ORIGINAL ARTICLE

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Correlation of Serum Ferritin with Insulin Resistance in Type 2 Diabetes Mellitus Patients and its Relationship with Components of Metabolic Syndrome

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Abstract

***Background:** Ferritin is a ubiquitous intracellular protein complex that reflects the iron stores of the body. Recent studies indicate that increased body iron stores have been associated with the development of glucose intolerance and type 2 diabetes mellitus. The present study was carried out to find out the correlation of serum ferritin with insulin resistance and its relationship with individual components of metabolic syndrome.*

***Objectives:** To determine relationship between serum ferritin and insulin resistance in type 2 diabetes patients and to find out relation of serum ferritin with individual components of metabolic syndrome.*

***Methods:** Study included 100 cases of type 2 diabetes mellitus compared with age and sex-matched 100 non-diabetic controls. Serum ferritin, fasting blood sugar, serum insulin, lipid parameters and waist circumference were estimated and Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated.*

***Results:** The mean age was 55.97 ± 10.36 years in patients with diabetes and 56.93 ± 10.06 years in control subjects. The mean serum ferritin in cases and controls were found to be 191.01 ± 94.27µg/l and 83.67 ± 51.38 µg/l respectively (p = 0.001). Mean HOMA-IR was significant higher in cases (4.22 ± 2.28) than controls (1.14 ± 0.48). There was also a positive linear correlation between serum ferritin and HOMA-IR in diabetes patients (r = 0.41, p < 0.05). Serum ferritin was significantly higher in hypertensive type 2 DM patients than hypertensive non-diabetic patients (p < 0.05). Mean serum ferritin was higher in the presence of other metabolic components, i.e., high waist circumference, high triglycerides, low HDL, high BP but this difference was not statistically significant.*

***Conclusion:** It was concluded that hyperferritinaemia may be an additional cause of insulin resistance in type 2 diabetes mellitus and metabolic syndrome.*

***Key words:** Metabolic syndrome, serum ferritin, insulin resistance, HOMA-IR.*

Introduction

Diabetes mellitus is one of the most common problems caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cells[1]. Type 2 diabetes has been rising globally. The worldwide spread of diabetes among general population is estimated to increase to 300 million in 2025[2,3].

The metabolic abnormalities in diabetes are abnormal muscle and fat metabolism, impaired insulin secretion and increased hepatic glucose and lipid production. Insulin resistance characterised by decreased ability of insulin to act effectively on target tissues especially muscle, fat and liver. In skeletal muscle, insulin receptors level and tyrosine kinase activity are reduced resulting in impairment of glycogen formation. Impaired fatty acid oxidation and lipid accumulation within skeletal myocytes also may generate reactive oxygen species such as lipid peroxides which may result in impaired insulin action[4].

Elevated iron stores may increase the risk of developing diabetes. Emerging scientific evidence has revealed unsuspecting influences between iron metabolism and type 2 diabetes. The relationship is bi-directional; iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways. It is increasingly recognised that iron influences glucose metabolism, even in the absence of significant iron overload[5]. Ferritin is a specialised iron storage protein, which reflects iron stores in the body[6].

Although a mechanism linking iron concentration and diabetes is not established, it is known that iron is a catalyst in the formation of hydroxyl radicals, which may contribute initially to insulin resistance, subsequently to decreased insulin secretion, and ultimately to the development of type 2 diabetes[7]. Animal models suggest that iron excess may result in beta-cells oxidative stress and decreased insulin secretion[8]. Excess iron may cause insulin resistance by

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interference with insulin inhibition of glucose production by liver. Also hyperferritinaemia may result in hepatic dysfunction by decreased hepatic extraction and metabolism of insulin[9].

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

Study design and subjects

This study was conducted at MBS hospital and Government Medical College, Kota, Rajasthan, between January 2017 and November 2017. The study consisted of 100 cases of type 2 DM admitted in medicine emergency and general wards and taking oral hypoglycaemic agents or insulin treatment. 100 people without diabetes irrespective of other risk factor, i.e., obesity, smoking, alcoholic were selected for the control group. Study groups were comprised of 30 - 80 years of age and statistically age- and sex-matched.

Exclusion criteria

Patients with type 1 DM, hemolytic anaemia, acute or chronic inflammation, iron deficiency anaemia, haemoglobinopathies, bleeding disorders, pregnancy, chronic liver disease, chronic kidney disease, patients with excessive alcohol intake (women > 40 g/day and men > 60 g/day were excluded), patient with hepatitis B and hepatitis C, infectious diseases like tuberculosis, sarcoidosis and septicaemia, patient on corticosteroid therapy, patients with overt thyroid dysfunction and patients with repeated blood transfusions were excluded from the study.

The study was approved by institutional ethics committee and written informed consent was obtained from all the study subjects after explaining the objectives of the study.

Questionnaire and data collection

A questionnaire was specifically designed to obtain information to select individuals according to the selection criteria of the study. The questions focused on socio-demographic data (age, sex) and background characteristics of diabetes (duration and type of diabetes mellitus, mode of anti-diabetic therapy, any complication). About 2 ml of venous blood was collected in fasting, post-prandial (FBS and PPBS) estimation. Blood sugar was estimated by Glucose oxidase-Peroxidase (GOD-POD) enzymatic end-point method (Kit: Manufatured by Siemens)[10]. Glycated haemoglobin (HbA1C) concentration was measured by iron exchange chromatography method[11]. Serum ferritin was measured by chemiluminescence method[12,13].

Statistical analysis

Statistical analysis was performed using SPSS 16.0. Significance in differences between mean values was assessed by independent t-test. Strength of association between two variables was judged by Pearson's correlation analysis, whereas significance of dependence and predictive values was analysed by linear regression study. Chi-square was test used for comparison of two groups for qualitative data. P value < 0.05 was considered to be statistically significant.

Calculation of HOMA-IR

Insulin resistance was estimated by using the formula of homeostasis model assessment insulin resistance (HOMA-IR fasting insulin [μIU/ml] X fasting glucose [mg/dl]/405), even though this investigation is not a gold standard method for insulin resistance, it correlates with the gold standard method. The respondents who had a HOMA score of more than 2.5 were deamed to have insulin resistance[14].

Results

A total 100 cases and an equal number of age- and sex-matched controls were studied. The mean age was 55.97 ± 10.36 years in patients with diabetes and 56.93 ± 10.06 years in control subjects. Mean haemoglobin in cases (13.65 gm%) and controls (13.13 gm%) was statistically matched; this was important because serum ferritin level varies directly with haemoglobin. Out of 100 cases, hypertensive and non hypertensive cases were 46% and 54%, respectively while in control group 26% were hypertensive and 74% were non-hypertensive. The prevalence of metabolic syndrome in case group was 68% while only 24% controls had metabolic syndrome. Table I shows that mean serum ferritin in cases and controls was found to be 191.01 ± 94.27μg/l and 83.67 ± 51.38 μg/l, respectively ($p < 0.05$). Mean HOMA-IR was significant higher in cases (4.22 ± 2.28) than controls (1.14 ± 0.48). There was also a positive linear correlation between serum ferritin and HOMA-IR in diabetes patients ($r = 0.41$, $p < 0.05$).

Table III shows that serum ferritin was significantly higher in hypertensive type 2 DM patients than hypertensive non-diabetic patients ($p < 0.05$). But, when we compared hypertensive cases with non hypertensive cases, results were statistically non significant ($p = 0.28$). Similarly, ferritin was significantly higher in non-hypertensive type 2 DM patients than non-hypertensive non-diabetic patients ($p < 0.05$).

Table II shows that mean serum ferritin was higher in the presence of other metabolic components, i.e., high waist circumference, high triglycerides, low HDL but this difference was not statistically significant.

Table I: Characteristics of case and control groups.

Parameters		Control group	Case group	P value
Age (years)		56.93 ± 10.06	55.97 ± 10.36	0.169
Sex (M/F)		53/47	57/43	0.108
Hb (gm%)		13.13 ± 0.64	13.65 ± 0.96	0.2
BMI (Kg/m^2)		24.76 ± 1.51	26.69 ± 1.91	0.001
FBS (mg/dl)		82.20 ± 4.08	134.92 ± 18.72	0.001
Serum ferritin (µg/l)	Over all	83.67 ± 51.38 (n = 100)	191.01 ± 94.27 (n = 100)	0.0001 (µg/l)
	Males	90.62 ± 50.94 (n = 57)	207.77 ± 94.74 (n = 53)	0.0001
	Females	74.46 ± 51.10 (n = 43)	171.69 ± 77.29 (n = 47)	0.0001
HbA1C (%)		5.27 ± 0.19	8.57 ± 1.90	0.001
Serum insulin (mU/l)		5.6 ± 2.23	12.43 ± 6.06	0.001
Triglycerides (mg/dl)		116.02 ± 15	154.23 ± 20.23	0.001
HDL cholesterol (mg/dl)		53.18 ± 4.7	38.47 ± 7.75	0.001
HOMA-IR	Overall	1.14 ± 0.48	4.22 ± 2.28	0.001
	Male	1.17 ± 0.50	4.56 ± 2.41	0.001
	Female	1.11 ± 0.39	3.83 ± 2.08	0.001

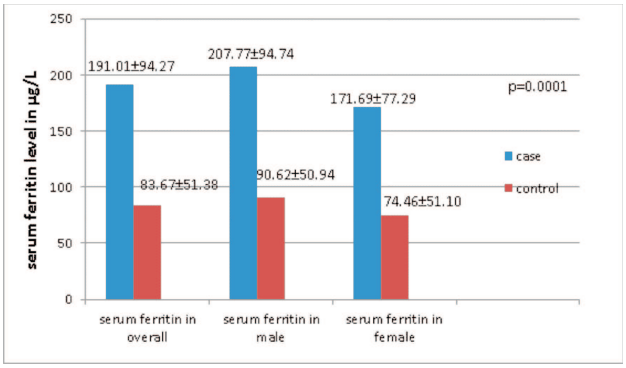

Fig. 1: *Distribution of serum ferritin, according to sex, in study and control groups.*

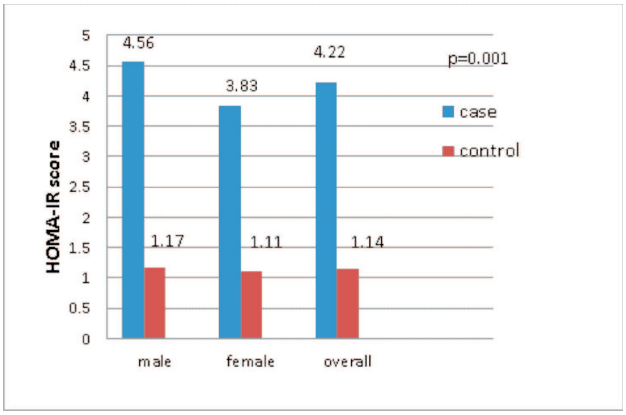

Fig. 2: *Comparison of mean HOMA-IR score, in cases and controls.*

Table II: Comparison of serum ferritin according to components of metabolic syndrome in diabetic and non-diabetic groups.

Components of metabolic syndrome	Mean serum ferritin (µg/l) Diabetics	Non diabetics	P value in case
(1) Waist circumference			
male ≥ 90 cm	210.25 ± 94.76	130.60 ± 64.68	
male < 90 cm	188.35 ± 126.02	78.81 ± 39.82	0.6
female ≥ 80 cm	183.48 ± 93.06	75.51 ± 51.25	0.08
female < 80 cm	129.22 ± 44.50	56.24 ± 29.84	
(2) triglycerides			
≥ 150 mg/dl	208.26 ± 103.24	80.15 ± 45.28	0.33
< 150 mg/dl	186.06 ± 91.68	65.12 ± 52.30	
(3) HDL			
Male < 40 mg/dl	227.07 ± 135.54	108.65 ± 61.98	
Male ≥ 40 mg/dl	204.84 ± 92.11	77.46 ± 36.84	0.57
Female < 50 mg/dl	199.31 ± 97.78	79.54 ± 53.76	0.25
Female ≥ 50 mg/dl	160.98 ± 73.40	48.34 ± 21.68	

Table III: comparison of mean serum ferritin in hypertensive and non-hypertensive cases and controls.

Group	Cases (mean ± SD)	Control (mean ± SD)	t-value	P value
Hypertensive	µg/l	µg/l		
Male	198.18 ± 96.35 (n = 17)	151.20 ± 64.23 (n = 14)		
Female	203.55 ± 112.13 (n = 29)	50.94±20.36 (n = 12)	4.86	p = 0.01
Overall	201.52 ± 85.25 (n = 46)	104.93 ± 36.35 (n = 26)		
Non-hypertensive				
Male	201.34 ± 90.12 (n = 24)	97.20 ± 44.25 (n = 43)		
Female	166.98 ± 82.36 (n = 30)	47.08 ± 19.36 (n = 31)	8.19	p = 0.01
Overall	182.25 ± 78.25 (n = 54)	76.20±41.59 (n = 74)		

Discussion

Ferritin is a universal intracellular protein that stores iron and releases it in a controlled fashion. The protein is produced by almost all living organisms, including algae, bacteria, higher plants, and animals. In humans, it acts as a buffer against iron deficiency and iron overload. Ferritin is found in most tissues as a cytosolic protein, but small amounts are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of

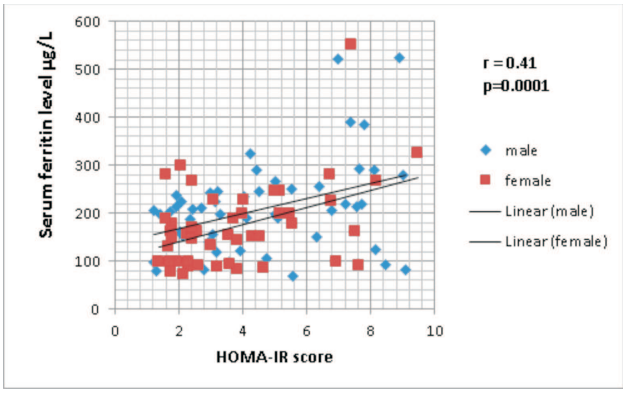

Fig. 3: *Correlation between mean serum ferritin (µg/l) and HOMA-IR score according to sex in case group.*

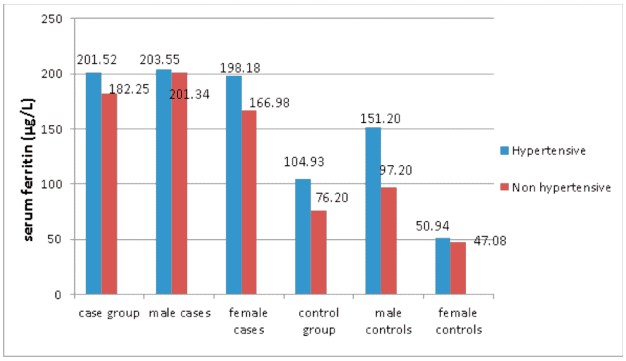

Fig. 4: *Graphical comparison of mean serum ferritin(µg/l) in hypertensive and non hypertensive cases and controls.*

Fig. 5: *Comparison of mean serum ferritin (µg/l) in relation to waist circumference in cases and controls.*

the total amount of iron stored in the body. Elevated ferritin levels are usually due to causes such as acute or chronic inflammation, chronic alcohol consumption, liver disease, renal failure, malignancy and overt thyroid dysfunction while ferritin levels are decreased in iron deficiency, excess menstruation, conditions that affect intestinal absorption

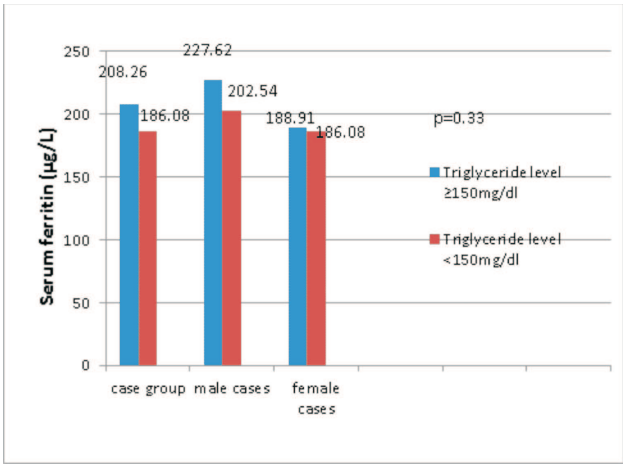

Fig. 6: *Comparison of mean serum ferritin (µg/l) in relation to Triglyceride (TG) level in cases and controls.*

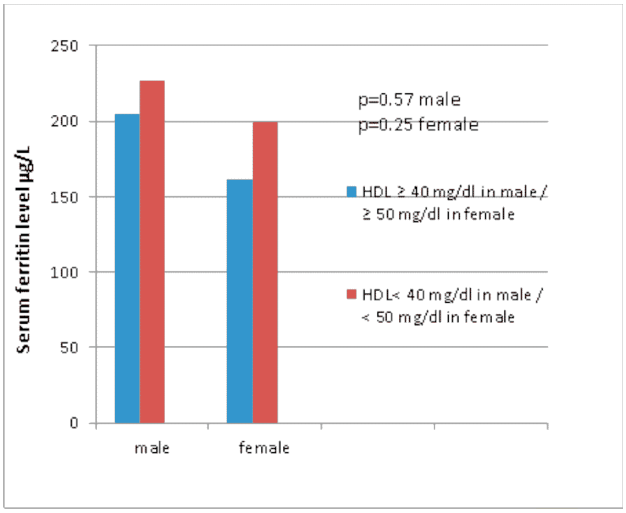

Fig. 7: *Comparison of mean serum ferritin (µg/l) in relation to serum HDL level in male cases and controls.*

of iron and any internal bleeding[15].

Increased serum ferritin is often associated with measures of insulin resistance such as elevated blood glucose and serum insulin level. The mechanism for the association between ferritin and type 2 DM is not established, but iron deposition in the liver may cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production. Iron is auto-oxidized to form highly reactive, lipid-soluble iron-oxygen complexes. These free radicals are powerful pro-oxidants, which can change membrane properties and result in tissue damage. Oxidative stress can also lead to hyperglycaemia through disturbed glucose metabolism. In addition, iron accumulation in hepatocytes may interfere with the insulin extracting capacity of the liver, and affect insulin synthesis and secretion in the pancreas. Iron excess probably contributes

to insulin resistance and subsequently to decreased insulin secretion[16,17].

In our study, mean serum ferritin in diabetic patients and controls was 191.01 µg/l and 83.67 µg/l, respectively. This difference in mean serum ferritin was statistically significant, irrespective of gender sex ($p < 0.001$). It was observed that in diabetic group, mean serum ferritin was lower in females (171.69 ± 77.29 µg/l) than males (207.77 ± 94.74 µg/l) but was statistically non-significant ($p = 0.06$). This difference in mean was consistent with previous studies[18,19].

High serum ferritin in diabetic patients was associated with high FBS and high serum insulin level. In our study diabetic patients were more insulin resistant than patients without diabetes. This finding was similar to study done by Bionapalli Sudhakar *et al*, who found that diabetic patients were more insulin resistant than non-diabetes controls (mean HOMA-IB 3.15 v/s 1.26 in control, $p < 0.05$)[18]. Wrede *et al*, reported a significant correlation between serum ferritin and insulin resistance in a large representative population[19].

Jiang *et al* have reported elaboration of hydroxyl radical in iron overload which causes cell damage and leads to insulin resistance. Desferrioxamine, a chelating agent with antioxidant properties improved fasting blood glucose in chronically transfused patients of thalassemia major, supporting this hypothesis[20].

In our study, mean serum ferritin was higher in hypertensive cases than non-hypertensive cases but this difference was not statistically significant. A Korean study done on 7,104 men showed that elevated serum ferritin level was independently associated with the incidental risk of hypertension in Korean men ($p < 0.003$). Serum ferritin was a significant predictor of hypertension in middle-aged Korean men. Fatty liver disease and insulin resistance may be mediators of this high ferritin in hypertensive patients[21].

In our study serum ferritin was higher in the presence of high TG and low HDL but this difference was not statistically significant. Sumesh Raj *et al*, found no correlation between serum ferritin and lipid profile (total cholesterol, LDL, triglyceride)[22]. Sumeet Samotra *et al*, showed significant relationship between raised serum ferritin and lipid profile (TC, TG) but not with LDL[23]. We advise further future studies to know the exact association of serum ferritin with lipid derangement.

Conclusion

It was concluded that raised serum ferritin level has a potential role in the development of insulin resistance and type 2 diabetes mellitus. Though mean serum ferritin level was consistently raised with each component of metabolic syndrome, this difference was not statistically significant. As insulin resistance is the key factor for metabolic syndrome, further studies are required to know the role of serum ferritin in metabolic syndrome. Ferritin may be used as an important biomarker in predicting diabetes mellitus and insulin resistance.

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