

Association of Serum Ferritin Levels with Metabolic Syndrome in India: a Cross-Sectional Study

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ABSTRACT

Background: Metabolic syndrome is a known risk factor for various diseases including coronary artery disease and is associated with subclinical-inflammation. Various inflammatory markers have been evaluated in metabolic syndrome. However, the data evaluating serum ferritin in metabolic syndrome is sparse. The current study aims to evaluate the correlation between serum ferritin and metabolic syndrome.

Materials and methods: This cross-sectional study included 100 subjects with metabolic syndrome and 50 gender matched healthy controls.

Results: The mean age (SD) in study and control groups was 52.34 (7.64) and 48.36 (9.16) years, respectively. Majority were females in both groups (60% vs 52%). The mean (SD) HbA1c amongst study vs control was 8.26 (2.33) vs 5.10 (0.51); <0.0001. Mean (SD) serum iron and hsCRP were significantly higher in the study group (115.50 ±42.6 vs 65.741±9.16; p<0.001) and (6.33±4.87 vs 3.45±3.5; p<0.007) respectively. Mean serum ferritin level was significantly higher in the study group (123.9 vs 59.02; p<0.0001). A statistically significant correlation was found between serum ferritin and waist hip ratio, triglyceride, BMI and HOMA IR (r=0.49, p<0.0001; r=0.50, p<0.0001; r=0.47, p<0.0001 and r=0.54, p<0.0001 respectively). An inverse correlation was found between serum ferritin and serum HDL levels (r=-0.46, p<0.0001). Even after adjusting for age, serum ferritin levels were found to be significantly associated with metabolic syndrome Coeff (95% CI) -65.6 (-84.23, -46.98); p<0.0001.

Conclusion: Significantly higher levels of serum ferritin were found in metabolic syndrome, and a significant correlation with its components was seen. Therefore, serum ferritin may be used as a marker of inflammation for an early intervention.

Keywords: ferritin, metabolic syndrome, inflammation.

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INTRODUCTION

Metabolic syndrome (MetS) is a complex constellation of metabolic abnormalities, characterized by elevated serum glucose, hypertension, abdominal obesity, and dyslipidaemia (1). Various studies have generated evidence that MetS was associated with development of cardiovascular disease (CVD), kidney disease, and diabetes mellitus (2). Studies have also demonstrated an association between high levels of acute phase reactant C-reactive protein (CRP), a sensitive marker of subclinical inflammation, and insulin resistance or MetS components (3-6). Ferritin, another acute phase reactant, has also been shown to be associated with insulin resistance (7, 8). In recent years, many studies have tried to elucidate the association between serum ferritin and MetS, but have yielded conflicting results among different races and genders (9, 10). Data on serum ferritin and MetS in Indian population is very scarce. We aimed to evaluate the association of serum ferritin with MetS in a cohort from North India. □

MATERIAL AND METHODS

This cross-sectional study was conducted in a tertiary care teaching institute in North India. The study was approved by the institutional ethics committee and included 100 definite cases of MetS and 50 gender matched healthy controls.

Primary and secondary objectives

The primary objective of our study was to evaluate the levels of serum ferritin in subjects with MetS.

Our secondary objective was to assess the association between serum ferritin and various components of MetS in individuals of any gender aged over 20 who met three or more of the following criteria as per current guidelines (11):

1. waist circumference ≥ 40 inch in men and ≥ 35 inch in women
2. serum triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
3. HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in male subjects, < 50 mg/dL (1.29 mmol/L) in

female subjects, or treatment for this lipid abnormality

4. blood pressure (BP): systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension

5. fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

All subjects with renal, liver, GI disease, haematological disease history of fever, alcohol intake, iron or vitamin B12 therapy, pregnancy, delivery within the last six months were excluded from the study. Subjects with history of aspirin, steroid, statin, supplemental iron, vitamin were also excluded.

Details of all enrolled subjects were entered in a predesigned proforma, detailed history was taken and physical examination was done. Anthropometric measurements, including height (meter) and weight (kilogram), were made. Blood pressure was measured by aneroid sphygmomanometer with patient in supine position after five minutes of rest, and an average of three consecutive readings was done. Fasting blood glucose and lipid profile was analysed using a fasting venous sample of blood.

Fasting serum insulin levels were also measured. Homeostasis model assessment of insulin resistance (HOMA IR) was used to assess insulin resistance. Serum levels of ferritin, iron, transferrin saturation and high sensitivity (hs) CRP levels have been also measured.

Statistical analysis

Data was entered into Microsoft excel 2013 and analysed using SPSS version 20. Continuous variables were presented as mean and standard deviation. Association of two categorical variables was done using Chi-square test. Statistically significant differences between two means were analysed using Student's t test. Pearson's test was used to estimate the strength of the correlation between variables. A p-value of ≤ 0.05 was considered statistically significant. □

RESULTS

The baseline characteristics of the study and control group is described in Table 1. Subjects in the study and control groups had a mean age of 52.34 (7.64) and 48.36 (9.16) years, re-

TABLE 1. Baseline characteristics of study and control groups

Variables	Study (n=100)	Controls (n=50)	P value
Age (years)	52.34 (7.647)	48.36 (9.167)	0.02
Males n (%)	40 (40)	24 (48)	0.42
Body mass index (kg/m ²)	27.57 (2.71)	23.45 (67)	<0.001
Waist circumference (cm)	87.40 (4.789)	79.90 (4.908)	<0.0001
Waist hip ratio	0.98 (0.04)	0.89 (0.052)	<0.0001
Systolic blood pressure (mm Hg)	136.28 (12.5)	120.3 (8.3)	<0.0001
Diastolic blood pressure (mm Hg)	85.3 (7.2)	76.3 (6.4)	<0.001
Fasting blood sugar (mg/dL)	147.52 (53.56)	91.24 (4.88)	<0.001
Glycated haemoglobin	8.26 (2.33)	5.10 (0.51)	<0.0001
Fasting insulin (μ IU/mL)	11.01 (4.22)	7.37 (0.95)	<0.0001
HOMA IR	3.88 (1.92)	1.66 (0.21)	<0.0001
Total cholesterol (mg/dL)	184.76 (27.83)	173.30 (20.82)	<0.02
HDL cholesterol (mg/dL)	42.34 (10.54)	58.12 (7.90)	<0.0001
Triglycerides (mg/dL)	174.08 (60.38)	112.34 (20.06)	<0.001
Serum iron (μ /dL)	115.50 (42.6)	65.74 (19.16)	<0.001
Serum ferritin (ng/mL)	123.9 (61.74)	59.02 (17.78)	<0.0001
hs-CRP (mg/dL)	6.33 (4.87)	3.45 (3.5)	<0.007

Values mentioned as mean (SD) unless specified; HDL=high density lipoprotein;

hs-CRP=highly sensitive C-reactive protein

spectively. The majority of participants were females in both study and control groups (60% vs 52%). The various components of MetS, including BMI, waist circumference, BP, blood glucose, lipid profile, etc, were significantly higher in the study group versus controls. The mean (SD) levels of HbA1c amongst study versus control groups were 8.26 (2.33) vs 5.10 (0.51); $p < 0.0001$. The mean (SD) value of serum iron was also noted to be significantly higher amongst the study group as compared to the control group (115.50 ± 42.6 vs 65.741 ± 9.16 ;

$p < 0.001$). Also, baseline hs-CRP was found to be significantly higher in study versus control groups (6.33 ± 4.87 vs 3.45 ± 3.5 ; $p < 0.007$).

Regarding the primary outcome, the mean serum ferritin level was significantly higher in the study population as compared to controls (123.9 vs 59.02; $p < 0.0001$).

We found a direct statistically significant correlation between serum ferritin and waist hip ratio, triglyceride, BMI and HOMA IR ($r = 0.49$, $p < 0.0001$; $r = 0.50$, $p < 0.0001$; $r = 0.47$, $p < 0.0001$ and $r = 0.54$, $p < 0.0001$, respectively)

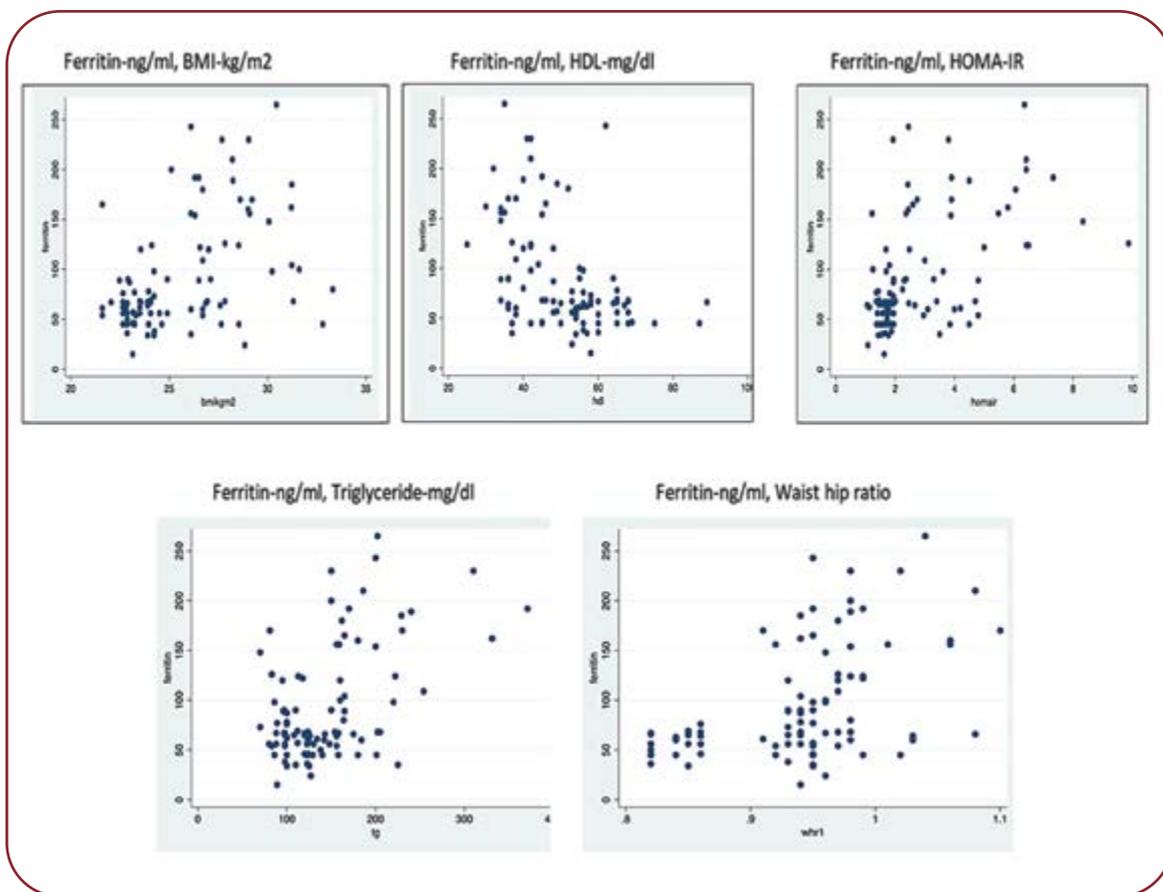


FIGURE 1. Scatter plot showing correlation between serum ferritin and waist hip ratio, triglyceride, BMI and HOMA IR

TABLE 2. Correlation of serum ferritin levels with parameters of metabolic syndrome

Variable	WHR (corr; p value)	HDL (corr; p value)	TG (corr; p value)	BMI (corr; p value)	HOMA IR (corr; p value)
Ferritin	0.49; <0.0001	-0.46; <0.0001	0.5; <0.0001	0.47; <0.0001	0.54; <0.0001

WHR=waist hip ratio; HDL=high density lipoprotein; TG=triglyceride; BM=body mass index; HOMA IR=homeostatic model assessment of insulin resistance

TABLE 2. Association of serum ferritin with metabolic syndrome after adjusting for age

Variable	Coeff (95% CI)	P value
Metabolic syndrome	-65.6 (-84.23, -46.98)	<0.0001
Age	--0.18 (-1.26, 0.90)	0.739

CI=confidence interval

(Figure 1). There was an inverse correlation between serum ferritin and serum HDL levels (r= -0.46, p<0.0001) (Table 2).

After adjusting for age as a potential confounder, serum ferritin levels were found to be significantly associated with MetS Coeff (95% CI) -65.6 (-84.23, -46.98); p<0.0001 (Table 3). □

DISCUSSION

The results of the current cross-sectional study suggest that serum ferritin is significantly higher in individuals with MetS. We also found a positive correlation between serum ferritin and components of MetS, including hypertriglyceridemia, BMI, waist hip ratio and HOMA-IR.

There was an inverse correlation between serum ferritin and serum HDL levels.

Various studies have evaluated the association between serum ferritin and MetS stratified by gender. Elevated serum ferritin was significantly associated with risk of MetS among the male gender after adjusting for other variables in a Chinese cohort; however, it was not significant among the females (12). A similar survey in Korea pointed to an increased risk of MetS in both male and female individuals with raised serum ferritin (10). Similar findings have been reported in a Chinese cohort where hypertriglyceridemia and elevated glucose were associated with serum ferritin among men (13). This gender difference in the association between SF and MetS was nullified in the present study, as the cohort were gender matched.

The association between serum ferritin and the components of MetS was found to be inconsistent in various studies. A prospective study conducted in Finland concluded that reduction in levels of serum ferritin was suggestive of resolving hypertriglyceridemia and hyperglycaemia (9). According to a recent meta-analysis, glucose and high triglyceride levels were two among the various components of MetS that were more strongly associated with serum ferritin levels (14). This finding is in agreement with our study, where hypertriglyceridemia and elevated HOMA-IR levels were found to be associated with serum ferritin.

Among other important components of MetS, BMI is considered to be an independent predictor of cardiovascular disease (15). Also, BMI, which is used to define obesity, has been found to be associated with increased serum ferritin levels (12, 15). Our study is in accordance with these findings.

The current study showed a statistically significant correlation between serum ferritin and waist hip ratio, triglyceride, BMI and HOMA IR, and an inverse correlation with serum HDL levels. Higher levels of iron deposits, as measured by the concentration of acute phase reactant such as serum ferritin and hs-CRP, have been also noted.

Although elevation of ferritin levels clearly seems to precede the development of diabetes, as demonstrated by various studies, its temporal relationship with MS is less clear (16-18). However, it seems that increased ferritin reflects both the involvement of inflammation, as CRP does, and independent actions of excess iron. It is known that increased accumulation of iron affects insulin synthesis and secretion in the pancreas, and interferes with the insulin-extracting capacity of the liver, thereby leading to peripheral hyperinsulinemia and impaired insulin secretion (19). Since insulin in turn stimulates cellular iron uptake by increasing the externalization of transferrin receptor, and may also stimulate the production of erythropoietin, a vicious circle leading to insulin resistance and diabetes may set in (18). □

CONCLUSIONS

The present study explores the correlation of serum ferritin with MetS, which is taking epidemic proportions owing to current lifestyle and food habits. Apart from various medications to treat individual components of MetS, monitoring and primary prevention is of utmost importance. Addition of an inflammatory marker, *i. e.*, serum ferritin, adds value to their available armamentarium to tackle the syndrome.

Elevated serum ferritin levels in patients with MetS tend to exhibit a certain degree of inflammation, which is likely to increase their risk of developing cardiovascular disease and/or diabetes. Thus, measuring serum ferritin concentrations might aid their evaluation as candidates for aggressive intervention against cardiovascular risk factors. However, prospective studies with long follow up are needed to determine whether raised serum ferritin precede the development of MetS and insulin resistance and contribute to the increased associated risk. □

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