ABSTRACT: BACKGROUND AND OBJECTIVES: The metabolic syndrome is a cluster of risk factors for cardiovascular disease (CVD). The present study was aimed to know the relationship between serum ferritin and metabolic syndrome and to evaluate its relationship with individual component of metabolic syndrome. METHODOLOGY: The present study was conducted in the Department of Medicine, SS Institute of Medical Sciences and Medical Research Centre, Davangere during the study period from January 2014 to December 2014. Based on NCEP ATP III criteria, 100 cases with metabolic syndrome were enrolled. Serum ferritin was measured on fasting blood samples using radio-immunoassay. RESULTS: In this study, male preponderance was noticed. The most common age group was 51 to 60 years (30%) and overall, the mean age was 55.84±15.04 years. The commonest component of metabolic syndrome was hypertension 88%. Lipid abnormalities revealed raised serum cholesterol, LDL, TG and low HDL among 61%, 15%, 86% and 81% respectively. Results of the present study showed serum ferritin was elevated significantly in individual components of metabolic syndrome (Hypertension, waist circumference, low HDL levels) though serum ferritin were elevated in patients of FBS and Triglyceride abnormality, but it was of statistically insignificant. CONCLUSION AND INTERPRETATION: Serum ferritin as a marker of metabolic syndrome was inconclusive but was raised significantly in individual components of metabolic syndrome.

KEYWORDS: Lipid abnormalities; Metabolic syndrome; Serum ferritin.

INTRODUCTION: The metabolic syndrome is a cluster of risk factors for cardiovascular disease (CVD), including obesity, hypertension, elevated triglycerides and low levels of HDL Cholesterol. It is a burgeoning global problem. Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America. Mets is also considered an emerging epidemic in developing East Asian countries including China, Japan, and Korea. The prevalence of metabolic syndrome may range from 8 to 13% in men and 2 to 18% in women depending on the population and definitions used.

The clinical manifestations of this syndrome may include hypertension, hyperglycemia, hypertriglyceridermia, reduced high-density lipoprotein cholesterol (HDL-C), and abdominal obesity. Abundant data suggest that patients meeting these diagnostic criteria have a greater risk of having significant clinical consequences, the two most prominent and dreaded of which are the development of coronary heart disease and diabetes mellitus (DM). It also increases risk of stroke, fatty liver disease, and several cancers. Initial laboratory studies in patients suspected of having metabolic syndrome include standard biochemical parameters to assess for hyperglycemia, renal dysfunction and lipid studies to assess for hypertriglyceridermia or low HDL levels.
Obesity and insulin resistance are considered central to the pathophysiology of this metabolic and cardiovascular syndrome.\textsuperscript{8} several studies have observed a positive association between elevated iron stores, measured by serum ferritin levels, and the prevalence of the metabolic syndrome. Studies have also reported positive correlation of ferritin levels with individual components of the metabolic syndrome, particularly serum triglycerides and plasma glucose, as well as markers of insulin resistance.\textsuperscript{9,10}

There is increasing evidence that moderately elevated body iron stores, below levels commonly found in genetic hemochromatosis, may be associated with adverse health outcomes. Elevated serum ferritin levels independently predicted incident type 2 diabetes in prospective studies in apparently healthy men and women.\textsuperscript{11,12} Although the mechanisms for the potential effect of iron on the risk of metabolic syndrome are unclear, it has been hypothesized that elevated iron stores may interfere with hepatic insulin extraction leading to peripheral hyperinsulinemia.\textsuperscript{13,14} Others have suggested that iron may catalyze the formation of hydroxyl radicals, which contribute to the development of insulin resistance.\textsuperscript{15,16}

The association between elevated iron stores and the metabolic syndrome, however, has been less well explored.\textsuperscript{10} However, there are very few studies done in this area especially in India. Hence, the present study was undertaken to know the relationship between serum ferritin and metabolic syndrome and to evaluate the relationship between serum ferritin and individual component of metabolic syndrome.

**METHODOLOGY:** The present one year cross sectional study was conducted at Department of Medicine, SS institute of medical sciences and Medical Research Centre, Davangere a tertiary care center over a period from January 2014 to December 2014. Prior to the commencement, the ethical clearance was obtained from the Ethical and Research Committee, SS institute of medical science and research center.

Considering the prevalence of metabolic syndrome as 50% a total of 100 patients with metabolic syndrome were selected for the study. Patients with metabolic syndrome were diagnosed as per National Cholesterol Education Program satisfying at least three of the criteria that is, central obesity [Waist circumference $\geq 102$ cm or 40 inches (male), $\geq 88$ cm or 36 inches (female)], dyslipidaemia [$T G \geq 1.695$ mmol/L (150mg/dL); $H D L - C < 40$ mg/dL (male), $< 50$ mg/dL (female)], blood pressure($\geq 130/85$ mm Hg) and fasting plasma glucose [$\geq 6.1$ mmol/L (110 mg/dL)] were selected for the study. Patients with anaemia, received treatment for anemia in last three months, hemolytic anemia, donated blood in last four months and positive inflammatory markers (WBC$>11,000$/mm$^3$ or WBC$<3000$/mm$^3$) were excluded from the study. All the patients fulfilling selection criteria were explained about the purpose of study and a written informed consent was obtained to participate in the study before enrollment.

Before the enrollment, demographic data such as age, sex, occupation, history regarding hypertension, diabetes mellitus and complications, cerebrovascular events viz, angina pain, myocardial infarction, ischemic disease were recorded.

A thorough physical examination such as anthropometry, vitals and systemic examination was conducted. These findings were recorded on a predesigned and pretested proforma.
A thorough clinical examination was conducted. Height and weight was recorded and body mass index was calculated. Body mass index in the range of less than 18.5 kg/m² were considered as underweight, 18.5 to 24.9kg/m² were considered as normal, 25.0 to 29.9 kg/m² were considered as overweight and more than 30 kg/m² were considered as obese. The waist circumference was measured using a standard measuring tape in cms. Waist circumference of ≥102 cm or 40 inches (male), ≥88 cm or 36 inches (female) was considered as abnormal. Investigations such as fasting blood sugar and lipid profile (total cholesterol, triglycerides, HDL, LDL) levels were done and the findings were recorded. Further these findings were interpreted according to NCEP ATP III criteria.¹⁷

Serum ferritin was measured on fasting blood samples using radio-immunoassay.¹⁸ The serum ferritin levels between 18.7 to 323 ng/mL for 18 to 30 years and 16.4 to 294 ng/mL for 31 to 60 years for males were interpreted as normal and 6.9 to 282.5 ng/mL in premenopausal and 14.0 to 233 ng/mL in post-menopausal in women were considered as normal.

**STATISTICAL ANALYSIS:** The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and comparison was done by student ‘t’ test. A probability value (‘p’ value) of less than or equal to 0.05 was considered as statistically significant.

**RESULTS:** Patients age ranged from 18 to 70 years. Maximum number of cases were in the age group of 51 to 60 (30%) and 21 cases were in the age group of 61 to 70(21%). Average age at presentation was 55.84±15.04 years. Majority of the patients were in 5th and 6th decade. Out of 100 patients 58(58%) were males and 42 patients (42%) were females, accounting a ratio of male to female was 1.38:1 suggesting male preponderance.

The commonest component of metabolic syndrome was hypertension 88%, followed by triglyceridemia 86%, low HDL 81%, fasting blood sugar 79%, waist circumference 73%. Majority of the patients were having hypertension, triglyceridemia and low HDL levels. 43% patients had metabolic syndrome with four components and 32% had five components. However 25% of the patients were noted with three components of metabolic syndrome (Graph 1).
The duration of hypertension was between 6 to 10 years in 40.96% patients and the overall mean duration was 9.68±8.52 years. The duration of type 2 diabetes mellitus was between 6 to 10 years in 30 patients and the overall mean duration was 9.52±9.52 years. Majority of patients with BMI between 25 to 29.99 Kg/m² were observed 72% followed by 19% between 18.5 to 24.99 Kg/m². Majority of the patients had waist circumference abnormality 73% and was normal in 27%. 83% of the patients were known hypertensive, 5% were newly detected, 12% of the patients were with normal blood pressure. 60% of the patients were known diabetic, 19% of patients were having FBS abnormality, 21% had no FBS abnormality. The lipid profile revealed raised serum cholesterol, Triglycerides, and low levels of HDL in patients of metabolic syndrome constituting a percentage of 39%, 86% and 81% respectively. LDL was elevated in 15%.

Serum ferritin was elevated in 43%, normal in 49% and below normal in 8% (Graph 2).

Patients with three components of metabolic syndrome elevated serum ferritin abnormality was seen in 14(56%), in 9(36%) it was within normal limits and in only 2(8%) it was below normal. In patients with 4 components the elevated serum ferritin was seen in 20(46.51%), normal in 20(46.51%), and below normal in 3(6.98%). In patients of all five components of metabolic syndrome elevated was seen in 9(28.13%), normal in 20(62.5%) and below normal in 3(9.38%). It was observed that in 43 patients serum ferritin levels were elevated, in 49 patients it was within normal limits and in 8 it was below normal.

Among 73 patients with abnormal waist circumference serum ferritin was elevated in 26(35.6) normal in 41(56.16%) below normal in 6(8.2). Of the 88 patients with hypertension, serum ferritin was elevated in 43(48.86%) normal in 37(42.05%) below normal in 8(9.0%). Among the 79 patients with abnormal FBS 30(37.9%) had elevated levels, 43(54.4%) had normal levels, 6(7.59%) had below normal levels. Out of 86 patients of triglyceridemia 38(44.19%) had elevated levels, 42(48.8%) had normal levels, 6(6.98%) had below normal.
In patients with HDL abnormalities (81%), 30 (37%) had elevated levels, 44 (54.3%) had normal levels, 7 (8.6%) had below normal levels (Table 2).

In patients with three components of metabolic syndrome, as well as four components, the mean serum ferritin levels were elevated in both males/females (Table 3).

The mean systolic blood pressure, diastolic blood pressure, FBS, triglycerides, low HDL abnormality was seen in 43 patients with elevated mean serum ferritin levels (Table 4).

**DISCUSSION:** In the present study 83% of patients were known hypertensive, 5% were newly detected, and remaining 12% were with normal blood pressure. The mean SBP was 143.48±14.25 mm Hg and DBP was 89.92±7.57 mm Hg. In the CURES-34 study[^19] done in Chennai, India, 430 subjects diagnosed with metabolic syndrome by the ATPIII criteria had raised blood pressure, which was seen in 31.2% (Males, 35.3% and females, 27.6%). A study[^20] of metabolic syndrome in Asian Indians, all the individual components of metabolic syndrome increased significantly with age, elevated blood pressure (63.1%) was the commonest abnormality observed.

In our study 60% of patients were known type 2 diabetes mellitus, 19% were newly detected. Out of 60% with known diabetes mellitus 50% had duration of diabetes mellitus ranged between 6 to 10 years. Overall, the mean duration of diabetes was 9.52±9.52 years. An Indian study[^20] the high prevalence of Diabetes and Hypertension, is supported by the fact that Diabetes and Hypertension have been found to be more widely prevalent in South Asians, thus, conferring a large and very real risk of adverse cardiovascular events and other attending complications. The possible explanations for this inordinately high prevalence can be attributed to a high prevalence of obesity, insulin resistance and a body fat structure that favors the development of metabolic syndrome, Diabetes and Hypertension[^21,22].

In the present study the waist circumference was abnormal in 73% of patients and 27% had normal waist circumference. The mean waist circumference was 96.78±7.33 cms. Another study[^23] done in Taiwan according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel III criteria, waist circumference abnormality was seen in 40% in 11411 adults. This sharp contrast in our study and study reported by Taiwan group may be because of number of patients in study group. Study done[^24] in China showed Waist circumference (WC) and body mass index (BMI) were good markers for MetS, WC was a good marker for T2DM and dyslipidemia, and BMI was a good marker for hypertension. The optimal BMI cut-off value of MetS was 24 kg/m², and the optimal WC cut-offs were 86 cm and 78 cm in men and women, respectively. Regional body fat distribution has an important influence on metabolic and cardiovascular risk factors. Increased abdominal (visceral) fat accumulation is a risk factor for coronary artery disease (CAD), dyslipidemia, hypertension, stroke, and Type 2 diabetes.[^25]

In our study lipid profile revealed raised serum cholesterol, Triglycerides, and low levels of HDL in patients of metabolic syndrome constituting a percentage of 39% 86% and 81% respectively. LDL was elevated in 15%. In a survey done by the US Department of Health and...
Human services, Triglyceride levels and HDL levels were found to be abnormal in 31.4% and 24.7% respectively.

In another study done in New Delhi, India, the age-adjusted HDL levels were found to be low in 64.91% of subjects. In a study done on Asian-Indians (Chennai), abnormal TG and HDL levels were seen in 76% and >90% of the study population. Asian Indians were found not only to have low HDL, but also have a preponderance of small, dense, dysfunctional HDL particles that are associated with less efficient reverse cholesterol transport and less protection against CAD. In a sub-study of the Chennai rural epidemiology study, abnormal Triglycerides and HDL was found in 25.2% and 63.5% of patients. However, in a study done only on urban south Indian men, abnormal TG was seen in 45.2%, whereas abnormal HDL was seen in 70.3% of subjects.

In the present study serum ferritin levels were normal among 49% patients and elevated serum ferritin levels were noted among 43% patients. The mean serum ferritin among males was 366.50±398.93 and in females it was 297.17±390.80 ng/mL. Based on NCEP III criteria 43% of patients had four components of metabolic syndrome, and 32% had five components. And 25% of the patients were with three components of metabolic syndrome. In patients with 3, 4 and all 5 components of metabolic syndrome in both males and females mean serum ferritin levels were elevated. But p-value was insignificant in all these patients of metabolic syndrome. Elevated serum ferritin levels were noted in 56% patients with three components, 46.51% with four components and 28.13% patients with five components. However, no statistically significant difference was observed between elevated serum ferritin levels and metabolic syndrome components.

The correlation of lipid profile with serum ferritin showed, significantly elevated serum ferritin levels in patients with abnormal waist circumference, hypertension and high density lipoprotein whereas no statistically significant difference was seen in patients with abnormal fasting blood sugar and triglycerides. Patient with Waist circumference abnormality 73(73%) as a component of metabolic syndrome elevated serum ferritin abnormality was seen in 26(35.6%), with significant p value 0.043. Patients with hypertension 88(88%), Serum ferritin was elevated in 43(48.8%) with significant p value of 0.0008. Patients with HDL abnormality 81(81%), serum ferritin was elevated in 30(37.04%) with significant p value of 0.045. In other components of metabolic syndrome that is FBS abnormality and Triglyceride abnormality of serum ferritin levels did not show significant reflection as far as statistical p value was concerned.

Serum ferritin is a widely used marker of iron status in epidemiological studies and accurately reflects differences in body iron stores by age and sex. However, serum ferritin is an acute-phase reactant and may be artificially elevated in the presence of inflammation. Several cross-sectional studies have previously examined the association between iron stores and individual metabolic cardiovascular risk factors, including hypertension, dyslipidemia, elevated fasting insulin and blood glucose, and central adiposity.

It is unclear whether elevated iron stores may simply be another marker of insulin resistance or whether elevated iron stores may contribute to the pathogenesis of altered metabolic states. Iron is a transition metal capable of causing oxidative tissue damage by catalyzing the formation of free radicals. Iron overload may contribute to insulin resistance.
through mechanisms related to both reduced extraction of insulin and impaired insulin secretion.\textsuperscript{33}

In a US study,\textsuperscript{9} mean reported moderately elevated iron levels were associated with an increased prevalence of metabolic syndrome and marker of insulin resistance. These associations were evident at moderately elevated iron levels, high levels associated with hemochromatosis. Given the high prevalence of elevated iron stores, especially in older ages, prospective studies are needed to determine whether moderately elevated iron stores precede the development of insulin resistance and contribute to the increased risk associated with it.

A cross-sectional study\textsuperscript{9} on 6,044 adults >20 years of age who participated in the Third National Health and Nutrition Examination Survey from Baltimore, USA examined the relationship among iron stores, the metabolic syndrome, and insulin resistance. Study concluded that, elevated iron stores were positively associated with the prevalence of the metabolic syndrome and with insulin resistance. Another a cross-sectional study\textsuperscript{34} of 1,444 adults over the age of 40 and under the age of 70 years lived in rural area showed that, moderately elevated serum ferritin levels were not independently associated with the prevalence of the MS after adjusting for other risk factors. Another cross-sectional study\textsuperscript{35} of 6311 adults older than 20 years demonstrated that, elevated serum ferritin concentrations are associated with an increased risk of MS and diabetes mellitus in a representative sample of the adult South Korean population. In a cross-sectional study,\textsuperscript{36} serum ferritin levels and metabolic syndrome and its components studied in 18,581 men and it was observed that elevated ferritin concentrations was, independently associated with metabolic syndrome and its components among healthy Korean men.

We analysed the data both qualitatively and quantitatively to find out correlation of elevated serum ferritin with individual component of metabolic syndrome. We found significant correlation of serum ferritin levels with hypertension, waist circumference and low HDL levels (significant p value for hypertension 0.0008, waist circumference 0.043, low HDL levels 0.045). This may not be a true reflection because of small sample size and other confounding factors. Studies with large sample size with proper adjustment of confounding variables may reflect significance of elevated serum ferritin in patients of metabolic syndrome or its individual components.

**CONCLUSION:** Amongst the patient presenting with metabolic syndrome, serum ferritin was elevated in hypertension (48.86%), waist circumference (35.62%), low HDL levels (37.04%). Metabolic syndrome was observed in elderly age groups than in younger age groups. In individual components of metabolic syndrome hypertension was commonly seen followed by triglyceridemia and low HDL levels. Serum ferritin as a marker of metabolic syndrome was inconclusive but was raised significantly in individual components of metabolic syndrome. To know significance of elevated serum ferritin levels in patients of metabolic syndrome may be a large sample size with proper adjustment of confounding variables may reflect importance of serum ferritin levels.
Table 1: Comparison of serum ferritin levels and metabolic syndrome components

| No. of Components | Serum ferritin levels | Total |
|-------------------|-----------------------|-------|
|                   | Normal limits | Elevated | Below normal |       |
|                   | No   | %     | No   | %     | No   | %    | No   | %    |
| 3                 | 9    | 36.00 | 14   | 56.00 | 2    | 8.00 | 25   | 100.00 |
| 4                 | 20   | 46.51 | 20   | 46.51 | 3    | 6.98 | 43   | 100.00 |
| 5                 | 20   | 62.50 | 9    | 28.13 | 3    | 9.38 | 32   | 100.00 |

$x^2=4.991$, DF=4, p=0.288.

Table 2: Comparison of other parameters with serum ferritin in individual components of metabolic syndrome

| Components of metabolic syndrome | Serum ferritin levels | Total |
|---------------------------------|-----------------------|-------|
|                                 | Within normal limits  | Elevated | Below normal |
|                                 | No. | %     | No. | %     | No. | %    | No. | %    |
| Waist Normal                    | 8   | 29.63 | 17  | 62.96 | 2   | 7.41 | 27  | 27.00 |
| Waist Abnormal                  | 41  | 56.16 | 26  | 35.62 | 6   | 8.22 | 73  | 73.00 |
| $x^2=6.276$; DF=2; p=0.043 (significant) |
| Hypertension Normal             | 12  | 100.00 | 0   | 0.00  | 0   | 0.00 | 12  | 12.00 |
| Hypertension Abnormal           | 37  | 42.05 | 43  | 48.86 | 8   | 9.09 | 88  | 88.00 |
| $x^2=14.192$; DF=2; p=0.0008 (significant) |
| Fasting blood Normal            | 6   | 28.57 | 13  | 61.90 | 2   | 9.52 | 21  | 21.00 |
| Fasting blood Abnormal          | 43  | 54.43 | 30  | 37.97 | 6   | 7.59 | 79  | 79.00 |
| $x^2=4.550$; DF=2; p=0.102       |
| Triglycerides Normal            | 7   | 50.00 | 5   | 35.71 | 2   | 14.29 | 14  | 14.00 |
| Triglycerides Abnormal          | 42  | 48.84 | 38  | 44.19 | 6   | 6.98 | 86  | 86.00 |
| $x^2=1.008$; DF=2; p=0.604       |
| HDL Normal                      | 5   | 26.32 | 13  | 68.42 | 1   | 5.26 | 19  | 19.00 |
| HDL Abnormal                    | 44  | 54.32 | 30  | 37.04 | 7   | 8.64 | 81  | 81.00 |
| $x^2=6.208$; DF=2; p=0.045 (significant) |

Table 3: Comparison of mean serum ferritin levels with metabolic syndrome components

| No. of Components | Males (n=58) | Females (n=42) | Overall (n=100) |
|-------------------|-------------|---------------|-----------------|
|                   | Mean | SD   | Mean | SD   | Mean | SD   |
| 3                 | 328.85 | 371.77 | 566.92 | 621.34 | 405.03 | 466.46 |
| 4                 | 391.58 | 387.05 | 225.21 | 201.45 | 325.81 | 333.77 |
| 5                 | 365.67 | 468.58 | 242.18 | 369.81 | 300.07 | 416.73 |

Table 3: Comparison of mean serum ferritin levels with metabolic syndrome components
| No. of Components | Mean serum ferritin levels (ng/mL) | Normal limits (n=49) | Elevated (n=43) | Below normal (n=8) |
|-------------------|-----------------------------------|----------------------|----------------|-------------------|
|                   | Mean | SD | Mean | SD | Mean | SD |
| WC (Cms)          | 96.67 | 6.84 | 97.39 | 8.12 | 93.62 | 5.95 |
| SBP (mm Hg)       | 140.57 | 16.87 | 146 | 10.98 | 147.75 | 8.71 |
| DBP (mm Hg)       | 87.87 | 8.14 | 92.04 | 6.64 | 91 | 5.75 |
| FBS (mg/dL)       | 150.48 | 122.00 | 131.62 | 40.72 | 125.12 | 27.52 |
| TGA (mg/dL)       | 189.79 | 95.69 | 186.14 | 35.41 | 168.37 | 48.28 |
| HDL (mg/dL)       | 41.95 | 10.85 | 39.9 | 12.04 | 37.75 | 6.73 |

Table 4: Comparison of mean metabolic components with mean serum ferritin

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