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Original Article

Clinical role of serum Copeptin in acute coronary syndrome

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ABSTRACT

Objective: To assess the role of Copeptin in diagnosis of acute myocardial infarction in troponin-blind period.**Subjects and methods:** This study was conducted on 40 patients who presented to emergency department complaining of chest pain and were highly suspicious to have acute cardiac ischemia, in addition to 10 subjects serving as a healthy control group. Blood samples were collected for determination of CK-MB, cTnI and Copeptin. These were measured twice (in patients' group); at 3 h and then at 6–9 h from admission time.**Results:** The first sample revealed a non-significant difference between UA group and AMI group as regards CKMB and troponin, however, high significant difference was found as regards Copeptin ($Z = 5.29$, $P < 0.001$). Moreover, ROC curve analysis of serum Copeptin for discriminating AMI group from UA group in the first sample showed diagnostic sensitivity and specificity of 100%.**In conclusion:** Determination of copeptin in early diagnosis of AMI has diagnostic value being superior to a conventional cTn-I within the first three hours after acute chest pain.© 2018 Egyptian Society of Cardiology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).¹

According to the latest third international definition of acute myocardial infarction (AMI), the electrocardiographic abnormalities together with changes of cardiac troponins (cTns) level represent the key diagnostic elements for diagnosis of AMI in the emergency department.² cTns are golden standards in diagnosis of AMI uniformly approved and recommended by guidelines.³

However, due to a delayed release of cTns into the bloodstream, cTns assays lack sensitivity within the first hours of myocardial injury, a phenomenon referred as the 'troponin-blind period'. cTns is raised within 6–9 h from the onset of symptoms giving sensitiv-

ity of 39–43% when the patient is admitted to the emergency department in the early three hours of onset.^{4,5}

In addition, multiple non-ischemic conditions may challenge the interpretation of causes of elevation in plasma cTns.^{2,3} Thus, addition of another biomarker such as, Copeptin may be more sensitive and informative in reflecting myocardial ischemia with a specific pathophysiological mechanism in AMI development.²

Copeptin, as an endogenous marker of stress⁶ and with its immediate release after the acute event, it seems to have a role in the early exclusion of AMI.⁷ It is the c-terminal part of the vasopressin prohormone and is secreted from the neurohypophysis in equimolar amounts with arginine vasopressin (AVP).⁸

2. Aim of the work

The aim of the present study was to examine the role of serum Copeptin in enhancing the sensitivity of diagnosis of AMI during the early hours of admission of patients in emergency department.

3. Subjects and methods

3.1. Subjects

This study was conducted on 40 patients who presented to emergency department complaining of chest pain and were highly

Abbreviations: ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; AMI, acute myocardial infarction; cTns, cardiac troponins; AVP, arginine vasopressin.

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suspicious to have acute cardiac ischemia, in addition to 10 subjects serving as a healthy control group.

Subjects included in this study were classified into the following groups:

(1) Patients' Group (I) (n = 40):

This group included 40 patients. Diagnosis was based on the combination of clinical presentation, ECG and routine laboratory markers (cTnI and CKMB). This group includes 20 males and 20 females. Their median age was 50 years. They were classified into two subgroups:

(a) Subgroup I-a [Unstable Angina (UA) Group]:

This subgroup included 15 patients with UA. Their median age was 60 years.

(b) Subgroup I-b [Acute Myocardial Infarction (AMI) Group]:

This subgroup included 25 patients with AMI. Their median age was 49 years.

(2) Control group (n = 10):

This group included 10 age and sex matched healthy subjects serving as a healthy control group. The median age of this group was 51 years.

Exclusion criteria:

Patients with stroke, traumatic brain injury, renal diseases and septic shock were excluded.

All individuals included in this study were subjected to laboratory investigations including assay of serum cardiac troponin I (cTn I), CK-MB and serum Copeptin. These were measured twice (in patients' group); at 3 h and then at 6–9 h from admission time.

3.2. Methods

(A) Analytical methods:

Five milliliters of venous blood were withdrawn under aseptic condition from patients on admission to emergency department and from control. Serum was separated by centrifugation at 3000g for 15 min and divided into two parts. The first part was used for immediate assay of CK-MB, cTnI, while the remaining part was stored within 2 h in aliquots at ≤ -80 °C for subsequent assay of Copeptin. Repeated freezing and thawing was avoided.

CK-total was assayed spectrophotometrically on the synchron CX9 auto-analyser (Beckman Instruments Inc.)^a which measures CK-total activity by an enzymatic rate method. CK-MB was assayed spectrophotometrically on the synchron CX9 auto-analyser (Beckman Instruments Inc.)^a by the immune-inhibition technique. cTn-I was assayed using Architect I 1000 from Abbott Diagnostics System.^b The used method is a two-step assay based on chemiluminescent microparticle immunoassay.

The level of Copeptin in samples was determined using a double-antibody sandwich ELISA kit supplied by Elabscience Co., Ltd.^c In this technique, samples or standards containing Copeptin was captured between two antibodies: the first was fixed to the inner wall of ELISA wells plate and the second was labeled with biotin to which Streptavidin-horse radish peroxidase was combined forming immune complex.

Addition of chromogen results in color development that measured spectrophotometrically at a wavelength of 450 nm. The color development is stopped by stopping solution. The concentration of Copeptin was proportional to the color intensity of the test sample. A standard curve was constructed from which the concentrations of Copeptin in the samples were determined.

(B) Statistical Methods:

Statistical analysis was performed by standard complete program of SPSS, version 20.0, IBM Corp., USA, 2012 Statistical Package.

Data was expressed descriptively as median and interquartile range for quantitative skewed data. Comparison between each two groups was done using Wilcoxon rank sum test for skewed data for dependent samples and Mann Whitney U Test for independent samples. $P < 0.05$ was considered significant and $p < 0.01$ was considered highly significant and $p > 0.05$ was considered non-significant. Furthermore, the diagnostic performance of the studied parameters was evaluated using receiver operating characteristic curve analysis, in which sensitivity% was plotted on the Y axis and 100-specificity on the x-axis. The best cut off value (the point nearest to the left upper corner of the curve) was determined.

4. Results

Results of the present study are shown in Tables 1–7 and Figs. 1–3.

Descriptive statistics of first sample (at 3 h from admission time) and second sample (at 6–9 h from admission time) regarding different cardiac markers among control group, UA group and AMI group are shown in Table 1.

Comparative statistics by using Wilcoxon Signed Rank Test between the first and second sample in AMI group revealed high significant difference as regards CKMB ($Z = 3.28$, $P < 0.001$), troponin ($Z = 4.37$, $P < 0.001$), and also a high significant difference was found as regards Copeptin ($Z = 4.19$, $P < 0.001$) as shown in Table 2.

Regarding UA group, a non-significant difference was found between first and second sample in all the studied markers as shown in Table 3.

Comparative statistics by using Mann Whitney U Test between UA group and AMI group in the first sample revealed a non-significant difference as regards CKMB ($Z = 3.36$, $P = 0.07$) and troponin ($Z = 1.77$, $P = 0.076$), however, high significant difference was found as regards Copeptin ($Z = 5.29$, $P < 0.001$). In the second sample, high significant difference was found as regards CKMB ($Z = 4.81$, $P < 0.001$), troponin ($Z = 5.24$, $P < 0.001$) and Copeptin ($Z = 5.03$, $P < 0.001$) as shown in Table 4.

Receiver operating characteristic (ROC) curve analysis was applied to assess the diagnostic performance of CKMB for discriminating AMI group from UA group in the first sample. The best cut-off level of CKMB was 22 IU/mL. This cutoff level had a diagnostic of sensitivity 64%, specificity of 93.33%, positive predictive value (PPV) 94.1%, negative predictive value (NPV) 60.9% and an area under the curve (AUC) of 0.82 as shown in Fig. 1 and Table 5.

Also for troponin, ROC curve analysis was applied to assess its diagnostic performance for discriminating AMI group from UA group in the first sample. The best cutoff level of troponin was 12.6 (pg/mL), its diagnostic sensitivity was 92%, specificity 46.67%, PPV 74.2%, NPV 77.8% and the AUC was 0.669 shown in Fig. 2 and Table 6.

Moreover, ROC curve analysis was applied to assess the diagnostic performance of serum Copeptin (pg/mL) for discriminating AMI group from UA group in the first sample. The best cutoff level

^a Beckman Instruments Inc.; Scientific Instruments Division, Fillerton, California 92634, 3100, USA.

^b Abbott Diagnostic System: 65,205 Wlesbaden, Germany, +49-6122-580.

^c Elabscience Co., Ltd. P.O. Box 5993, Bethesda, MD 20824, USA.

Table 1
Descriptive statistics of different cardiac markers in first (1st) and second (2nd) sample.

Parameters	First sample (3 h) median (IQR) [*]	Second sample (6-9 h) median (IQR) [*]
Troponin in AMI (pg/mL)	26.5 (22.6–34.8)	1134.2 (666.5–4444.2)
Troponin in UA (pg/mL)	21.6 (5.5–31.3)	28 (24.5–32)
Troponin in control (pg/mL)	8.05 (3.2–13)	
Copeptin in AMI (pg/mL)	1900 (1600–2000)	450 (350–700)
Copeptin in UA (pg/mL)	35 (25–50)	27 (21–33)
Copeptin in control (pg/mL)	23.5 (20–30)	
CKMB in AMI (IU/mL)	22 (16–32)	56 (38–89)
CKMB in UA (IU/mL)	18 (16–23.4)	21 (15–24)
CKMB in Control (IU/mL)	12.5 (9–20)	

^{*} IQR: Inter quartile range.

Table 2

Statistical comparison between first (1st) sample versus second (2nd) sample regarding CKMB, troponin and copeptin in acute myocardial infarction (AMI) group using wilcoxon signed rank test.

	1st sample versus second 2nd sample in AMI	
	Z	p value
CKMB 1st	3.28	<0.001 [*]
CKMB 2nd		
Troponin 1st	4.37	<0.001 [*]
Troponin 2nd		
Copeptin 1st	4.19	<0.001 [*]
Copeptin 2nd		

p < 0.001: Highly significant difference.

Table 3

Statistical comparison between first (1st) sample versus second (2nd) sample regarding CKMB, troponin and copeptin in unstable angina (UA) group Using Wilcoxon Signed Rank Test:

	1st sample versus second 2nd sample in UA	
	Z	p value
CKMB 1st	1.19	0.231 [*]
CKMB 2nd		
Troponin 1st	1.70	0.088 [*]
Troponin 2nd		
Copeptin 1st	2.11	0.09 [*]
Copeptin 2nd		

^{*} P > 0.05: non significant difference.

of Copeptin was 150 pg/mL, its diagnostic sensitivity was 100%, specificity 100%, PPV 100%, NPV 100% and AUC was 1.0 shown in Fig. 3 and Table 7.

5. Discussion

The gold standard for the diagnosis of AMI are ECG and determination of serum cTns concentration, together with clinical assessment.⁹ However, ECG is of little help in the exclusion of AMI in one quarter to one third of patients with AMI as no significant ECG changes are detected in the presence of ongoing acute cardiac ischemia.¹⁰

Moreover, the exclusion of AMI is still a demanding point of interest especially within the first hours of myocardial injury, in the so-called 'troponin-blind period'. This is due to the fact that cTns levels do not increase during the first few hours of AMI. Therefore, the exclusion of AMI requires monitoring of patients between a 6 to 9 h-period and serial blood sampling for measurement of cTns concentration.⁵

Therefore, many biomarkers are being evaluated, alone or in combination with cTns for enhancing the early diagnosis of AMI with higher sensitivity.

Table 4

Statistical comparison between unstable angina (UA) group versus acute myocardial infarction (AMI) group regarding different cardiac markers using Mann-Whitney U test.

	UA group versus AMI group	
	Z	P
CKMB 1st	3.36	0.07 ^{**}
CKMB 2nd	4.81	<0.001 [*]
Copeptin 1st	5.29	<0.001 [*]
Copeptin 2nd	5.03	<0.001 [*]
Troponin 1st	1.77	0.076 ^{**}
Troponin 2nd	5.24	<0.001 [*]

^{*} P < 0.01: Highly significant difference.

^{**} P > 0.05: Non significant difference.

Copeptin as a marker of acute stress, is excreted into circulation independent of necrosis of cardiac cells in cases of AMI.¹¹ Also, inadequate filling of the left ventricle caused by AMI stimulates cardiac baroreceptors or causes direct damage to baroreceptors which subsequently leads to AVP and Copeptin secretion from the posterior pituitary gland.¹²

Results of the present study revealed statistical significant difference between the levels of Copeptin in AMI group and UA group in first sample (3 h). This was in agreement with studies by Folli et al. and El Sayed et al.^{13,14} This result is attributed to two hypotheses; first, the stress hypothesis where Copeptin/AVP is a substantial part of the endocrine stress response. The second is the hemodynamic hypothesis where AMI results in hypotension leading to baroreceptor stimulation and finally secretion of Copeptin/AVP from the posterior pituitary gland.^{15,16}

In our study, the levels of Copeptin were declined afterwards in the second sample (6–9 h). These results were in agreement with Reichlin et al., Keller et al., Charpentier et al. and Folli et al.^{7,17,18,13} where Copeptin levels at admission were higher in the AMI group presenting zero to four hours after onset of symptoms with a falling pattern afterward from five to ten hours. They attributed this to the initiation of the formation of new angiogenesis of collateral coronaries which may reduce the ischemic symptoms, reduce the stimulation of cardiac baroreceptors and consequently decrease the Copeptin/AVP release axis.

Moreover, decreasing concentration of Copeptin may indicate adjustment to neurohumoral stress by activation of AVP system after AMI.¹⁹ A decrease in Copeptin concentration may also be due to the cessation or at least reduction of chest pain after the onset of AMI, or may be an inter-play of both reasons.⁷

Our study revealed that the levels of cTns in AMI group were significantly elevated in the second sample than the first sample. White suggested several potential pathobiological mechanisms for cTns elevations: myocyte necrosis, apoptosis, cellular release of proteolytic troponin degradation products, increased cell membrane permeability, formation and release of membranous blebs.²⁰

Table 5

Diagnostic performance of CKMB (IU/mL) in acute myocardial infarction group (AMI) group versus unstable angina (UA) in the first sample at cut-off level > 22.

Parameter	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC
CKMB (IU/mL)	>22	64	93.33	94.0	60.9	0.82

Table 6

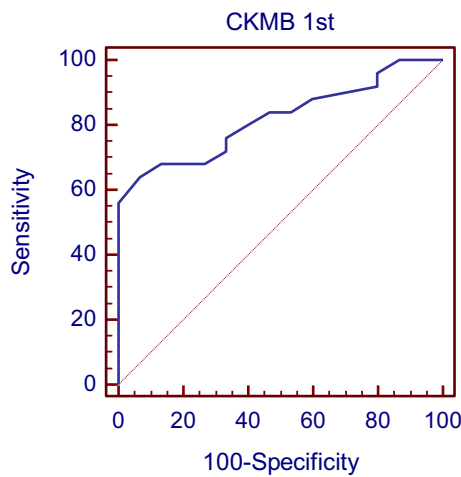
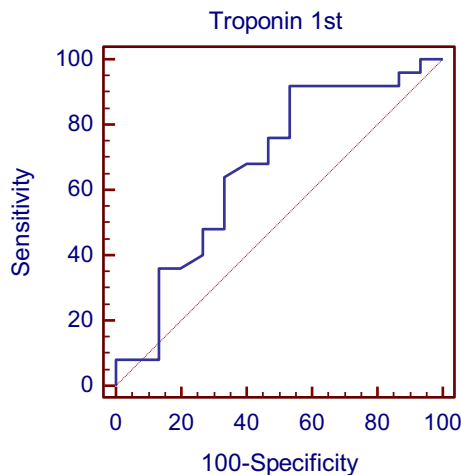
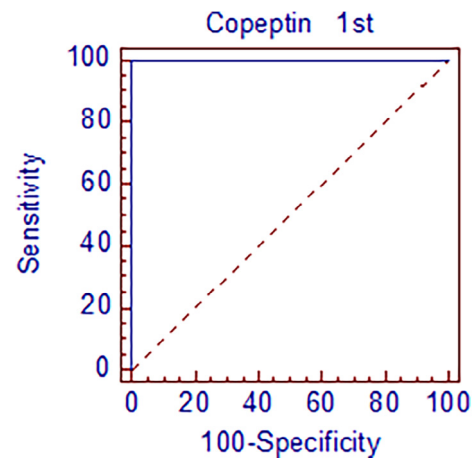
Diagnostic performance of troponin (pg/mL) in acute myocardial infarction group (AMI) group versus unstable angina (UA) in the first sample.

Parameter	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC
Troponin (pg/mL)	>12.6	92	46.67	74.2	77.8	0.669

Table 7

Diagnostic performance of copeptin (pg/mL) in acute myocardial infarction group (AMI) group versus unstable angina (UA) in the first sample group.

Parameter	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC
Copeptin (pg/mL)	150	100	100	100	100	1.0

**Fig. 1.** Receiver operating characteristic curve (ROC) analysis showing the diagnostic performance of CKMB (IU/mL) in acute myocardial infarction group (AMI) versus unstable angina (UA) in the first sample.**Fig. 2.** Receiver operating characteristic curve (ROC) analysis showing the diagnostic performance of troponin (pg/mL) in acute myocardial infarction group (AMI) versus unstable angina (UA) in the first sample.**Fig. 3.** Receiver operating characteristic curve (ROC) analysis showing the diagnostic performance of copeptin (pg/mL) in acute myocardial infarction group (AMI) versus unstable angina (UA) in the first sample.

Moreover, regarding cTns, our study revealed no significant difference in cTns levels between AMI and UA in the first sample. This is in agreement with other studies by Charpentier et al. and Chenevier-Gobeaux et al.^{18,21} that observed delayed increase of cTns level after admission of patients with AMI. This may be due to the fact that majority of cTns is bound to myofilaments, while the remainder is free in the cytosol. When myocyte damage occurs, the cytosolic pool is released first followed by a more protracted release from stores bound to deteriorating myofilaments.²²

Regarding CKMB, no significant difference was revealed in CKMB levels between AMI and UA in the first sample. These results agree with a study carried out by Esses et al.²³ The gradual increase in the level of CK-MB in AMI group was attributed to its location predominantly in a cytoplasmic pool of myocardial cells, therefore, after disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first.

Regarding the results of Copeptin in UA group, a non-significant difference was found between the first and second sample. These results may be due to partial occlusion in coronaries, therefore, there is a minimal oxygen supply and thus, there is no cardiac underfilling, thus, no baroreceptors stimulation leading to no release of Copeptin.²³ El Sayed et al.¹⁴ stated that UA is not accompanied by myocardial necrosis, thus, it does not cause enough endogenous stress for Copeptin release.

In concordance with these results, studies carried by Reichlin et al., Keller et al., Charpentier et al. and Folli et al.^{7,17,18,13} revealed that Copeptin values of UA subset of patients with ACS were normal and didn't show any difference from those observed in patients with benign causes of chest pain.

Similarly, the results of cTns in UA group shows a non-significant difference between the first and second sample. This could be explained by that there is no trigger for cTns release as the cardiac myocyte is still intact without any pathological necrosis, but the presence of minute amounts of serum cTns in the UA group may be due to the normal turnover rate of cardiac myocytes.

These results were in agreement with Aborehab et al.²⁴ where cTns levels in UA group of patients remained unchanged throughout the different samples regardless time from admission to hospital.

Also, the results of CKMB in UA group shows a non-significant difference between the first and second sample, as long as there is no myocardial necrosis so CKMB levels did not show elevation.

Assessment of the diagnostic performance by ROC curve analysis of serum cTns, CKMB and Copeptin showed that, in the first sample, cTns with cutoff value 12.6 pg/mL, revealed sensitivity 92%, specificity 46.67%, PPV 74.2% and NPV 77.8%. While CKMB with cutoff value 22 IU/mL, revealed sensitivity 64%, specificity 93.3%, PPV 94.1% and NPV 60.9%. Regarding Copeptin, the diagnostic accuracy in the first sample at cutoff value of 150 pg/mL was higher than that of cTns with sensitivity 100%, specificity 100%, PPV 100%, NPV 100%.

These results were in agreement with Keller et al.¹⁷ who reported that Copeptin is more sensitive than cTns within the first 3 h of AMI detection, the median serum Copeptin level in patients with AMI is significantly different from the non-ischemic patients. Moreover, the area under the curve for Copeptin alone was significantly higher than that for cTns alone.

However, in contrast, Lotze et al.¹⁹ reported a positive correlation between cTns and Copeptin at the time of initial AMI presentation ($r = 0.41$; $P < 0.001$).

Moreover, in this regards, Mockel et al. and Nursalim et al. reported that the combination of cTns and Copeptin at admission compared with use of only cTns increased detection of AMI.^{25,26} Meune et al. revealed that the combination of cTns and Copeptin at admission excludes AMI with a sensitivity of 86.7% and NPV of 82.6%.²⁷ The sensitivity of only cTns measured at admission was 73.3% and NPV was 76.5%, while sensitivity and NPV of cTns measured after 3 h were 83.3% and 83.9%, respectively. In addition, Reinstadler et al.²⁸ found that the combination of Copeptin and cTns reached sensitivity of 98.8% and NPV of 99.7% for ruling-out of AMI already at presentation. Thus, these studies proposed that in the final exclusion of AMI, Copeptin is not able to replace cTns, but adding Copeptin to cTns allows safe rule out of AMI.

In conclusion, our study revealed that Copeptin concentration is significantly higher in patients with AMI compared to patients with UA. Moreover, Copeptin rises at a time when other biomarkers namely the routinely used markers; cTns and CKMB are still undetectable.

However, being non-organ specific, the rapid rule-out of AMI is almost the only application of Copeptin in acute cardiac care as being adherent to the exclusion criteria sounds sometimes impractical. Practically, the use of Copeptin within a dual-marker strategy together with conventional cardiac troponin increases the diagnostic accuracy and particularly the negative predictive value of cardiac troponin alone for AMI.

Conflict of interest

None.

References

- Buja P, Tarantini G. Acute coronary syndrome: clinical assessment. In: Cademartiri F, Casolo G, Midiri M, eds. *Clinical applications of cardiac CT*. Milano: Springer; 2012:35–44.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551–2567.
- Mueller C. Detection of myocardial infarction – is it all troponin? Role of new markers. *Clin Chem*. 2012;58:162–164.
- Gu YL, Voors AA, Zijlstra F, Hillege HL, Struck J, Masson S. Comparison of the temporal release pattern of copeptin with conventional biomarkers in acute myocardial infarction. *Clin Res Cardiol*. 2011;100:1069–1076.
- Raskovalova T, Twerenbold R, Collinson PO, et al. Diagnostic accuracy of combined cardiac troponin and copeptin assessment for early rule-out of myocardial infarction: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovascular Care*. 2014;3:18–27.
- Pell JP. Cardiovascular risk scores. The national society journals present selected research that has driven recent advances in clinical cardiology. *EJH*. 2013;65:5–11.
- Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Eng J Med*. 2009;361:858–867.
- Morgenthaler NG, Struck J, Jochberger S, Duser WM. Copeptin: clinical use of new biomarker. *Trends Endocrinol Metabol*. 2007;19:43–49.
- Mohsen M, Shawky A. The diagnostic utility of High-Sensitivity Cardiac Troponin T in acute coronary syndrome. *EJH*. 2016;68:1–9.
- Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med*. 2017;12:147–155.
- Balmelli C, Meune C, Twerenbold R, et al. Comparison of the performances of cardiac troponins, including sensitive assays, and copeptin in the diagnosis of acute myocardial infarction and long-term prognosis between women and men. *Am Heart J*. 2013;166:30–37.
- Lippi G, Plebani M, Di Somma S, Monzani V, Tubaro M, Volpe M. Considerations for early acute myocardial infarction rule-out for emergency department chest pain patients: the case of copeptin. *Clin Chem Lab Med*. 2012;50:243–253.
- Folli C, Consonni D, Spessot M, Salvini L, Velati M, Ranzani G. Diagnostic role of copeptin in patients presenting with chest pain in the emergency room. *Eur J Int Med*. 2013;24:189–193.
- El Sayed ZH, Mahmoud HA, El Shall LY, El Sheshtawy FA, Mohamed MA. Impact of copeptin on diagnosis of acute coronary syndrome. *EJMHC*. 2014;15:241–247.
- Morgenthaler NG. Copeptin: a biomarker of cardiovascular and renal function. *Congest Heart Fail*. 2010;16:S37–S44.
- Maisel A, Muller C, Neath S, et al. Copeptin helps in the early detection of patients with acute myocardial infarction. *JACC*. 2013;62:150–160.
- Keller T, Tzikas S, Zeller T, Czyz E, Lillpop L, Ojeda MF. Copeptin improves early diagnosis of acute myocardial infarction. *J Am Coll Cardiol*. 2010;55:2096–2106.
- Charpentier S, Maupas-Schwalm F, Cournot M, Elbaz M, Botella JM. Combination of copeptin and troponin assays to rapidly rule out non-ST elevation myocardial infarction in the emergency department. *Acad Emerg Med*. 2012;19:517–524.
- Lotze U, Lemm H, Heyer A, Müller K. Combined determination of highly sensitive troponin T and copeptin for early exclusion of acute myocardial infarction: first experience in an emergency department of a general hospital. *Vasc Health Risk Manage*. 2011;7:509–515.
- White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol*. 2011;57:2406–2408.
- Chenier-Gobeaux C, Freund Y, Claessens Y, et al. Copeptin for rapid rule out of acute myocardial infarction in emergency department. *Inter J Cardiol*. 2013;166:198–204.
- Antman EM, Braunwald E. Acute coronary syndromes section of ST-elevation myocardial infarction. In: Libby P, Bonow RO, Zipes D, Mann DL, eds. *Pathology, Pathophysiology, and Clinical Features: a Textbook of Cardiovascular Medicine*. 8th ed:1210–1211.
- Esses D, Gallagher EJ, Iannaccone R, Bijur P, Srinivas VS. Six hour versus 12-hour protocols for AMI: CK-MB in conjunction with myoglobin. *Am J Emerg Med*. 2001;19:182–186.
- Aborehab NM, Salman TM, Mohamed OS, Boquiry AR, Mohamed MA. The clinical value of copeptin in acute coronary syndrome. *J Clin Exp Cardiol*. 2013;4:278.
- Möckel M. Copeptin adds to high-sensitivity troponin T in rapid rule out of acute myocardial infarction. *Clin Chem*. 2012;58:306–307.
- Nursalim A, Suryaatmadja M, Panggabean M. Potential clinical application of novel cardiac biomarkers for acute myocardial infarction. *IJIM*. 2013;45:136–149.
- Meune C, Balmelli C, Vogler E, et al. Consideration of high sensitivity troponin values below the 99th percentile at presentation: does it improve diagnostic accuracy? *Int J Cardiol*. 2013;72:506–542.
- Reinstadler SJ, Klug G, Feistritz H, Bernhard Metzler B, Mair J. Copeptin testing in acute myocardial infarction: ready for routine use? *Disease Markers*. vol. 2015; 2015. p. 1–9.