e-ISSN: 0976-822X, p-ISSN:2861-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(2); 166-172

Original Research Article

Association of Serum Ferritin Levels with Metabolic Syndrome in India

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Received: 10-12-2022/ Revised: 05-01-2023 / Accepted: 13-02-2023

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Conflict of interest: Nil

Abstract

Background: Iron can be stored and released by the common intracellular protein ferritin, which also serves as a buffer against iron overload and deficiency. Metabolic syndrome (MetS) characteristics have been linked to elevated serum ferritin concentrations. Serum ferritin concentrations vary widely by sex and ethnicity, and there is inconsistent evidence about the association between serum ferritin concentrations and MetS in Asian men and women. The prevalence of metabolic syndrome (MS), which affects 20–25% of adults worldwide, includes central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension. Insulin resistance, a common feature of metabolic syndrome, has been theorized to be a key factor in the association between MS and inactivity.

Aim: The present study was designed to explore the association of serum ferritin levels with metabolic syndrome and insulin resistance.

Material And Method: This case-control study was carried out in the Department of General Medicine with 50 instances of young adult metabolic syndrome in Group A and 50 cases of healthy, normal people in Group B. Patients with metabolic syndrome who were seen in the hospital's outpatient department made up the study population. According to the Adult Treatment Panel III (ATP III) criteria of the National Cholesterol Education Program, a person has a metabolic syndrome if at least three of the following symptoms are present. In agreement with the International Diabetes Federation (IDF), metabolic syndrome is described. Every study subject gave their written consent in accordance with the institutional ethics committee's rules and regulations. Patients who agreed to participate in the trial with their guardians' permission provided signed informed consent.

Results: There were 28 males amongst cases 27 males in controls while 22 and 23females amongst the case and control group respectively. the mean age was 33.48 ± 4.66 yrs. in patients with metabolic syndrome and 33.07 ± 4.49 yrs. amongst controls. It was observed that all 50 patients had 3 components, 43 patients had 4 components and 15 patients had all 5 components of metabolic syndrome. In metabolic syndrome group 12 (25.9) cases had History of Diabetes Mellitus, 20 (44.4) cases had History of Hypertension, 8 (18.5) cases History of Dyslipidemia, and 15 (33.3) cases had Family history of Metabolic syndrome while amongst the control group 2 (7.4%) had positive Family history of Metabolic syndrome. It was observed that serum ferritin was significantly increased amongst metabolic syndrome patient as compared to control group.

Conclusion: According to the findings, serum ferritin levels were considerably higher in metabolic syndrome sufferers compared to healthy persons in general. Comparing patients with 3, 4, and 5 components of the metabolic syndrome to controls, the association between

mean blood ferritin levels increased in a direct proportion to the number of components. A higher BMI is correlated with higher serum ferritin levels. Therefore, serum ferritin can be utilized as a clinical indicator of illness severity and a marker for the metabolic syndrome.

Keywords: Metabolic Syndrome, Serum Ferritin, Waist Circumference, Hypertension and Dyslipidemia.

Introduction

Elevated blood glucose, hypertension, abdominal obesity, and dyslipidemia are all characteristics of the metabolic syndrome (MetS), a complex constellation of metabolic disorders.[1] MetS has been linked to the emergence of diabetes mellitus, renal disease, and cardiovascular disease (CVD) in a number of studies.[2] A cluster of multiple cardiovascular risk factors known as the metabolic syndrome (MetS, Syndrome X, Insulin resistance syndrome, IRS) promotes atherosclerotic cardiovascular disease (ASCVD). It includes atherogenic dyslipidemia (more triglycerides, lower HDL-C), increased blood pressure and glucose levels, as well as prothrombotic and proinflammatory conditions. A complex web of metabolic variables known as metabolic syndrome increases the risk of diabetes by five times and cardiovascular disease by two times.[3]

The liver, heart, endocrine organs, and musculoskeletal system might have pathological changes as a result of iron, a required trace element that takes part in numerous biological oxidations and accumulates in tissue.[4,5] Increased iron accumulation may impact insulin production and secretion by the pancreas and impair insulin action in target tissues, according to several investigations in patients with hemochromatosis or hematologic disorders.[6,7] Iron can be stored and released by the common intracellular protein ferritin, which also serves as a buffer against iron overload and deficiency. It is crucial to identify iron shortage when using ferritin as a clinical biomarker to assess iron status. From infectious diseases and nutritional inadequacies to non-communicable diseases, India is going through an epidemiologic change and is now a burden on the entire world. Non-communicable disease is easily preventable, and the essence lies in their identification and reduction of them.[8] The hallmark of the management of non-communicable diseases (NCD) is Primary and Secondary prevention. The essence of prevention lies in risk factor identification and reduction.[9]

An increase in insulin secretion serves as a compensatory mechanism for a decrease in the tissue's sensitivity to the effects of insulin. According to a number of studies, significantly raised ferritin and iron levels are indicators of insulin resistance and are linked to an increased prevalence of metabolic syndrome. Increased endogenous iron reserves have been linked to the onset of insulin resistance syndrome (IRS), type 2 diabetes mellitus (T2DM), and glucose intolerance. There is accumulating evidence that even moderately higher iron reserves, as indicated by high-normal ferritin concentrations, are linked to diabetes. Iron overload causes oxidative damage to pancreatic beta cells.[10]

Studies have also shown a link between insulin resistance or MetS elements and high levels of acute phase reactant C-reactive protein (CRP), a sensitive marker of subclinical inflammation.[11,12]

Insulin resistance has also been linked to ferritin, another acute phase reactant.[13,14] Numerous investigations conducted in recent years to clarify the relationship between serum ferritin and MetS have shown inconsistent results among various racial and gender groups.[15,16] There are very few studies on serum ferritin and MetS in the Indian population. We sought to assess the relationship between serum ferritin and MetS in an Indian group.

Contrary to the current investigation, the majority of earlier analyses used blood ferritin levels to assess only the individual elements of the metabolic syndrome rather than the entire clustering illness.[17]

Material and Methods

This case-control study was carried out in the Department of General Medicine with 50 instances of young adult metabolic syndrome in Group A and 50 cases of healthy, normal people in Group B. Patients with metabolic syndrome who were seen in the hospital's outpatient department made up the study population. According to the Adult Treatment Panel III (ATP III) criteria of the National Cholesterol Education Program, a person has a metabolic syndrome if at least three of the following symptoms are present. In agreement with the International Diabetes Federation (IDF), metabolic syndrome is described. Every study subject gave their written consent in accordance with the institutional ethics committee's rules and regulations. Patients who agreed to participate in the trial with their guardians' permission provided signed informed consent.

Cases: Waist circumference: Using standardized methods, anthropometric measurements such as height, weight, and waist circumference were taken. The waist was measured by wrapping a measuring tape around it. Two readings of the patients' blood pressure were collected using a sphygmomanometer while they were lying on their right arms. Waist circumference of at least two of the following in South Asian individuals: >80 cm for women and >90 cm for men.

1. Triglycerides >150 mg/dl or a certain medicine cause hypertriglyceridemia.
2. Low HDL cholesterol: systolic blood pressure of 130 mmHg or higher, or treatment.
3. fasting plasma glucose less than 100 mg/dl, the use of a certain medication, or previous Type 2 diabetes diagnosis.

Controls: Normal healthy adults of 20 -40 years of age.

All subjects got thorough physical and clinical examinations after providing written informed permission. Their anthropometric data, such as height, weight, and waist circumference, were measured using accepted methods. The Spectrophometric Glucose Oxidase Per Oxidase (GOD-POD) method, which measures actual blood glucose enzymatically, specifically, accurately, and quickly, uses two ml samples of fasting serum and plasma.[18]

The automated Chemiluminescence Immunoassay system (CLIA) was used to assess serum ferritin levels. The non-competitive chemiluminescence immunoassay served as the basis for the methodology, which states that when a monoclonal biotinylated antibody, an enzyme-labeled antibody, and a serum containing native antigen are combined, there is no competition between the native antigen and the antibodies and no stearic hindrance, resulting in the formation of a soluble sandwich complex.[19]

Blood Sample Collection: The Spectrophometric Glucose Oxidase Per Oxidase (GOD-POD) method, which measures actual blood glucose enzymatically, specifically, accurately, and quickly, uses 2 ml fasting serum and plasma samples. We requested biochemical parameters. After centrifugation and serum separation, the

fasting lipid profile (FLP), which includes total cholesterol, TG, HDL, and LDL, was calculated using Roche reagents and an approved enzymatic method.

Statistical Analysis

Data entry was done in MS Excel data sheet for preparation of 'Master Chart.' Data analysis was done using Epi-info software. The categorical variables were assessed using Pearson chi-square. The test was considered significant only if the p value comes out to be less than 0.05.

Result

There were 28 males amongst cases 27 males in controls while 22 and 23 females amongst the case and control group respectively. The mean age was 30.42 ± 3.55 yrs. in patients with metabolic syndrome and 30.05 ± 3.36 yrs. amongst controls.

Table 1: Comparison of the diagnostic characteristics of cases and controls

		Cases	Control
Mean age		30.42 ± 3.55	30.05 ± 3.36
Gender	Male	28 (57.4)	27 (51.9)
	Female	22 (42.6)	23 (48.1)
Waist circumference	**Male**	93.12 ± 2.32	82.3 ± 3.1
	Female	95.18 ± 2.79	73.3 ± 3.4
Height (cm)		166.5 ± 4.58	160 ± 5.41
Weight (kg)		70.82 ± 6.17	68.5 ± 5.32
Mean BMI (m/kg2)		25.05 ± 1.729	23.1 ± 2.39
Systolic BP (mmHg)		139 ± 14.02	110 ± 11.3
Diastolic BP (mmHg)		77.2 ± 5.14	68 ± 5.1
Fasting glucose (mg/dl)		143.5± 57.04	84.1 ± 27.3
Cholesterol (mg/dl)		236.1± 68.7	176.2 ± 33.2
Triglyceride (mg/dl)		171.55 ± 59.5	136.2 ± 34.1
HDL (mg/dl)		33.62 ± 6.82	38.6 ± 5.49
LDL (mg/dl)		63.46 ± 14.52	58.1 ± 10.3
Serum ferritin(ng/ml)		295.03 ± 340.80	72.2 ± 55.6

It was observed that all 50 patients had 3 components, 43 patients had 4 components and 15 patients had all 5 components of metabolic syndrome. In metabolic syndrome group 12 cases had History of Diabetes Mellitus, 20 cases had History of Hypertension, 8 cases History of Dyslipidaemia, and 15 cases had Family history of Metabolic syndrome while amongst the control group 2 had positive Family history of Metabolic syndrome. It was observed that serum ferritin was significantly increased amongst metabolic syndrome patient as compared to control group. The mean serum ferritin was 295.03 ± 340.80 and 72.2 ± 55.6 ng/ml amongst metabolic syndrome patient and controls which was statistically significant but there was no statical significance when serum ferritin levels were compared amongst male and female patients with metabolic syndrome.

Table 2: Distribution of cases according to BMI

BMI	Metabolic syndrome	Control
Undernutrition (≤18.49)	0	2 (4.0%)
Normal (18.50-24.99)	11 (22%)	18 (36%)
Overweight (25.00-29.99)	33 (66%)	26 (52%)
Obese 1 (30.00-34.99)	5 (10%)	4 (8%)
Obese 2 (35.00-39.99)	1 (2%)	0
Total	50 (100)	50 (100)

Table 3: Serum ferritin level in grades of BMI

BMI	N	Mean	SD
18.50-24.99	11	166.53	136.13
25.0-29.9	33	265.33	278.03
30.0-34.9	5	326.55	235.68
35.0-39.9	1	1400.00	-
Total	50	295.0300	338.82772

It was observed that amongst cases mean serum ferritin with normal BMI (18.5 – 24.99) was 166.53 ± 136.13ng/ml, overweight BMI (25.0 – 29.99) was 265.33 ± 278.03 ng/ml, obese 1 BMI (30.0 – 34.99) was 326.5 ± 235.68 ng/ml and obese 2 BMI (35.0 – 39.99) was 1400ng/ml.

Discussion

In this analysis, we confirmed that there was a positive association between higher ferritin levels and the prevalence of MetS or MetS components in different sex groups. Halle M et al. 1997[20], reported 3.26 times higher risk for developing type 2 diabetes and 2.8 times higher risk for developing metabolic syndrome for individuals with the highest serum ferritin quartile compared with those of the lowest. Hämäläinen P et al. 2014[21], conducted a 6.5-year follow-up study on serum ferritin levels and development of metabolic syndrome and its components in Finnish adults. They found that the development of MetS in both men and women was associated with an increase in serum ferritin during a 6.5-year period. Conversely, resolution of hypertriglyceridemia in males and hyperglycemia in women over the same time period is linked with lesser increases in serum ferritin. Additionally, they noticed that serum ferritin levels and waist size were positively correlated in both sexes.

the study conducted by Young Suk Shim et al. 2017[22] mean BMI of the cases in first quartile of serum ferritin was 23.20 ± 0.07 kg/m^2, in second quartile of serum ferritin was 23.70 ± 0.07 kg/m2, in third quartile of serum ferritin was 24.16 ± 0.07 kg/m^2 and in fourth quartile of serum ferritin was 24.59 ± 0.08 kg/m^2.

Reactive oxygen species are produced when there is an excess of iron in the body. These species assault cell membranes, enhance lipid peroxidation, and cause DNA breakage and tissue damage. As a result, iron overload exacerbates IR by altering insulin receptor signaling, which impairs the liver's and muscles' ability to use carbs. The ATP III suggests using waist circumference rather than BMI as a measure of adiposity since abdominal obesity has a stronger correlation with metabolic risk factors and insulin resistance.[23,24]]

Liang Sun 2008[25] reported a strong positive association between elevated plasma ferritin concentrations and the risks of type 2 diabetes, impaired fasting glucose, and MetS among participants recruited from Beijing and Shanghai only. Studies in other areas of China had inconsistent or conflicting findings among Chinese men. One recent study by Park et al. 2012[26] reported that elevated serum ferritin levels were independently associated with future development of MetS during the 5-year follow-up period. The relationship between iron reserves and specific symptoms of the metabolic syndrome, such as hypertension, dyslipidemia, high fasting insulin and blood glucose, and central obesity, has been documented in a number of prior cross-sectional investigations.

Increased serum ferritin levels may be due to increased bodily iron reserves as well as systemic inflammation. Inflammation has

been observed to control the expression of ferritin's mRNA and protein levels as well as its release. Oxygen radicals created by excessive iron deposits lead to lipid peroxidation. DNA shatters as a result, causing tissue harm. Therefore, inflammation and oxidative stress, which are mediated by ferritin, are one of the pathways involved in the progression of MetS to CVDs and Type II DM.[27]

Indicators of insulin resistance and the prevalence of the metabolic syndrome were both raised by moderately elevated iron levels. When iron levels were only slightly raised, these relationships were clear. Prospective studies are required to ascertain if mildly raised iron stores precede the development of insulin resistance and contribute to the higher risk associated with it given the high prevalence of elevated iron stores, especially in older ages. Due to the small sample size and case-control design, our study is constrained. Longitudinal investigations are necessary to comprehend the ad hoc association between serum ferritin level and metabolic syndrome. As an acute-phase reactant, serum ferritin may increase in the context of inflammation. We made an effort to reduce this possible source by removing people who may have inflammation, infection, or liver illness. We cannot, however, rule out lingering confounding from further inflammatory diseases.

Conclusion

According to the findings, serum ferritin levels were considerably higher in metabolic syndrome sufferers compared to healthy persons in general. Comparing patients with 3, 4, and 5 components of the metabolic syndrome to controls, the association between mean blood ferritin levels increased in a direct proportion to the number of components. A higher BMI is correlated with higher serum ferritin levels. Therefore, serum ferritin can be utilized as a clinical indicator of illness severity and a marker for the metabolic syndrome. The progression of metabolic syndrome to Type II DM and other cardio metabolic derangements may be aided by these elevated serum ferritin levels. The pathophysiological mechanism of elevated ferritin levels in patients with insulin resistance syndrome has to be further studied.

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