

The Relationship between Serum Ferritin Level and Insulin Resistance in Metabolic Syndrome

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Introduction: Insulin resistance and metabolic syndrome (MetS) are risk factors for diabetes mellitus, and their prevalence is increasing. Ferritin has emerged as a biomarker of low-grade inflammation in addition to its role in iron metabolism. The study aims to determine the correlation between ferritin and insulin resistance (IR) in MetS.

Materials and Methods: In this study, ferritin, glucose (fasting), and HOMA-IR were measured from serum samples obtained from 98 MetS patients and 100 healthy volunteers. Serum ferritin, glucose, insulin, and HOMA-IR results were compared between the MetS and the control group. Correlation analysis was performed between ferritin and HOMA-IR in control and MetS patients.

Results: Serum ferritin (Control: 93,9±30,13; MetS:200±57,31 ng/ml), glucose (Control: 100,9±11,86, 123,9±21,52 ng/dl), insulin (Control: 4,11±2,57; MetS:15,99±5,71 µU/ml) and HOMA-IR (Control: 1,04±0,74; MetS:5,07±2,33) revealed to be higher in MetS compared to control. The correlation between serum ferritin level and HOMA-IR in MetS patients was revealed. This correlation was not found in the control group.

Conclusion: In MetS, high serum ferritin level increases insulin resistance. While the positive correlation of ferritin with insulin resistance occurs at high ferritin levels, this is not observed at low ferritin levels.

Keywords: Metabolic syndrome; glucose; insulin; HOMA-IR

Introduction

Metabolic syndrome (MetS) affects 20-25% of the adult population of the world and is recognized as an essential factor in the emergence of type 2 diabetes (DM), cancer, and cardiovascular disease (CVD) (1). MetS are characterized by clinical findings such as resistance to insulin, obesity of abdominal, hyperlipidemia, high blood pressure, and hyperglycemia (1, 2).

Ferritin is an essential molecule in regulating iron metabolism. This molecule, an intracellular protein, is a widely used biomarker to evaluate body iron stores (2). Conversely, the increase in iron stores is correlated with many health problems (2). Studies have reported that high ferritin levels are associated with dyslipidemia, hypertension, blood glucose levels, high fasting insulin levels, and abdominal adiposity (2, 3).

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The study aims to reveal the relationship between ferritin levels and HOMA-IR/fasting insulin resistance in MetS patients.

Materials and Methods

Ethical Statement

The Harran University Clinical Research Ethics Committee approved the study with the date of 30.03.2020 (decision no: HRU/20.06.24).

Study Design

Ninety-eight MetS who applied to the Internal Medicine Outpatient Clinic and 100 healthy individuals were included in the control. Metabolic syndrome was diagnosed when at least three National Cholesterol Education Program Expert Panel criteria were observed (4).

Participant Selection

Those with systemic diseases such as heart, kidney, and liver, endocrine abnormalities, such as thyroid diseases, clinical manifestations of hemochromatosis, serum ferritin >500 ng/ml, anemia (Hb<12 g/dl), blood transfusion in the last six months, iron or those with vitamin treatments, alcohol or drug abuse, any acute illness or existing inflammatory or infective disease evidence were excluded. All participants underwent a detailed clinical and physical examination. Anthropometric measurements were made according to Ozturk et al.' study (5).

Laboratory analysis

Blood samples from the patient and control groups were centrifuged at 2500 rpm for 15-20 minutes and stored at -80 °C until measurements were made. Ferritin, glucose, insulin, triglyceride, HbA1c, and HDL levels were measured in the Roche Cobas 8000 device using commercial kits. HOMA-IR fasting glucose was calculated using the insulin (6). BMI (body mass index) was calculated according to the method of Peterson et al. (7).

Statistical analysis

The data were analyzed using the SPSS v21. Mean, standard deviation, and percentages are given as descriptive statistics. The data were analyzed using Kolmogorov-Smirnov, t-test, and Mann-Whitney tests. Pearson r correlation test was performed because it showed normal distribution. The correlation coefficient was performed as described by Koo et al. (8). P-value<0.05 was considered significant.

Results

The demographic features (gender and age) of the control and patients participating in the study are given in Table 1. When the control and MetS were compared in terms of gender and age, there was no difference between them. Ferritin, glucose, insulin, HOMA-IR, triglyceride,

Table 1. Demographic characteristics of metabolic syndrome and control group

Variables	Control (n=100)	MetS (n=98)	P value
Age (years)	47.56±15.3	49.62±13.5	0.072*
Gender			
▪ Female	45 (57.7%)	45 (45%)	0.094**; $\chi^2=2.81$
▪ Male	33 (42.3%)	55 (55%)	
BMI	16.2±2.4	27.7±6	<0.0001*
HbA1c (%)	5.7±0.5	7.5±1.2	<0.0001*
Triglycerid (mg/dl)	112.3 ± 20.7	188.5±56.5	<0.0001*
HDL (mg/dl)	51.4±7.7	42.9±7.4	< 0.0001*
Ferritine (ng/ml)	93.9±30.13	200±57.31	<0.0001*
Glucose (mg/dl)	100.9±11.86	123.9±21.52	<0.0001***
Insulin (µU/ml)	4.11±2.57	15.99±5.71	<0.0001***
HOMA-IR	1.049±0.74	5.071±2.33	<0.0001***

*Unpaired t test; **Chi-squared test; ***Mann Whitney test; BMI; body mass index

HbA1c, and BMI were higher in MetS, while HDL was lower (Table-1 and Figure-1). A positive correlation was found between ferritin and HOMA-IR in MetS ($r=0.69$; $p<0.0001$) (Fig-2A). There was no correlation between ferritin and HOMA-IR in the control ($r=-0.024$) (Figure-2B). Ferritin and triglyceride ($r=0.19$; $p=0.059$), HbA1c ($r=-0.025$; $p=0.8$) HDL ($r=0.121$; $p=0.23$) and BMI ($r=0.1427$) was not correlated in the MetS group ($p=0.15$).

Discussion

In this study, serum ferritin and HOMA-IR were found to be increased in MetS patients. In addition, a positive correlation was found between increased ferritin levels and HOMA-IR in MetS patients. Significantly higher serum ferritin levels in metabolic syndrome have been reported in many studies (9, 10). In addition, It has been suggested that iron metabolism disorders in MetS affect hyperinsulinemia, insulin resistance, dyslipidemia, hyperglycemia, regional obesity, and hypertension (11). Our findings support these results. In this study, we

revealed that increased insulin resistance and high ferritin act together in MetS. We think that this finding will contribute to elucidating the pathophysiology of MetS.

In clinical studies in MetS patients, it has been suggested that the increase in ferritin correlates with the increase in insulin levels (12, 13). Iron metabolism affects liver functions. Accordingly, impaired iron hemostasis has been reported to be effective in the pathogenesis of insulin resistance and Type 2 diabetes (14). Serum ferritin concentration causes insulin sensitivity by affecting beta cell function (14). The molecular mechanism related to this issue has not yet been elucidated. Iron is a transition metal that catalyzes the formation of free radicals by causing oxidative damage in cells and tissues (15). Oxidative stress disrupts the oxidant-antioxidant balance and causes abnormal changes in intracellular signal transmission and gene expression. This can lead to pathological conditions such as insulin resistance (16). However, it has been reported

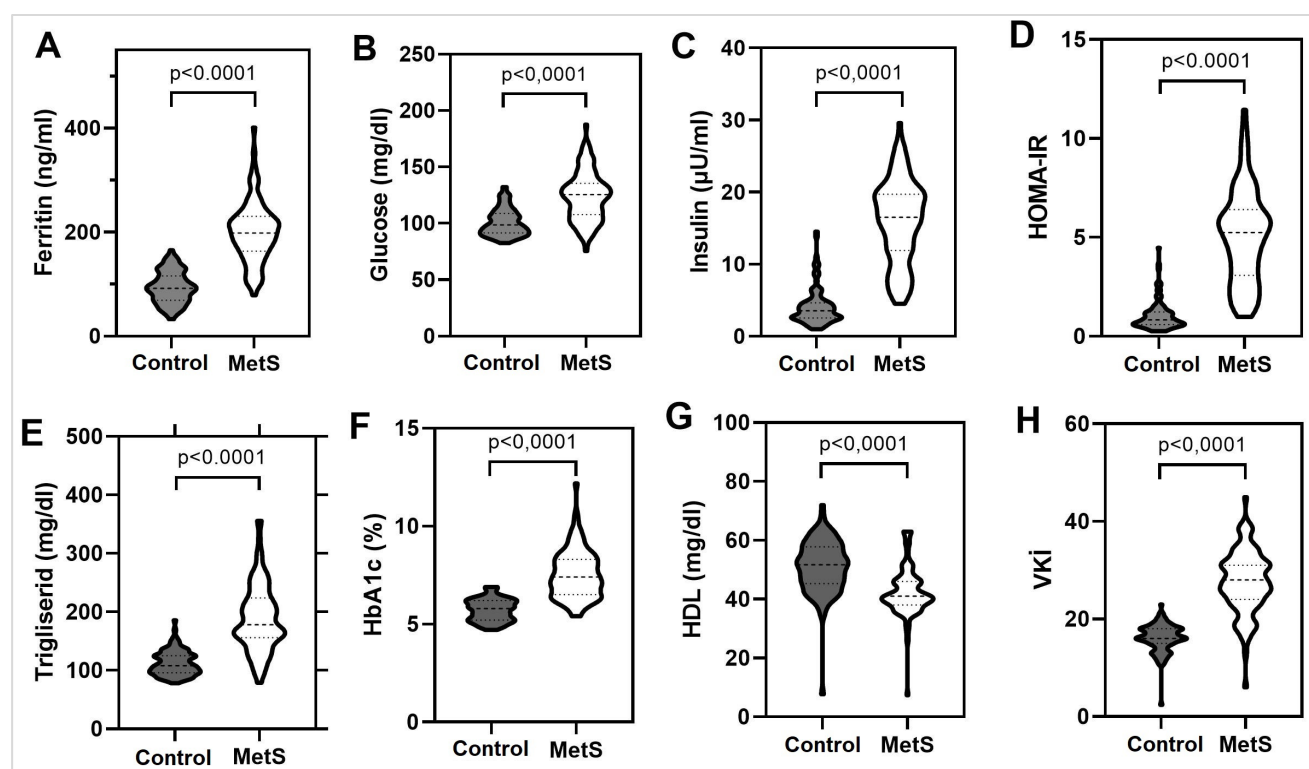


Figure 1. Serum ferritin (A), glucose (B), insulin (C), HOMA-IR (D), triglyceride (E), HbA1c (F), HDL (G), and Body mass index (H) in comparison of MetS and control groups

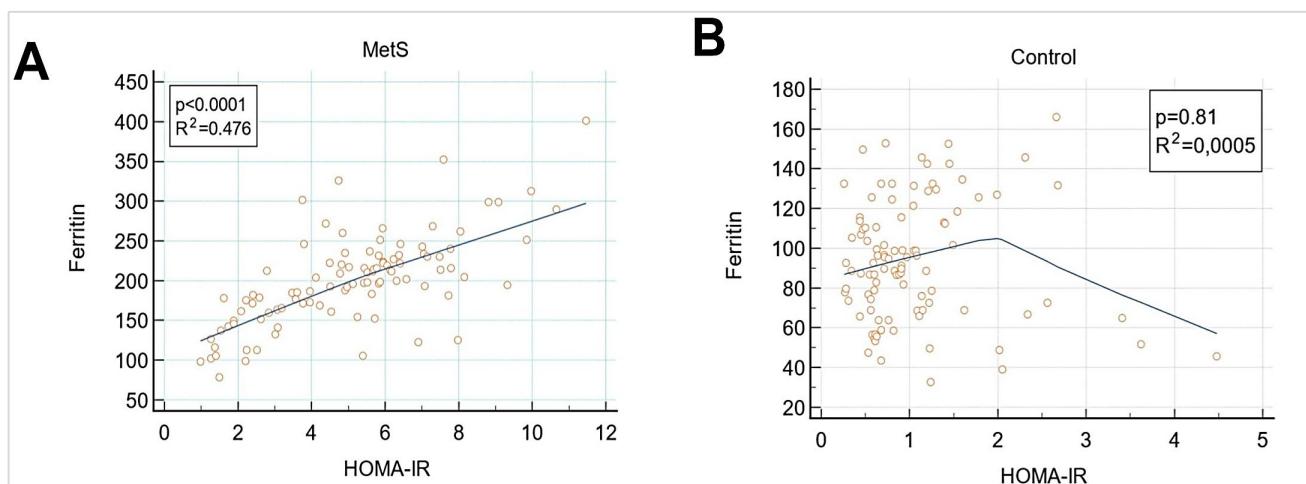


Figure 2. Correlation between serum ferritin level and HOMA-IR in MetS patients (A) and control group (B)

that an increase in ferritin levels can lead to chronic inflammatory reactions and increase body iron stores (17). Some cytokines involved in chronic inflammation are associated with the levels of NAD(P)H oxidase, which is a source of free radicals (18). An increase in NAD(P)H level increases oxidative stress. Increased oxidative stress activates intracellular signaling pathways that can produce products of cellular damage (18). Inflammation has been observed to regulate the expression and secretion of ferritin mRNA/protein levels. The increase in body iron stores produces hydroxyl radicals that lead to lipid peroxidation. This leads to DNA damage and tissue damage. Therefore, it has been suggested that the reason for the role of MetS in Type-2 DM and CVD is ferritin-mediated inflammation and oxidative stress (19). The increase in ferritin may affect insulin expression by affecting cytokine (20). However, there is not enough evidence on this subject. Further molecular studies are needed on this.

In this study, it was shown that there is a positive correlation between ferritin and insulin resistance in MetS patients. In addition, this effect was not found in healthy individuals. This was interpreted as high serum ferritin levels may cause pathological effects. Because it was found that there was no correlation between low serum ferritin levels and insulin resistance,

this finding demonstrates the effectiveness of ferritin-lowering treatment protocols in MetS.

The limitation of this study is that the drugs used by MetS patients were not questioned. The relationship between ferritin and metabolic syndrome components is not revealed.

Conclusion

The criteria used in diagnosing MetS largely overlap with the risk factors for Type 2 DM and CVD (20). Therefore, revealing the molecules involved in the pathophysiology of MetS is essential for diabetes and CVD. This study revealed the correlation between ferritin and insulin resistance in MetS patients. While there was no correlation between ferritin and insulin resistance in healthy individuals, a correlation was found in MetS patients. This situation reveals the importance of ferritin in MetS.

Conflict of Interest

The authors declare no conflict of interest for the present study.

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