

Study of Serum Ferritin and HbA1c Levels in Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

Diabetes is a metabolic disorder characterized by hyperglycaemia which is associated with rise in the HbA1c. Type 2 DM has several causes and no single cause is adequate to explain the progression from normal glucose tolerance to diabetes. The percentage of HbA1c represents the average values of glucose over preceding 6 to 8 weeks. The HbA1c fraction is elevated in chronic diabetic patients and it correlates positively with the glycaemic control. Increased body iron stores are associated with the development of glucose intolerance, type 2 DM and insulin resistance syndrome. Excess iron damages β -cells of pancreas due to oxidative stress which can contribute the pathogenesis of diabetes mellitus. Serum ferritin, an acute phase reactant a marker of iron stores in the body and its association with diabetes has been studied well recently. Plasma ferritin level is considered to be an indicator of body iron stores. This study was carried out to study the relationship of Serum Ferritin with Type 2 diabetes mellitus and to examine whether a correlation between S. ferritin and HbA1c exists.

METHODS

The study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine (u), Jawaharlal Nehru institute of Medical Sciences (JNIMS) Imphal, Manipur, from September 2017 to August 2019. 270 type 2 diabetes subjects (M:F - 135:135, mean age 46.40 ± 9 years) were studied and compared with 30 controls (mean age 47.27 ± 11 years). Serum ferritin, HbA1c and fasting lipid profile were measured. Statistical analysis was performed using SPSS software. Data were described using frequency, percentages and mean.

RESULTS

The mean serum ferritin level of the diabetic patients was significantly higher ($p < 0.013$) than that of the controls. There was a positive correlation ($r_p = 0.036$) between HbA1c and serum ferritin among diabetic patients.

CONCLUSIONS

There was a positive correlation between serum ferritin and HbA1c.

KEYWORDS

Diabetes Mellitus, Glycated Haemoglobin, Iron Overload, Serum Ferritin

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BACKGROUND

Diabetes mellitus (DM) is a group of metabolic disorders that share common phenotype of hyperglycaemia. Type 2 DM have several aetiologies and no single cause is adequate to explain the progression from normal glucose tolerance to diabetes. The fundamental molecular defects in type 2 DM are insulin resistance and impaired insulin secretion results from a combination of environmental and genetic factors.¹ It is a major public health concern both in developing and developed countries. It is one of the four major non-communicable diseases along with cardio-vascular disease, malignancy and chronic respiratory diseases. In type 2 DM, insulin resistance is the primary event followed by increasing degree of β -cells dysfunction.² Complications of DM are the cause of many deaths.³ The percentage of HbA1c represents the average values of glucose over preceding 6 to 8 weeks. The HbA1c fraction is elevated in chronic diabetic patients and it correlates positively with the glycaemic control.⁴ Chronic systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome, and type 2 DM. The process of inflammation induces hepatic synthesis of various acute phase proteins like serum ferritin which has some roles to play in insulin resistance as well as atherosclerosis. Higher incidence of type 2 DM has been observed with high levels of serum ferritin. Elevated blood glucose and insulin levels are measures of insulin resistance which is often reflected body iron overload resulting to increased serum ferritin.^{5,6} Diabetes may be induced by elevated iron stores through various mechanisms including oxidative damage to pancreatic beta cells, derangement of hepatic insulin extraction by the liver and suppress hepatic glucose production by insulin.^{5,6} Hcpidin regulates iron metabolism, hepcidin by directly stimulating the hepatocytes, causes excessive production of cytokines IL-6 in chronic inflammatory conditions specially T2DM.⁷ Chronic hyperglycaemia causes increased glycation of protein including haemoglobin resulting in the formation of Advanced Glycated End products (AGE).⁸ It has been suggested that in the diabetic patients a positive correlation between increased serum ferritin and poor glycaemic control reflected by higher HbA1c.⁹

Long term microvascular and macrovascular complications of diabetes may be due to raised serum ferritin.¹⁰ Iron is a transitional metal with strong pro-oxidant activity, leading to the production of reactive oxygen species that results in an increase in oxidative stress levels.¹¹ The probable role of ferritin as an iron overload marker in pancreatic damage or peripheral insulin resistance results in hyperglycaemia is not clear.¹² There is no much studies to show the best cut-off value for serum ferritin in type 2 DM.

The present study aimed at assessment of long-term glycemic control (HbA1c) among the subjects with type 2 diabetes mellitus along with correlation of HbA1c with biochemical parameters and other variables responsible for complications of diabetes mellitus.

METHODS

This is a cross sectional study carried out in the Department of Biochemistry in collaboration with the Department of Endocrinology, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur, from September 2017 to August 2019. A thorough history was taken, and detailed physical examination and relevant laboratory investigations was done for all subjects as per the proforma.

Inclusion Criteria

Subjects in the age group 30-60 years both male and female with already diagnosed as type 2 diabetes mellitus, who attended diabetic clinic or admitted in the ward in J.N. Institute of Medical Sciences, irrespective of socioeconomic status, who have consented for the study was randomly selected.

Case

This group consist of 270 subjects with already diagnosed as type 2 diabetes mellitus in the age group 30-60 years, who gives consent to participate in the study.

Control

Another group of 30 non-diabetic apparently healthy individuals who came for routine health check-up were also included as control group.

Exclusion Criteria

- Patient who are below 30 years or above 60 years.
- Type 1 diabetes mellitus.
- Patient with haemochromatosis, thalassemia, hemosiderosis.
- Patient with underlying liver, kidney, lung diseases.
- Patient with malignancy, hypertension and other systemic diseases.

Laboratory Tests Done

1. Serum ferritin
The test was performed on the LIAISON® Analyzer.
Method: Estimation of serum ferritin was based on sandwich chemiluminescence immunoassay.
2. Glycated haemoglobin (HbA1c)
HbA1c estimation was done using kit supply by Medsource Ozone Biomedicals Pvt. Ltd.
Method: Ion Exchange Resin Method 108

Ethics

This study was conducted after obtaining clearance and approval from the Institutional Ethics Committee, JNIMS, vide letter no. Ac/06/IEC/JNIMS/2017 (PGT). Written

informed consent of the patients or their relatives was taken prior to inclusion.

Statistical Analysis

Statistical analysis was performed using SPSS software. Data were described using frequency, percentages and mean. Pearson correlation was used to find out the relation between various data. Probability value (P-value) of less than 0.05 was taken as significant.

RESULTS

The age range in both the study group was 30 to 60 years. The mean age of the case was 46.40 ± 9.8 years and that of control was 47.27 ± 11.8 years. Out of the 270 cases, 135 (50%) were male and another 135 (50%) were female. Among the 30 controls group, 9 (30%) were male and 21 (70%) were female. When HbA1c was compared among cases and controls, it was significantly (p<0.05) more among cases (9.33±1.3%) than controls (5.52±0.7%) as shown in table 1. All the diabetic patients were having HbA1c more than 6.5% and mean HbA1c was 9.33% with a standard deviation of 1.34%.

HbA1c	Mean ± SD (%)	t-test
Controls (30)	5.52±0.7	t-15.211
Cases (270)	9.33±1.3	df-298, p-0.000

Table 1. Distribution of Diabetic Patients by HbA1c Levels Stratified by Cases and Controls

Serum Ferritin	Mean ± SD (ng/dL)	t-Test
Controls (30)	102.5±7	t-2.591
Cases (270)	172.7±11	df-298, p-0.013

Table 2. Distribution of Diabetic Patients by Serum Ferritin Level Stratified by Cases and Controls

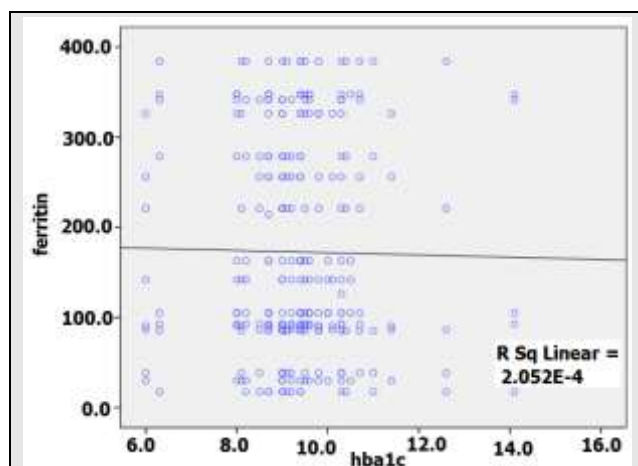


Figure 1. Scattered Diagram Showing Relation between Serum Ferritin and HbA1c

Variable	Pearson correlation
HbA1c	r _p = 0.036
Ferritin	N-270, p-0.0392

Table 3. Correlation between HbA1c and Serum Ferritin

The mean serum ferritin level of the case was 172.7 ± 11 ng/dL and that of control was 102.5 ± 7 ng/dL (Table 2). Serum ferritin level was significantly higher among cases

(172.7±11) than controls (102.5±7) and the finding was statistically significant (p<0.05). There was a positive correlation (rp= 0.036) between HbA1c and serum ferritin among diabetic patients as shown in table 3. The finding is statistically significant (p<0.05). The scattered diagram (Fig. 1) also showing clumping and direction of clumping was from left to right shown by a line on the graph.

DISCUSSION

There are many theories regarding the role of ferritin in DM. Pancreatic damage due to subclinical hemochromatosis has been considered in some cases of diabetes. These relationships are due to oxidative stress and inflammatory cytokines which potentiates the initiated events.¹³ 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 sell. High body iron stores that is serum ferritin have been linked to insulin resistance, metabolic syndrome and gestational diabetes. Excess iron damages β-cells of pancreas due to oxidative stress which can contribute to pathogenesis of diabetes mellitus. In a study by S Raj et al it is observed that there is significant higher levels of serum ferritin in diabetic than healthy controls and positive correlation between serum ferritin and HbA1c, which is in agreement with our study. The mean serum ferritin level of the case was 172.7 ± 11 ng/dL and that of control was 102.5 ± 7 ng/dL. The mean serum ferritin level of the diabetic patients was significantly higher (<0.013) than that of the controls. These findings are consistent with the studies conducted by Raghavani.¹⁴

Iron deposition in the liver may cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production but the mechanism for the association between ferritin and type 2 diabetes is not established.⁷ Iron is auto-oxidized to form highly reactive, lipid soluble iron-oxygen complexes. These free radicals are powerful pro-oxidants, which can change membrane properties and result in tissue damage.¹⁵ Oxidative stress can lead to hyperglycaemic through disturbed glucose metabolism. The insulin extracting capacity of the liver may be interfaced by iron accumulation in hepatocytes and affect insulin synthesis and section in the pancreas. Excess of iron contributes insulin resistance and subsequently insulin secretion is decreased.¹⁵ In the study of Sumeshraj et al. Serum ferritin levels increased as the duration of diabetes increased.⁵ The relationship between elevated serum ferritin levels and type 2 diabetes involves an elevation in oxidative stress through the increased formation of free radicals catalysed by iron, which may lead to insulin resistance and hyperglycaemia.^{16,17} There was a positive correlation (rp= 0.036) between HbA1c and serum ferritin among diabetic patients. The finding is statistically significant (p<0.05). Among the subjects (both cases and controls), those with higher ferritin level also showed high HbA1c. So higher serum ferritin level was associated with high HbA1c. This

finding corresponds with a study in India done by Prashant et al.¹⁸

Similar findings were evident in a study done by Raj et al. (2013) in India. Raghavani et al shown in their study that there was strong correlation of ferritin with FPG and moderate correlation with HbA1c.¹⁴ In diabetic subjects, a positive correlation between increased serum ferritin and poor glycaemic control, reflected by higher HbA1c, has been suggested by Eschwege et al.⁸

CONCLUSIONS

Serum ferritin levels was significantly increased in diagnosed cases of type 2 diabetes mellitus in comparison with healthy controls. Positive correlation between HbA1c and serum ferritin has also been found. Hyper ferritinemia may be one of the causes for development of insulin resistance before overt diabetes is seen. Routine screening for serum ferritin concentration in diabetes patients can be done to assess the glycaemic control. Further study is required to check whether a reduction in body iron storage can decrease the risk of type 2 diabetes.

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