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Research Article

SERUM FERRITIN LEVELS IN TYPE 2 DIABETES MELLITUS AND ITS RELATIONSHIP WITH HbA1c

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ABSTRACT

Diabetes Mellitus is a disease of metabolic dysregulation, affecting millions of people worldwide. Recent studies have emphasized the role of serum ferritin in insulin resistance. 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. The aim of this study is to establish an association between serum ferritin, FBS and HbA1c in type 2 diabetes mellitus and to evaluate the role of serum ferritin on glycemic status.

A case control study was conducted on 60 diabetic patients and 60 controls, aging between 30-65 years, admitted in the Department of Medicine, GMC, Jammu. The participants were categorized into three distinct groups. Estimation of blood glucose, HbA1C, and serum ferritin levels was performed on all subjects and controls.

Serum ferritin increased significantly in diabetes mellitus patients with high HbA1c or with complications, ie upto 293.9 ± 20.6 ng/ml from 168.5 ± 11.8 ng/ml, for those without complications and 100.6 ± 7.0 ng/ml amongst healthy controls. The present study showed positive correlation between increasing serum ferritin amongst Type 2 diabetics with complications, signalling towards an alarming development of hemochromatosis in a long standing diabetic patient.

INTRODUCTION

India is leading with larger number of diabetic patients than any other country, earning the dubious distinction of being the "capital of diabetes in the world". Prevalence of type 2 diabetes mellitus is expected to double between 2000 and 2030, with India predictably having largest number of type 2 diabetes patients than any other nation on the globe. (Wild *et al*., 2004) The prevalence of type 2 diabetes mellitus in India was estimated to be 7.8% in 2010 for a total of roughly 51 million people in accordance with International Diabetes Federation (IDF) Diabetes Atlas. Considering World Health Organization Criteria, the earlier study in urban India showed even higher prevalence, i.e. 12.1%. (IDF, 2009) It is expected that type 2 diabetes will rise to 9.3% by year 2030 with increase in percentage of Indians, the reasons might include migration of human beings from rural to urban areas with change in dietary habits, and the shift to an increasingly sedentary lifestyle. (Sudhakar *et al*., 2016)

Insulin resistance plays a major role in the development of IGT and diabetes.

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Insulin resistance is manifested by decreased insulin mediated glucose uptake and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. The symptoms and long term complications are influenced by the average blood glucose levels. Amongst the various markers of glycemic control, glycated haemoglobin has now been established as the most reliable, reflecting average glucose concentration over the previous two to three months. Emerging scientific evidences has disclosed unsuspected influence between iron metabolism and type 2 diabetes. The ability of iron to reversibly oxidize and reduce makes it potentially hazardous because of its ability to generate powerful oxidant species such as hydroxyl radicals. The relationship is bi-directional - iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways. Insulin influences the iron uptake and storage by increasing the cell surface transferrin receptors, reciprocally iron influences the insulin activity by interfering with glucose uptake and utilization. Iron causes hyperinsulinemia by decreasing the insulin uptake and metabolism by hepatocytes. Iron in its free form i.e., in non-transferrin bound form is known to induce oxidation of biomolecules through Heber-Weiss and Fenton reactions by producing harmful hydroxyl radicals. (Nitin *et al*., 2010)

Iron homeostasis in the body can be evaluated by measuring Ferritin, a key protein which regulates the homeostasis. (Jiang *et al*., 2004 a,b) Increased serum ferritin, reflecting body iron overload, is often associated with measures of insulin resistance, such as elevated blood glucose and insulin levels. Elevated iron stores may induce diabetes through a variety of mechanisms, including oxidative damage to pancreatic beta cells, impairment of hepatic insulin extraction by the liver, and interference with insulin's ability to suppress hepatic glucose production. (Vaitla and Vani, 2017) Hence, the present study was carried out to establish serum ferritin in type 2 diabetes and its correlation with Hb A1C.

MATERIAL AND METHODS

A case control study was conducted on 60 diabetic patients admitted in the Department of Medicine, Government Medical College Jammu, J&K, India. 60 age and gender-match healthy controls were also selected for the sake of comparison. Inclusion criteria were individuals willing to participate in the study either gender and age 30-65 years. The participants were categorized into three groups. They were: Group 1 (Healthy controls, matched for age and gender, with HbA1C <6.5%), Group 2 (Individuals with diagnosed type 2diabetes mellitus patients with HbA1C <8% and without complications) and Group 3 (Individuals with diagnosed Type 2 Diabetes mellitus patients with HbA1c > 8% or with complications).

Cases suffering from Anemia, Hypertension, Overt thyroid dysfunction, chronic kidney disease, Chronic liver disease, on corticosteroid therapy, history of recent blood transfusions, and family history of iron overload were excluded from this study. The data was collected through performa including gender, age, medical history, onset duration and complication of diabetes was filed. Physical examination was done. 5ml of venous blood was aseptically collected in vials and was separated for the estimation of blood glucose, HbA1c, and serum ferritin levels.

Blood glucose was estimated by Abott ARCHITECT c-Systems by hexokinase method following the principle: Glucose is phosphorylated by hexokinase in the presence of ATP and Magnesium ions to produce glucose -6-phosphate and Adenosine diphosphate. Glucose -6-phosphate dehydrogenase specifically oxidizes G-6-Phosphogluconate with the current reduction of NAD to NADH. One micromole of NADH is produced for each micromole of glucose consumed. The NADH produced, absorbs light at 340 nm and can be detected spectrophotometrically as an increased absorbance. (Burtis and Ashwood, 1994)

HbA1C was estimated on ARCHITECT c-Systems following the principle consisting of two separate concentrations' measurements: glycated Hb and total haemoglobin. Total haemoglobin is oxidized to stable methemoglobin azide by the action of sodium nitrite and sodium azide and the concentration of the hemoglobin is determined by measuring absorbance.

HbA1C alculations: The final result is expressed as %HbA1c (NGSP) or mmol/l/mol HbA1c (IFCC) and is automatically calculated by the system from the HbA1C/THb ratio as follows:

Mmol/mol HbA1c IFCC: HbA1c(mmol/mol) = (HbA1c/THb) x1000

% HbA1c DCCT/NGSP: HbA1c (%) = IFCC x 0.09148 + 2.152

The two concentrations are used to determine the percent HbA1C or the hemoglobin fraction in mmol/L. the individual concentration values of HbA1C and THb generated by HbA1C fraction, and must not be used individually for diagnostic purposes. (Table 1)

Table 1 Expected reference range of HbA1c values and their use for diagnostic purposes

HbA1c Value	Glycemic Goal
<8% HbA1c (64 mmol/mol)	Less stringent
<7% HbA1c (53 mmol/mol)	General (non-pregnant adults)
<6.5% HbA1c (48 mmol/mol)	More stringent

As recommended by ADA, patients in the range of 5.7% to 6.4% HbA1c would be in the category of increased risk of diabetes and results >6.5% HbA1c may aid in the diagnosis of diabetes. (ADA, 2012)

Ferritin levels was measured by chemiluminescent microparticle immunoassay (CMIA)with normal reference range 30-300 ng/ml for males, and 10-160 ng/ml for females. (NCCLS, 1992)

RESULTS

In the present study, a total of 120 subjects were studied in total with serum ferritin found significantly higher in cases (Group 2 and 3) as compared to controls (Group 1) ($p<0.001$) with mean ± sd of serum ferritin levels for group 1 being 100.6 ± 7.0 ng/ml. (Figure 1)

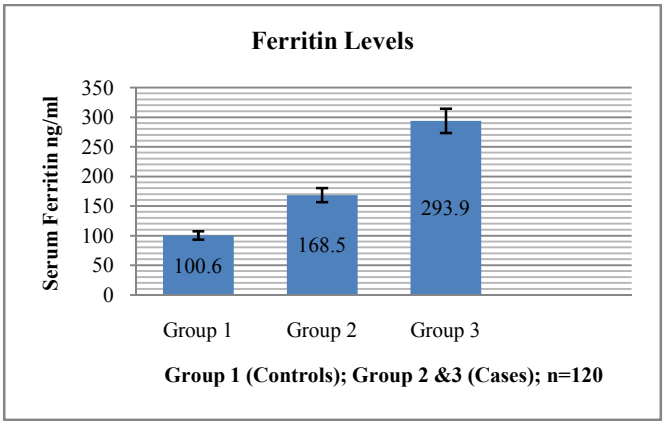

Fig 1 Graphical representation of mean ± SD of serum ferritin in 3 groups

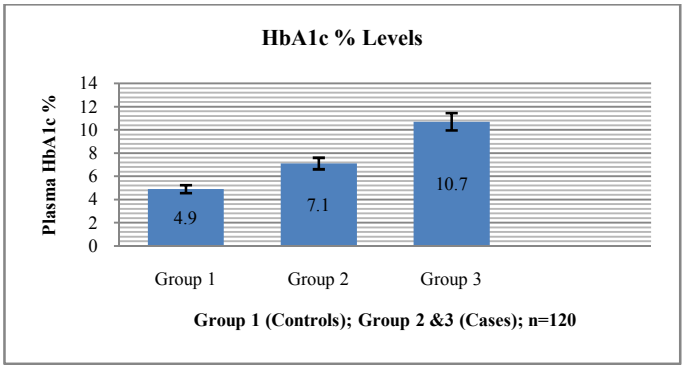

Fig 2 Graphical representation of mean ± SD of HbA1c % in 3 groups

In group 2&3, ferritin was positively correlated with FBS and PLBS but only correlation with PLBS was statistically significant. Figure: 2 shows that Ferritin was positively correlated with HbA1c and was significant in group 2 and

group 3 as well. Results go on to show that serum ferritin increased significantly in diabetes mellitus patients with high HbA1c or with complications as compared to those without complications with mean serum ferritin level being 293.9±20.6 ng/ml for group 3 as compared to 168.5±11.8 ng/ml for group 2.

DISCUSSION

The mechanism of iron-induced diabetes is not certain, but it is very likely to be mediated by three mechanisms: insulin deficiency, insulin resistance and hepatic dysfunction, shown by Swaminatha, *et al*. (2007). Halliday *et al*. (1979) has also discussed that in the conditions of iron overload, there is generally an increase in the expression of intracellular L-subunit rich ferritins, paralleled by an increase in these ferritins in the plasma. Serum ferritin was significant in group 3 compared to group 1 & 2, thus marking insulin resistance/deficiency, possibly due to iron deposition in the lever leading to hepatic insulin resistance and increased hepatic glucose production as also show by Forouhi *et al*. (2007) and by Fernandez-Real *et al*. (1998) Others (Sumesh and Rajan, 2013; Jiang, 2004a,b) have also studied and found that serum ferritin, a reflector of body iron stores, was significantly higher in diabetic patients when compared to controls and is significantly increased with the duration of diabetes. The present study showing positive correlation between increasing serum ferritin from 100.6 ± 7.0 ng/ml amongst healthy controls to 293.9±20.6 ng/ml amongst T2 diabetics with complications, reflects upon a possible development of hemochromatosis in a long standing diabetic patient. (Moczulski *et al*., 2001; Dymock *et al*., 1972)

CONCLUSION

It Was Concluded from the results of the present study that increased serum ferritin levels are associated with increased HbA1c reflecting poor glycemic control, which tends to exhibit a certain degree of inflammation that, in one way or another, is likely to increase their risk of developing diabetes or cardiovascular disease. A variety of limitations of this study, however, also need 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. It is suggested that serum ferritin can be used as an inflammatory marker for long-term complications in Diabetes mellitus. Iron may also negatively impact on glycemic control. Though we recommend further studies in this regard, we suggest that ideally the clinical approach should be a careful balance between insufficient iron stores and excess iron.

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