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Association Between 1, 5-Anhydroglucitol and HBA1C Among Prediabetics in Ekiti State Southwest Nigeria

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Abstract **Original Research**

Background: Prediabetes is a state or condition in which the blood glucose level though high is not diagnosed as type II diabetes. However, such individuals have increased risk of progression to diabetes mellitus and/or vascular disease. Prediabetes has an association with obesity, dyslipidemia and hypertension. The study aim to establish the association between levels of 1,5 Anhydroglucitol (1,5-AG and Glycated Haemoglobin in order to explore their usefulness as an early biological marker for detection of progression to diabetes mellitus.

Method: This case-control study consists of a total of 212 participants (male=106 and female=106) of 35 years to 54 years. Semi-structured questionnaire was used to collect socio-demographic data. Analysis of 1,5 Anhydroglucitol (1,5-AG) and Glycated Haemoglobin from each of the participants was done using blood sample. Colorimetric method using Chemistry Auto analyzer ChemRay 240 was used for 1,5 AG and Glycated Haemoglobin was analysed using Semi-Automatic Fine Care HbA1c Rapid Quantitative Test Analyzer.

Result: The mean level of 1,5 AG among prediabetes and control subjects was 18.3±5.6 µg/ml and 35.7±4.7 µg/ml respectively. 1,5 AG mean level of control group was higher than prediabetes subjects. Glycated hemoglobin was positively correlated to Age (r=0.237, p=0.014), BMI (r=0.195, p=0.045 but negatively correlated to 1,5 AG (r= -0.428, p<0.001). HbA1C (p=0.020) and 1,5 AG (p=0.047) are statistically significant for Age. The findings from this study showed that 1,5 AG (p=0.001) was predictors of prediabetes because of its sensitivity of 0.764.

Conclusion: Prediabetes is reversible when detected early. 1,5-AG examined alongside HBA1C underscore their usefulness in the diagnosis of prediabetes showed that these variables displayed a negative correlation to the prediction of prediabetes. The mean levels of HBA1C are higher in prediabetics than in Control groups and 1,5-AG which demonstrated higher levels in Control group than the Prediabetic group, hence, the reason for their negative correlation..

Keywords: 1,5 Anhydroglucitol (1,5-AG), Ceramide, Glycated Haemoglobin.

Introduction

Prediabetes is a state or condition in which the blood glucose level though high is not diagnosed as type II diabetes. It is the precursor stage before diabetes mellitus in which not all the symptoms required to diagnose diabetes are present, but in which blood glucose is abnormally high. Current understanding of prediabetes began with the 1980 definition of diabetes which recognized the category of impaired glucose tolerance (IGT) as intermediate between normoglycemia and diabetes mellitus, and which is associated with an increased risk of cardiovascular events. Based on pathophysiology, prediabetes can be classified into Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT). Prediabetes is marked by IFG or IGT, associated with resistance or deficiency of insulin (Taksali and Caprio, 2006).

In their classification of prediabetes, the American Diabetes Association (ADA,2018) classified individuals with a fasting plasma glucose of 100–125 mg/ dL [impaired fasting glucose (IFG)] or a 2-h postprandial glucose of 140–199 mg/dL [impaired glucose tolerance (IGT)] or an increased HbA1c [5.7%–6.4% (39–47 mmol/ mol)] as having prediabetes. The overlap of people with concurrent IFG, IGT and elevated HbA1c is small (Greiner *et al.,* 2020).

Prediabetes is a term frequently used to describe a condition of altered glucose metabolism which falls short of a full-blown diabetes mellitus yet confers an increased risk of progression to diabetes mellitus and/or vascular disease (Gale, 2017). Prediabetes should therefore not be viewed as a clinical entity but rather as a phase of increased risk for diabetes and cardiovascular disease (CVD) (American Diabetes Association, 2017). Without lifestyle changes, people with prediabetes are very likely to progress to type II diabetes.

Prediabetes has an association with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low High-Density Lipoprotein (HDL) cholesterol, and hypertension (American Diabetes Association, 2017). It is thus a metabolic diathesis. Prediabetes is a risk factor for a variety of cardiovascular diseases, primarily micro- and macro-vascular complications. Diabetes mellitus is an established risk factor for coronary heart disease (CHD) with Inflammation playing a role in the pathogenesis of CHD (NCEP, 2001). As a matter of fact, in type II diabetes mellitus (T2DM) patients, coronary artery disease (CAD) is a major cause of death (Frankel and Meigs, 2008; Van den Oever, 2010).

Chronic hyperglycemia leads to oxidative stress, dyslipoproteinemia, glycation of proteins, and endothelial dysfunction. Many studies have been carried out to evaluate markers of free radical induced lipid peroxidation and antioxidant status in diabetic patients (Maritim *et al.,* 2003).

Prediabetes usually occurs in people who have insulin resistance or whose beta cells in the pancreas are not producing enough insulin to maintain blood glucose within the normal range. The annual progression rate of prediabetes to diabetes is 5–10%, (Bansal, 2015) with older individuals. Those prediabetes with severe insulin resistance (IR), low insulin secretion, and other diabetes risk factors are likely to progress to diabetes. It was estimated that there were 318 million adults suffering from impaired glucose tolerance in the world by 2015 (Cefalu *et al.,* 2016).

In prediabetes, the long-term damage of diabetes associated complications — especially to the heart, blood vessels and kidneys — may already be starting, though most patients have no symptoms. An asymptomatic, preclinical prediabetes state generally precedes the onset of type II diabetes mellitus.

In 2015, the International Diabetes Federation estimated that the worldwide prevalence of impaired glucose tolerance (IGT) in adults was 318 million and will be expected to reach 482 million by 2040 (International Diabetes Federation, 2015). In Namibia, the prevalence of prediabetes was 6.8% on WHO grading and 20.1% using ADA criteria (Victor *et al.,* 2018) which was based on HBA1c and fasting blood glucose, hence, the reason for increment in ADA criteria. The prevalence of prediabetes ranges in adults from 2.2% to 16.2% with a prevalence of 7.3% in sub-Saharan Africa (Sicree *et al.,* 2009).

The development of prediabetes involves multiple

factors including genetics, peripheral insulin resistance (IR), defects in insulin secretion, glucotoxicity, lipotoxicity, impaired incretin release, amylin accumulation, inflammation, oxidative stress, and decreased β-cell mass leading to β-cell dysfunction (Festa *et al.,* 2004; Abdul-Ghani *et al.,* 2006[a]; Abdul-Ghani *et al.,* 2006[b]). Other factors associated with prediabetes are overweight or obesity, genetics or heredity and race.

Because most prediabetes patients progress to full blown diabetes, early diagnosis is expedient. However, clinicians are far from satisfied with the presently used method of monitoring glycemic level or for early diagnosis of prediabetes and diabetes because of the lagging in these methods. Fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) are used more as diagnostic rather as a predictive marker.

Glycated hemoglobin (HbA1c) is the most used biomarker to diagnose prediabetes and diabetes. HbA1c is formed when glucose attaches to the amino-terminal group of the β subunit of hemoglobin (Bookchin and Gallop, 1968). In the Norfolk prospective study, it was discovered that higher HbA1c levels were also associated with increased cardiovascular diseases (CVD), cancer, and all-cause mortality (Pfiste *et al.,* 2011). Additionally, HbA1c was more strongly correlated with retinopathy than fasting plasma glucose (FPG). Thus, HbA1c may be a better predictor of microvascular complications than FPG (Report of the expert committee on the diagnosis and classification of diabetes mellitus, 1997). HbA1c reflects chronic glycaemia rather than glucose levels at a single time point. Increased HbA1c levels are associated with increased morbidity and mortality.

Multiple cross-sectional and prospective cohort studies have implicated the impaired metabolism of branched-chain amino acid (BCAA), aromatic amino acid (AAA), free fatty acid (FFA), acylcarnitines and glycerophospholipid as being associated with insulin resistance, with many metabolites being considered as biomarkers for the prediction of prediabetes mellitus and diabetes mellitus (Zhao *et al.,* 2010; Wang *et al.,* 2011; Guasch-Ferre *et al.,* 2016; Pallares-Mendez *et al.,* 2016). More importantly, building a metabolic model for predicting the transition from prediabetes mellitus (pre-DM) to normal glucose regulation (NGR) or diabetes mellitus (DM) would be helpful for the early prevention and treatment among individuals with pre-DM.

The search for a more definitive early diagnostic tool for predicting prediabetes has led to investigating the usefulness of 1,5 Anhydroglucitol ($C_6H_{12}O_5$) and Ceramides as potential markers for predicting prediabetes (particularly as prediabetes is reversible when detected early it becomes more urgent to identify an early marker).

1,5 Anhydroglucitol (1,5-AG), is a naturally occurring dietary monosaccharide, metabolically inert polyol, which has been suggested as a prediabetes marker. As the proximal tubules in the kidney have a greater affinity for glucose reabsorption than 1,5-AG, high blood glucose levels prevent 1,5-AG reabsorption resulting in elevated 1,5-AG urinary excretion. 1,5-AG may thus be a useful biomarker as it reflects glucose levels within the preceding 10–14 days (Yamanouchi and Akanuma, 1994). It may be useful for identifying postprandial glycemic excursions and individuals at risk of complications as 1,5-AG has been associated with retinopathy and microvascular and macrovascular events. However, plasma 1,5-AG levels can change based on diet, sex and race (Brenda *et al.,* 2017).

METHODOLOGY

Study Design

The entire prediabetes and Control groups were randomly selected from individuals attending General Outpatient Department and Cardiology Outpatient Clinic of the Internal Medicine Department of Federal Teaching Hospital, Ido-Ekiti. A total of one hundred and six (106) participants, with equal representation of both sexes, identified as prediabetes were recruited. Another set of one hundred and six (106) healthy participants, with equal representation of both sexes, and screened to be non-diabetic or prediabetic were recruited to serve

as the control group.

Study Location

The study was conducted at Federal Teaching Hospital, Ido Ekiti, Nigeria. The hospital is located at the Northern part of the State. The hospital is a center of excellence and the only Tertiary Health Facility in the state. Its patient comes from all around the States of the Country. Federal Teaching Hospital Ido-Ekiti is in Ido Ekiti, the headquarters of Ido/Osi Local Government Area of Ekiti State with an estimated population of 107,000. It is geographically located in the northern part of Ekiti State which covers an estimated total area of 6353 km^2, 2453 square miles and an estimated population of 2,737,186, where the routes from Kwara and Osun State converge.

Study Population

Apparently healthy individuals (male and female) that visit the General Outpatient Department (GOPD) and Cardiology Outpatient Clinic of the Internal Medicine Department of the Federal Teaching Hospital, Ido Ekiti were recruited for this study. A structured questionnaire was administered to collect demographic information. Two of the three criteria of the American Diabetes Association (2018) were used in identifying subjects having prediabetes; individuals with a fasting plasma glucose of 100–125 mg/ dL (5.6 -6.9 mmol/L) [impaired fasting glucose (IFG)] and those with an increased HbA1c [5.7%–6.4% (39–47 mmol/ mol)]. Apparently healthy individuals, drawn from the same population but did not fall into the class of prediabetes after screening, were used as Controls.

Sample Size Determination

The sample size is determined based on the prevalence of 7.3% of prediabetes population (Sicree *et al.*, 2009) and calculated with the formula recommended by Daniel (1999). The estimate is desired to be with 5% margin of error and 95% confidence.

$$N = \frac{Z^2 \alpha P(1-P)}{d^2}$$

Where:

N= patient who should be sampled

Zα= the standard normal deviation corresponding, 95% of Confidence level =1.96

P= prevalence (7.3%)

d = the degree of accuracy desired (5%= 0.05).

$$N = \frac{(1.96)^2 \text{ X } 0.073\ (1 - 0.073)}{(0.05)^2} = 106$$

Inclusion Criteria

Participants aged 35 years and above and less than 54 years with prediabetes were enrolled. Similarly, participants aged 35 years and above and less than 54 years without prediabetes were enrolled as a healthy control group.

Exclusion Criteria

Participants having age less than 35 years and more than 54 years, diabetes mellitus, chronic kidney disease, end stage renal failure/disease, nephrotic syndrome, pregnancy, gestational diabetes and patient under steroid therapy were excluded from the study.

Ethical Consideration

Before the commencement of the study, an application was written to the ethical committee of Federal Teaching Hospital, Ido-Ekiti seeking approval of this study. After due processes, the approval was issued on 15th of May, 2020 with reference number ERC/2019/10/22/88A. Before the collection of the sample, information regarding the study was explained to the subjects. Oral and written

consent for participation in the study were obtained.

Informed Consent

Informed consent was sorted and obtained from participants prior to sample collection**.**

Statistical Analysis

Data collected were subjected to ANOVA, T-test, Chi-Square, ROC curve and BLR on IBM Statistical Package for Social Sciences (IBM-SPSS) version 27.0 statistical software with a 0.05% level of significance.

Collection of Blood Samples

For fasting glucose accuracy participants were enlightened to observe an overnight fast (10-12 hours) prior to the collection of samples. Using a sterile needle and syringe, 10ml of venous blood was collected from each participant after an overnight fast, 3mls was dispensed into a fluoride-oxalate container for Fasting blood glucose estimation, 3mls was dispensed into potassium ethyldiaminetetraacetic acid (EDTA) for estimation of glycated hemoglobin while the remaining 4mls was dispensed in plain bottle for the estimation of 1,5 anhydroglucitol.

Results

Table 4.1 show the comparison of Age and Gender between Pre-diabetic and Control groups. Age and Gender are not statistically significant to the prediabetic and control groups ($p>0.05$), however, for both Prediabetic and Control group, Age group (45 - 54) have more numbers of participants than Age group (34 - 44).

Table 4.2 compared the Body Mass Index (BMI) of Pre-diabetic and Control group. Normal BMI and Mean BMI are statistically significant to the groups with Mean BMI having a higher significant p-value = 0.001 than Normal BMI with a p-value = 0.012.

Table 4.3 is the comparison of the Mean levels of 1,5 Anhydroglucitol and HBA1C compared between the pre-diabetic and control groups. All parameters were statistically significant to the groups with a higher statistical p-value of <0.001.

Table 4.4 shows the correlation between Age, BMI and 1,5-AG of the Pre-diabetic group. All are

statistically significant. 1,5-AG ($p<0.001$) shows a higher significant and was more statistically significant than Age ($p=0.014$) and BMI ($p=0.045$).

Table 4.1: Age and gender compared between the pre-diabetic and control groups

Variable	**Case N = 106 n (%)**	**Control N = 106 n (%)**	**Chi square**	**p-value**
Age (in years)				
35 – 44	40 (37.7)	34 (32.1)	0.747	0.387
45 – 54	66 (62.3)	72 (67.9)		
Mean age ± SD	*45.8 ± 5.2*	*46.8 ± 5.4*	*-1.450*	*0.149*
Gender				
Male	53 (50.0)	53 (50.0)	0.683	0.409

Female	53 (50.0)	53 (50.0)		

Table 4.2: Body Mass Index (BMI) compared between the pre-diabetic and control groups

Variable	**Case** **N = 106** **n (%)**	**Control** **N = 106** **n (%)**	**Chi square**	**p-value**
Body Mass Index (kg/m^2)				
Normal	43 (40.6)	61 (57.5)	8.770	**0.012**
Overweight	50 (47.2)	41 (38.7)		
Obese	13 (12.2)	4 (3.8)		
Mean BMI ± SD	*26.4 ± 3.3*	*25.1 ± 2.4*	*3.292*	***0.001***

Table 4.3: Mean levels of Glycated Haemoglobin (HbA1c) and 1, 5 Anhydroglucitol compared between the pre-diabetic and control groups

Variable	**Case** **Mean ± SD** **N = 106**	**Control** **Mean ± SD** **N = 106**	**t test**	**p-value**
HbA1c (%)	7.44 ± *0.63*	5.12 ± *0.62*	27.059	**<0.001**
1,5-AG (µg/ml)	18.3 ± *5.6*	35.7 ± *4.7*	-24.522	**<0.001**

Table 4.4: Correlations between Age, BMI and HbA1c among the pre-diabetic group

Variable	**HbA1c**	
	Pearson correlation coefficient (r)	**p – value**
Age (in years)	0.237	**0.014**
Body Mass Index (Kg/m^2)	0.195	**0.045**
1,5-AG (µg/ml)	-0.428	**<0.001**

Table 4.5 shows the linear regression of Age, BMI and 1,5-AG for the prediction of HbA1c among the Pre-diabetic group 1,5-AG is statistically significant with p-values of 0.001.

Table 4.5: A linear regression for the predictors of HbA1c among the pre-diabetic group

Model	Coefficients		p-value
	B	**Std. Error**	
(Constant)	4.191	0.729	**<0.001**
Age (in years)	0.008	0.008	0.348
Body Mass Index (Kg/m^2)	0.011	0.016	0.486
1,5-AG (µg/ml)	-0.023	0.007	**0.001**

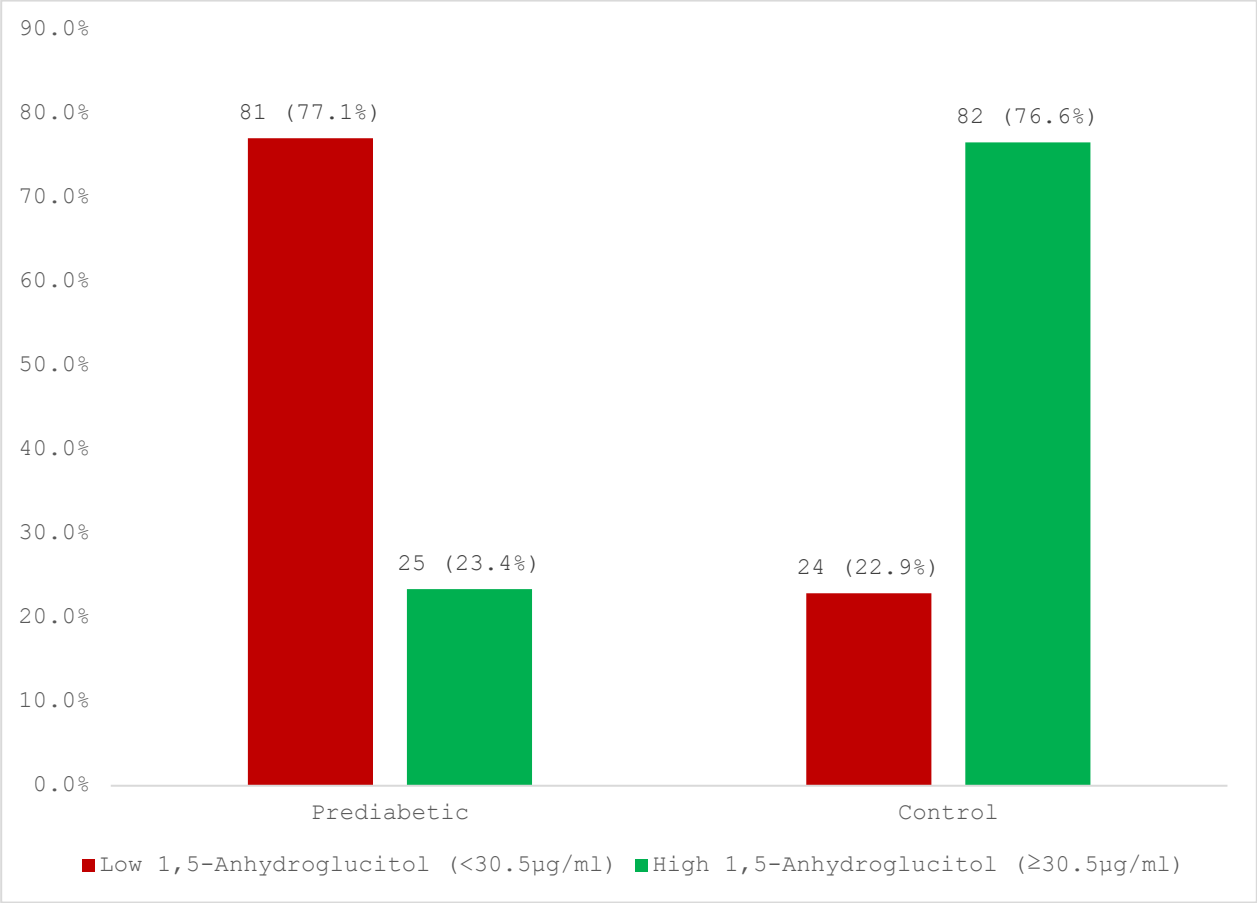

Figure 4.1: Shows the relationship in the levels of 1,5-Anhydroglucitol among the prediabetic and control group. The relationship shows that 1,5-AG value is low (<30.5µg/ml) in prediabetic group and high in control group (≥30.5µg/ml).

Table 4.6: Binary logistic regression for 1,5-AG as predictors of prediabetics

Variable	B	S.E.	AOR (95% CI)	p-value
1,5-Anhydroglucitol				
Low (<30.5 µg/ml)	1.262	0.727	3.534 (0.850 – 14.694)	0.082
High (≥ 30.5 µg/ml)			1.000	

Table 4.6 shows the Binary logistic regression for 1,5-AG and Ceramide as both predictors of prediabetes. Ceramide is more statistically significant in prediction of prediabetes than 1,5-AG with p-values of <0.001 and 0.082 respectively.

Discussion

Diabetes mellitus incidence has increased lately with change in the usual trends; many people developing diabetes not only in high income countries, but also in middle- and low-income countries (Satman *et al.,* 2013; Mahtab *et al.,* 2017). Putting the burden of prediabetes in Nigeria at a prevalence of 7.3%, making the number of individuals living with prediabetes in the country under the ADA criteria (15.8 million) is 35% of the whole number of adult Africans (45.3 million) with Impaired Glucose Tolerance (IGT) as estimated in 2019 and 2021. (Karuranga *et al.,* 2019; Musa *et al*., 2021). This means one in every three Africans with prediabetes is a Nigerian. Despite this upsurge in the prevalence of prediabetes, there had been little attention paid to it, the focus most clinical practice is on management of diabetes overlooking the fact that affected individuals would have had prediabetes for many years. Most pre-diabetic patients develop overt diabetes in 5 to 10 years and are at risk of complications including premature cardiovascular diseases (Huang *et al.,* 2017). The aim of this study was oriented on the usefulness of 1,5 Anhydroglucitol for a more definitive early diagnosis of prediabetes particularly as prediabetes is reversible when detected early it is helpful to identify an early marker.

Subjects recruited for this study were between the age range of 35years and 54years old, the mean of the prediabetic group being 45.8±5.2 while that of the control group was 46.8±5.4. Evaluation of age and gender in this study shows no statistically significant comparison between the prediabetic group and the control group, which suggest that results from this study do not admit age and gender as risk factors of pre-diabetes. This does not however overrule the scientific injunction that increasing age is associated with deterioration in beta cell function and a tendency to become insulin resistant (DECODA, 2003). More so, from table 4.1 ages of 45 - 54 years (62.3% and 67.9%) have more percentage values for both prediabetes and control group than ages 35 – 44 years (37.7% and 32.1%).

In addition, table 4.4 shows age to be statistically positively correlated to prediabetes (p=0.014). This assertion is in tandem with Alexandra *et al.,* (2019) clinical recommendations on sex and gender-specific aspects in prediabetes and diabetes mellitus, where it was discovered that age is a factor for the onset of prediabetes.

HbA1C is formed due to addition of glucose to N-terminal amino acid valine in α-hemoglobin chain. In this study a positive correlation (r=0.386, p=<0.001) was found between fasting blood glucose and HbA1C. Hence the reason both are being used for selection and diagnosis of prediabetes. While FBG measures the immediate overnight fast sugar level of an individual, glycated hemoglobin (HbA1C) depends on the concentration of blood glucose and lifespan of a red blood cell which is typically 120 days, which means the relative proportion of HbA1C at any one time depends on the mean circulating blood glucose level over that 3-month period (Shashanka *et al.,* 2016). HbA1C test and fasting blood glucose results are both useful as a basis for diagnosing and adjusting the treatment of pre-diabetes mellitus (Hajime *et al.,* 2017). Findings

from this study showed that this significant difference (*p*-value= <0.001) was also true for the mean levels of Glycated Hemoglobin (HbA1C) as that of the prediabetic subjects (7.44±0.63 %) was found to be significantly higher than the control group (5.12±0.62 %). The elevated levels of HbA1C in the prediabetic subjects is well established in previous studies (Jeon *et al.,* 2013, White *et al.,* 2015; Ria and Danny, 2019). Aside from the implication of HbA1C in measuring the blood glucose attached to the hemoglobin for a period of 3 months, elevated HbA1c is also an independent risk factor for dyslipidemia (Hussain *et al.,* 2017).

1,5 anhydroglucitol (1,5-AG) is a circulatory polyol originating mainly from foods and is structurally similar to glucose (Yamanouchi *et al.,* 1994). Due to this similarity, glucose inhibits renal reabsorption of 1,5-AG by competitive inhibition, (Buse *et al.,* 2003) resulting in an inverse correlation of 1,5-AG with hyperglycemia. 1,5-AG reflects the average maximum blood glucose level during the past 1-2 weeks and is reported to be a more sensitive marker of glucose variability and postprandial hyperglycemia than HbA1c, even for patients with prediabetes and for those with well or moderately controlled diabetes (Kim and Park, 2013). Findings from this study showed that the serum level of 1,5-AG was significantly (p<0.001) lower in the prediabetic subjects (18.3±*5.6* µg/ml) compared to the apparently healthy control group (35.7±*4.7* µg/ml). This agrees with the inverse correlation between the serum level of 1,5-AG and hyperglycemia (Dungan, 2008; Won *et al.,* 2009). More so, a significant negative correlation (r= -0.428, p=<0.001) between 1,5-AG and HbA1C was observed in this study, and this corroborates previous study of Pramodkumar *et al.,* (2016), where they observed similar observations. Furthermore, from the Linear Regression Analysis, 1,5-AG was established as a significant predictor of HbA1C among the prediabetic subjects. Though this study observed some insignificant difference in the average serum level of 1,5-AG between male and female prediabetic subjects, this was not supported by Wang *et al.,* (2017), nevertheless the prediabetic subjects between Ages 45-54years old (19.8±8.4µg/ml) had significantly (p=0.047) lower level of 1,5-AG compared to those between Ages 35-44years old (23.0±8.9µg/ml).

Conclusion

Prediabetes is reversible when detected early and 1,5-AG examined underscore its usefulness in the diagnosis of prediabetes. 1,5-AG which demonstrated higher levels in Control group than the Prediabetic group, hence, the reason for their negative correlation with HBA1C. Due to the increasing incidence of diabetes knowing fully well that prediabetes is often the precursor stage to full blown type 2 Diabetes Mellitus, it is recommended that 1,5-AG be included as part of routine test for prediabetes screening as this will go a long way in identifying prediabetes incidence earlier. Moreso, there are needs for more awareness for both male and female to live a healthy lifestyle with respect to daily intake and need for regular exercise.

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