

Serum Level of 1,5-anhydroglucitol in Sub Saharan Africans with Type 2 Diabetes Mellitus

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Citation

Dallatu Muhammad Kabiru, Jiya Muhammad Nma, Abdulrahman Muhammad Bashiru, Musa Badamasi. Serum Level of 1,5-anhydroglucitol in Sub Saharan Africans with Type 2 Diabetes Mellitus. *International Journal of Chemical and Biomedical Science*. Vol. 4, No. 2, 2018, pp. 30-33.

Received: August 30, 2017; **Accepted:** November 23, 2017; **Published:** March 2, 2018

Abstract: 1,5-anhydroglucitol (1,5-AG) has been suggested as a marker for short-term glycaemic control and postprandial hyperglycaemia. However, the role of 1,5-AG in glycaemic variability has not been established. The aim of this study was to demonstrate the usefulness of 1,5-AG as a marker for glycaemic variability in patients with type 2 diabetes. Eighty (80) diabetic patients and their sex and age matched controls from Kano (North – West Nigeria) were tested for serum 1,5-AG, glycated haemoglobin (HbA1c), and fasting blood glucose (FBG). Serum 1,5-AG level was negatively correlated with FBG ($p < 0.01$) in the control subjects and negatively with both HbA1c and FBG ($p < 0.01$) levels in the diabetic subjects. Serum 1,5-AG level was significantly higher in the controls ($17.72 \pm 1.22 \mu\text{mol/ml}$) than in diabetic ($4.51 \pm 0.57 \mu\text{mol/ml}$) subjects ($p < 0.01$). There was also very significant difference in HbA1c between the diabetic ($10.39 \pm 0.24\%$) and control ($6.12 \pm 0.10\%$) subjects ($p < 0.01$). Likewise, there was very significant difference in FBG between diabetic ($10.53 \pm 0.58 \text{ mmol/L}$) and control ($4.19 \pm 0.11 \text{ mmol/L}$) subjects ($p < 0.01$). Gender based analysis shows no significant difference in 1,5-AG, FBG, and HbA1c levels between diabetic males and females ($p > 0.05$). In the control subjects, males have significantly higher serum 1,5-AG level ($20.88 \pm 1.64 \mu\text{mol/ml}$) than females ($14.56 \pm 1.68 \mu\text{mol/ml}$). There was significant difference in BMI ($p < 0.05$) and weight ($p < 0.05$) between diabetic and control subjects, with diabetics having higher values (BMI in $\text{kg/m}^2 = 26.25 \pm 0.53$, W in $\text{kg} = 67.65 \pm 1.50$) than controls (BMI in $\text{kg/m}^2 = 24.70 \pm 0.37$, W in $\text{kg} = 62.96 \pm 1.11$). We recommend further investigations on the associations between this glycaemic marker and short – term glycaemic control and therefore in the management of diabetic patients.

Keyword: 1,5-anhydroglucitol, Sub Saharan, Africans, Type 2 Diabetes Mellitus

1. Introduction

The main purpose of treating diabetics is to prevent the onset and the progression of diabetic chronic complications. Since the mechanism of onset of chronic complications is still not well understood, the main strategy to achieve this purpose is to bring the plasma glucose level in diabetic patients as close as possible to that in healthy subjects and try to maintain good glycaemic control over the long term [1]. It is well known that poor control of blood glucose may lead to

both microvascular and macrovascular complications that are correlated with hyperglycaemia and blood glucose excursions [2]. Glucose excursions, especially in the postprandial state, are independent risk factors for macrovascular complications of diabetes mellitus [3]. In current clinical practices, the common indexes to evaluate the blood glucose states are glycated haemoglobin (HbA1c) and fructosamine (FA). However, these can only reflect the integrated average blood glucose concentration of the preceding 8–12 weeks or 2–3 weeks, respectively, and potentially overlook the important

hyperglycaemic excursions that may be balanced out by hypoglycaemia. Thus, neither HbA1c nor FA can reflect recent glycaemic excursions sensitively. In addition to HbA1c and FA, there is an imperative need for more intensive and sensitive blood glucose monitoring markers to reveal not only blood glucose levels but also recent hyperglycaemic excursions. The measurement of glycated hemoglobin (HbA1c) concentration is the gold standard of glycaemic control index in diabetes management and is well known as a marker for diabetes complications [4]. However, HbA1c level neither accurately reflect glucose fluctuations, nor does it provide a clear indication of glycemic control in recent days or weeks. HbA1c concentration measurement can be confounded in patients with anaemia, haemoglobinopathy, liver disease, or renal impairment [4].

1,5-anhydroglucitol (1,5-AG) was discovered in humans in 1972 [5]. It is reported that 99.9% of the filtered 1,5AG in the kidney is reabsorbed in the renal tubules, and the concentrations of 1,5-AG in the bloodstream are fairly constant because of the balance between intake and urinary excretion. When blood glucose is higher than the renal threshold for glucose, renal reabsorption of 1,5-AG is competitively inhibited by glucose in the renal tubule, and subsequently, the serum level of 1,5-AG decreases [6]. When blood glucose levels return to baseline, the reabsorption of 1,5-AG is restored, and the blood levels of 1,5-AG return to baseline values. Some studies have verified that 1,5-AG values are sensitive to the changes in blood glucose and can reflect even transient elevations of glycaemia within a few days. US FDA approved it as a short-term marker of glycaemic control in 2003 [7]. It is widely reported to be a good marker of glycaemia-induced glycosuria, since reabsorption of filtered 1,5-AG in the proximal tubule is competitively inhibited by glucose, hence an indicator to identify rapid changes in hyperglycemia [8]. It is reflective of short-term glucose status, postprandial hyperglycaemia, and glycaemic variability which are not captured by HbA1c assay and hence can serve as a warning sign of diabetes complications [9].

Although a low 1,5-AG concentration in plasma has been proposed to be an indication of metabolic derangement in diabetes mellitus, no any study on this marker was reported on the relationship between 1,5-AG concentration and other traditional markers of glycaemic control in our localities. The accurate and comprehensive assessment of glycemic control in patients with diabetes is important for optimizing glycemic management and for formulating personalized diabetic treatment schemes. To evaluate the significance of 1,5-AG in

Nigerian people with diabetes, we undertook this preliminary study to investigate and confirm the 1,5-AG levels in both healthy Nigerians adults and patients with diabetes mellitus (DM) and to examine the relationship of 1,5-AG levels with other markers of hyperglycaemia currently in use in our laboratories. This will provide an overview of the role of 1,5-AG as an adjunct glycaemic marker in patient with diabetes in Kano, North West Nigeria.

2. Materials and Methods

Eighty Type II male and female Diabetic patients, aged 50-55, attending Diabetic Clinic, Murtala Muhammed Specialist Hospital, Kano, and Eighty sex and age matched apparently healthy subjects as controls were used in the study. Institutional ethical approval was obtained from the Ethical Committee of the Hospital, and informed consent of all the participants were also sought before enrollment. Every subject was required to fast for at least 8 h. The following morning, 5 mL of venous blood, from the ulnar vein of each subject, was drawn into vacutainers and shaken gently to mix the additives with the blood. The samples were subjected to centrifugation, at 3000 rpm for 5 min at room temperature, and the supernatant serum was utilized to test FBG. Remaining samples were stored at 80°C prior to measurement of 1,5-AG and HbA1c. Anthropometry data recorded from each of the participant. Fasting blood glucose was measured by glucose oxidase method [10], Glycated haemoglobin was measured by Ion Exchange Resin method [11], while serum 1,5-AG was measured by Elisa method [12].

All continuous data in the study was expressed as Mean + SD. Data analysis was performed using SPSS software windows version 20.0. Chi-square test was performed to determine the relationship between serum 1,5-AG and other studied variables (fasting blood glucose and glycated haemoglobin). For all assessment a value of $p < 0.05$ was taken as statistically significant. The results obtained from the data analysis were also represented in form of tables.

3. Results

The results are presented in tables 1-3. Table 1 shows the anthropometry data of diabetics and controls. Significant difference was recorded in BMI and weight of the diabetics compared to controls, with diabetics having higher results than the controls ($p < 0.05$). Age and height were however similar in the two groups ($p > 0.05$).

Table 1. Anthropometry of Diabetics and Non-diabetics (Mean $\pm$ SEM).

Variable n	Age (yrs)	Weight (kg)	Height (m)	BMI (kg/m ²)
Diabetics 80	53.96 $\pm$ 1.57	67.65 $\pm$ 1.50	1.60 $\pm$ 0.01	26.25 $\pm$ 0.53
Controls 80	50.96 $\pm$ 1.65	62.96 $\pm$ 1.11	1.60 $\pm$ 0.01	24.70 $\pm$ 0.37
P value	0.190	0.013	0.545	0.018

N = sample size SEM = standard error of mean < = significant > = not significant

Table 2 show the association between serum 1,5-AG with anthropometry and biochemical parameters of the diabetic subjects. There was strong negative correlation of serum 1,5-AG levels with FBG and HbA1c ($p < 0.01$). There is also a weak positive relation of 1,5-AG with weight of the subjects ($p = 0.05$). Other parameters shows no significant association ($p > 0.05$).

Table 2. Biochemical Parameters of the Study Subjects (Mean $\pm$ SEM).

Variables n	FBG (mmol/l)	HbA1c (%)	1,5-AG (μ mol/ml)
Diabetics 80	10.53 $\pm$ 0.58	10.39 $\pm$ 0.24	4.51 $\pm$ 0.57
Controls 80	4.19 $\pm$ 0.11	6.12 $\pm$ 0.10	17.72 $\pm$ 1.22
P Value	0.000	0.000	0.000

N = sample size SEM = standard error of mean $<$ = significant $>$ = not significant

Table 3 show the concentration of FBG, HbA1c, and 1,5-AG levels of the diabetics and non-diabetic subjects. Diabetic subjects have significantly higher FBG and HbA1c and significantly lower serum 1,5-AG levels ($p < 0.01$).

Table 3. Correlation of 1,5-AG with Anthropometry and Biochemical Parameters of the Control Subjects.

Variables	R	p value
Age	-0.010	0.933
Weight	-0.066	0.561
Height	-0.047	0.679
BMI	-0.035	0.761
FBG	-0.700	0.000
HbA1c	-0.004	0.969

4. Discussion

Three key elements of glucose metabolic disturbance are fasting hyperglycaemic state, postprandial chronic hyperglycaemic state and changes in glycaemic excursions [13]. Chronic hyperglycaemia increases the risk of developing diabetic complications. *In vitro* experiments showed that damage to the vascular endothelium by periodical glycaemic excursions is probably more serious than chronic hyperglycaemia [14]. Furthermore, previous studies suggested postprandial glucose could predict more strongly mortality for all causes and cardiovascular than fasting blood glucose (FBG) [15, 16]. Therefore, the accurate and comprehensive assessment of glycaemic control conditions, especially the characteristics of glycaemic excursions in patients with diabetes, are of great significance for optimizing glycaemic management and formulating personalized treatment schemes.

In the past, measuring blood glucose levels at multiple times throughout a single day via self-monitoring blood glucose (SMBG) was generally used to evaluate the effects of postprandial hyperglycaemia on variations in blood glucose levels; however, this method cannot accurately reflect peaks and valleys in blood glucose levels since these values are limited to specific time points [7]. Although the continuous glucose monitoring system (CGMS) is regarded as the “gold

standard” for analyzing glycaemic excursions, it is invasive and expensive, thus limiting wide application of the system. Currently, this system is not available in our local settings.

All the data presented herein support the previously reported concept that diabetes is accompanied by reduction in plasma 1,5-AG concentration. In the current work, a significantly low level of 1,5-AG was recorded in diabetics. In our raw data (not shown), decreased level was seen in some patients with approximately normal FBG and HbA1c, indicative of very recent hyperglycaemia not reflected by FBG and HbA1c. Body of evidence has already reported that HbA1c and FBG levels neither accurately reflect glucose fluctuations, nor does it provide a clear indication of glycaemic control in recent days or weeks [7]. In this work again, all patients who showed marked increase in FBG and HbA1c, from 10.53 $\pm$ 0.58 mmol/l to 4.19 $\pm$ 0.11 mmol/l and 10.39 $\pm$ 0.24% to 6.12 $\pm$ 0.10% respectively patients and controls, also shows marked reduction in 1,5-AG concentration from 17.72 $\pm$ 1.22 μ mol/ml to 4.51 $\pm$ 0.57 μ mol/ml. Equally, a reversed order was recorded in the controls. Thus 1,5-AG concentration showed a marked response to the glycaemic state in both diabetics and controls. In a similar work reported else where, it was shown that neither glucose or insulin in the blood had an acute effect on 1,5-AG concentration [17]. They also reported that, stability of 1,5-AG concentration is due to the fact that, it underwent little diurnal change and no significant change was observed within a day in any of the studied subjects including non diabetics [17].

Glucose excursions, especially in the postprandial state, are independent risk factors for macrovascular complications of diabetes mellitus. Neither FBG nor HbA1c can reflect recent glycaemic excursions sensitively [18]. There is an imperative need for more intensive and sensitive blood glucose monitoring markers to reveal recent episodes. This information will facilitate adjusting diabetic treatment effectively and help to create more reasonable therapeutic regimes [18].

5. Conclusion

According to these results, we have demonstrated that the 1,5-AG values in diabetic patients were distinctly different from that seen in healthy individuals in Northern Nigerians, and these values had a negative correlation with hyperglycaemic index. We deduced that the lower value of 1,5-AG may also be a marker of the status of hyperglycaemia in Nigerian patients with Diabetes. We held the opinion that effective control of postprandial blood glucose is a key to reduce risk of diabetic complications and that 1,5-AG has been proposed as a marker of short term hyperglycaemia. If 1,5-AG measurements can be used regularly, in addition to HbA1c and FBG, it would be extremely helpful for adjusting treatment remedies to reduce the hazards that occur with hyperglycaemia and the hyperglycaemic excursions and ultimately effectively improve the prognosis of patients with

Diabetes. We recommend further investigations on the associations between this glycaemic marker and diabetes complications in our localities.

Acknowledgements

Authors want to acknowledge the study leave from Jigawa State Primary Health Care Development Agency, Dutse, Dahiru, SG of General Hospital Gumel and Halliru, AH of Bayero University, Kano.

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