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Pathology

Investigation of Glycated hemoglobin (HbA1C) and Serum Ferritin Levels in Diabetic Patients with Poor Glycemic Control in Benin City, Edo State, Nigeria

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Abstract **Original Research Article**

Aim/ Objective: Uncontrolled diabetes mellitus is a metabolic disorder characterized by persistent hyperglycaemia and associated complications. Assessing ferritin and glycated haemoglobin (HbA1c) levels in diabetic patients can provide valuable insights into the management and progression of the disease. This study was aimed at assessing the ferritin and HbA1c levels in patients with uncontrolled diabetes mellitus and evaluate the clinical implications of these assessments. ***Methodology*:** This was a case-control study, comprising of 60 consenting participants including 30 uncontrolled diabetes patients, 15 controlled diabetic patients, and 15 non-diabetic with no history of the disease serving as controls. Ferritin levels were measured using enzyme-linked immunosorbent assay (ELISA), and HbA1c levels were also determined using modified enzymatic reaction. Demographic and clinical data, including age, gender, diabetes duration, and medication history, were collected via questionnaires. ***Results*:** Analysis of variance (post-hoc) indicated significantly ($p < 0.001$) higher FBS, HbA1c and ferritin in patients with uncontrolled diabetes compared with the non-diabetic individuals. In contrast, there was no significant difference ($p = 0.973$) in mean ferritin between patients with controlled diabetes and those with uncontrolled diabetes. In the entire study population, there was a significant relationship between ferritin and FBS ($p = 0.001$) and HbA1c ($p < 0.001$) level. ***Conclusion*:** In this study, the levels of FBS, HbA1c and ferritin were higher among the uncontrolled diabetes patients. This suggests the need to include ferritin in the panel of assay when screening for diabetes mellitus and when monitoring the progression of the disease.

Keywords: Metabolic disorder, hyperglycaemia, glycated haemoglobin.

INTRODUCTION

Diabetes, commonly known as diabetes mellitus, comprises a set of prevalent endocrine disorders characterized by persistent elevation of glucose levels in the blood [1]. Frequently encountered symptoms include increased thirst, frequent urination, and heightened appetite. Untreated diabetes can lead to various health complications. Immediate complications may include diabetic ketoacidosis, hyperglycemic states, and, in severe cases, mortality. Long-term complications encompass cardiovascular disease, stroke, chronic kidney disease, foot ulcers, nerve damage, impaired vision, and cognitive issues [2]. The condition arises due to insufficient insulin production by the pancreas or inadequate response of the body's cells to the produced insulin. Individuals with diabetes face an increased risk of atherosclerotic cardiovascular disease, peripheral arterial disease, cerebrovascular disease, and hypertension [2]. Globally, an estimated 463 million

people, constituting 8.8% of the adult population, were diagnosed with diabetes in 2019, with type 2 diabetes accounting for approximately 90% of cases [2]. Occurrence rates are comparable among men and women, and diabetes stands as the ninth-leading cause of death worldwide [3].

Ferritin, a ubiquitous protein, stands at the crossroads of iron metabolism and cellular regulation. Primarily recognized as an intracellular iron storage protein, ferritin extends its influence beyond this role, serving as a valuable biomarker with implications for a wide range of physiological processes, including diabetes mellitus [4]. Elevated ferritin levels may indicate increased iron stores, potentially contributing to oxidative stress and exacerbating complications associated with diabetes [5]. Monitoring ferritin provides clinicians with a valuable tool to gauge the risk of complications related to iron overload. Studies by Fernández-Real *et al.*, (2002) [5] and Cooksey *et al*., (2004) [6] have highlighted a positive correlation between elevated ferritin and insulin resistance. Monitoring ferritin levels can aid in identifying individuals at higher risk of impaired glucose metabolism and guide interventions to improve insulin sensitivity. Elevated ferritin levels in diabetes have been implicated in cardiovascular complications. Ferritin's role in promoting oxidative stress and inflammation may contribute to atherosclerosis and cardiovascular events [5]. Clinicians can use ferritin as a risk stratification tool to identify individuals with diabetes who may be at an increased risk of developing cardiovascular complications.

Glycated haemoglobin, also known as glycohaemoglobin or haemoglobin A1C (HbA1c), is a type of hemoglobin that forms a chemical bond with sugar [7]. The presence of the sugar-hemoglobin linkage indicates an excess of sugar in the bloodstream, which is often a sign of diabetes when its concentration is high (HbA1c > 6.4%) [7]. HbA1c is particularly noteworthy because it is easily detectable. The process of sugars attaching to hemoglobin is termed glycation, and the reference system is based on HbA1c, defined as beta-N-1-deoxy fructosyl hemoglobin as a component [7]. HbA1c is primarily measured to determine the average blood sugar level over three months and can be used as a diagnostic test for diabetes mellitus. Normal glucose levels result in a normal amount of glycated hemoglobin. However, as the average plasma glucose levels rise, the proportion of glycated hemoglobin also increases in a predictable manner [7]. In diabetes, higher levels of glycated hemoglobin. Indicate poorer control of blood glucose levels and have been linked to cardiovascular disease, nephropathy, neuropathy, and retinopathy [7]. To the best of our knowledge, till date, no record of study of the assessment of ferritin and glycosylated haemoglobin in the controlled and uncontrolled diabetes mellitus in this part of the world.

MATERIALS AND METHODS

STUDY DESIGN

This study was a hospital-based and cross-sectional comprising of sixty (60) male and female participants (30 uncontrolled diabetes, 15 controlled diabetes, and 15 non-diabetic with no history of the disease serving as controls) with the age range between 18 and 70 years. The diabetics were recruited at University of Benin Teaching Hospital, Benin City, Edo State, where they are attending diabetic clinic. The uncontrolled diabetics were those who had earlier been diagnosed or recently diagnosed, but not on any treatment. All the diabetic patients were confirmed to have being diagnosed by the physician. The controlled group were recruited among the general populace; they are not diabetic, as well as their family members. Individuals who did not give their consent and or having any underlying disease were excluded. Also excluded were pregnant women. The pains and gains of the research were made known to each of the participants in order to seek their consent. A well-structured questionnaire was administered to every participant to obtain basic demographic details as well as anthropometric characteristics.

QUESTIONNAIRE/ETHICAL CONSIDERATION

The questionnaire comprised inquiries specifically formulated to obtain information regarding age, gender, state of origin, occupation, marital status, family history of diabetes mellitus, complications of diabetes mellitus, underlying disease condition, types of diabetes mellitus, degree/extent of smoking and alcohol consumption, supplement intake, and degree of activity or exercise. Ethical approval with reference number ADM/E 22/A/VOL. VII/14838152171 was obtained from the Health Research Ethics Committee, University of Benin Teaching Hospital, Benin City, Edo State to carry out this study.

BLOOD SAMPLE COLLECTION, PREPARATION AND ANALYSIS

10 millimeters of venous blood from the participants was collected from their ante-cubital veins using a sterile syringe and needle under aseptic conditions. Five millilitres of the samples was dispensed into the ethylenediaminetetraacetic (EDTA) container for the determination of the HbA1c levels by Modified Enzymatic method within 12 hours of collection, by following the manufacturer’s instructions. Three millilitres blood samples was dispensed into the fluoride oxalate container for the estimation of fasting blood glucose levels, using the commercially purchase kit from Randox Company Limited, United Kingdom. The remaining blood sample was dispensed into the plain container and left to clot, the clot was centrifuged at 5000rpm for 5 minutes to separate the serum from the clot. The serum was then dispensed into another clean dry plain container and used to determine the ferritin level of the patients.

SAMPLE ANALYSIS

GLUCOSE ESTIMATION

The concentration of glucose was determined using commercially purchased glucose kit from Randox company, United Kingdom. The glucose concentration was expressed in mg/dl.

GLYCATED HEAMOGLOBIN (HBA1C) LEVEL ESTIMATION

The estimation of was done by Modified Enzymatic method from the EDTA sample within 12hr by following the manufacturer's protocols. The kit was commercially purchased from Fortress with LOT number 220525. The diagnosis of diabetes was established considering the American Diabetes Association diagnostic criterion of Hb1c level ≥ 6.5% (IEC, 2009) and fasting blood glucose level ≥7.0 mmol/L (Sacks *et al.*, 2011) [8].

FERRITIN LEVEL ESTIMATION

The level of ferritin was determined using Enzyme Link Immunosobent Assay method. The kit was commercially purchased from Calbiotech, U.S.A. (Catalog Number: FR248T). Each patient's sample was analysed for ferritin according to manufacturer's instructions. Ferritin concentration was expressed in ng/ml. All assays were performed in technical duplicates.

MEASUREMENT OF ANTHROPOMETRIC INDICES

Weight of every participant was measured in kilograms using standard method, while height in meters was determined with stadiometer. Body mass index (BMI) was derived from the relationship between the ratio of height and weight (kg/m^2) of the participants. The reference normal value for BMI is taken as 18 - 25 kg/m^2.

STATISTICAL ANALYSIS

Descriptive data were expressed as mean and standard error of mean for continuous variables and as percentages for categorical variables. Comparative analysis between two groups was done using independent sample t-test. Association between two continuous variables was done using the Pearson's bivariate correlation test. Statistical significance was set at $P \leq 0.05$. All statistics were performed using SPSS for windows (version 25.0).

RESULTS

Table 1 shows the socio-demographic characteristics of the study population. The study population comprises 60 participants (diabetics, n = 45, and healthy controls, n = 15) of age ranging between 22 – 74 years (mean ± SD, 42.20 ± 13.21 years). A greater percentage of the participants were females (60%), middle-aged (40-59 years; 63.3%), married (71.7%), employed (66.7%), and from Edo state (60%). The lowest proportion of the participants were seen in males (40%), elderly aged ≥60 years (6.7%), single (28.3%), retirees (6.7%) and those from Bayelsa, Cross River, Lagos, Ondo and Oyo states (1.7%).

Some selected life-styles of the study population are shown in Table.2. Data shows that all of the non-diabetic group do not smoke or drink alcohol. Similarly, most of the diabetic patients do not smoke (88.9%), or drink alcohol (55.6%). Of the diabetic group that smoke (11.1%), 2.2% smoke 1 stick/day, while8.9% smoke two sticks/day. Of the diabetic patients that drink alcohol (44.4%), majority (20%) reported they take 2 bottles of alcoholic beverage daily. Similarly, a greater percentage (13.3%) of the non-diabetics drink 2 bottles per day. Majority of the participants (non-diabetics, 86.7%; diabetics, 52.3%) stated that they engage in one form of exercise or the other. However, the exercises were rarely done by the participants (non-diabetics, 66.7%; diabetics, 37.8%). Majority (66.7%) of the non-diabetics do not take supplements or vitamins, while most of the diabetics (53.3%) take the supplements. Majority of the participants (non-diabetics, 100% and diabetics 97.8%) reported they consume fish. Similarly, a greater percentage of the non-diabetics (86.7%) and the diabetic patients (77.8%) stated that they consume spinach. Furthermore, most of the participants (non-diabetic, 93.3% and diabetics, 84.4%) consume nuts.

Table 3 shows some of the clinical characteristics of the patients living with diabetes mellitus. Data indicated that majority (95.6%) of the patients were suffering from type 2 diabetes. A greater percentage (64.4%) of the patients had a family history of diabetes. As at the time of the study, 82.2% of the patients had underlying disease conditions, while 68.9% were taking diabetes medications.

Table 4 Analysis of variance (post-hoc) indicated significantly ($p < 0.001$) higher FBS, HbA1c and ferritin in patients with uncontrolled diabetes compared with the non-diabetic individuals. Patients with controlled diabetes indicated significantly higher HbA1c ($p = 0.007$) and ferritin ($p = 0.009$), but not FBS ($p = 0.125$) compared with the non-diabetic control. Furthermore, significantly ($p < 0.001$) lower FBS and HbA1c were observed in patients with controlled diabetes compared with the uncontrolled diabetes. In contrast, there was no significant difference ($p = 0.973$) in mean ferritin between patients with controlled diabetes and those with uncontrolled diabetes.

Table 5 shows the association between ferritin and fasting blood sugar and glycated hemoglobin among the nondiabetic control, diabetic patients and overall study population. Pearson's bivariate correlation test indicated no significant association between FBS and HbA1c and ferritin among non-diabetic control. In diabetic group, data indicated no significant association between ferritin and FBS ($p = 0.089$), on the other hand, there was a significant association between ferritin and

HbA1c (p = 0.05). Considering the entire study population, there was a significant relationship between ferritin and FBS (p = 0.001) and HbA1c (p < 0.001)

Table 1: Socio - Demographic Characteristics of the Participants

Characteristics	Number of Subjects	Percentage
Gender		
Males	24	40.0
Females	36	60.0
Age Groups		
Young Adults	18	30.0
Middle-Aged	38	63.3
Elderly	4	6.7
Marital Status		
Married	43	71.7
Single	17	28.3
Occupation		
Employed	40	66.7
Unemployed	6	10.0
Students	10	16.7
Retired	4	6.7
State of Origin		
Bayelsa	1	1.7
Cross River	1	1.7
Delta	17	28.3
Edo	36	60.0
Lagos	1	1.7
Ondo	1	1.7
Oyo	1	1.7
Rivers	2	3.3

Table 2: Selected Life - Style Profile of the Study Population

Lifestyle Variables	Non – Diabetics (n = 15) N (%)	Diabetes Patients (n = 45) N (%)
Smoking		
No	15 (100)	40 (88.9)
Yes	0 (0)	5 (11.1)
Number of Cigarette Sticks/Day		
None	15 (100)	40 (88.9)
1 stick/day	0	1 (2.2)
2 sticks/day	0	4 (8.9)
Alcohol Consumption		
No	12 (80.0)	26 (57.8)
Yes	3 (20.0)	19 (42.2)
Number of Bottles/Day		
None	12 (80.0)	26 (57.8)
1 bottle/day	1 (6.7)	6 (13.3)
2 bottles/day	2 (13.3)	9 (20.0)
3 bottles/day	0	4 (8.9)
Exercise Performance		
No	2 (13.3)	21 (46.7)
Yes	13 (86.7)	24 (53.3)
Frequency of Exercise		
None	2 (13.3)	21 (46.7)
Occasionally	1 (6.7)	3 (6.7)
Often	2 (13.3)	4 (8.9)
Rarely	10 (66.7)	17 (37.8)

Lifestyle Variables	Non – Diabetics (n = 15) N (%)	Diabetes Patients (n = 45) N (%)
Supplement/Vitamin Intake		
No	10 (66.7)	21 (46.6)
Yes	5 (33.3)	24 (53.3)
Fish Intake		
No	0	1 (2.2)
Yes	15 (100)	44 (97.8)
Spinach Intake		
No	2 (13.3)	10 (22.2)
Yes	13 (86.7)	35 (77.8)
Nuts Intake		
No	1 (6.7)	7 (15.5)
Yes	14 (93.3)	38 (84.4)

Table 3: Clinical Characteristics of the Patients Living with Diabetes Mellitus

Characteristics	Number of Patients	Percentage
Family History of Diabetes		
No	16	35.6
Yes	29	64.4
Type of Diabetes		
Type 1	2	4.4
Type 2	43	95.6
Underlying Disease		
No	37	82.2
Yes	8	17.8
Medication		
No	31	68.9
Yes	14	31.1

Table 4: Mean Fasting Blood Sugar, Glycated Hemoglobin and Ferritin Levels among Patients with Uncontrolled Diabetes, Controlled Diabetes and Non-Diabetic Controls

Variables	Type of Diabetes	N	Mean	Std. Error	Range		Statistics	
					Minimum	Maximum	F- Stat	P – Value
FBS (mg/dl)	Uncontrolled Diabetes	30	205.60	11.74	118.0	382.0	46.18	<0.001
	Controlled Diabetes	15	103.00	5.47	83.0	168.0		
	Non-Diabetic	15	76.06	2.93	56.0	103.0		
HBA1C (mmol/l)	Uncontrolled Diabetes	30	8.75	0.35	6.14	14.09	36.92	<0.001
	Controlled Diabetes	15	6.40	0.27	5.09	7.88		
	Non-diabetic	15	4.88	0.08	4.28	5.69		
Ferritin (ng/ml)	Uncontrolled Diabetes	30	200.22	36.77	11.23	762.10	5.63	0.006
	Controlled Diabetes	15	198.59	28.23	46.88	356.90		
	Non-diabetic	15	45.50	6.31	10.15	88.68		

Table 5: Association between Ferritin and Fasting Blood Sugar and Glycated Hemoglobin among the Nondiabetic Control, Diabetic Patients and Overall Study Population

Ferritin vs.	Non-Diabetic		Diabetic Patients		All Participants	
	R	P – Value	R	P - Value	R	P – Value
FBS (mg/dl)	-0.235	0.398	0.260	0.089	0.405	0.001
HBA1C (mmol/l)	-0.235	0.398	0.294	0.05	0.452	<0.001

DISCUSSION

Diabetes, also referred to as diabetes mellitus, is a collection of common endocrine disorders characterized by persistently elevated levels of glucose in the bloodstream [9]. Ferritin, a ubiquitous protein, stands at the crossroads of iron metabolism and cellular regulation. When cellular iron levels rise, ferritin efficiently sequesters the surplus, acting as a buffer against fluctuations in iron availability. This fundamental role makes ferritin a critical component in the regulation of cellular iron levels. Recently, it was observed that iron metabolism and increased activity of serum ferritin (hyperferritinemia) could influence the development of T2DM.

In this study, greater proportion of patients living with high ferritin were of the middle age and elderly age range (10), who found that the prevalence of high ferritin and inflammatory increased with advanced age with the highest prevalence for ages ≥ 60 years.

Many studies have linked smoking to be one of the causes of type 2 diabetes. In fact, people who smoke cigarettes are 30%–40% more likely to develop type 2 diabetes than people who don't smoke [11]. Also, study revealed that people with diabetes who smoke are more likely than those who don't smoke to have trouble with insulin dosing and with managing their condition. The more cigarettes you smoke, the higher your risk for type 2 diabetes [11]. The high levels of nicotine from smoking cigarettes can make the cells in the body less responsive to insulin, which makes the blood sugar levels higher. People with diabetes who are exposed to a high amount of nicotine may need more insulin to regulate their blood sugar levels. Majority 40 (88.9%) of the diabetics in this study do not smoke, while 5 (11.1%) do smoke. Of the 5 (100%) smokers among the diabetics, 1 (2.2%) smokes one stick per day, while 4 (8.9%) smoke two sticks per day.

According to Emmanuelle *et al*., it has been established that alcohol consumption by diabetics can worsen blood sugar control in those patients [12]. For example, long-term alcohol use in well-nourished diabetics can result in excessive blood sugar levels. Conversely, long-term alcohol ingestion in diabetics who are not adequately nourished can lead to dangerously low blood sugar levels. Out of the 45(100% diabetics in this study, 24(53.3%) do take vitamin supplements, while 21(46.6%) do not take. Forty-four (44) 98.4% supplemented with fish in addition to vitamin supplements, while 1(2.2%) do not eat fish. Thirty-five (35) 77.8% diabetics in this study consumed vegetables such as spinach, while 10 (22.1%) do not consume. Thirty eighty of the patients (38) 84.4%, eat nut such as groundnut, while 7 (15.5%) do not eat. Heavy drinking, particularly in diabetics, also can cause the accumulation of certain acids in the blood that may result in severe health consequences. Alcohol consumption can worsen diabetes-related medical complications, such as disturbances in fat metabolism, nerve damage, and eye disease. On alcohol consumption in this study, of the 45 (100%) of people living with diabetes mellitus, 19 (42.2%) do take alcohol, while 26 (57.8%) do not consume alcohol. Of the 19 (100%) participants who consumed alcohol, 6 (13.3%) take one bottle per day; 9 (20.0%) do take two bottles per day, while 4 (8.9%) were found to consume three bottles of alcohol daily.

HbA1c is primarily measured to determine the average blood sugar level over three months and can be used as a diagnostic test for diabetes mellitus. It is also employed as an assessment tool for glycemic control in people with diabetes. Greater proportion of patients living with uncontrolled diabetes mellitus were of the elderly age range in this study. This finding agrees with [13], they found out that the prevalence of diabetes increased with advanced age with the highest prevalence for ages ≥ 60 years. Higher participants in this study are female. This results disagree with [14], which reported that the rates of occurrence of diabetes mellitus are similar among men and women.

Selected life-style and clinical characteristics of the study population indicates that large percentage of patients with uncontrolled diabetes mellitus have inflammatory response (high ferritin level). Recent studies into the early recognition of type 2 DM have identified the presence of a significant relationship between serum ferritin levels and Fasting Blood Glucose (FBG) levels in patients with the disease, and these findings have shifted focus on the inflammatory markers of patients with type 2 DM. Normally, serum ferritin levels reflect the status of iron reserves in healthy individuals, and several studies have found increased ferritin levels in association with such diabetic complications as retinopathy, nephropathy, and vascular dysfunction in patients with DM and with elevated FBG [15, 16]. The present study aligned with the above studies, as marked elevated of ferritin, fasting blood glucose and glycated haemoglobin were recorded in the present study. A prospective cohort study conducted in China showed a significant correlation between serum ferritin levels and HbA1c and FBG [17], and epidemiological studies confirmed this correlation [18]. In their study, Chen *et al*., reported excessive iron as a cause of metabolic syndrome, while insulin resistance decreased with decreasing serum ferritin levels. The studies conducted by Kunutsor *et al*., also supported these findings. Many studies into this subject, however, have raised the question of whether serum ferritin levels and other inflammatory markers can serve as a marker in the early diagnosis of type 2 DM, although studies into the issue are lacking. This study also shows that the mean ferritin level of the study population indicates a significantly normal mean ferritin level in the control group and controlled diabetic compared to patients without treatment and supplement. This finding is in agreement with the study carried out by [19] which reported that ferritin level increases as a result of uncontrolled diabetes mellitus in diabetic patients.

Similarly, uncontrolled diabetic patients also indicated significantly higher mean HBA1c level compared with patients taking medications. Of the forty-five 45 (100%) diabetics in this study, 31 (68.9%) were not taken medications regularly, while 14 (31.1%) did take. This is in agreement with [20], which noted that higher levels of glycated haemoglobin in diabetics have been linked to lack of medications and uncontrolled lifestyle, and indicate poorer control of blood glucose levels.

Numerous studies have revealed that genetic vulnerability and familial aggregation are the causes of

DM in many populations [21, 22]. According to estimates, having one or both parents with non-insulin dependent diabetes mellitus increases the chance of the disease by two to four folds [23]. Between 25% and 33% of those with type 2 diabetes have family relatives who also have the disease [24]. In this study, the frequency of diabetes was more elevated in 29 (64.4%) patients with whom relations are living with the disease. Based on HbA1c and FBG criteria, respectively, having a diabetic mother was linked to 1.22 and 3.24 odds of developing diabetes, in comparison to having a diabetic father. These outcomes were consistent with earlier studies that found similar result [25-27]. However, other researches [28-30] did not show any appreciable variations between maternal and paternal transmissions. Our study agrees with these authors as 16 (35.6%) patients do not have any diabetics in their family. Lots of arguments have been put forth to explain the increased maternal transmission of DM, including behavioral risk factors such as, non-genetic variations in obesity that are passed on preferentially by the mother; intrauterine environments, and maternally transmitted mitochondrial DNA mutations and deletions [31, 32].

CONCLUSION

In this study, the levels of FBS, HbA1c and ferritin were higher among the uncontrolled diabetes patients. This suggests the need to include ferritin in the panel of assay when screening for diabetes mellitus and when monitoring the progression of the disease.

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AUTHORS CONTRIBUTIONS

Conceptualization, GUO., BIGA and FOO, methodology BIGA.,UCO and MOO, data curation, EOA,CEA and KIE, writing—original draft preparation, FOO and BIGA, writing—review and editing, SE and FOO supervision, BIGA, funding acquisition GUO and BIGA. All authors have read and agreed to the published version of the manuscript.

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