Study of serum ferritin and HbA1c in type 2 diabetes mellitus

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Abstract
Introduction: Diabetes is a metabolic disorder characterized by hyperglycaemia which is associated with rise in the HbA1c. Excess iron damages β-cells of pancreas due to oxidative stress which can contribute to pathogenesis of diabetes mellitus. Recent research reveals that HbA1c concentration also increases in iron deficiency anemia as well. This fact is hence important as in diabetic patient, the HbA1c may not be only correlated with blood sugar level but also iron status, if the patient happens to be suffering from iron deficiency anemia.
Objectives: Correlation of HbA1c and glucose level with serum ferritin.
Materials and Methods: A Cross sectional pilot study was conducted in 80 diabetic patients at Central Clinical Laboratory, MIMER Medical College, Talegaon.
Result: There was a positive correlation between serum ferritin and Fasting sugar, postprandial sugar, HbA1c. Serum ferritin is significantly related to Fasting Sugar (P value- 0.0028); postprandial sugar (P value- 0.0118) and glycated Haemoglobin (P value-0.0007). P value <0.05 is considered statistically significant.
Conclusion: Serum ferritin is elevated in patients with type 2 diabetes mellitus and can be used as a marker for glycemic control in diabetic patients.

Keywords: Serum ferritin, Glycated haemoglobin, Type 2 diabetes mellitus.

Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia from defects in insulin secretion, insulin action, or both.[1] People with type 2 diabetes mellitus develop characteristic microvascular complications such as retinopathy, nephropathy and neuropathy. There is also increased risk of macrovascular complications such as cardiovascular, cerebrovascular and peripheral vascular disease.[2] Approximately 5.1 million people aged between 20 and 79 years died from diabetes accounting for 8.4% of global all cause mortality in this age group.[3] In India 65.1 million in the age group of 20 to 79 have diabetes (8.56%) and expected to rise to 109 million by the year 2035.[4]

Individuals with (T2DM) show both insulin resistance and beta cell defects.[5] The complications of diabetes mellitus are influenced not only by the duration of the diabetes mellitus but also by the average level of blood glucose along with glycated haemoglobin.[2] HbA1c is currently the investigation of choice in monitoring the treatment of diabetes mellitus.[6] Measurement of HbA1c provides valuable information for management of diabetes mellitus[7] but HbA1c may be affected by a variety of genetic, haematologic and illness-related factors[8] like haemoglobinopathies (depending on the assay employed), certain types of anaemia, and disorders associated with accelerated red cell turnover such as malaria.[7,9]

Serum ferritin is an acute phase reactant, and is a marker of iron stores in the body.[10] Iron is a transitional metal that can easily become oxidized and thus act as an oxidant[11] An important role of ferritin during the acute phase response is to restrict the availability of iron by sequestration into the cavity of the ferritin protein shell[12] High body iron stores that is serum ferritin have been linked to insulin resistance,[13,14] metabolic syndrome,[13,15,16] and gestational diabetes.[17,18] Excess iron damages β-cells of pancreas due to oxidative stress which can contribute to pathogenesis of diabetes mellitus.[19] In diabetic patient, the HbA1c may not be only correlated with blood sugar level but also iron status if the patient happens to be suffering from iron deficiency anemia.[20] serum ferritin level had a relationship with hyperglycemia and its level decreased with lowering of serum blood glucose.[21]

This study hence proposes to study iron status in diabetes mellitus and correlate the same with HbA1c and blood sugar level.

Objectives
1. Estimation of Serum ferritin as iron status.
2. Fasting and Post-prandial blood sugar level as glucose status.
3. Estimation of HbA1c as a index of glycation.
4. Correlation of Serum ferritin with HbA1c and glucose.

Materials and Methods
A Cross sectional pilot study was conducted at MIMER Medical College Talegaon and Dr. Bhausaheb Sardesai Rural Hospital Talegaon Dabhade, (Tertiary

care). The study was approved by institutional ethical committee, MIMER Medical College.

The diabetic patients who attended the medicine OPD between 40 to 65 year irrespective of gender were included in the study population.

The details of patient's history, clinical presentation, diagnosis and treatment recorded. 1 ml fasting venous sample was collected from subjects in plain bulb for estimation of serum ferritin after written informed consent. 2 ml sample collected in EDTA for HbA1c. 2ml fasting and post-prandial sample in fluoride bulb for blood glucose estimation.

Inclusion Criteria: Clinically diagnosed cases of diabetes mellitus of 2 years duration irrespective of gender between 40-60 years of age.

Exclusion Criteria: History of illness like acute and chronic infections, malignancy, iron and copper metabolic disorders (hemosiderosis, Wilson's disease). Diabetic patients with anemia and diabetic complications were excluded from the study. The Hb level to specify the cut off for anemia were < 13 g/dl in male and < 12 g/dl in female.

All estimations were done by methods which are available in our hospital.

Serum ferritin was estimated by ELISA.[22] Blood sugar level by spectrophotometric method.[23] HbA1c by Immunoturbidimetric method.[24]

Statistical Analysis

A total of 80 blood samples were received during the study period. The data was collected and arranged in tables using Microsoft Excel 2010. Mean, standard deviation, maximum and minimum values were calculated. Correlation was calculated using Pearsons' correlation coefficient. $P < 0.05$ was considered statistically significant.

Results

Mean, standard deviation, maximum and minimum values of Fasting and Postprandial blood glucose, Glycated Haemoglobin and Serum ferritin are shown in following Table.

Table 1: Mean, standard deviation, maximum and minimum values of fasting blood glucose, post prandial blood glucose, glycated haemoglobin and serum ferritin level

	Fasting blood sugar level (mg/dl)	Postprandial blood sugar level (mg/dl)	HbA1c Glycated Haemoglobin Level (%)	Serum Ferritin level (ng/dl)
Mean	161.85	239.39	7.75	199
Standard deviation	22.5	24.16	0.75	32.66
Minimum	119	196	6.2	145
Maximum	215	302	9.6	290

Correlation of glycated haemoglobin, fasting and post prandial blood glucose with Serum ferritin is shown in following Table.

Table 2: Correlation of HbA1c, fasting and post prandial blood glucose with serum ferritin level

Finding	r value	P value
Correlation of HbA1c with serum ferritin level	0.3717	0.0007 **
Correlation of fasting blood glucose with serum ferritin level	0.3298	0.0028 *
Correlation of postprandial blood glucose with serum ferritin level	0.2803	0.0118 *

(** - significant at p < 0.001. * -significant at p < 0.05)

Correlation of Fasting blood glucose with Serum ferritin is shown in following graph.

## Graph 1: Correlation of fasting blood glucose level with serum ferritin
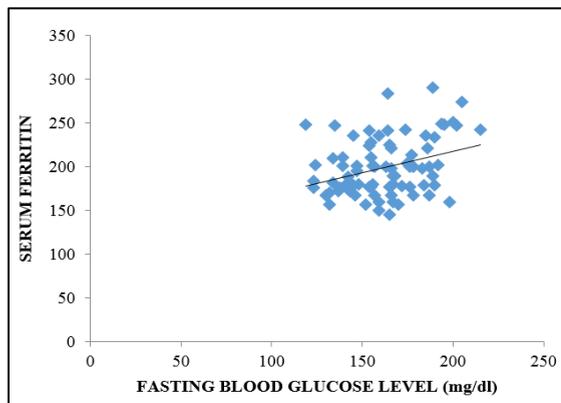
Correlation of post prandial blood glucose with serum ferritin is shown in following graph.

Graph 1: Correlation of postprandial blood glucose level with serum ferritin
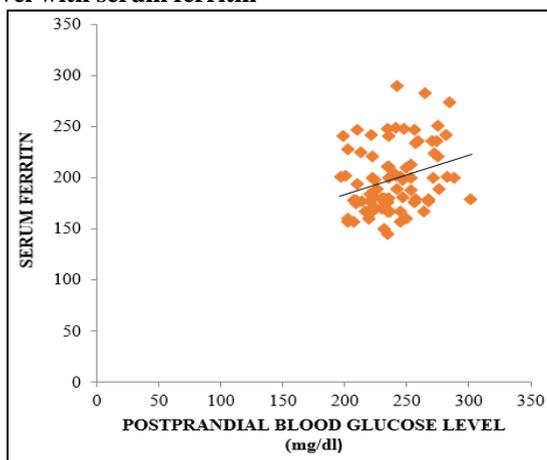
Correlation of glycated haemoglobin with serum ferritin is shown in following graph.

Graph 2: Correlation of glycated haemoglobin with serum ferritin
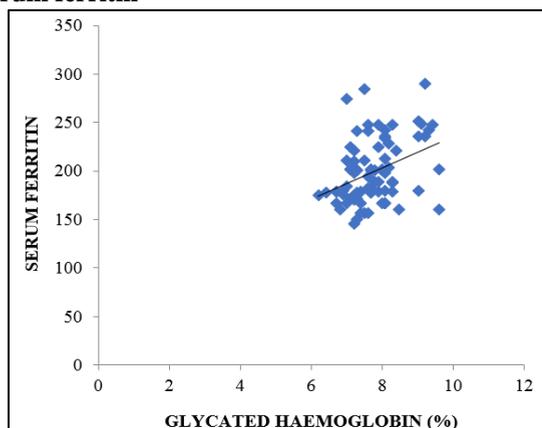
Discussion

Our study found a significance in comparing serum ferritin with glycated haemoglobin and blood glucose level in Type 2 Diabetes mellitus patient. Positive correlation between serum ferritin and HbA1c is seen, it may indicate increase iron status which may contribute to pathophysiology of diabetes mellitus.

Alap L Christy, Poornima A. Manjrekar, Ruby P. Babu, Anupama Hedge and Rukmini M.S. found a positive correlation between iron deficiency anemia and increased HbA1c levels especially in controlled diabetic individuals having FPG between 100-126 mg/dl.[25]

Sumesh Raj et al.[26] support this study in manner that in their study serum ferritin was significantly higher in the cases, when compared to controls ($p<0.01$) and serum ferritin was also significantly related to the duration of diabetes ($p<0.05$)

Researchers at University of Nottingham investigated studies between 1990 and 2014 in which HbA1c and glucose were measured as well as an index of anemia involving non-pregnant women not diagnosed with diabetes. The researchers recommend that when glucose and HbA1c level differs in diabetic patients, anemia or iron deficiency should be considered. If these abnormalities are identified, correction of high haemoglobin levels should be corrected before HbA1c is again used for diagnosis or monitoring. HbA1c is likely to be affected by iron deficiency and iron deficiency anemia with a spurious increase in HbA1c values. This may lead to confusion when diagnosing using HbA1c.[27]

Tarim O, Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I concluded that among type 1 DM patients with similar level of glycemia, iron deficiency anemia is associated with higher concentrations of HbA1c. In addition, iron replacement therapy leads to drop in HbA1c in both diabetic and non diabetic patients. The iron status of patient must be considered during the interpretation of HbA1c concentrations in type 1 DM.[28]

Recently, Jiang et al. carried out a nested case-control study within the nurses cohort with similar results.[29] In current study, mean serum ferritin of diabetic group was (271.4±47.755 μg/L) differed significantly ($p<0.05$) from the control group (203.6±42.877 μg/L) Poonam Arora concluded that serum ferritin is elevated in patients with type 2 diabetes mellitus when compared to healthy individuals and it indicates that serum ferritin can be used as a marker for glycemic control in diabetic patients.[30] Others has determined that ferritin just as a marker of pancreatic inflammation, while pancreatic damage due to some degree of subclinical hemochromatosis has been considered in some cases of diabetes.[31] Cantur KZ et al confirmed in their studies that poorly controlled diabetes patients had hyperferritinemia.[32] They also found a correlation between ferritin level and diabetic retinopathy. In diabetic subjects, a positive correlation

between increased serum ferritin and poor glycemic control, reflected by higher HbA1c, has been suggested by Eschwege et al[33] Ford checked serum insulin, hemoglobin A1C (HbA1c), fasting blood sugar (FBS), ferritin, and found a significant correlation between serum ferritin with HbA1c, FBS and serum insulin. He concluded that elevated serum ferritin is a risk factor for DM.[34]

Hence the current study concludes positive correlation between serum ferritin and glycated haemoglobin which implies the role of ferritin as an indicator of control of glycemia and diabetic complications. There was a positive correlation between serum ferritin with duration of diabetes. So serum ferritin could be used as a marker of insulin resistance.

Our study had some limitations such as we have not done estimation of Hb and RBC count to correlate with HbA1c and Serum ferritin. Also as we did not have facility of estimation of TIBC and Iron, it was not done. This study cannot be utilized to recommend protocols for diagnostic decision making as the mechanism of relationship between Ferritin and HbA1c is yet to be explained.

Conclusion

Based on this study it is concluded that serum ferritin is elevated in patients with type 2 diabetes mellitus and it indicates that serum ferritin can be used as a marker for glycemic control in diabetic patients. For right glycemic control, it is absolute necessity that iron stores should be adequate because if it is more, it causes damage to the pancreas and if less it elevates HbA1c level. This is a pilot study and further more extensive studies should be required to explain the relationship between ferritin and HbA1c.

Conflicts of Interest: The authors have none to declare.

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