



SERUM COPPER AND SERUM CERULOPLASMIN LEVELS IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Copper, a strong prooxidant, may play a role in atherogenesis. Serum Cu and caeruloplasmin levels have been suggested to be independent risk factors for coronary heart disease operating through oxidative modification of low density lipoprotein. Fifty cases of Acute Myocardial infarction and fifty age and sex-matched controls were recruited. Copper and ceruloplasmin levels were estimated in controls and in cases at the time of diagnosis and weekly. In cases copper and ceruloplasmin levels were statistically significantly elevated ($p < 0.0001$) compared to controls. And Serum copper and ceruloplasmin levels were maximum on 7th day of infarction, gradually declining from 7th to 28th day of infarction to normal ranges (P value is 0.0001). This suggests that serum copper and ceruloplasmin levels decreased in cases with institution of treatment.

KEY WORDS : *Coronary artery disease, Acute myocardial infarction, Copper, Ceruloplasmin, Acute phase reactant & Troponin i.*



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INTRODUCTION

Coronary heart disease has been defined as an impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart¹. It is the cause of 25-30% of deaths in most industrialized countries. Acute myocardial infarction (AMI) is defined as a part of acute coronary syndrome characterized by a typical clinical syndrome consisting of chest pain, dyspnoea with rise and fall in troponin or creatine kinase– MB to values greater than 99% of a normal reference population²

With 7.2 million deaths and 12.2 % of total deaths, coronary heart disease (CHD) is a worldwide disease. Mortality rates vary widely in different parts of the world. The highest coronary mortality is seen at present in the European region followed by South East Asia region³.

Ceruloplasmin is α_2 globulin – a glycoprotein carrying 6 copper atoms per molecule. It is one group of serum protein which rises after any form of tissue injury⁴. Ceruloplasmin being an acute phase reactant protein, its level rises immediately after cellular damage in acute myocardial infarction (AMI). Several prospective studies have indicated that serum copper or caeruloplasmin level may be an independent risk factor for cardiovascular disease^{5,6}. The increased risk has been attributed to the prooxidant function of caeruloplasmin, and recent experimental studies demonstrating the ability of caeruloplasmin to oxidatively modify low density lipoprotein (LDL)⁷ seem to underline concept. In one study a significant association between high baseline levels of serum caeruloplasmin and the subsequent risk of myocardial infarction⁶ and incidence of coronary heart disease (CHD)⁸ among individuals with high levels of serum caeruloplasmin have been reported. Therefore caeruloplasmin could be a pro oxidant in normolipidaemic AMI patients⁹. However, accessory factors derived from the vascular cells may be modulatory or requisite during lipoprotein oxidation within the vessel wall.¹⁰ Some studies have reported about the cardio

protective nature of caeruloplasmin¹¹ which could protect the myocardial tissue against the deleterious effects of oxygen free radicals. So we examined in our present study the changes in serum levels of copper and ceruloplasmin in Acute Myocardial Infarction patients and outcome of the AMI cases.

MATERIALS AND METHODS

A prospective study was undertaken in the Department of Biochemistry, Dr Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation, Chinnoutapalli, Gannavaram. Fifty diagnosed Acute Myocardial Infarction cases, who attended to our hospital and fifty age, sex matched controls were included in our study group. All cases in our study were diagnosed by Medicine Department of our Institute. All patients survive till the end of study period. Diagnosis of acute myocardial infarction (AMI) cases was done as per the E.C.G findings and by using biochemical parameters Creatinine phosphokinase (CPK), CPK-MB and Troponin I. Acute myocardial infarction (AMI) cases were diagnosed when any of these two criteria were present. The study was approved by the Ethics committee of our college. After fulfilling the inclusion and exclusion criteria, prior consent was obtained from the subjects.

Inclusion Criteria: Patients with symptoms and signs suggestive of Acute myocardial infarction (AMI) supported by ECG and cardiac markers (increased CPK, CPK-MB and Troponin I) were included in the study.

Exclusion criteria: Patients who were not willing to give consent were excluded from the study. Patients with diabetes mellitus, renal insufficiency, or hepatic disease, or patients with lipid abnormalities, who were taking lipid lowering drugs or antioxidant vitamins supplementation and current or past smokers, Patients with ≥ 600 mg/dl of C- Reactive protein were excluded from the study.

Sample collection and analysis: 5ml of Blood sample were collected from each Acute

myocardial infarction (AMI) patient for analysis of CPK, CPK-MB, Troponin- I, Copper and Ceruloplasmin levels at the time of admission. All patients were thrombolysed and given treatment according to standard protocol after blood samples were collected. Blood samples were collected On 7th, 14th, 21st and 28th day of infarction for analysis of copper and ceruloplasmin. And blood from the control subjects were also collected for analysis of Copper and Ceruloplasmin levels. CPK estimation was done by modified method of IJfcc¹² (Commercial kit ERBA Manheim) CK-MB estimation was done by method of IJfcc¹³ (Commercial kit ERBA Manheim) in Randox dytona autoanalyzer .Troponin I estimation was done by chemiluminescence immunoassay (CLIA) method.¹⁴(Commercial kit MONOBIND Master CLIA VAST Enabled kit) . Copper estimation was done by spectrophotometric method¹⁵(Commercial kit

Coral clinical systems). Ceruloplasmin estimation was done by Para- phenylene diamine oxidase method¹⁶ (Commercial kit CPC diagnostics pvt Ltd) .

RESULTS

The summary of data for serum Copper and serum Ceruloplasmin levels are tabulated in table No.1 and table No.2 respectively. Stat plus 2009 professional 5.8.4 was used to analyze the data. Analysis of variance (ANOVA) was used to study the data. The P value is < 0.05 is taken as statistically significant.

Copper : The P value is < 0.0001, considered extremely significant. Effective matching (or blocking) results in significant variation among the Means. With this data, the matching appears to be effective.

Table No.1

The summary of data for serum Copper levels in controls and AMI cases are tabulated in

Group	No of patients	Standard mean	Standard error of Deviation	Mean	Median
Control-cu	50	83.90	9.016	1.275	85.000
Cu-1 st day	50	126.36	15.349	2.171	128.00
Cu-7 th day	50	139.54	16.973	2.400	139.50
Cu-14 th day	50	123.80	16.173	2.287	123.50
Cu-21 st day	50	107.60	15.485	2.190	108.50
Cu-28 th day	50	91.860	11.725	1.658	92.500

Ceruloplasmin :The P value is < 0.0001, considered extremely significant. Effective matching (or blocking) results in significant variation among the Means. With these data, the matching appears to be effective.

Table No.2

The summary of data for serum Ceruloplasmin levels in controls and AMI cases are tabulated in

Group	No of Patients	Standard mean	Standard error of Deviation	Mean	Median
Control-ceru	50	27.180	2.775	0.3925	27.000
Ceru-1 st day	50	30.480	4.999	0.7070	30.000
Ceru-7 th day	50	37.880	5.279	0.7465	37.000
Ceru-14 th day	50	32.580	6.211	0.8784	32.000
Ceru-21 st day	50	24.220	5.108	0.7224	24.000
Ceru-28 th day	50	21.040	3.796	0.5368	21.000

DISCUSSION

Our study group includes fifty AMI cases and age and sex matched fifty controls. Serum Copper levels are higher in AMI cases on day one (1) compared to controls. In our study, serum Copper levels are maximum on the 7th day and gradually declining from 7th to 14th to 21st to 28th day of infarction to normal ranges, that is, just higher than the control levels by the end of 28th day (P value is 0.0001) statistically significant. Several other studies reported that associations of high levels of Copper to elevated risk of increased carotid intima-media thickness¹⁷, myocardial infarction¹⁸ and mortality from CHD or cardiovascular disease^{19, 20}. Our study is in accordance with Vallee et al (1952)²¹, who found in their study statistically significant raise in serum copper in all cases. The copper tend to rise in first five days after infarction, reaching a maximum or plateau in five to eleven days and then progressively fell to just above normal range within 19 to 30 days. Our study also in accordance with Khandekar et al²² who showed in his study that, serum Copper concentration increases in AMI, that is, ordinarily beginning on second day or third day⁶, reaching a maximum on fourth to sixth day²² or on fifth to eleventh day⁶ and gradually decreasing to normal within three or several weeks. The possible explanation for the increase of serum copper is discussed by Khandekar et al²².

In our study, serum Ceruloplasmin levels are maximum on the seventh day and gradually declining from 7th to 14th to 21st to 28th day of infarction to normal ranges, that is, just higher than the control levels by the end of 28th day(P value is 0.0001) is statistically significant. The association between elevated serum ceruloplasmin levels and increased incidence of CHD is its property as an acute phase protein. Since an increase of ceruloplasmin can be mediated by many unspecific factors causing tissue injury, a high ceruloplasmin levels may reflect response to injury and inflammation. Endothelial injury and inflammatory processes are thought to be involved in the pathogenesis of

atherosclerosis and markers of inflammation and infection, such as leucocyte count, fibrinogen and C-reactive protein have been shown to be independent risk factors for CHD²³⁻²⁷. This suggests that a substantial part of the increased risk is associated with high levels of ceruloplasmin may be attributed to inflammation process. In our study with the effective treatment of AMI cases, ceruloplasmin levels came down to almost normal levels by the 28th day of infarction. The remaining elevated risk may be due to other properties of ceruloplasmin, like its pro-oxidant activity, or it may reflect low level inflammation being involved in the cardiovascular disease process.

The prooxidant property of ceruloplasmin involves lipid peroxidation. Studies indicate that ceruloplasmin by itself can oxidize LDL in vitro and possibly in vivo^{17,183}. However, accessory factors derived from the vascular cells may be modulatory or requisite during lipoprotein oxidation within the vessel wall.²¹ Studies have reported about the cardio protective nature of ceruloplasmin²² which could protect the myocardial tissue against the deleterious effects of oxygen free radicals. Studies observing the role of transition metal ion- mediated oxidation of LDL molecules, centered on the role of human ceruloplasmin in this oxidative process, as it is the principal copper containing protein in serum.

Our study is in accordance with studies of Vallee et al (1952)⁶ who found in their study statistically significant serum oxidase activity increases gradually, after Myocardial Infarction, reaching a peak about the 9th day and thereafter falls slowly to normal . In some of their cases normal level is reached in between the 12th and 18th days, but in others the level does not return to normal by the end of 3 weeks. We did not carry out daily estimations in our study. Our study is also in accordance with Reunanen et al¹⁸, study of 104 AMI patients. In their study showed high concentration of serum Ceruloplasmin in patients with AMI and with other forms of coronary heart diseases and further showed

that Ceruloplasmin decreases slowly and reaches the baseline within a month¹⁸.

SUMMARY AND CONCLUSION

It is concluded that rise of serum copper, ceruloplasmin levels occurs as it promotes the oxidation of low density lipoprotein (LDL) cholesterol and thus increases its atherogenicity. However further study on

serum copper, ceruloplasmin levels and serial estimations of these level in AMI with more number of AMI patients can throw some light on this aspect. So early detection of high levels of Copper, Ceruloplasmin can intervene early and reduce the mortality and morbidity from AMI cases. And these parameters may be used as prognostic markers along with other traditional markers.

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