International Journal of Research in Medical Sciences
Saluja M et al. Int J Res Med Sci. 2022 Aug;10(8):1657-1662
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221975

Original Research Article

Association of serum ferritin and glycated haemoglobin in patients of type 2 diabetes mellitus and its correlation with components of metabolic syndrome

Manoj Saluja, Chetan Prakash Suman*, Saurabh Chittora, Dileep Meena

Department of Medicine, Government Medical College, Kota, Rajasthan, India

Received: 28 May 2022
Revised: 02 July 2022
Accepted: 07 July 2022

***Correspondence:**
Dr. Chetan Prakash Suman,
E-mail: chetansuman007@gmail.com

ABSTRACT

Background: Ferritin is a universal intracellular protein that stores iron and releases it in a controlled fashion, and reflects iron stores of the body. Recent studies indicate that increased body iron stores are associated with development of type 2 diabetes mellitus (DM) hence affecting the level of glycated haemoglobin. The aim and objectives of this study were to determine the relationship between serum ferritin and glycated haemoglobin in type 2 diabetes patients and to find out correlation between serum ferritin level and components of metabolic syndrome.
Methods: This study included 100 cases of type 2 DM compared with age and sex-matched 100 non-diabetic controls. Serum ferritin, fasting blood sugar, lipid parameters and waist circumference were estimated, and glycated haemoglobin was calculated by HPLC method.
Results: The mean serum ferritin in cases was 178.59±84.17 µg/l and in controls was 107.17±13.83 µg/l (p=0.0001). The mean age was 53.32±10.14 years in cases and 51.8±10.54 years in controls. Mean HbA1C level in cases was higher (8.40±1.22) as compared to controls (5.4±0.34) and it was statistically significant (p<0.0001). There was a positive linear correlation between HbA1C level and serum ferritin irrespective to gender in case group (r=0.342) and it was statistically significant (p<0.0001). Serum ferritin was significantly higher in hypertensive type 2 DM patients than hypertensive non-diabetic patients (p<0.0239).
Conclusions: The findings of this study suggest that increased level of serum ferritin is positively related to glycaemic control.

Keywords: Metabolic syndrome, Glycated haemoglobin, Serum ferritin, Fasting blood sugar, HDL

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder which is considered to result from multiple aetiologies, environmental and genetic acting together, which result in a chronic state of hyperglycaemia with disturbance in the metabolism of carbohydrate, fat and protein, due to relative or absolute deficiency of insulin secretion, or defects in insulin action or both. DM is a chronic disease and potentially disabling, which is reaching epidemic proportions in many parts of the world. DM is a major and growing threat globally. Largest number of diabetic patients are found in India, and India is earning the distinction of 'diabetic capital of world'. Type 2 diabetes has a rising trends around the globe. Worldwide expected number of patients of diabetes among the general population are estimated to increase to 300 million in 2025.[1,2] 65.1 million people in the age group of 20 to 79 have diabetes in India (8.56%), and it is expected to rise to 109 million by the year 2035.[3]

Increase in iron stores of the body may increase the risk of developing diabetes. Emerging evidence has revealed unsuspecting influences between iron metabolism and

type 2 diabetes. It is increasingly recognized that iron influences glucose metabolism, even in the absence of significant iron overload.[4] Iron affects the metabolism of glucose, and glucose metabolism impinges on several iron metabolic pathways.

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.[5] Although a mechanism linking iron concentrations and diabetes is not established, an animal models suggest that iron excess may result in beta-cell oxidative stress and decreased insulin secretion.[6]

Ferritin is a specialized iron storage protein, which reflects iron stores in the body.[7] Previous studies have demonstrated an association between increased serum ferritin levels and higher risks of diabetes.[8,9] Glycated haemoglobin (HbA1c) is a stable, irreversible product of non-enzymatic glycosylation of the haemoglobin by serum glucose. HbA1c is used to assess the state of glycemic control in previous 2 to 3 months, progression of diabetes and development of complications.[10,11]

This was a hospital based observational study, conducted to find out the correlation between serum ferritin, fasting plasma glucose and glycemic control in type 2 adult DM.

METHODS

Study design and subjects

This study was conducted at the government medical college and associated group of hospitals, Kota Rajasthan, between January 2019 and December 2019.All the patients as cases included in the study who given the consent for study during the study period after excluding the patient who excluded by exclusion criteria mentioned. Controls were selected as per no of cases.

The study included of 100 cases of type 2 DM admitted in various wards of our hospital and out-patients visiting medicine the OPD and were on OHA or injectable insulin therapy. 100 people without diabetes (irrespective of other risk factors, i.e., smoking, alcoholism, and obesity) were included in the control group. Age and sex matched patients and controls of 30-80 years of age were included in the study.

Exclusion criteria

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

Ethical clearance

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

Questionnaire and data collection

A special questionnaire was used to draw the information to select individuals according to the selection criteria of the study. Validity of questionnaire was tested by doing pilot study before the start of the study. The questions focused on socio-demographic data (age, sex) and background characteristics of diabetes (duration and type of DM, mode of anti-diabetic therapy, any complication). About 2 ml of venous blood was collected for fasting (FBS), post-prandial (PPBS) estimation. Serum ferritin was measured by chemiluminescence method. Blood sugar was estimated by glucose oxidase-peroxidase (GOD-POD) method. Glycated haemoglobin (HbA1C) concentration was measured by high performance liquid chromatographic method (HPLC).

Statistical analysis

Statistical analysis was performed using SPSS 20.0. Significance in differences between mean values was assessed by independent t test. Strength of association between two variables was assessed by Pearson's correlation analysis, whereas significance of dependence and predictive values was analysed by linear regression study. $P<0.05$ considered to be statistically significant.

RESULTS

This was a hospital-based study conducted at the Government Medical College, Kota. A total 100 cases and an equal number of age- and sex-matched controls were included in the study. The mean age was 53.32±10.14 years in patients with diabetes, and 51.8±10.54 years in the controls control subjects. Mean haemoglobin seen in cases (13.11 g%) and controls (14.14 g%); Out of 100 cases, hypertensive and non-hypertensive cases were 82% and 18%, respectively, while in control group, 80% were hypertensive and 20% were non-hypertensive.

Table-1 shows the mean serum ferritin in cases and controls. It was found to be 178.59±84.17 µg/l and 107.17±13.83 µg/l, respectively ($p<0.0001$). Mean glycated haemoglobin was significant higher in cases (8.40±1.22) than controls (5.7±0.34) ($p<0.0001$). There was also a positive linear correlation between serum ferritin and glycated haemoglobin in diabetes patients ($r=0.$ 0.342, $p<0.0001$). Average of serum ferritin level in

euglycemic diabetics is 93.45 and average of serum ferritin level in hyperglycaemic diabetics is 196.49.

Table 2 shows that serum ferritin was significantly higher in hypertensive diabetic patients than hypertensive non-diabetic patients ($p<0.0239$). But, when compared hypertensive cases with non-hypertensive cases, results statistically non-significant ($p=0.0999$). Similarly, ferritin significantly higher in non-hypertensive diabetic patients than non-hypertensive non-diabetic patients ($p<0.05$).

Table 3 shows that mean serum ferritin was higher in diabetic patients in the presence of other metabolic components, i.e., high waist circumference, high triglycerides, low HDL but this difference was not statistically significant. But in male having HDL>40 and females having HDL<50 serum ferritin found higher than fellow controls and statistically significant ($p<0.0001$).

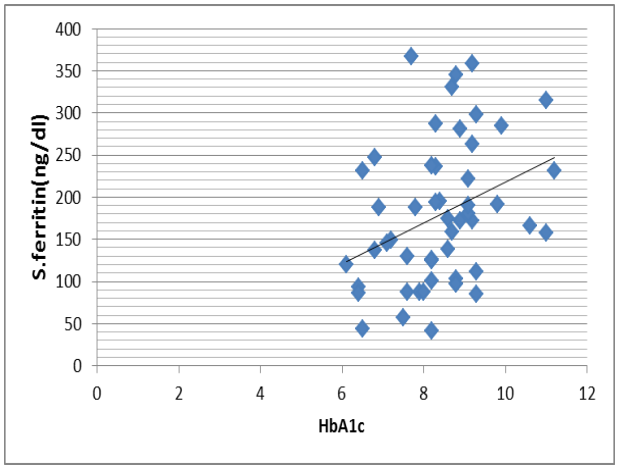

Figure 1: Correlation between serum ferritin and glycated haemoglobin in cases (r=0.342, p<0.0001).

Table 1: Characteristics of cases and controls.

Parameters	Cases	Controls	P value (Chi square test)
Age (years)	53.32±10.14	51.8±10.54	0.2999
Sex (F/M)	48/52	40/60	
Hb (g%)	13.11±1.04	14.14±1.0	0.0001
BMI (kg/m^2)	26.10±4.013	25.17±1.98	0.0436
FBS (mg/dl)	142.26±26.84	93.2±6.06	<0.0001
HbA1c (%)	8.40±1.22	5.4±0.34	<0.0001
Serum ferritin (µg/l)	178.59±84.17 M-153.78±69.27 F-208.79±90.58	107.17±13.83 M-107.41±0.41 F-106.8±15.18	<0.0001
Triglycerides (mg/dl)	203.48±16	168.8±23.56	<0.0001
HDL (mg/dl)	45.37±22.96	53.9±5.36	<0.0001

Table 2: Comparison of mean serum ferritin in hypertensive and non-hypertensive cases and controls.

Parameters	Cases	Control	P value (Chi square test) (cases)
Hypertensive (overall)	179.25±79.47, (n=82)	156.12±44.28, (n=80)	
Male	159.71±67.75, (n=52)	164.0±43.73, (n=55)	0.0239
Female	213.11±86.60, (n=30)	138.8±40.37, (n=25)	
Non-hypertensive (overall)	179.23±102.40, (n=18)	133.25±12.02 (n=20)	
Male	95.12±53.87, (n=6)	125.06±11.22 (n=5)	0.0536
Female	207.27±79.34, (n=12)	136.25±12.02(n=15)	

Table 3: Comparison of serum ferritin according to components of metabolic syndrome in diabetic and non-diabetic groups.

Component of metabolic syndrome	Serum ferritin		P value (Chi square test) (cases)
	Cases	Controls	
Waist circumference (cm)			
Male≥90	169.76±73.80, (n=38)	144.25±30.04, (n=40)	0.0055
Male<90	115.91±40.23, (n=18)	193.75±46.58, (n=20)	
Female≥80	210.20±84.94, (n=40)	141.33±37.29, (n=30)	0.6102
Female<80	234.24±133.24, (n=4)	127.60±21.7, (n=10)	
Triglycerides			
≥150	182.94±86.92, (n=86)	104.52±14.37, (n=84)	0.3567
<150	160.53±61.21, (n=14)	118.18±9.33, (n=16)	
HDL (mg/dl)			

Continued.

Component of metabolic	Serum ferritin		P value (Chi square test)
Male<40	157.84±71.81, (n=16)	112.36±12.4, (n=12)	0.9769
Male≥40	158.45±68.96, (n=36)	107.41±12.85, (n=48)	
Female<50	227.50±90.42, (n=37)	117±13.44, (n=15)	0.0011
Female≥50	130.25±32.09, (n=11)	104.215.34, (n=25)	

DISCUSSION

Type 2 DM is a chronic disease and its prevalence has been increasing everywhere around the globe. People living with type 2 DM are more at risk of complications both short and long term, which frequently result in their premature death.[12] Oxidative stress has been implicated within the pathogenesis of the complications seen in T2DM.[13] Superoxide species and oxide appear to be the first generated species. These species may then play a job within the generation of additional and more reactive oxidants, including the highly reactive hydroxyl in which iron plays a catalytic role in an exceedingly complex reaction. This reaction is usually named the metal catalyzed Haber-Weiss reaction and fenton.[14]

The most abundant element within the body is iron, and the majority iron occurs certain to proteins. In moderate quantities and leashed to proteins, it's a vital element altogether for cell metabolism and growth, but it's toxic when unleashed.[15] Iron is both a robust biological reductant and oxidant. As iron has the ability to generate hydroxyl radical from peroxide, iron can also breach the anti-oxidant safeguard like superoxide dismutase.[16] High iron content is being involved in oxidative damage to DNA, lipids and proteins resulting in various vascular and neurological complications.[17] Beta cells of pancreas are specially sensitive to oxidative stress and iron is involved in through multiple mechanism in dysregulation of functions of beta cells like decreasing insulin gene expression resulting in beta cell failure resulting in relative or absolute deficiency of insulin.[18] The central role of iron within the pathophysiology of disease springs from the benefit with which iron is reversibly oxidized and reduced. This property, while essential for its metabolic functions, makes iron potentially hazardous due to its ability to participate within the generation of powerful oxidant species like hydroxyl.[18]

Additional endogenous source of catalytic free iron is that the iron is released when the hame ring is opened by haemeoxygenase. The intracellular generation of apoferritin could be a cyto-protective antioxidant stratagem of endothelial cells.[19,20] Since serum ferritin is increased in T2DM, ferritin is taken into account as a positive acute phase protein and is up regulated intracellularly in many cell types, and extracellularly, within the plasma as a result of a rise in cellular secretion. A vital role of ferritin during the acute phase response is to limit the supply of iron by sequestration into the cavity of the ferritin protein shell.[12] The role of iron within the pathogenesis of diabetes is recommended by an increased incidence of type 2 diabetes in diverse causes of pathology and reversal or improvement in diabetes (glycemic control) with a discount in iron load achieved using either phelobotomy or iron chelation therapy.[21]

The importance of protein glycation is well-known within the pathogenesis of diabetic vascular complications. Transition metals also play a job in protein glycation induced by hyperglycemia. It has been shown that glycated proteins have a considerable affinity for the transition metals, and also the bound metal retains redox activity and participates in catalytic oxidation. Thus, should similar glycochelates form in vivo, reactions mediated by the chelates may well be involved within the vascular complications of diabetes.[22] Different theories regarding the role of ferritin in T2DM are suggested. Ferritin has been referred to as a marker of insulin resistance, possibly because of iron deposition within the liver resulting in hepatic insulin resistance and increased hepatic glucose production.[23] Ferritin has been determined even as a marker of pancreatic inflammation, while pancreatic damage because of a point of subclinical haemochromatosis has been considered in some cases of diabetes.

Two large epidemiological studies reported strong association between elevated serum ferritin concentration and increased risk for diabetes.[24,25] In our study we found a statistically significant increase in fasting plasma glucose, glycated hemoglobin and serum ferritin levels in patients of T2DM as compared to healthy controls. This finding is supported by various studies.[12,26] A prospective case control study conducted by Kumar et al reported that patients with T2DM had significantly higher serum ferritin level compared to healthy controls but there is no correlation between serum ferritin with mean glucose and HbA1c.[27] A study by Fernandez-real et al reported a correlation between serum ferritin with basal plasma glucose and no correlation with HbA1c in diabetics and normal controls.[23] So, there is a necessity for further studies to verify the implications of serum ferritin as a marker for type 2 DM and its role in pathogenesis of T2DM.

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 related to the incidental risk of hypertension in Korean men ($p<0.003$). Serum ferritin was a big predictor of hypertension in middle-aged Korean men. Liver disease and insulin

resistance could also be mediators of this high ferritin in hypertensive patients.[28]

In our study serum ferritin was higher within the presence of high TG and low HDL but this difference was not statistically significant. Raj et al found no correlation between serum ferritin and lipid profile (total cholesterol, LDL, triglyceride). Samotra et al showed significant relationship between raised serum ferritin and lipid profile (TC, TG) but not with LDL.[29,30] In our study, males having HDL>40 and females having HDL<50 serum ferritin was found higher then fellow controls and was statistically significant. We advise further future studies to understand the precise association of serum ferritin with lipid derangement.

Limitations

We found significant correlation with serum ferritin only in patients with waist ≥90 cm and in diabetic female with HDL <50 mg/dl. This could be due to the small sample size. Therefore, further studies on a larger scale are required to ascertain the role of serum ferritin in the prediction and management of diabetes, metabolic syndrome and its complications.

CONCLUSION

Increased level of serum ferritin may be one of the causes of development of insulin resistance, DM and related complications. The findings of this study suggest that increased level of serum ferritin is positively related to glycaemic control. Serum ferritin may be used as a tool in the screening of diabetic patients with poor glycaemic control who are at increased risk of developing diabetes complications.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ghazanfari Z, Haghdoost SA, and Mohammad A. Comparison of HbA1c and Fasting Blood Sugar Tests in General Population. Int J Prev Med. 2010;1(3):187-94.
2. Adeghate E, Schattner P, and Dunn E: An update on the etiology and epidemiology of diabetes mellitus. Ann NY Acad Sci. 2006;1084:1-29.
3. IDF Diabetes Atlas. Chapter-2.1, 6th edn. 2013;34.
4. Pankaj B, Puja B, Akshay R, and Kansal HM. Is serum ferritin associated with type II diabetes mellitus: A clinical study in a representative Indian population. J Med Sci Res. 2011;2:20-4.
5. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, and Hu FB: Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA. 2004;291:711-7.
6. Cooksey RC, Jouihan HA, Ajioka RS. Oxidative stress, beta-cell apoptosis, and The Relationship between Serum Ferritin and Glycosylated Hemoglobin 408 decreased insulin secretory capacity in mouse models of hemochromatosis. Endocrinology. 2004;145:5305-12.
7. Zafon C, Lecube A, and Sim´o R. Iron in obesity. An ancient micronutrient for a modern disease. Obesity Reviews. 2010;11(4):322-8.
8. Dekker LH, Nicolaou M, and Van Der ADL. Sex differences in the association between serum ferritin and fasting glucose in type 2 diabetes among South Asian, Surinamese African, Surinamese and ethnic Dutch: the population-based SUNSET study. Diabetes Care. 2013;36(4):965-71.
9. Sun L, Zong G, Pan A. Elevated serum ferritin is associated with increased incidence of type 2 diabetes in middle aged and elderly Chinese adults. J Nutr. 2013;143(9):1459-65.
10. Feldt-Rasmussen. Is there a need to optimize glycemic control in hemodialyzed diabetic patients? Kidney Int. 2006;70:1392-4.
11. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. Am J Med. 2010;123(3):S3-11.
12. Padmaja P, Shabana S and Shariq Mas. Serum ferritin and HbA1c in type 2 diabetes mellitus. Int J Clin and Biomed Res. 2015;1(3):30-7.
13. Radoi V, Lixandru D, Mohara M, Virgolici B. Advanced glyca- tion end products in diabetes mellitus: Mechanism of action and focused treatment. Proc Rom Acad Series B. 2012;1:9-19.
14. Halliwell B, Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: an overview. Meth Enzymol. 1990;186:1-85.
15. Herbert V. Everyone should be tested for iron disorders. J Am Diet Assoc. 1992;92:1509-76.
16. Jouihan HACP, Cooksey RC, Hoagland EA, Boudina S, Abel ED, Winge DR et al Iron- mediated inhibition of mitochondrial manganese uptake mediates mitochondrial dysfunction in a mouse model of hemochromatosis. Mol Med. 2008;14:98-108.
17. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology. 2011;283:65-87.
18. Kaneto H, Katakami N, Matsuhisa M, Matsuoka TA. Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. Mediators inflammation. 2010;2010:453892.
19. Balla J, Jacob HS, Balla G, Nath K, Vercellotti GM. Endothelial cell hemeoxygenase and ferritin induction by heme proteins: a possible mechanism limiting shock damage. Trans Assoc Am Phys. 1993;105.
20. Balla G, Jacob HS, Balla J, Rosenberg M, Apple F, Eaton JW et al. Ferritin: a cytoprotective antioxidant stratagem of endothelium. J Biol Chem. 1992;267:18148-53.

21. Swaminathan S, Fonseca VA, Alam MG, Shah SV. The role of iron in diabetes and its complications. Diabetes Care. 2007;30(7):1926-33.
22. Qian M, Liu M, Eaton JW. Transition metals bind to glycated proteins forming redox active "glycochelates": implications for the pathogenesis of certain diabetic complications. Biochem Biophys Res Comm. 1998;250:385-9.
23. Fernandez-Real JM, Richard- Engel W, Arroyo E, Balanca R, Casamitjana-Abella R. Serum ferritin as a component of the in- sulin resistance syndrome. Diabetes Care. 1998;21(1):62-8.
24. Ford ES, Cogswell ME. Diabetes and serum ferritin concentra- tion among U.S. adults. Diabetes Care. 1999;22:1978-83.
25. Tuomainen TP, Nyyssonen K, Salonen R, Tervahuta A, Korpela H, Lakka T et al. Body iron stores are associated with serum insulin and blood glucose concentration: Population study in 1,013 eastern Finnish Men. Diabetes Care. 1997;20(3):426-8.
26. Thanna RC, Nigosker S. Level of serum ferritin and glycated haemoglobin in type 2 diabetes mellitus. Int J Med and Health Sci. 2016;2(2):49-51.
27. Thilip Kumar G, Saravanan A, Ramachandran C and John Nitin Ashok. Mean blood glucose level and glycated haemoglobin level in patients of non-insulin dependent diabetes mellitus and its correlation with serum ferritin level. Int J Med Sci. 2011;4(1 and 2):13-7.
28. Ryoo JH, Kim SY Oh CM. The incidental relationship between serum ferritin levels and hypertension. Int J Cardiol. 2015;183:258-62.
29. Raj S, Rajan GV. Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus. Int J Res Med Sci. 2013;1(1):12-5.
30. Samotra S, Kudyar RP. Relationship between serum ferritin and type 2 diabetes mellitus. J Knowledge Sci. 2008;10:170-4.

Cite this article as: Saluja M, Suman CP, Chittora S, Meena D. Association of serum ferritin and glycated haemoglobin in patients of type 2 diabetes mellitus and its correlation with components of metabolic syndrome. Int J Res Med Sci 2022;10:1657-62.