

## REVIEW

# Assessing postprandial glucose using 1,5-anhydroglucitol: An integrative literature review

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### Abstract

**Purpose:** Recent studies have determined postprandial blood glucose is an independent risk factor for macrovascular complications. This risk exists, despite having HbA1C results within acceptable ranges for diabetes. 1,5-Anhydroglucitol (1,5AG) has been proposed as an appropriate indicator to detect and screen for postprandial hyperglycemia (PPHG). This review discusses the efficacy of 1,5AG to predict PPHG in order to reveal those who may be at risk for macrovascular complications.

**Data Sources:** An electronic search was conducted from 2003 to 2008 in the following databases: Medline, CINAHL, Health Source: Nursing/Academic Edition, and Pre-CINAHL. Any articles relating to 1,5AG as a marker for PPHG were used. The search was limited to any human research articles published in English. All articles were reviewed for additional relevant studies.

**Conclusions:** 1,5AG was found to be a reliable indicator of PPHG, even when HbA1C levels were within target ranges. 1,5AG may be a simple and effective tool for primary care providers to identify those at risk for macrovascular complications, who would otherwise go unnoticed if assessed by HbA1C alone.

## Introduction

Diabetes is a national epidemic in the United States. The Centers for Disease Control and Prevention (CDC) currently estimates that 20.8 million people have diabetes, while 6.2 million do not know they have the disease (CDC, 2005). Boyle et al. (2001) predict that by the year 2030, diabetes will affect 29 million people in the United States. Diabetes is the leading cause of kidney failure, blindness, nontraumatic amputations, and is currently the sixth leading cause of death in the United States (CDC, 2005). Of those who have diabetes, 65% will die from cardiovascular disease (CVD), such as heart disease or stroke (CDC, 2005). The morbidity, mortality, and cost of diabetes are major concerns for the healthcare system.

Vascular complications of diabetes, such as macro- and microvascular disease have been well demonstrated (DCCT Research Group, 1993; UK Prospective Diabetes Study Group, 1998). The risk of complications from hyperglycemia is generally measured by glycosylated

hemoglobin (A1C), a laboratory value that estimates the blood glucose average over the last 2–3 months. A1C is an important marker for complications risk; however, the 1995 landmark trial by the Diabetes Control and Complications Trial (DCCT) group states that A1C is not the total expression of the degree of glycemia, suggesting that the risk of complications may be more attributable to glycemic excursions resulting in postprandial hyperglycemia (PPHG) (DCCT Research Group, 1995).

### Postprandial hyperglycemia

PPHG occurs when the blood glucose rises above what is considered a normal glucose level after a meal. The American Diabetes Association (ADA) has defined PPHG as a blood glucose above 180 mg/dL 2-h postmeal, whereas the American Association of Clinical Endocrinologists (AACE) define PPHG as a 2-h postmeal glucose above 140 mg/dL (AACE Diabetes Mellitus

Clinical Practice Guidelines Task Force, 2007; ADA, 2007). Various studies have shown PPHG is an independent risk factor for increased CVD, even more so than A1C (Kim et al., 2007; Meigs, Nathan, D'Agostino, & Wilson, 2002; Temelkova-Kurktschiev et al., 2000; Tominaga et al., 1999). Furthermore, evidence has shown there is a linear relationship between increasing PPHG and cardiovascular mortality, whereas impaired glucose tolerance (measured by PPHG) was shown to be an independent risk factor for death (DECODE Study Group, 1999, 2003).

### Prevalence

The deleterious effects of PPHG on cardiovascular health are a concern because of its prevalence. Monnier, Lapinski, and Claude (2003) have shown that with improvement of A1C, the majority of hyperglycemia may be attributed to elevated postmeal glucose values. The findings of Monnier et al. are consistent with a U.S. cross-sectional analysis of 18,825 adults with diabetes which showed that PPHG (>200 mg/dL) after an oral glucose tolerance test (OGTT) was present in 74% of the subjects diagnosed with diabetes. PPHG was present in 99% of those with an A1C greater than 7%; however, of those whose A1C was <7% (considered by the ADA to be within the target range), 39% had a postprandial reading greater than 200 mg/dL (Erlinger & Brancati, 2001).

Similarly, Bonora et al. (2006) showed that of 3284 noninsulin dependent type 2 diabetic subjects in Italy, 84% had a 2-h PPHG episode of more than 160 mg/dL at least once a week. For those in good control (A1Cs <7%), 38% of the subjects had more than 40% of their total postprandial readings above 160 mg/dL.

### Measures for assessing PPHG

Evaluating PPHG is fairly straightforward when looking at individual blood glucose values; however, when evaluating for PPHG trends, variability becomes a reflective measure to assess PPHG. When PPHG occurs frequently, glucose values are said to be variable. Variability can be loosely defined as the amount of divergence of glucose levels from the mean. Because a normal glucose range is roughly 80–120 mg/dL, increasing variability usually equates to increased frequency of PPHG. So, although variability is not necessarily the same as PPHG, it is a reflective indicator that elevated glucose excursions are occurring.

Historically, data obtained from patient glucometers have been the primary method to evaluate for PPHG. However, with the advent of continuous glucose monitors (CGMs) and 1,5-anhydroglucitol (1,5AG), there are now other means to evaluate the degree of PPHG. A brief

description of self-monitoring blood glucose (SMBG), CGMs, and 1,5AG are important to discuss to enable clinicians to distinguish the differences among the various methods of glucose monitoring.

### Self-monitoring blood glucose

SMBG has been available since the 1970s with the invention of glucose monitors and has helped tighten glucose control (Bui, Perlman, & Daneman, 2005). Software enables providers to look at daily mean glucose values and glucose standard deviations. By using standard deviations, variability can be measured to help evaluate PPHG. Intrinsic problems exist, however, with self-monitoring of blood glucose. Varying brands of glucometers and various software platforms make it difficult for providers to accommodate all patients. As well, glucometers can individually vary in accuracy up to 15%, which may skew results from patient to patient (Johnson & Baker, 2001). In addition, measuring glucose standard deviations becomes valuable if there are enough readings to be representative of daily glucose trends. Without sufficient glucose data, or if the patient only tests when symptomatic, results are less representative of the larger glucose picture. Patients may need to test 5–10 times per day to get representative glucose samples to calculate the glucose standard deviation (Hirsch, 2005).

### Continuous glucose monitors

CGMs have been used to measure PPHG and the accuracy of other glycemic measures such as A1C (Consensus Committee, 2007; Dungan et al., 2006; Praet et al., 2006). CGMs are seemingly the most useful in getting a comprehensive look at glycemic PPHG, related to the amount of data they can obtain. CGMs can take as many as 288 readings per day and through software can calculate glucose variance. Still, as with SMBG, there are drawbacks to using CGMs. Accuracy is somewhat suspect and debate is ongoing as to the most appropriate algorithm to use in assessing variability. CGMs are also very expensive and are not readily reimbursed by insurance companies. CGMs can be time intensive to download and to evaluate glucose data in the office. CGMs require extensive education to use and can be somewhat technical for the average person with diabetes (Dexcom, 2007; Kollman et al., 2005; Kovatchev, Gonder-Frederick, Cox, & Clarke, 2004; Medtronic MiniMed Inc., 2007).

### 1, 5-Anhydroglucitol

1,5AG is a single lab value, which is indicative of the extent to which PPHG has occurred over the preceding

2–3 weeks. 1,5AG has been used for many years in Japan to detect PPHG and received Food and Drug Administration (FDA) approval for use in the United States in 2003 (U.S. Food and Drug Administration, 2003). GlycoMark is the only company currently marketing the 1,5AG laboratory test in the United States.

First discovered in 1888, 1,5AG is a monosaccharide polyol with a similar structure to glucose, however with only 1/40th the concentration of blood glucose (Yamanouchi & Akanuma, 1994). The distinguishing characteristic of 1,5AG is that blood levels are very stable. Ninety-nine percent of 1,5AG is reabsorbed by the kidneys and it is poorly metabolized in the body (Stickle & Turk, 1997; Yamanouchi & Akanuma). Intake of 1,5AG is balanced by urinary excretion, thus allowing 1,5-AG to remain fairly constant in the blood stream, except under conditions of hyperglycemia. 1,5AG is primarily found in food and the average intake is about 4.4 mg/day (Yamanouchi & Akanuma).

With elevated glucose levels above renal threshold (between 144 and 180 mg/dL of glucose), 1,5AG begins to be excreted in the urine depleting serum levels (Stickle & Turk, 1997; Yamanouchi et al., 1989). Plasma 1,5AG is selectively reabsorbed in the proximal tubule in direct competition with glucose, and thus it diminishes rapidly when blood glucose rises (Stickle & Turk, 1997). Persistent hyperglycemia above renal threshold results in 1,5AG being markedly low, whereas transient hyperglycemia (not revealed by A1C) will result in a slightly reduced 1,5AG value, indicating transient PPHG excursions. The normal reference range for 1,5AG without diabetes lies between 12 and 40 mg/L (Yamanouchi & Akanuma, 1994). Replenishment of 1,5AG occurs at a rate of approximately 0.3 µg/mL per day and body stores can be totally replenished in about 5 weeks with good glucose control (Stickle & Turk, 1997; Yamanouchi et al.).

### Purpose statement

The purpose of this integrative literature review is to evaluate the efficacy of 1,5AG in predicting PPHG to more effectively assess those who might be at risk for macrovascular complications. Based on the findings, clinical recommendations will be made.

### Methods

An electronic search was conducted to identify studies from 2003 to 2008 in the following databases: Medline, CINAHL, Health Source Nursing Academic, and Pre-CINAHL. Search terms used were 1,5AG or 1,5 anhydroglucitol or glycomark or 1,5 anhydro D glucitol, hyperglycemi\* and postprandial or postprandial

or glycemic excursion\*. The search was limited to any human research articles published in English. The references from all articles were reviewed for additional relevant studies. Older articles were included if they added information not found in more recent studies.

Inclusion criteria for this review focused on the use of 1,5AG as a glucose marker to identify postprandial blood glucose elevations. Any study related to the sensitivity, efficacy, and utility of 1, 5-anhydroglucitol was included. Exclusion criteria included any nonhuman trials or those not related to diabetes.

## Results

### 1,5AG versus A1C

A number of studies have evaluated the differences of 1,5AG and A1C. These findings are important to determine whether both parameters are necessary, given the relationship of PPHG with macrovascular complications.

A comparative study of 130 patients with type 2 diabetes tested their blood glucose eight times per day (fasting, 2-h postmeals and 10 p.m.). Their glucose profiles were then compared to A1C and 1,5AG values (Dworacka & Winiarska, 2005). Results of the study showed that subjects with an A1C above 6.5% had uniformly lower levels of the polyol 1,5AG (between 0.9 and 14.7 mg/L), signifying hyperglycemia above renal threshold for glucose; however, in the subjects who were considered to have good control (A1C <6.5%), the 1,5AG levels ranged broadly between 2.0 and 29.9 mg/L. The researchers concluded that 1,5AG variability among patients with similar A1C levels was explained by varying PPHG levels among subjects. Those deemed as low risk for complications as measured by A1C actually had increased risk for macroangiographic complications with decreased 1,5AG levels indicating PPHG.

Similar results were found by Kawasaki et al. (2005), who enrolled 172 hospitalized Japanese subjects with noninsulin dependent type 2 diabetes. They measured 7-point glucose profiles every third day and then compared the glucose values to 1,5AG, A1C, and glycated albumin (a marker for blood glucose average over 2–3 weeks). Their results showed that A1C and glycated albumin did not predict PPHG; whereas 1,5AG correlated well and could independently predict PPHG (>200 mg/dL). This study also identified the optimal cutoff level to reveal PPHG as 7.0 mg/dL, with a sensitivity of 86% and specificity of 78%.

An innovative study by Dungan et al. (2006) used continuous glucose monitoring as the evaluative tool for variability and PPHG. This study is compelling because of the amount of glucose data obtainable by using CGM

technology. Researchers enrolled 34 patients with type 1 or type 2 diabetes, with A1C levels ranging between 6.5% and 8.0%. The subjects completed 144 h (6 days) of continuous glucose monitoring. Serum 1,5AG, A1C, and fructosamine levels (a marker for blood glucose average over 2–3 weeks) were gathered on days 1, 3, and 7. 1,5AG, A1C, and fructosamine levels were compared with glucose results gathered by the CGMs. Measurement of glucose variability was determined by using the area under the glucose curve (AUC-180). Results showed that 1,5AG ( $r = -0.48$ ,  $p = .002$ ) correlated with total AUC-180 better than did A1C ( $r = 0.36$ ,  $p = .02$ ) or fructosamine ( $r = 0.33$ ,  $p = 0.03$ ). The results demonstrated that 1,5AG varied greatly among patients whose A1C values were similar. The researchers recommended using 1,5AG as an adjunct measure to A1C to tighten glycemic control.

Kawasaki, Ichiyanagi, and Yamanouchi (2007) further investigated the relationship of A1C and PPHG by determining whether there was a point at which the A1C value was low enough that PPHG would not be revealed by 1,5AG. This retrospective study took data from 82 nondiabetic and 139 diabetic Japanese subjects who had monthly A1C and 1,5AG values for up to 1 year. For all subjects (with or without diabetes) whose A1C was under 5.8%, results showed a 1,5AG glycemic excursion of  $15.1\% \pm 4.3\%$  for those with diabetes and  $3.8\% \pm 1.0\%$  for those without diabetes, demonstrating a significant variability of 1,5AG levels among those with diabetes, as compared to those without. Because A1C levels were considered in the normal range, they implicated PPHG as the cause of 1,5AG variability in those patients with diabetes.

### Short versus long-term marker

The main difference between A1C and 1,5AG is time. This difference is illustrated in a study by McGill et al. (2004). This U.S. study took 77 subjects whose A1C levels were  $\geq 7\%$ . Each subject received nutrition counseling, diabetes education, or additional medications, and/or medication adjustments to reduce mean A1C. They monitored A1C, 1,5AG, fructosamine, and random glucose measurements at 2, 4, and 8 weeks. Results showed that 1,5AG responded by two weeks, whereas A1C did not. They conclude that 1,5AG was highly correlated with A1C (Spearman  $\rho = -0.6459$ ,  $p < 0.0001$ ), showing that 1,5AG could predict longitudinal changes in A1C.

### Efficacy of use of 1,5AG in children

With the increase of both type 1 and type 2 diabetes in children, it is important to know whether the 1,5AG

values demonstrate the same findings in children as in adults. Nguyen, Rodriguez, Mason, and Heptulla (2007) evaluated 1,5AG concentrations in a U.S. pediatric population. This study used a small sample of 10 children ages 12–18 with type 1 diabetes and 10 age-matched children without diabetes. Inclusion criteria for those having diabetes, included an A1C less than 8%, on insulin pump therapy, a body mass index (BMI) less than the 90th percentile for age, a hemoglobin  $> 12$  g/dL, with no other chronic conditions other than hypothyroidism. A1C, 1,5AG, and PPHG were measured after a standardized meal. Results showed a 1,5AG concentration of  $24.60 \pm 3.99$   $\mu\text{g/mL}$  for those without diabetes versus  $4.75 \pm 2.95$   $\mu\text{g/mL}$  for those with diabetes. Despite having relatively good A1C values ( $7.72 \pm 0.37\%$ ), 1,5AG levels were diagnostically low, revealing considerable PPHG. Results showed that 1,5AG concentrations were comparable with previous studies performed on adults.

### Pregnancy

The use of 1,5AG in pregnancy is controversial. Kilpatrick, Keevilt, Richmond, Newland, and Addison (1999) found varying levels of 1,5AG in pregnant patients related to normal changes in renal threshold. In their study of 38 pregnant women whose blood glucose was normal, serum 1,5AG levels were measured after a 75-g glucose load. Sixteen of the subjects studied did not have glucose in their urine, whereas 22 subjects had glucosuria. The women who had glucosuria, however, did not have elevated blood glucose values. Eliminating the six subjects with the highest OGTT results, they examined the difference between the 16 patients with glucosuria and 16 without glucosuria, who had normal glucose blood levels. They found in the women without glucosuria that the 1,5AG ranged from 55 to 79  $\mu\text{g/dL}$  (9.0–12.9 mg/L) with a median of 72  $\mu\text{mol/L}$  (11.2 mg/L). Those with glucosuria ranged from 30 to 56  $\mu\text{mol/L}$  (4.9–9.2 mg/L) with a median of 46  $\mu\text{mol/L}$  (7.6 mg/L). Although these subjects were normoglycemic, they had varying degrees of plasma 1,5AG. The researchers attributed these variations to differences in normal renal threshold among pregnant patients and theorized that this variation may limit 1,5AG's usefulness in those with gestational diabetes.

In contrast, Dworacka et al. (2006) showed that monitoring 1,5AG during pregnancy was an important and reliable indicator of short-term glucose control. Their study consisted of 55 gestational diabetes mellitus (GDM) or pre-GDM patients without renal or hepatic insufficiency ranging in gestational age from 5 to 38 weeks. They measured a single 24-h glucose profile (11 glucose values), A1C, and 1,5AG. Multivariate regression analysis, with maximal glucose, gestational age, and 24-h

glucose profile, showed that maximal glucose level was the main determinant of 1,5AG levels ( $B = [-0.68]$ ,  $p = [.01]$ ) and that there was no correlation between 1,5AG and gestational age (when renal thresholds vary). They concluded that 1,5AG is a useful and effective measure to evaluate glucose short-term control in pregnant women.

### Renal impairment

A preponderance of older studies and a few more recent studies exist, which suggest limiting use of 1,5AG in renal impairment. Because 1,5AG is lost in the urine above renal threshold for glucose, impaired renal function limits the utility of 1,5AG as a marker for PPHG. Specifically, conditions such as end-stage renal disease or chronic renal failure have been shown to influence 1,5AG results (Emoto, Tabata, Inoue, Nishizawa, & Morii, 1992; Shimizu et al., 1999; Yamada, Hishida, Kato, & Yoneyama, 1996). 1,5AG may be useful in those with mild renal disease who have some albuminuria, however not in those with proteinuria (Shi, Fang, Yang, Shen, & Zhu, 1999).

### Other factors

Other factors may also affect the validity of the use of 1,5AG. For example cirrhosis, poor nutrition, and certain drugs such as acarbose may lower 1,5AG related to decreased production or uptake, whereas the Chinese herbal medicine Kampo has been shown to increase 1,5AG considerably, because of high amounts of 1,5AG in the herb. Medications, nutrition, herbs, and general condition of the patient need to be considered when interpreting 1,5AG results (Kawasaki et al., 2000; Watanabe et al., 2004; Yamagishi & Ohta, 1998; Yamanouchi & Akanuma, 1994).

### Discussion

A number of studies indicate that 1,5AG is able to detect frequent short-term elevations in glucose, which may contribute to macrovascular complications in patients with diabetes. Given the importance of managing PPHG, 1,5AG may be a useful marker in the detection and management of postmeal glucose spikes. 1,5AG is a simple laboratory test with a single value to interpret, reflecting a consistent pattern of glucose excursions. It may be viewed as a “sum of losses,” showing the relative loss of 1,5AG with multiple glucose excursions above renal threshold. 1,5AG is different from A1C in that it reflects a different aspect of glycemic control. Where A1C is a measure of glucose attached to the hemoglobin molecule

(glycated hemoglobin) and represents a glucose average over a period of months, 1,5AG is a total measure of the polyol in the serum and reflects PPHG over weeks. This time difference between the two measures is illustrated in the study by McGill et al. (2004), which showed that 1,5AG could predict A1C values because 1,5AG evaluates short-term glucose changes versus the long-term changes revealed by A1C. Indeed, the studies evaluated indicate that short-term glucose elevations are not detectable by A1C, reiterating the results from the DCCT trial which stated A1C was not the total expression of glycemic risk (DCCT Research Group, 1995).

### Utility

The usefulness of 1,5AG is its ability to detect those who are presumably in good glycemic control per A1C results, yet who may be at risk for complications because of PPHG excursions. If a patient has an A1C within target range, yet has a low 1,5AG value, it may indicate that the patient is having problematic PPHG.

The advantage of 1,5AG is its simplicity. 1,5AG can be likened to a PPHG counter, which marks each time glucose rises above renal threshold and gives a single result. Many patients test infrequently, making it difficult to evaluate glucose patterns. Infrequent glucose testing tempts providers to rely on A1C as the sole objective measure to evaluate total glycemic complication risk. 1,5AG may be an additional tool to detect poor glucose control in those with presumably good control per A1C results.

### Limitations

1,5AG is primarily a screening tool to see whether there is significant PPHG and is limited in this regard. Unlike CGMs or adequate SMBG, 1,5AG does not point out specific times of day or other factors contributing to PPHG. It is helpful in determining if there is a PPHG problem; however, it does not show when glucose excursions occur as would frequent SMBG or CGMs.

Using 1,5AG during pregnancy remains inconclusive. Although Kilpatrick et al. (1999) found that renal threshold for glucose varies among pregnant patients, Dworacka et al. (2006) showed that 1,5AG was accurate and efficacious at any stage of pregnancy. Additional studies need to be done to determine the usefulness of 1,5AG during pregnancy.

### Affordability

The 1,5AG laboratory test costs around \$50–\$80; however, it is reimbursable through Medicare and private

insurances (CPT code 84378). Medicare reimburses \$16 and private insurances coverage can range from \$25 to \$35 for the test. In contrast to 1,5AG, CGMs typically can cost up near \$250 and are covered on many health plans with preauthorization (CPT code 99250). The least expensive method to evaluate PPHG is to download and evaluate glucometer readings, where the cost is included in a normal provider billing.

It is conceivable that, in those patients with type 2 diabetes (who are not on insulin) 1,5AG could replace SMBG if both measures of 1,5AG and A1C levels are managed within target range showing no glucose excursions and a low glucose average. This would signify that both average and postmeal glucose levels are controlled and could possibly reduce expense associated with frequent glucose testing in those who may not need it.

## Study limitations

The limited number of studies and small sample sizes limit generalizability. As well, most of these studies have been performed in Asian countries where factors such as obesity, diet, culture and genetics differ from American culture and may also limit generalizability. In addition, no studies have been performed to evaluate 1,5AG with concurrent use of common diabetes medicines, such as aspirin, angiotensin-converting enzyme (ACE) inhibitors, or statins.

## Conclusions

1,5AG appears to be a reliable indicator of PPHG, despite A1C within target ranges. 1,5AG would be an additional tool used in conjunction with A1C to detect glycemic risk for complications. 1,5AG is a lab test which is perhaps best suited for use in a primary care setting as an initial screening tool. The simplicity of 1,5AG may give it preference over other tools, such as CGM technology or glucometer downloading; nevertheless, CGMs and glucometer downloading are important to appraise causes of PPHG when causative factors are not readily obvious. 1,5AG is a simple and effective tool for providers to identify those at risk for macrovascular complications, who may otherwise be missed if assessed by A1C alone.

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