the subjects' standard experimental characteristics, had serum copeptin levels (ng/mL) were higher in MI patients than in HCs (0,5384 vs. 0,279) with p-value less than 0.0001 as shown in fig. 12, also FSG, T.Cho, TG, LDL, VLDL, Ca+2, Cu+2, CPK (MB) and cTn-T were higher in MI patients than in HCs with P < 0.000l for all parameters, while T. Cho has P=0.4792, but HDL and Fe +2 were lower in MI patients than in controls with p= 0.01, as shown.Significant positive correlations were detected of copeptin with FSG, TG, VLDL, Cu, CPK (MB) and cTn-T (r=0.312 , P=0.004), (r=0.335, P=0.002), (r=0.324, P=0.003), (r=0.371, P<0.001),(r=0.484, P<0.001) and (r=0.553, P<0.001) respectively, as shown, while negative correlations of copeptin with HDL (r=-0.380, p<0.001), was detected as shown in (Table 1) and (Figures 1-12).

| Parameters | Controls | | | Patients | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | SEM | Mean | SD | SEM | P - value |
| FSG mg/dL | 84.73 | 5.01 | 0.9147 | 138.3 | 44.83 | 6.101 | <0.0001 |
| T.cholesterol mg/dL | 166.9 | 29.34 | 5.356 | 173.4 | 44.9 | 6.109 | 0.4792 |
| TG mg/dL | 99.87 | 31.44 | 5.739 | 155.6 | 48.32 | 6.575 | <0.0001 |
| HDL mg/dL | 45.67 | 4.866 | 0.8884 | 39.2 | 6.37 | 0.867 | <0.0001 |
| LDL mg/dL | 86.41 | 27.44 | 5.011 | 116.8 | 22.63 | 3.079 | <0.0001 |
| VLDL mg/dL | 19.63 | 5.711 | 1.043 | 30.3 | 7.25 | 0.987 | <0.0001 |
| Ca+2 mg/dL | 8.2 | 0.442 | 0.0807 | 7.67 | 0.44 | 0.06 | <0.0001 |
| Fe+2 mg/dL | 96.78 | 12.26 | 2.239 | 88.96 | 11.92 | 1.621 | 0.0055 |
| Cu+2 mg/dL | 122.3 | 28.61 | 5.223 | 132.1 | 15.78 | 2.147 | 0.0467 |
| CPK (MB) IU/mL | 83.47 | 30.08 | 5.491 | 198.2 | 44.84 | 6.102 | <0.0001 |
| Troponin-T ng/mL | 0.11 | 0.049 | 0.0089 | 14.9 | 5.17 | 0.704 | <0.0001 |
| Copeptin ng/mL | 0.28 | 0.127 | 0.0232 | 0.538 | 0.19 | 0.026 | <0.0001 |

**Table 1.** Biomarker Distribution in the HCs and MI Patients Group.

**Figure 1.** Mean+S.D. for F.S.G in control and patients.



**Figure 2.** Mean+S.D. for T. Cholesterol in control and patients.



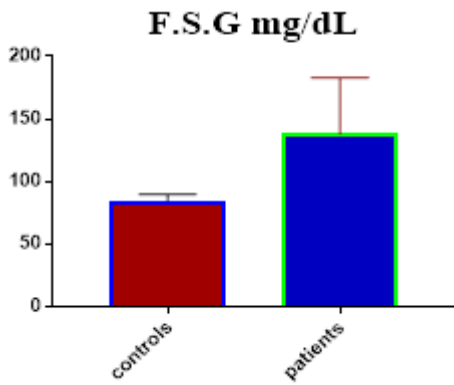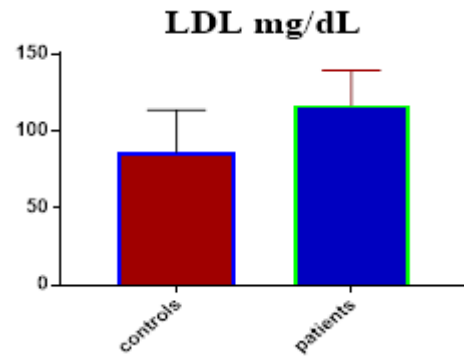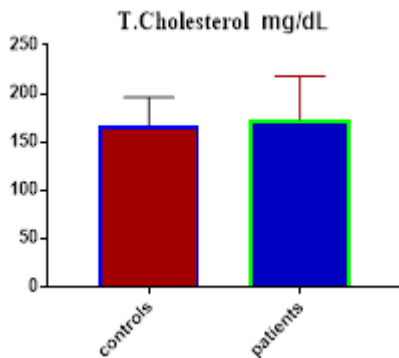**Figure 3.** Mean+S.D. for TG in control and patients.



**Figure 4.** Mean+S.D. for HDL in control and patients.



**Figure 5.** Mean+S.D. for LDL in control and patients.

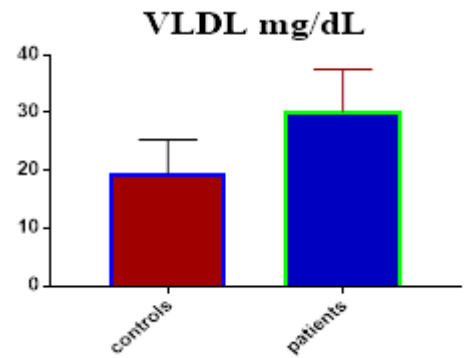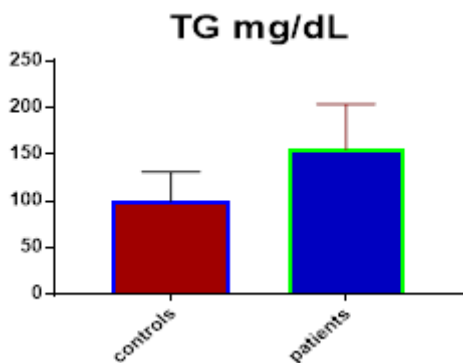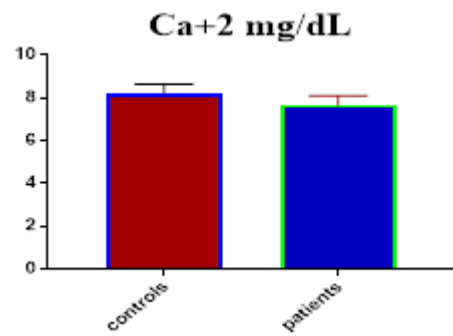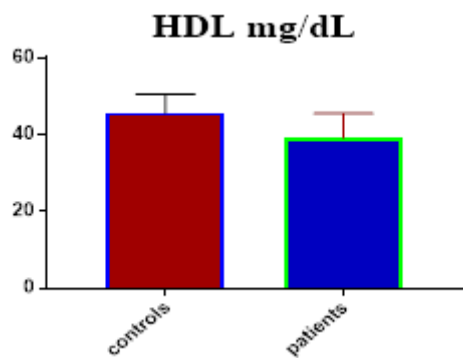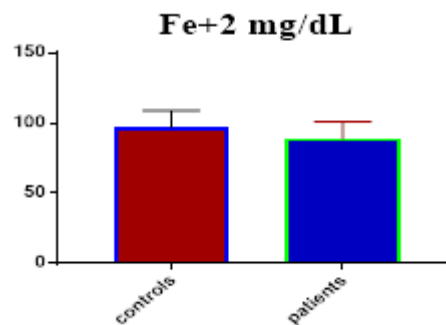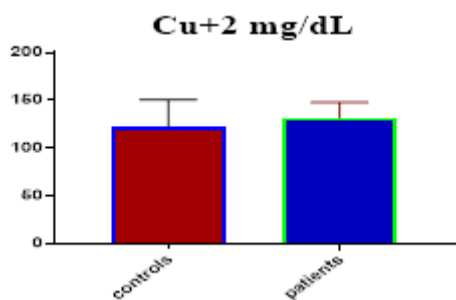

**Figure 6.** Mean+S.D. for VLDL in control and patients.



**Figure 7.** Mean+S.D. for $Ca^{+2}$ in control and patients.



**Figure 8.** Mean+S.D. for $Fe^{+2}$ in control and patients.

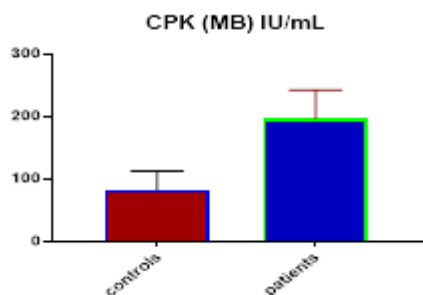**Figure 9.** Mean+S.D. for Cu$^{+2}$ in control and patients.



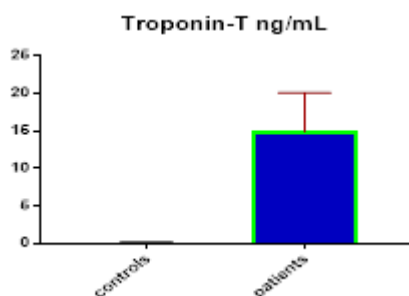**Figure 10.** Mean+S.D. for Cu$^{+2}$ in control and patients.



**Figure 11.** Mean+S.D. for Tropoxin T. in control and patients.
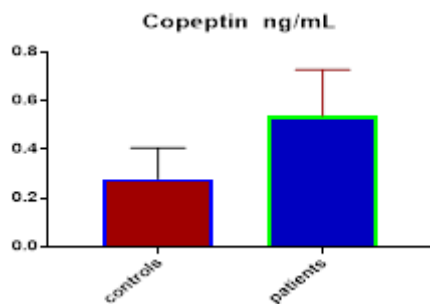


Figure 12. Mean+S.D. for Copeptin in control and patients.

Receiver operating characteristic (ROC) curve checking offered that the best biomarkers were fit to distinguish patients with MI from HCs is FSG [AUC = 0.9451 ; P < 0.0001; 95% Confidence Interval (CI) : Between 0.8938 and 0.9963 , SE: 0.02614 ] as shown while T.cholesterol was found to be a better predicator for MI [AUC =0.5225 ; P = 0.7333 ; 0.3961 to 0.649 , SE:0.0645 ] as shown and TG [AUC = 0.8639 ; P = < 0.0001; 95% CI: Between 0.7779 and 0.9498 and SE:0.04385 ] HDL [AUC = 0.788; P< 0.0001; 95% CI: Between 0.6903 and 0.8856 , SE:0.04983 ], LDL [AUC =0.804; P < 0.0001; 95% CI : Between 0.7108 and 0.8972 , SE: 0.04754 ],VLDL [AUC =0.8889; P<0.0001 ; 95% CI: Between 0.8122 and 0.9656 , SE:

0.03914 ],Ca [AUC =0.7948; P< 0.0001; 95% CI: Between 0.6977 and 0.8918 , SE:0.04952 ],Fe [AUC = 0.6951; P= 0.0032; 95% CI: Between 0.5815 and 0.8087 , SE:0.05796 ],Cu [AUC =0.6963 ; P = 0.0030; 95% CI: Between 0.574 and 0.8186 , SE:0.06239 ],CPK (MB) [ AUC = 0.9948 ; P < 0.0001 ; 95% CI: Between 0.9837 and 1.006 , SE:0.005652 ],Troponin-T [UC =1 ; P<0.0001 ; 95% CI:1 to 1 , SE: 0 ],Copeptin[AUC =0.8596 ; P < 0.0001; 95% CI : Between 0.7811 and 0.938 , SE:0.04002 ] respectively (Tables 2-3) and (Figures 13-24).

| Parameters | r | p-value |
|---|---|---|
| **Copeptin ng/mL** | | |
| FBS miligram / dL | 0.312 | 0.004 |
| T.cholesterol miligram /Dl | -0.018 | 0.869 |
| Triglycerides miligram /dL | 0.335 | 0.002 |
| HDL miligram / dL | -0.38 | <0.001 |
| LDL miligram / dL | 0.214 | 0.051 |
| VLDL miligram / dL | 0.324 | 0.003 |
| S.Ca+2 miligram / dL | -0.193 | 0.079 |
| S.Fe+2 miligram / dL | -0.16 | 0.147 |
| S.Cu+2 miligram / dL | 0.371 | <0.001 |
| CPK-MP IU/mL | 0.484 | <0.001 |
| Troponin-T IU/mL | 0.553 | <0.001 |

**Table 2.** Correlation of Copeptin with other Variables in Study.

| Parameters | AUC | Std. Error | 95% confidence interval | P-value |
|---|---|---|---|---|
| FSG miligram /dL | 0.9451 | 0.02614 | Between 0.8938 and 0.9963 | <0.0001 |
| T.cholesterol miligram /dL | 0.5225 | 0.0645 | Between 0.3961 and 0.649 | 0.7333 |
| TG miligram /dL | 0.8639 | 0.04385 | Between 0.7779 and 0.9498 | <0.0001 |
| HDL miligram /dL | 0.788 | 0.04983 | Between 0.6903 and 0.8856 | <0.0001 |
| LDL miligram /dL | 0.804 | 0.04754 | Between 0.7108 and 0.8972 | <0.0001 |
| VLDL miligram /dL | 0.8889 | 0.03914 | Between 0.8122 and 0.9656 | <0.0001 |
| Ca +2 miligram /dL | 0.7948 | 0.04952 | Between 0.6977 and 0.8918 | <0.0001 |
| Fe+2 miligram /dL | 0.6951 | 0.05796 | Between 0.5815 and 0.8087 | 0.0032 |

| Cu+2 miligram /dL | 0.6963 | 0.06239 | Between 0.574 and 0.8186 | 0.003 |
|---|---|---|---|---|
| CPK (MB) IU/ml | 0.9948 | 0.005652 | Between 0.9837 and 1.006 | <0.0001 |
| Troponin-T ng/ml | 1 | 0 | 1 to 1 | <0.0001 |
| Copeptin ng/ml | 0.8596 | 0.04002 | 0.7811 to 0.938 | <0.0001 |

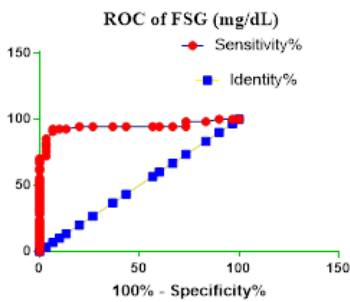**Table 3.** Standard of ROC Curves for Tested Variables in MI Patients.



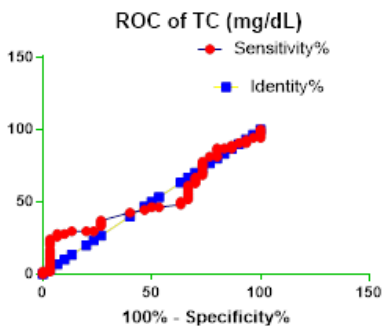**Figure 13.** AUC of ROC for FSG in MI patients.
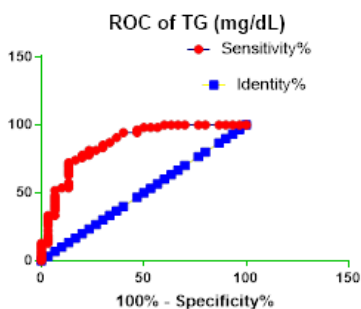


**Figure 14.** AUC of ROC for TCho in MI patients.



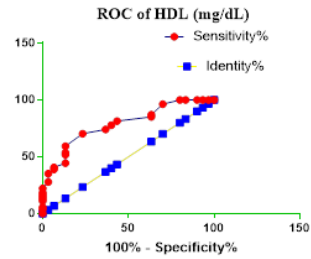**Figure 15.** AUC of ROC for TG in MI patients.
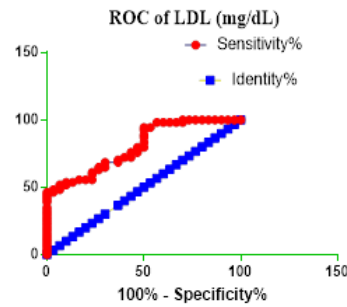


**Figure 16.** AUC of ROC for HDL in MI patients.
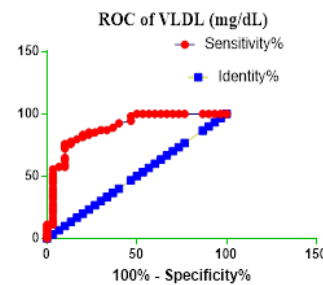


**Figure 17.** AUC of ROC for DL in MI patients.
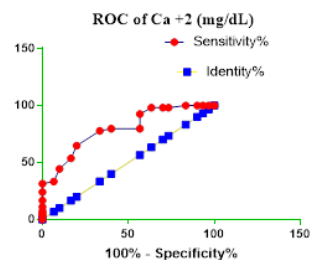


**Figure 18.** AUC of ROC for VLDL in MI patients.



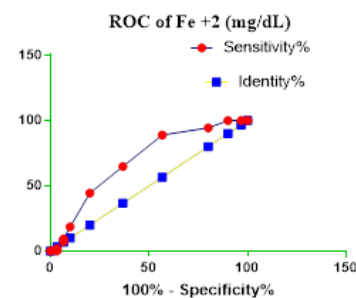**Figure 19.** AUC of ROC for $Ca^{+2}$ in MI patients.



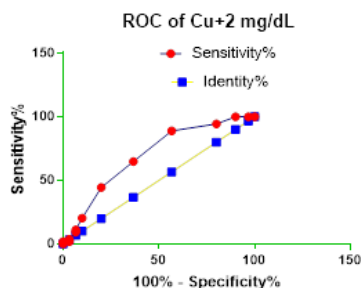**Figure 20.** AUC of ROC for $Fe^{+2}$ in MI patients.

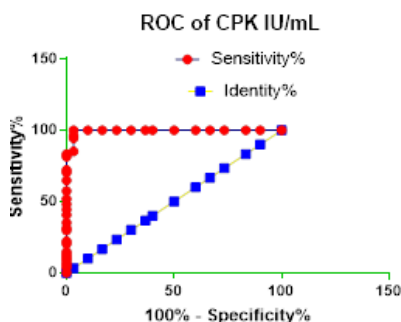**Figure 21.** AUC of ROC for $Cu^{+2}$ in MI patients.



**Figure 22.** AUC of ROC for CPK in MI patients.
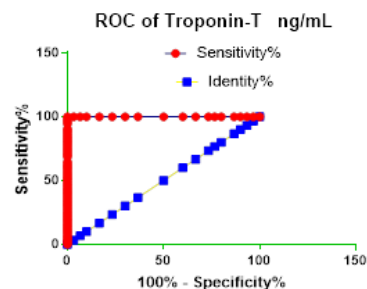

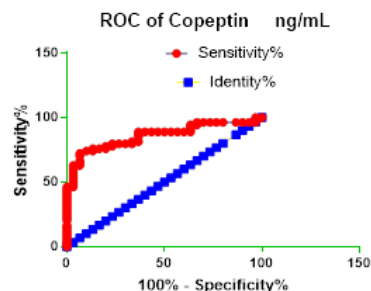
**Figure 23.** AUC of ROC for Troponin in MI patients.



**Figure 24.** AUC of ROC for Copoptin in MI patients.

## Discussion

Many different studies reference the relationship between T.Cho, TG, LDL, and MI, and MI risk factors in patients with high T. Cho, TG, LDL levels in patients and controls. The results of our study agreed with many previous studies, one of them which observed that lipid complications contain not only quantitative but also qualitative abnormality of lipoproteins that are likely atherogenic, quantitative abnormalities include elevated levels of overall serum T.Cho, TG, LDL, as well as reduced levels of HDL. The rates of TG and VLDL in

the MI population were substantially higher than in the control community in this study, which was consistent with other studies.

In this study, the findings showed significant differences in Ca +2, Fe+2, Cu+2 ions levels between patients and control groups, suggesting that these ions levels in research cases very effective in heart disease, especially MI. Several studies suggested that the low level of calcium in the serum is a major cause of MI, as the results of our current study showed that there is a close relationship between low calcium ions levels and MI patients, and this is in line with another study, which demonstrated that low serum calcium levels were one of the independent factors connected with MI after controlling for age, hypertension, smoking, and serum phosphorus, T.Cho, LDL, HDL, and FSG, this study agrees with the previous study which showed good relation in loss calcium level in MI patients than in HCs with p-value < 0.05 [2].

Data of this study showed good relation in loss serum iron level in MI patients than HCs with p-value < 0.05. In humans, iron can cause lipid peroxidation, which has been linked to ischemic myocardial injury. Atherosclerosis is believed to be caused by the degradation of low- LDLs. Copper deficiency increasing levels of LDL and other lipoproteins such as High-Density Lipoprotein (HDL) and Very-Low-Density Lipoprotein (VLDL) more susceptible to oxidation. When lipoproteins from copper-deficient animals are exposed to oxidative reactions involving iron, they produce more thiobarbituric acid reactive substances, indicating that copper can protect against iron-induced oxidation. Copper ions can catalyze lipoprotein oxidation, but enzymes must contain it to prevent oxidative modification. A copper deficiency in the body may lead to LDL oxidation, poor antioxidant enzyme levels, and dysfunctional mitochondria, all of which may contribute to MI development. Our study results are inconsistent with several studies. The role of trace elements in the formation and progression of CVD is becoming more widely understood in MI. However, there isn't always a clear cause-effect association between the production of MI and trace element status. This Troponin T protein has yet to be extracted from skeletal muscle. It's highly accurate as it relates to myocardial damage. They enter the bloodstream 6-8 hours after myocardial infarction, reach a plateau between 12 and 24 hours, and remain increased for 7 to 10 days. Creatine kinase is found throughout the body and is unspecific for myocyte damage; however, CK-MB is a myocardial tissue-specific enzyme. CK-MB can be identified in serum after 4 to 6 hours following Myocardial ischemia began, although it may take 12 hours for some people. CK-MB levels are frequently used to monitor for reinfarction since they recover to normal within 36 to 48 hours of the intervention. Because CK-MB is produced by weakening skeletal muscle, it should be used with caution if skeletal muscle damage or disease is still suspected [3].

Copeptin is now widely recognized as a quantifiable endogenous stress marker. Acute myocardial infarction, for example, causes it to grow fast. A single variable, it has only limited diagnostic sensitivity for an acute MI. In a dual-marker strategy, however, combining copeptin with standard cardiac troponin improves diagnostic accuracy and, in particular, the adverse predictive benefit of cardiac troponin alone for an acute MI, so our results correspond to many studies that show a significant increase in diagnostic sensitivity for acute myocardial infarction. CPP is a nonspecific marker, but its concentration rises early in an acute instance of AMI, most likely as a

result of a decrease in cardiac activity and/or blood pressure, making the pathophysiological model for ruling out AMI simple. Troponin, on the other hand, is 100% cardio-specific, although its concentration takes time to rise after myocardial necrosis.

## Conclusion

In conclusion, the current study found that the patients with MI have High levels of serum Copeptin, which may be the cause of their various complications during the disease course, and this may be used as possible biomarkers and predictor of MI, also they may be used in the manufacture of new treatments for MI disease.

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