

Evaluation of 1,5-Anhydroglucitol as a Biomarker for Type 2 Diabetes Mellitus in Patients without Overt Nephropathy

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1,5-Anhydroglucitol (1,5-AG) is a non-fasting glycemic marker that responds to hyperglycemia excursions. The reduction in serum levels of 1,5-AG is associated with an increase in postprandial glycemia and glycosuria, phenomena that increase the risk and severity of diabetic complications. The objective is to assess the ability of 1,5-AG to discriminate type 2 diabetes (T2D) patients without overt kidney disease, for screening or diagnostic purposes. The Human Research Ethics Committee of Universidade Federal do Paraná (UFPR) approved the project. Serum samples from 567 individuals classified as healthy subjects (n = 291) and T2D (n = 276) with moderate glycemic control (HbA1c of 7-8%), matched by gender, were analyzed. Serum 1,5-AG levels were measured using an automated enzymatic method (GlycoMark, Inc.). Receiver Operating Characteristic (ROC) curve analysis for 1,5-AG showed sensibility of 65.3% and specificity of 91.1% to detect T2D at cut-off point of 92 $\mu\text{mol/L}$. The results were similar to the groups' discrimination by glycemia (sensibility/specificity, 62.2%; 89.0%) at cut-off point of 6.3 mmol/L. HbA1c was the best discriminator (sensibility/specificity, 87.4%; 94.2%) at a cut-off point of 5.8% (40 mmol/mol). The serum 1,5-AG concentration was not able to discriminate T2D in the presence of moderate glycemic control with no overt nephropathy.

Key Words: 1,5-anhydroglucitol (1,5-AG). Diabetes biomarkers. ROC curves. Diabetes screening.

INTRODUCTION

Diabetes mellitus is a group of heterogeneous metabolic diseases of glucose metabolism, associated with chronic hyperglycemia (SBD, 2017; ADA, 2018). Type 2 diabetes mellitus (T2D) is responsible for over 90% of cases of diabetes, and it is caused due to insulin resistance and progressive loss of insulin secretion (ADA, 2018). T2D is a global public health emergency that affects the economies of all nations, particularly developing countries (Hu, 2011).

Postprandial hyperglycemia level is considered an independent risk factor for complications of diabetes (Bonora and Muggeo, 2001), and stringent glycemic control is therefore important in preventing such complications (UKPDS, 1998).

Leading global guidelines recommend three tests for the diagnosis and monitoring of diabetes: fasting blood glucose level, glucose level at 2 hours after a 75-g oral glucose tolerance test (OGTT), and HbA1c (glycated hemoglobin) (SBD, 2017; ADA, 2018).

Among the factors that may affect the diagnosis, when these biomarkers are used, are the requirement for fasting, difficulty with adherence to the test for many individuals, difficulty consuming glucose in the OGTT test, and the difficulty in finding a standardized HbA1c assay available at all clinical laboratories (Sacks, 2011).

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1,5-Anhydroglucitol (1,5-AG, 1-deoxyglucose, or 1,5-anhydro-D-glucitol; MW 164.157 g/mol) is a monosaccharide, originating mainly from foods and closely resembling glucose in structure (Yamanouchi *et al.*, 1992a; Buse *et al.*, 2003). Plasma 1,5-AG provides another option for assessing glycemia. In the normoglycemic setting, 1,5-AG is maintained at high but constant concentrations in the blood (Yamanouchi *et al.*, 1992a). 1,5-AG is freely filtered by the glomeruli and reabsorbed in the renal tubule, with a small amount excreted, corresponding to dietary intake (Yamanouchi *et al.*, 1989). However, in the setting of hyperglycemia, when glucose levels rise above the renal threshold for glycosuria (≥ 10 mmol/L), high amounts of glucose block tubular reabsorption of 1,5-AG, causing a decrease in serum 1,5-AG levels (Yamanouchi *et al.*, 1992b).

1,5-AG is inversely associated with postprandial glucose (PPG) (Yamanouchi, *et al.*, 1996, McGill *et al.*, 2004) and HbA1c levels $>7.0\%$ and $<8.0\%$, which makes 1,5-AG a marker for glucose excursions that occur primarily in the postprandial period, reflecting both fasting and PPG (Monnier *et al.*, 2007). The attractiveness of 1,5-AG for use in diabetes care is due to the possibility that it may capture additional information on glycemic excursions not reflected in values of HbA1c, the most common marker of glucose control.

Additionally, the measurement of 1,5-AG does not require fasting and the colorimetric assay has stable reagents and is easily automated and reproducible (Nowatzke *et al.*, 2004).

1,5-AG has been proposed to the FDA (Food and Drug Administration, federal agency of the United States Department of Health and Human Services) to be considered as an index of glycemic control in diabetic patients. Although not commercially available in Brazil, this test has been carried out since 1991 in Japan (Fukumura *et al.*, 1994) where it is routinely used.

1,5-AG levels can be influenced by race or ethnicity, with Asians and Africans showing higher concentrations compared to Caucasians (Herman *et al.*, 2009). In Euro-Brazilian populations, an overall reference interval (5-78 years and male + female) was 77-279 $\mu\text{mol/L}$ (Welter *et al.*, 2018).

More recently, 1,5-AG's application has expanded. It has been proposed that 1,5-AG can act as a predictor of (a) the 2-h plasma glucose value during a 75-g oral glucose tolerance test (OGTT) in routine medical checkups, (b) major adverse cardiac and cerebrovascular events (MACCE) even in non-diabetic

patients without coronary artery disease (Goto *et al.*, 2011) and (c) long-term cardiac mortality even in acute coronary syndrome patients with HbA1c levels $<7.0\%$ (Ouchi *et al.*, 2017).

It was suggested that 1,5-AG is a poor predictor of gestational diabetes mellitus (Kilpatrick *et al.*, 1999). In agreement with these results, Boritza *et al.* (2014) demonstrated that after 24 weeks 1,5-AG's concentration cannot discriminate efficiently between healthy and diabetic pregnant women; however, in early stages of pregnancy (≤ 23 weeks), 1,5-AG appears to be a useful marker for gestational diabetes.

Controversial reports regarding 1,5-AG's performance in screening T2D patients are available.

Here, we assess the ability of 1,5-AG to discriminate T2D patients with moderate glycemic control and without overt kidney disease, for screening or diagnostic purposes.

MATERIAL AND METHODS

Samples

Samples of serum and whole blood taken from 567 people, classified as T2D ($n = 276$) and healthy subjects (blood bank donors) (control group, $n = 291$) were studied. About 80% of all subjects were self-described as Euro-Brazilians. The characterization of diabetes was according to the criteria established by the American Diabetes Association (ADA, 2018) and the Brazilian Diabetes Association (SBD, 2017). Briefly, we used the following criteria: fasting glycemia (≥ 7.0 mmol/L) or 2-hour 75 g OGTT ≥ 11.1 mmol/L or HbA1c $\geq 6.5\%$ (48 mmol/mol). Subjects with diabetes were under oral hypoglycemic drugs (metformin, metformin/sulfonylurea and/or insulin therapy).

The groups were matched by gender. The inclusion criteria was established to mimic subjects with T2D usual characteristics at diagnostic observed in our population, such as age (> 45 years old), BMI (≥ 25 kg/ m^2) and glycemic control verify by HbA1c ($\geq 7.0\%$; poor glycemic control). Subjects with chronic diseases (such as cardiovascular, hepatic and kidney diseases) or diabetics with long-term complications (such as retinopathy, neuropathy, and myocardial infarction) were not included in the sample (exclusion criteria).

All subjects showed serum creatinine below 132 $\mu\text{mol/L}$ and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 , suggesting no overt nephropathy.

Hypertension was considered to be present if pulmonary artery systolic (PAS) pressure was ≥ 140 and pulmonary artery diastolic (PAD) pressure was ≥ 90 mmHg, or if there was use of antihypertensive drugs (Oliveira *et al.*, 2017). Dyslipidemia was considered to be present when fasting serum total cholesterol was ≥ 4.9 mmol/L, or HDL cholesterol was ≤ 1.0 mmol/L, or triglycerides were ≥ 1.7 mmol/L, or if there was use of lipid lowering drugs (Faludi *et al.*, 2017).

The Federal University of Parana's Ethics Committee approved this study (Protocol CEP-HC N° 071.EXT 0.25/2003-02).

Laboratory Measurements

1,5-AG was measured in serum by an enzymatic colorimetric method, GlycoMark™ (Tomen America, New York, NY, USA). Glycemia, glycated hemoglobin (HbA1c), albumin, and creatinine were measured with Labtest reagents (Labtest Diagnóstica S.A.), with standards and controls provided by the manufacturer. All measurements were conducted in an automated analyzer (Labmax 400, Labtest Diagnóstica S.A.).

Estimated glomerular filtration rates (eGFR) according to the Modification of Diet in Renal Disease (MDRD) study equation, with creatinine measured with conventional methodology, were calculated with a free software (<https://labtest.com.br/wp.../Estimativa-do-Ritmo-de-Filtração-Glomerular-08.12.16.xls>).

Statistical Analysis

Normality was tested using the Kolmogorov-Smirnov test. All studied continuous variables showed no normal distribution or homoscedasticity, and were described as median (interquartile range, 25th – 75th percentile), and compared with the Mann-Whitney U test.

Chi-square test was applied to compare categorical variables.

Spearman's rank-order correlations were applied to verify the association between variables.

Categorical variables were compared with the chi-square test.

The Receiver Operating Characteristic (ROC) curves and associated parameters were calculated using MedCalc version 18.5 (MedCalc Software bvba, Ostend, Belgium).

The program Statistica for Windows version 8.0 (StatSoft, Inc., Tulsa, OK, USA) was used. A probability of $< 5\%$ ($P < 0.05$) was considered significant in all analyses.

RESULTS

The characteristics of the study groups are shown in Table 1. The groups were matched by gender, with female prevalence ($> 70\%$). The healthy control group was significantly younger ($p < 0.001$) by about 5 years than those with T2D (median 49 vs. 54). The presence of obesity (BMI ≥ 30 kg/m²) was about 3 times higher in the T2D group (17.8% vs. 56.6%).

The T2D group showed high frequencies of family history of diabetes (69.5%), hypertension (78.2%), and dyslipidemia (75.1%).

As for glycemic markers for good glycemic control, criteria for fasting glycemia (< 7.2 mmol/L), HbA1c ($< 7.5\%$), and 1,5-AG (> 60 μ mol/L) showed that the majority of the subjects in the T2D group demonstrated moderate glycemic control, considering an HbA1c between 7.0% and 8.0%.

1,5-AG concentrations were about 2.4 times lower in the T2D group compared with the control group (median 57.3 vs. 137.3 μ mol/L).

Serum albumin, creatinine, and eGFR were significantly different between the groups but were nevertheless within the reference range, suggesting normal nutrition and kidney function.

1,5-AG showed a significant correlation ($P < 0.001$) with fasting glycemia ($r = -0.410$) and HbA1c ($r = -0.768$). No significant correlation ($P > 0.05$) was observed for the healthy subjects (data not shown).

The ROC curve analysis is shown in Figure 1. The area under the curve (AUC) for all tested biomarkers was significant ($P < 0.001$). The comparison of the AUC (\pm standard error) between 1,5-AG and glycemia (0.820 ± 0.018 vs. 0.851 ± 0.017) showed no difference ($P = 0.212$). The AUC for HbA1c (0.951 ± 0.009) was significantly higher ($P < 0.001$) compared to that for glycemia and 1,5-AG.

For the 1,5-AG, a sensitivity of 65.3% (95% CI, 59.4-71.0) and specificity of 91.1% (95% CI, 87.2-94.1) were observed at 92 μ mol/L (criterion) as the cut-off point (Figure 1).

TABLE 1 – Anthropometric, clinical and laboratory characteristics of the studied groups

Parameters	Control	T2D	P
n (567)	291	276	
Gender (M/F)	77/214	67/209	0.550*
Age (years)	49.0 (46-56)	54 (50-60)	<0.001
Duration of diabetes (years)	-	9.0 (5-14)	
BMI (kg/m ²)	26.0 (23.4-29.0)	30.7 (27.2-34.8)	<0.001
Obesity - BMI ≥30 kg/m ² , %	17.8	56.6	<0.001*
FH DM, %	-	69.5	
Hypertension, %	-	78.2	
Dyslipidemia, %	-	75.1	
Glycemia (mmol/L)	5.1 (4.5-5.8)	7.3 (5.8-9.7)	<0.001
HbA1c (%)	5.3 (5.1-5.6)	7.6 (6.3-9.2)	<0.001
1,5-AG (μmol/L)	137.7 (113.9-168.1)	57.3 (27.5-114.5)	<0.001
Albumin (g/L)	39.0 (38.0-40.2)	41.0 (39.0-43.2)	<0.001
Creatinine (μmol/L)	55.7 (44.2-67.2)	70.7 (61.8-79.5)	<0.001
eGFR (mL/min/1.73 m ²)	119 (98-148)	82 (71.5-94)	<0.001

BMI, body mass index; FH diabetes mellitus Introduce the word “mellitus”, Family history of diabetes (diabetes in father, mother, or siblings); 1,5-AG, 1,5 anhydroglucitol; eGFR, estimated glomerular filtration rate. P value, Mann-Whitney U test or *Chi-square test.

DISCUSSION

Type 2 diabetes is a global pandemic (SBD, 2017). Ethnic differences in susceptibility to diabetes is well recognized (Unnikrishnan *et al.*, 2017). Brazil has an admixture population. Our study focused on a population from southern Brazil, representing a majority (80%) of

European descendants. Only a few studies are available with regard to the response of biomarkers to diabetes in Brazilian populations.

1,5-AG is an interesting non-fasting biomarker for diabetes. It captures hyperglycemia (1-2 weeks) faster than HbA1c (2-3 months) and indicates effectiveness of therapy more promptly than the other traditional glycemic markers (Kim, Park, 2013).

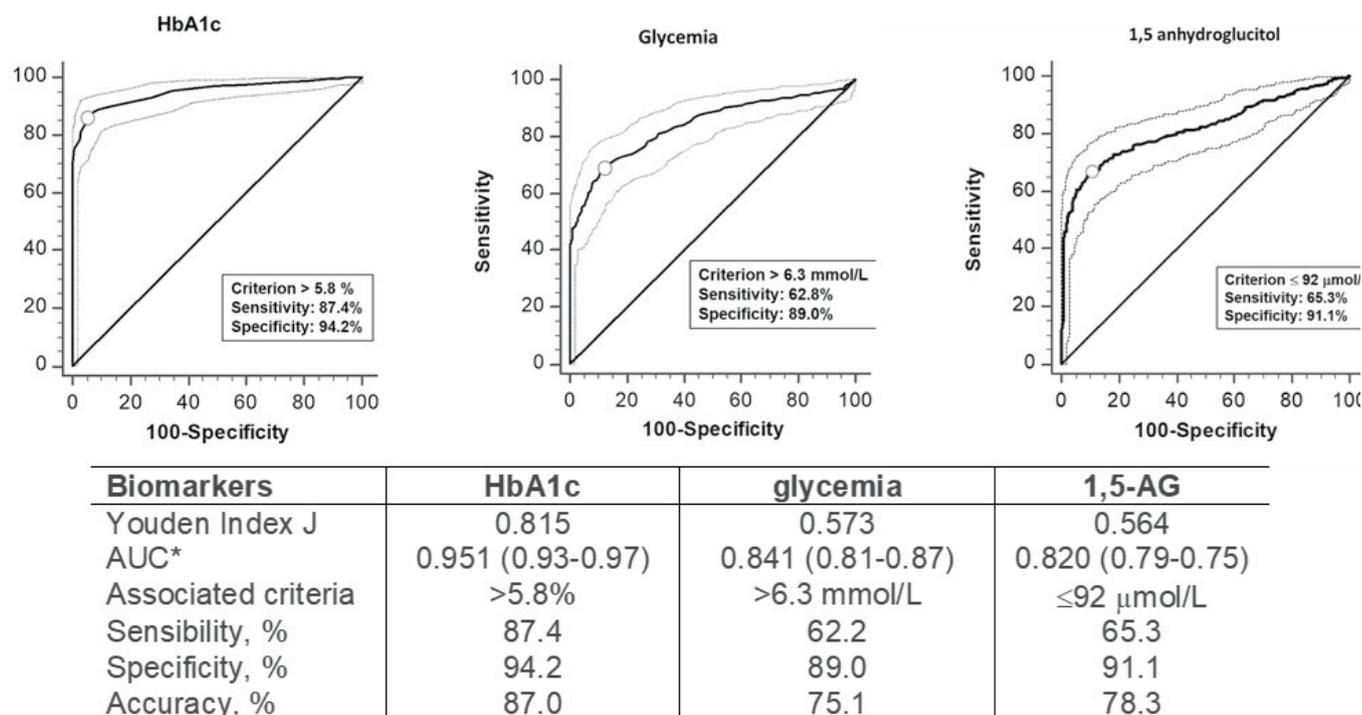


FIGURE 1 – ROC (receiver operating characteristic) for the glyceamic biomarkers HbA1c, glycemia, and 1,5-anhydroglucitol (1,5-AG). The circle indicates the cut-off point (associated criteria) and the dashed lines in the curve indicate the 95% CI. The table under the figure describes the relevant index. *AUC, area under the curve, all areas showed $P < 0.001$. Positive predictive value (%) / Negative predictive value (%) for HbA1c (93.2/82.2), glycemia (85.4/74.4) and 1,5-AG (87.3/73.2).

1,5-AG is stable in serum/plasma (plasma EDTA, NaF, citrate or heparin) and differently of glycemia, and it is not affected by the glycolysis (Yamanouchi *et al.*, 1991, McGill *et al.*, 2004). The measurement by enzymatic method, the most prevalent in literature, and applied in our present study, is not affected by moderate hemolysis, jaundice, lipemia (up to 11.3 mmol/L of triglycerides), or glucose (up to 55.5 mmol/L) as described by Nowatzke *et al.* (2004). Additionally, the 1,5-AG enzymatic method is easily automated, reproducible, and shows low analytical coefficient of variation ($CV_a = 3,83\%$) (Nowatzke, Sarno *et al.*, 2004), and the standardization is simpler than for HbA1c (Saglam *et al.*, 2017).

1,5-AG has been successfully applied as a marker for postprandial hyperglycemia, which is an independent risk factor for the development of complications of diabetes (Won *et al.*, 2009).

The use of 1,5-AG in diabetes screening or diagnosis is controversial. Yamanouchi *et al.* (1991) concluded

that 1,5-AG is sufficiently sensitive and specific for the diagnosis of diabetes, while Robertson *et al.* (1993) present an opposite viewpoint.

The present study focused on T2D subjects with moderate glyceamic control (HbA1c of 7-8%), median diabetes duration of 9.0 years, and no evidence of overt nephropathy. The study did not include subjects with renal insufficiency since it could affect the concentration of 1,5-AG (Hasslacher, Kulozik, 2016). The studied T2D group was selected bearing in mind glyceamic similarities with recent T2D subjects in our experience.

1,5-AG showed a performance to discriminate T2D, demonstrated by the ROC curve, similar to glycemia and was markedly inferior when compared with HbA1c (Figure 1). The capacity of 1,5-AG to discriminate T2D showed good specificity (91%) and poor sensibility (65%) at a cut-off point of 92 μmol/L (15 μg/mL). The ROC curves for glycemia and 1,5-AG showed a very good AUC index (0.8-0.9), with poor Youden Index J (< 0.7) (Ray *et al.*, 2010).

Our findings were in agreement with the study by Robertson *et al.* (1993) on Mauritian subjects (of Chinese ethnicity), which concludes that the diagnostic accuracy was poor for any cut-off of 1,5-AG to discriminate T2D.

On the other hand, Yamanouchi *et al.* (1991) found for 1,5-AG, with a cut-off value of 61 $\mu\text{mol/L}$, a 74.1% sensitivity and 97.4% specificity in the discrimination of T1D and T2D.

In our study, HbA1c at a cut-off point of 5.8% (40 mmol/mol; estimated average glucose 6.7 mmol/L) was the best discriminator (Figure 1). Two studies found both HbA1c and 1,5-AG to be excellent predictors of type 2 diabetes in obese youth (Shah *et al.*, 2009, Chan *et al.*, 2015). Tsukui and Kobayashi (1995) found that both HbA1c and 1,5-AG performed significantly better in the younger than in the older subjects, and that HbA1c is most likely to be superior to 1,5-AG as a screening test for T2D. These results are in agreement with ours.

A possible explanation for 1,5-AG failing to discriminate T2D in our study lies in the characteristics of the group in the study. These subjects with moderate glycemic control could not have hyperglycemic episodes with enough intensity and duration to promote significant changes to 1,5-AG in blood. 1,5-AG concentration is substantially lowered only when circulating glucose concentration is very high and exceeds the renal threshold, usually 10 mmol/L (Yamanouchi *et al.*, 1992b). In T2D, the renal threshold could be higher (11.1 – 13.9 mmol/L), which reinforces our hypothesis (Osaki *et al.*, 2016).

CONCLUSIONS

In conclusion, serum 1,5-AG was not able to discriminate T2D in the presence of moderate glycemic control and no overt nephropathy.

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