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Original Article

Biochemistry Section

Association of Serum Ferritin Levels with Metabolic Syndrome and Insulin Resistance

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ABSTRACT

Introduction: The impact of CVDs and Type II DM is increasing over the last decade. It has been estimated that by 2025 their incidence will double. Ferritin is one of the key proteins regulating iron homeostasis and is a widely available clinical biomarker of iron status. Some studies suggest that prevalence of atherosclerosis and insulin resistance increases significantly with increasing serum ferritin. Metabolic syndrome is known to be associated with increased risk of atherosclerosis as well as insulin resistance.

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

Materials and Methods: The present study was prospective, cross sectional. The study protocol was approved by IEC. The study group consisted of 90 participants (50 cases of metabolic syndrome and 40 age and sex matched controls). Diagnosis of metabolic syndrome was done as per NCEP ATP III criteria. Estimation of serum Ferritin and Insulin was done by Chemiluminescence Immunoassay (CLIA) while Glucose by Glucose Oxidase and Peroxidase (GOD-POD) method. Insulin Resistance was calculated by HOMA IR score.

Statistical Analysis: Data obtained was statistically analysed by using student t-test.

Results: We found statistically significant rise in the levels of serum ferritin (p=<0.001), glucose (p=<0.001), insulin (p=<0.001) and HOMA IR score (p=<0.0001) in cases of metabolic syndrome as compared with controls.

Conclusion: High serum ferritin levels though within normal range are significantly associated with both metabolic syndrome and insulin resistance.

Keywords: HOMA-IR, Iron overload, Type II DM

INTRODUCTION

Over the last decade there has been a global transition in the disease pattern. The relative impact of infectious diseases is decreasing while chronic diseases like cardiovascular disease (CVD) and diabetes are increasing [1]. It has been estimated that the incidence of DM and CVDs will double by 2025 [2].

The metabolic syndrome (MetS, Syndrome X, Insulin resistance syndrome, IRS) is a constellation of several cardiovascular risk factors promoting atherosclerotic cardiovascular disease (ASCVD). It consists of an atherogenic dyslipidemia (i.e. elevated triglycerides, low high density lipoprotein cholesterol (HDL-C)), elevation of blood pressure and glucose, prothrombotic and proinflammatory states. Metabolic syndrome is a complex web of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes [3].

Asian Indians are at a high risk of developing diabetes and CVD and the number of cases are consistently increasing. Recent data show that about one third of the urban population in India's major cities has metabolic syndrome [4].

Iron has important role in the normal physiological functions of the human body. Ferritin, one of the key proteins regulating iron homeostasis, is a widely available clinical biomarker to evaluate iron status and especially important for detecting iron deficiency. However, growing evidence has shown that even moderately increased iron stores represented by high-normal ferritin concentrations- are associated with diabetes [5].

Hyperinsulinemia resulting due to insulin resistance is the most striking feature of type 2 diabetes. The commonest causes are obesity which leads to down regulation of insulin receptors or genetic susceptibility. Insulin resistance leads to decreased cellular uptake of glucose in the tissues which are totally dependent on insulin, leading to hyperglycaemia.

Some studies demonstrate the strong associations between ferritin concentrations, obesity and inflammation, that contribute to the development of type II diabetes. It is well known that metabolic syndrome is a major risk factor for development of type 2 diabetes, it is now necessary to establish the link between the serum ferritin levels and risk of type 2 diabetes. Most of the previous studies have evaluated only the individual components of metabolic syndrome with serum ferritin levels rather than the clustered condition of metabolic syndrome per se unlike this present study [6].

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

MATERIALS AND METHODS

This study was prospective, cross-sectional type. It was conducted between 1st March 2013 to 30th September 2013 in University Medical College with Tertiary care hospital. Study population was patients of Metabolic syndrome visiting outpatient department of the hospital. Metabolic syndrome was defined in accordance with National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria [7] if atleast three of the following components were observed:

1. Central obesity: Waist circumference >102cm for men or >88cm for women.
2. Hypertriglyceridemia: Serum triglycerides >150 mg/dl.
3. Low HDL cholesterol <40 mg/dl for men or<50 mg/dl for women.
4. Arterial hypertension >130/85mmHg or patients on antihypertensive treatment.
5. Hyperglycaemia: fasting plasma glucose ≥110 mg/dl.

Inclusion Criteria

Total 50 cases of metabolic syndrome of age above 30 years of both the gender were enrolled. Forty age and sex matched healthy controls were chosen [Table/Fig-1].

Exclusion Criteria

1. Cardiac, renal, hepatic and other systemic diseases,
2. Any endocrinological abnormalities like thyroid disorders, etc.

3. H/O or clinical evidence of haemochromatosis, Serum ferritin >500 ng/ml.
4. Anaemia (Hb below 12 g/dl).
5. H/O blood transfusion, iron or vitamin therapies in last six months,
6. H/O drug or alcohol abuse,
7. Any Acute illnesses or current evidence of infective, inflammatory diseases.

All participants after their written informed consent underwent detailed physical and clinical examination. Their anthropometric measurements like height, weight, waist circumference were measured using standard procedures and techniques. Two ml fasting serum and plasma samples used for measurement of blood glucose by spectrophometric Glucose oxidase per oxidase (GOD-POD) method which is enzymatic, specific, accurate and rapid method of measurement of true blood glucose [8].

Estimation of serum ferritin and insulin was done by using automated Chemiluminescence Immunoassay system (CLIA). The working principle was based on non-competitive chemiluminescence Immunoassay stating that upon mixing monoclonal biotinylated antibody, the enzyme-labeled antibody and a serum containing the native antigen, reaction results between the native antigen and the antibodies, without competition or stearic hindrance, to form a soluble sandwich complex [9].

Insulin Resistance (IR) calculated by Homeostasis model for assessment of Insulin Resistance HOMA-IR score [10]:

(IR=Fasting Glucose (mg/dl) x Fasting Insulin (mlu/ml)/405).

Ethics

Research protocol was approved from Institutional Ethics committee.

STATISTICAL ANALYSIS

Microsoft Excel 2007 was used to calculate Z-test for finding the statistical significance between the means of Serum Ferritin, Blood glucose, Serum Insulin and HOMA-IR score in cases and controls.

RESULTS

Group	Male (n=41)		Female (n=49)	
A) Control	18	44%	22	45 %
B) Cases	23	56%	27	55 %

[Table/Fig-1]: Gender distribution each group

[Table/Fig-1] depicts the gender distribution in our study population. We found slightly higher percentage of metabolic syndrome in male population as compared to female population.

Group	Ferritin (ng/ml) Mean±SD	Glucose(mg/dl) Mean±SD	Insulin(µU/ml) Mean±SD	HOMA-IR Mean±SD
A) Control	88.10 ± 12.65	88.2± 9.17	3.91 ± 2.87	1.04 ± 0.59
B) Cases	187.97 ± 35.95	118.43± 28.59	16.2 ± 8.49	4.90 ± 2.92
Z-value	12.13	6.90	7.78	9.02
Normal range	10-220	70-150	0.7-9	-
P-value	< 0.001	< 0.001	< 0.001	< 0.001

[Table/Fig-2]: Comparison of ferritin, glucose, insulin & HOMA IR score in both groups

[Table/Fig-2] depicts the Comparison of Ferritin, Glucose, Insulin & HOMA IR score in both groups. The values of Serum Ferritin, Plasma Glucose, Serum Insulin and HOMA IR score are found to be statistically significant high in cases of Metabolic Syndrome as compared with controls. (p-Value< 0.001).

DISCUSSION

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

The percentage of males in the group of cases of metabolic syndrome was slightly higher, 56% as compared with females of the same group, 55%. However, with the limited number of cases in the present study group, we cannot comment on the incidence of metabolic syndrome in our study setting.

The normal ranges for above assays at our set up are as follows:

- Serum Ferritin: 15-220 ng/ml (Males), 10-124 ng/ml (Females)
- Blood Glucose: Fasting: 70-110 mg/dl
- Serum Insulin: Adult (Normal): 0.7-9.0 µU/ml, Diabetic (Type II): 0.7-25µU/ml

The finding of present study clearly indicates statistically significant increased concentration of serum ferritin in metabolic syndrome, though in the normal range, on the higher side of normal. These higher levels of serum ferritin in cases are associated with statistically significant increase in plasma glucose level, serum insulin and increased HOMA-IR score in cases as compared with controls.

Halle M et al., 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 [11]. The studies also noted geographic, urban-rural differences for the prevalence of obesity, metabolic syndrome and diabetes. Several cross-sectional studies have previously examined the association between iron stores and individual components of metabolic syndrome like hypertension [12], dyslipidemia [13], elevated fasting insulin and blood glucose [14] and central adiposity [15]. However, in present study significant association of serum ferritin levels with metabolic syndrome per se was found.

First Author and Year	Country	Population	Age	Sample size	Method for Estimation of Ferritin	Ferritin Concentration ng/ml
Soto González 2006 [16]	Spain	Patients of the Endocrinoloy and Nutrition Service of Hospital	38	598	RIAa	With MetS: 133.9±141.1 With out MetS: 66.8±71.8
Bozzini, 2005 [17]	Italy	Verona Heart Project	58	479	NIAb	With MetS: 124 (111–138) Without MetS: 83 (73–94)
Choi, 2005 [18]	Korea	Welfare Centers of Seoul Metropolitan	72	959	EIAc	With MS: 74±2 Without MetS: 59±2
Leiva, 2013 [19]	Chile	Research program of Risk Factors for Cardiovascular Disease of Talca	57	155	EIAc	With MS: 72 (47–112) Without MetS: 55 (36–96)

[Table/Fig-3]: Results of different cross-sectional studies on ferritin levels and metabolic syndrome
Abbreviations used:
a: Radioimmuno assay
b:Nephelometric Immunoassay c:Electrochemiluminescence Inmmunoassay

[Table/Fig-3] depicts the results from different cross-sectional studies on serum ferritin levels and metabolic syndrome. They show significantly raised serum ferritin levels in the subjects having metabolic syndrome as compared with those without metabolic syndrome.

Hämäläinen P et al., conducted a 6.5 year follow-up study on serum ferritin levels and development of metabolic syndrome and its components in Finnish adults [20]. They observed increased in serum ferritin over a 6.5 year period was associated with development of MetS in both men and women. Whereas, lower increases in serum ferritin over the same timeframe are associated with resolution of hypertriglyceridemia in men and hyperglycaemia in women. They also observed a positive correlation between waist circumference and serum ferritin levels in both the genders.

Elevated serum ferritin levels might reflect systemic inflammation in addition to increased body iron stores. It has been observed that inflammation regulates expression of ferritin mRNA & protein levels and its secretion. Excessive iron deposits produce hydroxyl radicals which cause lipid peroxidation. This leads to DNA fragmentation and tissue damage. Therefore, one of the mechanisms involved in progression of MetS to CVDs and Type II DM is inflammation and oxidative stress mediated through ferritin [15].

LIMITATIONS OF THE STUDY

Our study is limited by the small sample size and confined by the cross-sectional nature. In order to understand the casual relationship between serum ferritin concentrations and metabolic syndrome, longitudinal studies are required.

Serum ferritin is an acute-phase reactant and may be elevated in the presence of inflammation. We attempted to minimize this potential source by excluding individuals with suspected inflammation, infection and liver disease. However, we cannot rule out residual confounding by other inflammatory conditions.

CONCLUSION

From the findings of our study we can conclude that metabolic syndrome is associated with significantly increased serum ferritin though in the normal limits. These reflects iron overload, which can lead to increase in blood glucose level due to insulin resistance as indicated by high HOMA-IR score. These increased serum ferritin levels may be one of the key elements that progresses the journey of metabolic syndrome to Type II DM and other cardio metabolic derangements.

Further studies are required to investigate the pathophysiological mechanism of increased ferritin levels in patients with insulin resistance syndrome.

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