

# Elevated Ferritin Levels and the Relationship with Fasting Insulin Levels in Elderly Patients with Metabolic Syndrome

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## Abstract

**Introduction:** Elevated serum ferritin levels are associated with insulin resistance, type 2 diabetes and metabolic syndrome (MetS) as well as systemic inflammation and cardiovascular disease. The associations between ferritin and hemoglobin levels with individual components of MetS are unclear. The aims of the study were 1) to compare the ferritin levels, and 2) to investigate the relationships between ferritin, high-sensitivity CRP (hs-CRP), fasting glucose, fasting insulin and homeostasis model assessment (HOMA-IR) levels in elderly patients. **Subjects and Methods:** Study population included 121 (mean age  $64.3 \pm 14.1$  yrs) (80 female, 41 male) elderly patients. The study population was evaluated for MetS by Adult Treatment Panel III (ATPIII). Demographic and biochemical data such as fasting insulin, hs-CRP, fasting glucose and ferritin levels were evaluated. Biochemical data were evaluated retrospectively. Insulin resistance (IR) was estimated using the HOMA. **Results:** Metabolic syndrome was diagnosed in 39 elderly patients (32.2%). In elderly patients with MetS, mean levels of ferritin, hs-CRP, fasting glucose, fasting insulin and HOMA were found to be  $72.9 \pm 33.1$  ng/ml,  $0.90 \pm 0.01$ ,  $99.1 \pm 20.1$  mg/dl,  $13.4 \pm 1.1$   $\mu$ U/l,  $3.0 \pm 0.1$ , respectively. However, mean levels of ferritin, hs-CRP, fasting glucose, fasting insulin and HOMA were found to be  $54.1 \pm 33.1$  ng/ml,  $0.67 \pm 0.1$ ,  $91.9 \pm 17.0$  mg/dl,  $8.4 \pm 2.7$   $\mu$ U/l,  $2.71 \pm 0.9$ , in the other elderly patients, ( $p = 0.0012$ ), ( $p = 0.70$ ), ( $p = 0.70$ ), ( $p = 0.003$ ), ( $p = 0.80$ ) respectively. Mean levels of ferritin were positively correlated with diastolic ( $r = 0.850$ ,  $p = 0.03$ ), systolic blood pressures ( $r = 0.700$ ,  $p = 0.02$ ), and fasting insulin ( $r = 0.444$ ,  $p = 0.003$ ) in elderly with MetS. **Conclusions:** Mean levels of ferritin were increased in elderly patients with metabolic syndrome. And also, ferritin levels were positively correlated with systolic and diastolic blood pressures as well as fasting insulin but not with hs-CRP levels in elderly patients with metabolic syndrome.

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## Keywords

**Metabolic Syndrome, Ferritin, Fasting Insulin, Elderly**

### 1. Introduction

Increasing life expectancy is a worldwide phenomenon and has led to a progressive increase in the proportion of elderly people [1]. Iron is one of the essential inorganic substances for normal body physiology [2]. However, iron overload may be associated with adverse health outcomes [3]. Elevated serum ferritin levels are associated with insulin resistance [4]-[6], metabolic syndrome (MetS) [7] [8] systemic inflammation [4] [5], type 2 diabetes [9], and cardiovascular disease [10]. The associations between ferritin and hemoglobin levels with individual MetS components are unclear. Increased body iron may contribute to insulin resistance through mechanisms related to both reduced extraction of insulin and impaired insulin secretion [11]. Many studies have shown that subclinical iron overload in nonpathologic conditions leads to insulin resistance and an increased risk of type 2 diabetes mellitus [11]-[16]. Previously, *Tuomainen et al.* [17] suggested that serum ferritin levels were correlated with fasting serum glucose and insulin concentrations. In a latter study, it was found that there were significant positive correlations between the levels of ferritin, homeostasis model assessment of insulin resistance (HOMA-IR) and  $\beta$ -cell function (HOMA%B) [18]. However, according to our knowledge there are no efficient studies evaluating the characteristics of ferritin, fasting glucose, fasting insulin and HOMA-IR levels in elderly patients with or without MetS. Therefore, the aims of the study were 1) to compare the ferritin levels, and 2) to investigate the relationships between ferritin, high-sensitivity CRP (hs-CRP), fasting glucose, fasting insulin and HOMA-IR levels in elderly patients.

### 2. Subjects and Methods

Study population consisted of 300 consecutive patients over fifty years of age referred to outpatient clinic of internal medicine department of Ege University Hospital from January 1st, 2014 to April 8th, 2014.

Subjects with neoplastic disease, history of chronic inflammatory disease, acute infectious disease, anemia, abnormal liver enzyme levels (aspartate aminotransferase, AST and/or alanine aminotransferase, ALT  $\geq 2.5 \times$  upper limit of normal value), increased serum creatinine ( $>1.4$  mg/dl) and also high serum ferritin levels ( $>800$  ng/ml) as well as high hs-CRP (greater than 1.0 mg/dl) levels were excluded. Finally 121 patients (mean age  $64.3 \pm 14.1$  yrs) (80 female, 41 male) were included in the study. All study population was evaluated for MetS by Adult Treatment Panel III (ATPIII) [19]. Anthropometric measurements were made in all subjects such as body weight (kg), body mass index (BMI, kg/m<sup>2</sup>) and waist circumference (cm).

Habitual alcohol consumption and smoking were inquired with the following two questions: "Do you drink alcohol at least once a month? Yes/ No". "Do you smoke? Yes/No". If the answer is *Yes*, smokers were classified into two categories as ex-smokers and non-smokers [20].

Demographic and biochemical data such as fasting insulin, fasting glucose and ferritin levels were evaluated, retrospectively. High-sensitivity CRP was determined by a chemiluminescent assay on the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum ferritin was determined by an ELISA (Diagnostic Systems Laboratories, Webster, TX, USA). Insulin levels were measured with chemiluminance. Insulin resistance was calculated using the HOMA-IR as described by Matthews *et al.* [21] as follows: fasting serum insulin ( $\mu$ U/mL)  $\times$  fasting serum glucose (mg/dL)/22.5.

The study was approved by local Ethics Committee and informed consent was taken from the participants before they were taken into the study.

### Statistical Analysis

Statistical analysis was performed using the SPSS for Windows (13.0) software package. Data were expressed as mean  $\pm$  standard deviation (SD). The groups were compared using the Mann Whitney test. Pearson correlation coefficients were calculated to identify associations of clinical variables.

### 3. Results

Metabolic syndrome was diagnosed in 39 elderly patients (32.2%). Elderly patients without MetS were accepted as control group. Of 39 patients with MetS, 11 (28.2%) had a history of cardiovascular disease, 19 (48.7%) had dyslipidemia, 14 (35.8%) had hypertension and 6 (15.3%) had type 2 diabetes mellitus. In the control group, 10 (12.1%) had a family history of cardiovascular disease, 24 (29.2%) had dyslipidemia, 29 (35.3%) had hypertension and 9 (10.9%) had type 2 diabetes mellitus. Patients with MetS had higher mean values of waist circumference, systolic and diastolic blood pressures than those of patients without MetS ( $p = 0.03$ ,  $p = 0.01$ ,  $p = 0.05$ , respectively).

Among patients with MetS, 21.1% were smokers and 13.7% informed alcohol consumption. However, 19.0% of control subjects were smokers and only 15.1% of them consumed alcohol ( $p = 0.65$ ,  $p = 0.90$ ) (Table 1).

In elderly patients with MetS, mean levels of ferritin, hs-CRP, fasting glucose, fasting insulin and HOMA were found to be  $72.9 \pm 33.1$  ng/ml,  $0.90 \pm 0.01$ ,  $99.1 \pm 20.1$  mg/dl,  $13.4 \pm 1.1$   $\mu$ U/l,  $3.0 \pm 0.1$ , respectively. Ferritin, hs-CRP, fasting glucose, fasting insulin and HOMA were found to be  $54.1 \pm 33.1$  ng/ml,  $0.67 \pm 0.1$ ,  $91.9 \pm 17.0$  mg/dl,  $8.4 \pm 2.7$   $\mu$ U/l,  $2.71 \pm 0.9$ , in the other elderly patients, ( $p = 0.0012$ ), ( $p = 0.70$ ), ( $p = 0.70$ ), ( $p = 0.003$ ), ( $p = 0.80$ ) respectively (Table 2).

Mean levels of ferritin were positively correlated with diastolic ( $r = 0.850$ ,  $p = 0.03$ ), systolic blood pressures ( $r = 0.700$ ,  $p = 0.02$ ), and fasting insulin ( $r = 0.444$ ,  $p = 0.003$ ) in elderly with MetS. However, there was no correlation between ferritin and hs-CRP levels in elderly with MetS ( $r = 0.450$ ,  $p = 0.06$ ). And also, mean levels of ferritin were positively correlated with HOMA ( $r = 0.775$ ,  $p = 0.02$ ) in control.

### 4. Discussion

Increasing life expectancy is a worldwide phenomenon and has led to a progressive increase in the proportion of

**Table 1.** Demographic and anthropometric characteristics of elderly patients with metabolic syndrome and control were shown.

Parameters	Metabolic Syndrome (n = 39)	Control (n = 82)	p
Age (years)	69.5 $\pm$ 21.1	61.1 $\pm$ 17.8	0.80
Smokers, (%)	21.1%	19.0%	0.65
Smoking pocket/year	9.1 $\pm$ 1.5	6.1 $\pm$ 0.9	0.70
Alcohol consumption, no (%)	13.7%	15.1%	0.90
Body weight (kg)	70.0 $\pm$ 14.8	66.0 $\pm$ 19.1	0.70
Body Mass Index (kg/m <sup>2</sup> )	30.4 $\pm$ 5.8	26.1 $\pm$ 9.8	0.95
Waist circumference (cm)	109.5 $\pm$ 23.1	81.2 $\pm$ 15.5	0.03*
Systolic Blood Pressure (mmHg)	145.0 $\pm$ 34.0	131.9 $\pm$ 27.1	0.01*
Diastolic Blood Pressure (mmHg)	69.9 $\pm$ 15.3	58.1 $\pm$ 14.8	0.05*

\*Reflecting significant difference at the level of  $p < 0.05$ .

**Table 2.** Biochemical characteristics of elderly patients with metabolic syndrome and control were shown.

Parameters	Metabolic Syndrome (n = 39)	Control (n = 82)	p
Fasting glucose (mg/dl)	99.1 $\pm$ 20.1	91.9 $\pm$ 17.0	0.70
Fasting insulin ( $\mu$ U/ml)	13.4 $\pm$ 1.1	8.4 $\pm$ 2.7	0.003
HOMA-IR	3.0 $\pm$ 0.1	2.71 $\pm$ 0.9	0.80
T-Cholesterol (mg/dl)	241.5 $\pm$ 35.1	206.8 $\pm$ 29.1	0.90
HDL-Cholesterol (mg/dl)	39.1 $\pm$ 10.7	41.8 $\pm$ 13.1	0.80
LDL-Cholesterol (mg/dl)	140.0 $\pm$ 21.0	131.9 $\pm$ 27.1	0.04*
Triglyceride (mg/dl)	138.1 $\pm$ 22.5	125.3 $\pm$ 31.8	0.001*
Hematocrit (%)	34.0 $\pm$ 3.1	35.1 $\pm$ 7.1	0.01*
Ferritin (mg/dl)	72.9 $\pm$ 33.1	54.1 $\pm$ 33.1	0.0012*
hs-CRP (mg/dl)	0.90 $\pm$ 0.01	0.67 $\pm$ 0.1	0.70

\*Reflecting significant difference at the level of  $p < 0.05$ .

elderly people within the population [1]. The prevalence of MetS in different regions depends on defining criteria. The unhealthy lifestyle which is defined by sedentary character of people and unhealthy diets is significantly associated with MetS [22]. The metabolic syndrome is directly related to the accumulation of visceral adiposity in middle age associated with overeating and a decline in exercise. It has been estimated that 15% to 20% of persons aged over 70 years have metabolic syndrome [23]. Among the elderly population, the prevalence of MetS was reported to be higher in Turkey (61.7%) [24]. Likewise, the prevalence of MetS in Turkish adults aged 40 years or over, currently standing at 53%, shows significant differences across geographic regions, being highest in the two southern regions and lowest in the Aegean region [25]. In the present study, we found that the frequency of MetS in elderly was 32.2%. This finding might be different from other studies due to nutrition and physical activity characteristics in our region.

Serum ferritin concentration is considered to be a good measure of body iron stores in healthy people [11]. Higher levels of ferritin at baseline were associated with the metabolic syndrome [26], hyperinsulinemia, high HOMA-IR, and low HOMA%B and with an increased prevalence of the MetS [27]. To previous knowledge, most common defect in patients with an earlier stage of damage induced by iron overload is liver mediated insulin resistance [28]. And also, *Haap et al.* [14] reported that reduced hepatic insulin extraction, resulting in hyperinsulinemia correlated with the degree of iron overload. In some studies, it has been shown that there are positive correlations between levels of serum ferritin and those of fasting glucose, insulin, and glycosylated hemoglobin [29]-[32]. An independent and significant positive association between higher plasma ferritin, and increased risk of developing type 2 diabetes has been reported in middle-aged and elderly adults [33]. In a recent study, it was found that, dyslipidemia, obesity, and insulin resistance might be important risk factors for higher serum ferritin levels in the elderly [34]. Furthermore, *Oshaug et al.* [35] have found that diastolic blood pressure was a significant predictor for serum ferritin levels. In another study, *Canturk et al.* [36] showed that there was an independent positive association between serum ferritin concentrations and markers of glucose homeostasis. In another study, *Salonen et al.* [37] reported that serum ferritin concentrations had a significant positive correlation with blood glucose, serum triglycerides, and serum apolipoprotein B concentrations, and an inverse correlation with serum HDL cholesterol. However, in the present study, we found that there were positive correlations between ferritin and some of metabolic syndrome components such as diastolic and systolic blood pressures as well as fasting insulin levels, but not with lipid levels in elderly with MetS. And also, we found a positive correlation between ferritin and HOMA-IR levels in the control group. Those findings showed that there was association between serum ferritin levels and insulin resistance in elderly with and without MetS.

Subclinical inflammation, which is usually observed in individuals with obesity and the metabolic syndrome, is associated with increased risk of type 2 diabetes [38]. And also, increased body iron may contribute to insulin resistance via chronic inflammation and oxidative stress [39]. In many studies [11] [40], it has been suggested that formation of hydroxyl radicals catalyzed by iron might be associated with incident diabetes. Because, highly active radicals could attack cell membrane lipids, proteins, and DNA and cause tissue damage. In addition, oxidative stress may impair insulin secretion and insulin extraction [39]. Based on the data from the study of *Sharifi et al.* [40], elevation in serum ferritin levels could be seen in pre-diabetes stage, before the occurrence of an overt diabetes mellitus. Likewise, *González et al.* [15], reported that MetS and insulin resistance are associated with elevated serum CRP and ferritin levels. However, to our findings, there was no statistically significant difference between the two groups with regard to hs-CRP levels. And also no correlations were found between ferritin and hs-CRP levels in elderly with and without MetS, probably because of sample size. Future studies are needed in the elderly patients with MetS.

In summary, mean levels of ferritin were increased in elderly patients with metabolic syndrome. And also, ferritin levels were positively correlated with systolic and diastolic blood pressures as well as fasting insulin but not with hs-CRP levels in elderly patients with metabolic syndrome.

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## Abbreviations

HOMA-IR = Homeostasis model assessment-insulin resistance;

LDL = Low-density lipoprotein;

HDL= High-density lipoprotein;

hs-CRP = High sensitivity C-reactive protein.