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Serum Iron Profile in Type 2 Diabetes, A Role Beyond Anemic Marker!

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Abstract

Background: There are evidences of controversial study findings that iron profile has a significant role in maintenance of glycemic status. This study has therefore been done to estimate the markers of iron in subjects with type 2 diabetes mellitus as compared to impaired glycemic status and apparently healthy individuals and to look for correlation between these various iron markers and glycemic control. Methods: One hundred and fifteen (115) subjects were enrolled for the study and divided into three groups: fifty (50) each of diabetic & impaired glycemic status and fifteen (15) apparently healthy individuals based on HbA1c level. Basic demographic profile like age and sex and estimation of serum random glucose, urea, ceatinine, iron, ferritin, transferrin and soluble transferring receptor (stfR) were done. Results: ANOVA test has shown a significant difference in the mean for stfR (F=11.055, p=0.000) as well as for stfR/ferritin index (F=8.68, p=0.000). ANOVA for serum iron, transferrin, and ferritin were not statistically different for the groups. A significant correlation was found between HbA1c & stfR -ferritin index and between HbA1c and stfR in diabetic group. Conclusion: Iron and its markers are not only important in detecting and study of iron deficiency anemia but also might have a strong role in glucose homeostasis as well as development of intolerance and hence diabetes. stfR and stfR- ferritin index is comparatively stable and might be therefore used as additional marker along with HbA1C for monitoring blood glucose homeostasis.

Keywords: Glycemic control, HbA1c, Iron, stfR, stfR-ferritin index.

INTRODUCTION

Glycosylated hemoglobin (HbA1c) is used as a reliable indicator of the blood sugar level of an individual during the previous three months, and the World Health Organization has included it in diagnostic criteria for diabetes [1]. It has been suggested that disturbances of iron metabolism are part of the metabolic syndrome, which associates insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and central obesity [2]. In another prospective study in healthy women showed that higher iron stores (reflected by ferritin concentrations and the ratio of transferrin receptors to ferritin) were associated with an increased risk of type 2 diabetes mellitus (DM), independently of known diabetes risk factors [3].

Besides blood glucose level which is the main factor affecting HbA1c, the other factors which might influence its level are: hemolytic anemia, hemoglobinopathies, pregnancy, and altered by deficiency of nutritional factors, such as vitamin B12, folate, and iron leading to false-negative or false-positive results [4,5]. Previous studies reported that in subjects irrespective of status of diabetes, iron deficiency anemia (IDA) is associated with higher HbA1c levels, which decrease upon iron supplementation [6,7]. Other studies reported that, in subjects with iron deficiency but without diabetes, HbA1cmeasurements had no significant changes [8]. But in one study done by Sinha et al, HbA1c levels in anemic subjects was found to be significantly lower than in the control group [9]. In another retrospective case control study done by Jari Intra et al found that means of HbA1c were significantly higher in anemic subjects, than those measured in individuals without anemia [10]. The influence of IDA on HbA1c is therefore found to be controversial.

This study was therefore undertaken to estimate the markers of iron (serum iron, ferritin, transferrin, soluble transferrin receptor and soluble transferrin receptor- ferritin index) in subjects with type 2 DM as compared to impaired glycemic status and apparently healthy individuals and to look for correlation between these various iron markers and glycemic control in the participants irrespective of their anemic status.

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MATERIALS AND METHODS

Study design:

It was a hospital-based observational single centered cross-sectional controlled study. The study was done in the department of Biochemistry. Total no. of subjects enrolled for the study was 115 and divided into three groups based on glycemic control:

Group I: Diagnosed Type 2 DM patients (n = 50), with HbA1c level than≥ 6.4%.

Group II: Subjects with impaired glycemic status (n = 50), with HbA1c level 5.7% to 6.4%.

Group III: Age- and sex-matched healthy subjects (n=15) free from any ailment which may affect the parameters under study. They were chosen from the general population and HbA1clevel less than 5.7%.

Inclusion criteria:

All the subjects selected for study were within age group of 20-70 years. The subjects were enrolled in the study based on their glycemic control level and divided into 3groups as mentioned above.

Exclusion criteria:

Presence of ailments like hemochromatosis, chronic alcoholics, overt thyroid dysfunction, presence of medical renal disease, corticosteroid therapy, chronic inflammatory conditions like SLE, RA etc. pregnant women, primary hyperparathyroidism or any malignancy which might affect progression of the disease.

Methods:

Basic demographic profiles were recorded for all the subjects and then blood samples were collected in EDTA vile for HbA1c and in sterile empty vacutainer (SEV) for estimation of serum random glucose, urea, ceatinine, iron, ferritin, transferrin and soluble transferring receptor (stfR). Estimation of serum glucose, urea, creatinine, iron and transferrin were done by photometric method in fully automated chemistry analyzer: Beckman coulter AU2700. Serum ferritin and stfR estimation were done by chemiluminiscence method in automated immunoassay machine: DXI 300, Beckman Coulter. Estimation of HbA1c was done by HPLC method in Arkray HbA1c analyzer.

Research ethics

The protocol was approved by Institute's ethics committee. An informed written consent was taken from each subject selected for the study.

Statistical methods

A database was prepared for all the subjects and statistical analysis was done in SPSS software (version 20.0, Chicago, U.S.) for windows .The value of the biochemical parameters estimated in the participants are being expressed as Mean ± SD units. One way ANOVA was done to look for significant difference in the levels of the estimated iron markers in the groups of participants. Post hoc Games Howell test (GHT) was done for comparisons of quantitative variables. Pearson correlation test was done to find out if there is association between these various iron markers and glycemic control in the participants.

RESULTS

The present study included total of 115 subjects: 50 subjects each of diagnosed type 2DM with HbA1c more than or equal to 6.4% (Group I) and impaired glycemic status with HbA1clevel 5.7- 6.4% (Group II) and 15 apparently healthy volunteers (Group III) with HbA1c less than 5.7%. The number of males and females in Group I are 33 & 17, in Group II 28 & 22 and in Group III 8 & 7 respectively. The mean ± SD of age of Group I, II and III are 54.82 ± 11.22 years, 46.48 ± 10.08 years and 44.14 ± 14.13 years respectively.

Table 1: The biochemical parameters of the study groups

Variables	**Group I** n= 50 Male= 33, Female= 17	**Group II** n=50 Male= 28, Female= 22	**Group III** N=15 Male= 8, Female = 7	ANOVA*	
				F	p
Age (in years) mean	54.82 ± 11.22	46.48 ± 10.08	44.14 ± 14.13		---
Urea (mg/dl)	30.96± 19.81	26.58 ± 18.41	21.13 ± 10.85	1.85	0.16
Creatinine (mg/dl)	0.90 ± 0.58	0.81± 0.31	0.73 ± 0.21	1.11	0.33
HbA1C (%)	9.36 ± 2.09	5.93 ± 0.26	5.33 ± 0.21	93.17	0.000†
RBS (mg/dl)	186 ± 74.8	92.3 ± 16.7	79.53 ± 18.8	98.36	0.000†
Ferritin (ng/ml)	111 .24 ± 66.97	104.8 ± 24.75	140.37 ± 67.5	0.239	0.79
Iron (µg/dl)	77.04 ± 42.41	79.96 ±43.78	83.33 ± 17.25	0.156	0.86
Transferrin (mg/dl)	279.56 ±132.87	270.88 ±66.95	241.13 ±48.03	0.854	0.43
sTfR nmol/l	75.46 ±88.60	20.83 ±6.60	33.27±20.39	11.055	0.000†
sTfR/log (ferritin) index	3.04 ±2.33	1.7 ±0.68	3.04 ±1.56	8.69	0.000†

* Welch's ANOVA was done to look for equality of means for different parameters in the groups of participants.

† p value is significant at 0.001 level.

Table 1 shows the various biochemical parameters of the study groups. Welch's ANOVA for stfR /ferritin index has been done to look for equality of means and it has been found that there is a statistically significant difference in the mean± SD between the groups (F=8.68, p=0.000). Levene's test shows that our samples violates the rule of homogeneity of variances (p value= 0.000). Post hoc GHT has been therefore done to see the equality of means between the groups and it has been found that there is a statistically significant difference between Group I & Group II (p value=0.001) and Group II & Group III (p value=0.015). Welch's ANOVA for stfR shows statistically significant difference in the mean ± SD of the groups (F=11.055, p=0.000) with post hoc GHT has been found to be statistically significant between the Group I & Group II (p value= 0.000) and Group I & Group III (p value=0.008). There is no significant difference between Group II & Group III (p value=0.083). ANOVA for serum iron, transferrin, and ferritin were not statistically different for the groups.

Pearson correlation test was done between HbA1C & different iron markers iron, transferrin stfR, ferritin, stfR, stfR - ferritin index in all the three groups (I, II, III). Statistically significant positive correlation was found in Group I, between HbA1c & stfR -ferritin index *(r= 0.37, p = 0.008)* (Figure 1) and between HbA1C and stfR*(r= 0.4, p =0.012)* at 0.05 level, (Figure 2). The correlation of other parameters with HbA1c is not statistically significant. No significant correlation has been found between RBS and iron markers among the groups.

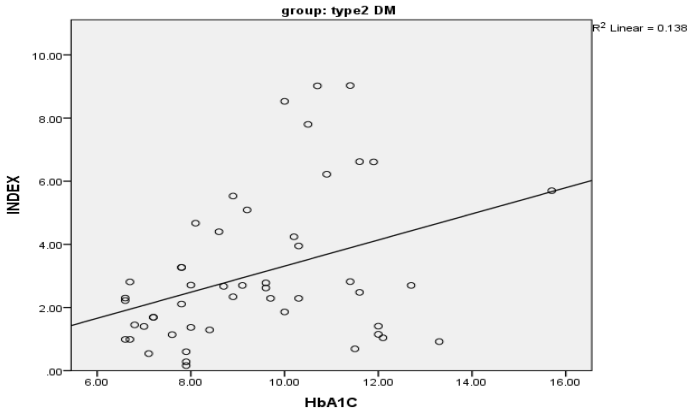

Figure 1: Pearson correlation between HbA1C & stfR- F index in type2DM (r=0.37, p=0.008)

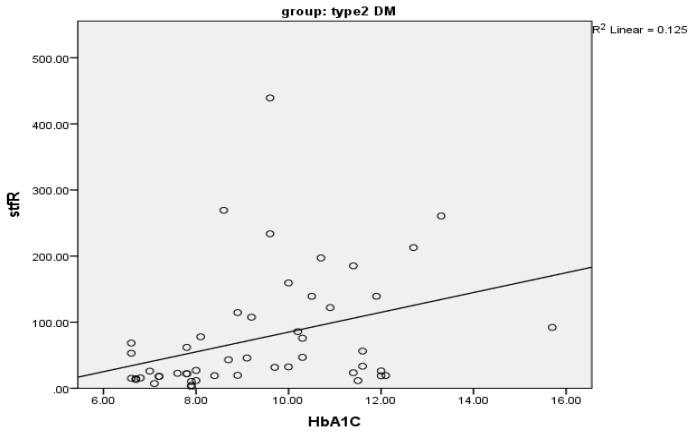

Figure 2: Correlation between HbA1C and stfR (r= 0.4, p =0.012)

DISCUSSION

Serum iron concentration in all the three groups are within reference range and are not significantly different in diagnosed cases of type 2DM, impaired glycemic group as well as healthy controls. The finding is similar to the result of the study done by G.K. Veerabhadra Goud et al [11]. In contrary to the findings of Gunjan Misra et al who found higher level of serum iron level in uncontrolled diabetes, we found low serum iron in type 2DM than in to impaired glycemic group than in healthy controls [12]. This might be because of more caloric/dietary restriction in diagnosed cases and also may be aggravated by already existing iron deficiency in normal population of India.

Our study has shown a significantly higher expression of soluble transferrin receptor (stfR) level in type 2 DM as compared to impaired glycemic group irrespective of iron status. The difference in level of stfR is not significant between impaired glycemic group and healthy group. Our findings are correlating with the findings by Hernandez et al who described increased stfR concentration in type 2 diabetic patients. In a sample of obese participants from the Diabetes Prevention Program (DPP) cohort they observed that high levels of stfR (indicative of low body-Iron store) were directly related to the risk of T2DM [13,14]. Studies evaluating the relationship between stfR and risk of T2DM are scarce and inconclusive. In a general German population from the EPIC-Potsdam and Cooperative Health Research in the Region of Augsburg (KORA) cohorts, and in Spanish population at high cardiovascular risk from the PREDIMED cohort serum ferritin, but not stfR, was associated with a higher risk of T2DM [15-17].

In this study we have found that stfR /ferritin index in type 2 DM is significantly higher than in impaired glycemic group and in healthy control. Significant difference has been found irrespective of iron status. The reason might be that insulin resistance may lead to increased stfR levels and therefore stfR-ferritin-index may also increase. Rather than only as iron deficiency indicator it might also be overlapped with insulin resistance where there is evidence of increase in serum stfR and stfR-ferritin index.

A positive association has been found in our study among diabetic group, between stfR& HbA1C and stfR-ferritin index & HbA1c, as compared to impaired glycemic group and healthy control. This indicated that it might be because of more prevalence of insulin resistance in type 2 diabetic people as compared to other groups. It has been shown in various studies that transferrin is an important determinant of the lipolytic activity of human serum in adipocytes and adipose tissue lipolysis has been recognized as a major determinant of insulin resistance [18,19]. Thus, higher levels of transferrin, although usually negatively correlated with ferritin, could also be involved in the risk of insulin resistance and type 2 diabetes.

In this study the correlation between ferritin and HbA1c was assessed but was not found significant. The findings are similar to Christy et al and Sharifi and Sazandeh where there was also lack of significant correlation between ferritin and HbA1c [20,21]. Several studies have shown elevated ferritin in diabetic people, though its mechanism is debatable. In a study by Raj and Rajan, ferritin showed positive correlation with HbA1c in diabetic people. In another study, Canturk et al found that serum ferritin was elevated as long as glycemic status was not achieved, thus they found normal ferritin levels in diabetic individuals. We could not explain the lack of correlation of serum ferritin levels with HbA1c in this study [22,23].

CONCLUSION

The study of iron and its markers are not only important in detecting and study of iron deficiency anemia but also might have a strong role in glucose homeostasis as well as development of intolerance to glucose and hence leading to type 2 diabetes mellitus. The parameters like ferritin and transferrin level might be altered by other factors like: level of serum iron, inflammatory status of the body etc. but stfR and stfR-ferritin index are comparatively stable and might be used as additional marker along with HbA1C for monitoring blood glucose homeostasis. It might have a role towards the development of insulin resistance or may be a result of it. Further studies if taken up by some researchers including the insulin resistance measurement may put some light in the fact.

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Conflicts of Interest of each author/ contributor: None

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