Elevated Serum Ceruloplasmin Levels in Subjects With Metabolic Syndrome: A Population-Based Study

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Serum ceruloplasmin was reported to be an independent risk factor for cardiovascular disease. We investigated whether serum ceruloplasmin level is elevated in subjects with metabolic syndrome (MS, insulin resistance syndrome) in a community-based population. A total 883 subjects over 40 years of age were studied among a population of the Chongup district, a rural area of South Korea. Serum ceruloplasmin levels were measured, and oral glucose tolerance tests were performed. Known cardiovascular risk factors, such as serum lipids, fasting insulin level, and urinary albumin excretion rate (UAER), were also measured. Serum ceruloplasmin levels in the subjects with MS (n = 167, 325 ± 141 mg/L) were significantly higher than in those without MS (278 ± 93 mg/L, *P* < .001). The mean ceruloplasmin level also increased as the glucose tolerance worsened (278 ± 95 mg/L in normal glucose tolerance [NGT], 303 ± 108 mg/L in impaired glucose regulation, and 328 ± 148 mg/L in diabetes; *P* < .001). Serum ceruloplasmin level was positively correlated with age, fasting glucose, postload 2-hour glucose, total cholesterol, triglyceride, systolic blood pressure, diastolic blood pressure, and UAER and negatively with high-density lipoprotein (HDL)-cholesterol. In multiple regression analysis, serum ceruloplasmin level was independently associated with age, fasting glucose, triglyceride, HDL-cholesterol, and UAER. In conclusion, serum ceruloplasmin level is elevated in the subjects with MS, as well as in subjects with impaired glucose regulation or diabetes mellitus. In addition, serum ceruloplasmin level is associated with various cardiovascular risk factors. These results suggest that elevated serum ceruloplasmin level can be a marker for metabolic stresses associated with MS.
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CERULOPLASMIN, THE MAIN copper-carrying protein, is one of the acute-phase reactants and antioxidant proteins in serum.[1] Elevated levels of serum copper and ceruloplasmin were reported to be predictive factors of acute myocardial infarction,[2-5] and serum level of ceruloplasmin was positively correlated with severity of coronary atherosclerosis.[6] However, the mechanism by which elevated serum ceruloplasmin is associated with atherosclerosis and coronary artery disease is still largely unknown.

Atherosclerosis is considered to be a chronic inflammatory process.[7,8] As ceruloplasmin is an acute-phase protein, a high serum ceruloplasmin level can be a reaction to systemic inflammations associated with unidentified infections,[9,10] which, in turn, is associated with atherosclerotic events.[7] In fact, the Rotterdam Study[11] showed that excessive risk of myocardial infarction for the highest quartile of ceruloplasmin was reduced by 33% after adjustment for markers of inflammation, such as C-reactive protein and leukocyte count.

On the other hand, several previous studies have reported a significant association between serum ceruloplasmin concentration and conventional cardiovascular risk factors.[12-15] There was a strong positive association of copper and ceruloplasmin levels with lipid peroxide, total cholesterol, and triglycerides.[14] Ceruloplasmin levels were independently associated with intra-abdominal fat thickness, in addition to total cholesterol and triglycerides.[15] Several studies also indicated that the serum ceruloplasmin level is increased in patients with type 1[13,16] and type 2[12,17] diabetes mellitus. Therefore, the association between ceruloplasmin level and cardiovascular morbidity might be due to metabolic stresses rather than systemic infections.

It has long been noted that certain common cardiovascular risk factors, such as glucose intolerance, hypertension, and dyslipidemia simultaneously occur in certain subjects.[18] In 1998, the World Health Organization (WHO) proposed a working definition of the metabolic syndrome (MS) for this syndrome, including central obesity and microalbuminuria as additional components.[19] To our knowledge, there has been no population-based study on the serum level of ceruloplasmin in subjects with MS. Therefore, we investigated whether serum ceruloplasmin level is elevated in subjects with MS. We also studied the association of ceruloplasmin levels with various conventional cardiovascular risk factors.

SUBJECTS AND METHODS

Subjects

The study subjects were selected by a random cluster sampling among the rural population of the Chongup district, located in the southwestern part of Korea. The area occupies 692 km^2 and includes about 151,000 people. We randomly selected 6 villages, which included 1,791 registered residents aged over 40 years. Among them, 1,108 subjects (61.9%) agreed to participate in the study. We analyzed the data of 883 subjects after excluding the subjects with the following exclusion criteria: subjects with history or signs of cardiovascular disease, chronic inflammatory processes, infection, or acute inflammation within the last 6 months; subjects with leukocytosis (blood leukocyte count $> 10{,}000 \times 10^3/\mu L$), pyuria, hematuria, or overt proteinuria

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by urine dipstick test. This study was approved by the Institutional Review Board, and all subjects gave written informed consent.

Methods

Detailed information on current health status, medical history, drug use, smoking, and alcohol intake was obtained by a questionnare during interview. Subjects' weight and height were measured in light clothing without shoes, and body mass index (BMI, kg/m^2) was calculated from these measurements. The waist circumference was measured at the level of umbilicus, and hip circumference was measured at the level of greatest hip girth. The ratio of waist-to-hip circumferences (waist-to-hip ratio [WHR]) was used as an index of central obesity. Blood pressure (BP) was measured after a 10-minute rest in the sitting position, with a standard 12.5-cm cuff mercury sphygmomanometer. Diastolic BP was recorded at the disappearance of the Korotkoff sounds (phase V).

After an overnight fast, a 75-g oral glucose tolerance test was performed in subjects not known to have diabetes. The subjects were classified as normoglycemia, impaired glucose regulation (IGR, impaired glucose tolerance or impaired fasting glycemia), or diabetes mellitus according to the WHO clinical staging.[19] MS was defined as the coexistence of glucose intolerance (IGR or diabetes) together with 2 or more of the following 4 components: hypertension (arterial pressure $\geq$ 140/90 mm Hg), dyslipidemia (triglyceride $\geq$ 1.7 mmol/L and/or HDL-cholesterol $<$ 1.0 mmol/Ll for women, $<$ 0.9 mmol/L for men), central obesity (WHR $>$ 0.90 for men, $>$ 0.85 for women) and/or BMI $>$ 30 kg/m^2, and microalbuminuria (urinary albumin excretion rate [UAER] $\geq$ 20 μg/min).

Venous blood samples were collected before and 2 hours after the glucose load for measurements of plasma glucose and insulin levels. Plasma glucose was determined by glucose oxidase method (Hitachi 736-40 automatic analyzer; Hitachi, Tokyo, Japan). Plasma insulin concentrations were determined by an insulin-specific immunoradiometric assay kit (Linco Research, St Louis, MO), in which the cross-reactivity with proinsulin was less than 0.2%. Fasting serum triglyceride and total cholesterol levels were measured using an autoanalyzer with enzymatic techniques. HDL-cholesterol was measured after heparin and manganese chloride precipitation. Albumin concentration of the timed overnight urine sample was determined by a commercial double-antibody immunoradiometric assay kit (Diagnostic Products, Los Angeles, CA). Serum ceruloplasmin concentration was measured by nephelometry (Beckman Coulter, Fullerton, CA).

Statistical Analysis

Results are expressed as mean $\pm$ SD. Statistical analysis was performed using SPSS computer software (SPSS, Chicago, IL). Student's *t* test and 1-way analysis of variance (ANOVA) were used in comparison of continuous variables, and χ^2 test or stratified Mantel-Haenszel analysis was used for evaluating prevalence. Variables that showed skewed distribution, such as insulin, triglyceride, ceruloplasmin, and UAER, were log-transformed before analyses and then back-transformed to their natural units for presentation. A 2-tailed partial correlation analysis was used to assess the association of various atherosclerotic risk factors with ceruloplasmin. To find the independent factors associated with ceruloplasmin, multiple linear regression analysis was also performed. A *P* value less than .05 (2-tailed) was considered statistically significant.

RESULTS

Among the 883 subjects, 167 (18.9%) had MS. The clinical characteristics of these subjects are shown in Table 1. Serum ceruloplasmin level in the subjects with MS (325 $\pm$ 141 mg/L) was significantly higher than in the subjects without MS (278 $\pm$ 93 mg/L, $P < .001$). The percentage of subjects with low ceruloplasmin values ($<$ 200 mg/L) was similar between the subjects with and without MS (2.4% *v* 4.6%, $P = .28$). In contrast, the percentage of subjects with high ceruloplasmin values ($>$ 350 mg/L) was greater in the subjects with MS than without (20.4% *v* 7.7%, $P < .001$). The mean ceruloplasmin levels also increased as the glucose tolerance worsened (278 $\pm$ 95 mg/L in normal glucose tolerance [NGT], 303 $\pm$ 108 mg/L in IGR, and 328 $\pm$ 148 mg/L in diabetes; $P < .001$). Among the subjects with MS, diabetic patients (n = 71) had slightly higher, but not statistically significant, ceruloplasmin levels compared with nondiabetic subjects (341 $\pm$ 161 *v* 313 $\pm$ 123 mg/L, $P > .05$).

Table 1. Clinical and Biochemical Characteristics of the Study Population

	Without MS (n = 716)	With MS (n = 167)	*P*
Sex (M/F)	280/436	53/114	NS
Age (yr)	60.6 $\pm$ 9.5	63.1 $\pm$ 9.7	$<$.01
Smoking (%)	30.1	25.5	NS
Diabetes mellitus (%)	1.9	38.6	$<$.001
Hypertension (%)	47.4	79.2	$<$.001
BMI (kg/m^2)	23.4 $\pm$ 2.9	25.3 $\pm$ 3.2	$<$.001
WHR	0.87 $\pm$ 0.05	0.91 $\pm$ 0.05	$<$.001
Ceruloplasmin (mg/L)	278 $\pm$ 93	325 $\pm$ 141	$<$.001
FBS (mmol/L)	4.9 $\pm$ 1.1	7.1 $\pm$ 2.6	$<$.001
PP2 (mmol/L)	6.3 $\pm$ 1.6	11.2 $\pm$ 4.8	$<$.001
Systolic BP (mm Hg)	138 $\pm$ 22	154 $\pm$ 23	$<$.001
Diastolic BP (mm Hg)	83 $\pm$ 11	89 $\pm$ 12	$<$.001
Triglyceride (mmol/L)	1.76 $\pm$ 1.05	2.87 $\pm$ 2.01	$<$.001
HDL-cholesterol (mmol/L)	1.19 $\pm$ 0.28	1.06 $\pm$ 0.26	$<$.001
Total cholesterol (mmol/L)	5.09 $\pm$ 0.91	5.56 $\pm$ 0.96	$<$.001
UAER (μg/min)	8.4 $\pm$ 23.0	24.5 $\pm$ 49.1	$<$.01
Fasting insulin (pmol/L)	59 $\pm$ 61	79 $\pm$ 63	$<$.01

Abbreviations: BMI, body mass index; WHR, waist-to-hip circumference ratio; FBS, fasting plasma glucose; PP2, postload 2-hour glucose; BP, blood pressure; HDL-cholesterol, high-density lipoprotein-cholesterol; UAER, urinary albumin excretion rate; NS, not significant.

Serum ceruloplasmin level was positively correlated with age, fasting glucose, postload 2-hour glucose, total cholesterol, triglyceride, systolic and diastolic blood pressure, and UAER and negatively correlated with HDL-cholesterol levels (Table 2). The serum triglyceride level especially showed the strongest association with the ceruloplasmin level (Fig 1A). The correlation was stronger in the diabetic subjects (Fig 1B). An independent relationship with serum ceruloplasmin level was maintained in age, fasting glucose, triglyceride, HDL-cholesterol, and UAER in multiple regression analysis (Table 3).

Since it was reported that the serum ceruloplasmin level is increased in subjects with diabetes mellitus,[12,13,16,17] we separately analyzed the data after excluding the subjects with diabetes. In nondiabetic subjects, the serum ceruloplasmin level was also positively correlated with age, systolic and diastolic blood pressure, and triglyceride levels and negatively correlated with HDL-cholesterol (Table 2). In multiple regression analysis, the serum ceruloplasmin level was independently related to age, BMI, triglyceride, HDL-cholesterol, and UAER (Table 3).

DISCUSSION

The working definition of MS by the WHO includes not only the subjects with glucose intolerance, but also the subjects with

Table 2. Correlations Between Serum Ceruloplasmin Concentration and Clinical, Biochemical Parameters

	Coefficient (*R*)	*P*
All subjects (N = 883)		
Age	.072	<.05
BMI	−.051	NS
WHR	.059	NS
FBS	.139	<.001
PP2	.144	<.001
Systolic BP	.081	<.05
Diastolic BP	.067	<.05
Triglyceride	.426	<.001
HDL-cholesterol	.245	<.001
Total cholesterol	.096	<.01
Fasting insulin	.012	NS
UAER	.074	<.05
Nondiabetic subjects (n = 796)		
Age	.115	<.01
BMI	−.086	<.05
WHR	.034	NS
FBS	.072	<.05
PP2	.109	<.01
Systolic BP	.096	<.01
Diastolic BP	.096	<.01
Triglyceride	.364	<.001
HDL-cholesterol	−.224	<.001
Total cholesterol	.053	NS
Fasting insulin	.010	NS
UAER	.061	<.05

Abbreviations: BMI, body mass index; WHR, waist-to-hip circumference ratio; FBS, fasting plasma glucose; PP2, postload 2-hour glucose; BP, blood pressure; HDL-cholesterol, high-density lipoprotein-cholesterol; UAER, urinary albumin excretion rate; NS, not significant.

insulin resistance determined by glucose uptake under hyperinsulinemic, euglycemic conditions.[19] Since we did not perform the glucose clamp study in this population-based study, the prevalence of MS must have been underestimated. With this limitation in mind, we report that serum ceruloplasmin level is elevated in subjects with MS, as well as in subjects with diabetes mellitus. In addition, serum ceruloplasmin level is associated with various cardiovascular risk factors, such as serum triglyceride, HDL-cholesterol, glucose levels, and UAER.

Although several prospective studies have indicated that serum ceruloplasmin level could be an independent risk factor for cardiovascular disease,[2-5] the mechanism by which ceruloplasmin is linked to cardiovascular disease is not established. Ceruloplasmin can function as a pro-oxidant[20] and can oxidatively modify LDL in vitro.[21,22] Ceruloplasmin also can act synergistically with other cardiovascular risk factors in vivo.[2,6] Moreover, serum copper, which the level changes in parallel with that of ceruloplasmin, is the major independent determinant of serum lipid peroxide level, suggesting that serum copper bound to ceruloplasmin contributes to lipid peroxidation.[14]

On the other hand, ceruloplasmin is generally considered to be one of the major physiologic inhibitors of lipid peroxidation.[1] In vitro studies showed that ceruloplasmin has ferroxidase activity, which inhibits the ferrous ion-dependent formation of hydroxyl radicals and lipid peroxidation.[23,24] In addition, it has also been proposed that ceruloplasmin might decompose the lipid peroxide[25] or act as a scavenger of superoxide radicals.[26] Recently, it has been suggested that an increase in intracellular oxidative stress plays an important role in the development of atherosclerosis.[8,27] It is suggested that various risk factors for atherosclerosis, including hypertension, hyperlipidemia, diabetes, and hemodynamic shear stresses generate oxidative stress in the vascular cells, and this increase in oxidative stress causes endothelial dysfunction and atherosclerosis.[8] Previous studies reported that plasma markers of oxidative stress are increased in subjects with impaired glucose tolerance.[28,29] In line with this, we reported that plasma malondialdehyde (MDA) levels, a marker of oxidative stress, were higher in the subjects with MS than in the controls.[30] Therefore, elevated ceruloplasmin levels in vivo could be a defense mechanism against increased oxidative stress.

As stated earlier, ceruloplasmin is one of the acute phase proteins, and a high serum ceruloplasmin level may reflect systemic infection, which, in turn, is associated with atherosclerotic events.[9,10] However, the present study shows that ceruloplasmin levels are elevated in subjects with MS in an otherwise healthy, community-based population. Because of the cross-sectional nature of the study, we cannot make a firm conclusion whether there

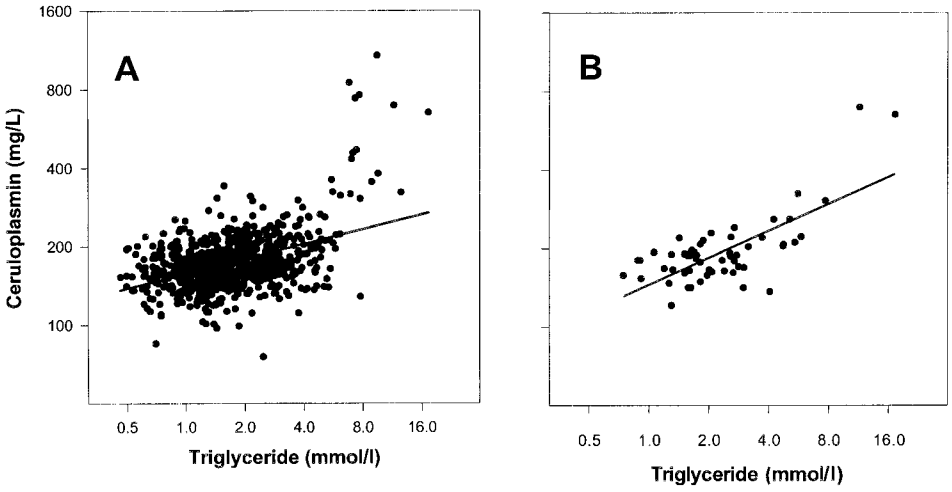

Fig 1. Correlation between serum ceruloplasmin and triglyceride levels in (A) the entire group of subjects ($r = .426$, $P < .001$), and (B) in the diabetic subjects only ($r = .648$, $P < .001$).

Table 3. Multiple Regression Analysis of the Relationship Between Serum Ceruloplasmin Concentration and Clinical Parameters

Parameter	Beta*	95% CI	*P*
All subjects (N = 883)			
Triglyceride	0.369	0.304~0.447	<.001
Age	0.142	0.090~0.225	<.001
HDL-cholesterol	−0.102	−0.232~−0.045	<.01
FBS	0.075	0.043~0.130	<.05
UAER	0.068	0.012~0.379	<.05
Nondiabetic subjects (n = 796)			
Triglyceride	0.296	0.227~0.386	<.001
Age	0.160	0.092~0.277	<.001
HDL-cholesterol	−0.135	−0.248~−0.073	<.001
UAER	0.093	0.036~0.238	<.01

Abbreviations: HDL-cholesterol, high-density lipoprotein-cholesterol; FBS, fasting plasma glucose; UAER, urinary albumin excretion rate.
*Beta is standardized coefficients, and the 95% CI is 95% confidence interval for the standardized coefficients.

is a causal relationship between serum ceruloplasmin levels and MS. However, our data at least suggest that an increase in the serum ceruloplasmin level is associated with metabolic factors rather than with systemic infectious processes.

One of the limitations of our study is that we measured ceruloplasmin concentration by nephelometry. This method measures ceruloplasmin protein regardless of copper content and does not measure the ceruloplasmin activity, which better reflects copper nutritional status.[31] Therefore, we could not discriminate whether abnormal copper nutritional status or increased serum ceruloplasmin protein per se is associated with MS. In fact, the effect of abnormal copper nutritional status on cardiovascular disease in humans is uncertain.[32,33] In contrast to the epidemiologic studies showing increased ceruloplasmin is associated with increased cardiovascular risk factors, animal studies have shown that copper deficiency decreases serum ceruloplasmin, but increases blood pressure[34] and serum cholesterol levels,[35,36] and results in overt cardiovascular diseases (eg, cardiac enlargement and rupture, coronary artery thrombosis, and myocardial infarction).[37] The reason for such apparent discrepancy is not clear at present. However, considering the antioxidant action of ceruloplasmin, it can be suggested that increased ceruloplasmin in MS be a compensatory mechanism to overcome oxidative stress induced by other metabolic stresses. On the other hand, ceruloplasmin deficiency in copper deficiency may not adequately overcome oxidative stress in the body. In this regard, it should also be noted that in the state of copper deficiency, activities of many copper-dependent enzymes important in redox regulation (eg, superoxide dismutase, glutathion peroxidase, glutathion transferase, etc) are also altered. However, the exact relationship between copper nutritional status, serum ceruloplasmin level, and risk of cardiovascular disease in humans remains to be established.

In this study, the independent factors associated with serum ceruloplasmin levels were age, serum triglyceride, HDL-cholesterol, fasting glucose levels, and UAER in the whole subjects and BMI instead of fasting glucose in nondiabetic subjects. There have been only a few studies that have reported a significant association between serum ceruloplasmin concentration and conventional cardiovascular risk factors.[11,14,15] Reunanen et al[2] reported that there was no significant correlation between serum ceruloplasmin and conventional cardiovascular risk factors and suggested that the association between ceruloplasmin level and cardiovascular morbidity was not mediated through conventional risk factors. In contrast, Craig et al[14] reported that there was a strong positive association of copper and ceruloplasmin levels with lipid peroxide, total cholesterol, and triglyceride. In the study of Cignarelli et al,[15] ceruloplasmin levels were independently associated with intra-abdominal fat thickness, in addition to total cholesterol and triglyceride. Our data confirmed that serum lipids, especially triglycerides, are strongly associated with ceruloplasmin levels. However, it should be noted that the magnitude of the coefficients of determination (R^2) is only modest ($\approx$ 17% for triglycerides). One possible explanation for the strong association between serum triglyceride and ceruloplasmin would be that triglyceride increases oxidative stress in the cell.[38] Excluding phagocytes, the majority of reactive oxygen species (ROS) are generated by the mitochondrial electron transfer chain (ETC).[39] Cytosolic long-chain acyl-CoA (LCAC), the metabolically active form of fatty acids, has been shown to inhibit mitochondrial adenine nucleotide translocator, the rate-limiting enzyme for exchange between mitochondrial adenosine triphosphate (ATP) and cytosolic adenine diphosphate (ADP).[40] When the mitochondrial ADP concentration drops, the proton gradient becomes higher. This impairs the flow of electrons through the ETC and increases the likelihood of accidental transfer of a single electron from the ETC to oxygen.[41] By this way, increased cytosolic LCAC as a consequence of an increase in serum triglycerides can increase ROS generation in the cells.[38] Enhanced production of ROS in vascular endothelial or smooth muscle cells will increase the induction of vascular inflammatory (atherogenic) genes[8] and the subendothelial oxidation of LDL,[42,43] resulting in accelerated atherosclerosis. In this regard, it is quite possible that an increased serum level of ceruloplasmin in MS is a compensatory mechanism for increased oxidative stress in association with high serum triglyceride, but future studies are needed to prove this hypothesis.

In summary, serum ceruloplasmin level is elevated in subjects with MS, as well as in subjects with diabetes mellitus in a Korean community-based population. In addition, serum ceruloplasmin level is associated with various cardiovascular risk factors, suggesting that elevated serum ceruloplasmin level can be a marker for metabolic stresses associated with MS.

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