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ORIGINAL ARTICLE

Impact of copeptin on diagnosis of acute coronary syndrome

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KEYWORDS

Copeptin;
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Abstract *Background:* Acute coronary syndrome remains the principal cause of death, so the early diagnosis is of great importance. Cardiac troponin is the preferred biomarker for acute myocardial infarction. Cardiac chest pain immediately increased copeptin secretion. The combination of copeptin and cardiac troponin I is being suggested for early diagnosis of acute coronary syndrome.

Subject: It was done to emphasize the importance of association of copeptin, cardiac troponin I and high sensitive C reactive protein to confirm the diagnosis of acute myocardial infarction or unstable angina pectoris in patients with a cardiac chest pain.

Method: The current study enrolled 22 patients with acute myocardial infarction as group i and 33 patients with unstable angina pectoris as group ii. The third group consisted of 23 apparently healthy persons. Patients and controls were subjecting to laboratory investigations, which include the levels of copeptin, high-sensitivity cardiac troponin high sensitive C reactive protein creatine kinase MB fraction, lipid and I profile.

Results: We found a significant increase of copeptin in group i when compared to group iii (30.01 ± 12.92) (9.54 ± 3.55), respectively, p value = 0.000 and group ii (30.01 ± 12.92) (11.16 ± 4.58) respectively, p value 0.000, but a non-significant difference in group ii when compared to group iii (11.16 ± 4.58) (9.54 ± 3.55) respectively, p value = 0.160. Also cardiac troponin

Abbreviations: ACS, acute coronary syndrome; cTn, cardiac troponins; AMI, acute myocardial infarction; UAP, unstable angina pectoris; AVP, arginine vasopressin; hs-cT I, high-sensitivity cardiac troponin I ; hs-CRP, high sensitive C reactive protein; CK-MB, creatine kinase MB fraction.

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I showed a significant increase in group i when compared to group ii (136.73 ± 26.07) (11.18 ± 3.79), p value = 0.000, and group iii (136.73 ± 26.07) (9.61 ± 3.70) respectively, p value = 0.000, but a non-significant difference between group ii (11.18 ± 3.79), and group iii (9.61 ± 3.70), p value = 0.129. There was a positive correlation between copeptin and cardiac troponin I within group i, r = 0.718, p value = 0.000.

Conclusion: In suspected acute coronary syndrome, determination of copeptin and cardiac troponin I provides a remarkable negative predictive value, which aids in early and safe ruling out of myocardial infarction.

1. Introduction

Acute coronary syndrome (ACS) remains the principal cause of death around the world in 2011 [1]. Diagnosis and accurate exclusion are of great importance in the emergency department to ensure early effective treatment. Cardiac troponins (cTn) are the preferred biomarkers for detection of myocardial cell necrosis and they are essential for the diagnosis of acute myocardial infarction (AMI) [2]. However, there remains a troponin-blind interval after onset of chest pain due to the delayed release of cTn following a cardiac injury [3], and requires repeat measurement of cTn to discriminate between AMI and unstable angina pectoris (UAP) [4]. Therefore, there is a need for a biomarker that is released immediately in the event of AMI [3]. The hope is that this new biomarker will enable early decision making in clinical practice. AMI activates the main hypothalamic stress hormone, arginine vasopressin (AVP) [2]. Hence, AVP becomes an important marker; however, due to its unstable nature and rapid clearance from plasma, measurements of AVP are rarely reproducible [5]. Copeptin is stored in the neurohypophyseal vesicles together with AVP until they are secreted [2]. Copeptin is stable and easier to measure. Therefore, its level represents the production of AVP. Thus, copeptin is a mirror of AVP concentration with high prognostic accuracy [6]. Therefore, in patients with ACS, the new biomarker copeptin as a marker of acute endogenous stress [7] is expected to be elevated very early after AMI [8]. Therefore, the combination of a marker of endogenous stress and a marker of cell necrosis has been suggested to improve the diagnostic performance in chest pain patients at presentation in the emergency department [9].

1.1. Aim of work

This study was done to emphasize the importance of association of copeptin, cardiac troponin i, high sensitive C reactive protein and creatine kinase MB fraction, to confirm the diagnosis of acute myocardial infarction or unstable angina pectoris in patients with a cardiac chest pain.

2. Patients and methods

2.1. Patients and controls

AMI was the final diagnosis in 22 patients (14 males and 8 females), their ages ranged between 46 and 73 years, and 33 patients with UAP (24 males and 9 females), and their ages ranged between 47 and 71 years. They presented to the emergency department of the National Heart Institute, Imbibe, Giza, Egypt, complaining of typical cardiac chest pain between January 2013 and June 2013. Patients with hepatic or renal disease were excluded. Other 23 apparently healthy persons of matching age served as the healthy control group of this study for baseline normal value assessment. All investigations and diagnosis of AMI and UAP were performed in accordance with a standardized protocol in the National Heart Institute, Health and Human Ethics Clearance Committee guidelines for Clinical Researches. Local ethics committee approved the study protocol and informed consents were obtained from all subjects.

Patients and controls were divided into the following groups (According to the current guidelines) [10]:

1- AMI patients as group i: consisted of 22 patients with a mean age/years and SD of 59.59 ± 6.75.
2- USP as group ii: consisted of 33 patients with a mean of age/years and SD of 58.82 ± 6.20.
3- Healthy control as group iii: consisted of 23 age matched, with mean age/years and SD of 56.04 ± 6.27.

Comprehensive adult health history was taken and comprehensive physical examination was done for all studied participants.

All studied participants were subjected to the following:

1- Standard 12-lead electrocardiography (ECG).
2- Trans-thoracic echocardiography.
3- Chest radiography (postero-anterior and lateral).
4- Laboratory investigations:-
   a) Serum random blood glucose level.
   b) Serum lipid profile (total cholesterol, serum low-density lipoprotein – cholesterol (LDL-c) and triglycerides).
   c) Liver function tests (total serum bilirubin, total serum protein, prothrombin time, and international normalized ratio).
   d) Renal function tests (serum creatinine, serum blood urea).
   e) Total serum creatine kinase (CK).
   f) Serum creatine kinase-MB fraction (CK-MB) .
   g) Serum highly sensitive cardiac troponin i (hs-cTn I).
   h) Serum copeptin.
   i) Serum highly sensitive C reactive protein (hs-CRP).

2.2. Sampling collection

- Five ml of venous blood was withdrawn, under aseptic condition, from each patient and control. Then it was divided as follows:

- 3 ml without anticoagulant to measure the concentration of serum creatine kinase (CK), serum creatine kinase-MB fraction (CK-MB), alanine aminotransferase (ALT), highly sensitive cardiac troponin I (hs-cTn I), Glucose, Urea and highly sensitive C reactive protein (hs-CRP).
- 2 ml without anticoagulant (serum) to measure concentration of copeptin. The samples were lifted for 2 h at room temperature before centrifugation for 20 min at approximately 1000*g* and stored at −20 °C.

2.3. Quantitative determination of human copeptin (CPP) by ELISA

The kits were supplied by Uscn Catalog NO E90365Hu.

2.3.1. Principle of this procedure

The microtiter plate provided in this kit had been pre-coated with a monoclonal antibody specific to copeptin.

Standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for copeptin. Next, Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. After TMB substrate solution was added, only those wells that contain copeptin, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme–substrate reaction was terminated by the addition of sulfuric acid solution and the color change was measured spectrophotometrically at a wave length of 450 nm ± 10 nm. The concentration of CPP in the samples was then determined by comparing the O.D. of the samples to the standard curve .The detection range is 15.6–1000 pg/ml.

This assay has high sensitivity and excellent specificity for detection of copeptin.

2.4. Determination of concentration of C- reactive protein by ELISA

The kit supplied by GenWay Catalog NO 40-052-115042.

2.4.1. Principle of this procedure

The hsCRP ELISA was based on the principle of a solid phase enzyme-linked immunosorbent assay.

The assay system utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the CRP molecule. This mouse monoclonal anti-CRP antibody was used for solid phase immobilization (on the microtiter wells). A goat anti-CRP antibody is in the antibody-enzyme (horseradish peroxidase) conjugate solution. The test sample was allowed to react simultaneously with the two antibodies, resulting in the CRP molecules being sandwiched between the solid phase and enzyme-linked antibodies. After a 45-min incubation at room temperature, the wells were washed with water to remove unbound labeled antibodies. A tetramethylbenzidine (TMB) reagent was added and incubated for 20 min, resulting in the development of blue color. The color development was stopped with the addition of 1 N HCl changing the color to yellow. The concentration of CRP was directly proportional to the color intensity of the test sample. Absorbance was measured spectrophotometrically at 450 nm.

2.5. Statistical analysis

All information was recorded in a database created with Microsoft Office Access 2007. Calculations were done by means of statistical software packages namely SPSS (Statistical Package for the Social Sciences), version 17.

Data were tabulated and statistically analyzed to evaluate the difference between the whole groups under investigations as regards the various parameters. Together, correlation was tried in between the essential studied parameters. The statistical analysis included the arithmetic mean value, standard deviation, and hypothesis student's *t* test. Pearson's test was used to study the correlation "*r*" and the significance of result (*p*).

3. Results

3.1. Baseline characteristics of all groups

Table 1 provides the baseline characteristics of the overall study population. Discharge diagnosis of AMI was made in 22 patients, having an ST segment elevation, pathological Q and T wave inversion. Furthermore, they had highest levels of copeptin, hs-cTn I, hs-CRP, LDL-C, and CK-MB. The diagnosis of UAP was made in 33 patients. Traditional risk factors were present in AMI and UAP patients. All UAP patients and controls had normal ECG.

3.2. Comparison between AMI patients and controls

When comparing between group i and group iii patients, we found a highly significant increase of all serum CK-MB, serum LDL-c, serum random blood glucose level, hs-CRP, hs-troponin I and serum copeptin. There were non-significant differences when comparing between group i and iii as regards the mean of all; age, height and BMI, as shown in Table 2 and Fig. 1.

3.3. Comparison between UAP patients and controls

Table 3 showed that, there were non-significant differences as regards the age, height, weight, BMI, CK-MB, hs-cTn i and copeptin, when compared between group ii and group iii patients. The comparison of both random blood glucose and hs-CRP in previous groups, was significantly increased in random blood glucose, and highly significant in hs-CRP, as shown in Fig. 1.

3.4. Comparison between UAP and AMI patients

Table 4 showed that, there were highly significant increases between group ii and group i patients as regards CK-MB, LDL-c, random blood glucose level, hs-CRP, hs-Tcn I and copeptin while a non-statistically significant difference was found between the two groups as regards age, height, weight and BMI, as shown in Fig. 1.

3.5. Correlation between copeptin in AMI patients

Table 5 shows the correlation coefficient of copeptin and other parameters within AMI patient group. We found that, there

Table 1 Baseline characteristics and presentation in the overall population according to final diagnosis.

Parameters	Group i (mean ± SD)	Group ii (mean ± SD)	Group iii (mean ± SD)
Age/years	(59.59 ± 6.75)	(58.82 ± 6.2)	(56.04 ± 6.27)
Sex (men/women) (*n*)/%	(14/8)–(70/30%)	(22/9)–(71/29%)	(16/7)–(70/30%)
Height (m)	1.70 ± 0.07	1.71 ± 0.08	1.71 ± 0.08
Weight (kg)	90.00 ± 13.54	88.24 ± 11.16	84.65 ± 8.38
Body mass index (m^2/k)	31.04 ± 5.03	30.13 ± 4.41	29.38 ± 3.24
Hypertension	18	30	No
Hypercholesterolaemia	22	33	No
Diabetes mellitus	15	23	No
Family history	22	32	No
Smoking	14	22	No
Aspirin	22	33	No
Beta-adrenergic blocker	22	33	No
ACE inhibitor[a] or ARB[b]	22	30	No
Statin	22	33	No
Clopidogrel	10	No	No
Duration of chest pain (h)	6–8/h	8–10/h	No chest pain
Electrocardiogram:			
Pathological Q wave	All 22 patients had these changes	All patients have normal ECG	All patients have normal ECG
ST-segment elevation			
T-wave changes			
LDL(U/L)[c]	394.55 ± 101.71	323.67 ± 84.07	227.00 ± 44.50
CK-MB(U/L)[d]	45.59 ± 12.04	7.76 ± 3.43	6.22 ± 1.90
Random blood glucose (mg/dL)	149.09 ± 79.90	93.15 ± 10.93	87.39 ± 8.66
hs-cTnI (pg/ml)[e]	136.73 ± 26.07	11.18 ± 3.79	9.61 ± 3.70
Copeptin (pmol/L)	30.01 ± 12.92	11.16 ± 4.58	9.54 ± 3.55
CRP (mg/L)[f]	25.66 ± 13.41	15.24 ± 6.99	4.89 ± 3.59

[a] Angiotensin-converting enzyme.
[b] Angiotensin II receptor blocker.
[c] Low density lipoprotein.
[d] Creatine kinase-MB.
[e] High-sensitivity cardiac troponin.
[f] C reactive protein , means ± standard deviations or numbers of observations in the corresponding group.

Table 2 Comparison between group (i) and group (iii).

Parameters	Group i		Group iii		Independent *t*-test		Significant
	Mean	SD	Mean	SD	*t*	*p*-value	
Height/m	1.70	0.07	1.71	0.08	0.245	0.808	NS
Weight/kg	90.00	13.54	84.65	8.38	1.601	0.117	NS
BMI (m^2/k)[a]	31.04	5.03	29.38	3.24	1.322	0.193	NS
CK-MB (U/L)[b].	45.59	12.04	6.22	1.90	15.216	0.000	HS
LDL (U/L)[c]	394.55	101.71	227.00	44.50	7.214	0.000	HS
Random blood glucose (mg/dL)	149.09	79.90	87.39	8.66	3.683	0.001	HS
CRP (mg/L)[d]	25.66	13.41	4.89	3.59	7.168	0.000	HS
hs-cTnI (pg/ml)[e]	136.73	26.07	9.61	3.70	22.650	0.000	HS
Copeptin (pmol/L)	30.01	12.92	9.54	3.55	8.660	0.000	HS

[a] Body mass index.
[b] Creatine kinase-MB.
[c] Low density lipoprotein.
[d] C reactive protein.
[e] High-sensitivity cardiac troponin I.

was a non-significant difference but positive correlation between copeptin and CK-MB $r = 0.201$ and $p = .370$, and between copeptin and LDL-c, $r = 0.298$ and $p = 0.196$. But there was a highly significant positive correlation between copeptin and both hs-cTn i and hs-CRP, ($r = 0.718$ and $p = 0.000$), ($r = 0.699$ and $p = 0.000$) respectively, as shown in Fig. 1.

4. Discussion

ACS comprises life-threatening conditions that require immediate and efficient medical care to improve outcome. A previous study reported that nearly one third of patients with ACS have normal levels of hs-cTn T and the majority of these pa-

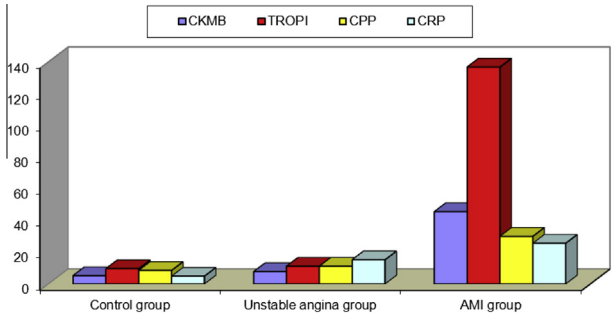

Figure 1 Show the relations of cardiac biomarkers in all groups.

tients had unstable angina. Hs-cTn T and hs-cTn I remain superior biomarkers for AMI diagnosis [11]. The new biomarker copeptin was expected to be elevated very early after an AMI [12].

In the current study, we observed that, the copeptin levels were significantly increased in AMI than in unstable angina patients. While there was a non-significant difference between UAP patients and healthy controls. This result suggested that, AMI induces a higher level of copeptin secretion than UAP patients and control subjects. This finding was well in agreement with Folli and his college study that showed the increase in copeptin levels was strictly related to stress occurring immediately with the onset of AMI [13]. Karakas and his colleague suggested that, copeptin may be of less value in diagnoses of unstable angina patients [14]. This is because; the unstable angina pectoris is not accompanied by necrosis and does not cause sufficient endogenous stress for copeptin release [9]. Kaplan–Meier analysis showed that copeptin levels above the diagnostic cut-off (< 14 pmol/L) were associated with elevated intermediate-term (180 days) mortality, while no patient with copeptin values below the cut-off died [15] Therefore the use of copeptin was proposed in AMI patients who present soon after symptom onset (0–4 h) while troponin is still negative [16].

Another study reported that, copeptin provided a little clinical information when measured alone [17], because the exact trigger cause for copeptin release in AMI was unknown; it was generally considered a marker of acute life-threatening

Table 3 Comparison between group ii and group iii.

Parameters	Group ii		Group iii		Independent *t*-test		Significant
	Mean	SD	Mean	SD	*t*	*p*-Value	
Height/m	1.71	0.08	1.71	0.08	0.753	0.454	NS
Weight/kg	88.24	11.16	84.65	8.38	1.306	0.197	NS
BMI (m^2/k) [a]	30.13	4.41	29.38	3.24	0.691	0.493	NS
CK-MB (U/L)[b]	7.76	3.43	6.22	1.90	1.540	0.056	NS
LDL (U/L) [c]	323.67	84.07	227.00	44.50	5.036	0.000	HS
Random blood glucose (mg/dL)	93.15	10.93	87.39	8.66	2.106	0.040	S
CRP (mg/L) [d]	15.24	6.99	4.89	3.59	6.518	0.000	HS
hs-cTn I (pg/ml) [e]	11.18	3.79	9.61	3.70	1.543	0.129	NS
Copeptin (pmol/ L)	11.16	4.58	9.54	3.55	1.423	0.160	NS

[a] Body mass index.
[b] Creatine kinase-MB.
[c] Low density lipoprotein.
[d] C reactive protein.
[e] High-sensitivity cardiac troponin I.

Table 4 Comparison between group (ii) and group (i).

Parameters	Group ii		Group i		Independent *t*-test		Significant
	Mean	SD	Mean	SD	*t*	*p*-Value	
Height/m	1.71	0.08	1.70	0.07	0.490	0.626	NS
Weight/kg	88.24	11.16	90.00	13.54	0.525	0.602	NS
BMI (m^2/k) [a]	30.13	4.41	31.04	5.03	0.711	0.480	NS
Serum CK-B (U/L) [b]	7.76	3.43	45.59	12.04	17.108	0.000	HS
LDL (U/L) [c]	323.67	84.07	394.55	101.71	2.815	0.007	HS
Random blood glucose (mg/dL)	93.15	10.93	149.09	79.90	3.985	0.000	HS
CRP (mg/L) [d]	15.24	6.99	25.66	13.41	3.772	0.000	HS
hs-cTnI (pg/ml) [e]	11.18	3.79	136.73	26.07	27.359	0.000	HS
Copeptin (pmol/L)	11.16	4.58	30.01	12.92	7.712	0.000	HS

[a] Body mass index.
[b] Creatine kinase-MB.
[c] Low density lipoprotein.
[d] C reactive protein.
[e] High-sensitivity cardiac troponin I.

Table 5 Correlation between CPP and the other studied parameters within group (i).

Parameters	Copeptin		
	Group i		
	r	*p*-Value	Significant
CK-MB[a]	0.201	0.370	NS
LDL(U/L) [b]	0.298	0.196	NS
hs-cTn i(pg/ml) [c]	0.718	0.000	HS
CRP (mg/L) [d]	0.699	0.000	HS

[a] Creatine kinase-MB.
[b] Low density lipoprotein.
[c] High-sensitivity cardiac troponin I.
[d] C reactive protein.

conditions [18] and may be a clinically useful non-specific prognostic marker reflecting disease severity in patients with a wide array of diseases [5]. For this reason it should be assessed along with other more specific biomarkers, such as cardiac troponins.

In the current study, there were highly significant increases of both copeptin and hs-cTnI levels in AMI patients when compared to unstable angina patients. Nursalim and his colleague described a negative predictive value of up to 99.7% using the combination of low level of copeptin and low level of hs-cTnT for ruling out AMI [18]. The combination of hs-cTnT and copeptin decreased the number of false negative as compared to hs-cTnT alone [9]. The results of our study are in accordance with the known fact that copeptin is an endogenous stress hormone reaching markedly elevated levels in critically ill patients [12]. However, in the final exclusion of AMI, copeptin is not able to replace cTnT [19], but adding copeptin to cTnI allowed safe rule out of AMI with a negative predictive value >99% in patients presenting with suspected acute coronary syndromes [8]. The recent presentation of the Biomarkers In Cardiology-8 (BIC-8) was the first interventional clinical trial to study whether it is safe to discharge suspected ACS patients who test troponin and copeptin negative at admission on emergency department [20]. The limitation of our study is that, the present measurements of copeptin and hscTnI concentrations were performed after a time interval elapsed since onset of chest pain and presentation to the emergency department and this might be responsible for the lack of an association between copeptin and ACS.

In our study, we found that, hs-CRP level was highly significantly increased in AMI patients than in those with UAP patients. Accordingly, it seems that hs-CRP could be helpful in differentiating AMI patients from UAP patients. As we found, there was a highly significant increase in patients with UAP than in healthy controls. Accordingly, hs-CRP could be assessing its diagnostic value in ACS. Madadi and his colleague found that, patients with AMI had higher levels of hs-CRP in comparison with unstable angina [21]. Yip and his colleague reported hs-CRP levels of 2.95 mg/L in patients with AMI and 1.35 mg/L in subjects with UAP [22]. But Madadi and his colleague showed that, hs-CRP levels were equal to or higher than 3.27 mg/L more likely to be associated with AMI, so the cut-off point for differentiating between the two diseases was calculated as 3.27 mg/L. [21]. Another study, found that hs-CRP level is a predictor of mortality over the next five years in patients with ACS [21]. This is because the inflammation is one of the pathophysiological mechanisms of most acute cardiovascular conditions including ACS [19] [23], and the benefits of elevated hs-CRP post ACS are indicating the level of myocardial inflammation [24]. Also, this biomarker was associated with atherosclerotic plaque rupture, which is probably a reason for AMI. Patients with unstable angina who had higher levels of hs-CRP had been suggested to be at greater risk of mortality and AMI [25].

In our study, there was a highly positive correlation between copeptin and hs-cTnI ($r = 0.718$, $p = 0.000$) within AMI patients. Karakas and his colleague found a modest positive correlation between copeptin and hs-cTnT in AMI patients [14]. Also, in a study by Lotze and his colleague, they reported a positive correlation between hs-cTnT and copeptin at the time of initial AMI presentation ($r = 0.41$; $p < 0.001$) [3].

5. Conclusion

In suspected ACS patients, determination of copeptin and hs-troponin i provides a remarkable negative predictive value which aids in early and safe ruling-out of myocardial infarction.

Conflict of interest

The authors declare no conflict of interest.

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