Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol

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The growing attention to alternative glycemic biomarkers including fructosamine, glycated albumin (GA), 1,5-anhydroglucitol (1,5-AG), is attributable to the limitations of the glycated hemoglobin (HbA1c) assay. It is important to recognize the conditions in which HbA1c levels may be difficult to interpret. Serum fructosamine and GA have been proposed useful tools for monitoring of short-term glycemic control. These biomarkers not only reflect well glycemic control in hematologic disorder, but also represent postprandial glucose fluctuation. Serum 1,5-AG may be useful for estimating within-day glucose variation. Use of these nontraditional tests can be more helpful in the management of diabetes as complement traditional measures. Further larger cohort studies are warranted to determine whether nontraditional biomarkers have potential utility for early diagnosis, management of diabetes, and prevention of diabetic complications.

Keywords: Diabetes mellitus, Fructosamine, Glycosylated serum albumin, 1,5-anhydroglucitol, Biological markers

Introduction

Diabetes mellitus (DM) is a chronic metabolic syndrome exhibiting hyperglycemia. Strict glycemic control is essential for preventing the complications of diabetes. Serum glycemic biomarkers have been effective measures used to monitor glycemic control in clinical practice[1]. Traditionally, glycated hemoglobin (HbA1c) has been used as the standard measure for long-term glucose control. In addition, the role of HbA1c was further broadened as the guidelines from the American Diabetes Association[2] and the World Health Organization[3] introduced HbA1c for the diagnosis of DM in 2009.

There has been increasing interest in nontraditional glycemic markers as alternatives to HbA1c[4,5]. Because of the situations that can be reduced the validity of HbA1c test, it is important to interpret HbA1c values in various conditions. This article will review the limitations of HbA1c measurement and the current knowledge about alternative glycemic biomarkers, including fructosamine, glycated albumin (GA), and 1,5-anhydroglucitol (1,5-AG).

Limitations of HbA1c

HbA1c are influenced by red blood cells (RBC) survival. Because the average lifespan of RBC is 120 days, HbA1c reflects mean glucose levels over the preceding two to three months. Falsely elevated HbA1c in relation to a mean blood glucose concentrations can be achieved when RBC turnover is decreased, resulting in a disproportionate number of older RBC. This problem can occur in patients with iron, vitamin B12, or folate deficiency anemia. Inversely, increased RBC turnover leads to a greater proportion of younger RBC and falsely lowed HbA1c values, such

as in conditions with acute and chronic blood loss, hemolysis or pregnancy, anemia and patients treated for iron, vitamin B12, or folate deficiency, and treated with erythropoietin[6-8]. HbA1c values may be falsely high or low in those with end-stage renal disease[9].

HbA1c cannot be used as a glycemic marker in neonatal DM. During the perinatal period, fetal hemoglobin (HbF) is the main component of hemoglobin and less than 10% is hemoglobin A. HbA1c values typically are low in relation to hyperglycemia in neonatal diabetes. HbA1c is influenced by changes according to age in HbF, and does not precisely reflect glycemic control in neonate[10,11].

In addition, HbA1c levels are no accurate in reflecting short-term glycemic changes. While glycemic control changes rapidly, HbA1c changes gradually. As a result, measuring HbA1c to evaluate responses to glucose-lowering treatment in DM patients may be useful after twelve weeks[12]. In patients with fulminant type 1 DM (in which hyperglycemia rapidly occurs), HbA1c may not be a reliable indicator due to its normal or only slightly elevated levels[13].

Mean HbA1c values are associated with the development and progression of diabetic complications[14-16]. Several studies have noted the relationship between postprandial hyperglycemia and cardiovascular disease[15]. Better control of glycemic variability is one of the most important ways to prevent cardiovascular disease in diabetes. HbA1c is a measure that mainly reflects average serum glucose concentration, but it does not separately reflect postprandial hyperglycemia and fasting hyperglycemia[15,16].

Alternative biomarkers

There are several alternative biomarkers to HbA1c in use today, including fructosamine, GA, 1,5-AG, and continuous glucose monitoring, described below.

1. Fructosamine

Fructosamine is a ketoamine formed from the binding of fructose to total serum protein, mostly albumin, through glycosylation[17]. The term fructosamine includes all glycated proteins. Fructosamine assays are cheaper and easier to perform than HbA1c assays. Serum fructosamine values reflect mean blood glucose concentrations over the previous two to three weeks, which can be used clinically as markers of recent changes in glycemic control. When used in combination with other measures, it may play a role in identifying fluctuating glucose levels in DM patients with stable HbA1c. There is a good correlation between HbA1c values and serum fructosamine[18,19].

There are also several limitations to the use of serum fructosamine measurements. The higher within-subject variation for fructosamine than that for HbA1c means that frequent measurements must be conducted[20]. Serum fructosamine values must be adjusted if the serum albumin concentration is abnormal[21]. Falsely low levels in relation to mean blood glucose levels will occur with rapid albumin turnover, such as in nephrotic syndrome, severe liver disease, or protein-losing enteropathy. The level of fructosamine in young children is lower than that in adults, which is also partly due to their lower serum protein concentration[22].

2. Glycated albumin

GA is the proportion of the serum GA to the total albumin. GA is similar to serum fructosamine, except that is not affected by serum albumin levels[23]. The level of GA is approximately three times higher than that of HbA1c. Since the half-life of albumin is shorter than that of RBC, GA reflects a shorter duration, two to three weeks, of glycemic control, than that of HbA1c[24]. GA and fructosamine are strongly associated with HbA1c and fasting glucose[25-27].

1) Clinical usefulness of GA
GA has several advantages for monitoring for glucose control. The first is that it is not influenced by abnormal RBC lifespan or variant hemoglobin. GA is a particularly useful indicator of glycemic control in hematologic disorders, such as in anemia, hemorrhage, renal anemia, pregnancy, liver cirrhosis, and neonatal DM. The second advantage is that GA may be quite useful for conditions in which glycemia improves rapidly, or in which glycemia deteriorates rapidly, such as in fulminant type I DM. GA will provide a more accurate assessment of recent glycemia. Finally, when compared with HbA1c values, GA values have more correlation with postprandial glucose levels and glucose excursions[28,29]. Because the glycation speed of GA is ten times faster than HbA1c, GA is likely to reflect variations in blood glucose and postprandial hyperglycemia in combination with HbA1c and its value[30]. It has been reported that GA is related to daily glucose fluctuation[20].

2) Limitations of GA
GA has abnormal values in diseases that result in abnormal albumin metabolism. The rise of albumin metabolism leads to low GA levels in diseases including nephrotic syndrome, hyperthyroidism, glucocorticoid administration, Cushing's syndrome, and in neonates[10,31-33]. Whereas albumin metabolism decreases, high GA levels are seen in diseases such as liver cirrhosis and hypothyroidism[34].

Unlike HbA1c, GA is inversely influenced by obesity. GA tends to be lower in obese subjects with a high percentage of body fat mass[35]. In addition, GA levels in infants significantly increase with age[36]. The serum glucose levels of infants are lower than that of adults, and higher albumin metabolism is associated with lower GA levels.

3. 1,5–anhydroglucitol

The 1-deoxy form of glucose known as 1,5-AG is a naturally occurring dietary polyol. During euglycemia, serum 1,5-AG concentrations are maintained at a constant steady state due

to renal tubular reabsorption of all of the serum 1,5-AG. The normal serum concentration of 1,5-AG has been reported to be 12–40 μg/mL[37]. Serum 1,5-AG competes with very high levels of glucose for reabsorption into the kidney. Within 24 hours of a rise in serum glucose to >180 mg/dL, serum circulating 1,5-AG falls as urinary losses increase[38,39]. Lower serum 1,5-AG levels reflect high circulating glucose and the occurrence of glycosuria over the past 1 to 2 weeks[40,41]. Measurement of serum 1,5-AG may reflect postprandial glycemic excursion rather than HbA1c[42-44]. While 1,5-AG may have clinical implications for the evaluation and treatment of glycemic excursions in type 1 diabetes[45], this test is affected by alteration in renal hemodynamics.

4. Continuous glucose monitoring

Although the use of continuous glucose monitoring can accurately evaluate the glycemic variability of within-day and between-day, the current continuous glucose monitoring systems are expensive without national health insurance coverage and are not easily available in clinical practice. Furthermore, they are relatively inaccurate in the lower glucose range, and should be used in conjunction with self-monitoring of blood glucose[46].

Conclusions

The growing attention to nontraditional glycemic biomarkers is attributable to the limitations of the HbA1c assay[47-49]. It is important to recognize the conditions in which HbA1c levels may be difficult to interpret. Use of these alternative markers can be more helpful in the management of diabetes as complement standard measures. There are generally good correlations of HbA1c with serum fructosamine and GA. Fructosamine and GA have been proposed to be useful tools for monitoring short-term glycemic control. These biomarkers not only reflect well glycemic control in hematologic disorder, but also represent postprandial glucose fluctuation. Serum 1,5-AG may be useful for estimating within-day glycemic excursion. Nevertheless, there are no definitive guidelines for using alternative biomarkers as adjuncts to standard markers of glycemia, such as HbA1c, fasting glucose, or self-monitoring blood glucose measures[49]. Long-term prospective studies are still lacking. Further larger cohort studies are warranted to determine whether alternative biomarkers have potential utility for early diagnosis, management of diabetes, and prevention of diabetic complications.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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