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Serum 1,5-Anhydroglucitol (GlycoMark™): A Short-Term Glycemic Marker

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ABSTRACT

1,5-Anhydroglucitol (1,5-AG), the 1-deoxy form of glucose, has been measured and used clinically in Japan for over a decade to monitor short-term glycemic control. Evaluation of glucose control otherwise requires measuring plasma glucose or glycated proteins whose levels reflect average glucose concentration over the half-life of the protein analyzed. Hemoglobin A1c measurements reflect blood glucose levels over that past 2–3 months, while fructosamine can be used to evaluate glycemic control over 10–14 days. In contrast, 1,5-AG levels in blood respond within 24 h as a result of glucose's competitive inhibition of 1,5-AG reabsorption in the kidney tubule. When glucose levels rise, even transiently, urinary loss of 1,5-AG occurs, and circulating levels fall. Because of changes in renal hemodynamics in normal pregnancies, 1,5-AG appears of limited usefulness in evaluation of gestational diabetes. However, the characteristics of 1,5-AG levels in patients with moderate to near-normal glycemic control suggest that it may be a valuable complement to frequent self-monitoring or continuous monitoring of plasma glucose to confirm stable glycemic control. Measurements performed daily or weekly in a given patient would suggest that overall glycemic control has been stable or improved if 1,5-AG levels are stable or increasing. If 1,5-AG levels fall, greater attention to glucose monitoring and both lifestyle and medical management could be prescribed to correct the glycemic excursions that would underlie such changes. The behavior of this analyte is different from all others used in the management of diabetes, creating potential opportunities for its use in clinical practice.

INTRODUCTION

IT HAS BEEN WELL ESTABLISHED that control of glycemia helps to reduce or prevent complications of diabetes mellitus.[1–6] In managing diabetes, patient self-monitoring of blood glucose and measurement of various biochemical markers of glycemic control are approved by the U.S. Food and Drug Administration (FDA). Capillary, venous, and arterial glucose can be measured in plasma, serum, or blood. Each provides a slightly different index of instantaneous glycemic control.[7–9] Continuous intermittent interstitial glucose monitoring can be

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performed to provide trends over hours to days in glucose control.[10–12] Various glycated serum protein assays, such as fructosamine (FA), can be used to monitor average glycemia over a period of 2–3 weeks.[7,8,13,14] Glycosylated hemoglobin, most commonly hemoglobin A1c (A1C), can be measured as an index of average glycemia over a period of 2–3 months and is the marker best validated in prospective interventional and epidemiological studies to predict risk of complications of diabetes.[1–8,13,15,16]

A diagnostic test measuring the level of 1,5-anhydroglucitol (1,5-AG) has recently been proposed to the FDA as an index of glycemic control in patients with diabetes. Although not currently available in the United States, this blood test has been commercially available since 1991 in Japan, where considerable effort has been devoted to the characterization of 1,5-AG levels in plasma and serum in diabetes mellitus.

The aim of this review is to summarize the extensive research conducted on 1,5-AG with a specific focus on its potential clinical utility and comparison with other glycemic markers that are currently available in the United States.

PHYSIOLOGICAL SIGNIFICANCE OF 1,5-AG

1,5-AG is a six-carbon monosaccharide, specifically the 1-deoxy form of glucose. It was first detected in 1888 in plants and in 1972 in humans. 1,5-AG in bodily fluids originates mostly from ingestion of these plant sources.[17] Although the 1,5-AG content of most foods is similar, soybeans are particularly high (approximately 23 μg/g). Other foods with moderate levels include rice, bread, and beef (2–4 μg/g). Although the physiological function of 1,5-AG is not known, its structural similarity to glucose allows glucose to competitively inhibit the absorption of 1,5-AG in the renal tubules (Fig. 1). Normally, 99.9% of 1,5-AG filtered by the kidney is reabsorbed, maintaining a large internal pool of 1,5-AG (Fig. 2A). Oral intake is balanced by urinary excretion to maintain consistent blood levels of 1,5-AG. However, when glucose levels are high in diabetic patients (Fig. 2B), glucose prevents 1,5-AG reabsorbtion in the renal tubules, leading to net excretion of 1,5-AG in the urine and thus decreasing levels in serum.[17,18]

ASSAY METHODOLOGY

Although a gas chromatography–mass spectroscopy assay can accurately measure the very small amount of 1,5-AG in both urine and other biological samples,[17] the majority of clinical data generated in Japan are based on the two-step enzymatic method described by Fukumura et al.[19] Basically, levels of 1,5-AG are measured through colorimetric detection of hydrogen peroxide following the oxidation of 1,5-AG by pyranose oxidase. Since glucose could interfere with this reaction, the sample is first

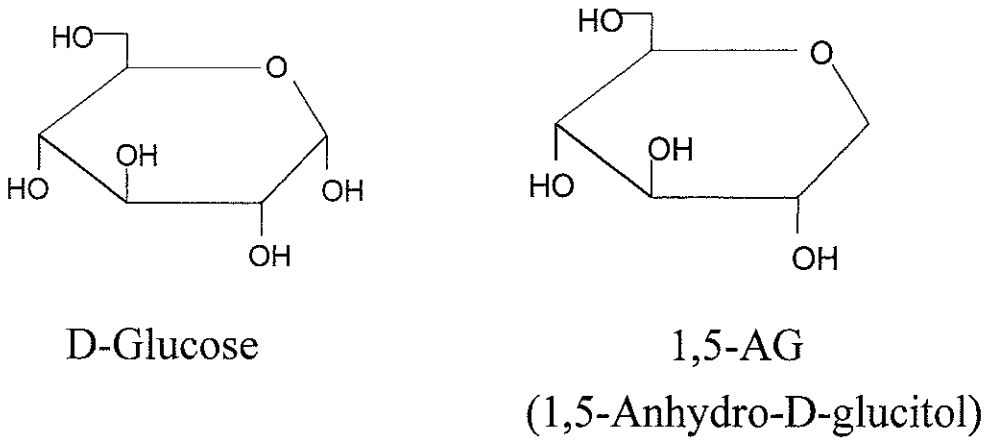

FIG. 1. Chemical structures of glucose and 1,5-AG. The difference between glucose (**left**) and 1,5-AG (**right**) is demonstrated.

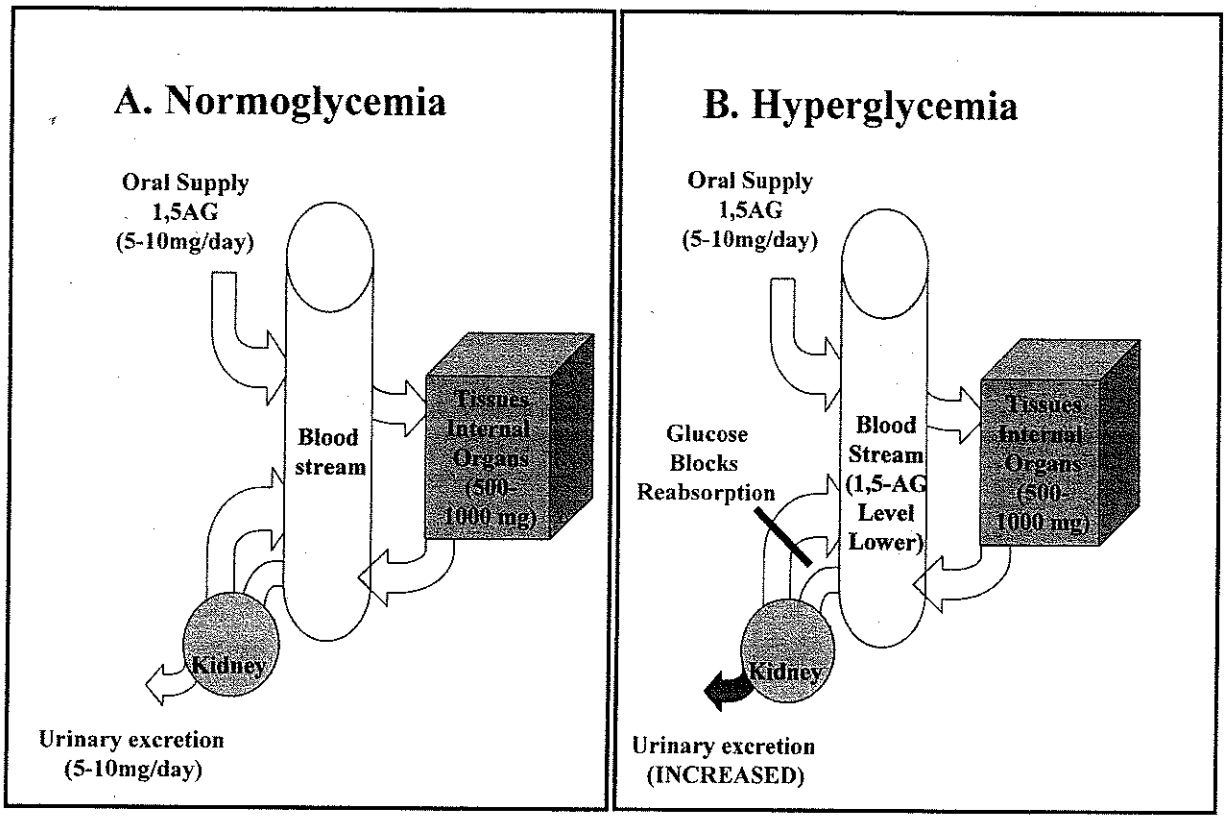

FIG. 2. Reabsorbtion of 1,5-AG in normal and hyperglycemic states. **A:** In normoglycemia, the oral intake and urinary excretion of 1,5-AG are balanced, maintaining a constant level of circulating 1,5-AG. **B:** In hyperglycemia, high levels of glucose block the reabsorbtion of 1,5-AG in the proximal tubule, resulting in increased excretion and decreased serum levels of 1,5-AG.

exposed to glucokinase to convert glucose to glucose-6-phosphate. This assay is available in a kit (GlycoMark™; Tomen America, New York, NY) that is being evaluated in the United States. Another automated system was reported by Tanabe et al.[20] using a flow-injection system. In this system, glucose and other interfering substances are adsorbed by an on-line anion-exchange column prior to the enzyme reaction. 1,5-AG is then detected using the colorimetric detection of hydrogen peroxide as described above.[19] Measurement of 1,5-AG is not affected by EDTA, NaF, citrate, or heparin, nor is it affected by meals or exercise. Therefore, time of day of sampling is not a factor.[17]

CLINICAL UTILITY OF GLYCOMARK

Normal versus diabetic

Numerous studies have examined 1,5-AG's ability to differentiate between normal and diabetic individuals.[17] Figure 3 demonstrates the clear differences in 1,5-AG levels between healthy subjects and patients with diabetes mellitus.[21] 1,5-AG levels among a healthy population do vary widely (12–40 μg/ml), with the mean serum 1,5-AG level in healthy males significantly exceeding that of healthy females.[17] Despite the wide variation in population levels of 1,5-AG, few normal individuals show substantial changes in 1,5-AG levels with repeated measures over a period of 2–3 years.[17] Although individual variance in renal threshold for glucose (the concentration of serum glucose above which urinary losses occur as a result of the kidney tubule being unable to reabsorb all the glucose filtered) does not appear to seriously influence the clinical utility of 1,5-AG, caution should be taken when evaluating levels in patients whose renal threshold are markedly different from normals,[17,22–24] such as individuals with chronic renal failure or tubular defects.

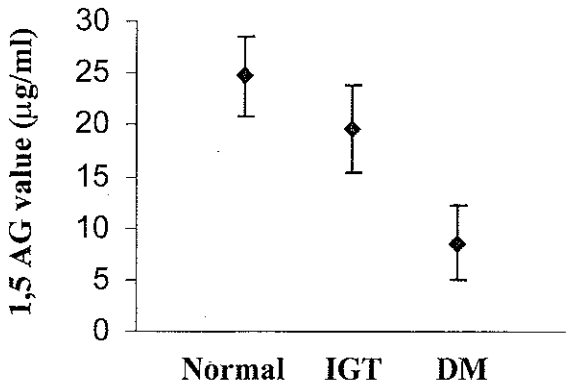

FIG. 3. Evaluation of 1,5-AG levels in individuals with normal glucose tolerance, IGT, and diabetes mellitus (DM). Individuals were grouped according to their 2-h plasma glucose values by 75-g oral glucose tolerance test as normal (<6.7 mmol/L, $n = 450$), IGT (6.8–11.0 mmol/L, $n = 364$), or DM (>11.1 mmol/L, $n = 217$). The mean and SD of 1,5-AG values reported by Yamanouchi et al.[21] are as follows: normal, 24.7 ± 7.5 μg/mL; IGT, 19.6 ± 8.4 μg/mL; DM, 8.5 ± 7.3 μg/mL.

Whether these observations from Japan will hold true in a more ethnically and culturally diverse population like in the United States is uncertain. Furthermore, extremes of dietary intake such as vegetarian diets high in soy as well as low carbohydrate diets will need to be evaluated as transient adherence to fad diets is quite common in overweight Americans. Finally, a normal range and values associated with good glycemic control will need to be established for men and women in the United States with the assay under development.

Increases and decreases

Several factors contribute to the stability of serum 1,5-AG levels in healthy individuals. The large pool and metabolic inertness of 1,5-AG combined with the large degree of reabsorption that occurs in the kidney maintain consistent serum levels of 1,5-AG in a normal glycemic state. Additionally, studies examining fluctuations based on time of day or dietary load have shown no substantial variations in 1,5-AG levels.[17]

In hyperglycemic states, this renal balance is disrupted, resulting in a rapid and significant *decrease* in 1,5-AG levels. Decreases in serum levels of 1,5-AG result when high levels of glucose induced by hyperglycemia competitively inhibit the renal reabsorption of 1,5-AG in the proximal tubule. The 1,5-AG level falls immediately as urinary glucose appears, generally at plasma glucose of approximately 160–190 mg/dL.[25,26]

Upon return of strict glycemic control, Yamanouchi et al.[26] demonstrated, in a study of 82 patients, that the average daily increase in serum 1,5-AG appears constant at approximately 0.3 μg/mL daily and is not influenced by treatment, sex, age, body weight, or duration of diabetes mellitus. This consistent recovery rate in 1,5-AG levels provides a rapid indication of the patient's response to intensification of lifestyle management or increases in antidiabetic medication.

Monitoring

A reliable, rapid monitoring tool to evaluate daily glucose levels of patients with diabetes can provide clinicians with valuable information regarding treatment effectiveness. 1,5-AG has demonstrated in numerous studies a sensitive and rapid response to serum glucose levels.[17] A cohort study[27] underscores the clinical usefulness of serum 1,5-AG levels to monitor glycemic control following changes in antidiabetic medication. Fifty-six patients were treated with oral hypoglycemic agent for 4 weeks. As expected, 1,5-AG levels steadily increased, as plasma glucose levels decreased. At week 4, oral medical treatment of half the patients was discontinued; 1,5-AG levels in these patients decreased sharply over the following 2 weeks. The mean change of 1,5-AG paralleled that of fasting and mean (of seven daily measurements) plasma glucose, demonstrating serum 1,5-AG's sensitive and rapid response to serum glucose levels. Neither A1C nor FA displayed significant correlations to serum glucose levels in this 2-week follow-up period, although FA levels were beginning to change.[27] Most interesting were the results of an extension of this study in which 20 patients demonstrated "near-normoglycemia" with average A1C values of 6.5% during the final 8 weeks of the 16-week study. When these patients were divided into those with mean serum 1,5-AG above or below 10.0 μg/mL, though there was no difference in A1C, the mean (±SD) daily plasma glucose levels were, respectively, 159 ± 21 and 123 ± 26 mg/dL.[27]

In another clinical study, a second interesting feature of the 1,5-AG measure was observed. Seventy-six patients with well-controlled type 2 diabetes (mean A1C 7.1%) treated with diet, oral antidiabetic agents, conventional insulin therapy, or multiple daily injections were examined for 1,5-AG levels as well as daily excursions in glucose.[28] The multiple daily injection group had less glycemic excursion with fewer glucoses over 180 mg/dL and fewer glucoses less than 70 mg/dL than the other three groups. Across groups there was good correlation with the degree of glycemic excursion with 1,5-AG levels despite similar A1C, suggesting a role of 1,5-AG as an index of consistency of control through the day. This could prove exceptionally useful as an adjunct to A1C testing and perhaps an alternative to frequent glucose monitoring to detect glycemic excursions.

Screening

The usefulness of 1,5-AG for screening populations for glycemia is less well defined. Yamanouchi et al.[21] conducted a multi-institutional study involving 1,034 Japanese including 342 with normal glucose tolerance, 232 with impaired glucose tolerance (IGT), and 460 with diabetes. 1,5-AG was highly specific (93%) and quite sensitive (84%) for the diagnosis of diabetes by World Health Organization criteria in existence at that time. This performance was superior to both A1C and FA (Fig. 4). Robertson et al.[29] demonstrated similar results in a hospital population. However, a larger community-based population study of Mauritian Chinese subjects conducted by Robertson et al.[30] was not able to confirm these results. Though there were significant differences between normal and both newly diagnosed and known diabetes subjects, the overlap between the groups was too great for the measure to be clinically useful.[30]

The utility of 1,5-AG as a screening test for diabetes and IGT has not been conclusively demonstrated. Furthermore, there is little information available regarding its performance in an ethnically and culturally diverse popula-

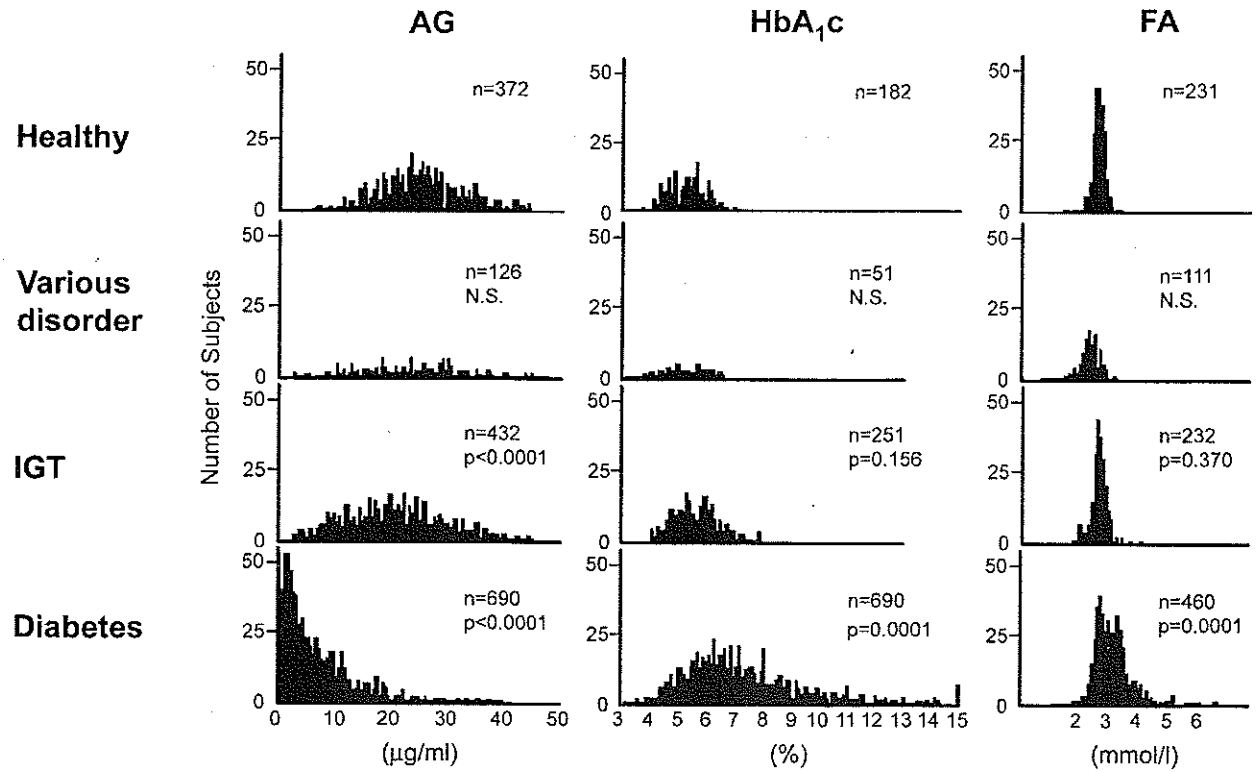

FIG. 4. Comparison of distribution of 1,5-AG, A1C, and FA in various populations. *y*-Axes give number of subjects. Significance of differences compared with healthy subjects was estimated by Scheffe's test for single subgroups. Data are from Yamanouchi et al.[21] © 1991 by the American Diabetes Association.

tion such as in the U.S. Because of the deficiencies in current glucose screening methods, studies in the United States examining the usefulness of 1,5-AG for screening should be undertaken.

Gestational diabetes screening

Tam et al.[31] evaluated the predictive value of 1,5-AG to identify pregnancies for increased risk of gestational diabetes. Results showed no significant difference in plasma 1,5-AG, implying that 1,5-AG is a poor predictor. Because of factors including considerable decrease of 1,5-AG in pregnant women around 34 weeks and the change in renal function that occurs during pregnancy, 1,5-AG does not appear to be a useful marker for gestational diabetes.[22] However, there is a tremendous need for short-term monitoring of the glycemic state in pregnancy, and the utility of 1,5-AG in this setting should be more fully explored.

COMPARISON WITH OTHER GLYCEMIC MARKERS

Measurement of glucose in various body fluids, glycohemoglobin measures such as A1C, and glycoprotein measures such as FA are currently FDA-approved methods of monitoring glycemia in the United States. Table 1 compares these two markers with 1,5-AG. The nature of A1C and FA is to respond over a slower period of time than 1,5-AG. A1C testing historically has suffered from a lack of standardization due in part to the large number of assays that are commercially available. Efforts are underway to develop new traceable standards that will allow for direct comparison of A1C assays in the near future in addition to efforts to make the values reported worldwide similar to the assay employed in the Diabetes Control and Complications Trial. Since the A1C values represent changes over the last 90 days, considerable lag times exist between actual glycemic changes and A1C response. Response of FA to changes in glucose is generally detected after approximately 2 weeks but suffers somewhat from day-to-day variability in levels.

In contrast, the combination of a large internal 1,5-AG pool to produce a stable baseline, a rapid response to increased glucose levels, and the demonstrated accuracy and reproducibility of commercial assays allows for clear analytical detection of small variations in blood glucose levels in periods of days. The direct competition between glucose and 1,5-AG in the kidney tubule throughout the day and the immediate lowering of 1,5-AG pools following elevated glucose levels provide a reflection of average glycemia over prolonged periods of time in a single measurement, and with repeated measures demonstrate changes in glucose levels over much shorter periods of time.[17] An issue with 1,5-AG that has not yet been adequately explored is the notion that in patients with more extreme levels of hyperglycemia (e.g., A1C over 10%), measurements of 1,5-AG are less sensitive to modest changes in glycemic control as a result of persistent glycosuria. Likewise, 1,5-AG will not identify episodes of hypoglycemia.

SUMMARY

Considerable data are available to suggest that 1,5-AG may be a useful marker of both overall glucose control and changes in glycemic control over periods of days. Its greatest utility may be in the form of a self-monitoring device used on a weekly basis to ensure that their overall glucose levels remain stable or improve. Increases in 1,5-AG would indicate improvement, and decreases would indicate interval worsening of glycemic control. Algorithms could be developed for patients to increase treatment or to perform more capillary glucose self-monitoring when 1,5-AG levels indicate worsening control. These techniques could reduce the burden of monitoring in stable patients and perhaps the expense. This is an exceptionally relevant issue in a time of budgetary constraints and an increasing reliance on evidence-based health care to determine what payors will reimburse.

There is little support from randomized clinical trials that self-monitoring of glucose is useful in improving average glycemic control in

TABLE 1. COMPARISON OF THREE GLYCEMIC MARKERS

	Hemoglobin A1c	*Fructosamine*	*1,5-Anhydroglucitol*
Response to high serum glucose	Glycation of hemoglobin	Protein glycation	Reabsorption competitively inhibited
Correlation with glucose level	Direct	Direct	Inverse
Reflects glucose level	Past (average past 2–3 months)	Past (average past 2–3 weeks)	Recent (1–2 days to a week)
Variance in hyperglycemia	Small	Small	Large
Largest changes observed in	Medium–high hyperglycemia	Medium–high hyperglycemia	Modest hyperglycemia–near-normoglycemia
Potential interferences	Hemolytic anemia	Serum albumin; bilirubin; daily activities	Impaired renal function, pregnancy

patients with type 2 diabetes.[32] Certainly 1,5-AG measurements could not supplant the role of current glucose monitoring techniques as safety measures in patients with type 1 diabetes at high risk of hypoglycemia and much more dynamic changes in glucose levels. FA has been somewhat disappointing as a measure of short-term glycemic control, in part because of its inherent variability through the day and in part because the time course it reflects is perhaps too long for it to function as a behavioral change aide. A1C has been exceptionally well validated as a measure of risk for complications in patients with type 1, type 2, and gestational diabetes. The availability of a short-term marker of glycemic control would certainly be a welcome addition to the tools available to monitor glycemia.

GlycoMark, a kit developed for automated measurement of venous plasma 1,5-AG in Japan, is currently being evaluated at a number of centers around the United States. Since 1,5-AG is largely derived from dietary sources and its levels are in part dependent on renal blood flow and filtration fraction, it is unknown whether assays for 1,5-AG will perform similarly in a country as ethnically and culturally diverse as the United States and in a population of people with diabetes who exhibit such variable body mass and renal function. Whether it will obtain FDA approval and whether its utility can be adequately demonstrated to health care providers are still unknown. Pending those results, development of a home-use diagnostic based on an enzymatic assay holds considerable promise based on review of the literature, though careful patient and provider education would be needed to incorporate its very different pattern of change, as compared with currently used monitoring techniques, into a management program. In clinical research studies in which short-term changes in glucose need to be evaluated, 1,5-AG assays may be useful as ancillary endpoints. As control of hyperglycemia produces a reduction in the morbidity associated with diabetes, novel techniques for monitoring glycemia to facilitate improvement are particularly needed in patients with type 2 diabetes. To this end, further exploration of 1,5-AG is clearly warranted.

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