ORIGINAL RESEARCH

Relationship between Serum Ceruloplasmin level and Dyslipidemia

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ABSTRACT

Introduction: Several recent reports have indicated that Cp levels are elevated in patients with heart failure (HF), both in acute and chronic states and regardless of etiology. Furthermore, serum Cp levels appeared to be inversely correlated with LV ejection fraction but directly correlated with symptom severity especially in the non-ischemic group. **Materials and Methods:** 40 Individuals with abnormal lipid profile without any associated diseases like DM, HTN etc. Kinetic method amenable to automation for ceruloplasmin estimation with inexpension-50 µl sample + 1 ml reagent(1) → kept at room temperature for 1 min → 150 µl reagent(2) → measure in kinetic mode with factor 2012, lag time 10 secs. Lipid profile was assessed by standard methods. The data was analyzed by using Microsoft Excel. **Results:** However when correlations were seen separately for tests and controls, ceruloplasmin was positively correlated with LDL in dyslipidemics and with no other parameter of lipid profile ($r = 0.434$, $p < 0.05$) but not in control. Ceruloplasmin was negatively associated with TG in controls, but the correlation is not statistically significant. **Conclusion:** The present study showed that serum ceruloplasmin levels of dyslipidemics are significantly higher than normal healthy subjects. Thus raised ceruloplasmin can be considered as an added risk factor in dyslipidemic patients with regard to coronary artery disease.

Keywords: Serum ceruloplasmin, Dyslipidemics, Coronary artery disease.

INTRODUCTION

The World Health Organization (WHO) predicts that deaths due to circulatory system diseases are projected to double between 1985 and 2015.[1] The presently available risk factors to predict the risk of morbid coronary events fail to do so in about 30% to 40% of the cases, so a search must be done for new risk factors that can add to the current list and will help for further evaluation. Ceruloplasmin[1] is and α-2 globulin that carries most of the copper in the blood. Although its elevation after inflammation and trauma has led to its classification as an acute phase reactant, its physiological role is still uncertain and has been a subject to various speculations, investigations and contradictions. Multiple biochemical activities of ceruloplasmin have been described including oxidation of various amines, oxidation of Fe^{++} to Fe^{+++} for its subsequent uptake by transferrin and antioxidant activity against lipid peroxidation.

In contrast to this; ceruloplasmin is also considered as a pro-oxidant which may be central in its primary function that is as a participant in the host defence system through an injurious oxidant action on host biomolecules. The oxidant activity of ceruloplasmin may be a causative factor for atherosclerosis.[2]

Dyslipidemia is elevation of plasma cholesterol and or triacylglycerol or a low high-density lipoprotein or decreased serum high density lipoprotein level that contributes to the development of atherosclerosis. It is a primary major risk factor for coronary artery disease (CAD) and may even be a pre-requisite for coronary artery disease occurring before other major risk factors come into play.

The potential mechanistic link between Cp and cardiovascular disease has been debated, although the focus has been primarily on its contribution to the development of atherosclerosis and lipid oxidation rather than its protective capacity.[3] High levels of Cp were observed to be an independent risk for CAD[4] and our group has further demonstrated that elevated Cp is an independent predictor of major adverse cardiovascular events . Several recent reports have indicated that Cp levels are elevated in patients with heart failure (HF), both in acute and chronic states and regardless of etiology. Furthermore, serum Cp levels appeared to be inversely correlated with LV ejection fraction but directly correlated with symptom severity especially in the non-ischemic group.

There is now abundant evidence that particles resembling oxidatively modified LDL are present in atherosclerotic lesions. The monocytic cells achieve optimal oxidation rates by utilizing their own

transition metal ions. Macrophage derived hypochlorous acid or nitric oxide may be precursors of highly reactive hydroxyl radicals by metal ion independent mechanisms.

MATERIAL AND METHODS

The subjects for the study were selected with written informed consent. Assuming the prevalence of dyslipidemia in all lipid profile samples to be 50% and with an allowable error of ±10/20% and confidence interval of 95% the estimated sample size is 80 samples. Out of which approximately 50% would be dyslipidemic. These subjects were categorized under following groups:-

Control group: 40 age and sex matched healthy individuals with normal lipid profile.

Test group: 40 Individuals with abnormal lipid profile without any associated diseases like DM, HTN etc.

The procedure for serum ceruloplasmin estimation is as follows

Kinetic method amenable to automation for ceruloplasmin estimation with inexpension

50 µl sample + 1 ml reagent(1) → kept at room temperature for 1 min → 150 µl reagent(2) → measure in kinetic mode with factor 2012, lag time 10 secs.

Lipid profile was assessed by standard methods: Cholesterol: Cholesterol oxidase[6] method Serum Triacylglycerol: Trinder's[7] method Serum LDL: Direct LDL kit[8] method

Serum HDL: Direct HDL kit[8] method

Criteria for Dyslipidemia: According to adult treatment panel III guidelines

Serum Total Cholesterol: >200 mg/dl

Serum Low Density Lipoprotein: >100 mg/dl Serum High Density Lipoprotein: < 40 mg/dl Serum Triacylglycerol: >150 mg/dl

With presence of one or more of the above parameters, the individual is considered as dyslipidemic.

Inclusion criteria: Dyslipidemia

Exclusion criteria: Associated major illness like Hypothyroidism, HTN, DM etc that can independently increase the risk of CAD.

Statistical Analysis: The data was analyzed by using SSPS version 14.0.

Values were expressed as mean +/- SD. Mann Whitney test for significance was used Correlation was calculated using Pearson's correlation

RESULTS

Statistically significant for dyslipidemics and controls for all values except HDL with test values being significantly higher. The test applied was Mann Whitney test for significance. Table 1.

- There was a statistically significant rise in TC, LDL and TG levels in dyslipidemics when compared with controls whereas serum HDL levels did not show any significant change.
- Serum Ceruloplasmin levels were significantly raised in dyslipidemics when compared with control group

Table 1: Comparison of lipid profile in Group I and Group II

	Total Cholesterol	LDL	TG	HDL	Ceruloplasmin
Group II (Test)	163.05 +/- 44.06	129.5 +/- 34.67	208.92 +/- 115	39.2 +/- 8.71	825.1
Group I (controls)	120.76 +/- 29.08	89.05 +/- 13.21	107.5 +/- 18.56	388 +/-0.75	422
Z	4.950	5.944	7.068	0.113	5.440
P	0.0001	0.001	0.0001	0.912	0.0001

Z = value of significance according to Mann Whitney test P = P value

Correlations were calculated using Pearsons correlation coefficient. However when correlations were seen separately for tests and controls, ceruloplasmin was positively correlated with LDL in dyslipidemics and with no other parameter of lipid profile ($r = 0.434$, $p < 0.05$) but not in control. Ceruloplasmin was negatively associated with TG in controls, but the correlation is not statistically significant. Table 2

Table 2: Correlation of Serum Ceruloplasmin and Lipid profile in cases and controls

	Control		Test	
Total Cholesterol	0.117	0.508	0.140	0.466
LDL	0.114	0.520	0.434	0.018
TG	0.115	0.056	0.115	0.449
HDL	0.113	0.523	0.114	0.554

The normal serum ceruloplasmin level is 325 – 520 IU/Lit Thus the **Odds ratio as high as 15.54** shows a positive correlation of serum ceruloplasmin and dyslipidemia supporting our hypothesis pointing that,

raised ceruloplasmin levels in dyslipidemic patients can form an added risk factor for coronary heart disease.

Association of LDL is more consistent with raised ceruloplasmin values than any other dyslipidemic parameter. Also the percentage of the control group showing raised ceruloplasmin levels is as low as 10%. Table 3

Table 3: Odds ratio

	Serum Ceruloplasmin (less than 520 IU/Lit)	Serum Ceruloplasmin (more than 520 IU/Lit)
Control Group	32 subjects	8 subjects
Dyslipidemic Cases	16 subjects	24 subjects

DISCUSSION

Atherosclerosis represents the pathological process that typically underlies cardiovascular morbidity and mortality, formation of plaques in the intima and media of the arterial wall[3]. Atherosclerotic plaque results from the progressive accumulation of cholesterol, diverse lipids in native and oxidized forms, extracellular matrix materials and inflammatory cells.[5]

Atherogenic dyslipidemia; a highly prominent cardiovascular risk factor is intimately associated with premature atherosclerosis and correspond to an imbalance between excess circulating levels of apoB containing lipoproteins (LDL, TG) compared with levels of antiatherogenic apoA1 containing lipoproteins (HDL).[6] In our study dyslipidemics had raised levels of LDL, TC, TG whereas HDL was in the normal range in both the groups. There was statistically significant rise in serum total cholesterol, TG and LDL levels when dyslipidemics were compared with the normal group (Table no 1).

LDL is the major vehicle for transport of cholesterol not only to the peripheral tissues but also to the arterial wall [7]and ionic interaction of positively charged domains of apoB and negatively charged proteins of extracellular matrix including proteoglycans, collagen and fibronectin leads to intimal retention of apoB containing lipoproteins a major initiating factor in atherogenesis.[8]

Ceruloplasmin has varied biochemical roles in the body like ferroxidase activity and as a marker of inflammation as acute phase reactant. There was a significant rise observed in the dyslipidemics ($p < 0.001$) than the normal subjects in the study. An increase in ceruloplasmin levels in dyslipidemics may be due to its synthesis by the activated macrophages.

These findings are similar to Virgolici et al. an increase in serum ceruloplasmin levels could generate an excess of oxidized LDL which causes atherosclerosis[9] In this study when the ceruloplasmin levels were compared between dyslipidemics and normal healthy subjects the odds ratio was 15.54 which means the dyslipidemics are more prone for rise in ceruloplasmin levels than the healthy subjects supporting our hypothesis that raised serum ceruloplasmin levels could enhance the risk for coronary artery diseases.

When the levels of ceruloplasmin were correlated with the levels of TC, TG, LDL and HDL; in dyslipidemics we found a statistically significant strong positive correlation between ceruloplasmin and LDL levels. It was seen only with the LDL levels. This may have a bearing on the fact ceruloplasmin being a pro-oxidant may increase the levels of oxidized LDL.[10] Thus raised serum ceruloplasmin may further enhance the risk of CAD in patients with raised LDL levels. Further studies are required to find out whether there is any cause and effect relationship between LDL and serum ceruloplasmin levels.

CONCLUSION

The present study showed that serum ceruloplasmin levels of dyslipidemics are significantly higher than normal healthy subjects. Thus raised ceruloplasmin can be considered as an added risk factor in dyslipidemic patients with regard to coronary artery disease. LDL values in dyslipidemic patients require special attention because of the great significance associated with the raised ceruloplasmin levels, and if found raised then addition of antioxidants to the conventional ways of treatment may prove therapeutically useful.

Thus, Serum Ceruloplasmin level in association with LDL values in dyslipidemics should be considered as an added risk factor with a special role of antioxidants in the conventional therapy. Further follow up of such cases can thus be done as a future part of the study.

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