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Original Article

Correlation of Serum Ferritin in Type 2 Diabetes with Glyscosylated Haemoglobin and its relation after 3 months of follow up

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Abstract

Background: *Iron metabolism is involved with the development of diabetes. A few studies have suggested a causal relationship between high iron stores and diabetes. The patho-physiology behind this relationship is largely unknown, however, it is proposed that iron mediated free radical injury is the responsible factor.*

Objective: *The objective of this study was to study Serum Ferritin levels in Type 2 DM patients and its relation with Glycosylated Hemoglobin (A1C) and the relation of Serum Ferritin with HbA1c level after follow up at 3 months.*

Method: *In this observational case control study, Adults, aged > 18 years, with T2DM as per the Diagnostic criteria by the American Diabetes Association (ADA) were included. We measured FBG, PPBG, A1C, Serum Ferritin, Serum Creatinine in all the patients.*

Result: *We enrolled 93 patients with diabetes. Mean serum ferritin of all patients was 354.22 ± 22.31 ng/ml and mean A1C % of all patients was 8.41 ± 0.41%. Significant correlation was found between serum ferritin and FBG levels. Patients with A1C ≥8.5% had significantly higher serum ferritin level (435.99 ± 53.45 ng/ml) in comparison to those with A1C levels between 7.6 and 8.5% (223.59 ± 16.88 ng/ml) as well as than those with ≤7.5% (207.98 ± 6.54 ng/ml). On follow up at 3 month A1C levels changed significantly, but there was no significant change in serum ferritin level.*

Conclusion: *We found that serum ferritin was significantly high in patients with diabetes both males and females as compared to normal population. Serum ferritin levels correlate significantly with FBG levels but not with PPBG and HbA1C. Patients with A1C>8.5% have significantly higher serum ferritin levels. During a follow-up period of 3 months of treatment, A1C level reduced signifacantly while serum ferritin levels did not fall significantly.*

Keywords: *Serum Ferritin, T2DM, A1C , T2DM.*

Introduction

Iron metabolism is involved with the development of diabetes[1,2,3,4]. Studies have suggested a causal relationship between high iron stores and diabetes[5,6]. Apart from diabetes, studies have also linked serum ferritin with obesity, metabolic syndrome and insulin resistance[7,8,9]. The patho-physiology behind

this relationship is largely unknown, however, it is proposed that iron mediated free radical injury is the responsible factor. Iron can be very easily oxidised and reduced reversibly, and this property, vital for its metabolic function, also makes it potentially hazardous by generating oxidative stress[10]. It has also been shown that iron causes hyperinsulinaemia by decreasing the insulin uptake and metabolism by hepatocytes[11].

We performed this study to find the correlation of serum ferritin, marker of body iron stores, with serum glycated haemoglobin (A1C), marker of long term glycemic status. We also studied the relation of Seum Ferritin with HbA1C over a period of 3 month follow up.

Although various studies, have supported involvement of iron in association with diabetes, the hypothesis is still not considered valid. In a recently published data from the EPIC-Interact study[12], higher serum ferritin levels were associated with higher risk of diabetes, yet the authors concluded that the relationship is more complex than simple direct correlation. Therefore, the association between iron parameters and diabetes must be further established with more prospective studies.

Oobjective

Aim of this study was to study Serum Ferritin levels in Type 2 DM patients and its relation with Glycosylated Hemoglobin (A1C) and the relation of Serum Ferritin with HbA1c level after follow up at 3 months

Material and Method

This is an observational case control study. Adults, aged > 18 years, with T2DM as per the Diagnostic criteria by the American Diabetes Association (ADA) were included in the study- Fasting blood glucose (FBG) level of 126 mg/dl (7.0 mmol/L) or higher, *or* 2-hour plasma glucose level of 200 mg/dl (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), *or* Random plasma glucose of 200 mg/dl (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

We measured FBG, PPBG, A1C, serum ferritin, serum creatinine at the first visit. Serum ferritin and A1C was done after 3 month follow up.

Exclusion Criteria : Patients with Anemia (Hb<10 g/dL), taking steroids for more than a week and patients with illness that cause hyperferritinemia or affecting serum ferritin level e.g. Acute and chronic liver disease, Sepsis , End-stage renal disease and Autoimmune diseases were excluded from the study.

Statistical Analysis

All data was collected into Microsoft Excel. Results were expressed as Mean ± Standard Error. All statistical analysis was done using Statistica-8 software. Categorical data were compared using Chi-square test. Continuous data were compared using one-way analysis of variance (ANOVA).

Results

We enrolled 93 patients with diabetes. 63 (67.74%) were males and 30 (32.26%) were females. Mean age of all patients was 56 ± 11.69 years. Mean serum ferritin of all patients was 354.22 ± 22.31 ng/ml and mean A1C % of all patients was 8.41 ± 0.41% (Table 1).

Table 1 Basic Characteristics of all patients included in the study (n=93)

	Mean + SE	Range
Age (years)	56 ± 1.82	30 - 87
Sex: Males	63 (67.74%)	
Females	30 (32.26%)	
FBG (mg/dl)	154.59 ± 7.76	79 - 334
PPBG (mg/dl)	232.47 ± 10.33	109.00 - 454.00
A1C (%)	8.41 ± 0.41	4.60 - 15.90
Serum Ferritin (ng/ml)	354.22 ± 22.31	51.20 - 1149.00
Serum Creatinine (mg/dl)	1.30 ± 0.11	0.45 – 3.97

FBG= Fasting Blood Glucose, PPBG= Post Prandial Blood Glucose, GFR= Glomerular Filtration Rate, SE= Standard Error

Comparison of ferritin categories

We categorized all patients into two groups- Normal and High Ferritin groups. Normal ferritin group (NF Group) included 28 (30.10%) patients with serum ferritin levels between 12 and 204 ng/ml. High ferritin group (HF group) group included 65 (69.89%) patients with serum ferritin above 204 ng/ml. The proportion of males and age were similar in both the groups (Table 2). The mean serum ferritn levels of NF and HF groups were 134.09 ± 8.09 ng/ml and 449.05 ± 32.73 ng/ml

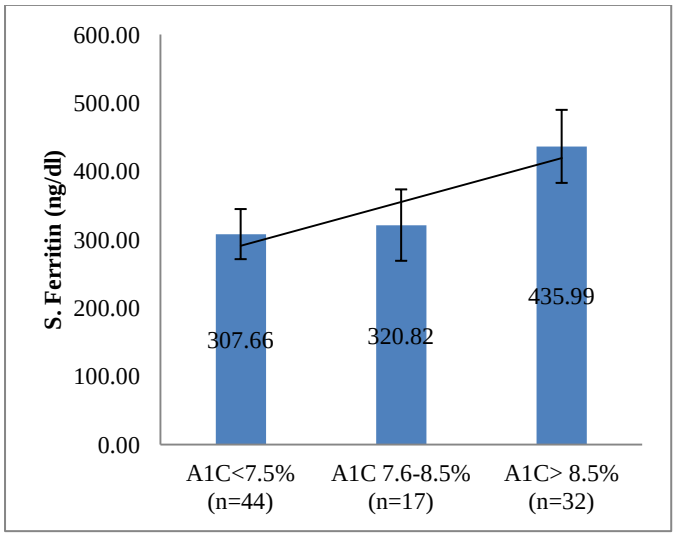
respectively. The mean A1C, FBG and PPBG levels were similar in both the groups. The mean serum creatinine, urine micralbumin and GFR were also similar between both the groups.

Table 2 shows comparison of basic characteristics between normal ferritin and high ferritin groups

	Normal Ferritin Group (n=28)	High Ferritin Group (n=65)	p-value
Males	17 (60.71%)	46 (70.77%)	p=0.141 (χ^2=0.905)
Females	11 (31.29%)	19 (29.23%)	
Age ± SE (years)	55.29 ± 1.89	57.05 ± 1.54	0.508
FBG ± SE (mg/dl)	143.88 ± 9.33	159.22 ± 7.37	0.234
PPBG ±SE (mg/dl)	231.23 ± 10.76	233.02 ± 8.39	0.903
A1C1 ± SE (%)	8.11 ± 0.37	8.55 ± 0.25	0.338
Ferritin1 ± SE (ng/ml)	134.09 ± 8.09	449.05 ± 32.73	0.001
S. Creatinine± SE (mg/dl)	1.17 ± 0.12	1.37 ± 0.09	0.206

All subjects were classified on the basis of their A1C levels into 3 groups. There were 44 (47.31%) patients with A1C levels less than 7.5%, there were 17 (18.28%) patients with A1C levels between 7.6 and 8.5% and 32 (34.41%) patients had A1C more than 8.5%. Those with A1C ≥8.5% had significantly higher serum ferritin level (435.99 ± 53.45 ng/ml) in comparison to those with A1C levels between 7.6 and 8.5% (223.59 ± 16.88 ng/ml) as well as than those with ≤7.5% (207.98 ± 6.54 ng/ml).

Figure 1 shows serum ferritin levels in groups with A1C≤7.5%, A1C 7.6-8.5% and A1C>8.5%



Correlation

Correlation analysis was performed between serum ferritin and various other parameters. Significant correlation was found between serum ferritin and FBG levels (r=0.213, p=0.040). Correlation was not significant between serum ferrritn and A1C level, PPBG, serum creatinine, urine micalbumin or GFR.

Follow-up analysis

We followed up patients after 3 months interval to study association of serum ferritin with glycemic changes. Follow up data was available from 63 patients, while 30 patients were lost to follow. Mean A1C levels of these 63 patients significantly decreased from first visit to second visit (after 3 months). A1C levels decreased from 8.58 ± 2.21% to 8.05 ± 1.63% (p=0.00019). Mean serum ferritin levels did not decrease from first to second visit (after 3 months). Serum ferritin at first visit was 355.51 ± 269.82 ng/ml, which was statistically similar to serum ferritin levels at second visit 350.11 ± 232.14 ng/ml (p=0.830). (Table 3).

Table 3. Comparison A1C and serum ferritin at 0 month and at subsequent visit at 3rd month in all patients who were followed up

n=63	At 0 months	At 3rd month	t-value	p- value
A1C ± SD (%)	8.58 ± 2.21	8.05 ± 1.63	3.97	0.00019
Ferritin (ng/ml) ± SD	355.51 ± 269.82	350.11 ± 232.14	0.22	0.830

Discussion

We studied serum ferritin levels in T2DM patients. The mean serum ferritin was raised in the diabetes patients of our study (354.22 ± 22.31 ng/ml).Similar to our study, Jiang R et al in 2004 reported that patients with diabetes had mean serum ferritin of 109 ng/ml, significantly higher than non-diabetics, who had mean serum ferritin of 71.5 ng/ml[3].

We further analysed all the patients by dividing them into groups of normal ferritin (NF) and high ferritin (HF). Both groups were matched with respect to age and sex. Although the serum A1C levels of HF group was higher in comparison to NF group, the difference was not statistically significant (8.55 ± 0.25 vs 8.11 ± 0.37 ng/ml, p=0.338). Similarly, mean FBG and PPBG levels were also higher in HF group than NF group but the difference was statistically not significant (159.22 ±

7.37 vs 143.88 ± 9.33 ng/ml, p=0.234). Halle M et al., reported 3.26 times higher risk for developing type 2 diabetes and 2.8 times higher risk for developing metabolic syndrome for individuals with the highest serum ferritin quartile compared with those of the lowest[13]. But there is not enough evidence to prove that the relation is causal, that is, high iron is sufficient to cause diabetes. In a meta-analysis published in 2013[14], it was found that elevated levels of ferritin may help identify individuals at high risk of type 2 diabetes.

In our study, we found a significant correlation of serum ferritin with fasting blood glucose levels (r=0.213, p=0.04) but not with post-prandial blood glucose level or A1C level (r=0.071, p=0.878 and r=0.160, p=0.125 respectively). The correlation between serum ferritin and A1C levels has been studied by a few other studies with variable results. Christy et al [15] found no significant correlation between A1C and ferritin levels. However, they showed that a positive correlation exists between iron deficiency anemia and increased A1C levels, and therfore, A1C levels increase in anemia. Kunduet al[16] showed that serum ferritin levels were highest in diabetics with A1C >8% (p<0.001) but they also did not find direct correlation between ferritin and A1C. In a small study by Padwal MK et al[8] high serum ferritin levels were found to be correlated to metabolic syndrome and insulin resistance. Thus, in terms of relation of ferritin with A1C, our results are similar to study by Christy et al. While interpreting results of the above studies, it must also be emphasized that A1C levels can be influenced by multiple factors. Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, hemolyticanemia) will falsely lower A1C test results regardless of the assay method used[17].

Follow up data showed that after 3 months of treatment, A1C levels decreased significantly (8.58 + 2.21 vs 8.05 + 1.63, p=0.00019) but serum ferritin levels did not fall significantly (355.51 ± 269.82 vs 350.11 ± 232.14 ng/ml, p=0.830). This is in contrast to Momeni et al who had shown that after 3 months follow up, with proper glycemic control, as the A1C levels decreased, serum ferritin levels also decreased significantly (115+109.4 to 91.4+61.9 ng/ml)[18]. No other study has assessed effect of anti-diabetic treatment on serum ferritin levels.

There are many unanswered questions in regards to association of diabetes and ferritin. We do not know the optimum levels of tissue iron in diabetes patients and if it is possible to provide different treatment modalities to diabetics with high serum ferritin. We further need to understand the effect of "normal" iron concentrations on diverse metabolic processes in tissues including liver, fat, muscle, pancreas, gut, and brain, the molecular mechanisms for these effects and if they can be targeted by approaches other than changing global iron levels. The patho-physiological association needs to be decoded before reliably commenting on clinical implications.

Conclusion

In this study we found that serum ferritin was significantly high in patients with diabetes both males and females as compared to normal population. Serum ferritin level correlated significantly with FBG level, but not with PPBG and HbA1C. Patients with A1C>8.5% have significantly higher serum ferritin levels**.** During a follow-up period of 3 months of treatment, A1C level reduced signifacantly while serum ferritin levels did not fall significantly**.**

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