

Pattern of iron profile in type 2 diabetes mellitus patients: experience from outpatient department of Bangladesh Diabetic Network

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ABSTRACT

Background: Worldwide diabetes mellitus (DM) has been recognized as the most prevalent endocrine disorder. Excess iron has been implicated in the pathogenesis of diabetes and its complications. Iron is a transitional metal and a potential catalyst in cellular reaction that produces reactive oxygen species. Free iron causes the assembly of reactive oxygen species that invariably steer the body's homeostasis towards oxidative stress-mediated diabetic complications. On the other hand, ferritin is an index of body iron stores and acts as an iron overload marker. Elevated iron indices are more common in patients with diabetes. Excess iron may have a role in the development of diabetes and subsequently in glycemic control. In this context, this study was aimed to assess the pattern of plasma iron profile in type 2 DM patients and compare with healthy controls.

Methods: This cross-sectional study included 284 subjects attending the outpatient department of Endocrinology of Bangladesh Diabetic Network Ltd. (BDN) from January 2021 to June 2021. This study was done to evaluate the serum iron, total iron binding capacity (TIBC) and ferritin of 284 subjects divided into two groups (I and II) of 182 Type 2 DM patients constituted Group I and Group II consisted of 182 healthy individuals (controls).

Results: Mean serum free iron concentration in Group I and Group II were 14.24 ± 6.7 and 11.29 ± 4.1 $\mu\text{mol/l}$ respectively. Mean TIBC in Group I and Group II were 54.19 ± 9.8 and 64.08 ± 7.5 $\mu\text{mol/l}$ respectively. However, mean serum ferritin concentration were 169.50 ± 15.1 and 121.29 ± 11.9 mg/ml respectively. The difference between serum iron, TIBC and ferritin between Group I and Group II were highly significant with the *p* values 0.003, 0.016 and 0.042 respectively. In Group I, glycated hemoglobin (HbA1c) and fasting blood glucose levels both increased. However In this investigation, HbA1c levels were found to have a substantial relationship with serum iron levels and TIBC. However, there was no significant link between serum ferritin and HbA1c.

Conclusion: The results obtained from this study suggests that serum iron and serum ferritin were increased and TIBC was decreased in T2DM patients as compared to healthy control. In patients with T2DM, there was a potentiated disparity in the readings. The findings suggest that these micronutrient levels can be employed as biomarkers for T2DM patients.

Key words: Serum iron, TIBC, ferritin, T2DM patients, HbA1c.

(BIRDEM Med J 2022; 12(2): 124-128)

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Received: August 12, 2021

Revision received: February 18, 2022

Accepted: February 28, 2022

INTRODUCTION

Diabetes mellitus (DM) is the most prevalent chronic non-communicable disease all over the world. It is frequently preventable.¹ This disease is responsible for millions of deaths annually. Diabetes is undoubtedly one of the most challenging health problems in 21st century.² Middle and low income countries see more than 80% of the deaths owing to diabetes.³ By 2030 the seventh leading cause of mortality in the world will be diabetes which is projected by the World Health Organization (WHO). Emerging scientific evidences has disclosed unsuspected influence between iron metabolism and T2DM. The relationship is bi- directional iron affects glucose metabolism and glucose metabolism impinges on several iron metabolic pathways.^{4,5} In T2DM increased blood glucose changes the blood osmolality which may cause hemolysis and can interfere with hemoglobin and iron metabolism. Emerging scientific evidences also have suggested that iron status can influence glucose metabolism and can lead to insulin resistance in diabetic patients.³

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.^{6,7} Increased serum ferritin is often associated with measures of insulin resistance, such as elevated blood glucose and insulin levels.⁸

On the other hand, it is increasingly being recognized by few researchers that serum iron influence glucose metabolism even in absence of significant iron overload or even in a state of iron deficiency. Iron is a transitional metal and a potential catalyst in cellular reactions that produces oxygen reactive species such as hydroxyl radical (OH⁻) and superoxide anion (O⁻) that can initiate and propagate the cascade leading to oxidative stress and finally cell death.⁹ In DM, there is decrease in update of iron and increase circulatory pool of catalytic iron. In DM, increased blood glucose stimulates non enzymatic glycosylation of several proteins including hemoglobin. Glycosylation of hemoglobin also leads to increase in iron release from protein.¹⁰

In different studies variable findings have been obtained for iron profile status in type II DM. In Bangladesh, there is very limited study about association of serum iron profile and type 2 DM. Present study had been designed to determine the levels of serum iron, TIBC, ferritin and HbA1c in type 2 DM patient and normal healthy individuals. By this study we also analyzed whether there is any association between type 2 DM and iron status.

METHODS

This study was cross sectional which conducted over a period of six months, from January 2021 to June 2021. The study was done using oral glucose tolerance test for healthy control and fasting and post prandial plasma glucose for type II DM patients with 21 to 80 years age group attending the outpatient department of endocrinology of Bangladesh Diabetic Network Ltd. (BDN). The data was collected through a questionnaire which included their personal data, family history, smoking habits and recent blood donation. Pregnant and lactating women, patients who were smokers and alcoholics and who were taking medication that affects iron level (tetracycline, ciprofloxacin, drug used for hypothyroid and seizures) were excluded from this study.

Sample collection

After overnight fasting for 8-10 hours about 6 ml of venous blood was drawn with aseptic precautions from anticubital vein from all the subjects and dispersed 2 ml in Ethylenediamine Tetra Acetic Acid (EDTA) tube for HbA1c and 4 ml was delivered in a plain tube for estimation of fasting blood glucose, serum iron profile respectively. 2 ml in fluoride tube for estimation of fasting blood glucose and 2 ml for iron profile.

Statistical analyses

Statistical analysis were performed with the help of MS Excel (version 2016) and SPSS (23) version. Data were presented as mean \pm SD. Data were compared using appropriate statistical method like chi square test, pearson correlation test and Independent sample Kruskal-Willis test. Tests was considered significant at the level of $d \leq 5\%$ and considered as test of significance when $P < 0.05$.

RESULTS

Total patients were 284 and the mean age of Group I and Group II were of 55.983.48 and 55.323.36 years, respectively. Comparison of age and glycemic parameters (fasting blood glucose and HbA1c) of both groups were shown in (Table I). Whereas comparison of Iron status of both groups were shown in (Table II). In this study, a positive correlation of serum iron and ferritin were found with HbA1c. Also a negative correlation of TIBC was found with HbA1c, that was shown in (Table III).

Table I Comparison of age, fasting blood glucose and HbA1c among groups

Variables	Group I	Group II	P value
	(n=142)	(n=142)	
	Mean ±SD	Mean ±SD	
Age(Years)	55.98±3.48	55.32±3.36	0.131
Fasting Blood glucose (mmol/l)	8.61 ± 3.47	5.78±1.05	<0.001**
HbA1c(%)	8.33±2.16	5.72±0.53	<0.001**

Statistical analysis was done by Independent t- test to compare among groups. Values are expressed as the mean± SD. *= significant. **p*>0.05, ***p*<0.01, ****p*<0.001

Table II Comparison of Serum Iron, TIBC and Ferritin levels among the groups

	Cases	Control	P-Value
	(Group I)	(Group II)	
	Mean±SD	Mean±SD	
Serum Iron(imol/l)	14.24±6.7	11.29±4.1	0.003**
TIBC(imol/l)	54.19±9.8	64.08±7.5	0.016**
Serum Ferritin (mg/ml)	169.50±15.1	121±11.90	0.042*

Statistical analysis was done by Independent t- test to compare among groups. Values are expressed as the mean± SD. *= significant. **p*>0.05, ***p*<0.01, ****p*<0.001.

Table III Correlation of Serum Ferritin, TIBC and Iron with HbA1c in Diabetic Patients

variables	r	p-Value
Serum Iron	0.267	0.042
Serum TIBC	-0.423	0.002
Serum Ferritin	0.033	0.714

r, Pearson correlation coefficient

*=significant. **p*<0.05; ** *p*<0.01. *** *p*<0.001

Pearson correlation was used for statistical analysis.

DISCUSSION

In our study we found out that serum iron and serum ferritin were significantly higher in cases (type2DM) as compared to controls (healthy subjects) while serum TIBC was lower in the case Group I as compared to control Group II. Fasting blood sugar and HbA1c were expectedly higher in cases in contrast to controls.

In this study serum iron in group I(case) and group II(control) were 14.24±6.7 and 11.29±4.1 imol/l respectively. It was significantly different among two groups (*p*<0.01). Renuka and Vasanta,2016 found in their research, serum iron were 9.7 ± 6.45 and 7.2 ± 4.75 imol/l in type 2 diabetic patients and healthy control respectively with a significant difference among groups (*p*<0.001).¹¹ In this study, there was significant positive correlation of serum iron with HbA1c. Saha and Murgod, in 2019 spilled that serum iron is higher in diabetic patients than age and sex matched healthy subjects.¹² In this study, there were significant positive strong correlation of serum iron with HbA1c. There is a close relationship between iron profile and serum ferritin with T2DM because altered glucose metabolism can alter the iron profile vice versa. This bidirectional relationship occurs because of the alter iron profile or free iron induces oxidative stress and produces inflammatory cytokines¹³

Glycation of hemoglobin contributes to substantial affinity for transitional metals and glycation of hemoglobin decreases ability of transferring to bind ferrous iron. When concentrations of antioxidants are low, reducing potential and anaerobiosis progressively increases, thereby facilitating a rapid release of iron from ferritin. Additionally, the ferroxidase activity of the heavy chain in apoferritin is also down regulated in this setting resulting in an increase in free iron as pro oxidant agent. reactive oxygen species have been shown to interfere with insulin signaling at the cellular level.¹³ Via Haber-Weiss and Fenton reactions, Hydroxyl radical generated and causes damage cellular membrane potentiated nucleic acid. These events lead to insulin resistance and finally type2 diabetes mellitus¹⁴ (Misra et al,2016) and thereby contributing diabetic complications. But one study had done by Sowjanya et al in 2017 and they had found there was no increase in serum iron among the patients of DM.¹⁵

The different kind of result has been observed by

Dinneen et al¹⁵ who found no role of iron in diabetes mellitus. They determined distribution of iron histochemically by evaluating hepatic iron stores in autopsy specimens. No significant difference was observed. Similar type of result was also obtained by the study of Elis et al¹⁶ whose study population comprised three subject groups with severe diabetic retinopathy, without retinopathy and non diabetic non retinopathy subjects. Serum iron and ferritin levels did not differ significantly between the three groups and there was no correlation between HbA1C level and serum iron and ferritin levels between the diabetic patients group. The different kind of result has been observed by Dinneen et al¹⁵ who found no role of iron in diabetes mellitus. They determined distribution of iron histochemically by evaluating hepatic iron stores in autopsy specimens. No significant difference was observed. Similar type of result was also obtained by the study of Elis et al¹⁶ whose study population comprised three subject groups with severe diabetic retinopathy, without retinopathy and non diabetic nonretinopathy subjects. Serum iron and ferritin levels did not differ significantly between the three groups and there was no correlation between HbA1C level and serum iron and ferritin levels between the diabetic patients group. The different kind of result has been observed by Dinneen et al¹⁵ who found no role of iron in diabetes mellitus. They determined distribution of iron histochemically by evaluating hepatic iron stores in autopsy specimens. No significant difference was observed. Similar type of result was also obtained by the study of Elis et al¹⁶ whose study population comprised three subject groups with severe diabetic retinopathy, without retinopathy and non diabetic nonretinopathy subjects. Serum iron and ferritin levels did not differ significantly between the three groups and there was no correlation between HbA1C level and serum iron and ferritin levels between the diabetic patients group.

TIBC in group I and II was 54.19 ± 9.8 and 64.08 ± 7.5 (imol/l) respectively. It was significantly different among 2 groups ($p < 0.01$). Also observed significant positive correlation of TIBC and HbA1c. study of Dhakad et al. in 2019.¹⁶ Ferritin, an iron storage protein may function as a source of iron for promotion of superoxide-dependent lipid peroxidation.¹⁷ Some previous studies has been reported to negatively correlate with insulin

sensitivity.¹⁸ Bertelsen et al. 2001 concluded in their research that oxidative stress impels insulin resistance. By that influences glucose metabolism through decreasing internalization of insulin and increases ferritin synthesis thereby influences iron metabolism.¹⁹ Our study spill that serum ferritin level were increased in type 2 DM when compared with non diabetes subjects. Nevertheless there are no significant difference when analogized between male along with female Type2DM. Furthermore in this study the serum ferritin is positively correlated with glycemic status of the diabetic individual which is not significant. Consequently serum ferritin is commonly used as a marker of body iron stores and has been reported to negatively correlate with insulin sensitivity.²⁰ Inconsistent with a previous study of Forouhi et al. 2007 found no significant association observed between fasting blood glucose and serum ferritin level as well as not significantly associated with HbA1c.^{21,22} Other authors suggested that iron may catalyse the formation of hydroxylradicals, which contribute to the development of insulin resistance.^{23,24}

By our study it was perceived that type 2 diabetic patients have significantly increased serum fasting blood glucose, HbA1c, serum iron and ferritin nonetheless TIBC which was significantly decreased when compared with healthy controls.

Limitation

Although optimal care had been tried in every step of the study, there were some facts to be considered while reviewing the report as limitations of this present study. This study was done only in one diabetic care center of Bangladesh, hence may not represent the whole population of the country, detailed dietary habit could not be considered.

Conclusion

Accordingly this study evinced that serum iron and serum ferritin have a significant positive correlation though TIBC has negative correlation of with HbA1c levels respectively. Therefore, in congruency with previous researches showed that estimation of iron profile will be useful in diabetes mellitus patients and the risk of development of diabetic complications by reactive oxygen species, associated inflammatory disorders, all of these which in turn will help in overall management of diabetic patients.

Authors' contribution: AH prepared the study design, Collected data, Sample, Prepared the manuscript, MMB reviewed and edited the manuscript, SMS helped in data collection, supervised patient management and also sample processing, SS performed statistical analysis and interpretation, S drafted and edited the research manuscript preparation, FN compiled data and writing, MFA supervised this study. All authors read and approve the final version for submission.

Conflicts of interest: Nothing to declare.

Funding: There was no funding for this study.

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