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STUDY OF SERUM FERRITIN IN METABOLIC SYNDROME

General Medicine

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ABSTRACT

The metabolic syndrome consists of a constellation of metabolic abnormalities that confers increased risk of cardiovascular disease (CVD) and Diabetes mellitus (2). In cross-sectional studies, elevated ferritin levels have been associated with hypertension, dyslipidaemia, elevated fasting insulin and blood glucose and central adiposity (3). Elevated serum ferritin levels independently predicted incident of type 2 diabetes in prospective studies Serum ferritin may also be an independent determinant of poor metabolic control in the diabetic patient. Hence this study was taken up to see correlation of ferritin to metabolic syndrome and to evaluate the relationship between serum Ferritin & components of metabolic syndrome

MATERIALS AND METHODS: 100 patients of metabolic syndrome diagnosed as per National Cholesterol Education Program Adult Treatment Panel III (2001). - BMI, Waist hip ratio, waist circumference and BP were measured. Afer general and systemic examination Fasting Blood sugar, Post prandial sugar, Blood urea and serum creatinine, Fasting Lipid Profile, Baseline ECG, C-reactive protein, Urine routine/microscopy, Complete blood counts with peripheral blood smear,Fasting serum ferritin levels (immunoradiometric assay)

OBSERVATIONS -There were 62 males & 38 females with mean Age distribution of 58.02 ± 8.15year. Majority of patients (40%) were in their sixth decade of life. Mean BMI in our study was 29.50 (±1.837), 87 (87%) of patients had blood pressure recording of more than 135/85mmhg. Sixty six patients (66%) patients were known hypertensives on treatment., seventy five patients (75%) were known diabetics on treatment, 25 (25%) patients did not have history of diabetes.

46(46%) patients had abnormal total cholesterol (>200mg/dl), 72(72%) patients had abnormal triglycerides (>150mg/dl), 80(80%) patients had abnormal HDL (<40mg/dl in males, <50 in females). There were 35 (35%) patients with 3 components of metabolic syndrome, 37 (37%) with 4 components and 28 (28%) with 5 components of metabolic syndrome. Central obesity was increasing significantly with increasing number of components of metabolic syndrome $p<0.05$. dyslipidemia (TG) was increasing significantly with increasing number of components of metabolic syndrome $p<0.05$. Serum ferritin was increasing significantly with increasing number of components of metabolic syndrome with $p=0.05$. It also showed that individual components of metabolic syndrome had significant correlation with increasing number of components of metabolic syndrome

CONCLUSION -There is a positive association between elevated iron stores, measured by serum ferritin levels, and the prevalence of the metabolic syndrome.

2. Serum ferritin levels proportionally correlated with increasing number of components of the metabolic syndrome

KEYWORDS

Ferritin,metabolic syndrome,CV risk

INTRODUCTION

Metabolic syndrome is also known as metabolic syndrome X, Syndrome X, Insulin resistance syndrome, Reaven's syndrome (1). The metabolic syndrome consists of a constellation of metabolic abnormalities that confers increased risk of cardiovascular disease (CVD) and Diabetes mellitus (2). In cross-sectional studies, elevated ferritin levels have been associated with hypertension, dyslipidaemia, elevated fasting insulin and blood glucose and central adiposity (3). Elevated serum ferritin levels independently predicted incident of type 2 diabetes in prospective studies in apparently healthy men and women (4). The association between elevated iron stores and the metabolic syndrome, however, has been less well explored . Ferritin, a ubiquitous intracellular protein that is key in the regulation of iron homeostasis, is an accepted biomarker to evaluate body iron stores (5). Study by JM Fernandez et al(6) showing correlations among serum ferritin and diastolic blood pressure, HDL quotient, glucose suggest that serum ferritin could be a marker of the insulin resistance syndrome. Serum ferritin may also be an independent determinant of poor metabolic control in the diabetic patient. Hence this study was taken up to see correlation of ferritin to metabolic syndrome.

Aims and objectives

1. To study the relationship between serum ferritin & metabolic syndrome.
2. To evaluate the relationship between serum Ferritin & components of metabolic syndrome

MATERIALS AND METHODS:

100 patients of metabolic syndrome diagnosed as per National Cholesterol Education Program Adult Treatment Panel III (2001) from Sassoon general Hospitals Pune Maharashtra, satisfying both the inclusion and exclusion criteria as stated below. Study was done after obtaining ethical committee approval. A written informed consent was taken from every selected case. The study was conducted from December 2013 to June 2015.

Method of Collection of Data-

After initial screening, demographic details of the patient like patient identifier, age, gender, height, weight, smoking history, alcoholism history were recorded in case record form. Other relevant history like history of hypertension or diabetes, history of coronary artery disease (CAD), history of blood donation ,history of blood transfusion ,treatment for anaemia, history of jaundice or liver disease. BMI, Waist hip ratio, waist circumference were measured.Blood pressure was taken in a supine position after 5 min of rest General and systemic examination was done. All the patients have undergone following investigations: Fasting Blood sugar, Post prandial sugar, Blood urea and serum creatinine, Fasting Lipid Profile, Baseline ECG, C-reactive protein, Urine routine/microscopy, Complete blood counts with peripheral blood smear,Fasting serum ferritin levels (immunoradiometric assay)

Inclusion criteria:

All patients with metabolic syndrome as per NCEP ATP III (2001) criterion.

Exclusion criteria:

1. Anemic patents or those who received treatment for anemia in last 3 months
2. Patients who donated blood in last 4 months
3. Patients with hemochromatosis

4. Positive inflammatory markers (CRP> 1mg/dl, WBC>11,OOO/cu mm or WBC < 3000/cu mm)
5. Patients with hemolytic anemia
6. Patients with liver disease

Method of Statistical Analysis: Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients,

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

OBSERVATIONS

Table 1-Correlation of components of metabolic syndrome with Severity

Variables	Severity of Metabolic syndrome			P value
	3components (n=35)	4 components (n=37)	5 components (n=28)	
central obesity: waist circumference ≥ 102 cm in male , ≥ 88 cm in female	16 (45.7%)	30 (81.8%)	28 (100%)	<0.001(VHS)
dyslipidaemia:TG ≥ 150 mg/dl	19 (54.2%)	25 (67.6%)	28 (100%)	<0.001(VHS)
dyslipidaemia: HDL-C < 40 mg/dl (male), < 50 mg/dl (female)	18 (51.4%)	34 (91.9%)	28 (100%)	<0.001(VHS)
blood pressure ≥ 130/85 mmHg	27 (77.1%)	32 (86.5%)	28 (100%)	0.006 (HS)
fasting plasma glucose ≥ 100 mg/dl	32 (91.4%)	32 (86.5%)	28 (100%)	0.141 (NS)

The individual components of metabolic syndrome had significant correlation with increasing number of components of metabolic syndrome. Central obesity was associated with increasing number of components of metabolic syndrome with a significant p value of <0.001, dyslipidaemia (both triglycerides and HDL criteria) also showed similar correlation of statistical significance (p value of <0.001). Blood pressure also significantly correlated with a p value of 0.006 .blood sugars did not show statistical significance (p=0.141).

Table2 -Mean Serum ferritin ng/l according to Number of components of metabolic syndrome of patients studied

Components	Serum ferritin (ng/ml)		p value
	Mean	±SD	
3 components	114.4	42.39	
4 components	140.2	50.87	0.004 (Significant)
5 components	156.7	56.24	
ANOVA f = 5.858 df =2			

Mean serum Ferritin was increasing significantly (p 0.004) with increasing number of components of metabolic syndrome.

Table 3-Association of Gender and Components of Metabolic Syndrome

Components	Gender		Total	p value
	Male (%)	Female (%)		
3 components	28 (80.0)	7 (20.0)	35 (100.0)	
4 components	22 (59.5)	15 (40.5)	37 (100.0)	0.01 (Significant)
5 components	12 (42.9)	16 (57.1)	28 (100.0)	
Total	62 (62.0)	38 (38.0)	100 (100.0)	

χ^2=9.270 df= 2

In our study there were more males patients in 3 and 4 components subset of metabolic syndrome. 57% of 5 components patients were females.

Table-4 Association of Components of Metabolic Syndrome and BMI

Components	Mean	±SD	p value
3 components	28.6	1.49	
Components	Duration of DM (in years)		p value
5 components	29.9	1.98	
ANOVA f =6.897 df =2			

Mean BMI in patients with metabolic syndrome was increasing significantly.

Table5--Association of Triglycerides and Components of Metabolic Syndrome

Components	Mean	±SD	p value
	HDL (mg/dl)		
4 components	158.1	26.4	(Very Highly Significant)
5 components	182.9	23.0	
ANOVA f =15.994 df =2			

TG concentration in relation to components of metabolic syndrome .As the number of components increase, there is significant increase (p<0.001) in TG concentration.

Table-6-Association of HDL and Components of Metabolic Syndrome

	Mean	±SD	
3 components	40.6	6.0	
4 components	38.0	5.1	<0.013 (Significant)
5 components	36.6	5.1	
ANOVA f =4.568 df =2			

HDL concentration in relation to components of metabolic syndrome .As the number of components increase, there is significant decrease in HDL concentration.

DISCUSSION— AGE,**BMI,WHR** In a study conducted by Claudia et al (**9**) , the mean age distribution among study population was 58.7 years. In a study done by Bilgilli et al (10), mean age of the patients was 51.1±11.8year. Mean BMI in our study was 29.50 (±1.837) , with 75% of patients meeting criteria for central obesity according to NCEP ATPIII guidelines. All the patients had BMI > 25 Kg/m2. Mean BMI in patients with metabolic syndrome was increasing significantly(**Table2**) In a study conducted by Vasilis Tsimchodimos et al (**11**), mean BMI in study population was 29.1±3.4. In a study done by BilgilliSebel et al (10), all subjects of metabolic syndrome had BMI >25 Kg/m2. In a study conducted by M Sarah et al (**12**), The waist circumference for 56% participants was above the cut point. Of these participants, 28% met the criteria for metabolic syndrome, whereas only 1% of participants with a waist circumference below the cut point met the criteria for metabolic syndrome. They also concluded that waist circumference was a better predictor of metabolic syndrome than was BMI.

A Bener et al (**13**) in a study, compared WC - WHR- BMI, to identify the best predictor of metabolic syndrome among Qatari adult population. They concluded that WC followed by WHR was best parameter to predict metabolic syndrome. BMI had the lowest sensitivity and specificity in both genders.

HYPERTENSION- In our study 87 (87%) of patients had blood pressure recording of more than 135/85mmhg. Sixty six patients (66%) patients were known hypertensives on treatment.In a study done by Jing Wang et al (**13**), diastolic blood pressures were significantly high in males when compared with females. Our study did not show such correlation.

In a cross-sectional study conducted by Rantana O et al (14), the prevalence of metabolic abnormalities associated with arterial hypertension in individuals in the control and hypertensive groups ranged from 0.8 to 35.3%, respectively. Around 91.3% of the hypertensive patients had at least one associated cardiovascular risk

factor.

DIABETES MELLITUS- In the present study, seventy-five patients (75%) were known diabetics on treatment, 25 (25%) patients did not have history of diabetes. In a study done by Jing Wang et al (**13**) fasting blood sugar was significantly high in females when compared with males**.**

LIPID PROFILE- In our study, 46(46%) patients had abnormal total cholesterol (>200mg/dl), 72(72%) patients had abnormal triglycerides (>150mg/dl), 80(80%) patients had abnormal HDL (<40mg/dl in males, <50mg/dl in females)(**Table5,6**). In a study done by Jing Wang et al (13), HDL cholesterol was significantly high in females when compared to males.

In a study done by BilgiliSebel et al (**10**) metabolic syndrome patient had significantly higher BMI, waist and hip circumference, systolic and diastolic pressure, fasting glycaemia, two-hour postprandial serum glucose, total cholesterol, triglycerides, lower HDL cholesterol.

NUMBER OF COMPONENTS- The study population was categorized in to those having 3, 4 and 5 components of metabolic syndrome. Based on the serum ferritin levels in ng/l, they were divided into 5 quartiles as >50, 51-100, 101-150, 151-200 &>200(71).(**Table 1,2**)
There were 35 (35%) patients with 3 components of metabolic syndrome, 37(37%) with 4 components and 28 (28%) with 5 components of metabolic syndrome. In our study, we analysed the association of serum ferritin and other parameters of metabolic syndrome with each group containing 3, 4 and 5 components of metabolic syndrome.

SIGNIFICANCE---The present study revealed that Serum ferritin(**Table 2**) **-** was increasing significantly with increasing number of components of metabolic syndrome with p=0.05. It also showed that individual components of metabolic syndrome had significant correlation with increasing number of components of metabolic syndrome.

central obesity was increasingly associated with increasing number of components of metabolic syndrome with a significant p value of <0.001, dyslipidemia (both triglycerides and HDL criteria) also showed similar correlation of statistical significance (p value of <0.001). Blood pressure also significantly correlated with a p value of 0.006. However there was no significant association between fasting blood glucose and number of components of metabolic syndrome in our study. An explanation could be that in our study 75% of patients were known diabetics on treatment and majority of them falling in the group containing 4components and 5 components of metabolic syndrome.

In a study conducted by Claudia et al (**9**) , a higher concentration of ferritin was associated with the metabolic syndrome at baseline.

In a similar study conducted by Megan jehn et al (**15**) ,it was revealed that the highest prevalence of the metabolic syndrome occurred in those with higher levels of serum ferritin. Mean serum ferritin values in premenopausal women, postmenopausal women, and men were 33.6, 93.4, and 139.9 µg/l, respectively. Metabolic syndrome was more common in those with the highest compared with the lowest levels of serum ferritin in premenopausal women (14.9 vs. 6.4%, P = 0.002), postmenopausal women (47.5 vs. 28.2%, P < 0.001), and men (27.3 vs. 13.8%, P < 0.001). Insulin resistance also increased across quartiles of serum ferritin for men and postmenopausal women and persisted after adjustment for age, race/ethnicity, C-reactive protein, smoking, alcohol intake, and BMI. The prevalence of elevated blood pressure, elevated plasma glucose, elevated triglycerides, and abdominal adiposity all increased significantly with increasing serum ferritin. The prevalence of elevated triglycerides and abdominal adiposity also increased with increasing levels of serum ferritin. The greater the number of metabolic syndrome components present, the greater was the serum ferritin level. The results of this study were similar to our observations.

A study by Liang Sun et al (**19**), Median ferritin concentrations was 155.7 ng/ml for men and 111.9 ng/ml for women .They concluded that Elevated circulating ferritin concentrations were associated with higher risk of type 2 diabetes and metabolic syndrome in middle-aged and elderly Chinese independent of obesity, inflammation, adipokines, and other risk factors.

A study conducted by Vasilis tsimchodimos et al (**11**) revealed that patients with metabolic syndrome exhibited increased concentration of serum ferritin compared to control group supporting our findings.

Study by Istvan et al(**7**), showed that the incidence of metabolic syndrome was increased in men & both pre and post menopausal women, among those with higher serum ferritin levels. Ferritin levels also correlated with increasing number of components of metabolic syndrome. They also observed that individual components of the metabolic syndrome correlated well with increasing number of components of metabolic syndrome. This is the first prospective study associating ferritin and transferrin with the metabolic syndrome and its components.

M ledesma et al did a Cross sectional study in 3386 male Spanish adults between the ages of 19-65 year, Metabolic syndrome prevalence was 27.1%. They found a positive association between elevated iron stores, measured as serum ferritin concentration, and metabolic syndrome. Participants within the highest serum ferritin quintile had a higher risk than those in the lowest quintile for central obesity, hypertriglyceridemia , and metabolic syndrome. The association was non-linear and occurred at serum ferritin concentrations above 100 µg/L. Ferritin was also associated with insulin resistance, measured by HOMA-IR suggesting that ferritin could be an early marker of metabolic damage in the development of metabolic syndrome (**16**).

S Seo et al examined 280 postmenopausal women who visited the health promotion center of hospital for a routine health checkup. The proportion of postmenopausal women with metabolic syndrome and coronary atherosclerosis in the highest ferritin quartile was significantly higher compared with that in the lowest quartile. Serum ferritin levels were independently associated with the presence of metabolic syndrome and coronary atherosclerosis, after adjusting for confounding factors (**17**). . Median levels of serum ferritin were significantly higher in men compared with women (121.9 vs. 51.0 ng/ml, P < 0.001), and significantly lower in non metabolic syndrome population with Metabolic Syndrome population (73.2 vs. 106.0 ng/ml, P < 0.001).(**20**)

In a study conducted by L Han et al Ferritin concentrations were higher in men than women. Elevated ferritin concentrations were associated with higher body mass index, waist circumference, lipids, insulin, glucose . Elevated concentration of ferritins was significantly related with higher risk of metabolic syndrome, obesity, overweight and diabetes among men, but not among women. There was a gender difference in associations between ferritin and Metabolic Syndrome, obesity, and diabetes in Chinese adults according to L Han et al in their study. (**21**). We did not such gender differences in our study(**Table 3**). Further evaluations of the variation in gender on these associations are warranted to understand the mechanisms behind gender differences.

Similarly, many epidemiological studies have reported statistically significant associations of body iron with diabetes, although results from all studies are not entirely consistent.
Sun et al (2012),(**20**) in a prospective study in China, a country with the largest diabetic population in the world, an almost twofold increased risk of type 2 diabetes was observed among middle aged and elderly persons in the highest quintile of ferritin level compared with those in lowest after adjusting for known risk factors including high sensitivity C reactive protein (hsCRP), BMI, γ-glutamyl transferase (GGT), and adiponectin . .

In a case cohort study by Montonen et al, (2012) (**18**) ,among 27,548 participants of the EPIC Postdam study in Germany, the sTFR-ferritin ratio was significantly inversely related to the risk of type 2 diabetes, and ferritin concentration was associated with higher risk . The result was independent of biomarkers of inflammation, hepatic fat, IR, and dyslipidemia. In evaluating these studies, a few considerations must be borne in mind. In epidemiological studies investigating the relation between iron and diabetes, serum ferritin is the most commonly used indicator of body iron stores. As mentioned in the introduction, the use of ferritin in assessing body iron stores has been somewhat challenging because ferritin can be elevated in inflammation, cancer, and liver disease (Wang et al., 2010)(8).

CONCLUSION

1. There is a positive association between elevated iron stores, measured by serum ferritin levels, and the prevalence of the metabolic syndrome.

2. Serum ferritin levels proportionally correlated with increasing number of components of the metabolic syndrome

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