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Invited critical review

Glycated albumin; clinical usefulness

Masafumi Koga *

Department of Internal Medicine, Kawanishi City Hospital, Hyogo, Japan

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ABSTRACT

The main purpose of treating diabetes is to prevent the onset and progression of diabetic chronic complications. Since the mechanism of onset of chronic complications is still not well understood, the main strategy to achieve this purpose is to bring plasma glucose levels as close as possible to those in healthy subjects and maintain good glycemic control over the long term. Since glycation among various proteins is increased in diabetic patients compared with non-diabetic subjects, glycated protein can be used as a glycemic control indicator. Currently, among these glycated proteins, HbA1c is used as the gold standard of glycemic control indicators. However, HbA1c does not accurately reflect the actual status of glycemic control in some conditions with rapid changes in glycemic control and in patients with anemia (hemolytic anemia, iron deficiency anemia, etc.) and variant hemoglobin. In comparison, glycated albumin (GA) more accurately reflects changes in plasma glucose during the short term and postprandial plasma glucose. GA also reflects glycemic control in patients with hematologic disorders whereas GA does not reflect glycemic control in patients with disorder of albumin metabolism. GA is a glycemic control indicator which overcomes most of the disadvantages of HbA1c, and could be therefore expected to replace HbA1c as the standard glycemic control indicator in the near future. However, it is necessary to accumulate more evidences from large research studies on the effective directions for measuring GA.

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1. Introduction

In clinical practice of diabetes mellitus, HbA1c is widely used as the gold standard of glycemic control indicators [1]. This indicator has

* Tel.: +81 72 794 2321; fax: +81 72 794 6321.
E-mail address: m-koga@kawanishi-city-hospital.com.

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made it possible to select a method for treating diabetes mellitus and to evaluate its appropriateness. In addition, large-scale clinical trials and studies such as the Diabetes Control and Complications Trial (DCCT) and U.K. Prospective Diabetes Study (UKPDS) have demonstrated that the onset and progression of diabetic microangiopathy are correlated with HbA1c [2,3]. Therefore, it is possible to delay the onset and progression of diabetic microangiopathy by achieving excellent glycemic control by using HbA1c as an indicator. In the past, diabetes mellitus had been diagnosed by fasting plasma glucose, randomly measured plasma glucose, or plasma glucose after oral glucose tolerance test. However, the American Diabetes Association (ADA) introduced HbA1c for the diagnosis of diabetes mellitus in 2009 for such reasons as: (1) The HbA1c assay has several advantages over laboratory measures of glucose; (2) Diabetes should be diagnosed when HbA1c is >6.5%. A repeat HbA1c test should be done for conformation in asymptomatic patient; (3) if HbA1c testing is not available, previously recommended diagnostic methods remain acceptable [4].

However, HbA1c is known to have several disadvantages (Table 1). HbA1c reflects glycemic status during a relatively long period (past 1 to 2 months), and does not reflect glycemic control accurately under conditions with rapid changes in glycemic control. In addition, it is known that in hematologic disorders such as anemia and variant hemoglobin, abnormal HbA1c levels are observed. Glycated albumin (GA), on the other hand, reflects short-term glycemic control and is not influenced by hematologic disorders. Under these conditions, it is necessary to judge glycemic control by GA or another glycemic control marker (fructosamine). HbA1c mainly reflects mean plasma glucose, but hardly reflects postprandial plasma glucose or glycemic excursion which contributes to the development and progression of diabetic macroangiopathy. HbA1c is related to macroangiopathy as shown in the DCCT/EDIC study [5], but the sensitivity is lower than for diabetic microangiopathy for that reason. On the other hand, it has recently become clear that GA reflects postprandial plasma glucose and glycemic excursion as well as mean plasma glucose. This review summarizes the usefulness of GA in clinical practice of diabetes mellitus.

2. Hematologic disorders

There are a large number of hematologic disorders with abnormal HbA1c levels including hemolytic anemia and variant hemoglobin (Table 1). Conditions such as pregnancy and neonates/infants, which are seemingly not hematologic disorders, are included in this category, because pregnant women often complicate with iron deficiency and composition of hemoglobin in neonate/infant is different from adult. These main disorders are outlined below.

Table 1
Conditions with possible inaccurate HbA1c levels.

Conditions with abnormally high HbA1c levels
Rapid improvement of glycemic control
Iron deficiency anemia
Pregnancy
Variant hemoglobin[a]
Conditions with abnormally low HbA1c levels
Rapid deterioration of glycemic control
Diseases with shortened lifespan of red blood cells
Hemolytic anemia, hemorrhage, liver cirrhosis
Chronic kidney disease (renal anemia)
During treatment of iron deficiency anemia
Variant hemoglobin[a]
Neonates[b], neonatal diabetes mellitus[b]
Hereditary persistence of fetal hemoglobin (HPFH)[b]

[a] HbA1c in majority of variant hemoglobin majority shows low value, but HbA1c shows high value in a small number of variant hemoglobin. HbA1c in majority of variant hemoglobin can be measured correctly depending on the model of HPLC [29,30].
[b] HbA1c can be measured in whose HbF is 30% or less depending on the model of HPLC [30].

2.1. Hemolytic anemia

Hemolytic anemia is one of the representative diseases with low HbA1c levels. Anemia occurs as a result of the destruction of red blood cells due to various etiologies [6,7]. In order to compensate for anemia, synthesis of red blood cells increases, and the lifespan of red blood cells is shortened. As a result, HbA1c levels decrease. HbA1c in patients with hemolytic anemia is influenced by plasma glucose as well as anemia. Low HbA1c levels are also observed in hemolytic patients without anemia because of compensation by increased synthesis of red blood cells [8]. It was shown that GA, on the other hand, accurately reflects glycemic control in hemolytic anemia because GA is not influenced by the lifespan of red blood cells [9].

2.2. Iron deficiency anemia

It is known that low HbA1c levels are observed in most types of anemia but that high HbA1c levels are observed in iron deficiency anemia [10,11]. We found that high HbA1c levels are observed not only in iron deficiency anemia but also in iron deficiency without anemia [12]. Iron deficiency anemia is the most frequent type of anemia; more than half of premenopausal women are in a state of iron deficiency. It has become clear that apparently high HbA1c levels are observed in such women because of iron deficiency [13]. On the other hand, if iron deficiency anemia is treated with iron preparations, synthesis of red blood cells increases, and the lifespan of red blood cells is shortened; therefore, HbA1c temporarily decreases and then returns to the former level. Because GA is not influenced by these factors, it can be used to evaluate glycemic control in patients with iron deficiency anemia [13,14].

2.3. Pregnancy

GA has been recommended for a long time as a glycemic control indicator during pregnancy since it reflects plasma glucose during a shorter period than HbA1c. Although HbA1c is known to increase from the middle to the end of pregnancy [15,16], the cause was unknown for a long time. Because the demand for iron increases at the end of pregnancy, most women at the end of pregnancy become iron deficient; based on this finding, we demonstrated that increased HbA1c at the end of pregnancy is caused by iron deficiency [17,18]. According to a report by the Japan Glycated Albumin Study Group of the Japanese Society of Diabetes and Pregnancy, the frequencies of neonatal complications (neonatal hypoglycemia, polycythemia, and respiratory disorder) and large for dates (LFD) babies were significantly higher in the group whose GA value at the end of pregnancy was 15.8% or higher compared with those of the group whose GA value was less than 15.8% [19]. On the other hand, no significant relationship was observed between HbA1c and the frequency of maternal and neonatal complications. One of the causes of this phenomenon is considered to be apparently high HbA1c levels at the end of pregnancy due to the state of iron deficiency. Based on these results, the Japanese Society of Diabetes and Pregnancy strongly recommended that GA measurement is useful for the prevention of perinatal complications in mothers and fetus/infants [19].

2.4. Liver cirrhosis (chronic liver disease)

In liver cirrhosis, apparently low HbA1c levels are observed because of the shortened lifespan of red blood cells associated with hypersplenism [20]. On the other hand, apparently high GA levels are observed because of the prolonged lifespan of albumin associated with impaired albumin synthesis [21]. Therefore, neither HbA1c nor GA can be used alone as a glycemic control indicator. When we calculated HbA1c estimated from diurnal variations in plasma glucose in patients with chronic liver disease including liver cirrhosis, measured