Clinical impact of glycated albumin as another glycemic control marker

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Abstract. It is known that glycation among various proteins is increased in diabetic patients compared with non-diabetic subjects. Currently, among these glycated proteins, glycated hemoglobin (HbA₁C) is used as the gold standard index of glycemic control in clinical practice for diabetes treatment. However, HbA₁C does not accurately reflect the actual status of glycemic control in some conditions where plasma glucose changes during short term, and in patients who have diseases such as anemia and variant hemoglobin. In comparison, another index of glycemic control, glycated albumin (GA), more accurately reflects changes in plasma glucose during short term and also postprandial plasma glucose. Although GA is not influenced by disorders of hemoglobin metabolism, it is affected by disorders of albumin metabolism. This review summarizes diseases and pathological conditions where GA measurement is useful. These include the status of glycemic control changes during short term, diseases which cause postprandial hyperglycemia, iron deficiency anemia, pregnancy, chronic liver disease (liver cirrhosis), chronic renal failure (diabetic nephropathy), and variant hemoglobin.

Key words: Glycated albumin, Glycated hemoglobin (HbA₁C), Postprandial hyperglycemia, Iron deficiency anemia, Chronic liver disease
1. Change in Short-term Glycemic Control Status

Since the half-life of serum albumin is shorter than that of erythrocytes, GA changes rapidly in cases where the status of glycemic control changes during short term [6, 14]. Intensive insulin therapy was performed as the initial treatment in 8 patients with type 2 diabetes mellitus with poor glycemic control (Fig. 2) [15]. There was only a mild decrease in averaged HbA1c from 10.9% to 10.0%, while averaged GA decreased markedly from 35.6% to 25.0%. The changes of HbA1c and GA during 2 weeks were -0.9% and -10.6%, respectively, and the decrease of GA was as an index of glycemic control.
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approximately 10 times greater than that of HbA1C. When glycemic control changes shortly due to the start or change of diabetes treatment, GA is a more suitable index of glycemic control than HbA1C.

On the other hand, GA increases prior to HbA1C when glycemic control status worsens during short term. Therefore in such conditions, GA allows the worsening of glycemic control to be detected at an earlier stage. It is known that HbA1C remains normal or only mildly elevated at the diagnosis of fulminant type 1 diabetes mellitus in which pancreatic β cells are rapidly destroyed, resulting in an increase in plasma glucose and ketoacidosis in the very short term [16]. We examined HbA1C and GA at diagnosis in patients with fulminant type 1 diabetes mellitus. Although there was a significant positive correlation between HbA1C and GA, its regression line was shifted upper compared with patients with untreated type 2 diabetes mellitus (Fig. 3A). Namely, due to the increase of plasma glucose during very short term, the extent of the elevation of GA is suggested to be larger than that of HbA1C at the diagnosis of fulminant type 1 diabetes mellitus. As a result, the GA/HbA1C ratio was significantly higher in patients with fulminant type 1 diabetes mellitus at diagnosis than those with untreated type 2 diabetes mellitus (Fig. 3B). When a GA/HbA1C ratio
≥3.2 is regarded as a cutoff value, the sensitivity and specificity of differentiating fulminant type 1 diabetes mellitus at diagnosis from untreated type 2 diabetes mellitus were 97% and 98%, respectively. Therefore, we suggested that a high GA/HbA<sub>1c</sub> ratio is helpful for diagnosing fulminant type 1 diabetes mellitus [17].

2. Postprandial Hyperglycemia

A number of epidemiological studies have shown that postload hyperglycemia becomes a risk factor for cardiovascular diseases. The DECODE study [18] or Funagata study [19] revealed that postload plasma glucose in the glucose tolerance test is a more potent risk factor for cardiovascular events than fasting plasma glucose. Furthermore, it has been reported that administration of the α glucosidase inhibitor acarbose to patients with impaired glucose tolerance or diabetes mellitus was associated with cardiovascular risk reduction (STOP-NIDDM trial) [20, 21].

HbA<sub>1c</sub> is considered primarily to be an index which reflects the mean plasma glucose levels. On the other hand, there have been recently several reports suggesting that GA is an index which more strongly reflects postprandial plasma glucose rather than mean plasma glucose. The GA/HbA<sub>1c</sub> ratio in patients with type 1 diabetes mellitus was shown to be significantly higher than in patients with type 2 diabetes mellitus [22]. In general, plasma glucose fluctuates over a greater range in patients with type 1 diabetes mellitus compared with patients with type 2 diabetes mellitus. In view of this phenomenon, in patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus who show no difference in HbA<sub>1c</sub> value, the GA value is significantly higher in the former. The authors speculated that GA may more strongly reflect postprandial plasma glucose and range of plasma glucose fluctuations than HbA<sub>1c</sub>.

When relationship between HbA<sub>1c</sub> and GA was examined in patients with type 2 diabetes mellitus, GA/HbA<sub>1c</sub> ratio was found to be significantly higher in patients receiving insulin treatment than in patients receiving diet therapy or oral hypoglycemic drugs [23]. Insulin secretion determined by the homeostasis model assessment pancreatic β–cell function (HOMA-%β) was significantly lower in the patients receiving insulin treatment than that in the patients not receiving insulin treatment. There was a significant inverse correlation in GA/HbA<sub>1c</sub> ratio and HOMA-%β (Fig. 4), reflecting decreased endogenous insulin secretion is involved in increased value of the GA/HbA<sub>1c</sub> ratio. Combining the results that maximum plasma glucose is involved in the GA/HbA<sub>1c</sub> ratio in patients with type 1 diabetes mellitus [22], it is suggested that a decrease in the insulin secretion increases the glycemic excursion, causing increase of the GA/HbA<sub>1c</sub> ratio.

Recently, plasma glucose levels throughout the day can be measured by means of the continuous glucose monitor (CGM) system. A study on the relationship between the CGM system data and the index of glycemic control was reported. Among the patients with diabetes mellitus showing poor glycemic control, GA indicated a more potent relationship with differences of plasma glucose levels and plasma glucose fluctuation index than HbA<sub>1c</sub> and 1,5-anhydroglucitol (1,5-AG) [24].

In gastrectomized subjects, oral glucose tolerance test often shows marked hyperglycemia (oxyhyperglycemia) 30 to 60 min after glucose loading. We showed that in non-diabetic subjects who underwent gastrectomy, GA and HbA<sub>1c</sub> were both higher than in controls but the GA/HbA<sub>1c</sub> ratio was also significantly higher. Namely, the extent of increase of GA was greater than that of HbA<sub>1c</sub> in the gastrectomized subjects, thus better reflecting postprandial hyperglycemia [25].

The reasons why serum GA reflects postprandial hyperglycemia better than HbA<sub>1c</sub> are unknown. The shortened lifespan of erythrocytes in diabetic patients with poor glucose control [26], lagging GLUT1-
mediated glucose uptake by erythrocyte resulting in a relatively lower degree of rise in HbA1c [27], different glycation rates between albumin and hemoglobin [28] and a direct effect of insulin and oral hypoglycemic agents on serum albumin metabolism [29] may be involved. These mechanisms need to be clarified in future studies.

If GA presents relatively higher values than HbA1c in patients associated with postprandial hyperglycemia, it may be more appropriate to measure GA as an index of glycemic control in patients with diabetes mellitus. Recently, it has been revealed that GA is an index that predicts the development of coronary artery disease (CAD) as well as its severity [30, 31]. The relationship between GA and diabetic vascular complications will be further investigated.

3. Anemia (Hemolytic Anemia, Iron Deficiency Anemia, Iron Deficiency Status, Treatment by Iron Preparations)

It is well known that HbA1c presents lower values in relation to glycemia in patients with hemolytic anemia, because lifespan of erythrocytes is shortened in these patients [7]. Meanwhile, patients with iron deficiency anemia conversely presents higher HbA1c values relative to plasma glucose levels [32, 33]. We found that HbA1c also shows higher levels in relation to glycemia even in iron deficient state without anemia [34]. Iron deficiency anemia is the most frequently seen anemia. Since approximately one half of premenopausal women are in iron deficient status, a great number of premenopausal women present high HbA1c values relative to plasma glucose levels [33, 35]. On the other hand, when patients with iron deficiency anemia are treated with iron supplements, HbA1c transiently decreases because lifespan of erythrocytes shortens [36, 37]. In contrast, GA is not influenced by these conditions, and thus GA is a preferable index of glycemic control in premenopausal women who frequently suffer from iron deficiency anemia (Fig. 5) [37].

4. Pregnancy

In pregnant women displaying diabetes mellitus and those with gestational diabetes, intensive glycemic control during pregnancy is needed to lower the risk of intrauterine fetal death, fetal growth disorders and maternal complications [38, 39].

Phelps et al. [40] showed biphasic changes in HbA1c levels during pregnancy, with HbA1c levels lowest at gestational week 24. A longitudinal study also demonstrated similar biphasic changes in HbA1c levels [41]. One of the reasons why HbA1c decreases from the first trimester to the second trimester of pregnancy is considered to be the decrease in plasma glucose levels, although the reason why HbA1c increases from the second trimester to the third trimester is unknown. Sanaka, et al. [42] reported the phenomenon that HbA1c increases from the second trimester to the third trimester in non-diabetic cases, whereas GA does not change much during this period. Based on this result, it was suggested that HbA1c show high values independent of plasma glucose levels from the second trimester to the third trimester during pregnancy. It is known that iron demand is increased and iron deficiency often occurs in the third trimester of pregnancy. Our investigations in non-diabetic pregnant women demonstrated that HbA1c increased from the second trimester to the third trimester of pregnancy while GA did not show any significant change. Mean corpuscular hemoglobin (MCH), transferring saturation, and serum ferritin decreased from the second trimester to the third trimester of pregnancy, and thus most women became iron...
deficient in the third trimester. Since HbA1c showed significant inverse correlations with these values, it was concluded that the increase of HbA1c in the third trimester of pregnancy was caused by iron deficiency [43]. In our further investigations of pregnant women with diabetes mellitus, HbA1c increased and transferrin saturation and serum ferritin decreased from the second trimester to the third trimester of pregnancy, while GA showed no significant change (Fig. 6). Since HbA1c again showed a significant inverse correlation with transferrin saturation, it was concluded that HbA1c increases due to iron deficiency in the third trimester also in pregnant women with diabetes mellitus [44]. These findings suggest that HbA1c is not an appropriate index of glycemic control during pregnancy. Meanwhile, GA is not affected by iron deficiency and has the advantage of reflecting the short-term status of glycemic control, and is thus considered to be a preferable index of glycemic control during pregnancy.

Since the threshold of reabsorption of glucose decreases in renal tubules resulting in renal glycosuria during pregnancy, serum 1,5-AG indicates a low value [45, 46]. Therefore, serum 1,5-AG is inadequate as an index of glycemic control during pregnancy.

5. Chronic Liver Diseases (Liver Cirrhosis)

Since liver is a pivotal organ regulating plasma glucose levels, glucose metabolic abnormalities occur frequently in patients with chronic liver diseases (CLD), such as chronic hepatitis and liver cirrhosis. In patients with CLD, about 70-90% are diagnosed as impaired glucose tolerance and 30-60% of them as diabetes mellitus [47]. It is important to maintain a good glycemic control status because CLD patients with poor glycemic control have been shown to offer poor prognosis [48].

HbA1c has been shown to be apparently lower in relation to glycemia due to shortened half-life of erythrocytes [49] originating from hypersplenism in CLD patients. On the contrary, GA and fructosamine levels are apparently higher in relation to glycemia in these patients due to prolonged half-life of serum albumin originating from reduced capacities of albumin synthesis in vivo [50, 51]. Similarly, it has been reported that serum 1,5-AG levels do not reflect glycemic control state accurately in CLD patients [52]. Taken together, it was difficult to monitor glycemic control status accurately in CLD patients, because none of the
Clinical impact of glycated albumin values relative to glycemia in CLD patients, the GA/HbA1C ratio is set higher in these patients. We revealed that although there was a significant positive correlation between HbA1C and GA in CLD patients, its regression line was shifted higher in comparison with that in patients with type 2 diabetes mellitus (Fig. 7A). There was no correlation between GA/HbA1C ratio with mean plasma glucose, while there were significantly inverse correlations with hepaplastin test (HPT), cholinesterase and platelet count, which are indices of hepatic function (Fig. 7B). These results showed that GA/HbA1C ratio reflects the hepatic function independently of plasma glucose levels [55].

Therefore, simultaneous measurement of HbA1C and GA can give the glycemic control index CLD-HbA1C as well as the hepatic function index GA/HbA1C ratio in CLD patients (Fig. 8).

We investigated the relationship between plasma glucose levels and glycemic control markers in CLD patients [51]. In comparison with HbA1C estimated from the mean plasma glucose levels [53], measured HbA1C showed lower values and GA/3 (GA indicates approximately 3 times the value of HbA1C, thus the HbA1C value can be predicted from GA/3) showed higher values in CLD patients. The discrepancy between HbA1C or GA/3 and estimated HbA1C increased when hepatic function decreased. Instead, CLD-HbA1C calculated as the mean of HbA1C and GA/3 was found closely matched with HbA1C estimated from the mean plasma glucose levels. Therefore, CLD-HbA1C was shown to be useful as an index of glycemic control in CLD patients [54].

Since HbA1C shows lower and GA shows higher values relative to glycemia in CLD patients, the GA/HbA1C ratio is set higher in these patients. We revealed that although there was a significant positive correlation between HbA1C and GA in CLD patients, its regression line was shifted higher in comparison with that in patients with type 2 diabetes mellitus (Fig. 7A). There was no correlation between GA/HbA1C ratio with mean plasma glucose, while there were significantly inverse correlations with hepaplastin test (HPT), cholinesterase and platelet count, which are indices of hepatic function (Fig. 7B). These results showed that GA/HbA1C ratio reflects the hepatic function independently of plasma glucose levels [55]. Therefore, simultaneous measurement of HbA1C and GA can give the glycemic control index CLD-HbA1C as well as the hepatic function index GA/HbA1C ratio in CLD patients (Fig. 8).
6. Chronic Renal Failure (Diabetic Nephropathy)

In patients with chronic renal failure, HbA1c shows lower values in relation to glycemia due to renal anemia. Furthermore, when erythropoietin is administered to patients with renal anemia, HbA1c shows even lower values because lifespan of erythrocytes is shortened [56, 57]. Meanwhile, it has been reported that GA is a useful index of glycemic control in hemodialysis patients with diabetes because GA is not affected by renal anemia [56-58]. Additionally, in the examination of patients with diabetes mellitus receiving peritoneal dialysis, it was shown that GA reflects properly the status of glycemic control whereas HbA1c does not [59]. In contrast, in patients with diabetic nephropathy (stage III or IV) presenting marked proteinuria, it should be noted that GA shows a lower value relative to plasma glucose levels as a result of the increased turnover of albumin metabolism.

Observations of 98 hemodialysis patients with diabetes mellitus for 11 years indicated that the prognosis in the group with a GA value ≥29.0% at the start of hemodialysis was significantly poorer than that in the group with a GA value <29.0% [60]. These results show that glycemic control status in hemodialysis patients with diabetes is also involved in their prognosis, and that glycemic control status should be judged by GA, not by HbA1c.

7. Variant Hemoglobin

Conventionally, abnormal hemoglobin has been found through other symptoms such as anemia and cyanosis. In HbA1c analysis by the high-performance liquid chromatography (HPLC) method, the substituted glycated products of variant hemoglobin by amino acids are eluted in a different position from HbA1c, and a number of asymptomatic variant hemoglobins have been found recently by abnormal peaks and abnormal HbA1c values on HPLC charts [9]. When variant hemoglobin is suspected, HbA1c measurement by an immunological approach is considered to be useful. However, since some variant hemoglobins include unstable hemoglobin and hemoglobin with increased or decreased glycation, these cases affect HbA1c values measured by the immunological approach. Thus, the HbA1c value does not necessarily reflect the glycemic control status [9]. Since variant hemoglobin affects HbA1c measurements through various mechanisms, the glycemic control status should be determined by using GA in patients with variant hemoglobin [61].

8. Disorders of Albumin Metabolism

Although GA is not influenced by anemia and variant hemoglobin, it is influenced in patients with disorders of albumin metabolism [62]. GA shows lower values in relation to glycemia in patients with nephrotic syndrome, hyperthyroidism [63], and glucocorticoid administration in which albumin metabolism increases. Meanwhile, GA presents higher values relative to plasma glucose levels in patients with liver cirrhosis [51, 54] and hypothyroidism [63] in which albumin metabolism decreases.

Moreover, in obese subjects GA values were found to set lower in relation to glycemia [64-66]. It is known that chronic micro-inflammation is evoked by inflammatory cytokines (adipocytokine) secreted from adipocytes in obese subjects [67], and there was a significant positive correlation between BMI and high-sensitive C-reactive protein as well. Furthermore, we found a significant inverse correlation between high-sensitive C-reactive protein and GA [66]. Based on these results, we propose the theory that chronic micro-inflammation increases albumin catabolism in obese subjects [68], and as a result of the shortened half life of albumin, GA decreases relative to plasma glucose levels [66]. Indeed, it has been shown that GA was set lower in relation to plasma glucose levels in smokers, hyperuricemic patients, hypertriglyceridemia and men with nonalcoholic fatty liver disease (NAFLD) with high alanine aminotransferase (ALT) levels in whom chronic inflammation is evoked [69-72].

9. Use of HbA1c and GA Measurement to Diagnose Diabetes Mellitus

Measurements of HbA1c have not been world-wide ly standardized. By the measurement standardized by Japan Diabetes Society (JDS), HbA1c levels are shown to set approximately 0.4% lower compared with those standardized by National Glycated Hemoglobin Standard Program (NGSP) [73]. Thus, GA/HbA1c ratio based upon the measurement standardized by JDS is approximately 3.0, whereas GA/HbA1c ratio based upon the measurement standardized by NGSP is approximately 2.8.
Recently, HbA1c has been introduced as a test to diagnose diabetes mellitus [74]. It is reasoned by that the laboratory measure that captures long-term glycemic exposure can provide a better marker for the presence and severity of the disease than single measures of plasma glucose concentration. However, there are some conditions leading to spurious HbA1c results, as shown above. Clinicians should be aware of these conditions, particularly in populations in which they are more prevalent.

It is unknown whether or not serum GA is useful for the diagnosis of diabetes mellitus. In addition, the most appropriate cut-off point of serum GA for the diagnosis of diabetes mellitus is not clear. Further analyses should be necessary to prove which of HbA1c and GA is a better index of the diagnosis of diabetes mellitus.

### Table 2  Diseases and pathologic conditions for which GA measurements are recommended

1. At rapid improvement or aggravation of glycemic control status
2. At onset of fulminant type 1 diabetes mellitus
3. Type 1 diabetes mellitus
4. Type 2 diabetes mellitus under insulin therapy
5. Patients with marked postprandial hyperglycemia (e.g., gastrectomy)
6. Patients treated with drugs targeting postprandial hyperglycemia
7. Hemolytic anemia, hemorrhage, blood transfusion, etc.
8. Variant hemoglobin
9. Chronic renal failure (in particular, receiving hemodialysis)
10. Liver cirrhosis (calculation of CLD-HbA1c)
11. Iron deficiency anemia, iron deficiency status
12. Treatment phase of iron deficiency anemia
13. Pregnant women, premenopausal women

### 10. Conclusion

HbA1c is not always an ideal index of glycemic control, and it does not accurately reflect the status of plasma glucose control in various pathological conditions. The diseases and pathological conditions in which GA rather than HbA1c better reflects glycemic control status are shown in Table 2.

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### References

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