

Serum ceruloplasmin ,copper and iron levels as a risk factors for coronary heart diseases(CHD)

Asmaa M. Salih*

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Abstract

Ceruloplasmin (Cp) is one of the acute phase protein, in this review ,we studied the level of ceruloplasmin with copper (Cu) and iron in 90 patients with coronary heart diseases (those patients are divided into three groups, whom are stable angina , unstable angina and myocardial infarction compared with 30 healthy volunteers) and the roles of them as diagnostic and prognostic tools. The diagnosis was attend by a clinical examination carried out by the consult medical staff in Ibn AL-Nafis hospital.

The result: ceruloplasmin recorded a significantly($p<0.05$)higher level in all patient groups compared with the control, so this result supports the hypothesis that a high serum ceruloplasmin level is a risk factor for coronary heart disease and agrees with immunological theory about tissue damage of myocardial muscle. The same conclusion is reported for serum copper level.

Key word :ceruloplasmin, coronary heart disease,copper,iron,risk factors.

Introduction

coronary heart diseases (CHD) is totally or partially occlusion in blood vessels which leads to oxygen deprivation oxidative modification of low density lipoprotein(LDL) by lipid peroxidation. These process enhance uptaking of LDL by macrophages and cellular accumulation of cholesterol in the arterial walls leading to increased the formation of atherosclerosis [1]. Therefore, during myocardial ischemia deprives the myocardium of oxygen leads to reduced fatty acid utilization, increased lactate and reduction in PH, which means increased oxidative stress and liberating free radical formation, a matter which causes a wide spectrum of myocardium damage [2] . Antioxidant plays an important role in preventing free radical damage, ceruloplasmin (Cp) is an important extra cellular antioxidant also it is an α_2 -glycoprotein[3] (which is synthesized mostly in the liver) with molecular mass of 132 KDa and

contains about 9% carbohydrate . The Cp molecule binds 6-8 copper atoms so it is officially known as ferroxidase [4]. ceruloplasmin is synthesized in the hepatocyte as apo Cp , the copper atoms are incorporated post transitionally followed by the binding of the carbohydrate side chains Incorporation of cu atoms into apo Cp. occurs intracellular by an ATP ase, which maintains cu in a reduced state [3] .physiological functions of cp include the following :

1. A major part of the antioxidant activity of human plasma is due to ceruloplasmin [5].
2. Regulation transport ,availability and redox potential of iron (Fe) as a result of its ferroxidase activity for instance , if functional iron required for erythropoiesis , Fe^3 and Fe^2 is immediately oxidized to Fe by Cp [3].
3. ceruloplasmin reacts either as a ferroxidase enzyme by catalyzing

the oxidation of Fe^{2+} to Fe^{3+} and thus prevents peroxidation of membrane lipids because this could lead to cell injury, which means ceruloplasmin acts as an antioxidant through ferroxidase activity and it scavenges superoxide anion radical [5]

4. It is one group of serum protein, which rises after any tissue damage that called acute phase proteins like C-reactive protein, α_1 antitrypsin, fibrinogen, haptoglobin, seromucoid, serum amyloid A protein [6]. Therefore Cp acts as a host defense mechanism by its radical scavenging and copper donor activity.

All previous antioxidants are designed to prevent the occurrence of free radical-induced injury under normal conditions. However, these protective mechanisms may be overwhelmed and severe free radical mediated injury may occur [1], also during ischemia cellular injury facilitates the production of free radicals [6], and damage can develop, when a generator of reactive oxygen species (ROS) is present in a suppressed antioxidant [7], that may be happened even with temporary coronary occlusion which causes myocardial damage [6]. At the same time, ischemia of myocardium induces an active inflammatory response in myocardial tissue with an early phase of neutrophil accumulation that is accelerated by reperfusion. Neutrophil may exacerbate tissue injury through the release of free radicals (FRs) and proteolytic enzyme [8]. Copper (Cu) is an essential cofactor for many enzymes including cytochromes, but it's toxic in its unbound form. The vast majority of serum copper is transported bound to ceruloplasmin, the rest is bound to

albumin, transcuprein and copper - amino acid complexes [7], at the same time LDL oxidation process dependent on high concentration of transition metals such as copper and iron in vitro because these free ions can company in oxidation and reduction reactions forming most toxic radical which is hydroxyl [9].

All that make copper has both pro-oxidant and antioxidant effects [10], while iron can induce lipid peroxidation in vitro and in vivo in humans and has promoted ischemic myocardial injury in experimental animals [11]. According to the previous information submitted by many epidemiological data which suggest that Cp and metal ions (copper and iron) might be involved in human coronary heart disease, we tested these hypothesis in present study by investigating whether Cp, Cu and iron were coronary risk factors in Iraqi patients, and can use them as prognostic and diagnostic factors.

Materials and Methods

Ninety Iraqi patients with coronary heart disease (CHD), who admitted to Ibn-AL-Nafis teaching hospital were studied. All patients were classified into three clinical subgroups: 30 with myocardial Infarction (MI), 30 with stable angina (SA) and 30 with unstable angina (UA), according to a clinical examination by physicians and electrocardiogram (ECG).

The other group (control) consist of 30 Iraqi healthy individuals were age, sex and ethnic Matching with patients group.

The laboratory investigation includes:-

1. -Estimation of serum ceruloplasmin levels by single radial immunodiffusion (SRID) plates for accurate quantitative determination of human

(Biomaghreb-Tunisia) , using specific endoplate , with incubation for 48hr at 23C' in case of ceruloplasmin Cp , the concentration of Cp was determined from the standard curve (reference Cp concentration ,versus squares of ring diameter)and expressed as:-

Normal value g /l {Cp
19 - 57 mg/dl — 1.9 - 5.7 g/l .

2. -Determine free copper (cu) by using colorimetric test with kit of Randox England .
3. -Determine free Iron (Fe) by using colorimetric test (Ferrozine)with kit of Biomeghreb , Tunisia

The statistical analysis were done using spss version 7.5 computer software , further exploration of significance difference were assessed by Dancan test.

Results

Table-1. shows the mean level of ceruloplasmin in patient groups and healthy control ,the UA. group had the highest mean ± SD (0.566 ± 0.128) followed by the mean of MI group (0.561±0.119) and SA group without significant differences among patient groups , further more , there were significant differences among each of patient groups and healthy control (0.439 ± 0.081) .

All patient groups revealed a significant increase in their mean compared to control group .

Table-1- statistical analysis among the study groups according to the concentration of ceruloplasmin (g/L).

Group	No.	Means±SD	Duncan*
Control	30	0.493±0.081	a
MI	30	0.561±0.119	b
S.A	30	0.548±0.174	b
U.A	30	0.566±0.128	b

*the similar letters means there are no significant differences (p<0.05).

Table -2- statistical analysis among the study groups according to the concentration of copper (m mol/L).

Group	No.	Means±SD	Duncan*
Control	30	1.9±0.217	a
MI	30	2.56±0.138	b
S.A	30	3.10±0.113	c
U.A	30	2.30±0.10	b

*the similar letters means there are no significant differences (p<0.05).

Table - 2 illustrate mean levels of copper in patient groups and healthy control (1.9±0.217) a significant (p<0.05) increase in the mean level of Cu were obtained in all patient groups compared with healthy control .

The S.A group recorded the highest mean compared to the others groups with significant differences (3.10 ± 0.113) . At the same time, there were no significant differences between MI (2.56 ±0.13) and UA. group (2.3 ± 0.1)

Table-3- statistical analysis among the study groups according to the concentration of iron (m mol/L).

Group	No.	Means±SD	Duncan*
Control	30	1.30±0.07	a
MI	30	1.210±0.06	b
S.A	30	1.225±0.09	ab
UA	30	1.192±0.07	c

*the similar letters means there are no significant differences (p<0.05).

Table -3- revealed a Non significant decrease in the means of iron level for all patients groups vs. control (1.31 ± 0.07) except in UA. group. However, there were no significant differences among patient groups themselves.

Discussion

the present study is an attempt to look for the diagnostic and prognostic importance of serum ceruloplasmin , copper and iron levels in CHD patients

In present data , Cp level of all patient groups showed a significant rise as compared with the control group ,

these result agree with previous study like [12],[13]. Furthermore, another researcher [14] submitted that the patients with unstable angina appears Cp levels from 6 hours of onset chest pain until 6 months were significantly higher during follow up, these finding agrees with present study because present sample were collected during the 6 hours from onset chest pain. Moreover, patients with CHD having in common risk factors such as obesity, hypertension, Glucose intolerance and dyslipidemia have elevated Cp. levels [8],[15].

ceruloplasmin is an important intravascular antioxidant and it protects tunica intima against free radical injury [11], also it is an acute phase protein synthesized by liver in response to tissue damage and inflammation, therefore Cp can used as coronary risk factor as reported by a previous study that emphasized high level of cp used as a coronary risk factor [13],[15],[16],[17], furthermore Cp exhibits a cardio protective effect and prevents oxygen free radical induced release of noradrenalin, a powerful vasoconstrictor [1],[10].

Previous study showed an increase risk of cardiac events especially in patients with myocardial infarction in Cp concentrations (>0.36 g/L) [17], comparing with present data, which demonstrate an increase in Cp level in all patients group even in control group, so it has been suggested that inflammation may reduce plaque stability and increase thrombogenesis and may stimulate macrophages to produce various cytokines [18]. Which are mainly stimulate hepatocyte to release the inflammatory or acute phase proteins [17], and there is associations between CHD and plasma proteins involved in the acute phase protein response to tissue damage or inflammation [15], which may be releases before the onset symptoms of

chest pain that makes sensitive plasma proteins are associated with higher risks of atherosclerosis and CHD in apparently healthy subjects [17], which means that the inflammatory component of the atherosclerotic process could be simply elevating CP levels secondarily [7].

In present study, the gradient increased level of Cp in all patients group especially MI patients illustrated that the inflammation induced elevation of Cp in CHD patients, which was associated with inflammatory process as acute phase protein and not with the pro-oxidant activity of Cp. [7],[2]. our result agrees with recent report which it concluded that the MI patients recorded the highest statistically mean of Cp [2], thus leads to consider Cp level as a sensitive index of prognosis and diagnosis for CHD, especially with MI. Furthermore, present results agree with a previous report [4], which suggested that Cp could use as prognostic and diagnostic factor for acute MI.

Previous study emphasized that elevated serum copper concentration is an independent risk factor for CHD [14]. There was a positive relation between copper and aggregation of classical risk factors for CHD [18]. Moreover, prospective study, was found elevated serum copper level to be associated with cardiovascular disease [9]. All these findings agree with present results, which demonstrated an increase in Cu level. Furthermore, these agrees with another report illustrated the same findings in Iraqi CHD patients [19]. In experimental study of animals, elevated level of Cu causes changing in the vascular wall structure because there was a reduction in intimal collagen fibers of the animal which received copper supplement in there dietary, which means that dietary Cu

can significantly affect the composition and progression of atherosclerotic lesions by modulates the formation of atherosclerotic lesions [7]. Moreover Cu can contribute to excess production of damaging reactive oxygen species (ROS), known to be involved in atherogenesis [8], while another study submitted that the excess serum Cu and Cp may be immunosuppressive, especially in older organisms because lymphocyte culture in vitro appears reduction response when lymphocyte taken from mice with higher serum Cu concentration [20].

present data submitted an information about serum Cp and Cu level in Iraqi CHD patients, an elevated level of Cp and Cu in all three patient groups, this result agrees with prior study, which recorded a finding that an elevated level of serum Cp was synergistic with an elevated level of serum Cu in European CHD patients [7], also the same result was recorded in another study about Iraqi CHD patients [19], especially present sampling was collected within 6 hours from onset symptoms of chest pain, thus these phenomenon is basis for constantly observed sudden increase in serum Cu and Cp levels, which decreases slowly and reaches to baseline with a month [21]. All these events, facilitate the appearance of ischemia onset symptoms, accordingly Cp and Cu can be used as a factor to predict CHD. Moreover, many of AMI may be occur after a period of time from plaque rupture, thrombi and bleeding because blockage the lumen after at least 3 days [22]. this concept provide important fundamental knowledge for understanding the mechanism, which leads to initiate the CHD, and uses a new factors like Cp and Cu as an auxiliary predicting factor to determine the risk, in order to provide a suitable medical care to prevent the progress of disease into

more complex states.

Another study recorded that serum level of Cu and iron were significantly higher in patients with CHD in both rural and urban Indian population [23], that's agree with present data about Cu, on the other hand, it was disagree with present analysis about iron that differences belongs to fluctuating decreasing iron levels with three patient groups which may be explain as a non specific reaction common to other disease like anemia [8] even excessive body iron stores are not associated with risk of CHD [25], or may be related to the antagonistic relation between Cu and Fe [26], therefore present data not allowed to used free serum iron as a risk factor for CHD.

Number of papers has studied stored iron overload, as assessed by increased serum ferritin concentration [6][11][23][25][26], did not confirm a role for serum ferritin as risk factor for the extent of CHD [6] while other research reported that excessive body iron stores are associated with risk of CHD [11], because iron can induce lipid peroxidation in vitro and vivo in humans and has promoted CHD in experimental animals [16], in contrast, the present evidence illustrating that iron depletion is positive in all patient group with CHD that agree with other reported [8].

Finally, from present research, it's conclude that rise of serum Cp and Cu level with all CHD patients groups were found to be highly - significant and used as a risk factor for prognostic and diagnostic disease. At the same time, follow - up study has to be done for further investigation. however, further studies are necessary to arrest the role of Cp and Cu amongst persons of high risk groups such as hypertensive, hyperlipaemic, smokers and family members of patients with CHD, on the other hand, further study

on serum iron level and serial estimation of this level in persons of high risk group and CHD patients can throw some light on this role.

The present study is an attempt to look for the diagnostic and prognostic importance of serum ceruloplasmin, copper and iron levels in CHD patients. In present data, Cp level of all patient groups showed a significant rise as compared with the control group, these results agree with previous study like [12],[13]. Furthermore, another researcher [14] submitted that the patients with unstable angina appear Cp levels from 6 hours of onset chest pain until 6 months were significantly higher during follow up, these findings agree with present study because present samples were collected during the 6 hours from onset chest pain. Moreover, patients with CHD having in common risk factors such as obesity, hypertension, Glucose intolerance and dyslipidemia have elevated Cp levels [8],[15].

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السيريولوجيا والتهنحاس والحديد كعوامل خطورة لامراض شرابين القلب الاكليلية

اسماء صالح*

*قسم علوم الحياة، كلية العلوم للبنات، جامعة بغداد

الخلاصة:

يعد بروتين السيريولوجيا من احد بروتينات الطور الحاد وفي هذا البحث تمت دراسة مستوى السيريولوجيا والتهنحاس والحديد في مصل المرضى المصابين بامراض شرابين القلب الاكليلية وهي الذبحة الصدرية المستقرة والذبحة الصدرية غير المستقرة واحتشاء العضلة القلبية ودور كل من هذه العوامل كادوات تنبؤية وتشخيصية. شمل البحث تسعين مريضا بامراض شرابين القلب الاكليلية وهؤلاء المرضى تم تقسيمهم الى ثلاثة مجاميع حسب الامراض اعلاه كل مجموعة مكونة من ثلاثين مريضا. وتمت مقارنة نتائجهم بثلاثين متطوعا من الاصحاء وقام الملاك الطبي الاستشاري في وحدة الطوارئ بمستشفى ابن النفيس بتشخيص الحالات المرضية. اظهرت النتائج ان السيريولوجيا من سجل ارتفاعا معنويا في مصل دم كل المرضى للمجاميع الثلاثة مقارنة بمجموعة السيطرة والنتيجة هذه تؤكد فرضية ان المستوى العالي من السيريولوجيا من بعد كعامل خطورة لامراض شرابين القلب الاكليلية والارتفاع يرافق التغييرات المناعية لتلف نسيج العضلة القلبية وبنفس الوقت رافقه ارتفاع في مستوى النحاس وبالتالي يمكن استخدام كل منهما كادوات في تشخيص الاصابة المرضية