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Original Research Article

A Case Control Study to Assess the Level of Serum Ferritin and Correlation between Serum Free Iron Concentrations in Type-2 Diabetics

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Abstract

Aim: The aim of the present study was to assess the level of serum ferritin in type 2 diabetes patients with good and poor glycemic control and also assessed the correlation between serum free iron concentrations with glycemic control.

Methods: The study was conducted in the Department of General Medicine, JLN Medical College and Hospital, Bhagalpur, Bihar, India for the period of two years. Study population was patients of type 2 diabetes mellitus visiting outpatient department of our hospital. This study comprises 200 patients with type 2 diabetes mellitus (treated with hypoglycemic drugs), as cases and 200 patients, age and sex matched apparently healthy adults as a control group.

Results: Age and sex difference between two groups was statistically non-significant. On comparison of serum ferritin levels between cases and controls it was found that the mean serum ferritin of diabetic population was 139.85 ± 62.98 ng/mL and that of control group was 61.97 ± 26.64 ng/mL (p value< 0.05). Serum ferritin of case group is therefore significantly higher than the control group. Similarly, BMI, fasting blood glucose (mg/dl) and glycated haemoglobin (HbA1C) values were significantly higher in diabetic group as compared to control group. We compared serum ferritin values with HbA1C values in diabetic patients. Increase in serum ferritin levels was noted with increasing values of HbA1C. Correlation between serum ferritin and HbA1c was also assessed. The correlation between glycated haemoglobin and serum ferritin was done by Pearson correlation test and it showed a significantly positive correlation (r=0.512) with serum ferritin.

Conclusion: The present study concluded that positive correlation between serum ferritin levels and increased HbA1c reflecting poor glycemic control. This highlights the need for strict glycemic control in these subjects. Further studies are needed to verify the importance of screening of hyperferritinemia in type 2 diabetic patients and to define cut-off level of serum ferritin for possible early detection and subsequent prevention or delaying of impaired glucose tolerance and diabetes in those participants.

Keywords: Fasting blood glucose, HbA1c, Serum ferritin, Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (DM2) is an important health problem worldwide affecting about 8 percent of population. [1] The prevalence of disease continued to rise over the recent decades. [2-6] The probable role of inflammatory factors and cytokines in producing DM was described by Pickup JC in 1998. [7] Similar results also were found by other studies which showed that acute phase reactants may be useful for predicting DM [8-11] however, these findings were not found in some other studies. [12]

Acute phase reactants are proteins that respond to acute stress such as infection, trauma, surgery and tissue necrosis. Some of these agents are alpha-acid glycoprotein, haptoglobin, fibrinogen, C-reactive protein (CRP) and ferritin. [13-15] CRP is produced by liver cells and could activate complement system and T and B lymphocytes. Erythrocyte Sediment Rate (ESR), as an acute phase reactant, is less important than CRP for evaluation of inflammation. [9,16] Ferritin is a complex globular protein that stores iron as soluble and non-toxic component. In

oxidative stress, Fe2+ enters to cells and then changes to Fe3+, linked to ferritin and then protect cells from oxidative stress. [17] Increasing concentration of iron and ferritin in cells could cause resistance to insulin and dysfunction of β cells of pancreases. Hyperinsulinemia due to resistance to insulin may be responsible for increasing serum ferritin. It has been suggested that disturbance of iron metabolism could cause insulin resistance, hyperinsulinemia, dyslipidemia, HTN and central obesity. [18,19]

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. [20] 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. [21] Ferritin is a specialized iron storage protein, which reflects iron stores in the body. [22] Previous studies have demonstrated an association between increased serum ferritin levels and higher risks of diabetes. [23,24] 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. [24,25]

The aim of the present study was to assess the level of serum ferritin in type 2 diabetes patients with good and poor glycemic control and also assessed the correlation between serum free iron concentrations with glycemic control.

Materials and Methods

The study was conducted in the Department of General Medicine, JLN Medical College and Hospital, Bhagalpur, Bihar, India for the period of two years.Study population was patients of type 2 diabetes mellitus visiting outpatient department of our hospital. This study comprises 200 patients with type 2 diabetes mellitus (treated with hypoglycemic drugs), as cases and 200 patients, age and sex matched apparently healthy adults as a control group.

Inclusion Criteria

Diabetic patients (type 2, treated with hypoglycemic drugs), age more than 30 years of both the gender. Diabetic patients met the criteria American Diabetes Association.9

Exclusion Criteria

Patients with anaemia (Haemoglobin levels less than 12g/dl in women and less than 13g/dl in males) or receiving treatment for anaemia in the past three months, Patients receiving iron supplements, pregnant women. Patients with history of blood donation in the last three months, Patients with diagnosed type 1 diabetes mellitus, Patients with hepatic disorders, renal disorders, malignancies, acute infections, fever, myocardial infarction, bleeding disorders or Patients with history of drug or alcohol abuse. Patients on medication with possible influence on serum ferritin levels. Patients who do not give consent to the study.

All participants after their written informed consent underwent detailed physical and clinical examination. BMI was calculated using standard formula. Under all aseptic and antiseptic conditions 5 ml of blood sample was collected from each subject (with overnight fasting) and divided into a sterile empty vial and an EDTA vial. EDTA vials are used for estimation of glycated hemoglobin and blood glucose. The rest of the sample was then allowed to stand for some time and then centrifuged for separation of serum. Blood glucose measurement by spectrophometric Glucose oxidase per oxidase (GOD-POD) method which is enzymatic, specific, accurate and rapid method of measurement of true blood glucose. Estimation of serum ferritin was done by using automated Chemiluminescence Immunoassay system (CLIA).

Statistical analysis Arithmetic mean and standard deviation were calculated to assess the levels of various parameters in both groups. Students 't' test was used for comparison of quantitative variables. Co-relation between serum ferritin and HbA1c% in patients and co-relation between serum ferritin and fasting blood glucose levels was evaluated using Pearson Co-relation Co-efficient. All tests were considered statistically significant if the p-value was <0.05.

Results

Table 1: Comparison of means of the different anthropometric, clinical and biochemical characteristics

Parameters	Diabetic group	Control group	P value
Age (years)	53.06 ± 12.58	51.89+13.27	>0.05
Male / female	92 / 108	85 / 115	>0.05
Serum ferritin (ng/mL)	139.85 ± 62.98	61.97 ± 26.64	<0.01
BMI (Kg/m2)	26.32 ± 3.06	24.86 ± 2.68	<0.01
Fasting blood glucose (mg/dL)	162.28 ± 46.54	82.86 ± 13.27	<0.01
Glycated haemoglobin (HbA1C) (%)	8.94 ± 2.22	5.35 ± 0.75	<0.01

Age and sex difference between two groups was statistically non-significant. On comparison of serum ferritin levels between cases and controls it was found that the mean serum ferritin of diabetic population was 139.85 ± 62.98 ng/mL and that of control group was 61.97 ± 26.64 ng/mL (p value< 0.05). Serum ferritin of case group is therefore significantly higher than the control group. Similarly, BMI, fasting blood glucose (mg/dl) and glycated haemoglobin (HbA1C) values were significantly higher in diabetic group as compared to control group.

Table 2: Comparison of serum ferritin with HbA1C in diabetic patients

HbA1C Range (%)	No.	Mean ± SD HbA1C%	Serum Ferritin (ng/mL)
6 -7.5	65	6.84 ± 0.64	94.42 ± 36.54
7.51- 9	55	8.07 ± 0.84	118.22 ± 22.83
9.01-10.5	45	9.95 ± 0.43	155.65 ± 38.22
> 10.5	35	11.85 ± 1.12	229.11 ± 12.74

We compared serum ferritin values with HbA1C values in diabetic patients. Increase in serum ferritin levels was noted with increasing values of HbA1C.

Table 3: Correlation between serum ferritin and HbA1c levels Group

	Mean±SD	Pearson Correlation
Serum Ferritin (ng/mL)	139.85 ± 62.98	.512
Glycated haemoglobin (HbA1C)	8.94 ± 2.22	

Correlation between serum ferritin and HbA1c was also assessed. The correlation between glycated haemoglobin and serum ferritin was done by Pearson correlation test and it showed a significantly positive correlation (r=0.512) with serum ferritin.

Discussion

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. [26,27] 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. [28]

Scientific studies had 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. [29] Other mechanisms related to serum ferritin are, potent hydroxyl radicals from iron by Heber–Weiss and Fenton reactions impair mechanism of vasodilatation, disrupt endothelium, accelerate development of atherosclerosis, diabetic nephropathy, and other microvascular complicat ions associated with type II diabetes within 7 years. [30] Age and sex difference between two groups was statistically non-significant. On comparison of serum ferritin levels between cases and controls it was found that the mean serum ferritin of diabetic population was 139.85 ± 62.98 ng/mL and that of control group was 61.97 ± 26.64 ng/mL (p value< 0.05). Serum ferritin of case group is therefore significantly higher than the control group. Similarly, BMI, fasting blood glucose (mg/dl) and glycated haemoglobin (HbA1C) values were significantly higher in diabetic group as compared to control group. We compared serum ferritin values with HbA1C values in diabetic patients. Increase in serum ferritin levels was noted with increasing values of HbA1C. Correlation between serum ferritin and HbA1c was also assessed. In present study levels of BMI, fasting blood glucose, HbA1c and serum ferritin were significantly higher in diabetic patients as compared to controls. Similar findings were noted by Chandrashekhar et al [31] and Kundu et al[32] A significant increase in serum ferritin levels was observed in diabetic patients with raised HbA1c compared to well controlled ones, findings are consistent with the study of Chandrashekhar et al.

The correlation between glycated haemoglobin and serum ferritin was done by Pearson correlation test and it showed a significantly positive correlation (r=0.512) with serum ferritin. Pramiladevi et al noted a significant correlation in diabetics compared with individuals with normal blood sugar regarding

increased serum ferritin, and hyperferritinemia may be one of the causes for development of insulin resistance before overt diabetes. [33] Contrary to present study, Thilip Kumar G et al. reported that patients with type 2 diabetes had significantly higher serum ferritin level when compared to healthy controls but there is no correlation between serum ferritin with mean blood glucose and HbA1c. [34]

Conclusion

The present study concluded that positive correlation between serum ferritin levels and increased HbA1c reflecting poor glycemic control. This highlights the need for strict glycemic control in these subjects. Further studies are needed to verify the importance of screening of hyperferritinemia in type 2 diabetic patients and to define cut-off level of serum ferritin for possible early detection and subsequent prevention or delaying of impaired glucose tolerance and diabetes in those participants.

References

1. Hughes E, McCracken M, Roberts H, Mokdad AH, Valluru B, Goodson R, Dunn E, Elam-Evans L, Giles W, Jiles R. Surveillance for certain health behaviors among states and selected local areas--behavioral risk factor surveillance system, United States, 2004. MMWR Surveill Summ. 2006 Jul 14;55(7):1-124.
2. McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. Lancet. 20 00 Aug 26;356(9231):757-61.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
4. National Center for Health Statistics (US). Chartbook on Trends in the Health of Americans. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2002.
5. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med. 2010 Mar 25;362(12):1090-101.
6. Fox CS, Pencina MJ, Meigs JB, Vasan RS, Levitzky YS, D'Agostino RB Sr. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham Heart Study. Circulation. 2006 Jun 27;113(25):2914-8.
7. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? Diabetologia. 1998 Oct;41(10):1241-8
8. Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, Koenig W. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Arch Intern Med. 2003 Jan 13;163(1):93-9.
9. Festa A, D'Agostino R Jr, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP, Haffner SM. The relation of body fat mass and distribution to markers of chronic inflammation. Int J Obes Relat Metab Disord. 2001 Oct;25(10):1407-15.
10. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N; West of Scotland Coronary Prevention Study. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes. 2002 May;51(5):1596-600.
11. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes. 2004 Mar; 53(3):693-700.
12. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, Kobes S, Tataranni PA, Hanson RL, Knowler WC, Lindsay RS. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. Diabetes Care. 2003 Jun;26(6): 1745-51.
13. Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H. Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. Proc Natl Acad Sci U S A. 1987 Oct;84(20):7251-5.
14. Moshage HJ, Janssen JA, Franssen JH, Hafkenscheid JC, Yap SH. Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. J Clin Invest. 1987 Jun;79(6):1635-41.
15. Kushner I. The phenomenon of the acute phase response. Ann N Y Acad Sci. 1982;389:39-48.
16. Hoffmann JA, Kafatos FC, Janeway CA, Ezekowitz RA. Phylogenetic perspectives in innate immunity. Science. 1999 May 21;284 (5418):1313-8.
17. Theil EC. Ferritin: structure, gene regulation, and cellular function in animals, plants, and microorganisms. Annu Rev Biochem. 1987;56: 289-315.
18. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. Diabetes Care. 2004 Oct;27(10):2422-8.
19. Ashourpour M, Djalali M, Djazayery A, Eshraghian MR, Taghdir M, Saedisomeolia A. Relationship between serum ferritin and inflammatory biomarkers with insulin resistance in a Persian population with type 2

diabetes and healthy people. Int J Food Sci Nutr. 2010 May;61(3):316-23.
20. 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;145:5 305-12.
21. 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.
22. 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.
23. 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.
24. Feldt-Rasmussen. Is there a need to optimize glycemic control in hemodialyzed diabetic patients? Kidney Int. 2006;70:1392-4.
25. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. Am J Med. 2010; 123(3):S3-11.
26. 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.
27. 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.
28. IDF Diabetes Atlas. Chapter-2.1, 6th edn. 2013;34.
29. Mellitus TI, Bansal P. Is serum ferritin associated with type II diabetes mellitus: A clinical study in a representative Indian population. Journal of Medical Science & Research. 2011;2(1).
30. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in US adults. Diabetes care. 2004 Oct 1;27(10):2422-8.
31. Chandrashekhar HR, Shekar HS, KiranNagaraju, Chikkalingiah and Bhagavan BC (2014): Association of Serum Ferritin Levels with Glycemic Control in type-2 Diabetes Mellitus. Indian J. of Pharmacy Practice, 7 (1): 58-61.
32. Kundu AR, Mandal T, Bandyopadhyay U, Ghosh E, and Ray D (2013): Relation of iron stores to oxidative stress in type 2 diabetes. Nigerian Journal of Clinical Practice, 16(1):10 0-103.
33. Pramiladevi R, Boke U, Kora S. Serum ferritin levels in type II diabetes mellitus. Sch J App Med Sci 2013; 1:472– 475.
34. 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 (1and 2): 13-17.