https://doi.org/10.29309/TPMJ/2024.31.02.7869

The Professional Medical Journal
www.theprofesional.com
2024, Volume, 31 Issue, 02

ORIGINAL ARTICLE

Influence of serum ferritin on glycemic control in patients with type 2 diabetes mellitus.

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Article Citation: Memon S, Das B, Noor un Nisa, Anjum S, Rafique S, Memon R. Influence of serum ferritin on glycemic control in patients with type 2 diabetes mellitus. Professional Med J 2024; 31(02):183-188. https://doi.org/10.29309/TPMJ/2024.31.02.7869

ABSTRACT… Objective: To determine the influence of serum ferritin levels on glycemic control in patients with type 2 diabetes mellitus (T2DM) patients. **Study Design:** Cross-sectional study. **Setting:** Department of Medicine, Liaquat University Hospital, Hyderabad, Pakistan. **Period:** July 2021 to December 2021. **Material & Methods:** A total of 180 patients of 30-60 years of age and either gender, and known cases of diabetes mellitus for ≥3 year duration were included. Demographic, clinical and laboratory data was recorded. HbA1c below 7% was labeled as good glycemic control while HbA1c above or equal to 7% was designated as poor glycemic control. The serum ferritin ≥307 μg/L was considered as raised. Association of glycemic control with respect to serum ferritin levels was noted. **Results:** In a total of 180 patients of T2DM, the mean age, duration of diabetes, and HbA1c were 53.62 ± 5.82 years, 11.91±4.92 years, and 12.41 ± 5.73% respectively. The mean serum ferritin was 512±22.53 ug/L, whereas serum ferritin was raised in 109 (60.5%). The serum ferritin levels were significantly higher in patients with poor glycemic control than those having good glycemic control (56.0% versus 44.0%, p=0.044). **Conclusion:** In contrast to individuals with good glycemic control, patients with poor glycemic control more frequently had elevated serum ferritin levels, according to the current study. In order to properly manage diabetes patients and prevent the negative effects of elevated serum ferritin levels, serum ferritin should be included in the usual screening protocol of diabetic patients while monitoring their glycemic status.

Key words: Diabetes Mellitus, Glycemic Control, HbA1c, Screening, Serum Ferritin.

INTRODUCTION

One of the common metabolic illnesses known as diabetes mellitus (DM) exhibits the phenotype of hyperglycemia. Nearly 90% of all diabetic patients are having T2DM. Among T2DM, reduction in response of insulin is defined by terminology "insulin resistance".[1] Depending on the cause of the DM, factors that affect glucose levels include decreased insulin secretion, decreased glucose absorption, and increased glucose production.[2,3] The use of symbols "HbA1c" refers to glycated haemoglobin, which is progressed when the oxygen-carrying protein haemoglobin combines with blood glucose to form a compound known as "glycation".[4] It is used to evaluate long term control on glycemic condition and to track a therapy aim in the avoidance. By evaluating HbA1c, broad view of typical blood sugar levels over a period of 6 to 8 weeks can be obtained.[5]

One of the vital trace elements for a human organism is iron. 3–5 grams of iron are found in the human body. Mostly through absorption, the body controls the amount of iron in the body. The organism becomes dysfunctional when iron levels are either inadequate or excessive.[6] Diabetes risk may be increased by elevated iron storage. Recent scientific studies have found unexpected links between iron metabolism and T2DM. The impact of glucose metabolism on various iron metabolic pathways has an impact on iron metabolism. Iron has influence on glucose metabolism, unexpectedly in nonappearance of substantial iron excess, is becoming more commonly known.[7]

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Article received on: 16/09/2023
Accepted for publication: 22/11/2023

Existing data suggests a link between raised blood ferritin levels and poor glycemic control in diabetic individuals, as determined by their higher HbA1C levels.[8] When ferritin levels are high, a variety of events, including as oxidative damage to pancreatic beta cells, decreased liver ability to extract hepatic insulin, and interference with insulin's ability to control hepatic glucose synthesis, may result in diabetes.[9] Ferritin levels have also been found to correspond with specific symptoms of the metabolic syndrome, including serum lipids, plasma glucose, and insulin resistance markers.[10] There is growing concern regarding the connection between T2DM and evidence that mildly elevated body ferritin stores below those typically found in genetic hemochromatosis may result in poor glycemic status. Raised serum ferritin has been reported to have a positive influence of 66%, while normal serum ferritin has a negative influence of 34%, and the glycemic control is good (38%) and poor (35%) in the type 2 diabetes mellitus (T2DM) population, respectively.[11,12]

The relationship between serum ferritin levels and glycemic management in Pakistani T2DM patients is little understood. Hence the present study was planned to determine the influence of serum ferritin levels on glycemic control in patients with T2DM.

MATERIAL & METHODS

This cross-sectional study was performed at Department of Medicine, Liaquat University Hospital, Hyderabad, Pakistan. The study was performed during July 2021 to December, 2021. The study was commenced when ethical approval letter was sought from hospital ethics committee (IRB#: LUMS/REC/115). Patients of 30-60 years of age and either gender with history of diabetes mellitus (known cases) for ≥3 year duration. Patients with primary or secondary hemochromatosis, iron deficiency anemia, porphyria cutanea tarda, malabsorption syndrome and auto-immune disorders (SLE, rheumatoid arthritis) were excluded from this study. Old hospital records and diagnosis cards provided by relevant consultation doctors were used to evaluate the illnesses. By reviewing pertinent drug / prescription histories, patients receiving chemotherapy, iron, and mineral supplements that may alter the blood ferritin level were confirmed, and pregnant women and nursing moms were also excluded from consideration. Sample was estimated using two proportion formula on WHO sample size calculator. Taking anticipated frequency of raised serum ferritin as 66% among poor glycemic control diabetic patients[13], with 95% confidence level and 7% margin of error, the sample size turned out to be 176. We considered 180 patients for this study using non-probability consecutive sampling.

The serum ferritin ≥307 µg/L was considered as raised serum ferritin. When the patient's blood pressure was measured upon presentation and was found to be at 140/90, hypertension was diagnosed. Anemia was considered when hemoglobin concentration of less than 11 g/dL (laboratory maneuver). Smoking was considered when patients having having history of tobacco (≥ 3 cigarettes per day) use for ≥ 03 years duration. Obesity was considered when BMI ≥ 27 kg/m2 (Asian population). By looking for any abnormalities, such as minute bulges within blood vessels, bleeding in the retina, new blood vessels, scar tissue, or blood vessel leakage, an ophthalmoscope was used to assess diabetic retinopathy. Hyperlipidemia was evaluated as abnormally elevated levels of any one or all lipoproteins (cholesterol>200 mg/dl or triglycerides >150 mg/dl). Diabetic nephropathy was labeled when urinary albumin excretion (microalbuminuria) is greater than 30 mg / 24 hours. When a patient's foot was treated with a soft nylon fibre (monofilament) to reduce touch sensitivity, diabetic neuropathy was taken into account.

All participants in the study provided written informed consent before being evaluated for their glycemic status according to the operational definition using the HbA1c (the principal researcher took a 2 cc venous blood sample). The population was then classified as having good or poor glycemic control. HbA1c below 7% was labeled as good glycemic control while HbA1c above or equal to 7% was designated

as poor glycemic control. The lead investigator collected a 3 cc sample of venous blood after one month and delivered it to the lab for examination in a sterilized disposable 5 cc syringe. The senior pathologist having more than 5 years clinical laboratory experience was evaluate the specimen.

For statistical analysis, "Statistical Package for Social Sciences (SPSS)", version 21 was used. Categorical variables were summarized as frequency and percentage while numerical variables were expressed as mean standard deviation. To ascertain the relationship between elevated blood ferritin levels and patient characteristics, the Chi-square or Fisher-exact test was used. P values under 0.05 were considered statistically significant.

RESULTS

During six months study period total 180 patients of DM for ≥3 year duration of 30-60 year either gender were equally enrolled in to the study groups. Mean age, duration of DM and HBA1C levels were 53.62 ± 5.82, 11.91 ± 4.92 and 12.41 ± 5.73 respectively. Table-I summarizes the demographic and clinical findings.

The mean serum ferritin level was 512±22.53 µg/mL, whereas serum ferritin level was raised in 109 (60.5%) patients. Statistical significance was observed for raised serum ferritin with age ($p<0.001$), gender ($p=0.08$), residence ($p<0.001$), duration of diabetes ($p<0.001$), hypertension ($p=0.042$), smoking ($p=0.231$), hyperlipidemia ($p<0.001$), obesity ($p=0.050$), raised HbA1c ($p=0.05$), diabetes neuropathy ($p=0.047$), retinopathy ($p=0.050$), nephropathy ($p=0.032$), anemia ($p=0.049$), and glycemic status ($p=0.044$) and the details are shown in Table-II.

DISCUSSION

A biomarker for quantifying iron in human body is the complex of proteins and iron phosphorus known as ferritin. Elevated iron concentrations cause tissue and organ damage.[13,14] Increased iron accumulation impacts insulin synthesis, its discharge from pancreas, and the capability of liver for absorbing insulin. A consequence of muscle injury, iron buildup in muscles decreases glucose uptake. Conversely, by enhanced transferring receptor externalisation, insulin promotes cellular absorption of iron. Thus, iron and insulin may interact to amplify one other's effects, eventually resulting in diabetes and insulin resistance.[15]

Study Variables	Frequency (%)
Age Groups	
30-40	53 (29.4%)
41-50	81 (45.0%)
51-60	46 (25.6%)
Gender	
Male	105 (58.3%)
Female	75 (41.7%)
Residence	
Urban	73 (40.6%)
Rural	107 (59.4%)
Diabetes Duration	
3-5 years	42 (23.3%)
5-8 years	53 (29.4%)
>8 years	85 (47.2%)
Smoking	
Yes	94 (52.2%)
Obesity	
Yes	103 (57.2%)
Hypertension	
Yes	134 (74.4%)
Diabetes Neuropathy	
Yes	122 (67.8%)
Hyperlipidemia	
Yes	108 (60.0%)
Diabetes Retinopathy	
Yes	87 (48.3%)
Diabetes Nephropathy	
Yes	113 (62.8%)
Anemia	
Yes	98 (54.4%)

Table-I. Summary of demographical and clinical features

In the current investigation, patients with poor glycemic control had ferritin levels that were considerably higher than those with adequate glycemic control (56% versus 44%). The correlation between body iron reserves and the likelihood of acquiring DM has been the subject of numerous studies conducted globally. Elimam H et al study found a strong positive association between HbA1c and serum ferritin levels.[16]

Study Variables	Raised Serum Ferritin		P-Value
	Yes (n=109)	No (n=71)	
Age Groups			
30-40 years	39 (35.8%)	14 (19.7%)	<0.001
41-50 years	39 (35.8%)	42 (59.2%)	
51-60 years	31 (28.4%)	15 (21.1%)	
Gender			
Male	58 (53.2%)	47 (66.2%)	0.080
Female	51 (46.8%)	24 (33.8%)	
Residence			
Urban	53 (48.6%)	20 (28.2%)	<0.001
Rural	56 (51.4%)	51 (71.8%)	
Diabetes Duration			
3-5 years	33 (30.3%)	9 (12.7%)	<0.001
5-8 years	21 (19.3%)	32 (45.1%)	
>8 years	55 (50.5%)	30 (42.3%)	
Hypertension			
Yes	87 (79.8%)	47 (66.2%)	0.042
Smoking			
Yes	53 (48.6%)	41 (57.7%)	0.231
Hyperlipidemia			
Yes	56 (51.4%)	52 (73.2%)	<0.001
Obesity			
Yes	56 (51.4%)	47 (66.2%)	0.050
Diabetic Neuropathy			
Yes	80 (73.4%)	42 (59.2%)	0.047
Diabetic Retinopathy			
Yes	59 (54.1%)	28 (39.4%)	0.050
Diabetic Nephropathy			
Yes	78 (71.6%)	35 (49.3%)	0.032
Anemia			
Yes	66 (60.6%)	32 (45.1%)	0.049
Glycemic Control			
Poor control	61 (56.0%)	29 (40.8%)	0.044
Good control	48 (44.0%)	42 (59.2%)	

Table-II. Comparison of study variables with respect to serum ferritin levels (n=180)

Others have also shown link between high blood sugar and insulin levels and increasing body iron stores.[17] Additionally, Wolide AD et al[18] study in Ethiopia found that patients with T2DM had elevated ferritin, BMI, blood pressure and waist circumference with a substantial dissimilarity from the control group. In a study by Andrews M, et al. to evaluate the association between indicators indicating body iron storage, obese patients with T2DM were compared with a control group, and the study discovered greater blood ferritin levels among T2DM patients than the control group.[19] A similar study by Sun L. et al. and Shetty J.K. et al. discovered elevated serum ferritin levels. They also observed that diabetics with elevated serum ferritin levels had considerably poorer glycaemic control, as evidenced by higher levels of HbA1c.[20,21] In a cohort study conducted by Chen L. and colleagues[22], researchers investigated the association between serum ferritin levels and the susceptibility to develop T2DM in a Chinese population. The study enrolled a total of 2,225 participants aged between 25 and 75 years. Among these participants, 112 individuals were diagnosed with T2DM during the course of the study. Several key findings emerged from the comparison between individuals with diabetes and those without the condition. Firstly, individuals with T2DM exhibited higher baseline serum ferritin levels compared to their non-diabetic counterparts. Additionally, several other parameters, including BMI, and HbA1c levels were notably elevated in the group of patients with diabetes in comparison to the non-diabetic group.

Our results along with what we found in the literature collectively suggest a potential link between elevated serum ferritin levels and an increased risk of developing T2DM. These finding underscores the importance of further research to elucidate the underlying mechanisms and implications of iron metabolism in diabetes as well as the potential for serum ferritin levels to serve as a predictive marker for poor glycemic control. The present study analyzed patients at a single center with a limited sample size. Conducting similar studies with higher sample size in multiple institutes with a cohort evaluation would further validate finding of the present study.

CONCLUSION

In contrast to individuals with good glycemic control, patients with poor glycemic control more frequently had elevated serum ferritin levels, according to the current study. In order to properly manage diabetes patients and prevent the negative effects of elevated serum ferritin levels, serum ferritin should be included in the usual screening protocol of diabetic patients

while monitoring their glycemic status.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Sughandh Memon	Conceptualized the study, designed study protocol initial manuscript writing.	
2	Bhagwan Das	Literature search, Protocol designing and critical review and revision.	
3	Noor un Nisa	Involved in drafting initial manuscript draft.	
4	Sarwat Anjum	Involved in drafting initial manuscript draft.	
5	Saima Rafique	Involved in data analysis and result interpretation.	
6	Rafia Memon	Involved in data collection, analysis and result interpretation.