J Cardiovasc Disease Res., 2018; 9(3):134-140
A Multifaceted Peer Reviewed Journal in the field of Cardiology
www.jcdronline.org | www.journalonweb.com/jcdr

Original Article

Linkage of Some Trace Elements and Cardiac Markers in Assessment of Acute Coronary Syndromes

Ahmed Hosny El-Adawy[1,*], Ayat Tharwat Hassib Mohamad[2], Ehsan Abd El-Aty Rizk[2], Hamdy Fouad Ali Marzouk[2]

[1]Department of Cardiolovascular Medicine, Faculty of Medicine, Mansoura University, EGYPT.
[2]Department of Clinical Pathology, Faculty of Medicine, Mansoura University, EGYPT.

ABSTRACT

Background: Acute coronary syndrome (ACS) is accounting for any condition causing sudden reduced blood flow to the heart. Some trace elements play role in the development of ACS. **Aim:** This study aimed to evaluate the linkage between serum zinc, copper, iron level and cardiac markers in acute coronary syndromes. **Methods:** Eighty patients were divided into four groups. Group I (patients with unstable angina), Group II (acute myocardial infarction early 6 h), group III (acute myocardial infarction late 6 h) and group IV (patients with reperfusion therapy). Fifteen apparently healthy individuals served as a control group. Different risk factors as age, sex, diabetes and dyslipideamia were addressed in different groups. The correlation between Fe, Zn and Cu versus cardiac enzymes were demonstrated. The receiver operating characteristic (ROC) analysis was conducted. **Results:** Male and diabetic patients were significantly higher. The CK and Tn were significantly increased in groups I, II and III. The CK-MB levels were significantly increased in group II and group III. The AST levels were significantly increased in group III. The serum iron level was significantly lower in group I, II and III. Serum zinc show slight decrease in groups II and III. No significant correlation was obtained concerning serum Cu. In group II, there were significant positive correlation between Fe versus Tn, CK-MB and CK. The (ROC) analysis was identified the optimal Fe, Zn and Cu plasma level for potential prediction of development of ACS. **Conclusion:** Fe and Zn values were lower in ACS patients. Cu values did not show difference.

Key words: Acute coronary symdrome, Cardiac biomarkers, Risk factors, Zinc, Iron, Copper.

Correspondence
Dr. Ahmed Hosny El-Adawy
Department of Cardiovascular Medicine, Faculty of Medicine, Mansoura University, Mansoura 35516, EGYPT.
Ph.no: +20-100-1029806
E-mail: dr_ahmed_hosny@msn.com

Submission Date: 25-06-2018;
Revision Date: 12-08-2018;
Accepted Date: 05-09-2018.
DOI : 10.5530/jcdr.2018.3.30

INTRODUCTION

Acute coronary syndromes (ACS) encompass myocardial infarction, non-Q-wave myocardial infarction and unstable angina, which are common causes of emergency hospital admission and a major cause of morbidity and mortality worldwide.[1-4]

ACS describes the range of myocardial ischemic states that includes unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) or ST-elevated myocardial infarction (STEMI). The most common manifestation of ACS is acute myocardial infarction (AMI).[5-6] The pathogenesis of ACS is complex, but the syndromes are usually due to abrupt myocardial ischemia, which is itself a sequela of plaque rupture, thrombus formation and partial or complete occlusion of the coronary artery.[1,7]

Cardiovascular risk factors may be divided into modifiable and non-modifiable entities. Genetics disorders play a key role in the atherosclerosis development and currently as non-modifiable factor.[8] Chronologic age has been linked to increased risk for coronary disease and represents a significant non-modifiable risk factor for coronary artery disease.[9] Gender and family history may also be linked to an increased statistical risk for atherosclerosis.[10-12]

Early diagnosis of ACS is essential because of improvement in prognosis following timely interventions. Currently, the diagnosis of ACS is based on elevation of high-sensitive cardiac troponin I or T (cTnI or cTnT) in the context of clinical and ECG findings.[13-14]

The biochemical marker of myocardial ischemia should provide a diagnostic window. Cardiac troponins are the only accepted biomarkers for diagnosing myocardial injury and acute myocardial infarction (AMI).[15] In 1954, aspartate aminotransferase (AST), has been identified as the first biochemical marker for diagnosis of AMI.[16] Lactate dehydrogenase (LDH) increased in patients with AMI and were described as possible biomarkers of AMI.[17-18] Plasma creatine kinase (CK) is rapidly released in blood 3–9 h after an AMI.[19-21] Cardiac isoforms-cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are subunits exclusively expressed in myocardial tissue.[22]

Copeptin is a surrogate of vasopressin release and indicates neurohormonal stress activation and vasoactive response.[23] The additional use of copeptin to cTnT allows for a rapid triage of chest pain patients to an early diagnosis of non-ST elevation myocardial infarction.[24] Choline is is considered a marker of plaque instability, as well as a marker of severe myocardial ischaemia.[25] Creatine kinase (CK) and creatine kinase-MB (CK-MB) were considered as the gold standard for AMI diagnosis.[21] Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are more sensitive and specific markers than CK-MB in detecting myocardial necrosis and useful prognostic indicator in patients with ACS.[26]

Trace elements are being increasingly recognized as essential mediators for the development and progression of cardiovascular diseases (CVD).[27-28]

Zinc (Zn) and copper (Cu) levels in the body interact with and balance each other. Zinc (Zn) interacts with cardiovascular cells and its deficiency leads to cellular damage and atherosclerosis and cause an increase in endothelial cell apoptosis.[29] The impact of Cu on cardiovascular diseases has not been clearly elucidated. However, Cu may contribute to myocardial dysfunction in heart failure and dietary Cu deficiency reduces the activity of cardiac cytochrome c oxidase and favors the development of hypercholesterolemia.[30-31] There is increasing epidemiological evidence concerning the role of iron in atherosclerosis and ischemic heart disease. Iron plays a role in the process of atherosclerosis.[32] Patients with myocardial infarction showed higher serum copper and iron levels and lower selenium and zinc levels.[33]

This study aims to investigate the value of some trace elements: Fe, Cu and Zn and cardiac markers in acute coronary syndrome.

SUBJECTS AND METHODS

The present study was conducted on 95 adult subjects. Eighty patients were suffering from ischemic heart disease (46 males and 34 females)

with ages ranged from 45 to 65 years. Fifeen apparentely healthy individuals (9 males and 6 females) with ages ranged from 45 to 65 years, who served as a control group. The control group had no clinical evidence of coronary artery disease (CAD) or family history of CAD.

The patients were selected from Cardiology Department of Internal Medicine Hospital, Mansoura University in 2015-2016. The analysis was carried out at clinical chemistry lab of Clinical Pathology department, Mansoura University, Egypt.

Patients were classified according to their clinical data and investigation into 4 groups each comprise 20 patients. Group I, (6 males and 14 females) with ages range from 40 to 65 years had unstable angina. Group II, (17 male and 3 female) their ages range from 40 to 60 years with acute myocardial infarction (AMI early 6 h). Group III, (12 males and 8 females) their ages range from 50 to 65 years with acute myocardial infarction (AMI late 6 h). Group IV, (11 males and 9 females) their ages range from 45 to 60 years with reperfusion therapy.

All selected patients had diagnosed as acute coronary syndrome. Subjects with the following diseases had been excluded: Valvular heart diseases, Congenital cardiac lesions, Cardiomyopathy, Renal diseases, Hepatic diseases, CNS manifestations, Heart failure, Pregnant females, Patient on estrogen therapy and Female on oral contraceptive pills.

All study participants were subjected to full history taking including Age, Sex, socioeconomic status and occupations, smoking, history of Diabetes Mielletes, hypertension, coronary artery disease, ischemic heart disease and previous myocardial infarction. A written consent was obtained from every participant.

Clinical examination

The general, chest and cardiac clinical examination were performed for all participant.

Standard 12-lead Electrocardiography (ECG) was taken at speed of 25 mm/sec and a sensitivity of 1 mv/cm using Hellige simplicriptor EK 31. Electrocardiography (ECG) was used for analyze the signs of ischemia and/ or infarction. Observation of any arrhythmia, conduction defect or signs of chamber enlargement were also observed.

Echocardiography was used for measuring left ventricle ejection fraction (LVEF%).

Laboratory investigations

Sample collection and routine laboratory investigations

Eight ml of peripheral venous blood were withdrawn for every subject by venipuncture under complete aseptic conditions and aliqueted into 2 tubes. One ml was delivered to tube containing EDTA for CBC. Seven ml were placed in plain polypropylene tube and allowed to clot; then centrifuged at 3000 rpm for 10 min and serum was separated for assessment of Serum glucose level: (Human; Wiesbaden, Germany), Liver function tests (LFTs) (Human; Wiesbaden, Germany), Renal function tests (RFTs) (Human; Wiesbaden, Germany), Serum total cholesterol using enzymatic colorimetric method (Diasys; Holzheim, Germany), Serum total triglyceride using enzymatic colorimetric method (Diasys; Holzheim, Germany), Serum total high density lipoprotein (HDL) using enzymatic colorimetric method (Diasys; Holzheim, Germany) and Serum total low density lipoprotein (LDL).

Cholesterol was calculated from total serum cholesterol (TC), the HDL cholesterol and the triglyceride concentration (TG) according to the equation of Friedewald *et al*. provided that TG does not exceed 400 mg/dl and LDL= serum cholesterol- (1/5 Triglyceride + HDL).[34]

Measurement of specific cardiac markers

Serum level of lactate dehydrogenase (LDH), Serum level of creatine kinase (CK), Serum level of creatine kinase-isoenzyme (CK-MB) and Serum level of troponin (Tn) were measured using kinetic enzymatic method (Roche Diagnostics; GmbH, Mannhein, Germany).

Assessment of serum trace elements via colorimetric principle

Serum samples were preserved in 1.5 ml eppendorf tubes at – 80°C for subsequent estimation of Serum level of zinc (Zn), copper (Cu) and iron (Fe) by colorimetric method. The assessment of serum Zn and Cu were measured via colorimetric principle using a commercial kits (Centronic GmbH, Wartenberg, Germany) according to the manufacturer's instruction. The assessment of serum iron via colorimetric principle was measured using commercial kit (Biotechnology, S.A.E., Cairo, Egypt) according to the manufacturer's instruction.

Statistical Analysis

The program used was SPSS version 16. Quantitative data were analyzed using mean and standard deviation, while frequency and percentage were used with qualitative data. Student *t* test and F test were used to compare means of different groups, while chi square test was used to compare frequencies.

Ethical statement

Study protocol approved by Medical Ethics research Committee of the faculty of medicine, Mansoura University, Egypt and from the mangers of the hospital in which the study conducted. Informed written consent obtained from each participant in the study. Confidentiality and personal privacy respected in all levels of the study. Collected data will not be used for any other purpose.

RESULTS

There is no significant differences between group I, group II, group III, group IV regarding age, sex, weight, height and BMI (Table 1).

The blood glucose (BG) and lipogram (total cholesterol TC and triglyceride TG levels) of studied groups demonstrated that Group II, III and IV showed higher BG and TG. Group III and IV showed higher TC (p=0.17, 0.027) as shown in Table 2.

There was significant difference between different groups regarding diabetes ($P < 0.001$), but no significant difference regarding total cholesterol and triglyceride (P =0.902, 0.294), respectively (Table 3).

The serum cardiac enzymes levels showed significant variation in the studied groups Table 4. The CK levels were significantly increased in group II and group III ($p< 0.001$). Group I show significant decrease than control ($p< 0.001$).

The CK-MB levels were significantly increased in group II and group III ($p< 0.001$, =0.012), respectively as compared to control group. Also, group II was significantly higher than group I ($p< 0.001$).

The AST levels were significantly increased in group III ($p< 0.001$) as compared to control group. Also, group III was significantly higher than group I, group II and group IV ($p< 0.001$).

The Tn levels were significantly increased in group I, group II and group III (p=0.017, 0.006 and 0.001), respectively. There were significantly differences on comparing Tn levels among patients; group II and III were significantly higher than group I (p=0.006, 0.001 respectively), group I, group II and III (p=0.011, 0.003, < 0.001 respectively). No significant difference was found between group II and group III (p=0.904).

Table 1: Demographic data of the studied groups.

Parameter		Group I n=20	P-value*	Group II n=20	P-value*	Group III n=20	P-value*	Group IV n=20	P-value*	Control Group n=15	P-value*
Age / year		52.90 ± 5.99	0.907	51.90 ± 6.07	0.977	53.55 ± 5.98	0.500	51.10 ± 7.60	0.543	52.13 ± 4.67	0.907
Sex; n (%)	Male	6 (30%)	0.334	17 (85%)	0.164	12 (60%)	0.751	11 (55%)	0.751	9 (60%)	0.334
	Female	14 (70%)		3 (15%)		8 (40%)		9 (45%)		6 (40%)	
Weight /kg		89.2 ± 11.95	0.184	94.30 ± 9.15	0.733	93.60 ± 10.59	0.615	94.800 ± 8.08	0.906	95.00 ± 7.31	0.184
Height / cm		171.05 ± 11.26	0.338	179.95 ± 6.02	0.389	177.45 ± 7.57	0.973	178.90 ± 8.78	0.696	176.33 ± 11.62	0.338
BMI**		30.13 ± 4.41	0.398	31.46 ± 12.45	0.419	29.22 ± 3.11	0.915	29.08 ± 3.14	0.877	29.15 ± 3.94	0.398

*P-value significance between investigated group and healthy control

**BMI, body mass index.

Table 2: Serum blood glucose, total cholesterol and triglyceride levels (mean±SD) among the studied groups.

Parameter	Group I n=20	P1	Group II n=20	P2	Group III n=20	P3	Group IV n=20	P4	Control Group n=15
BG (mg/dl)	93.25 ± 18.45	0.924	198.50 ± 90.35	0.002*	247.15 ± 89.91	< 0.001*	226.05 ± 100.70	< 0.001*	96.73 ± 19.91
TC (mg/dl)	199.00 ± 64.74	0.095	199.95 ± 78.87	0.062	215.35 ± 79.89	0.017*	217.20 ± 76.82	0.027*	160.80 ± 18.76
TG (mg/dl)	187.00 ± 70.26	0.0337	205.65 ± 63.03	0.003*	193.40 ± 63.03	0.021*	207.15 ± 69.26	0.021*	153.60 ± 15.94

* P1, significance between group I vs. healthy control; p2, significance between group II vs. healthy control; p3 significance between group III vs. healthy control; p4, significance between group IV vs. healthy control.

**BG, blood glucose; TC, total cholesterol; TG, triglyceride

Table 3: Prevalence of some risk factors in the studied groups.

Parameter		Group I n=20	Group II n=20	Group III n=20	Group IV n=20	Control Group n=15	X^2	P-Value
Diabetes Mellitus	Diabetic n (%)	1 (0.5%)	15 (75%)	20 (100%)	17 (85%)	3 (20%)	55.12	< 0.001*
	Non Diabetic n (%)	19 (99.5%)	5 (25%)	0 (0.00%)	3 (15%)	12 (80%)		
Obesity BMI >30	Obese n (%)	11 (55%)	8 (40%)	7 (35%)	8 (40%)	7 (46.7%)	1.924	0.750
	Non Obese n (%)	9 (45%)	12 (60%)	13 (65%)	12 (60%)	8 (53.3%)		
Hyper cholesterol	n (%)	8 (40%)	7 (35%)	8 (40%)	10 (50%)	0 (0.00%)	0.576	0.902
Hyper triglyceride	n (%)	12 (60%)	16 (80%)	13 (65%)	15 (75%)	6 (40%)	4.935	0.294

*highly significant

The serum Fe, Zn and Cu levels among the studied groups were demonstrated in Table 5. No significant differences were found between patient groups and control group. Group II showed significantly lower iron level than group I (p=0.025). Also, group III showed significantly lower iron level than group I and group IV (p=0.015, 0.042 respectively). Serum zinc was significantly lower in group II than group I and group IV (p= 0.033, 0.002). No other significant correlation was observed. No significant correlation was obtained for the serum copper levels among the studied groups (Table 5).

The correlation between cardiac enzymes and Fe demonstrated significant positive correlation between Fe versus Tn, CK and CK-MB. In subjects with positive Tn, the mean value ± S.D of Fe was 153.56 ± 89.28 compared to 191.07 ± 117.78 in subjects with negative Tn. The difference was found to be statistically significant (p< 0.001). In subjects with high CK, the mean value ± S.D of Fe was 147.82 ± 89.93 compared to 194.60 ± 117.71 in subjects with low CK. The difference was found to be statistically significant (p< 0.001). In subjects with high CK-MB, the mean value ± S.D of Fe was 152.16 ± 84.24 compared to 196.24 ± 121.36 in subjects with low CK-MB. The difference was found to be statistically significant (p< 0.001).

Regarding to the correlation between cardiac enzymes and Zn, there were significant positive correlation between Zn versus Tn, CK and CK-MB. In subjects with +ve Tn, the mean value ± S.D of Zn was 104.09 ± 32.32 compared to 113.00 ± 38.69 in subjects with-ve Tn. The difference was found to be statistically significant (p< 0.001).

In subjects with high CK, the mean value ± S.D of Zn was 100.00 ± 30.77 compared to 114.76 ± 38.88 in subjects with low CK. The difference was found to be statistically significant (p< 0.001).

In subjects with high CK-MB, the mean value ± S.D of Zn was 107.06 ± 31.02 compared to 112.77 ± 39.98 in subjects with low CK-MB. The difference was found to be statistically significant (p< 0.001).

While the correlation between cardiac enzymes and Cu showed significant positive correlation between Cu versus Tn, CK and CK-MB. In subjects with +ve Tn, the mean value ± S.D of Cu was 124.60 ± 110.87

Table 4: Comparison of serum cardiac markers levels in the studied groups.

		CK (U/L) (Mean ± S.D.)	CK-MB (U/L) (Mean ± S.D.)	AST (U/L) (Mean ± S.D.)	Troponin (U/L) (Mean ± S.D.)
Group I (n=20)		92.25 ± 44.75	4.25 ± 1.80	31.80 ± 12.21	0.032 ± 0.026
Group II (n=20)		729.90 ± 600.11	8.43 ± 3.95	36.20 ± 10.25	0.322 ± 0.409
Group III (n=20)		1126.45 ± 812.27	29.57 ± 87.98	170.95 ± 131.28	0.311 ± 0.312
Group IV (n=20)		197.35 ± 57.94	5.17 ± 9.04	36.45 ± 12.91	0.014 ± 0.006
Control Group (n=15)		189.13 ± 51.03	2.94 ± 1.03	32.13 ± 13.07	0.014 ± 0.009
G-I vs Control	t-value	4.491	0.921	0.031	2.846
	p-value	< 0.001*	0.226	0.939	0.017*
G-II vs Control	t-value	3.445	4.713	0.940	3.384
	p-value	0.001*	< 0.001*	0.309	0.006*
G -III vs Control	t-value	4.414	3.391	4.245	4.106
	p-value	< 0.001*	0.012*	< 0.001*	0.001*
G -IV vs Control	t-value	0.437	0.829	0.661	0.000
	p-value	0.665	0.303	0.337	1.000
G -I vs G -II	t-value	4.821	4.428	0.988	3.114
	p-value	< 0.001*	< 0.001*	0.335	0.006*
G -I vs G -III	t-value	5.763	1.279	4.812	4.041
	p-value	< 0.001*	0.216	< 0.001*	0.001*
G -I vs G -IV	t-value	8.182	0.468	0.982	2.835
	p-value	< 0.001*	0.645	0.338	0.011*
G -II vs G -III	t-value	1.957	1.081	4.496	0.122
	p-value	0.065	0.293	< 0.001*	0.904
G -II vs G -IV	t-value	4.118	1.660	0.069	3.385
	p-value	0.001*	0.113	0.946	0.003*
G -III vs G -IV	t-value	5.069	1.222	4.679	4.248
	p-value	< 0.001*	0.236	< 0.001*	< 0.001*

* highly significant

compared to 132.11 ± 88.73 in subjects with -ve Tn. The difference was found to be statistically significant (p< 0.001). In subjects with high CK, the mean value ± S.D of Cu was 144.57 ± 121.11 compared to 125.68 ± 82.62 in subjects with low CK. The difference was found to be statistically significant (p< 0.001). In subjects with high CK-MB, the mean value ± S.D of Cu was 139.03 ± 115.13 compared to 126.68 ± 82.96in subjects with low CK-MB. The difference was found to be statistically significant (p< 0.001).

The correlation between Fe, Zn and Cu versus Tn, CK and CK-MB in all studied groups were demonstrated in Table 6. There were significant positive correlation only between Fe versus Tn and CK-MB in group II (r=0.532, p=0.016), (r=0.522, p=0.018) respectively.

There were significant negative correlation between Zn versus CK-MB in group I (r=-0.491, p=0.028). Otherwise no significant correlation were obtained between Zn versus Tn and CK in all studied groups and versus CK-MB in group II, group III, group IV and group V.

There is no significant correlation were obtained between Cu versus Tn, CK, CK-MB in all studied groups.

A receiver operating curve (ROC) analysis showed that the best cut-off values were established for Fe, Cu and Zn plasma level as 216, 124 and 132, respectively. This cut-off values showed the highest accuracy to predict Fe usage (sensitivity of 76.25% and specificity of 73.3%), Cu usage (sensitivity of 85% and specificity of 86.6%) and Zn usage (sensitivity of 80% and specificity of 80%). The area under the curve was 0.400 (95% CI=0.094 – 0.706, P= 0.513) for Fe, 0.640(95% CI=0.337 – 0.943, P= 0.359) for Cu and 0.520 (95% CI=0.243 – 0.797, P= 0.869) for Zn (Figure 1).

DISCUSSION

This study was aimed to access the relation between some trace elements (Fe, Zn and copper) and acute coronary syndrome (ACS).

There is no difference regarding age, sex, weight, height and BMI was found between patients and healthy control.

In the current study, group II, III and IV showed higher BG (p=0.002 in gp II, < 0.001 in gp II, III), higher TG (p= 0.003, 0.021, 0.021 respectively) than control group. Also, group III and IV showed higher TC (p=0.17, 0.027) when compared to control group.

In the present study, there was a statistically significant difference (p< 0.001) concerned diabetes and no significant difference regarding obesity (p=0.750) or dyslipideamia (p=0.902, 0.294). These results harmonize with the INTERHEART Study that the risk of MI increases 2.48 folds in presence of diabetes mellitus.[35]

This study showed statistically significant differences between patients with UA and AMI (p< 0.001) as compared to control group in CK enzyme, statistically significant relation between patients with UA and others with AMI, also we found statistically significant relation between patients with UA and AMI and those who received reperfusion therapy.

Table 5: Comparison of serum iron, Zinc and Cupper levels among the studied groups.

Mean (µg/ml)		Serum Fe			Serum Zn			Serum Cu		
		± S.D.	Range	Mean (µg/ml)	± S.D.	Range	Mean (µg/ml)	± S.D.	Range	
Group I (n=20)		194.40	± 77.73	106 - 401	118.20	± 30.34	78 - 178	117.22	± 91.10	10.50 - 315
Group II (n=20)		131.42	± 96.32	10 - 320	96.45	± 36.20	19 - 151	119.00	± 42.83	45 - 195
Group III (n=20)		128.99	± 76.56	11 - 300	100.40	± 38.23	23 - 150	115.400	± 36.71	48 - 178
Group IV (n=20)		176.77	± 73.25	9.50 - 296	128.45	± 40.85	28 - 178	121.60	± 66.68	69 - 318
Control Group (n=15)		195.53	± 121.58	85 - 441	111.86	± 3380	75 - 210	116.98	± 32.38	62 - 200
G-I vs Control	t-value		0.633			0.149			0.184	
	p-value		0.973			0.565			0.992	
G-II vs Control	t-value		2.10			1.64			1.53	
	p-value		0.091			0.209			0.328	
G -III vs Control	t-value		1.33			0.481			0.194	
	p-value		0.056			0.363			0.397	
G -IV vs Control	t-value		0.606			0.919			0.695	
	p-value		0.554			0.211			0.807	
G -I vs G -II	t-value		2.43			2.39			1.05	
	p-value		0.025*			0.033*			0.303	
G -I vs G -III	t-value		2.66			1.64			1.03	
	p-value		0.015*			0.189			0.315	
G -I vs G -IV	t-value		0.978			0.530			0.153	
	p-value		0.341			0.337			0.880	
G -II vs G -III	t-value		0.096			0.301			0.117	
	p-value		0.925			0.767			0.908	
G -II vs G -IV	t-value		1.65			3.55			0.842	
	p-value		0.115			0.002*			0.410	
G -III vs G -IV	t-value		2.17			1.85			0.677	
	p-value		0.042*			0.080			0.506	

Table 6: Correlation between Fe, Zn and Cu versus Tn, CK and CK-MB in the studied groups.

		Serum Fe			Serum Zn			Serum Cu		
Groups	*Corr.	Tn	CK	CK-MB	Tn	CK	CK-MB	Tn	CK	CK-MB
Group I (n=20)	r-value	0.239	-0.417	-0.388	0.011	-0.315	-0.491*	-0.048	-0.044	0.053
	p-value	0.310	0.067	0.091	0.962	0.175	0.028	0.839	0.854	0.825
Group II (n=20)	r-value	0.532*	0.439	0.522*	0.294	0.403	0.296	-0.072	-0.033	0.029
	p-value	0.016	0.053	0.018	0.208	0.078	0.205	0.762	0.890	0.904
Group III (n=20)	r-value	-1.93	0.162	-0.360	-0.092	-0.202	0.281	0.135	-0.295	0.375
	p-value	0.414	0.494	0.119	0.700	0.392	0.230	0.572	0.206	0.103
Group IV (n=20)	r-value	-0.051	0.085	-0.083	0.194	0.294	0.275	-0.207	-0.212	-0.123
	p-value	0.830	0.721	0.728	0.413	0.208	0.241	0.380	0.31	0.605
Control Group (n=15)	r-value	0.085	0.284	0.460	-0.249	-0.343	-0.138	-0.160	-0.463	-0.472
	p-value	0.763	0.305	0.084	0.371	0.211	0.624	0.570	0.082	0.076

*r-value; p-value

However, no significant relations were observed among patients with AMI (early or late 6 h).

Concerning CK-MB, there was statistically significant difference in patients with AMI ($p< 0.001$) as compared to control group and in patients with AMI within 6 hr and those with UA.

In a previous study, the increase in serum levels of Cu and Fe and the decrease in serum levels of Zn and Se in patients with higher levels of Tn and CK-MB reveal that trace element levels are related to the degree of myocardial damage.[33] Moreover, zinc levels were significantly inversely correlated with CK, CKMB and cTnT levels and the prevalence of AMI decreased with increasing zinc level.[36]

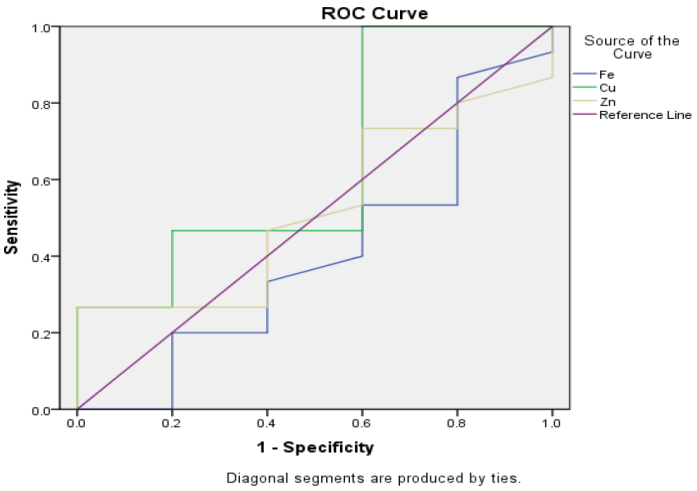

Figure 1: A receiver operating curve (ROC) analysis for Fe, Cu and Zinc plasma level for the prediction of acute coronary syndrome in comparison with control subject.

As regard to AST, levels were significantly different in patients with AMI within six hrs ($p< 0.001$) as compared to control group, patients with UA and others with AMI (late six hrs), patients with AMI and patients with AMI (late six hrs) and those who received reperfusion therapy. No other significant correlation was observed.

Tn levels were significantly different in patients with UA and AMI (p=0.017, 0.006 and 0.001 respectively) as compared to control group, also there was significant correlation between patients with UA and AMI and in patients with UA and AMI and those who received reperfusion therapy.

The serum iron level was decreased in patients with AMI either in first six hrs or after six hrs (the mean value ± S.D was 96.45 ± 36.20, 100.40± 38.23 respectively) as compared to other subjects. There were statistically significant differences between patients with UA and AMI patients and statistically significant differences between patients with AMI and those who received reperfusion therapy.

The current finding is consistent with the results of Regnström *et al.* 1994 showed that serum iron was significantly lower in patients than in controls and suggested that low stored iron levels are a risk factor for premature coronary atherosclerosis and MI.[37]

Study conducted by Kervienen *et al.* 2004 was proved that their is association between serum iron and CHD as the subjects with low iron, high-sensitivity C-reactive protein (hs-CRP) and a high total leukocyte count were at an increased risk.[38]

The presence of anaemia was associated with a 1.4 times increased risk of a cardiovascular event.[39]

Contrary to previous findings, Morrison *et al.* 1994 were observed a significantly higher risk of acute myocardial infarction in the highest category of serum iron (i.e., more than 175 µg/dl, versus less than 120 µg/dl) with rate ratios of 2.18 (95 % confidence interval (CI) 1.01–4.74) for men and 5.53 (95 % CI 1.69–18.12) for women. The risk was further increased in people with elevated levels of LDL cholesterol. No association was found with dietary iron or the use of iron supplements.[40]

In a cross-sectional study, the total iron binding capacity (TIBC) was significantly increased in the high-frequency blood donors when compared with the low-frequency blood donors (mean ± standard error of the mean (SEM) = 363 ± 10 µg/dL versus 325 ± 7 µg/dL; p = 0.003.[41]

However, other studies were found no association between body iron stores and risk of CHD. For example, Daphne et al. 2006, Sun et al. 2008 and Sempase *et al.* 2010 reported lack of association between serum ferritin and CHD in both men and women.[42-44]

There was no significant difference in serum zinc level between patients and control. Patients with AMI showed significant decrease in serum zinc level than patients with UA and those who received reperfusion therapy (p= 0.033 and 0.002, respectively).

These results were in agreement with the study of Giannoglou *et al.* 2010 and Cebi *et al.* 2011 showed that serum Zn was not significantly associated with CHD risk and severity (P = 0.320).[45-46]

In contrast, a study of Islamoglu *et al.* 2011 found that serum Zn was significantly lower in patients than in healthy control (P < 0.010).[47] Moreover, in the study of Bayir *et al.* 2013, serum Zn concentration was significantly less in the CHD group compared to the control group ($p< 0.010$).[30] Also, Lui *et al.* 2015 meta-analysis study indicated that subjects with MI had lower Zn levels than healthy controls (SMD=−1.848, 95 % CI=(−2.365, −1.331).[48]

However, other study suggested that the occurrence of lower serum Zn in MI patients may be an acute phase response rather than a cause of cardiovascular disease.[48]

Serum copper level did not show any significant change among the studied groups in this study which in agreement with study of Oster *et al.* 1993 that found no association between concentrations of Zn and Cu in serum and the corresponding concentrations in heart tissue.[49]

In contrary, Klevay (1992) had proposed that Cu deficiency rather than excess is a risk factor for CAD and it had effects on various risk factors including cholesterol level, blood pressure, glucose tolerance and electrocardiographic abnormalities.[50] In addition, Shokrzadeh *et al.* 2009 revealed that the mean Cu level of the ischemic cardiomyopathy (ISCMP) group (1.54 ± 0.52 mg/L) was significantly higher than the Cu levels of the healthy volunteers (1.31 ± 0.24 mg/L; p = 0.048).[51]

Recommendation and limitation: More number of patients are recommended to evaluate association between iron, zinc and copper and ACS patients. Study the effect of iron, zinc and copper supplementation or chelation on treatment or even preventing complication of the disease.

The major limitations of our study are that it is an observational non randomized study; also, it is a single center study, with a small number of patient subgroups.

ACKNOWLEDGEMENT

We express our sincere gratitude to the patients who participated in the study. We thank the technical staff at Mansoura Specialized Medical Hospital, Mansoura, Egypt for their excellent technical assistance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACS: Acute Coronary Syndrome; **AMI:** Acute myocardial infarction; **AST:** Aspartate aminotransferase; **BG:** Blood Glucose; BMI: Body mass Index; **CBC:** Complete Blood Count; **CHD:** Coronary Heart Disease; **CK:** Creatine Kinase; **CK-MB:** Creatine Kinase MB; **cTn:** Cardiac Troponin; **Cu:** Copper; **CVD:** Cardiovascular Diseases; **ECG:** Electrocardiography; **Fe:** Iron; **HDL:** High Density Lipoprotein; **hs-CRP:** high Sensitivity C-reactive Protein; **ISCMP:** Ischemic Cardiomyopathy; **LDH:** Lactate dehydrogenase; **LDL:** Low Denisity Lipoprotein; **LFT:** Liver Function Test; **LVEF:** Left Ventricle Ejection Fraction; **RFT:** Renal Function Test; **ROC:** Receiver Operating Characterististics; **STEMI:** ST-elevated myocardial infarction; **TC:** Total Serum Cholesterol; **TG:** Triglyceride; **TIBC:** Total Iron Binding Capacity; **UA:** Unstable Angina; **Zn:** Zinc

SUMMARY

Some trace elements as iron, zinc and copper play a vital role in the development of acute coronary syndrome (ACS). Serum iron and zinc were significantly lower in ACS patients and no significant correlation was obtained concerning serum Copper. Cardiac enzymes, CK, Tn, AST and CK-MB were significantly increased in investigated group as compared to control group. Many risk factors are involved in the pathogenesis of ACS. Diabetic and male patients were significantly at high risk.

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Cite this article : El-Adawy AH, Mohamad ATH, El-Aty Rizk EA, Marzouk HFA. Linkage of Some Trace Elements and Cardiac Markers in Assessment of Acute Coronary Syndromes. J Cardiovasc Disease Res. 2018; 9(3):134-40.