Evaluation of Serum Level of Copeptin as an Endogenous Stress Biomarker in the Early Diagnosis of Subtypes of Acute Coronary Syndrome in Iraqi Patients

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Abstract

Background: Acute coronary syndrome (ACS) is still one of the main causes of morbidity and mortality worldwide, and an early diagnosis of acute myocardial infarction (MI) aims to decrease mortality in MI patients. The ACS is manifested as one of three subtypes. These subtypes include MI with the electrocardiogram (ECG) is showing ST-segment elevation (STEMI), the other is MI with the ECG is showing no ST-segment elevation (NSTEMI), and the third type is unstable angina (UA). **Objectives:** The objectives of this study were to evaluate the role of serum copeptin (CPP) level in early diagnosis of subtypes of ACS. **Materials and Methods:** One hundred and twenty patients (72 males and 48 females) aged ≥30 years were consecutively selected from those who were admitted and diagnosed as ACS. The ACS patients comprised three subgroups: STEMI, NSTEMI, and UA, while apparently, healthy subjects were recruited as controls for this study. For each study subject, serum CPP was measured. **Results:** The CPP mean level showed an overall significant difference among study groups. On paired comparison, the CPP mean level was significantly higher in STEMI and NSTEMI subgroups ($P < 0.001$) as well as in UA subgroup of ACS patients than in controls ($P < 0.05$). On receiver operator characteristic analysis, the CPP levels showed good sensitivity and specificity in differentiation of each ACS subtype patients from controls as well as in differentiation of patients among subtypes of ACS. **Conclusion:** Serum CPP level is significantly higher in all subtypes of ACS than in controls in the first hours after the onset of acute chest pain in ACS patients in addition to having better sensitivity and specificity in the differentiation of patients among the subtypes of ACS.

Keywords: Acute coronary syndrome, copeptin, ST-segment elevation myocardial infarction

Introduction

Coronary heart disease (CHD) is caused by an inadequate myocardial oxygen supply due to narrowing or obstruction of the coronary arteries and is the most common cause of death worldwide.[1] Clinically, the major acute clinical manifestation of CHD is termed acute coronary syndrome (ACS) which includes an acute myocardial infarction (MI) with the electrocardiogram (ECG) showing ST-segment elevation myocardial infarction (STEMI), an acute MI with no ST-segment elevation myocardial infarction (NSTEMI), and a third subtype which is the unstable angina (UA).[2] The management of the three subtypes of ACS is variable, so a finding of efficient cardiac biomarkers for the early diagnosis would be of great importance. Cardiac-specific troponins of the type I high sensitive cardiac troponin-I (hscT-I) and of the type T high sensitive cardiac troponin-T (hscT-T) have been regarded as favorable biomarkers for the diagnosis of MI since 2000[3] and are still having a vital role in assessing cardiac injury through measuring their total levels[4] or their specific isoforms.[5] The pattern of traditional troponin elevation was documented by many studies; troponin level rises in serum 4–10 h after onset of acute MI, and it peaks at 12–48 h and remains elevated for 4–10 days. Accordingly, and in the context of acute chest pain and to reliably rule out

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acute MI, patients need to repeat the measurement of troponin level 6–12 h after initial assessment.[6] In addition, a newer generation of cardiac troponin tests has emerged and is referred to as the high-sensitivity troponins. They can detect cardiac injury more efficiently and more immediate than conventional cardiac troponins by their ability to detect very low serum troponin levels. Such tests were Food and Drug Administration approved for hscT-T in 2017 and for hscT-I in 2019.[7]

Copeptin (CPP) is a polypeptide molecule that is derived from the precursor peptide prepro-vasopressin (164 amino acids) which consists of arginine vasopressin (AVP), neurophysin II, and CPP.[8] It has recently been reported that the level of CPP, the C-terminal part of AVP precursor, was elevated within 30 min after the onset of chest pain in patients with MI as a result of endogenous stress response.[9] The CPP level did not require serial sampling in contrast to troponin and so may represent an accurate anchor point to diagnose MI in patients admitted to emergency department (ED).[9] Hence, CPP level may confirm or rule out ACS in patients admitted to ED at an earlier time if it were of high sensitivity and specificity, and such a property would reduce the mortality rate and decrease the economic costs of management of ACS patients.

Materials and Methods

Study patients were recruited from the coronary care unit at Al-Yarmouk Teaching Hospital during the period between November 1, 2022, and September 1, 2023. One hundred and twenty patients (72 males and 48 females) aged ≥30 years were consecutively selected from those who were admitted and diagnosed as ACS by specialist cardiologists. The diagnosis of ACS was based on the presence of two out of three criteria:

- Clinical presentation of the patient
- ECG changes
- A positive troponin test.

Based on the same adopted criteria, ACS patients comprised three subgroups, namely STEMI, NSTEMI, and UA. The apparently healthy subjects as a controls group were recruited from those who had no current illness with consideration of age and sex matching with the ACS patients. They had no history of CHD or other systemic diseases and have had normal ECG recording.

Blood analysis

Blood samples were collected from patients and controls. Serum was separated, divided into aliquots, and used for measurement of CPP. The assays of CPP depended on the use of enzyme-linked immune sorbent assay kits that were supplied by MyBioSource Company, USA. Serum cholesterol, glutamate oxaloacetate transaminase (GOT), and fasting blood sugar (FBS) were measured by a fully automated Cobas c 111 analyzer.

Statistical analysis

Data were analyzed using the statistical package of SPSS Inc., (Chicago, IL, USA). After assuring that the data were normally distributed, data presentation was done by simple measures such as mean, standard error or standard deviation of the mean, and percentage. The analysis of variance (ANOVA) test was used to detect the presence of difference in means among more than two groups, while the Least significant difference (LSD) test was used for the difference between two means. $P < 0.05$ was considered statistically significant. A receiver operator characteristic (ROC) curve analysis with measurement of the area under the curve (AUC) was done for CPP level for differentiation of study subjects according to the method of Hanley and McNeil.

Ethics approval

This study was approved by the ethical committee of Department of Biochemistry, Medical College, Al-Mustansiriyah University, Baghdad, Iraq, on 3rd of June 2023. Verbal consent was obtained from the participants before filling the questionnaire. Participants were informed that their participation in this study is voluntary, no incentives or compensations will be offered in return, and that they have the right to withdraw from the study at any stage.

All the participants' information was kept private by keeping it in a secured folder in a password-protected computer owned by the study investigators. No information was shared with any other individuals or entities.

Results

The clinical characteristics of study subjects are shown in Table 1. The patients and the control subjects had a similar sex distribution (60% males and 40% females). The study patients who were ≤50 years in age constituted 33.3%, and those who were >50 years constituted 66.66%. In regard to BMI, 20% of patients were of normal weight, 47.5% were overweight, and 32.5% were within the obese category.

Table 1: Clinical characteristics of study subjects

Characteristic	Patients ($n=120$), n (%)	Controls ($n=80$), n (%)
Age (years)		
≤50	40 (33.3)	27 (33.75)
>50	80 (66.66)	53 (66.2)
BMI (kg/m^2)		
Normal weight	24 (20)	16 (20)
Overweight	57 (47.5)	38 (47.5)
Obese	39 (32.5)	26 (32.5)
Sex		
Male	72 (60)	48 (60)
Female	48 (40)	32 (40)
ACS subgroups		
STEMI	40 (33.3)	80 (100)
NSTEMI	40 (33.3)	
UA	40 (33.3)	

BMI: Body mass index, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, UA: Unstable angina, ACS: Acute coronary syndrome

The ACS patients included those with STEMI (40 patients), NSTEMI (40 patients), and UA (40 patients).

The result of the comparison of levels of study parameters among subgroups of ACS patients (STEMI, NSTEMI, and UA) and controls is shown in Table 2. The comparison revealed significant differences among the study groups or subgroups in regard to the CPP mean level as well as to the mean levels of cholesterol, GOT, and FBS.

Further analysis by LSD test revealed that CPP level mean was significantly higher in both STEMI and NSTEMI subgroups than in controls ($P < 0.001$) as well as in UA subgroup than in controls ($P < 0.05$) [Table 3]. The mean level was also significantly higher in STEMI than in both NSTEMI ($P < 0.001$) and UA ($P < 0.001$). Furthermore, a significant difference in CPP level was detected between NSTEMI and UA subgroups ($P = 0.015$).

The ROC analysis was done to reveal the discriminative ability of CPP between paired ACS subgroups and between them and the controls group. Table 4 shows AUC and the best discriminative cutoff value of CPP that best predicted STEMI versus NSTEMI subgroups of ACS patients. The CPP showed that the AUC was 0.847 with a cutoff value of 236.23 pg/ml, and 92.3% was the sensitivity of the test, while the specificity was 82.2%, and the diagnostic accuracy was 87.2%.

Table 5 shows the results of AUC and the best discriminative cutoff value of CPP that best predicted STEMI versus UA subgroups of ACS patients. The CPP level showed that the AUC was 0.951 with a cutoff value of 203.04 pg/ml, and 95% was the sensitivity of the test, while the specificity was 88.2%, and the diagnostic accuracy was 92.1%.

Table 6 shows the results of AUC and the best discriminative cutoff value of CPP (pg/ml) that best predicted NSTEMI versus

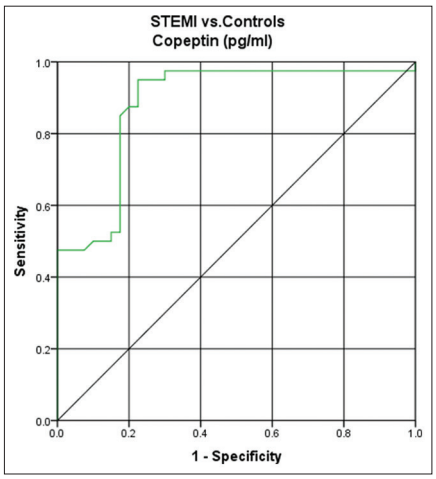

Figure 1: Receiver-operating characteristic curve of copeptin levels in STEMI subgroup of acute coronary syndrome patients versus controls

Table 2: Demographic, clinical characteristics, baseline laboratory tests, and study biomarkers in subgroups of acute coronary syndrome patients and controls

Characteristic	STEMI ($n=40$), mean±SE	NSTEMI ($n=40$), mean±SE	UA ($n=40$), mean±SE	Controls ($n=80$), mean±SE	*P*
Age (years)					
Range (years)	45–75	45–78	47–80	34–77	0.065
Mean	59±2	60±3	61±3	57±2	NS
BMI (kg/m^2)	28.53±0.57	28.17±0.53	27.53±0.57	23.37±0.46	0.032 significant
FBS (mg/dL)	194.27±8.78	173.79±11.32	152.77±6.81	92.67±2.37	>0.001 significant
Cholesterol (mg/dL)	211.42±5.2	173.87±5.93	153.18±4.58	141.64±2.73	>0.001 significant
GOT (IU/L)	146.1±14.86	58.69±3.17	15.74±1.2	14.42±0.56	>0.001 significant
Copeptin (pg/mL)	341.41±13.65	214.18±8.02	185.82±5.69	162.65±3.19	>0.001 significant

ANOVA test was performed. STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina, BMI: Body mass index, FBS: Fast blood sugar, GOT: Glutamate oxaloacetate transaminase, NS: Not significant, SE: Standard error

Table 3: Comparison of copeptin levels between paired study groups

		LSD				
(I) groups	(J) groups	Mean difference (I−J)	SE	*P*	95% CI	
					Lower bound	Upper bound
STEMI	NSTEMI	127.23800*	11.57613	0.000	104.3956	150.0804
	UA	155.58975*	11.57613	0.000	132.7474	178.4321
	Controls	178.75894*	10.43458	0.000	158.1691	199.3488
NSTEMI	UA	28.35175*	11.57613	0.015	5.5094	51.1941
	Controls	51.52093*	10.43458	0.000	30.9311	72.1108
UA	Controls	23.16919*	10.43458	0.028	2.5794	43.7590

*Significant difference between groups ($P \leq 0.05$). LSD test was performed. STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-STEMI, UA: Unstable angina, SE: Standard error, CI: Confidence interval, LSD: Least significant difference test

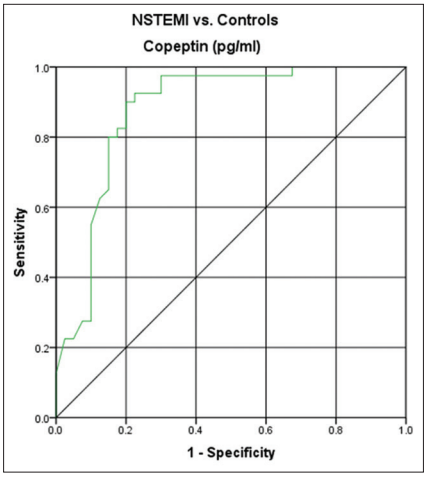

Figure 2: Receiver-operating characteristic curve of copeptin levels in the NSTEMI subgroup of acute coronary syndrome patients versus controls

UA subgroups of ACS patients. The CPP showed that the AUC was 0.845 with a cutoff value of 179.99 pg/ml, and 85% was the sensitivity of the test, while the specificity was 88.2%, and the diagnostic accuracy was 87.9%.

Table 7 and Figure 1 show the results of AUC and the best discriminative cutoff value of CPP (pg/ml) that best predicted STEMI versus controls subgroups of ACS patients. The CPP showed that the AUC was 0.894 with a cutoff value of 196.24 pg/ml, and 87.9% was the sensitivity of the test, while the specificity was 84.03%, and the diagnostic accuracy was 87.5%.

Table 8 and Figure 2 show the results of AUC and the best discriminative cutoff values of CPP (pg/ml) that best predicted NSTEMI versus controls subgroups of ACS patients. The CPP showed that the AUC was 0.825 with a cutoff value of 166.92 pg/ml, and 85.5% was the sensitivity of the test, while the specificity was 77.5%, and the diagnostic accuracy was 73.7%.

Table 9 and Figure 3 show the results of AUC and the best discriminative cutoff values of CPP (pg/ml) that best predicted UA subgroup of ACS patients versus controls. The CPP showed that the AUC was 0.833 with a cutoff value of 157.69 pg/ml, and 80% was the sensitivity of the test, while the specificity was 85%, and the diagnostic accuracy was 83.1%.

Discussion

Early identification of ACS patients among those presenting with acute chest pain to the ED in the real-life daily clinical practice is important. Patients with ACS can benefit from rapid and aggressive medical and interventional treatment. The CPP level, if were to be an efficient diagnostic tool in such patients, could rule out individuals with noncardiac chest pain and so increase the efficiency of work in ED.

In the present study, there was a significant difference in CPP level in subgroups of patients with ACS when compared with

Table 4: The discriminative cutoff value of copeptin level that best predicted ST-segment elevation of myocardial infarction versus non-ST-segment elevation of myocardial infarction subgroups of acute coronary syndrome patients

Parameter	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.847	236.23	92.3	82.2	87.2

CPP: Copeptin, AUC: Area under the curve

Table 5: The discriminative cutoff value of copeptin level that best predicted ST-segment elevation of myocardial infarction versus unstable angina subgroups of acute coronary syndrome patients

Parameter	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.951	203.04	95.0	88.2	92.1

CPP: Copeptin, AUC: Area under the curve

Table 6: The discriminative cutoff value of copeptin level that best predicted non-ST-segment elevation of myocardial infarction versus unstable angina subgroups of acute coronary syndrome patients

Parameter	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.845	179.99	85	88.2	87.9

CPP: Copeptin, AUC: Area under the curve

Table 7: The discriminative cutoff value of copeptin level that best predicted ST-segment elevation of myocardial infarction versus controls subgroups of acute coronary syndrome patients

Study biomarker	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.894	196.24	87.9	84.03	87.5

CPP: Copeptin, AUC: Area under the curve

Table 8: The discriminative cutoff value of copeptin level that best predicted non-ST-segment elevation of myocardial infarction versus controls subgroups of acute coronary syndrome patients

Study biomarker	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.825	166.92	85.5	77.5	73.7

CPP: Copeptin, AUC: Area under the curve

Table 9: The discriminative cutoff values of some study parameters that best predicted unstable angina versus controls subgroups of acute coronary syndrome patients

Study biomarker	AUC	Cutoff value	Sensitivity	Specificity	Diagnostic accuracy (%)
CPP (pg/mL)	0.833	157.69	80.0	85.0	83.1

CPP: Copeptin, AUC: Area under the curve

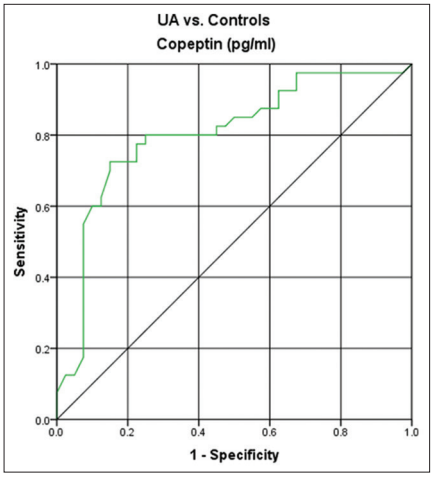

Figure 3: Receiver-operating characteristic curve of copeptin levels in unstable angina subgroup of acute coronary syndrome patients versus controls. UA: Unstable angina

controls in the first few hours after the onset of chest pain. On further comparison of paired ACS subgroups and controls, then, the STEMI subgroup showed the highest level compared with other subgroups (NSTEMI and UA). This agrees with other studies that found that CPP level was elevated even within 30 min after the onset of acute chest pain in patients with MI. Moreover, it did not require serial sampling like troponin and may represent an accurate anchor point to diagnose ACS patients, particularly those with MI, early at the time of their admission to ED.[9] This role of CPP level was explained as an acute endogenous stress response to ischemia and seemed real and effective[10] because myocardial ischemia acts as an endogenous stressor leading to rapid activation of neurohormonal system and increased CPP release.[11] Such a role for CPP is further reinforced by the study finding that it has a good AUC and high sensitivity and specificity in early diagnosis of ACS patients and their differentiation from controls as well as in differentiation of patients among subtypes of ACS (STEMI, NSTEMI, and UA). However, it was also found that a combination of CPP level and hscTn-I level are even more sensitive to rule out ACS patients compared with either of these markers tested independently.[11]

It may be concluded that serum CPP level may enable to confirm or to rule out ACS with high sensitivity and specificity and may serve to reduce mortality among ACS patients and to decrease the economic costs of management of ACS patients in ED.[12]

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Conflicts of interest

There are no conflicts of interest.

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