

Association Between Serum Ferritin Level and Glycemic Control in Patients of Type 2 Diabetes Mellitus With and Without Retinopathy

Ferritin Level
and Glycemic
Control in Type 2
Diabetes

Ali Raza¹, Maliha Hameed², Anus Bashir³, Hussain Farooq⁴, Hadia Rafique Rana⁵ and Muhammad Javed Asif⁶

ABSTRACT

Objective: To determine the significance of serum ferritin level in Pakistani diabetic population with or without retinopathy and its association with glycemic control.

Study Design: Cross-sectional

Place and Duration of Study: This study was conducted at the Department of Hematology, Shaikh Zayed Hospital, Lahore from January 2015 to June 2015.

Materials and Methods: Twenty one normal healthy controls and 42 known diabetics of disease duration more than five years (21 without retinopathy and 21 with retinopathy) were included. All were tested for serum ferritin and Hb A1c levels.

Results: Ferritin levels were found to be higher in diabetic groups as compared to normal control group. Both diabetic groups with or without retinopathy had significantly higher levels of HbA1c as compared to normal controls. Higher serum ferritin levels were observed with longer duration of diabetes.

Conclusion: Ferritin levels are higher in diabetic groups with and without retinopathy as compared to controls and correlated with poor glycemic control.

Key Words: Diabetes, Diabetic Retinopathy, Ferritin, Glycemic Control

Citation of articles: Raza A, Hameed M, Bashir A, Farooq H, Rana HR, Asif MJ. Association Between Serum Ferritin Level and Glycemic Control in Patients of Type 2 Diabetes Mellitus With and Without Retinopathy. Med Forum 2019;30(6):82-85.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia and one of the leading causes of morbidity and mortality in human population.¹ There are two types of DM. Type 1 diabetes is insulin dependent whereas type 2 diabetes is non-insulin dependent and more common than type 1. Both types are associated with microvascular and macrovascular complications like retinopathy, nephropathy, neuropathy and coronary artery disease.^{2,3}

¹. Department of Pathology, Sahara Medical College Narowal.

². Department of Medicine, Lahore General Hospital Lahore.

³. Physician, Tehsil Head Quarter Hospital, Ferozwala.

⁴. Shaikh Zayed Hospital. Lahore.

⁵. Department of Pathology, Central Park MC, Lahore.

⁶. Department of Haematology, University Medical & Dental College, University of Lahore, Lahore.

Correspondence: Dr. Ali Raza, Senior of Pathology, Sahara Medical College, Narowal.

Contact No: 03334707689

Email: draliraza@live.com

Received: December, 2018

Accepted: April, 2019

Printed: June, 2019

According to the International Diabetic Federation (IDF), Pakistan currently ranks at number 2 in MENA region for number of diabetic patients aged 18-99 years. The diabetics in Pakistan were estimated at 7.6 million in 2017.⁴ In a country wide population based survey conducted in Pakistan, 16.98% of the general population aged 20 years or above is suffering from type 2 diabetes mellitus.⁵

American diabetic association has recently approved HbA1c as a reliable test both for diagnosis of DM and assessment of glycemic control in known diabetic patients. The value of HbA1c for non-diabetic people is less than 5.7 %, for pre-diabetics is 5.7% to 6.4% and for diagnosis of DM is 6.5%.^{3,6} Studies have shown variable cut off thresholds of HbA1c for increased risk of retinopathy.⁷

The advantage of HbA1c is that there is no need to fast and lower variability than FBS and OGTT. It also gives excellent estimate of glycemic control for the period of preceding 3-4 months which is equal to the life span of red blood cells.^{1,6}

Iron is a major factor in the causation of glucose intolerance, gestational diabetes, type 2 diabetes and insulin resistance syndrome. Patients of DM with poor diabetic control exhibited elevated levels of serum ferritin which is also associated with diabetic

complications like retinopathy, nephropathy and vascular dysfunction.^{8,9}

Elevated iron stores are also responsible for damage to liver, heart, endocrine organs and skeletal muscles.¹⁰ Researchers in a retrospective study showed that iron excess (by measuring ferritin) could increase risk of diabetes mellitus by three times.¹¹

Serum ferritin is a simple index of iron stores and a cost effective test. The measurement of ferritin in serum by immune assay is a non-invasive, reliable and easy test for body iron stores as compared to previously used measures e.g liver and bone marrow biopsy which are invasive and expensive.¹²

Diabetic Retinopathy (DR) is an important etiological factor of blindness in developing countries. Several studies have been conducted to find prevalence of DR in Pakistan. Results vary from 15 % to as high as 43%.¹³

In diabetics with retinopathy, the metabolism of iron is impaired and its role is bidirectional. There is hyperglycemia induced destruction of heme molecule, over expression of proteins related to iron metabolism like hepcidin and ferroportin and intra retinal and vitreal hemorrhages. All lead to iron overload in diabetic eye. Iron overload, in turn, causes retinal neurodegeneration of rods and cones due to increased oxidative stress. Iron overload also causes defective phagocytosis and synthesis of cytokines which worsen the pathogenesis.¹²

Duration of diabetes is one of the important factors involving in its pathogenesis. Studies have shown odds ratio of 1.13 and 1.16 for per year increase of DR. However about 20% diabetics with type 2 DM may present with retinopathy at the moment of diagnosis In type 2 diabetes, prevalence of retinopathy is 50 percent after 10 years.¹⁴ This emphasizes the role of factors other than duration and glycemic control alone.

MATERIALS AND METHODS

It was a cross sectional analytical study conducted at Department of Hematology, Sheikh Zayed Hospital from 1st January 2015 to 30th June 2015 on 63 subjects aged 30-60 yrs with normal hemoglobin level. Study population was divided into three groups consisted of 21 normal healthy controls, 21 diabetics without retinopathy and 21 diabetics with retinopathy with duration more than five years. Subjects with hypertension and hypertensive retinopathy, haemochromatosis, iron supplements, history of blood transfusion or iron loss like gastrointestinal bleed and history of blood donation were excluded. Subjects having chronic diseases, acute and chronic infections, malignancies and autoimmune diseases were also excluded. CBC was performed on haematology analyzer KX-21 by electric impedance method, HbA1c on chemistry analyzer Dimension-System by turbidmetric inhibition immunoassay (TINIA) and

Serum ferritin on Immulite 100-System by chemiluminescence immunoassay. Data of diabetic patients visiting diabetic clinic and ophthalmology departments of Shaikh Zayed

Hospital, was collected according to inclusion criteria. Data was analyzed using SPSS 20. P-value <0.05 was taken as significant.

RESULTS

There were 15 males in group A, 13 in group B and 12 in C. The difference of gender among groups was insignificant with p-value = 0.619. The age distribution for three groups was insignificant with p-value = 0.061. There were 15 cases with age < 40 years, 20 cases with age 40-50 years and 28 cases with age > 50 years. The average ages for the three groups were 37, 50 and 55 years (Tables 1-2).

There were 0, 2 and 5 cases with high ferritin levels in three groups respectively. The mean ferritin levels for group A, B and C were 92.2±73.2, 121.6±113.0, and 199.5±162.1 µg/l respectively. The median ferritin levels recorded for three groups were 58.6, 83.6 and 139.0 µg/l and the difference among groups was significant with p-value 0.021 by chi-square. Hyperferritinemia was not found different among males and females. There was 1 male and 1 female in group B, and 3 males and 2 females in group C with high ferritin levels (Table 3).

Table No.1: Gender distribution of cases

Gender	Group A (n=21)		Group B (n=21)		Group C (n=21)	
	No.	%	No.	%	No.	%
Male	15	71.4	13	61.9	12	57.1
Female	6	28.6	8	38.1	9	42.9

Chi-square = 0.96, p-value = 0.619 (Not significant)

Table No.2: Age distribution of cases

Age (years)	Group A (n=21)		Group B (n=21)		Group C (n=21)	
	No.	%	No.	%	No.	%
<40	9	42.9	4	19.1	2	9.5
40-50	7	33.3	7	33.3	6	26.6
>50	5	23.8	10	47.6	13	61.9

Chi-square = 8.8, p-value = 0.061 (Significant)

Table No.3: Distribution of ferritin levels for three study groups

Ferritin level (µg/l)	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
High ferritin	-	-	2	9.5	5	23.8
Normal	21	100.0	19	90.5	16	76.2
Total	21	100.0	21	100.0	21	100.0
Mean±SD	92.2±73.2		121.6±113.0		199.5±162.1	
Median (Q1 – Q3)	58.6 (36.5 – 111.0)		83.6 (37.1 – 185.0)		139.0 (96.4 – 262.0)	

Chi-square = 7.69, p-value = 0.021 (Significant)

Table No.4: Distribution of hemoglobin A_{1c} levels for study groups

Hemoglobin A _{1c} (%)	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
≤ 5.70	21	100.0	-	-	-	-
6.5 - 7.00	-	-	6	28.6	2	9.5
>7.00	-	-	15	71.4	19	90.5
Total	21	100.0	21	100.0	21	100.0
Mean±SD	5.26±0.29		8.10±1.38		8.40±2.04	
Median (Q1 – Q3)	5.3 (5.1 – 5.5)		7.9 (6.9 – 10.1)		8.1 (7.8 – 9.1)	

Chi-square = 82.76 p-value < 0.001 (Significant)

Table No.5: Distribution of duration of diabetes for the diabetic groups

Duration of DM (years)	Group B		Group C	
	No.	%	No.	%
≤ 10	16	76.2	10	47.6
11 - 15	5	23.8	7	33.3
>15	-	-	4	19.0
Total	21	100.0	21	100.0
Mean±SD	9.0±2.6		12.0±4.0	
Median (Q1 – Q3)	8 (7 – 10)		11 (10 – 15)	

Chi-square = 7.28 p-value = 0.026 (Significant).

Table No.6: Association of ferritin level with HbA_{1c}

HbA _{1c}	Ferritin levels				Total	
	Hyperferritinemia		Normal		No.	%
	No.	%	No.	%		
≤ 5.70	-	-	21	37.5	21	33.3
6.5 - 7.00	1	14.3	7	12.5	8	12.7
>7.00	6	85.7	28	50.0	34	54.0
Total	7	100	41	100	63	100.0

Chi-square = 6.24, P-value = 0.047

HbA_{1c} levels for three groups were measured and the mean levels were 5.26±0.29 %, 8.10±1.38 % and 8.46±2.04% for the three groups with median levels of 5.3%, 7.9% and 8.1% respectively. HbA_{1c} >7.0% was seen, it was noted that there were 15 (71.4%) in group B and 19 (90.5%) in group C. The differences for frequencies was significant with p-value <0.001 (Table 4). The mean duration of diabetes for group B was 9.0±2.6 years and that for group C was 12.0±4.0 years. Majority (76.2%) of cases in group B and nearly half (47.6%) in group C had the disease for <10 years respectively. Difference for categories of duration was significantly different with p-value 0.026 (Table 5). In the end all groups were studied together for the association between HbA_{1c} and hyperferritinemia. It was observed that the association was significant with p-value 0.047. (Table 6).

DISCUSSION

Diabetes mellitus (DM) is a major public health concern, affecting millions of people across the globe. In our study, there were 15 males in group A, 13 in

group B and 12 in C. The difference of age, gender and hemoglobin level among groups was insignificant. It was in accordance with results of study by Smotra et al.¹⁵

There were 0, 2 and 5 cases with high ferritin levels in groups A, B and C respectively. The ferritin levels were found to be higher in diabetic groups as compared to normal control group. The difference among groups was significant. It was in accordance with studies conducted by Chen¹⁶, Borah¹⁷ and Farhan.¹⁸

Both diabetic groups with or without retinopathy had significantly higher HbA_{1c} levels as compared to normal controls. Increased HbA_{1c} levels in both diabetic groups correlated with the level of hyperferritinemia in the same groups. It was similar to the observations of Momeni¹⁹ and Raj.²⁰

Higher serum ferritin levels were seen in patients with longer duration of diabetes. Diabetics with retinopathy in Group C had significantly increase duration of diabetes and also exhibited higher Ferritin Levels when compared with group B. It is in accordance of study conducted by Kundu²¹ and Jaganatha et al.²² Whereas the findings of above referred international studies are in line with conclusion made in our present study, some other studies reported different observations.

One study was performed by Elis et al²³ by making three study groups like ours. The groups were compact and similar in parameters like age, gender and hemoglobin concentration. Serum ferritin concentrations did not diverge noticeable among three groups. No statistical significant relationship between glycemic control and serum iron or ferritin concentration in two diabetic groups was seen. In studies conducted by Sharifi et al²⁴ and Pramiladevi et al²⁵ reported that there was no relationship between serum ferritin and HbA_{1c} in diabetic patients of both sexes.

CONCLUSION

Hyperferritinemia can predict retinopathy in diabetics with poor glycemic control (HbA_{1c} > 7) and a duration longer than ten years. It is suggested that estimation of HbA_{1c} level may be used as a routine test for diagnosis of DM and to check the glycemic control in diabetics respectively. Pakistani diabetics shall also be evaluated for hyperferritinemia and be trialed with iron chelators and blood donations to reduce iron overload and consequent diabetic complications, as being practiced in developed countries.

Author's Contribution:

Concept & Design of Study: Ali Raza
Drafting: Maliha Hameed, Anus Bashir

Data Analysis: Hussain Farooq, Hadia Rafique Rana, Muhammad Javed Asif

Revisiting Critically: Ali Raza, Maliha Hameed
 Final Approval of version: Ali Raza

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Masharani U. Diabetes mellitus and hypoglycemia. In: Papadakis MA, McPhee SJ, editors. *Current Medical Diagnosis & Treatment*. United States of America: McGraw Hill; 2019.p.1222-66.
- Endocrinology. In: Wilkinson IB, Raine T, Wiles K, Goodhart A, Hall C, O'Neill H. *Oxford Handbook of Clinical Medicine*. 10th ed. United Kingdom: Oxford University Press; 2017.p.202-41.
- Pearson ER, McCrimmon RJ. Diabetes mellitus. In: Ralston SH, Penman ID, Strachan MWJ, Hobson RP eds. *Davidson's Principles and Practice of Medicine*. 23rd ed. China:Elsevier; 2018.p.719-62.
- Diabetes in MENA. International Diabetes Federation.2019. [Internet][cited:2019 May 1] Available from: <https://www.idf.org/our-network/regions-members/middle-east-and-north-africa/diabetes-in-mena.html>
- Aamir AH, Haq Z, Mahar SA, Qureshi FM, Ahmad I, Jawa A, et al. Diabetes Prevalence Survey of Pakistan (DPS-PAK): prevalence of type 2 diabetes mellitus and prediabetes using HbA1c: a population-based survey from Pakistan. *BMJ Open* 2019; 9(2): e025300.
- Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus abbreviated report of WHO consultation. World Health Organization 2011.
- Zhang R, Li Y, Zhang S, Cai X, Zhou X, Ji L. The Association of Retinopathy and Plasma Glucose and HbA1c: A Validation of Diabetes Diagnostic Criteria in a Chinese Population. *J Diabetes Res* 2016.
- American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2014; 37:S14-S16.
- Sanjeevi N, Freeland-Graves J, Beretvas SN, Sachdev PK. Trace element status in type 2 diabetes: A meta-analysis. *J Clin Diagn Res* 2018; 12(5) : OE01 -08.
- Camaschella C, Hoffbrand AV, Domenica M. Iron overload. In: Hoffbrand AV, Higgs DR, Keeling DM, Mehta AB, editors. *Postgraduate Haematology*. 7th ed. UK: John Wiley & Sons; 2016.p.40-52.
- Salem Z, Vazirinejad R, Sheikholeslami NZ, Hashemi Z, Tashakiry M. The comparison of serum ferritin concentration between healthy people with and without family history of diabetes. *Pak J Med Sci* 2008;24:296-9.
- Ciudin A, Herandez C, Simo R. Iron overload in diabetic retinopathy: a cause or consequence of impaired mechanism. *Exp Diabetes Res* 2010:1-8.
- Hakeem R, Awan Z, Memon S, Gillani M, Shaikh SA, Sheikh MA, et al. Diabetic retinopathy awareness and practices in a low-income suburban population in Karachi, Pakistan. *J Diabetol* 2017; 8:49-55.
- Solomon SD, Chew E, Duh EJ, Sobrin L, Sun JK, VanderBeek BL. Diabetic retinopathy: a position statement by the American diabetes association. *Diabetes Care* 2017; 40(3): 412-8.
- Smotra S, Kudyar RP. Relationship between Serum ferritin and type 2 Diabetes Mellitus. *JK Science* 2008;10:170-174.
- Chen L, Li Y, Zhang F, Zhang S, Zhou X, Ji L. Elevated serum ferritin concentration is associated with incident type 2 diabetes mellitus in a Chinese population: a prospective cohort study. *Diabetes Res Clin Pract* 2018;139:155-62.
- Borah M, Goswami RK. Evaluation of serum ferritin in in type II diabetes mellitus: a hospital based observational study from Dibrugarh, Assam, India. *Int J Res Med Sci* 2016; 4(11):4916-21.
- Farhan M. Ahmed U. Anwar MK. Association of Serum ferritin and CRP levels with development and severity of diabetic retinopathy. *Pak J Physiol* 2017; 13:11-3.
- Momeni A, Behradmanesh MS, Kheiri S, Abasi F. Serum ferritin has correlation with HbA1c in type 2 diabetic patients. *Adv Biomed Res* 2015; 4:74.
- Raj S, Rajan GV. Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus. *Int J Res Med Sci* 2013; 1:12-5.
- Kundu D, Roy A, Mandal T, Bandyopadhyay U, Ghosh E, Ray D. Relation of iron stores to oxidative stress in type 2 diabetes. *Niger J Clin Pract* 2013;16(1):100-3.
- Jaganatha SB, Nagarappa K, Mallikarjuna CR. Serum ferritin a novel risk factor for diabetes? *International J Innov Res Sci* 2013;2:475-479.
- Elis A, Ferencz JR, Gilady G, Assia EI, Lishner M. Is serum ferritin high with patients of diabetic retinopathy? A controlled study. *Endocr Res* 2004; 30:141-147.
- Sharifi F, Sazandeh S. Serum Ferritin in Type 2 Diabetes Mellitus and its relationship with HbA1c. *Acta Medica Iranica* 2004;42(2):142-145.
- Pramiladevi R, et al. Serum ferritin level in type 2 Diabetes Mellitus. *Sch J App Med Sci* 2013;1(5): 472-5.