EVALUATION OF SERUM FERRITIN AS PREDICTOR OF HbA1c IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

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ABSTRACT

Background: Serum Ferritin is an acute phase protein and it is a marker of iron stores in the body. The HbA1c fraction is abnormally elevated in chronic hyperglycemic diabetic patients. **Objective:** To determine the association between serum ferritin and long term glycemic control by HbAIc in patients with diabetes mellitus type 2. **Methodology**: This was a case control study which was carried out in the chemical pathology department of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, from 1ST July 2016 to 31ST January 2017. A total of 290 study subjects were included in this study. 110(38%) were the cases (diabetics with high HbA1c). Ferritin, hemoglobin, HbA1c, and fasting blood sugar were measured in blood samples. Exclusion criteria included anemia, or any other disease or drug that could affect ferritin levels. Results were analyzed statistically by t-test and Pearson correlation test. The data was entered and analyzed by SPSS version 17. **Results**: A total of 290 study subjects were included in this study.110 were the cases (diabetics with high HbA1c), and 180 normal subjects were included. The mean serum ferritin among cases was significantly higher than control group (137±64 vs. 94±61ng/ml). (*P*<0.00). **Conclusion**: There is strong association and positive correlation between serum ferritin and blood glucose control HbA1c in diabetics of type 2 DM. We propose that more studies be performed about the role of ferritin in DM patients with impaired glucose tolerance.
Key Words: Diabetes mellitus, Ferritin, Fasting blood glucose, Glycosylated hemoglobin A1c

INTRODUCTION

Diabetes mellitus is a common metabolic disorder characterized by absolute or relative deficiency in insulin secretion and/or insulin action associated with chronic hyperglycemia.[1,2] The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and it is expected to increase to 4.4% by 2030.
Similarly in Pakistan the current prevalence of type 2 diabetes mellitus is high.[4,5] However, since the risk of type 2 diabetes is to a large extent modifiable through lifestyle changes, there is a huge potential to slow down and eventually reverse this pandemic. Long term control of glucose in people with diabetes mellitus can be effectively monitored by measurement of glycated proteins primarily HbA1c (glycosylated hemoglobin) which shows the previous control of blood glucose over the period of last six to eight weeks. But HbA1c may be affected by a variety of genetic, hematologic and illness-related factor.[6] So it is important to have another tool which could be useful in this regard. Diabetes may be induced by elevated iron stores 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.[7] Elevated ferritin leveIs have also been observed to be closely correlated with the individual component of metabolic syndrome especially with triglycerides, plasma glucose and markers of insulin resistance.[8] Moreover, it has been documented by two prospective studies that there is an independent association between baseline elevations in iron stores and the incidence of diabetes while low Vitamin D levels is also a risk factor for impaired glucose tolerance and T2DM.[9,10]
Overall there is paucity of literature showing any direct relation of diabetes mellitus with iron excess. This study was planned to determine the association of serum ferritin with HbA1c level in patients with type 2 DM and correlation of serum ferritin levels with HbA1c.

METHODOLOGY

This case-control study was conducted in the chemical pathology department of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, from 1st July 2016 to 31st January 2017 after obtaining approval from the Institutional Review Board for of Sheikh Zayed Medical College Rahim Yar Khan. It included adults patients having hemoglobin level more than 10 gram percent in the age group ≥ 35 years with or without vascular complications who were known to have diabetes mellitus type2 and were on diet control, hypoglycemic drugs or insulin for treatment of Type 2 DM for 6 months to 2 years. Age and sex matched healthy subjects (Non diabetic) coming to the hospital as patient`s attendant and also from medical or paramedical staff, persons attending OPD for routine checkup were taken as a control

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group. A detailed proforma was developed for each patient which included the age, sex, drug history and history of heart disease, hypertension along with their physical examination. For each subject the weight and height were measured and their body mass index (BMI) was calculated using weight /(height)^2 formula.

Exclusion criteria was, Type 1 diabetes mellitus, other states associated with altered serum ferritin levels like: Hemochromatosis, Chronic alcoholics, Chronic inflammatory conditions like SLE/ rheumatoid arthritis, Hepatitis, History of repeated blood transfusions, Iron deficiency anemia, Hypothyroidism, Chronic kidney disease were excluded.

All cases were selected by random sampling technique and the control subjects were also selected randomly. The study parameters were analyzed on Fully Automated Biochemistry Analyzer and Ferritin was analyzed by Electrochemiluminescence technique (ECLIA). After taking informed consent blood samples were collected in fluoride vacutainer for Fasting Blood glucose, in plain vacutainer for Ferritin and Lipid profile and in EDTA vacutainer for HbA1c. Samples for PP2BG were collected after 2 hours of taking a meal. Diabetic patients tested for HbA1c were arranged into 3 groups-Well controlled: < 7%, moderately controlled: ≥7%-8%, poorly controlled: > 8%. Reference range of serum ferritin was taken for Men ; 30-220 ng/mL and in Females; 20-110 ng/mL. Statistical analysis was done by using SPSS 17.

In data analysis, comparison of all parameters between control and study group was carried out by applying t-test and correlation of ferritin with other parameters were also studied by applying Pearson correlation test. $p < 0.05$ was considered significant.

RESULTS

A total of 290 study subjects were included in this study. 110 (38%) Cases (diabetics with high HbA1c), with 52 (47.3%) males and 58 (52.7%) females and 180 (62%) normal subjects (Control), with male 88 (48.9%) and 92 (51.1%) females. (p=0.7) Mean age for diabetic group was 52±8 years and for control group was 46±7 years.(p=0.00) (Table I) The mean BMI in diabetics was 28 ±4 kg/m2 and for control group was 25±3kg/m2. (p=0.00) The mean level of hemoglobin in diabetics (13.6±1.2g/dl) was not

significantly different from normal controls (13.6±1.5.g/dl). (p=0.06) The mean serum ferritin among cases was significantly higher than control group (137±64 vs 94±61ng/ml). (P<0.00) The mean ESR among diabetics was 20±14 while in controls was 14±5.(p=0.00) The overall mean serum ferritin level among males was 141±72ng/ml as compared to 81±42ng/ml among female. (p=0.00)

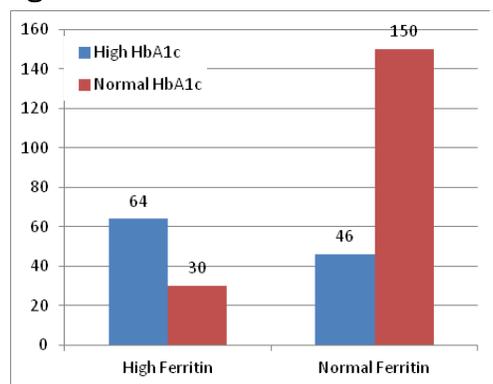**Table I: Mean values of different variables among cases and and controls**

Variable	Study Group	Mean±SD	P value
Serum ferritin (ng/ml)	Case	137±64	0.000
	Control	94±61	
Hemoglobin (gm/dl)	Case	13±1.2	0.6
	Control	13±1.5	
ESR	Case	20±14	0.000
	Control	14±5	
FBG (mg/dl)	Case	180±55	0.000
	Control	101±16	
PP2BG (mg/dl)	Case	301±86	0.000
	Control	144±38	
HbA1c	Case	7±1.4	0.000
	Control	5±1.4	
Total Cholesterol (mg/dl)	Case	200±47	0.06
	Control	191±31	
Triglyceride (mg/dl)	Case	199±82	0.000
	Control	157±45	
LDL	Case	123±39	0.07
	Control	130±27	
HDL (mg/dl)	Case	43±7	0.000
	Control	46±6	
BMI	Case	28±4	0.000
	Control	25±3	

Figure I shows that out of 94 cases with high serum ferritin levels, 64(68%) were also having high HbA1c as compared to those with normal ferritin levels where 46(23.5%) has high HbA1c. (p=0.000) Among cases with high serum ferritin category, 51(54.3%) were having poor diabetic control, 34(36.2%) have moderate diabetic control while only 9(9.6%) were having good diabetic control, whereas among normal ferritin category, 18(9.2%) were having poor diabetic control, 20(10.2%) were

having moderate diabetic control and 158(80.6%) have good diabetic control. (p=0.000) Statistical analysis showed the correlation coefficient between serum ferritin and HbA1c (r=0.49,p=0.00), BMI (r=0.04,p=0.1), FBS(r=0.22,p<0.00), PP2BS(r=0.27,p<0.00), and with Triglycerides. (r=0.17,p<0.00).

Figure I: HbA1c level among subjects having high and normal ferritin.

Table II: Mean values of variables among three groups showing glycemic control.

Variables	Groups according to Glycemic Control	N	Mean	SD	95% Confidence Interval for Mean		Min.	Max.	P value
					Lower Bound	Upper Bound			
Serum Ferritin	Good	167	80	46.2	73.1557	87.2905	20.00	228.00	
	Moderate	54	150	66.9	131.9590	168.5113	34.45	280.00	0.000
	Poor	69	152	67.8	136.2668	168.8729	25.70	236.00	
HbA1c	Good	167	5.1	.8	5.0740	5.3241	3.40	6.70	
	Moderate	54	7.4	.3	7.3509	7.5242	7.00	7.90	0.000
	Poor	69	9	.8	8.8554	9.2556	8.00	12.90	
ESR	Good	167	15.57	6.698	14.55	16.59	6	53	
	Moderate	54	19.11	16.040	14.73	23.49	5	90	0.05
	Poor	69	17.90	11.685	15.09	20.71	7	60	
Triglyceride	Good	167	154.69	51.258	146.86	162.53	47	400	
	Moderate	54	181.04	68.522	162.33	199.74	65	464	0.000
	Poor	69	213.65	74.976	195.64	231.66	82	494	
PP2BG	Good	167	149.56	48.859	142.09	157.02	15	380	
	Moderate	54	239.83	81.300	217.64	262.02	130	520	0.000
	Poor	69	309.33	100.61	285.16	333.50	2	587	
FBG	Good	167	106.11	28.675	101.73	110.49	67	282	
	Moderate	54	151.70	57.581	135.99	167.42	70	314	0.000
	Poor	69	177.75	57.981	163.83	191.68	100	318	

Table II shows the mean values of different variables in three groups; good, moderate and poor.

DISCUSSION
The results of this study showed that serum ferritin level in diabetic patients was significantly higher than non- diabetics and additionally increased body iron stores as reflected by high serum ferritin levels has a statistically significant correlation with FBS, PP2BS and HbA1c. Another study which was recently carried out in nurses cohort has shown the same results.[11] Subclinical hemochromatosis may contribute significantly for development of type 2 diabetes. Ferritin is known to be a marker of inflammation and also an index for body iron stores. In some epidemiological study conducted in S.Korea serum ferritin was the among the strongest determinant of blood glucose in regression models.[12] Another prospective study done among apparently healthy men and women showed that the incidence of type2 diabetes can be independently predicted by elevated serum ferritin levels.[13]

Iron in stored form gets deposited in various tissues and organs. In pancreas it may cause damage to β cell and decreased insulin secretion and in liver it may cause insulin resistance.[14] Our study clearly showed that there is positive correlation between the high HbA1c and high serum ferritin which in turn also reflects the short and long term relation between serum ferritin and glycaemic control. Study carried out by Cantur KZ et al also showed that those diabetic patients with poor glycemic control also had hyperferritinemia showing the poor long term glycemic control.[15] Sumesh Raj et al, also found that serum ferritin was significantly higher in the cases (p<0.01) when compared to controls which correlates with the present study (p<0.05) and as well as found positive correlation between serum ferritin and FBS, HbA1c.[16]

CONCLUSION
Our study showed that there is association between serum ferritin and poor glycemic controI. It is therefore suggested that serum ferritin levels should be included in the screening of patient with high risk for the development of diabetes mellitus and also for the assessment of long term glycemic status of patients with established diabetes mellitus. Furthermore, large scale studies are suggested as well.

Conflict of interest
There is no conflict of interest among all authors.

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