Increased Iron Overload and Glycated Hemoglobin in Diabetes Mellitus-II Patients in Sulaimani city

Sirwan Mustafa Mohammed

Dept. of Biology, School of Science, University of Sulaimani, Kurdistan Region-Iraq,
e-mail: sirwan.mohammed@univsul.net

Abstract:

The purpose of the current study was to assess the correlation between the iron overload and increased glycated hemoglobin (HbA1c) among some diabetic patients in Sulaimani outpatient clinics. The studied samples included 60 randomly selected patients diagnosed with diabetes mellitus-II, having mean age of 51 years. Oppositely, 20 non-diabetic persons (having normal blood glucose and HbA1c within the normal range (2-6%) with mean age of (46) years; were enrolled as a control group. Serum ferritin (SF) was used for measuring iron storage status, correspondingly, blood glucose and mean values of glycemia, measured as glycated hemoglobin (HbA1c) are measured. The results of the current study revealed highly significant increasing of iron storage (P-value <0.001) and percentage of glycated hemoglobin (p< 0.05) among the diabetic patients. Further studies with larger samples should be conducted to examine the possible role of iron overload in the emergence of diabetes.

Keywords: Iron overload; glycated Hemoglobin(HbA1c); Diabetes mellitus-II.

Introduction:

Iron is the most abundant transitional metal in the body. The crucial role of iron in the pathophysiology of disease is derived from the easiness with which iron is reversibly oxidized and reduced. This property, while essential for its metabolic functions, makes iron potentially hazardous because of its ability to participate in the generation of powerful oxidant species such as hydroxyl radical [1, 2].

Ferritin, like hemoglobin, is a major iron storage protein. Isoferritin moieties have been identified for liver and spleen (L isoferritin) and for heart and kidney (H isoferritin). Circulating plasma ferritin is most like the L isoferritin. A serum ferritin assay provides a much more sensitive indicator of iron body stores than a traditional serum iron assay [3].

Serum ferritin levels increase as a result of iron overload, aging, infection, inflammation, liver disease, juvenile rheumatoid arthritis, leukemia, and Hodgkin's disease; and they decrease as a result of iron deficiency [4, 5].

Iron is not actively excreted through the-liver or kidneys. Iron is not actively excreted through the-liver or kidneys. It is lost from the body only when cells are lost, particularly epithelial cells from the gastrointestinal tract, epidermal cells of the skin, and, in menstruating women, red blood cells. Thus, iron balance is primarily, if not exclusively, achieved by control of absorption rather than by control of excretion [6].

As a predominant public and medical issue, the emergence of diabetes had increased dramatically in recent years. Lately, it is recognized that, increased body iron stores are associated with the

development of glucose intolerance, gestational diabetes & Type-2 diabetes [7,16].

According to the World Health Organization (WHO), 30 million people worldwide had diabetes in 1985. By 2000 the number was up to 171 million, and by 2030 it is estimated to be a whopping 366 million. In the United States one-third of all children born today are projected to develop diabetes during their lifetime [8].

According to the data of "Diabetes and Endocrine Center in Sulaimani" 7205 diabetic patients visited the center during the first six months of 2012, and underwent various diabetes-related investigations.

It has long been recognized that iron overload can increase the risk of diabetes, particularly in iron-overload states such as hemochromatosis and recurrent transfusions in diseases like thalassemia. Furthermore, a large body of epidemiological evidence- suggests that an increase in dietary iron (as heme, mainly from meat and meat products) is associated with an increased risk of diabetes [2]. In contrast, iron deficiency (over time one of the most common nutritional deficiencies in the world) may lower the risk of diabetes. Indeed, it has been suggested that recurrent phlebotomy may protect against diabetes [9].

Many recent studies suggest that iron overload plays a significant role in the development of diabetes and its complications. Iron may contribute to the pathogenesis of type 2 diabetes mellitus by inducing oxidative stress and interfering with insulin secretion or by losing β-cell mass [10, 11].

The issue of the health effects caused by iron overload has gained considerable visibility. An increase in serum ferritin has been infrequently reported in diabetic patients who have no clinical or biological signs of genetic hemochromatosis. Consequently, such patients might undergo unjustifiable liver biopsies. However, in view of the heterogeneity of the populations included in most studies, this association with ferritin remains questionable and the data are conflicting about whether elevated SF, an independent risk factor for diabetes and whether higher levels reflect inflammation or increased iron stores [12, 13].

On the other hand HbA1c, glycated haemoglobin, is formed by the glycosylation of haemoglobin. Its value represents the glycaemic status of a person over the last two to three months. It is measured in diabetics as well as in those with impaired glucose tolerance to assess the glycaemic status over the last two to three months [16, 17]. Some studies suggested that poor glycemic control and increase in glycation of haemoglobin is contributing to the increase in free iron pool which is known to increase oxidant generation, and enlarged microvascular complication of diabetes [16, 18].

Objectives: To observe the relationship between iron storage and hemoglobin glycation in diabetic patients.

Methodology:

Subjects:

The present study included 60 randomly selected diabetic patients visiting the Medya clinical laboratory in Sulaimani city from the period between February 2012 and October 2012. Their age were ranged from (32-71) years, with mean age of 51 years.

On the other hand 20 non-diabetic persons with their age ranged (24-60) years (having normal blood glucose and HbA1c within the normal range 2-6%) enrolled as a control group. The questionary form for each case included in the current study was filled out and the inappropriate cases were removed. The methodology used in this study also involved, collection, preparation, and

storage of the samples. As well as included the different laboratory tests that used to investigate iron storage, blood glucose, and hemoglobin glycation.

Sample collection and preparation:

About 5 ml of venous blood were drawn from each person and separated into two parts; one was collected in EDTA containing tube, used for measurement of HbA1c immediately on the same day of collection and the other part in a non-anticoagulated plain tube to obtain the serum samples. The blood samples were left for about 15 minutes in the water bath 37 C° to allow blood to clot. Later, tubes were centrifuged at 2500-3000 RPM for about 5 minutes to obtain the serum samples. After centrifugation the serum samples were used for the measurement of the serum ferritin (SF) by the ELFA method. Then the blood glucose were measured by using automated chemical analyzer KENZA from BioLabo,While the HbA1c values were obtained by using the NycoCard HbA1c ReaderΠ as in [19,20].

Statistical Analysis:

In the current study the statistical analysis used was in included; independent t-test to compare means. The data were analyzed by using the Statgraphics Plus Version 4.0.

Results:

I. Iron overload:

The current study included sixty diabetic patients and twenty control personnel; the questionaries' and laboratory obtained data were organized and tabulated as shown in Table (1).

The t-test comparison of iron storage, measured as SF showed highly significant rising among the diabetic patients (P=0.001) as exposed in Table (1) and Fig.(1).

Table. I: Comparison of serum ferritin between diabetic patients and control group.

Subject Cases	№	Mean age years	Mean SF ng/ml	SD
Diabetes	60	51	183.3	15.28
Controls	20	38	60.5	65.3
Correlation			P < 0.001	P<0.00091

SD: Standard Deviation

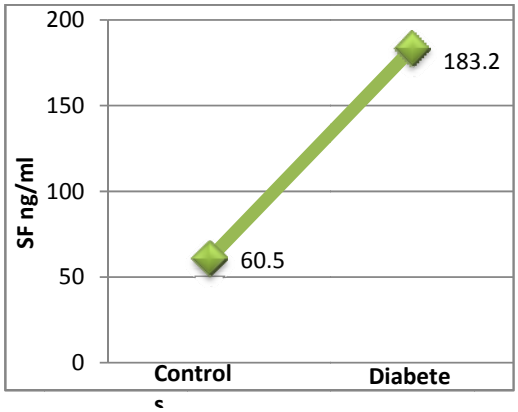

Fig.1: Mean of serum ferritin levels in diabetic patients when compared with control group.

II. Glycated Haemoglobin:

In regard to the HbA1c defining normal values (2-6%), The t-test comparison of the means between the haemoglobin glycation level in both control and diabetic patients showed statistically significant differences (P< 0.05), as shown in Table (2) and Fig. (2).

Table. II: Intensity of glycaemic status among the diabetic patients and control group.

Subject Cases	№	Mean age years	Mean HbA1c %	Mean Glucose Mg/dl
Diabetes	60	51	8.1	221
Controls	20	38	3.9	97
Correlation			p< 0.05	p< 0.05

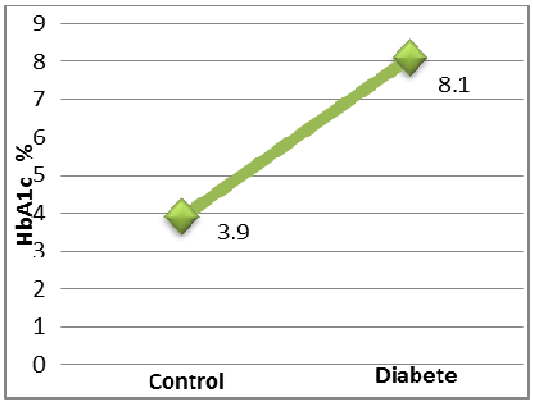

Fig.2: Mean of Hba1c levels in diabetic patients when compared with control group.

Discussion:

The current study was carried out to assess the correlation between increased serum ferritin and elevated levels of glycated hemoglobin among some diabetic patients in Sulaimani city. As well as, to draw attention to the possible role of iron overload in the emergence of diabetes.

The pathological effects of iron accumulation in tissue in iron-overload states are well known [1]. The newest event in the field is the recognition that iron plays an important role in the pathophysiology of disease in the absence of systemic iron overload [2].

The concept of iron contributing to diabetes is supported by a few important recent animal studies [14], which have demonstrated that, in obese mice with type 2 diabetes treated with an iron-restricted diet as well as an iron chelator, there were improvements in glucose metabolism without causing obvious iron deficiency. Thus, even at "normal" levels iron exerts a harmful effect on β-cell function that may be reversible with removal of iron, either through phlebotomy or possibly iron chelation. Serum ferritin concentration offers an indirect estimate of body iron stores because it is highly-correlated with bone marrow iron. Ferritin is also a positive acute-phase reactant and increases in the presence of various acute or chronic disease conditions. Elevated serum ferritin levels have been found in many chronic inflammation– related diseases [12].

The results of the current study showed increased level of both SF and hemoglobin glycation (measured by HbA1c) among studied sample of diabetic patients, which came in parallel with some other recent finding [6, 17, 18]. Unfortunately, ferritin is an acute-phase reactant and it is unclear whether adjustment for one marker of inflammation, C-reactive protein (CRP) is adequate or whether the association is affected by residual confusing, in addition,HbA1c is also not affected by blood sugar levels alone, and there are various unclear factors when measuring HbA1c [17, 15]. There is now growing evidence for the association of incident diabetes with both the adipocytokine adiponectin and hepatic function as measured by the hepatic enzymes glutamate-pyruvate transferase (GPT) and γ- glutamyl transferase (GGT). In addition, excess iron deposition in the pancreas is known to cause a secondary form of diabetes, which has led to speculation that higher concentrations of iron may increase the risk of developing diabetes [4, 16]. Yet, their association with ferritin has not been widely studied, nor are there any studies that have adjusted for these markers to test the independence of the- ferritin-diabetes association.

In brief, current study might be much more reliable and intensive with taking to the count the other interfering factors such as assessment of CRP as an inflammation marker and other liver function tests to differentiate between targeted cases and the intrusive cases, to obtain more accurate results.

Conclusion:

Iron stores, measured by serum ferritin were significantly higher in diabetic patients compared to normal subjects.The studied sample of diabetic patients showed significantly increased level of haemoglobin glycation, in comparison with normal subjects.

Acknowledgment

I would like to express my sincere gratitude to whom they helped me to fulfill this work; especially, Medya clinical laboratory and Miss Suaad Hassan at the"Diabetes and Endocrine Center in Sulaimani" for their generous cooperation, as well as, I would like to thank all persons who participated in this study and I wish them all healthy life.

References

[1] S. Swaminathan and *et al*., "The Role of Iron in Diabetes and Its Complications" Diabetes Care; 30:1926–33, (2007).

[2] S.V. Shah, and V.A. Fonseca, "Iron and Diabetes Revisited". Diabetes Care; 34:1676–77, (2011).

[3] J.P. Greer and *et al*., "Wintrobe's clinical hematology". 12th eddion. Lippincott Williams & Wilkins. ISBN-13: 978-0-7817-6507-7.P:857-61, (2009).

[4] N.G. Forouhi and *et al.*, "Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study". Diabetologia.; 50:949–956, (2007).

[5] M. Manuel, G.J.Antonio and A.F Remacha, "Disorders of iron metabolism. Part II: iron deficiency and iron overload". J Clin Pathol; 64:287-296, (2011).

[6] S. Liang and *et al*., "Ferritin Concentrations, Metabolic Syndrome, and Type 2 Diabetes in Middle-Aged and Elderly Chinese". J Clin Endocrinol Metab. 93: 4690–96, (2008).

[7] S. Smotra, Tandon V.R. and Sharma S., "Ferritin and Type-2 Diabetes Mellitus". Review Article. JK Science;9 (4):164-66, (2007).

[8] M.D. Johnson, "Human Biology Concepts and Current Issues".6th edition, Pearson Education, Inc. ISBN 10: 0-321-70167-4. P300-301, (2012).

[9] J.M. Fernández-Real, López-Bermejo A, Ricart W., "Cross-talk between iron metabolism and diabetes". Diabetes; 51:2348–2354, (2002).

[10] S.N. Rajpathak and *et al*., "Biomarkers of body iron stores and risk of developing type 2 diabetes". Diabetes Obes Metab; 11(5):472-9, (2009).

[11] H. Jingyu and *et al*., "Iron Overload and Diabetes Risk: A Shift From Glucoseto Fatty Acid Oxidation and Increased Hepatic Glucose Production in a Mouse Model of Hereditary Hemochromatosis". Diabetes; 60:80-86, (2011).

[12] X. Chen, Scholl O.T, and Stein TP., "Association of Elevated Serum Ferritin Levels and the Risk of Gestational Diabetes Mellitus in Pregnant Women". Diabetes Care; 29:1077–1082, (2006).

[13] M. Yukiko and *et al*., "Iron restriction improves type 2 diabetes mellitus in Otsuka Long Evans Tokushima fatty rats". Am J Physiol Endocrinol Metab; 298: 1140–49, (2010).

[14] R.C. Cooksey, Jones D, Gabrielsen S, *et al*. "Dietary iron restriction or iron chelation protects from diabetes and loss of beta-cell function in the obese (ob/ob lep-/-) mouse". Am J Physiol Endocrinol Metab; 298:1236-1243, (2010).

[15] R. Jiang, Manson JE, Meigs JB et al., "Body iron stores in relation to risk of type 2 diabetes in apparently healthy women". JAMA;291:711–717, (2004).

[16] J.S. Skyler., "Atlas of Diabetes",4th edition. Springer LLC. ISBN 978-1-4614-1027-0, PP: 149-51, (2012).

[17] S. Nitin., "HbA1c and factors other than diabetes mellitus affecting it". Singapore Med J; 51(8): 616-20, (2010).

[18] K. S. Jeevan, Mungli P and Mohammad S.I., "Relationship between free iron and glycated hemoglobin in uncontrolled type 2 diabetes patients associated with complications". Indian journal of clin biochem;23:67-70, (2008).

[19] "European Reference laboratory for Glycohaemoglobin".Manufacturer Check up Certification of NycoCard® HbA1c, (1998).

[20] B.D. Sacks and *et al*. "Guidlines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus".Clin Chem;57(6):e1-e47, (2011).