Plasma Glucose and Serum Ceruloplasmin in Metabolic Syndrome and Diabetes Mellitus Type 2
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Abstract
Diabetes mellitus type 2 and metabolic syndrome are conditions associated with insulin resistance and hyperglycemia. Metabolic syndrome a risk factor for diabetes mellitus type 2. Plasma glucose (fasting/postprandial) and serum ceruloplasmin levels and their relationship were studied. Study population consisted of 150 individuals—50 individuals with diabetes mellitus type 2, 50 individuals with metabolic syndrome, and 50 age- and sex-matched healthy controls. Plasma levels of fasting and postprandial glucose were measured along with serum ceruloplasmin. Data was analyzed by ANOVA and Pearson correlation. The fasting and postprandial plasma glucose levels in metabolic syndrome and diabetes mellitus 2 were increased when compared to control. Serum ceruloplasmin level was 327.8 ± 68.9 in control, 227.3 ± 46.8 in metabolic syndrome, and 194.0 ± 49.6 in diabetes mellitus type 2 individuals. There was a statistically significant negative correlation between the fasting, postprandial plasma glucose, and serum ceruloplasmin in type 2 diabetes mellitus.

Keywords: Diabetes mellitus; Metabolic syndrome; Ceruloplasmin; Glucose

1. INTRODUCTION
Diabetes mellitus is a metabolic disorder due to defect in the secretion of insulin and/or defect in the action of insulin characterized by hyperglycemia [1]. Diabetes mellitus type 2 and metabolic syndrome are conditions associated with insulin resistance [2]. Metabolic syndrome may be associated with dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state [3]. It increases the risk of diabetes mellitus by fivefold and cardiovascular risk by twofold over the next 5-10 years [4,5].

Ceruloplasmin is an enzyme (E.C. 1.16.3.1) [6]. It is an acute-phase protein synthesized in the liver and a member of blue multicopper oxidase. The physiological functions of ceruloplasmin are uncertain, but ceruloplasmin has a role in copper transport, coagulation, angiogenesis, defense against oxidative stress, and iron homeostasis [6,7]. There has been conflicting data on serum ceruloplasmin in metabolic syndrome and diabetes mellitus type 2. Some studies show significantly increased serum level of ceruloplasmin in metabolic syndrome and diabetes mellitus [8,9]. Data available mainly explains the association between increased ceruloplasmin levels and cardiovascular diseases [10-12]. Few studies have also shown a decrease in plasma ceruloplasmin in type 2 diabetes mellitus [13-15]. This study was conducted to evaluate the relationship between the fasting plasma glucose, postprandial plasma glucose, and serum ceruloplasmin level in metabolic syndrome and diabetes mellitus type 2.

2. MATERIALS AND METHODS
Study population consisted of 150 individuals who came to the hospital for health checkup. It was divided into cases and controls. Cases consisted of 50 individuals who fulfilled the criteria for metabolic syndrome according to the National Cholesterol Education Program (NCEP): ATP III and 50 individuals with diabetes mellitus type 2. Control group consisted of 50 age- and sex-matched healthy individuals. The study was conducted after obtaining approval from the Institutional Ethics Committee.

After obtaining written informed consent from the subjects, blood samples were collected under aseptic precautions in fasting condition from cases and controls in plain and sugar tubes (containing sodium fluoride as antiglycolytic agent and potassium oxalate as anticoagulant). Blood samples for postprandial plasma glucose were collected exactly 2 h after the meal. Blood samples were immediately processed to obtain serum for the estimation of ceruloplasmin and plasma for the estimation of glucose.

The ceruloplasmin level in serum was assayed by the colorimetric method described by Sudderman and Nomato [16]. Plasma glucose was measured by using the commercially available Identi glucose kit and the fully automated analyzer (Olympus AU400) that used the glucose oxidase/peroxidase (GOD-POD) method described by Trinder [17].

The data was analyzed statistically by ANOVA for multiple group comparison, and Pearson correlation was used to find the correlation between the parameters.
3. RESULTS

We observed statistically significant ($p < 0.001$) increase in fasting plasma glucose in metabolic syndrome (111.0 ± 8.49 mg/dl) and diabetes mellitus type 2 (153.2 ± 22.58 mg/dl) when compared to controls (99.2 ± 9.23 mg/dl) (Figure 1). The post prandial glucose levels were significantly ($p < 0.001$) increased in metabolic syndrome (105.0 ± 39.41 mg/dl) and diabetes mellitus type 2 (176.4 ± 52.28 mg/dl) in comparison with the control group (111.7 ± 41.47 mg/dl) (Figure 2). Serum ceruloplasmin level in control was 327.8 ± 68.9, whereas in metabolic syndrome 227.3 ± 46.8 and in diabetes mellitus type 2, 194.0 ± 49.6. The decrease in plasma ceruloplasmin level between the groups is statistically significant with $p$ value < 0.001 (Figure 3). There was a statistically significant ($<0.05$) negative correlation between serum ceruloplasmin and levels of fasting as well as postprandial plasma glucose in diabetes mellitus type 2 (Table 1).

4. DISCUSSION

Metabolic syndrome and diabetes mellitus are conditions associated with insulin resistance and hyperglycemia. The primary clinical outcome of metabolic syndrome is cardiovascular disease. But majority of the individuals with metabolic syndrome will have insulin resistance and this can later result in increased risk for type 2 diabetes mellitus.

We found a statistically significant increase in the fasting and postprandial plasma glucose levels in diabetics when compared to metabolic syndrome. Our study shows a statistically significant decrease in the serum ceruloplasmin in metabolic syndrome and diabetes mellitus type 2, when compared to control group. Further, when compared to metabolic syndrome, a statistically significant decrease in serum ceruloplasmin level was observed in diabetes mellitus type 2. The correlation between the plasma glucose levels (fasting and postprandial) and serum ceruloplasmin in diabetes mellitus type 2 was statistically significant. We observed that in metabolic syndrome, serum ceruloplasmin levels were decreased, but they are independent of plasma glucose (fasting and postprandial) levels. Our observation is consistent with study by Sarkar et al. where they observed that plasma ceruloplasmin in diabetes mellitus type 2 was decreased when compared to controls, and plasma ceruloplasmin was negatively correlated with fasting plasma glucose in diabetics [13]. Ramakrishna and Jailkhani also demonstrated decreased levels of ceruloplasmin in non-insulin dependent diabetes mellitus compared to normal healthy controls [15]. Abou-Seif and Youssef observed decrease in the serum ceruloplasmin along with other antioxidant enzymes like superoxide dismutase and catalase in...
diabetes mellitus [18]. Rangaswamy and Santhosh too observed a statistically significant decrease in plasma ceruloplasmin in diabetics when compared to the control group [14]. Awadallah et al. concluded that levels of serum ceruloplasmin, glutathione, zinc, copper and sodium levels were decreased in juvenile diabetes [19]. In contrary to our finding, Chul-Hee Kim et al. found a statistically significant increase in plasma ceruloplasmin in metabolic syndrome [8]. Similar observations were made by many other researchers [20].

The decrease in the serum ceruloplasmin in the metabolic syndrome and diabetes mellitus observed in our study may be due to the increased utilization of the antioxidants, including ceruloplasmin, to neutralize the reactive oxygen species produced in excess in these conditions. Significant negative correlation was observed between the plasma glucose and ceruloplasmin in diabetes mellitus type 2 but not in metabolic syndrome. It may be due to the damage caused by the glycation of the antioxidant enzymes, including ceruloplasmin, due to hyperglycemia. Ceruloplasmin has got a role in copper and iron metabolism. About 95% of the copper present in plasma is transported with the help of ceruloplasmin [13]. Ceruloplasmin possesses antioxidant activity due to its ferroxidase activity. Reactive oxygen species prevent the binding of copper to the ceruloplasmin and disrupt normal protective function and liberate copper. Copper is toxic in the free form. This may promote oxidative stress by Haber-Weiss reaction [21]. Due to the ferroxidase activity, ceruloplasmin can oxidize ferrous iron to ferric iron; this will not allow the iron to be available for Fenton reaction, so there is limited generation of hydroxyl radical [22]. Reactions involving copper (Haber-Weiss reaction) and iron (Fenton reaction) are important reactions responsible for oxidative stress in the atherosclerotic plaques [23].

Normal healthy endothelium is a producer of nitric oxide. Oxidative stress impairs the endothelium-dependent vasodilation due to the quenching of endothelial nitric oxide, which allows endothelium to become net producer of reactive oxygen species, especially superoxide (since endothelial nitric oxide synthase is uncoupled to produce superoxide instead of nitric oxide). Nitric oxide is the target for reactive oxygen species (ROS). Superoxide converts nitric oxide to peroxynitrite. The peroxynitrite is a source for hydroxyl radicals that cause endothelial damage. Hyperglycemia poses an additional burden by inducing oxidative stress. Defect in the endothelium-dependent relaxation of the vessels is observed in diabetes mellitus [24-26]. Studies had shown that ceruloplasmin-induced lipid peroxidation is accelerated by glucose [27,28]. All these may contribute to the progression of atherosclerosis and coronary vascular disease.

5. CONCLUSION

Ceruloplasmin is a copper containing enzyme. It acts as an antioxidant through its ferroxidase activity. In diabetes mellitus, increased oxidative stress is a risk factor for atherosclerosis and coronary heart disease. Antioxidant proteins like ceruloplasmin

![Figure 3: Serum ceruloplasmin level in control and cases (metabolic syndrome, diabetes mellitus type 2)](image)

![Table 1: Correlation between fasting and postprandial glucose with serum ceruloplasmin](table)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fasting plasma glucose and serum ceruloplasmin</th>
<th>Postprandial plasma glucose and serum ceruloplasmin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson correlation coefficient ($r$)</td>
<td>$p$</td>
</tr>
<tr>
<td>Control</td>
<td>$-0.08$</td>
<td>0.577</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>0.173</td>
<td>0.241</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>0.563</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*p < 0.05 (significant).
may be damaged by the accelerated glycation due to hyperglycemia. Increased oxidative stress may utilize antioxidants, including ceruloplasmin. Decrease in serum ceruloplasmin in metabolic syndrome and type 2 diabetes mellitus may contribute to the increased risk of atherosclerosis and coronary artery disease by increasing oxidative stress.

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Author Contributions
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Conflict of Interest
None.

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