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Diagnostic Usefulness of 1, 5 Anhydroglucitol in Diabetes Mellitus: A Review

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ABSTRACT

1,5 AG is a six carbon chain monosaccharide and is one of the major polyols present in humans. The approximate normal levels of 1,5AG are about 20 -40 µg/mL. The main source of 1,5AG is diet containing carbohydrates, and this 1,5AG undergoes similar metabolic pathways like other saccharides and is distributed in all organs and tissues. Once DM is confirmed and treatment initiated, it is important to monitor glycemic control at regular intervals of time. While HbA1c has been used as a gold standard to monitor diabetic control during the preceding 2-3 months, GA and FA were used to monitor short time glycemic control. But none of the above three serves to monitor glycemic excursion after meals. 1,5AG has been emerging as an alternative short-term diabetic control monitoring marker to assess short term glycemic excursions. 1,5 AG has also been found to be useful to monitor CVD, CLD patients as well in the clinical usefulness of subtypes of DM. This review article gives a condensed version of research findings during the last two decades and will be very useful for future researchers to expand the clinical usefulness of 1,5AG in other areas of human health.



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INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder due to insufficient secretion of Insulin, the chief hormone that helps the uptake of glucose by cells. Many factors are involved in the development of DM due to a cluster of metabolic disorders. The first line of screening for DM is urine analysis followed by plasma glucose measurement and then doing glucose tolerance test (GTT) to confirm it. Following treatment by medications, diabetic control is monitored mainly by measuring glycosylated haemoglobin (HbA1c) at regular intervals of time. Tests

such as 1,2 Anhydroglucitol (1,5AG) are now emerging as the test of choice to monitor glycemic control during a short period so that alternations in medication could be initiated before uncontrolled DM emerges. This review article gives a condensed summary of the clinical usefulness of 1,5AG along with its merits and demerits compared to HbA1c, Glycated Albumin (GA) and Fructosamine (FA).

Symptoms of increased hyperglycemia include polyuria, weight loss, impaired growth, susceptibility to infections, blurred vision, chronic hyperglycemia and diabetic ketoacidosis. Longtime complications include retinopathy, neuropathy, nephropathy, renal failure, and peripheral neuropathy, foot ulcer, cardiovascular and sexual dysfunctions. Uncontrolled DM may lead to atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Further, hypertension and abnormalities of lipoprotein metabolism are often found in people with DM (American Dietary Association., 2011).

HbA1c test has been used as the gold standard to monitor diabetic control and management and has been considered as a marker for DM complications.

However, recent findings predict that HbA1c level neither accurately reflect glucose fluctuations, nor does it provide a clear indication of glycemic control and does not find usefulness in patients co-founded with anaemia, hemoglobinopathy, liver disease or renal impairment. 1,5AG, a molecule that structurally resembles glucose is greatly influenced by diet, medication, gender and race, renal failure and various pathological conditions. 1,5AG may serve as the reflective of short term glucose status. While HbA1c does not predict short term glucose status and postprandial hyperglycemia, 1,5AG may serve as an alternative index of subtypes and a warning for DM complications (Kim WJ and Park CY., 2013).

Studies have validated 1,5AG as the best marker of short term glycemic control. 1,5AG is a metabolically inert polyol which competes with glucose for reabsorption in the kidneys. And it was found to be decreased when the renal threshold for glucose increases. Hence 1,5AG may predict accurately rapid changes in glycemia than HbA1c, GA or FA. A tight association was found between glucose fluctuations due to postprandial initiation. Hence 1,5AG may serve as a complementary test to HbA1c (Dungan KM., 2008).

Clinical laboratories in Japan has been using 1,5AG test for nearly a decade for monitoring short term glycemic control. While HbA1c level reflects the average glucose levels during the preceding 2-3 months and fructosamine 10-14 days, 1,5AG levels respond within 24 hours due to competitive glucose inhibition of 1,5AG reabsorption in the kidney tubules. Even a transient increase in plasma glucose (PG) will induce the loss of 1,5AG into the urine, and the circulating blood level will fall. Due to changes in renal hemodynamics in normal pregnancies, the usefulness of 1,5AG in Gestational Diabetes Mellitus (GDM) is limited to monitoring of 1,5AG in moderate or near-normal glycemic control, and it may serve as a valuable alternative for self-monitoring to confirm an individual's glycemic control. While increasing 1,5AG levels suggest improvement decrease may need alteration in medication as well as lifestyle modification. The metabolic aspect of this new 1,5AG marker was being different from all others in the management of DM and is being recommended as the best alternate marker in clinical practice (Buse JB *et al.*, 2003).

Of late, postprandial hyperglycemia was found to be a risk factor for the development of cardiovascular (CV) mortality. Routinely used parameters such as Fasting Plasma Glucose (FPG) and HbA1c does not serve as a reliable marker for monitoring daily excursion. 1,5AG is now emerging as the short-term retrospective marker of glycemic con-

trol and its level reflects acute episodes of hyperglycemic peaks. Plasma 1,5AG levels accurately predict the maximum glycemic status of a diabetic person. Hence monitoring 1,5AG level will serve as a self-monitoring glucose excursions compared to both FPG and HbA1c. Further, in non-diabetic patients, monitoring of 1,5AG may serve as a screening marker for post-PPG associated CV risk (Dworacka M *et al.*, 2002).

Serum 1,5AG may be a useful marker in diabetic whose HbA1c levels are < 8.0 %. In a study involving Type 1 Diabetes Mellitus (T1DM) patients and controls, T1DM patients HbA1c values > 8.5 % had lower 1,5AG, and higher glucose and males were found to have higher 1,5AG than females within the patient's group. 1,5AG showed a significant correlation to glucose for patients and not for controls. The widest range demonstrated by 1,5AG was not predicted by HbA1c as it was found to be narrowly distributed among patients with HbA1c \geq 8.0 %. Hence 1,5AG will give good information better than HbA1c in the mid-term assessment of glycemic control in young patients with T1DM (Mehta SN *et al.*, 2012).

Although 1,5AG has been suggested as a marker for short-term glycemic control and post-prandial hyperglycemia, its role in glycemic variability has not yet been studied in T2DM patients. 1,5AG showed correlation to FPG, HbA1c and PPPG; however, no correlation was found between 1,5AG to net glycemic action, glycemic excursion and daily mean PG. A significant correlation was found between 1,5AG to HbA1c and mean PPPG for T2DM patients when HbA1c levels were < 8.0%. However, in patients with HbA1c > 8.0%, no correlations were found between 1,5AG to any glycemic markers, oxidative stress (OS) and urine markers. These observations suggest that only limited usefulness of 1,5AG has been established between glycemic variability and OS. Measurement of 1,5AG may be useful to predict mean glucose and postprandial hyperglycemia only in well-controlled diabetic patients (Min Joo Kim *et al.*, 2013).

Since 1,5AG is reabsorbed by the renal tubule, its level in serum may be influenced by diet. A study done on a large number of males and females with normal FPG showed that habitual intake of dairy products exerted a significant negative variable for serum 1,5AG levels. Serum 1,5AG was found to be low in subjects with habitual intake of dairy products compared to those who do not eat such food. However, no differences were observed between the groups in the levels of HbA1c, GA, FPG and 2 hrs PPPG. Hence, habitual intake of dairy products was associated with low serum levels of 1,5AG independently of PG levels (Kogura M *et al.*, 2010).

In a study, a positive correlation was found between serum uric acid (UA) to both FPG and 1,5AG. Serum 1,5AG levels were not different between hyperuricemia and normal uricaemia subjects. Even after adjustment with 2 hours PG concentrating there was an association between 1,5AG and UA. Multivariate analysis further demonstrated that serum UA was found to be independently related 1,5AG level and vice-versa (Koga M *et al.*, 2009).

Serum 1,5AG has now become a known marker to evaluate recent glycemic control. In a study involving Chronic Liver Disease (CLD) and those free of CLD, calculated HbA1c levels using Rohling formula were low among the CLD patients, and those with HbA1c < 7.0 % showed significantly low 1,5AG levels compared to these without CLD. Multivariate analysis further confirmed that estimated HbA1c served as the significant explanatory variable for 1,5AG levels in CLD patients and when the estimated HbA1c levels were < 5.8%, the only hepaplastin test was the significant explanatory variable for 1,5AG. Hence, serum 1,5AG levels were found to be low in CLD patients with and without DM. The CLD patients with low 1,5AG were associated with a deteriorated liver function (Koga M *et al.*, 2011).

In a study done on T2DM based on estimated Glomerular Filtration Rate (eGFR) and Chronic Kidney Disease (CKD) in different stages in comparison with controls has revealed that the patients study group differed significantly with respect to 1,5AG and FPG, age, duration of DM, Blood Pressure (BP), High-density lipoprotein cholesterol (HDL-c), use of antihypertension or antidyslipidemic medication. While 1,5AG levels in control groups could be explained based on the above parameters, eGFR was the only independent determinant of 1,5AG levels in CKD stages 4-5. When 1,5AG was logarithmically transformed, significant inverse correlations to HbA1c and FPG levels were observed for CKD stages 1-3, but no significant when compared with CKD stages 4-5 (Kim WJ *et al.*, 2012).

1,5AG may offer therapeutic value when patients are treated with insulin. Lispromix insulin-treated patients HbA1c levels were <7% in 73.4% of patients and 60.9% in patients treated with glargine dose. The baseline value of 1,5AG was below the median in 70.8% of patients treated with lispro and 63.7% in patients treated with glargine. Hence regular measurement of 1,5AG levels in Insulin-treated patients will help to monitor glycemic control (Dungan KM *et al.*, 2012).

Studies have shown that short term insulin therapy may induce long term glycemic remission in newly diagnosed T2DM patients. But the prediction of re-

mission is still not proved. In T2DM patients, continuous subcutaneous Insulin infusion (CSII) showed a decrease in HbA1c and FA along with increased 1,5AG, but FA was lower in the remission group. Logistic regression analysis proved that 1,5AG level after 1 month of CSII as the independent marker of remission rather than FA and the cut off point for 1,5AG was 8.9 ug/dL (Liehua Liu *et al.*, 2012).

In a study to assess the clinical usefulness of 1,5AG in postprandial hyperglycemia (PPH), it was found that fasting serum 1,5AG levels were lower in T2DM group compared to normal glucose tolerance (NGT), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) groups and correlated with glycemic values from oral glucose tolerance test (OGTT) and 2 hours PPPG emerged as the independent predictor of 1,5AG based on multiple regression analysis. Further, 1,5AG significantly correlated to PPPG during each quartile of HbA1c, and the coefficient increased with higher HbA1c quartiles. It was further observed that subjects with increased 1,5AG levels had both raised Insulin Resistance (IR) and decreased insulin secretion. Decreased 1,5AG levels also showed a correlation to PPH and decreased the capacity of Insulin secretion across a wide range of glycemia as well as in well-controlled DM (Won JC *et al.*, 2009).

Recent studies recommended the effective management of PPG in order to reduce risks of macroangiopathy complications as well as CV risks. The 1,5AG level may predict the short - term hyperglycemic excursion. In a study done on elderly T2DM patients, it was found that plasma 1,5AG level was negatively and HbA1c was positively correlated to FPG and mean PG. This study further proved that patients with low HbA1c might have decreased 1,5AG plasma level. It is recommended that 1,5AG levels in plasma should be monitored to identify well-controlled T2DM patients who show transient hyperglycemia to prevent patients at risk of macroangiopathic complications (Dworacka M *et al.*, 2005).

In a Chinese army based hospital study, 1,5AG was significantly correlated to mean PG, glycemic excursion, PPPG in moderately well-controlled patients based on defined HbA1c levels. Multivariate analysis revealed a negative correlation between 1,5AG and the above parameters but not HbA1c and GA. HbA1c and GA showed positive correlation to mean PG, FPG and 1,5AG was found to be a better marker than HbA1c and GA for glycemic excursion in T2DM patients suggesting that 1,5AG will serve as the best metric for assessing PPPG in moderately and well-controlled diabetic patients while HbA1c and GA will be superior markers for monitoring mean PG and FPG (Sun J *et al.*, 2011).

In another Chinese study, it was found out that serum 1,5AG levels in T2DM patients were found to be lower than in healthy adults. Correlations were found between 1,5AG and HbA1c, FFG and PPPG. A continuous glucose monitoring (CGM) system gave a negative correlation of 1,5AG to mean PG, the standard deviation of glucose for 7 days. This study has demonstrated that 1,5AG may serve as a marker of hyperglycemia as well as 7 days' hyperglycemic excursions compared to HbA1c (Wang Y *et al.*, 2012).

Many studies have demonstrated that PP hyperglycemia is a risk factor for many macrovascular complications and hence it is important to investigate the early stages of glucose intolerance. A study conducted on 77 healthy Japanese men has revealed that in OGTT, 1,5AG levels measured at 0,30,60,90,120 and 180 minutes after 75g glucose load did not show any significant difference in 1,5AG until 90 minutes after the glucose load. Regression analysis showed an inverse correlation between 2hr post-challenge glucose to baseline 1,5AG, and the correlation was still significant even after adjusting for age and other variables. A receiver operating curve confirmed that 1,5AG might provide a role as an ancillary predictor of 2h PG of 75g OGTT in routine medical checkups (Goto M *et al.*, 2011).

For acute and short term glycemic control monitor, the two markers currently used, HbA1c and GA are not sensitive and postprandial hyperglycemia associated with DM has now become a serious risk factor for CVD. 1,5AG has been reported as a reliable marker in adults with both T1 and T2DM for postprandial hyperglycemia. However, no reliable normal range for 1,5AG in normal children and adult with T1DM has not yet been established. In a study conducted on normal children and those with T1DM, the levels of 1,5AG in normal children were found to be higher than those with T1DM. Further, 1,5AG was negatively correlated to HbA1c. Although good glycemic control was maintained, the PP glucose levels were found to be elevated, and 1,5AG levels showed a difference between normal and T1DM children. Both 1,5AG and HbA1c should be used concurrently to evaluate therapy to target PP hyperglycemia (Nguyen TM *et al.*, 2007).

Many previous studies have reported that 1,5AG reflects glycemic control and increases with reduction in HbA1c and PP glucose. In a study on the use of biphasic insulin aspart 30 (Bi Asp30) and Insulin glargine (IGlar), greater reductions in PP excursions were achieved with BiAsp30 compared with IGLar and it was associated with increased 1,5AG levels. Even a moderate increase in HbA1c was

found to lower 1,5AG levels. Hence 1,5AG measurements will help to identify patients with excessive PP glucose excursions at the upper level of HbA1c (Moses AC *et al.*, 2008).

In a study conducted on T1DM subjects in the age group of 4-17 years and measurement of 4 different glycemic control markers, it was found that GA and FA showed a higher correlation with each other. Very low correlation was found between 1,5AG and HbA1c. All the 4 glycemic control markers, HbA1c, 1,5AG, GA and FA, showed a similar degree of correlation with CGM of mean PG as well as with hyperglycemia at 180 mg/dL. You are using Area Under the Curve (AUC) method. However, 1,5AG did not correlate with hyperglycemia AUC 180 better than did HbA1c (Beck R *et al.*, 2011).

In untreated fulminant T1DM (FT1DM) and T2DM patients studied, HbA1c showed no significant difference between both groups. Serum 1,5AG levels were significantly lower in FT1DM patients than T2DM. Serum 1,5AG were < 5 µg/mL in 86% of FT1DM compared to only 3% of T2DM patients. Hence serum 1,5AG and not HbA1C will reflect short-term exacerbation of glycemic in patients with FT1DM (Koga M *et al.*, 2010).

Several forms of DM have been characterized based on a molecular basis, and they will be useful for informed decisions regarding treatment and prognosis. Three subtypes of DM have been identified viz Maturity-On Set Diabetes of the Young (MODY) due to HNF1A mutations (HNF1A-MODY) derived from T2DM, MODY due to glucokinase mutations (GCK-MODY) of T1DM and latent autoimmune diabetes in adult (LADA). In a study done on all the above sub-types of DM, the measured 1,5AG mean levels were 13.06, 4.23, 3.09, 3.46 and 5.42 µg/ml for GCK-MODY, HNF1A-MODY, T1DM, LADA and T2DM. Adjusting for HbA1c revealed a difference between HNF1A-MODY and T2DM. The 1,5AG levels were highest in HNF1A-MODY group of patients. Hence 1,5AG was found to be a useful marker in discriminating GCK-MODY from other diabetes subtypes, particularly HNF1A-MODY. Hence measurement of 1,5AG could help diagnostic decisions regarding MODY diagnostic testing (Pal A *et al.*, 2010).

1,5AG has been used as a short-term marker of metabolic control in DM. In hyperglycemic conditions, the renal loss is stimulated by glycosuria resulting in its lower level in plasma. Due to the low renal threshold for glucose, the 1,5AG level may be altered in MODY due to hepatocyte nuclear factor 1 α (HNF -α). In a study conducted in Poland on T2DM patients with an equal number of non-diabetic, the mean plasma 1,5AG level in diabetic HNF-α mutation carriers was lower than in T2DM pa-

tients (5.9 vs 11.0 $\mu\text{g/mL}$), and its level in non-diabetic control was 23.9 $\mu\text{g/mL}$. The Receiver Operating Curve (ROC) analysis revealed 85.7% sensitivity and 80.0% specificity for 1,5AG during screening for HNF- α MODY with HbA1c levels between 6.5 and 9.0 %. Hence 1,5AG may serve as a useful biomarker for differential diagnosis of patients with HNF- α MODY with a range of HbA1c values. However, further studies are required to confirm these findings (Skupien J *et al.*, 2008).

In a study done at Seoul under diabetic prevention program on T2DM patients using multivariate logistic regression analysis, 1,5AG showed a close association with diabetic retinopathy among patients with moderate glucose control but not with patients having albuminuria. Hence 1,5AG may serve as a complementary targeting marker for high-risk group patients (W. J. Kim *et al.*, 2012).

Many studies have proved that 1,5AG was a useful clinical marker for both short term glycemic status and PP hyperglycemia. Also, studies have shown that increased PPPG during OGTT as a risk factor for CVD. However, the laboratory has not yet proved an association between 1,5AG levels and risk of CVD. In a study done in Japan on healthy male and females with a mean age of 58.5 years with no previous history of coronary heart disease (CHD), and during follow-up for 11 years the adjusted Hazard Ratio (HR) for men with CVD increased linearly. The HR with serum 1,5AG was 14.0 $\mu\text{g/mL}$ compared to the reference group of 24.5 $\mu\text{g/mL}$. Similar results were also observed in non-diabetic men. However, no significant relationship between 1,5AG and CVD were observed for women. The outcome of this study strongly suggests that 1,5AG levels may be useful to detect individuals, especially men at a higher risk for CVD irrespective of the presence or absence of DM (Watanabe M *et al.*, 2011).

It has been shown that serum 1,5AG level drops when PG increases above the renal threshold for glucose and hence 1,5AG may serve as a useful marker to assess PP hyperglycemia. In T1 and T2 DM patients, measurements were done for mean glucose, Mean Post Meal Maximum Glucose (MPMG) and ROC for glucose above 180 mg/dL showed that 1,5AG varied considerably between patients. Mean 1,5AG correlated with AUC- 180 more robustly than HbA1c. MPMG correlated more strongly with 1,5AG than with HbA1c. These observations confirm that 1,5AG reflected glycemic excursion particularly with PP state and better than HbA1c or FA. Hence 1,5AG may serve as an additional marker along with HbA1c to assess glycemic control in moderately controlled patients with DM (Dungan KM *et al.*, 2006).

Differences in HbA1c levels have not been firmly established across racial/ethnic groups. In a study with a large population of T2DM from 11 countries in the age group of 30-80 years have shown that the baseline means PG did not differ between Caucasian and non-Caucasian groups. HbA1c was higher in Hispanics, Asians and patients of other racial/ ethnic groups compared with Caucasian, while 1,5AG was higher for Asian and African patients compared to Caucasians. After adjusting factors affecting glycemia, HbA1c was higher in Hispanics, Asians, Africans patients of other racial/ ethnic groups. Differences in HbA1c and 1,5AG were found among racial/ethnic groups but not for MPG. This type of comparisons of glycemic status across racial/ethnic groups must be done based on uniformity in the methods of measuring the above parameters (Herman WH *et al.*, 2009).

The three principle Bio-Markers of glycemic control are HbA1c, GA and 1,5AG. While HbA1c primarily reflect MPG, 1,5AG and GA represent PP glycemic excursion in addition to MPG. Studies have shown that in gastrectomized subjects, OGTT showed increased hyperglycemia 30 minutes after a glucose load and it is called oxyhyperglycemia. GA in gastrectomized subjects were found to be lower than non-gastrectomized, while 1,5AG levels were lower. Hence measurements of both GA and 1,5AG may be useful in gastrectomized patients (Jun Murai *et al.*, 2014).

1,5AG is metabolically stable and will get excreted in urine when its plasma levels exceed the renal threshold value. 1,5AG is reabsorbed by renal tubules, and it is competitively inhibited by glycosuria leading to its reduction in plasma level. Good correlation was found between plasma 1,5AG and urine glucose, and hence 1,5AG could be used as a sensitive day to day marker of glycemic control. It may provide useful information on current glycemic control and hence superior to both HbA1c and FA in detecting near normoglycemia (Yamanouchi T *et al.*, 1994).

A Japanese study has demonstrated that reduced 1,5AG was observed in hyperglycemic patients compared to euglycemic and 1,5AG comes back to normal if antihyperglycemic therapies are effective. A study done in USA on T1 and T2DM patients who were given multiple therapies such as diabetes education, nutritional counseling and dose adjustment of various brands of insulin or hypoglycemic drugs in order to measure HbA1c at 1.0 % over monitoring period revealed that 1,5AG, FA and glucose values progressed significantly towards euglycemia during a two weeks monitoring period and the median changes for 1,5AG, FA and glucose were 97.7 and 13% respectively. However, HbA1c

values did not respond significantly to therapy until week 4. 89.6% of patients 1,5AG changed from baseline after 8 weeks, and there was a good correlation between 1,5AG with HbA1c and FA. This study has confirmed that 1,5AG responds sensitively and rapidly to changes in glycemic and monitors glycemic control in accordance with other established markers (Janet B *et al.*, 2004).

In a study done in Japan covering 11 institutions on 4 groups of patients for screening DM, 1,5AG values between each group (Non-diabetic, IGT, DM and patients with other disorders without IGT) was less than that of HbA1c or FA values. 1,5AG levels were positively correlated to FPG, HbA1c and FA and decreased 1,5AG levels from the mean value of 14µg/mL for DM. The 1,5AG level was found to be superior to HbA1c or FA for screening DM. Among the three markers measured, 1,5AG and HbA1c together were slightly better than 1,5AG alone. The wide variation in 1,5AG values with relatively fair glycemic control with negligible influence of sampling 1,5AG has a more potential value than HbA1c or FA for screening DM (Yamanouchi T *et al.*, 1991).

In a study on two groups of T2DM patients aged 30-59 and 60-82 years, paired ROC indicated that HbA1c was superior to 1,5AG only in younger age groups. However, when ROC was compared for these two groups, both parameters performed better with younger than other subjects. Hence in the younger subjects, HbA1c was sensitive, but for older subjects both HbA1c and 1,5AG were poor screening tests with reference to OGTT standard (Tsukui S *et al.*, 1995).

In a study involving four groups of T1DM patients treated with four different treatments, diet, Oral Hypoglycemic Agents (OHA), Conventional Insulin Therapy (CIT), and multiple insulin therapies (MIT), HbA1c values were found to be similar for all the groups. The MIT groups showed significantly higher 1,5AG, lower M-Value and little glycemic risk compared with CIT Group. No significant differences were found for CIT and MIT based on insulin dose. M-value shared significant correlation only to 1,5AG and not with HbA1c Hence plasma 1,5AG measurement will be a useful index for daily excursions of PG in well-controlled T1DM patients (Kishimoto M *et al.*, 1995)

The mean 1,5AG values in chronic renal failure (CRF) patients were significantly lower than in controls in spite of normal glycaemia. However, the levels in CRF groups were similar to the diabetic group. During the OGTT test, while PG in CRF was not significantly different compared to controls, Fasting Estimated Average Glucose (FEAG) in CRF patients were significantly higher than controls. These finding suggest that the decrease in 1,5AG

levels in patients with CRF may be due to decrease in 1,5AG reabsorption, independently of glucose excretion and that serum/ urine 1,5AG may serve as useful markers for renal tubular dysfunction, since 1,5AG reabsorption is more vulnerable than glucose reabsorption (Shimizu H *et al.*, 1999).

CONCLUSION

While HbA1c level reflects the average glucose levels during the preceding 2-3 months and fructosamine 10-14 days, 1,5AG levels respond within 24 hours due to competitive glucose inhibition of 1,5AG reabsorption in the kidney tubules. In non-diabetic patients, monitoring of 1,5AG may serve as a screening marker for post PPG associated CV risk. 1,5AG showed correlation to FPG, HbA1c and PPPG; however, no correlation was found between 1,5AG to net glycemic action, glycemic excursion and daily mean PG. A significant correlation was found between 1,5AG to HbA1c and mean PPPG for T2DM patients when HbA1c levels were < 8.0%.

Serum 1,5AG levels were found to be low in CLD patients with and without DM. The CLD patients with low 1,5AG were associated with deteriorated liver function. Regular measurement of 1,5AG levels in Insulin-treated patients will help to monitor glycemic control. HbA1c and GA showed a positive correlation to mean PG, FPG and 1,5AG were found to be a better marker than HbA1c and GA for the glycemic excursion. 1,5AG will be very useful as an ancillary predictor of 2hour PG of 75g OGTT in routine medical checkups. Both 1,5AG and HbA1c should be used concurrently to evaluate therapy to target PP hyperglycemia. 1,5AG may serve as a useful biomarker for the differential diagnosis of patients with HNF- α MODY with a range of HbA1c values. 1,5AG reflected glycemic excursion particularly with PP state and better than HbA1c or FA. Hence 1,5AG may serve as an additional marker along with HbA1c to assess glycemic control in moderately controlled patients with DM. M-value shared significant correlation only to 1,5AG and not with HbA1c and hence plasma 1,5AG measurement will be a useful index for daily excursions of PG in well-controlled T1DM patients.

REFERENCES

- American Diabetes Association, Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011, 33, S62-S69.
- Beck R, Steffes M, Xing D, Ruedy K, Mauras N, Wilson DM, et al. The interrelationships of glycemic control measures: HbA1c, glycated albumin, fructosamine, 1,5-anhydroglucitol, and continuous glucose monitoring. *Pediatr Diabetes*, 12(8), 2011, 690-5.

- Buse JB, Freeman JL, Edelman SV, Jovanovic L, McGill JB. Serum 1,5-anhydroglucitol (GlycoMark): a short-term glycemic marker. *Diabetes Technol Ther*, 5(3), 2003, 355-63.
- Dungan KM, Buse JB, Herman WH, Arakaki RF, Jiang HH, Jacobson JG, et al. Potential for the use of 1,5-anhydroglucitol when initiating insulin therapy in people with type 2 diabetes and suboptimal control with oral antidiabetic drugs. *Diabetes Res Clin Pract*, 96(3), 2012, e66-9.
- Dungan KM, Buse JB, Largay J, Kelly MM, Button EA, Kato S, et al. 1,5-anhydroglucitol and postprandial hyperglycemia as measured by the continuous glucose monitoring system in moderately controlled patients with diabetes. *Diabetes Care*, 29(6), 2006, 1214-9.
- Dungan KM. 1,5-anhydroglucitol (GlycoMark) as a marker of short-term glycemic control and glycemic excursions. *Expert Rev Mol Diagn*, 8(1), 2008, 9-19.
- Dworacka M, Winiarska H, Szymanska M, Kuczynski S, Szczawinska K, et al. 1,5-anhydro-D-glucitol: a novel marker of glucose excursions. *Int J Clin Pract Suppl*, (129), 2002, 40-4.
- Dworacka M, Winiarska H. The application of plasma 1,5-anhydro-D-glucitol for monitoring type 2 diabetic patients. *Dis Markers*, 21(3), 2005, 127-32.
- Goto M, Yamamoto-Honda R, Shimbo T, Goto A, Terauchi Y, Kanazawa Y, et al. Correlation between baseline serum 1,5-anhydroglucitol levels and 2-hour post-challenge glucose levels during oral glucose tolerance tests. *Endocr J* 58(1): 2011; 13-7.
- Herman WH, Dungan KM, Wolffenbittel BH, Buse JB, Fahrback JL, Jiang H, et al. Racial and ethnic differences in mean plasma glucose, haemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab*, 94(5), 2009, 1689-94.
- Janet B. McGill, Md1 Thomas G. Cole, Phd1 William Nowatzke, et al. Circulating 1,5-Anhydroglucitol Levels in Adult Patients With Diabetes Reflect Longitudinal Changes Of Glycemia, 27, 2004, 1859-1865.
- Jun Murai, Masafumi Koga, Hiroshi Saito, Mikio Mukai, Soji Kasayama, Serum 1,5-anhydroglucitol is low in gastrectomized men. *Acta Diabetologica*, 51 2, 2014, 337-338.
- Kim WJ, Park CY, Lee KB, Park SE, Rhee EJ, Lee WY, et al. Serum 1,5-anhydroglucitol concentrations are a reliable index of glycemic control in type 2 diabetes with mild or moderate renal dysfunction. *Diabetes Care*, 35(2), 2012, 281-6.
- Kim WJ, Park CY. 1,5-Anhydroglucitol in diabetes mellitus. *Endocrine*, 2013, 33-40.
- Kishimoto M, Yamasaki Y, Kubota M, Arai K, Morishima T, Kawamori R, Kamada T. 1,5-Anhydro-D-glucitol evaluates daily glycemic excursions in well-controlled NIDDM. *Diabetes Care*. 18(8), 1995, 1156-9.
- Koga M, Murai J, Saito H, Mukai M, Kasayama S, Imagawa A, et al. Serum 1,5-anhydroglucitol levels in patients with fulminant type 1 diabetes are lower than those in patients with type 2 diabetes. *Clin Biochem*, 43(15), 2010, 1265-7.
- Koga M, Murai J, Saito H, Mukai M, Kasayama S, Moriwaki Y, et al. Close relationship between serum concentrations of 1,5-anhydroglucitol and uric acid in non-diabetic male subjects implies common renal transport system. *Clin Chim Acta*, 410(1-2), 2009, 70-3.
- Koga M, Murai J, Saito H, Mukai M, Kasayama S. Habitual intake of dairy products influences serum 1,5-anhydroglucitol levels independently of plasma glucose. *Diabetes Res Clin Pract*, 90(1), 2010, 122-5.
- Koga M, Murai J, Saito H, Mukai M, Toya D, Tanaka N, et al. 1,5-Anhydroglucitol levels are low irrespective of plasma glucose levels in patients with chronic liver disease. *Ann Clin Biochem*, 48(2), 2011, 121-5.
- Liehua Liu, Xuesi Wan, Juan Liu, Zhimin Huang, Xiaopei Cao, Yanbing Li. Increased 1,5-Anhydroglucitol Predicts Glycemic Remission in Patients with Newly Diagnosed Type 2 Diabetes Treated with Short-Term Intensive Insulin Therapy. *Diabetes Technology & Therapeutics*. Aug, 14(9), 2012, 756-761.
- Mehta SN, Schwartz N, Wood JR, Svoren BM, Laffel LM. Evaluation of 1,5-anhydroglucitol, haemoglobin A1c, and glucose levels in youth and young adults with type 1 diabetes and healthy controls. *Pediatr Diabetes*, 13(3), 2012, 278-84.
- Min Joo Kim, Hye Seung Jung, Yul Hwang-Bo, Sun Wook Cho, Hak Chul Jang, Seong Yeon Kim et al. Evaluation of 1,5-anhydroglucitol as a marker for glycemic variability in patients with type 2 diabetes mellitus, *Acta Diabetologica*, 50(4), 2013, 505-510.
- Moses AC, Raskin P, Khutoryansky N. Does serum 1,5-anhydroglucitol establish a relationship between improvements in HbA1c and postprandial glucose excursions? Supportive evidence is utilizing the differential effects between biphasic insulin aspart 30 and insulin glargine. *Diabet Med*, 25(2), 2008, 200-5.

- Nguyen TM, Rodriguez LM, Mason KJ, Heptulla RA. Serum 1,5-anhydroglucitol (Glycomark) levels in children with and without type 1 diabetes mellitus. *Pediatr Diabetes*. 8(4), 2007, 214-9.
- Pal A, Farmer AJ, Dudley C, Selwood MP, Barrow BA, Klyne R, et al. Evaluation of serum 1,5-anhydroglucitol levels as a clinical test to differentiate subtypes of diabetes. *Diabetes Care*. 33(2), 2010, 252-7.
- Shimizu H, Shouzu A, Nishikawa M, Omoto S, Hayakawa T, Miyake Y, et al. Serum concentration and renal handling of 1,5-anhydro-D-glucitol in patients with chronic renal failure. *Ann Clin Biochem*, 36 (6), 1999, 749-54.
- Skupien J, Gorczyńska-Kosiorz S, Klupa T, Wanic K, Button EA, Sieradzki J, et al. Clinical application of 1,5-anhydroglucitol measurements in patients with hepatocyte nuclear factor-1alpha maturity-onset diabetes of the young. *Diabetes Care*. 31(8), 2008, 1496-501.
- Sun J, Dou JT, Wang XL, Yang GQ, Lü ZH, Zheng H, Ma FL, et al. Correlation between 1,5-anhydroglucitol and glycemic excursions in type 2 diabetic patients. *Chinese Medical Journal*. 01 Nov 2011, 124(22):3641-3645.
- Tsukui S, Kobayashi I, Effects of age and obesity on glycated haemoglobin and 1,5-anhydroglucitol in screening for type 2 diabetes mellitus. *Diabet Med*, 12(10), 1995, 899-903.
- W. J. Kim, C. Y. Park, S. E. Park, E. J. Rhee, W. Y. Lee, K. W. Oh, S. W. Park, et al. Serum 1,5-anhydroglucitol is associated with diabetic retinopathy in Type 2 diabetes, 29, 2012, 1184-1190.
- Wang Y, Zhang YL, Wang YP, Lei CH, Sun ZL. A study on the association of serum 1,5-anhydroglucitol levels and the hyperglycaemic excursions as measured by continuous glucose monitoring system among people with type 2 diabetes in China. *Diabetes Metab Res Rev*, 28(4), 2012, 357-62.
- Watanabe M, Kokubo Y, Higashiyama A, Ono Y, Miyamoto Y, Okamura T. Serum 1,5-anhydro-D-glucitol levels predict first-ever cardiovascular disease: an 11-year population-based cohort study in Japan, the Suita study. *Atherosclerosis*, 216(2), 2011, 477-83.
- Won JC, Park CY, Park HS, Kim JH, Choi ES, Rhee EJ, et al. 1,5-Anhydroglucitol reflects postprandial hyperglycemia and a decreased insulinogenic index, even in subjects with prediabetes and well-controlled type 2 diabetes. *Diabetes Res Clin Pract*. 84(1), 2009, 51-7.
- Yamanouchi T, Akanuma Y, Toyota T, Kuzuya T, Kawai T, Kawazu S, et al. Comparison of 1,5-anhydroglucitol, HbA1c, and fructosamine for detection of diabetes mellitus. *Diabetes*. 40(1), 1991, 52-7.
- Yamanouchi T, Akanuma Y. Serum 1,5-anhydroglucitol (1,5AG): a new clinical marker for glycemic control. *Diabetes Res Clin Pract*, 24, 1994, 261-8.