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The effect of weight loss on serum ceruloplasmin levels in obese patients

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ABSTRACT

Introduction and aim. Serum ceruloplasmin level may be a biomarker associated with obesity and cardiovascular risk. We aimed to evaluate the effect of body weight lost by diet and exercise program on metabolic parameters and serum ceruloplasmin levels in obese patients.

Material and methods. A total of 120 obese patients with BMI ≥30 kg/m^2 were enrolled in a 16-week balanced diet program with the goal of losing 10% or more of body weight while maintaining a daily energy deficit of 500-1000 kcal/day.

Results. Mean weights of the patients decreased from 93.2±15.1 kg to 83.2±13.1 kg ($p<0.001$) and mean BMI decreased from 35.8±5.6 kg/m^2 to 31.9±4.9 kg/m^2 ($p<0.001$). Mean ceruloplasmin decreased from 25.2±4.7 mg/dL to 23.6±4.9 mg/dL ($p<0.001$), mean total cholesterol from 191.8±37.1 mg/dL to 153.8±28.7 mg/dL ($p<0.001$), mean LDL from 120.3±31.4 mg/dL to 91.1±27.7 mg/dL ($p<0.001$) and mean fasting blood glucose from 108.2±35 mg/dL to 103.3±81.1 mg/dL ($p<0.001$). There was a statistically significant and weak correlation between the change in ceruloplasmin and the change in BMI ($p=0.016$, $R=0.233$). There was a statistically significant and weak correlation between ceruloplasmin change and weight change ($p=0.010$, $R=0.251$).

Conclusion. Obese patients' serum ceruloplasmin levels were found to decrease with weight loss.

Keywords. ceruloplasmin, obesity, weight loss

Introduction

Obesity is a chronic metabolic disease characterized by an increase in body fat stores caused by an excess of energy intake over energy expenditure. Obesity has been linked to type 2 diabetes, dyslipidemia, metabolic syndrome, atherosclerosis, and cardiovascular disease.[1] Obesity considered to be one of ten most dangerous diseases by the World Health Organization (WHO) has also been found to be intricately linked to cancer in recent studies conducted by the same organization.[2]

In the report prepared by the Commission on Methods and Measures to Combat Obesity, it was announced that 34% of the population of Turkey was overweight in 2021, and the obesity rate was 39.1% in women and 24.5% in men. Because obesity is one of the leading causes of morbidity and mortality worldwide, numerous studies have been conducted to better understand the pathophysiologic mechanism of obesity and related diseases.[3,4] The most prominent of these mechanisms is that obesity-induced inflammation causes metabolic disorders and chronic diseases.[5] A host of metabolic abnormalities, oxidative stress, mitochondrial dysfunction, immune dysfunction, and chronic low-grade inflammation have been identified in the overweight obese patients.[6] Some studies have reported positive correlations between body fat mass and weight gain and plasma concentrations of inflammation-sensitive plasma proteins (ISP).[7] White adipose tissue serves as the largest endocrine organ to secrete adipokines systemically.[8] Adipocytokines which are proinflammatory cytokines are thought to increase the hepatic synthesis of ISPs.[9] Ceruloplasmin is one of these ISPs. It is a copper-containing protein that is synthesized in the liver and is involved in copper transport, iron homeostasis, oxidant stress defense, angiogenesis and coagulation.[10] There are studies in the literature suggesting that serum ceruloplasmin level may be a biomarker associated with obesity and cardiovascular risk.[11,12] However, it is unclear whether losing weight will reduce serum ceruloplasmin levels in obese patients who are expected to have high serum ceruloplasmin levels.

Aim

The aim of our study was to investigate how fasting glucose, lipid profile, and serum ceruloplasmin levels were affected in obese patients who were enrolled in a low-calorie nutrition program, and whether ceruloplasmin is a biomarker of obesity status.

Material and methods

Ethical approval

Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University approved our study (date: 25.05.2022/Decision No: 477) and it was carried out in accordance with the Helsinki Declaration principles.

Study design

The study was designed as a single-center cross-sectional study. 157 patients (44 males and 113 females) who applied to internal medicine department of Istanbul Medipol University between June 2022 and August 2022, aged 18 and older with a BMI of 30 kg/m^2 or higher were included the study.

Patients with coronary artery disease and cerebrovascular disease, renal, hepatic, and thyroid dysfunction, diagnosed with diabetes and/or hyperlipidemia and taking medication for these reasons, acute or chronic inflammatory diseases, orthopedic limitations, pregnant women, breastfeeding women, smokers and those on medical treatment for obesity were excluded from the study.

Intervention

Patients were thoroughly informed about the content of the study and written informed consent forms were obtained. Detailed anamnesis and physical examinations were carried out and demographic data such as age, gender, height, weight, BMI and chronic diseases were obtained. Body weight and height were measured in the morning while fasting, naked and barefoot. Body mass index (BMI) was calculated as body weight in kilograms divided by height in square meters (kg/m2). After 12 hours of fasting, venous blood samples were collected. Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), lipid profile including triglycerides (TG), fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, thyroid stimulating hormone (TSH), C-reactive protein (CRP), complete blood count and serum ceruloplasmin levels were all measured in the laboratory. The enzyme immunoassay was used to measure the level of ceruloplasmin in the blood (AssayMax Human Ceruloplasmin Elisa Kit, AssayPro, MO, USA). Patients were enrolled in a 16-week balanced diet program (55% carbohydrates, 25% lipids, and 20% protein) with the goal of losing 10% or more of body weight while maintaining a daily energy deficit of 500−1000 kcal/day and advised to walk for 30−45 minutes a day, 3−4 days a week, at a pace of 5−6 kilometers per hour.

Patients were weighed every two weeks. The patients' weight measurements were re-measured at the end of the 16-week follow-up period, their BMI was calculated, blood tests were repeated, and the effect of weight loss on these values was examined. Due to noncompliance with the diet, failure to achieve weight loss, or study discontinuation, 13 male and 24 female patients were excluded from the study and the study was completed with a total of 120 patients, 31 males and 89 females.

Diabetes mellitus was defined as fasting blood glucose 126 mg/dl.

Dyslipidemia was defined as TG >150 mg/dl and/or LDL >130 mg/dl and/or HDL <40 mg/dl in men and <50 mg/dl in women.

Statistical analysis

In the reference "Plasma ceruloplasmin as a biomarker for obesity: A proteomic approach," the correlation between BMI and serum ceruloplasmin level was found to be 0.265.[11] In our study, Type 1 Error was calculated as α=0.05, the power of the study was calculated as 1-β=0.80 and the sample size was calculated as 109. The MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program was used for the sampling calculations.

Continuous variables were described using descriptive statistics (mean±standard deviation, minimum, median, and maximum).

The conformity of continuous variables with normal distribution was examined by the Shapiro-Wilk test.

The relationship between two continuously dependent variables that did not fit the normal distribution was examined using the Wilcoxon Signed Rank test.

The correlation between two continuous variables that did not fit the normal distribution was examined using the Spearman Rho Correlation Coefficient.

The statistical significance level was set at 0.05. The MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) program was used for the analyses.

Results

Demographic data including age, gender and comorbidities are given in Table 1.

Table 1. Demographic data

	n	**%**
Sex, n (%)		
Male	31	25.8
Female	89	71.8
Age	Mean±SD	Med (min–max)
	52.2±10.8	53.5 (23–71)
	n	%
Diabetes		
Yes	15	12.5
No	105	87.5
Dyslipidemia		
Yes	104	86.7
No	16	13.3

Dyslipidemia criterion 1 (HDL <40 in males, <50 for females, mg/dL)		
Yes	76	63.3
No	44	36.7
Dyslipidemia criterion 2 (Triglyceride >150 mg/dL)		
Yes	58	48.3
No	62	51.7
Dyslipidemia criterion 3 (LDL >130 mg/dL)		
Yes	32	26.7
No	88	73.3

When the patients' weight parameters (kilograms and BMI) were compared before and after the study, there was a significant difference. The patients' mean kilogram and BMI decreased statistically significantly ($p<0.001$). When the laboratory parameters (ceruloplasmin, total cholesterol, HDL, LDL, TG, and fasting blood glucose) were compared before and after the study, there was a significant difference. Mean ceruloplasmin, total cholesterol, LDL, fasting blood glucose decreased, and HDL increased statistically significantly ($p<0.001$) (Table 2).

Table 2. Weight parameters and laboratory parameters*

	Before	**After**	**p**
BMI (kg/m^2)			
Mean±SD	35.8±5.6	31.9±4.9	<0.001
Med (min–max)	34.1 (24.2–54.4)	31.2 (21.5–45.8)	
Final weight (kg)			
Mean±SD	93.2±15.1	83.2±13.1	<0.001
Med (min–max)	90 (70–141)	83 (60–123)	
Ceruloplasmin (mg/dL)			
Mean±SD	25.2±4.7	23.6±4.9	<0.001
Med (min–max)	25.3 (7.2–35.7)	23.9 (8.1–32.5)	
Total cholesterol (mg/dL)			
Mean±SD	191.8±37.1	153.8±28.7	<0.001

Med (min–max)	188 (112–278)	148 (108–231)	
HDL (mg/dL)			
Mean±SD	43.7±10.7	47.7±12.3	<0.001
Med (min–max)	40 (27–68)	47 (26–74)	
LDL (mg/dL)			
Mean±SD	120.3±31.4	91.1±27.7	<0.001
Med (min–max)	119.4 (58–205.4)	85.8 (30.4–146)	
TG (mg/dL)			
Mean±SD	163.9± 84.7	104.9±55.7	<0.001
Med (min–max)	141 (35–427)	104 (34–285)	
Fasting blood glucose (mg/dL)			
Mean±SD	108.2±35	103.3±81.1	<0.001
Med (min–max)	98 (72–292)	90.5 (69–713)	

* Wilcoxon Signed Rank test

There was a statistically significant and weak correlation between change in ceruloplasmin and change in BMI (p=0.016, R=0.233). There was a statistically significant and weak correlation between ceruloplasmin change and weight change (p=0.01, R=0.251, Table 3).

Table 3. Examination of the correlation between change in ceruloplasmin and BMI change/weight change*

	R	**p**
BMI x Ceruloplasmin	0.233	0.016
Weight x Ceruloplasmin	0.251	0.01

* Spearman's rho test

Discussion

In the present study fasting blood glucose, total cholesterol, LDL, TG, and ceruloplasmin levels were found to be lower in obese patients who lost weight with a 16-week balanced diet program, while HDL levels increased.

It is known that lifestyle change including diet and exercise is the first step and one of the most effective approaches in the treatment of obesity and related diseases.[13] Dietary therapy has been shown in studies to have a significant effect on lipid levels.[14] It has been reported that a 5-10% decrease in body weight results in a 20% decrease in triglycerides, a 15% decrease in LDL cholesterol, and an 8-10% increase in HDL cholesterol.[15] According to the results of this study, 86.7% of the obese patients examined had dyslipidemia,

and the lipid profile improved significantly with weight loss, which is consistent with the findings of other studies in the literature.

Similar to dyslipidemia, dysglycemia improves dramatically with weight loss. American Association of Clinical Endocrinologists has prioritized the fight against obesity in the treatment algorithm for type 2 diabetes. Excess weight loss improves blood glucose control and reduces the need for medication.[16,17] According to studies, a 7% reduction in body weight is enough to reduce the risk of type 2 diabetes by 58%. It has been emphasized that losing weight reduces the risk of diabetes even if it does not result in an ideal weight.[18,19] In this study, 12.5% of the patients had overt diabetes and there was a significant change in fasting blood glucose averages with diet.

The chronic low-grade inflammation associated with obesity and the subsequent altered metabolism has been termed "metaflammation."[20]

For many years, adipose tissue was thought to be static tissue; however, it is now known that it is an endocrine organ that secretes a large number of bioactive proteins known as adipocytokines.[21]

These adipocytokines stimulate the production of ISPs such as ceruloplasmin. The regression of ceruloplasmin levels with weight loss, as seen in our study, may be related to a decrease in adipocyte pool and cytokine synthesis.

There are some studies in literature examining the relationship between obesity and ceruloplasmin. Kim et al. looked into new biomarkers that could be used in obesity and found that C-reactive protein, fibrinogen and ceruloplasmin levels were higher in obese people than in non-obese people.[11] Böyük et al. evaluated the change in serum ceruloplasmin levels in obese patients who achieved weight loss after laparoscopic adjustable gastric banding operation. Weight loss was found to be 12.9±3.3 kg between the preoperative period and the 3rd month of the postoperative period, while the serum ceruloplasmin level decreased from 33.3±15.7 mg/dL to 23.9±8.8 mg/dL. A positive correlation was found between weight loss and a decrease in serum ceruloplasmin levels.[22]

Some studies have reported that high ceruloplasmin concentrations represent an elevated risk for cardiovascular diseases. Considering that conditions such as diabetes, hyperlipidemia, hypertension, and obesity are associated with inflammation and each of them is a factor contributing to cardiovascular risk, it is possible to explain this relationship.[23]

The relationship between obesity and ceruloplasmin has been investigated not only in adults but also in children. In a cross-sectional study that included 976 patients investigating the relationship between metabolic syndrome, systemic inflammation markers and ceruloplasmin in adolescents, adolescents with metabolic syndrome had higher TNF-α, IL-6, CRP and ceruloplasmin levels than those without metabolic syndrome, all values were associated with metabolic syndrome components and especially insulin resistance. However, it was determined that the marker with the highest correlation was ceruloplasmin.

Serum ceruloplasmin level in adolescents has been identified as the most useful marker for inflammation and future cardiovascular disease risk.[24]

The reason for the increase of ceruloplasmin due to inflammation in obesity is because it is a powerful antioxidant. Myeloperoxidase is a neutrophil enzyme that increases oxidative stress in many inflammatory pathologies and catalyzes the production of free radicals via hydrogen peroxide. Ceruloplasmin is a potent inhibitor of myeloperoxidase. In other words, it rises to compensate for the oxidative stress caused by inflammation in obesity.[25]

Ceruloplasmin inhibits lipoperoxidation through iron metabolism. There is a similar mechanism not only in obesity but also in every disease that progresses with inflammation. For example Taysi et al. found that serum ceruloplasmin levels were higher in patients with rheumatoid arthritis than in those without a diagnosis in their study. Patients with rheumatoid arthritis have higher levels of free radicals in their blood. Peroxidation caused by free radicals damages lipid cell membranes, and ferrous (++) iron acts as a catalyst for lipoperoxidation. Ceruloplasmin is an antioxidant that prevents lipoperoxidation by converting ferrous iron to ferric iron (+++).[26]

Study limitations

Our study is a single-center study with 120 patients. Multicenter studies with more patients are needed. In addition, since it is a cross-sectional study, the causality relationship could not be established clearly. Cohort studies that give clearer cause-effect relationships are needed.

Conclusion

In this study, ceruloplasmin levels were found to be higher in obese patients in accordance with other studies in the literature and in addition to the results of these studies it was determined that ceruloplasmin levels decreased with weight loss. The results of the study suggest that ceruloplasmin may be a marker of obesity.

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Declarations

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No funding was done for this study.

Author contributions

Conceptualization, E.Y.; Methodology, E.Y. and I.S.; Software, E.Y. and I.S.; Validation, I.S.; Formal Analysis, E.Y.; Resources, E.Y. and I.S.; Data Curation, E.Y. and I.S.; Writing - Original Draft Preparation, E.Y.; Writing – Review & Editing, E.Y. and I.S.; Supervision, I.S.; Project Administration, E.Y.

Conflicts of interest

The authors declare no competing interests and no conflict of interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was approved by Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University approved our study (date: 25.05.2022/Decision No: 477) and it was carried out in accordance with the Helsinki Declaration principles.

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