Assessment of Biomarkers of Glycation in Type I, Type II and Gestational Diabetes Mellitus

ABSTRACT

Diabetes Mellitus, a leading cause of death worldwide, requires accurate diagnostic and management indicators. This study aimed to assess various diabetes indicators and glycation markers associated with glycemic status. Conducted in Port Harcourt (Obio-Akpor LGA), the study included 120 participants diagnosed with Type I, Type II, or Gestational diabetes. Each group had 40 subjects. Blood samples were collected after fasting to evaluate parameters including Insulin (INS), Fasting Blood Glucose (FBG), Albumin (ALB), Total Protein (TP), Glycated Hemoglobin (A1c), Glycated Albumin (GA), Fructosamine (FA), 1,5-anhydroglucitol (1,5-AG), Alpha-tocopherol, and Glutathione (GSH). Results showed that FBG levels did not significantly differ across the groups (F-value = 2.14, P = 0.12). INS levels were significantly higher in Type I, Type II, and Gestational groups (F-value = 16.1, P < 0.05). Other markers, including ALB, TP, FA, GA, A1c, and 1,5-AG, showed no significant differences between the groups. Correlation analysis revealed that A1c, GA, and FA levels had significant relationships with FBG. In particular, the correlation between FBG and A1c was strongest in Type II (r^2 = 0.99) and Gestational diabetes (r^2 = 0.99). For Type I, the correlation was lower (r^2 = 0.56). The study also found negative correlations between FBG and 1,5-AG, and between FBG and GSH, particularly in Type II and Gestational groups. This study suggests that A1c is the most reliable indicator of blood glycemic status among the markers tested, providing valuable insight into diabetes management and diagnosis.

Keywords: **Diabetes indicators, Glycation markers, HbA1c, Fasting Blood Glucose.**

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by impaired glucose metabolism and elevated blood glucose levels. The condition can result from various etiological factors, including reduced insulin secretion, insulin resistance, and excessive glucose production. Diabetes is a multifactorial disease, with causes ranging from autoimmune responses and genetic predispositions to environmental and lifestyle factors such as diet, obesity, physical inactivity, smoking, and alcohol consumption. Additional contributing factors include vascular diseases, infections, and complications such as diabetic ketoacidosis, stroke, kidney disease, and nerve damage. (1). Although uncontrollable risk factors such as genetics and age cannot be changed, individuals can lower their risk by making healthier lifestyle choices, including a balanced diet and regular physical activity (1).

Diabetes presents in various forms, classified according to its underlying pathogenic mechanisms. Type 1 diabetes mellitus (T1DM), typically diagnosed in children and young adults, results from autoimmune destruction of pancreatic beta cells, leading to insulin deficiency (1).

Insulin therapy is crucial for managing T1DM, which often presents suddenly with severe symptoms, such as ketosis. In contrast, Type 2 diabetes mellitus (T2DM), typically developing in adulthood, is characterized by insulin resistance and reduced insulin secretion, with factors like obesity, aging, and lifestyle choices often contributing to its progression. (2). Type 3 diabetes, also referred to as gestational diabetes, occurs during pregnancy and is associated with a higher risk of developing Type 2 diabetes later in life (3).

In tropical regions, a form of diabetes known as Malnutrition-related diabetes mellitus (MRDM), or "tropical diabetes," is prevalent. This type results from pancreatic dysfunction

caused by malnutrition, often associated with the consumption of cassava, a root crop that contains cyanide (2). Regardless of the type, diabetes can lead to serious health complications, such as cardiovascular disease, kidney damage, and vision impairment.

Diabetes is diagnosed and monitored using various glycemic biomarkers, with glycated hemoglobin (HbA1c) traditionally serving as the gold standard. However, alternative biomarkers such as fructosamine, glycated albumin (GA), and 1,5-anhydroglucitol have gained attention for their potential to provide more timely and accurate insights into glycemic control, particularly in situations where HbA1c may be unreliable (4). These markers are especially valuable in cases of anemia, renal dysfunction, or gestational diabetes, where HbA1c may not accurately capture short-term fluctuations in blood glucose levels.

The increasing global prevalence of diabetes is concerning. According to the International Diabetes Federation (IDF), more than 537 million adults worldwide are living with diabetes, a number expected to rise to 643 million by 2030 and 783 million by 2045. In Sub-Saharan Africa, Nigeria has the highest number of diabetes cases, with an estimated 11.2 million affected adults (5,6,24). This underscores the urgent need for improved diagnostic tools and management strategies to tackle the expanding diabetes epidemic, especially in resource-limited regions.

The incidence of diabetes mellitus is increasing, and late-stage presentations with poor prognosis are common. In Nigeria, despite the establishment of diagnostic centers, many patients continue to present with advanced symptoms, such as excessive hunger, fatigue, blurred vision, and slow-healing wounds, often resulting from uncontrolled blood sugar levels. This highlights the need for enhanced diagnostic techniques and regular monitoring to prevent complications and improve patient outcomes. This study aims to investigate more effective methods for diagnosing and monitoring diabetes mellitus in patients at the University of Port Harcourt Teaching Hospital in Rivers State, Nigeria.

Given the rising prevalence and poor prognosis of diabetes-related complications, this study aims to identify improved diagnostic and monitoring strategies for diabetes mellitus in Nigeria. The findings may contribute to the development of more reliable biomarkers for early detection and better management, ultimately enhancing treatment outcomes and reducing complications. This research will benefit researchers, healthcare providers, and educators, and serve as a valuable reference for future studies on diabetes management in the region. Additionally, it will address the need for more comprehensive policy development and programs to combat diabetes in Nigeria and Sub-Saharan Africa as a whole (7).

This study primarily aims to evaluate glycation biomarkers in Type I, Type II, and Type III Diabetes Mellitus, with the goal of identifying the most reliable marker for diagnosing, monitoring, and managing the disease. It seeks to examine the relationship between various glycation markers and blood glucose levels, determining which marker provides the most accurate index for diabetes diagnosis and monitoring. Additionally, the study will assess whether long-term glycation markers, such as HbA1c, offer more precise insights compared to short-term markers like fructosamine and glycated albumin in the diagnosis and management of Diabetes Mellitus. To achieve this, the study will analyze several biomarkers, including insulin, fasting blood glucose, albumin, total protein, glycated hemoglobin (HbA1c), fructosamine, glycated albumin, 1,5-anhydroglucitol, alpha-tocopherol (Vitamin E), and glutathione, evaluating their effectiveness in diagnosing, monitoring, and treating diabetes mellitus.

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2. **MATERIAL AND METHODS**

This study was conducted in Port Harcourt, specifically within the Obio-Akpor Local Government Area (25). and involved 120 subjects diagnosed with Type I, Type II, and Type III diabetes who were attending healthcare facilities in the region. The Type I group consisted of

40 participants, the Type II group also included 40 participants, and the Type III group comprised 40 participants.

The inclusion criteria for the study required that participants be registered with the hospital, diagnosed with diabetes, attending a diabetes clinic for treatment, and aged between 18 and 60 years. Conversely, the exclusion criteria included suspected diabetes patients who were not registered with the healthcare facility, as well as unconfirmed diabetes patients.

Subjects who met these eligibility criteria and provided written consent were recruited for the study. A simple randomization technique was used to select participants. Each subject drew a number from a container, which contained the numbers "0" and "1." Those who picked "1" were included in the study, while those who picked "0" were excluded.

For sample collection, 5 ml of blood was drawn from each participant. After withdrawing the needle from the vein, the puncture site was pressed with dry cotton wool to stop any bleeding. Of the collected blood, 3 ml was transferred into a heparin bottle for the preparation and analysis of various biomarkers, excluding glycated hemoglobin. The remaining 2 ml was placed into an EDTA tube for glycated hemoglobin determination. Blood samples collected in heparin bottles were processed by centrifuging at 4000 rpm for 5 minutes. After spinning, the plasma was separated from the blood cells and stored at -20°C until analysis.

The biomarkers analyzed in the study included insulin, fructosamine (FA), 1.5 anhydroglucitol (1,5 AG), and glycated albumin (GA), which were measured using the ELISA technique. Fasting blood glucose (FBG) was measured using the glucose oxidase method, albumin was analyzed using the bromocresol green (BCG) method, and total protein (TP) was assessed using the biuret method. Glycated hemoglobin (HbA1c) was measured using the i-Croma sandwich immunoassay, while alpha-tocopherol (Vitamin E) and glutathione (GSH) were measured using the colorimetric method.

For statistical analysis, a one-way ANOVA was performed to determine if there were significant differences in the biomarker concentrations across the three diabetes groups (Type I, Type II, and Type III). Additionally, Pearson's correlation analysis and regression were used to explore the relationships between the biomarkers and to assess cause-and-effect patterns. The statistical significance level was set at $p < 0.05$.

3. RESULTS AND DISCUSSION

Table 1 shows the demographic parameters of diabetic subjects in their various groups. The mean±SD age of Type 1 diabetic subjects was 20±7years, the mean±SD age of Type 2 diabetic subjects was 42±10years and the mean±SD age of Type 3 was 33±8years.
Out of a total of 120 subjects recruited for the study, 43 were males and 77 were females. The Type 1 group comprised 22 males and 18 females, giving a total of 40 participants that made up the group. Type 2 group comprised 21 males and 19 females, giving a total of 40 participants that made up the group. Type 3 group comprised only females which were 40 participants. The values for other analytes, including Fasting Blood Glucose, Insulin, Albumin, Total Protein, Fructosamine, Glycated Albumin, Glycated Hemoglobin, 1,5-Anhydroglucitol, Glutathione, and Alpha-Tocopherol, are presented in Table 2.

Table 1: Demographic Parameters

	Type 1 subjects	Type 2 subjects	Gestational
Age (yrs)	20±7	42±10	33±8
Males	22	21	0
Females	18	19	40

Table 2: Comparing Glycation Biomarkers in Type 1, Type 2 and Gestational Diabetes Groups

	Type 1	Type 2	Gestational	F-value	P-value	Remark
FBG	5.9±4.9	7.2±4.8	8.2±5.5	2.14	0.12	NS
INS	21.5±1.1	75.9±16.5	144.5±20.8	16.1	<0.05	SS
ALB	3.5±0.5	3.4±0.6	3.3±0.7	1.92	0.15	NS
TP	5.9±1.2	5.9±1.2	5.6±1.3	0.91	0.41	NS
FA	236.8±5.4	234.1±4.7	247.5±5.3	1.86	0.16	NS
GA	15.7±4.2	14.8±3.7	14.1±5.4	1.27	0.29	NS
A1C	6.05±4.5	7.2±4.9	8.6±6.0	2.35	0.10	NS
1,5 AG	16.0±7.5	16.1±10.9	14.7±7.8	0.31	0.74	NS
GSH	4.9±0.5	4.2±0.4	5.3±0.5	1.22	0.29	NS
Toco	16.0±0.9	15.4±0.9	17.0±1.1	1.46	0.24	NS

Key:
Diabetes subjects:
Type I: N = 40
Type 2: N = 40
Gestational: N = 40

The result presented in Table 2 shows that the mean level of fasting glucose was statistically insignificant in all groups of the diabetic population studied. This implies that fasting blood glucose does not serve as a differential diagnostic marker for diabetes because it does not discriminate or differentiate among type 1, type 2 and type 3 diabetes. This finding was consistent with other parameters evaluated in this study except for insulin. Therefore, insulin can serve as a differential marker for the types of DM

4. DISCUSSION

Diabetes is a group of disease that is characterized with too much glucose in the blood and the laboratory diagnosis for diabetes requires the determination of routine investigations such as fasting blood glucose, random blood glucose, postprandial glucose estimation, oral glucose tolerance, urinalysis and glycated haemoglobin. Insulin measurement may be required to determine the type of diabetes as it is often deficient in type 1 diabetes, hence the name Insulin Dependent Diabetes. Glycated haemoglobin is the commonly used glycation marker to measure how the body managed glucose for a period of 3months based on that erythrocytes have a life span of 3months and glucose generally binds with proteins in the body in a term referred to as glycation; when the concentration of glucose is high in the blood it leads to corresponding increase in protein glycation. Generally, glycated haemoglobin has been the glycation marker of choice but this study seeks to identify other glycation markers like fructosamine and glycated albumin to determine their suitability in diabetes diagnosis relative to glycated haemoglobin and their relationship with blood glucose level.
The demographic parameters, samples were collected from carefully selected group of 120 patients with type I, II and III diabetes mellitus, the subjects were 43 male and 77 female within different ages, blood samples were carefully collected from 40 patients with type I diabetes mellitus within the age of 20±7, 40 samples were also collected from patients with type II diabetes mellitus within the age of 42±10 and another 40 samples were carefully collected from pregnant women within the age of 33±8 years of age to test for type III diabetes mellitus.

The result presented in Table 4.2 shows that the mean level of fasting glucose was statistically insignificant in all groups of the diabetic population studied. This implies that fasting blood glucose does not serve as a differential diagnostic marker for diabetes because it does not discriminate or differentiate among type 1, type 2 and type 3 diabetes. This finding was consistent with other parameters evaluated in this study except for insulin. Reports have shown that diabetes is classified based on insulin activity; Insulin-dependent diabetes and Non-insulin dependent diabetes. This classification is based on insulin dependency which implies that insulin was the differentiating marker between those types of diabetes; therefore, there should be a significant difference in insulin level among the groups. The findings on insulin were consistent with current knowledge because insulin showed significant difference in mean level among the groups studied. Comparing the three groups, insulin had the lowest level in type 1 diabetes than in other groups.
Certain other non-glycemic markers like protein and albumin showed no significant difference in their mean levels among the groups. This implies that the various types of diabetes does not impact of the distribution on concentration of protein in the blood. The same finding was consistent with albumin. Albumin level had not any significant difference among the three types of diabetes. On a differential basis, glutathione levels were consistent in three diabetic groups, meaning that there was no significant difference in the mean levels among the groups. This finding was also consistent with tocophenol. There was no significant difference among the mean levels of tocophenol in the three diabetic groups studied.

For a glycation marker to be considered more effective, it should be associated with blood glucose levels. Therefore, Table 4.4 presents the correlation and regression analysis between fasting blood glucose (FBG) levels and fructosamine (FA). The results show a moderate positive correlation in Type I and Type II diabetes, while a weak positive correlation was observed in Type III diabetes.
According to a study by (8)The findings of this study revealed a significant association between Fasting Blood Glucose (FBG) and fructosamine, with notable correlations observed between serum fructosamine levels and FBG. (9) Blood glucose levels have been previously reported. While both fructosamine and HbA1c are reliable indicators of glycemic control, fructosamine is considered the better predictor of blood glucose levels. (9). In a study of 25 patients with Type I, II, and III diabetes, serum fructosamine was found to be a better indicator of average blood glucose concentrations over the previous 3-6 weeks, while HbA1c was more useful for reflecting glucose levels over the past 8-10 weeks (10). The effectiveness of Fasting Blood Glucose (FBG) for the routine detection of Type I, II, and III diabetes has been documented (11) Several other studies have indicated that FBG alone is not an efficient or

reliable screening method for types I, II, and III (12). Likewise, relying solely on fructosamine for screening types I, II, and III may not be justified. In this study, the serum fructosamine assay showed a 3.125% false positive rate and a 9.375% false negative rate when compared to FBG values for assessing hyperglycemia. Previous studies have also reported a 2.7% false positive rate and a 32.6% false negative rate using a serum fructosamine cutoff value of 2.65 mmol/L. (13). (14) Error rates of 23-26% were observed for fructosamine, c-fructosamine, and HbA1c in a cohort of 450 diabetic patients. In another study, the c-fructosamine test demonstrated 79.4% sensitivity and 77.3% specificity in diagnosing type III (15). Therefore, the combined assessment of fructosamine and FBG offers a more reliable approach for identifying type III compared to measuring either parameter alone. As fructosamine reflects the average glucose levels over the past 2-3 weeks, it is not influenced by food intake on the day of testing. Furthermore, no significant difference was observed between the measured serum fructosamine levels (16). Therefore, fructosamine can be measured at any time of the day, and the same blood sample can be used to analyze both FBG and fructosamine. As a result, paired values of FBG and fructosamine could be employed for diagnosing type III, potentially eliminating the need for unnecessary OGTT in many cases, as previously suggested (17).

The results, as shown in Table 4.5, present a correlation and regression analysis between glucose levels and GA (FBG and GA). The analysis indicates a positive association between these parameters in Type I, Type II, and Type III. A study on the relationship between fasting blood glucose and glycemic indices found that GA levels correlate more strongly with plasma glucose levels and the glucose fluctuation index than HbA1c or 1,5-AG, particularly in individuals with poor glucose control (18).In this study, the relationship between FBG and GA was more positive compared to FA, with correlation coefficients of 0.64, 0.61, and 0.59 for Type I, Type II, and Type III, respectively. Albumin, being the most abundant serum protein, is likely the primary glycated component in fructosamine. As such, any changes in albumin levels affect both GA and FA. There are varying reports on the suitability of glycated albumin (GA) or fructosamine (FA) as independent indicators for the assessment and management of diabetes. The present review highlights that, in certain clinical conditions, GA offers significant advantages for monitoring glycemic status compared to other currently available biomarkers. However, in pathological conditions characterized by altered albumin metabolism (such as nephrotic syndrome and hyperthyroidism, where albumin metabolism is increased), the value of GA may underestimate actual glycemic levels. Specifically, in patients with kidney disease, GA is considered reliable if the albumin concentration in the urine does not exceed 3.5 g/24 h. Additionally, chronic inflammation, as seen in smokers, patients with non-alcoholic liver disease, hypertriglyceridemia, and hyperuricemia, can also influence GA levels. Conversely, in conditions where albumin metabolism is reduced (such as cirrhosis and hypothyroidism), GA levels may be higher than the actual mean glycemia, thus limiting its use in glycemic monitoring due to the reduced synthesis of albumin. Notably, in patients with cirrhosis, the GA/HbA1c ratio correlates with liver function, offering an indirect assessment of liver health. While literature supports the use of GA as a reliable biomarker for glycemic status, consensus on the appropriate decision thresholds for different clinical conditions remains lacking.

The results shown in Table 4.6 present a correlation and regression analysis between glucose levels and HbA1c (FBG and HbA1c). A strong positive association was observed in Type I, Type II, and Type III. According to a study, fasting blood glucose (FBG) shows a positive correlation with HbA1c in non-diabetic patients, while it negatively correlates with random blood sugar due to LDL levels. In diabetic patients, however, FBG remains highly correlated with HbA1c (19). Currently, HbA1c is widely accepted as the preferred indicator for assessing glycemic control, rather than glycated albumin (GA) or fructosamine (FA). This is largely due to the extensive body of research supporting HbA1c, which has demonstrated greater stability and standardization for clinical use. In contrast, FA and GA are more commonly utilized in veterinary medicine than in human clinical practice..

This study considered both short-term and long-term glycation markers. Theoretically, short-term markers (FA and GA) are expected to show a stronger association with FBG than long-term markers (A1c), but the opposite was observed. A1c exhibited a more positive correlation with FBG across all types of diabetes, except in Type 1. This finding suggests that A1c is the preferred glycation marker in this study, relative to the other markers. In Type 1, the

correlation strength was seen as follow: GA>A1c>FA. In Type II, the correlation strength was seen as follow: A1c>GA>FA while in Type III, A1c>GA>FA. A 2006 study evaluated blood glucose, A1c, and FA in both fasting conditions and 2 hours postprandial (PP) after a standard meal. The results showed a stronger correlation between 2-hour PP glucose levels and A1c compared to FA. (20) This finding is consistent with the results of this study, suggesting that the glycation process may vary across different proteins. Some proteins glycated more rapidly and respond to changes in blood glucose levels faster than others. Therefore, attention should be directed more toward the glycation process itself rather than the half-life of the protein. Based on this, A1c remains a relatively reliable marker for the diagnosis and management of diabetes.
Due to the competitive inhibition of 1,5-AG reabsorption in the kidney tubule by glucose, blood 1,5-AG levels may respond with high sensitivity within 24 hours (21), indicating even transient elevations in glucose levels over the course of a few days (22), (23). By implication, an increase in glucose levels should result in a decrease in blood 1,5-AG levels. This observation aligns with the findings of this study. In all the groups studied there were negative relationships between FBG and 1, 5-AG so that increase in one leads to the decrease of the other and vice versa. This pattern if well understood can be used as complementary marker for glycemic monitoring.

This study also evaluated some antioxidants such as glutathione and tocophenol with the view of determinining the the level of relationship they have with fasting blood glucose. Table 4.8 revealed a significant negative correlation between FBG and glutathione in Type I and Type II diabetes but a weak positive correation in Type III. This means that increase in blood sugar will lead to a decrease in glutathione and vice versa. Table 4.9 revealed a significant negative correlation between FBG and tocophenol in Type I and Type II diabetes but a weak positive correation in Type III. This means that increase in blood sugar will lead to a decrease in tocophenol and vice versa. This finding is in tune with current knowledge because diabetes is believed to increase oxidative stress which in turn deplicts antioxidant levels.

5. CONCLUSION

The growing interest in nontraditional glycemic biomarkers stems from the limitations of the HbA1c assay. It is crucial to recognize the conditions under which HbA1c levels may be difficult to interpret. The use of alternative markers can be valuable in diabetes management as complementary tools alongside standard measures. There is generally a strong correlation between HbA1c and serum fructosamine as well as glycated albumin. While fructosamine and glycated albumin have been proposed as useful tools for monitoring glycemic control, they should not be considered independent markers for diabetes management but rather as additional assessment tools. Currently, there are no definitive guidelines for incorporating alternative biomarkers as adjuncts to standard glycemic markers, such as HbA1c and fasting blood glucose. Therefore, including serum 1,5-anhydroglucitol may be useful for assessing day-to-day glycemic excursions. In conclusion, GA, FA, and 1,5-AG play a significant clinical role in supporting the management of diabetes.

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