ORIGINAL ARTICLE

Relationship Between Serum Ferritin Level and Hba_{1c} in Bangladeshi Type 2 Diabetic Patients

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ABSTRACT

Background: Diabetes mellitus (DM) type 2 is one of the most common endocrine disorders affecting more than 135 million people in the world. The etiology of the disease is not fully understood, but recently subclinical hemochromatosis has been considered as one of the probable causes of DM. This study was carried out to examine the relationship between serum ferritin as a marker of iron overload with DM and HbA1c.

Materials & Method: This study was conducted in the Biochemistry department of Sir Salimullah Medical College, Dhaka; over a period of 18 months from July 2013 to December 2014. In this case control study, 46 patients with type 2 diabetes were taken as case, who were referred to theoutpatient department of "Ibrahim General Hospital & Diabetic care & Educational Center"(DCEC). 46 normal individuals were included as the control group, who were matched with the case group regarding age, sex, BMI and Hb%. Ferritin, hemoglobin, HbA_{1c} and fasting plasma sugar were measured in blood samples. Exclusion criteria included anaemia, or any other disease or drug that could affect ferritin levels.

Result: Results were analyzed statistically by Chi-square test, Student's t-test, Pearson correlation coefficient test and Odds ratio.Mean serum ferritin was significantly higher in diabetics than in the control group (197.97 ± 75.99 μgm/L vs. 64.24 ± 27.83 μgm/L, $p < 0.001$). There was significant positive correlation between serum ferritin and HbA1cin diabetic patients ($p < 0.001$). In this study, OR of 11.64 was also found.

Conclusion: Serum ferritin is positively correlated with type 2 Diabetes Mellitus. And this may be an important and independent predictor for development of diabetes mellitus.

Key Words: Diabetes mellitus, ferritin, HbA1c, relationship

Introduction

Diabetes mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycemia. It is caused by a complex interaction of genetics and environmental factors.[1] Type 2 DM is an extremely heterogenous disease 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.[2] It is a major public health concern both in developing and developed countries. It is one of the four priority non-communicable diseasesalong with cardio-vascular disease, malignancy and chronic respiratory diseases. Complications of DM are the cause of many deaths. It is the leading cause of adult blindness, amputation, renal failure, heart attacks and strokes.[3]

A minor hemoglobin derivative called glycated

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hemoglobin (HbA_{1c}) is produced by glycation, the covalent binding of glucose to hemoglobin. In assessment of glycemic status, the percentage of HbA_{1c} represents the integrated values of glucose over preceding 6 to 8 weeks.[2] At the present time, the HbA1cis used worldwide as the marker of long term glycemic control and also a therapeutic target in the prevention and delay of the development of hyperglycemic complications.[4,5]

It is recently recognized that increased body iron stores are associated with the development of glucose intolerance, type 2 DM and insulin resistance syndrome.[6,7,8] Some researches had shown that, there is difficult control of hyperglycemia in patients with iron overload.[7,9] Normally, there is little ferritin in human plasma proportionate to the total stores of iron in the body. Plasma ferritin levels are thus considered to be an indicator of body iron stores. Ferritin is one of the key proteins that play an important role in regulating iron homeostasis.[10]

The mechanism for the association between serum ferritin and type 2 DM is not established yet, but iron deposition in the liver may cause insulin resistance by interfering the ability of insulin to suppress hepatic glucose production.[8,9] Iron is auto oxidized to form iron-oxygen complexes. These free radicals can change membrane properties and result in tissue damage.[11,12] Oxidative stress can also lead to hyperglycemia through disturbed glucose metabolism.[13] This study was performed in order to find a link between serum ferritin and DM and also HbA_{1c} as a blood glucose control marker in diabeticpatients.

Materials and Method

This case-control study was conducted in Dhaka from July 2013 to December 2014 and was carried out in a group of diabetic patients who had been referred to the outpatient department of Ibrahim General Hospital & DCEC, and a normal control group. Patients with Chronic kidney disease, Chronic liver disease, individuals on corticosteroid therapy and other states associated with altered serum ferritin like haemochromatosis, bleeding disorder, chronic alcoholics, anaemia were excluded from our study. Also the individuals with repeated blood transfusion were not included. Our criteria for the diagnosis of anemia were based on laboratory investigation and a hemoglobin level of lessthan 13 g/dl. in male and 12 gm/dl in females. In case of CRP level as the acute phase protein marker the cut-off value was taken as 6 mg/dl.

The control group consisted of individuals who had no history of diabetes mellitus. They had fasting blood sugar levels of less than 6 mmol/L and hemoglobin levels of more than the cut-off value. They did not have a history of medication use, and were matched with the diabetic group regarding age, sex and BMI. One standard questionnaire was completed for each subject, which included their personal data, drug usage, disease history and physical examination. Weight and height were measured by a standard device and body mass index (BMI) was calculated based on weight / (height)2 formula. The blood sugar was measured after 12 h of fasting by glucose oxidase method in the biochemical laboratory of Sir Salimullah Medical College, Dhaka. HbA1cby modified HPLC method and ferritin by by DRG Ferritin ELISA kit in the BSMMU laboratory. Results were analyzed with SPSS software and t-test was used for quantitative variables, Chi-square test for qualitative variables and Pearson's regression for correlation between variables. Odds Ratio was also done to find the risk factor.

Results

The mean age of the diabetic patients was 54.91 ($\pm$6.46) years and that of the controls was 53.19 ($\pm$7.31) years. 56.5% of the cases were male and 43.5% were female. On the other hand, in the control group 58.7% was male and 43.1% was female. Mean BMI was 27.95 ($\pm$2.21) kg/m² and 27.19 ($\pm$2.98) kg/m² in cases and controls respectively.There was no significant differences between the two groups regarding age, sex and BMI. Table I reflects these demographic features of the study subjects.

Table II Shows the comparison between the case & control group regarding Hb concentration, fasting plasma glucose (FPG), HbA_{1c} and serum ferritin.

Table III showing the association between serum ferritin among the subjects with normal level (≤6%) of HbA1c and the subjects with high level (≥6.1%) of HbA1c. 150 μgm/L was the cut off value of Serum ferritin level. Most of the study subjects with normal of HbA1c (%) were showing the lower Ferritin level and vice versa.

There was positive and significant correlation between HbA1c and serum ferritinin diabetic subjects as shown in Fig I.

On the other hand, the control group was also positively correlated regarding serum ferritin and HbA1c, but their correlation was not statistically significant. (Fig II)

Table IV is for the measurement of serum ferritin as a risk factor for type 2 diabetes mellitus. In this study, OR of 11.64 was observed which indicates that the individuals with higher serum ferritin level are in 11.64 times at risk to develop type 2 DM than those with lower serum ferritin level.

Table-I: Demographic characteristics of the subjects in groups

Demographic v ariables	Group		p value
	Case (Type 2 diabetic) n=46	Control (Non diabetic) n=46	
Age (mean ±SD)	54.91±6.46	53.19 ± 7.31	0.236
Male n (%)	26 (56.5%)	27 (58.7%)	
Femalen(%)	20 (43.5%)	19 (41.3%)	0.833
BMI (kg/m²)	27.95 ± 2.21	27.19 ± 2.98	0.150

Student's 't' test was done

Table-II: Comparison between the study groups regardingBiochemical parameters

Biochemical parameters	Case Mean (n=46)	Control Mean (n=46)	P value
FPG (mmol/L)	7.88±1.57	5.09±0.65	0.001
HbA1c (%)	8.53±2.31	5.44±0.48	0.001
S. Ferritin (μgm/L)	197.97±75.99	64.24±27.83	0.001
Hb (gm%)	13.07±1.27	13.42±0.98	0.726

Student's 't' test was done

Table-III: Association of serum ferritin level with HbA_{1c} among the study subjects.

HbA1c (%)	Serum ferritin (≤150μgm/L)	Serum ferritin (≥150μgm/L)	p value
≤6	48	4	≤0.001
≥6.1	11	29	

Chi-squire test was done

Table-IV: Risk measurement of serum ferritin in type 2 DM.

Serum Ferritin (μgm/L)	With DM (n=46)	Without DM (n=46)	OR
≥151	34	9	11.64
≤150	12	37	

Serum Ferritin

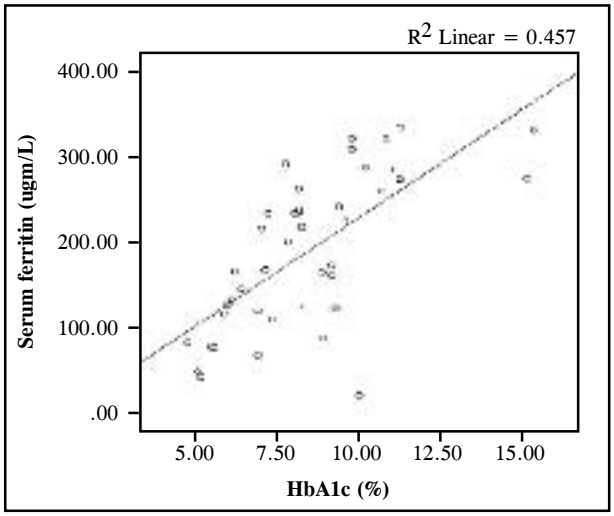

Figure-I: Correlation between serum ferritin and HbA1c in cases

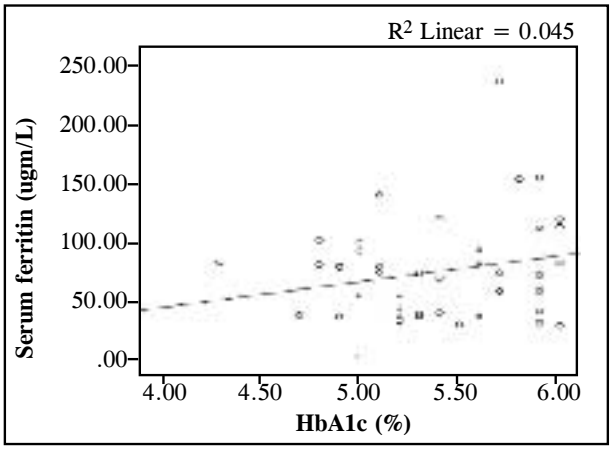

Figure-II: Correlation between serum ferritin and HbA_{1c} between controls.

Discussion

Type 2 diabetes mellitus is a global problem that causes many life-threatening complications. Impaired insulin secretion as well as insulin resistance are the main factors in the development of type 2 DM. Now-a-days, increased serum iron store, indicated by serum ferritin is thought to have an influence in the development of type 2 DM.[8]

In this study, cases were the diabetic patients. So, their fasting plasma glucose level were higher in comparison to the controls. There was significant difference of HbA1c between cases and controls ($p \leq 0.001$). Similar observation was found in other two studies in India and China.[14,15]

The mean serum ferritin level of the diabetic patients was significantly higher (<0.001) than that of the controls. These findings are consistent with the studies conducted by Raghavani.16We have also found significant ($p \leq 0.001$) association between HbA_{1c} and serum ferritin. Among the subjects (both cases and controls), those with higher ferritin level also showed high HbA_{1c}. So higher serum ferritin level was associated with high HbA_{1c}. This finding corresponds with a study in India done by Prashant *et al.*[17] Another study found in general population that increased body iron store was possibly associated with the occurance of glucose intolerance, type 2 DM and gestational diabetes.[11]

We also found that serum ferritin level was positively & significantly correlated withHbA_{1c} ($p=0.001$) in diabetic patients. 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 HbA_{1c}.[16] A significant correlation between iron and HbA_{1c} was found in a study in India.[18]

From the above discussion, it seems that ferritin may have a role in the pathogenesis of type 2 DM. The mechanism for the association between serum ferritin and type 2 DM is not yet established. But iron deposition in the liver may resist the action of insulin on liver (Mozulski *et al.*, 2001& Fernandez Real *et al.*, 2002).[11,19] There is some evidence that iron overload also affects skeletal muscle. Deposited iron in muscle decreases glucose uptake because of muscle damage. Increased accumulation of ironin the pancreas causes decreased insulin synthesis and secretion (Fernandez Real *et al.*, 2002).[11]

Besides insulin resistance, iron may also has a role in DM through oxidative stress. Pancreatic β-cells, which are at increased risk of oxidative damage may be the cause of developing diabetes (Lenzen *et al.*, 1996). However, in a study in Iran by Sharifiet al. found no correlation of serum ferritin with HbA_{1c}.[20] Another study in Indiaalso did'nt find significant correlation between serum ferritin and HbA_{1c}.[14]

There was positive correlation of serum ferritin with HbA_{1c} ($p=0.06$) in the non-diabetic controls also, but that was not significant. Similar finding was observed in another study done by Sumesh Raj *et al* in India.[21]

It was also evident in our study that serum ferritin is a strong risk factor (OR= 11.64) for type 2 DM. Scholl (2005) had performed a study on women and found that high ferritin levels (170ng/ml)in women augment the risk of developing type 2 DM.[23] This augmentation was about three times within ten years. A large population based study in Taiwan by Chang *et al.* (2013) had shown that individuals with moderately high serum ferritin level had 1.3 times (95% CI) higher risk for developing hyperglycemia. They also shown that this risk increased to 2.16 times (95% CI) for individuals with severely high serum ferritin level.[22]

Therefore, this study shows that Serum ferritin is positively correlated with HbA_{1c} in diabetic subjects and also a potential risk factor for type 2 diabetes mellitus. Our findings can be explained well enough by the findings of other studies.

Conclusion

Our findings of the present study supported that there is significant increase in serum ferritin in diabetes mellitus compared to control group. Positive correlation between HbA_{1c} and serum ferritin hasalso beenfound. And hyper ferritinemia may be one of the causes for decreased insulin production and development of insulin resistance in diabetes mellitus.

Conflict of interest: None

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