



SERUM FERRITIN LEVELS AS A RISK FACTOR IN TYPE II DIABETES MELLITUS

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ABSTRACT

Diabetes Mellitus is a predominant public health concern, affecting millions of people worldwide. Recently, it has been recognized that, increased body iron stores are associated with Type-2diabetes mellitus. Increased Serum Ferritin have been reported to negatively correlate with insulin sensitivity and the presence of insulin resistance syndrome. The relationship between iron metabolism and type 2 diabetes mellitus is bi-directional. Iron affects glucose metabolism and glucose metabolism impinges on several iron metabolic processes. Iron overload decreases insulin sensitivity and cause earlier complications in diabetes mellitus. This study attempts to evaluate the significance of serum ferritin level as an early predictor of type 2 diabetes mellitus and its relationship with HbA1c.

KEY WORDS : Type II diabetes mellitus, Ferritin, Glycated haemoglobin HbA1c



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INTRODUCTION

Diabetes mellitus, a metabolic disorder due to absolute or relative insulin deficiency characterized by chronic hyperglycemia, disturbance of fat & protein metabolism. The insulin deficiency may either be due to defects in insulin secretion or action. Type 1 diabetes mellitus is insulin dependent & is mainly immune mediated. Type 2 diabetes mellitus is non –insulin dependent where the circulating insulin level is normal or slightly elevated or decreased, depending on the stage of the disease¹. According to the Diabetes Atlas 2006 published by the International Diabetes Federation ,the number of people with Diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025.^{2,3} Several studies have shown that there is increased oxidative stress in Diabetic patients with Iron overload⁴. Ferritin is an index of body iron stores & acts as an iron overload marker. Iron is a transition metal & a potential catalyst in cellular reaction that produces reactive oxygen species . More recently the results from prospective studies from Caucasian populations suggested that Iron overload could predict the development of abnormal glucose metabolism⁵. The aim of this study is to find the influence of body iron stores on type II diabetes mellitus and its correlation with HbA1c.

MATERIALS AND METHODS

Blood sample (5 ml) , serum separated is obtained from 100 individuals [50 diabetics and 50 healthy controls) attending medicine / diabetology outpatient department of our institute, Sree Balaji Medical College And Hospital , Chromepet , Chennai , India.

EXCLUSION CRITERION

Those individuals with history of iron supplementations, recent blood transfusions, family history of iron overload states, liver dysfunction and renal insufficiency were excluded from the study.

INVESTIGATIONS , performed

1. HbA1c by ion exchange chromatography
2. Serum ferritin levels by particle enhanced turbidimetric immunoassay

3. Fasting blood sugar and post prandial blood sugar by GOD – POD [glucose oxidase – peroxidase method], Diatek Kit , Fully Automated Analyser
4. Serum Creatinine By Jaffes Kinetic Method , Erba Biochem
5. 12 lead ECG [electrocardiogram]

The association of serum ferritin with HbA1c was evaluated by using pearsons correlation coefficient . Statistical analysis was done with SPSS 15 software. The study was approved by the institutional ethical committee of Sree Balaji Medical College And Hospital . An informed consent was obtained , both in English and in vernacular languages from the participants of the study..

RESULTS OF THE STUDY

1. Among diabetics, mean serum ferritin : 120.44 ng/ml
2. Among healthy controls, mean serum ferritin : 62.27 ng/ml
3. Student t test, level of significance, $t = 5.201$ [$p < 0.000$]
4. There was a positive correlation between ferritin & HbA1C [Pearson correlation between ferritin & HbA1C is 0.34]

DISCUSSION

DIABETES MELLITUS TYPE II – IMPACT

Diabetes Mellitus is a predominant public health concern, affecting millions of people worldwide. The disease causes substantial morbidity and mortality and long term complications. Recently, it has been recognized that, increased body iron stores are associated with the gestational diabetes & Type-2diabetes¹. Increased Serum Ferritin (SF) have been reported to negatively correlate with insulin sensitivity^{2,3}and the presence of insulin resistance syndrome⁴. associated with significant long term sequelae, particularly damage or dysfunction of various organs especially kidneys, eyes, nerves, heart and blood vessels⁵.

FERRITIN IN TYPE II DIABETES MELLITUS

Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. The reference ranges for serum ferritin are 30-300 ng/mL for males, and 10-160 ng/mL for females. Numerous prospective epidemiological studies have shown that serum ferritin is an important and independent predictor for the development of diabetes mellitus. The publication of report about the relationship between excess ferritin, coronary heart disease and insulin resistance has increased interest in ferritin, as a possible risk factor for diabetes mellitus.

RELATIONSHIP BETWEEN IRON AND GLUCOSE METABOLISM

Free iron exerts a positive feedback on ferritin synthesis, and oxidative stress increases the release of iron from ferritin⁶. Iron overload decreases insulin sensitivity and cause earlier complications in diabetes mellitus. In addition to pancreatic beta cell damage, insulin resistance may be the other explanation for hyperglycemia following iron overload. Furthermore abnormalities in ferritin metabolism following glycation in a hyperglycaemic state might be a primary cause of hyperferritinaemia in type 2 diabetes mellitus. Inflammation was suggested to regulate not only ferritin mRNA and protein levels but also its secretion. As a result, elevated ferritin concentrations might reflect systemic inflammation in addition to elevated body iron stores. Meanwhile, inflammation was postulated to be involved in the physiopathological mechanisms behind metabolic syndrome and diabetes.

SERUM FERRITIN – A RISK FACTOR IN TYPE II DIABETES MELLITUS

Ferritin has been known as an index for body iron stores and also as an inflammatory marker. In some epidemiological studies, serum ferritin was the second strongest determinant of blood glucose (after BMI) in regression models and the third strongest determinant of serum insulin (after BMI and age)⁶. Its concentration also correlated positively with plasma triglycerides and apolipoprotein B concentrations, and negatively with HDL2 cholesterol⁵. It was then hypothesized that serum ferritin could be a

marker of insulin resistance. The probable correlation between ferritin and DM was considered first in 1993 by Kayet al.⁶, after which other studies were focused on this subject. In 1999 a survey by Ford and his colleagues in United States on 9486 diabetic adults determined high levels of ferritin in diabetics⁷. Another study by Kwant⁸ on the prevalence of C282Y mutation of hemochromatosis gene, determined the higher prevalence of this mutation in type 2 DM, that could be considered as an evidence for some relationship between these two disorders. Fernandez in 1998 studied the relationship between serum ferritin and the results of glucose tolerance test and insulin sensitivity in healthy subjects. In this study the correlation between serum ferritin and diastolic blood pressure, HDL, glucose area under the curve and insulin sensitivity suggest that serum ferritin could be a marker of insulin resistance. Such results have also been reported by Kim et al. There are different theories regarding the role of ferritin in DM. Pancreatic damage due to some degree of subclinical hemochromatosis has been considered at least in some cases of diabetes¹⁸. Others have determined ferritin just as a marker of pancreatic inflammation, and some have referred to it as a marker for insulin resistance as mentioned above. Fernandez et al, studied the effect of ferritin reduction by blood letting on insulin sensitivity and HbA1c levels in diabetic patients⁹. In this study the positive effect of ferritin reduction on blood glucose control was used for confirmation of the probable role of ferritin in DM pathogenesis but, the use of blood letting may affect total hemoglobin level and HbA1c as well, so the use of HbA1c as a marker of blood glucose control has not been appropriate. Recently some studies have investigated the effect of chelator agents such as Desferal on the control of diabetes mellitus¹⁰. There are different results in this regard. Some studies have determined a higher level of ferritin in people who are high risk for atherosclerosis¹¹. Since insulin resistance has been considered as the basic factor in the pathogenesis of atherosclerosis¹² higher ferritin in atherosclerotic patients can be due to insulin resistance. Poorly controlled patients of DM have hyperferritinemia which

co-relates with diabetic retinopathy, diabetic nephropathy and vascular dysfunction¹¹⁻¹³. Jiang et al¹⁴ have reported elaboration of hydroxyl radical in iron overload which causes cell damage and leads to insulin resistance. Deferroxamine, a chelating agent with antioxidant properties improve fasting blood glucose in chronically transfused patients of thalassemia major support this hypothesis. Recently, it has been suggested that transferrin and iron induce IR of glucose transport in adipocytes¹⁵. Some studies found a positive correlation between increased SF and poor glycemic control reflected by higher HbA1C, supporting the findings of Eschwege et al¹⁶. DyMock et al¹⁷ reported influence of the increased body iron stores on diabetic nephropathy and vascular dysfunction. In patients with increased SF glycemic control is poor and there is vascular

damage. Insulin resistance has been documented by Ralpa&Fronzo¹⁸ in such patients.

LIMITATIONS

A variety of limitations of this study need however also to be addressed. The sample size is small which did not allow a multivariate approach for incorporating additional, potentially meaningful factors for modifying the levels of serum ferritin and HbA1c. Nevertheless it seems reasonable that routine screening for serum ferritin levels among diabetics provide additional information and so pave the way for more clinical trials on research for serum ferritin levels in a larger population and thereby intervening iron metabolism as one of the possible modalities in treating diabetic individuals.

REFERENCES

1. Fernandez-Real JM, Lopez-Bermejo A, Ricart. Cross talk between iron metabolism and diabetes. *Diabetes* 2002; 51:2348-54.
2. Dmochowski K, Finegood DT, Francombe W, Tyler B, Zinman B. Factors determining glucose tolerance in patients with thalassemia major. *J ClinEndocrinolMetab* 1993;77:478-83.
3. Cavallo-Perin P, Pacini G, Cerutti F, Bessone A, Condo C, Sacchetti L, et al. Insulin resistance and hyperinsulinemia in homozygous β -thalassemia. *Metabolism* 1995; 44: 281-86.
4. Wrede CE, Buettner R, Bollheimer LC, Scholmerich J, Palitzsch KD, Hellerbrand C. Association between serum ferritin and the insulin resistance syndrome in a representative population. *Eur J Endocrinol* 2006;154:333-40.
5. Suvarna J, Ingle H, Deshmukh CT. Insulin resistance and beta cell function in chronically transfused patients of thalassemia major. *IndPediatr* 2006; 43:393-400.
6. Ascherio A, Rimm EB. Blood Donation and risk of coronary heart disease in men. *Circulation* 2001; 103: 52-57.
7. Dymock IW, Cassar J, Pyke DA, Oakley WG.. Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis. *Am J Med* 1972; 52:203-10.
8. Facchini FS. Effect of phlebotomy on plasma glucose and insulin concentrations. *Diabetes Care* 1998; 21:2190.
9. Facchini FS. Effect of phlebotomy on plasma glucose and insulin concentrations. *Diabetes Care* 1998; 21:2190.
10. Jiang R, Ma J, Ascherio A, Stampfer MJ, Willett WC, Hu FB. Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am J Clin Nutr* 2004;79:70-5.
11. Canturk Z, Cetinarslan B, Tarkun I. Serum ferritin levels in poorly- and well-controlled diabetes mellitus. *Endocr Res* 2003; 29: 299-306.
12. Loebstein R, Lehotay DC, Luo X, Bartfay W, Tyler B, Sher GD. Diabetic nephropathy in hypertransfused patients with beta-thalassemia. The role of oxidative stress. *Diabetes Care* 1998; 21:1306-9.
13. Sumeet Smotra and R.P. Kudyar. Relation between serum ferritin and type 2 diabetes mellitus. *JK Science*, vol. 10, no. 4, Oct-Dec 2008:170-174.

14. Bansal Pankaj, Bansal Puja, Raizada Akshay and Kansal H.M. Is serum ferritin associated with type 2 diabetes mellitus: A clinical study in a representative Indian population. *Journal of Medical Science and Research*, 2011, vol. 2, issue:1: 20-24.
15. N G Forouhi, A H Harding, M Allison, M S Sandhu, A Welch, R Luben, S Bingham, K T Khaw and N J Wareham. Elevated serum ferritin level predict new-onset type 2 diabetes mellitus: results from the EPIC-Norfolk prospective study. *Diabetologia* 2007, vol. 50: 949-956.
16. Jeevan K Shetty, Mungli Prakash and Mohammad S Ibrahim. *Indian Journal of Biochemistry* 2008/23(1): 67-70.
17. Earl S. Ford and Mary E. Cogswell. Diabetes and serum ferritin concentration among US adults. *Diabetic Care* December 1999, vol. 22, number 12: 1978-1983.
18. Jose Manuel Fernandez-Real, Abel Lopez-Bermejo and Wifredo Ricart. Cross-talk between iron metabolism and diabetes. *Diabetes*, August 2002, vol. 51, no. 8: 2348-2354.