Review Article



# A proposed glycemic control marker for the future: glycated albumin

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**Abstract:** The goal of treatment of diabetes is to prevent the onset and the progression of chronic diabetic complications. Since the mechanism of the onset of the chronic complications is still not well understood, the main strategy is to bring the patient's glycemic control status as close as possible to that of healthy subjects and to keep good glycemic control over the long term. Glycated protein can be used as a glycemic control indicator, and currently, HbA1c is used as the gold standard. HbA1c reflects the average glycemic value over approximately three months. However, HbA1c is affected by red blood cell (RBC) turnover, and HbA1c does not provide a measure of plasma glucose fluctuation or hypoglycemia. Glycated albumin (GA) assay is albumin specific measurement different form fructosamine, which can change due to a fluctuation of other serum proteins concentrations. GA reflects the glycemic control status for about the previous two to three weeks because of the half-life of albumin. GA is likely to reflect the plasma glucose fluctuation, whereas GA is also influenced by albumin metabolism including obesity. Here, we focused on GA as a biomarker for hyperglycemia.

**Keywords:** Diabetes; HbA1c; glycated albumin (GA); complication; pregnancy

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## Introduction

HbA1c reflects average glycemia over approximately three months, and clinical significance for the prevention of complications has been established through large-scale clinical trials, including the Diabetes Control and Complications Trial (DCCT) (1) and the United Kingdom Prospective Diabetes Study (UKPDS) (2). Additionally, HbA1c was used as a diagnostic criterion for diabetes by the International Expert Committee (3), the American Diabetes Association (ADA) (4), and the World Health Organization (WHO) (5). However, in the ADA standards of Medical Care in Diabetes 2017 statement described that, when using HbA1c to diagnose diabetes, it is important to recognize that HbA1c is an indirect measure of average plasma glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, including age, race, ethnicity, and anemia, variant hemoglobin (6). Furthermore, HbA1c does not reflect glycemic variability or hypoglycemia.

In Japan, HbA1c and glycated albumin (GA) are mainly used as glycemic control markers (7). Since, the lifespan of an erythrocyte is around four months, HbA1c reflects the average glycemic control status of previous two to three months. By contrast, since the half-life of albumin is around 17 days, GA reflects that of around previous two to three weeks (8). It is reported that GA is useful for patients with short-term changes in glycemic control, or in patients with anemia or on dialysis, in whom HbA1c values are inaccurate (9-12). Moreover, GA values have more of a correlation with postprandial plasma glucose levels compared with HbA1c. But, the GA prognostic significance is not as clear as for HbA1c, and, the GA level would be affected by any

change in albumin metabolism.

Here, we focused on the biomarkers of hyperglycemia, especially on the basic medicine of GA and the role of glycemic markers in pregnant women and dialysis patients.

## Differences between HbA1c, fructosamine and GA

HbA1c and GA are both glycemic control markers, but there are many differences not only reflecting the glycemic change period but also its distribution and glycation sites. HbA1c is defined as the stable adduct of glucose to the N-terminal valine of the β-chain of hemoglobin (13). Since hemoglobin localizes in red blood cells (RBC), the amount of HbA1c is proportional to the glucose concentration and the life span of RBC. It is known that glucose transport across the RBC membrane is complete within seconds (14), but it has identified inter-individual heterogeneity in glucose gradients across RBC membranes (15).

On the other hand, GA is defined as albumin containing lysine residues bound to glucose (16). Since, GA localizes throughout the whole body, including the blood, interstitial fluid, lymph, and cerebrospinal fluid, the amount of GA is proportional to the glucose concentration in the whole body and the half-life of albumin. Since GA is not related to hemoglobin metabolism, it is possible to be an important glycemic control marker in patients with diabetes and diverse comorbidities.

It was known that GA changes more quickly than HbA1c because of the half-life of albumin is shorter than the life span of erythrocyte. In addition, it was also reported that GA changes more markedly than HbA1c. Mo *et al.* reported that a 1% increase in HbA1c was associated with a 2.84% increase in GA involving 953 participants without known diabetes (17). It would be based on the differences of the glycation reaction between the N-terminal valine of the β-chain of hemoglobin and lysine residues of albumin, including the number of glycation sites, and the reaction speed of each of the glycation sites. It was reported that albumin has multiple glycation sites, and glucose becomes attached to Lys-199, Lys-281, Lys-439, and Lys-525, as well as to some other lysine residues (18). A recent study using the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) analysis has shown that *in vitro* glycation rates differ for each amino group in human serum albumin. Specifically, the glycation rates at Lys-199, Lys-439, Lys-525, and the N- terminal amino acid are faster than at other glycation sites (19). Glycation rate have also been reported for hemoglobin, too (20). Ueda *et al.* reported that the glycation speed was approximately 4.5 times faster for GA than HbA1c (21).

Cohen *et al.* developed an index for the glycation gap (GG), a measure of the disparity between intracellular in RBCs, HbA1c, and the extracellular, glycated serum protein (GSP) measured as fructosamine. GG is calculated as "measured HbA1c-predicted HbA1c by fructosamine". They reported that in longstanding type 1 diabetes, there is a greater than two-fold increase in the prevalence of nephropathy in patients with high GG (22). GG is also a predictor of retinopathy (23). Moreover, inter-individual heterogeneity in the erythrocyte transmembrane glucose gradient might explain the discordance between HbA1c and fructosamine (15). A case cohort study of DCCT/EDIC (24) and an Atherosclerosis Risk in Communities (ARIC) Study (25) revealed reported that HbA1c and GA were independently associated with diabetic complications.

For the differences between GA and fructosamine, since, albumin is the major component of serum protein (around 60–70%), fructosamine is mainly measured GA, although other serum proteins such as glycated lipoproteins and glycated globulins may affected the concentration of fructosamine. Rodriguez-Segade *et al.* reported that the fructosamine is significantly influenced by the immunoglobulin levels, in particular IgA (26).

Various methods have been available to measure fructosamine, remains poorly standardized. The assays are rapid, inexpensive, and available for automation, but affected by changes in ambient temperature, and reducing material including bilirubin and vitamin due to due to the technical nature of assay. Moreover, fructosamine has few clinical evidences. The enzymatic GA assay is also better standardized and less affected by preanalytical variables than fructosamine (27).

In summary, HbA1c is a long-term intracellular glycemic control marker in RBCs, and GA is an intermediate extracellular marker. They are different and independent biomarkers for micro and macrovascular complications. As to available evidence, the overall diagnostic efficiency of GA seems superior to that of fructosamine.

## End stage of renal diseases (ESRD)

### *Glycemic control marker for hemodialysis patients with diabetes*

Diabetes is the leading cause of chronic kidney disease (CKD). According to a report issued by the ADA, HbA1c has limitations in the general population and is even less

 

precise in the setting of diabetic kidney disease (DKD); erythrocyte lifespan become shorter as eGFR falls, which results in lower HbA1c. However, GA is less affected by low eGFR or other confounding conditions (28).

There were many reports that HbA1c levels significantly underestimated glycemic control in hemodialysis patients with diabetes. Inaba *et al.* reported that HbA1c underestimated the glycemic control status in Japanese hemodialysis patients with diabetes due to the increase of young erythrocytes by the use of erythropoietin (11). Conversely, GA was a better assay to estimate glycemic control after comparing with the mean blood glucose (MBG), HbA1c, and GA. Similar results were shown in a U.S. study with 307 hemodialysis patients with diabetes (12).

Important results related to survival and the hospitalizations of hemodialysis patients with diabetes from a prospective study followed 444 patients for up to 2.33 years were reported by Freedman *et al.* (29). According to their results, "Unadjusted analyses paradoxically revealed lower death with high HbA1c, while the negative effect disappeared after adjustment for demographic characteristics. In contrast to the HbA1c and random plasma glucose values, GA accurately predicts the risk of death and hospitalizations in hemodialysis patients with diabetes". Similar results had been obtained in a study that reported that GA measurement could predict cardiovascular hospitalization (30). Moreover, Inaba *et al.* reported that, on the analysis of the hemodialysis patients without history of cardiovascular events, the survival was significantly longer in GA <20.0% group than GA 20.0% to 24.5% group or >24.5% group (31). An analysis of a national prospective cohort study in the United States (CHOIS Study) revealed that GA was a risk factor for mortality and morbidity in hemodialysis patients (32).

Based on these evidences, the Japanese Society for Dialysis Therapy published the "Guide: Best Practice for Diabetic Patients on Hemodialysis 2012" (33). The Guide stated the targets for glycemic control, showed that the glycemic control of dialysis patients with diabetes should be measured by GA, and stipulated that HbA1c should be used as a reference. GA levels <20.0% were suggested as tentative targets for glycemic control in patients without a history of cardiovascular events. For patients with a history of cardiovascular events, however, GA levels <24.0% were suggested. For all hemodialysis patients with diabetes, the GA level should be monitored once a month. For hemodialysis patients without diabetes, plasma glucose and GA levels should be monitored at least once a year.

Therefore, in hemodialysis patients, GA is considered to more accurately reflect glycemic control than HbA1c and will be able to predict the prognosis of hemodialysis patients.

### *Glycemic control marker for pre-dialysis patients with diabetes*

In pre-dialysis patients with diabetes, although falsely low HbA1c values caused by renal anemia and erythropoiesis stimulating agent (ESA) administration, GA values can also be falsely low due to hypoproteinemia with proteinuria, therefore both HbA1c and GA do not reflect plasma glucose accurately. For that reason, the glycemic control status cannot be accurately determined based on both the HbA1c and GA in pre-dialysis patients with diabetes.

The risks of cardiovascular events become higher with the progression of renal failure, and patients with advanced nephropathy can frequently develop a cardiovascular event (34). Therefore, more efforts should be made for suppression of cardiovascular events in the higher extent of advanced nephropathy. However, there is no evidence indicating that strict glycemic control improves cardiovascular events or the prognosis in patients with stage 4 nephropathy. The results may be because the analyses were conducted based on HbA1c as a glycemic control marker. On the other hand, albumin metabolism may be facilitated in patients with proteinuria, and GA also does not accurately reflect glycemic control status in those with stage 4 nephropathy. Consequently, analyses with GA cannot be expected to obtain significant results.

We considered that a glycemic control marker that accurately reflects plasma glucose could be obtained by adjustment of GA with some factor in patients with stage 4 nephropathy. Hypoalbuminemia can be observed with proteinuria; hypermetabolism of the albumin may be correlated with proteinuria or serum albumin. Therefore, GA adjusted by urinary protein or serum albumin concentration may accurately reflect plasma glucose. Since quantitative urinary protein measurement has not always been measured, we investigated whether GA adjusted by serum albumin may be useful as a glycemic control marker (35).

In patients with stage 4 nephropathy (eGFR <30 mL/min/1.73 $m^2$), plasma glucose was measured 7 times a day (before and after each meal and before bed) to calculate estimated HbA1c or GA values based on the obtained MBG levels. Measured HbA1c levels were significantly lower than the estimated HbA1c. The measured HbA1c values had no

 

significant correlation with hemoglobin, while a significant negative correlation of the estimated HbA1c values with hemoglobin was observed. From the findings above, patients with HbA1c values equal to or lower than the target value may be aimlessly followed without reinforcement of treatment for diabetes because glycemic control has also been determined based on the HbA1c values in patients with stage 4 nephropathy. No significant correlation was observed between the measured and estimated HbA1c values. Since, a significant positive correlation between the measured HbA1c/estimated HbA1c and hemoglobin was observed that it assumed that the progression of anemia affected the measured HbA1c levels.

Although a significant positive correlation was observed between the measured and estimated GA values, the regression line was shifted lower than the line of equivalence. It was shown that a significant correlation between the measured GA/estimated GA and serum albumin resulted in a larger discrepancy between them with a decrease in serum albumin. Then, a formula for computation of adjusted GA based on a regression equation for serum albumin and GA was found [adjusted GA = GA ×19.2/(4.32× serum albumin +4.81)]. A significant correlation between the adjusted and estimated GA values was observed, and a regression equation was found that was approximate to the line of equivalence. No significant correlation was indicated between the adjusted GA/estimated GA and serum albumin (35).

Moreover, adjusted GA was not affected by serum albumin and showed significant correlations with various markers of glycemic fluctuation (36). Those results suggest that strict glycemic control with adjusted GA as a glycemic control marker may improve suppression of cardiovascular events and the prognosis in patients with stage 4 nephropathy. Yajima *et al.* investigated the relationship of glycemic control markers with the prognosis in diabetic patients with a relatively short duration of dialysis (37). HbA1c and GA values were not significant indices of the prognosis, while the adjusted GA was a significant index of the prognosis. The result may be because self-urination was observed after introduction of dialysis with abnormalities in albumin metabolism due to proteinuria.

## Pregnancy

The diabetic population has currently been increasing in the world (38), and this tendency is no exception in women of child-bearing age. Furthermore, the report of the Hyperglycemia and Adverse Pregnancy Outcomes Study indicated strong and continuous associations of maternal plasma glucose levels below the diabetic level with increased birth weight (39). In Japan, the frequency of gestational diabetes mellitus (GDM) was increased 4.1 times from 2.92% to 12.08% that may be affected by changes in the diagnostic criteria for GDM (40). Peripartum maternal and fetal complications can be suppressed with favorable glycemic control by finding any abnormalities in the maternal glycemic metabolism status early during pregnancy (41,42). Based on a report of the meta-analyses of 20 studies, the relative risk of development of postpartum type 2 diabetes in patients with GDM was 7.43 times higher than in pregnant women with normal glucose tolerance (43), and maternal follow-up after delivery was important, too. In addition, concepts of developmental origins of health and diseases have been proposed in recent years (44), and the long-term effects on the fetuses of mothers with abnormal glucose tolerance after birth have been discussed. For the reasons above, appropriate maternal glycemic control during pregnancy is an important issue not only to protect maternal and fetal health but also the subsequent health of mothers and the next generation. Glycemic control markers for the management of pregnant women with abnormal glycemic metabolism are described below.

As for a report many years ago, Phelps *et al.* reported changes in HbA1c values during pregnancy in 377 non-diabetic pregnant women and shown that HbA1c values were lowest at the 24$^{th}$ week of gestation with two-phase changes (45). Similarly, in a report by the Japanese Society of Diabetes and Pregnancy (JSDP) (46), analyses of 574 normal pregnant women showed that HbA1c values became lower during the second trimester of the pregnancy and then higher during the third trimester, and GA values tended to be gradually decreased over the third trimester. Given the report, the reference ranges for HbA1c and GA values in Japanese normal pregnant women were 4.4% to 5.7% and 11.5% to 15.7%, respectively. It is certain that discrepancies between in the changes of HbA1c and GA values were observed during pregnancy; an issue of which value should be believed as a glycemic control marker has been raised. It has been shown that HbA1c values were lower in most conditions with anemia but higher with iron deficiency anemia (47,48). We found that HbA1c values might become higher not only in iron deficiency anemia but also in latent iron deficiency (49,50). HbA1c levels were significantly increased from the second trimester through the third trimester but not GA levels. All of the mean

 

corpuscular hemoglobin (MCH), transferrin saturation (%Tf), and serum ferritin that reflect the iron deficiency were decreased over the third trimester with significant negative correlations of HbA1clevels. From the findings above, it was shown that HbA1c values were increased with the progression of the iron deficiency during the third trimester in normal pregnant women. Therefore, it was shown that HbA1c could have issues for reliability as a glycemic control marker during pregnancy, particularly in the third trimester. However, HbA1c values might not be increased from the second to third trimesters without the iron deficiency by adequate iron intake during pregnancy.

As expected, glycemic control is important for pregnant women with diabetes and GDM, and detailed changes in HbA1c and GA values have also been reported by an Investigation Review Committee for Glycated Albumin by the JSDP (51). Based on that report, HbA1c values became lower during the second trimester and then higher during the third trimester in 193 pregnant women with diabetes and GDM similar to normal pregnant women. In the meantime, GA values decreased with gestational age. Such changes were comparable to those in normal pregnant women, and discrepancies in the changes were observed between the glycemic control markers. For that reason, we conducted a similar study in 11 pregnant women with diabetes, as well as 6 pregnant women with GDM, and revealed that HbA1c values significantly increased from the second trimester ($20^{th}$ to $23^{rd}$ weeks) through the third trimester ($32^{nd}$ to $35^{th}$ weeks) similar to normal pregnant women, while GA values showed no significant changes (52). Since, all of MCH, %Tf, and serum ferritin values decreased during the third trimester with a significant positive correlation between the %Tf and the ratio of GA to HbA1c (GA/HbA1c), the iron deficiency was aggravated, and HbA1c values increased during the third trimester. Moreover, we performed continuous glucose monitoring (CGM) to compare HbA1c and GA values to MBG obtained by CGM in pregnant women with diabetes; HbA1c had no correlation with MBG, while a significant correlation was observed between GA and MBG (53). A significant negative correlation of HbA1c/MBG-estimated HbA1c with MCH was observed, which suggested that HbA1c values might be falsely high due to the effects of the iron deficiency during pregnancy. On the other hand, it was shown that GA values were similar to the MBG-estimated GA levels and reflected the glycemic control status accurately during pregnancy.

The Japan Glycated Albumin Study Group of the JSDP has also studied the relationships of neonatal complications and birth weight with HbA1c and GA values (49). With analyses given HbA1c of 5.7% and GA of 15.7% as the upper limits of normal range, frequencies of neonatal complication showed higher tendency of neonatal complications in the incidence of polycythaemia (P=0.094) and heavy-for-date (P=0.071) in the GA ≥15.8% group, no significant increase in the frequency was observed in a group with HbA1c ≥5.8%.

Sugawara *et al.* retrospectively investigated 42 Japanese diabetic mothers and their infants and reported that GA levels of mothers were significantly higher in infants with hypoglycemia, respiratory disorders, hypocalcemia, myocardial hypertrophy, and large-for-date status (54). On the other hand, considering hypoglycemia, HbA1c was not significantly different between the two groups.

According to the reports above, it was shown that the effects of iron deficiency on HbA1c values were significant in pregnant women compared to non-pregnant women. The reason is that the iron deficiency may develop after hemorrhage during menstruation, and HbA1c is affected by shortened RBC survival with hemorrhage in non-pregnant women, while pregnant women may develop the iron deficiency because of the increased demand for iron without hemorrhage, and the effects of the iron deficiency on HbA1c can therefore be greater (55).

## Reference range for GA and diabetes screening and diagnosis

### *Reference range for GA*

*Table 1* summarized the reference range for GA at around 11% to 16% and did not find any differences among race and ethnicity, except for African American. In the Japanese population, the Committee on the Standardization of Laboratory Testing related to Diabetes Mellitus of the Japan Diabetes Society reported that the reference range for GA in the Japanese population selected as a reference population by oral glucose tolerance test (OGTT) was 12.3% to 16.9% (n=699) (56). In the Chinese population, the reference range for GA has been reported as 10.8% to 17.1% (n=380) (57).

In the American population, we reported that the reference range for GA was determined as 11.9% to 15.8% (mean =18.83%, n=201, SD =0.96), and race between black and white persons impacted the assay results (58). Selvin *et al.* reported that the differences between black and white persons in GA, fructosamine, and 1,5-anhydroglucitol

 

**Table 1** Summary for the reference range study

| No. | Country | Reference range (%) | Number | Age | Reference |
|---|---|---|---|---|---|
| 1 | Japan | 12.3–16.9 | 699 | 23–91 | Tominaga 2006 |
| 2 | China | 10.8–17.1 | 380 | 20–69 | Zhou 2009 |
| 3 | USA | 11.9–15.8 | 201 | – | Kohzuma 2011 |
| 4 | USA | 10.7–15.1 | 1,799 | Mean 55 | Selvin 2018 |
| 5 | Europe | 9.0–16.0 | 252 | 17–92 | Testa 2017 |
| 6 | Italy | 11.7–16.9 | 32 | – | Paroni 2007 |

levels parallel that in HbA1c (59). For black individuals, a systematic and larger study is needed to determine their reference range. Selvin *et al.* also reported that in a healthy reference population of 1,799 individuals (mean age 55 years, 51% female, 15% black), the 2.5$^{th}$ and 97.5$^{th}$ percentiles, respectively, were, 10.7% and 15.1% for GA (60).

For a normal European population of 252 subjects [age range from 17 to 92 years (median age 56); sex ratio: 167/85 females/males], the preliminary reference value for GA% was 9.0% (90% CI, 8.7% to 9.5%) to 16.0% (90% CI, 15.6% to 16.4%) (61). In the Italian population, the normal group of GA ranged from 11.7% to 16.9% (n=32) (62).

In summary, the reference interval for GA in the Japanese, Chinese, American, and European populations are almost the same. For black individuals, an additional study is needed to determine their reference range separately.

### *Screening and diagnosis of diabetes*

OGTT measurement is a standard in the diagnosis of diabetes and pre-diabetes, but the method is not widely used because of its complexity and poor reproducibility. The International Expert Committee (3), the ADA (4), and the WHO (5) proposed the use of HbA1c to diagnose diabetes and pre-diabetes at a threshold of 6.5% (48 mmol/mol) and 5.7%, respectively. This threshold was developed as a HbA1c levels associated with a higher prevalence of diabetic retinopathy (DR) (63,64).

In the Japanese population, Mukai *et al.* reported that they studied 2,681 subjects aged 40–79 years, and the prevalence of DR increased sharply above the ninth decile for GA (16.2% to 17.5%) (65). The ROC analysis revealed that the optimal thresholds for DR were 17.0% for GA. The sensitivity and specificity of these thresholds for GA were 86.5%, and 89.0%, respectively. Parrinello *et al.* in an analysis of 12,306 persons (958 with diabetes) in the ARIC Study found an independent association of GA with retinopathy (66). DR increased sharply above the ninth decile for HbA1c [6.4% to 15.9% (46–150 mmol/mol)], and for GA (15.2% to 51.5%). In the ARIC study, Juraschek *et al.* also reported that GA was significantly associated with diabetes risk [hazard ratio (HR) 5.22 (2.49–10.94)] (67). For the Chinese population, Ma *et al.* also reported the GA cutoff to diagnose diabetes using OGTT (68). These data suggested that GA was independently associated with retinopathy and could be a tool for the screening and diagnosis of diabetes.

The cutoff value to diagnose diabetes was also studied. For the Japanese population (1,575 subjects, aged 26–78 years), the threshold for GA that best predicted diabetes was 15.5% with a sensitivity of 83.3% and a specificity of 83.3% (69). For the cutoff of GA, many results were reported from Japan (70), Korea (71,72), Taiwan (73,74), and China (75) (*Table 2*).

In addition, for prediabetes in African-Americans, Sumner *et al.* reported that detection of prediabetes, the sensitivities of HbA1c (threshold =5.7% (39 mmol/mol) and GA (threshold =13.77) were similar in non-obese immigrants (37% *vs.* 42%, P=0.75), and the sensitivity of the combined HbA1c and GA was better than that of HbA1c alone (72% *vs.* 37%, P=0.01) (76). GA contributes by identifying prediabetes not detected by HbA1c in non-obese African immigrants.

*Table 1* summarized data of the GA reference range and the cutoff values for detecting and screening diabetes. These data revealed that the diagnostic cut-point for GA could be useful in identifying persons with hyperglycemia in settings where fasting glucose or HbA1c is not available.

## Relationship with diabetes complications and biomarkers of hyperglycemia

A large study showed that strict glycemic control could suppress the development or progression to diabetic

 

**Table 2** GA Threshold, sensitivity and specificity for diagnose and screening of diabetes

| No. | Country/region | Threshold (%) | Sensitivity (%) | Specificity (%) | n | Reference | Definition |
|---|---|---|---|---|---|---|---|
| Diagnose diabetes (GA only) | | | | | | | |
| 1 | Japan | 17.0 | 86.5 | 89.0 | 2,618 | Mukai 2014 | Retinopathy |
| 2 | China | 17.1 | 76.8 | 76.8 | 1,971 | Ma 2010 | OGTT |
| Screening of newly diagnosed diabetes | | | | | | | |
| 3 | Japan | 15.5 | 83.3 | 83.3 | 1,575 | Furusyo 2013 | FPG + HbA1c |
| 4 | Japan | 15.2 | 62.1 | 61.9 | 980 | Ikezaki 2015 | OGTT |
| 5 | Korea | 14.7 | 66.4 | 88.3 | 852 | Hwang 2014 | OGTT |
| 6 | Korea | 15.6 | 95.1 | 97.5 | 265 | Park 2016 | – |
| 7 | Taiwan | 14.9 | 78.5 | 80.0 | 2,192 | Hsu 2015 | FPG + HbA1c |
| 8 | Taiwan | 15.0 | 74.0 | 85.0 | 1,559 | Wu 2016 | OGTT |
| 9 | China | 15.7 | 73.3 | 80.1 | 1,211 | Yang 2012 | OGTT |

GA, glycated albumin; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose.

microvascular complications in patients without any diabetic complications and those with mild diabetic complications (1,2). Since it has been reported, targeting HbA1c and maintaining the value as low as possible became a standard treatment in the suppression of the development of or progression to diabetic complications. Subsequently, since GA has been increasingly used as a glycemic control marker, studies have come to be performed to examine whether GA might predict diabetic complications.

There are some epidemiological reports supporting the use of not only HbA1c but also GA as a good marker of glycemic control based on clinical outcomes. For microvascular complications, a case cohort study of DCCT/EDIC (24) revealed that HbA1c and GA had similar associations with retinopathy and nephropathy, which were strengthened when both measures were considered together.

The ARIC study is a prospective cohort originally of 15,792 persons from US communities. Selvin *et al.*, measured GA, fructosamine, and HbA1c in 11,104 participants with and without diabetes of ARIC study, and evaluated the associations of these biomarkers of hyperglycemia with the risk of coronary heart disease, ischemic stroke, heart failure, and mortality. GA was significantly associated with the outcomes with strong associations in persons with diabetes, and these associations were similar to those observed for HbA1c (77). Recently they reported that these glycemic markers were associated with incident peripheral artery disease (PAD), and an especially a strong association with PAD and critical limb ischemia (CLI) in ARIC participants (78).

Many epidemiological studies have come to show that development of and progression to diabetic macroangiopathy may be more associated with hyperglycemia after a glucose load than MBG. Large studies, such as the DECODE and Funagata studies showed that post-load plasma glucose in an OGTT might be a stronger risk factor for cardiovascular events compared to fasting plasma glucose (79,80). HbA1c has been considered a marker that primarily reflects MBG values but not really postprandial plasma glucose. Therefore, although there is substantial evidence for a relationship with diabetic microvascular complications, evidence for diabetic macroangiopathy (arteriosclerosis) has been limited. On the other hand, GA has recently been reported to reflect postprandial plasma glucose as well as mean plasma glucose values one after another. It has been shown that the GA/HbA1c of patients with type 1 diabetes were significantly higher than that with type 2 diabetes (81). The study revealed that GA might better reflect postprandial plasma glucose levels and the amplitude of glycemic fluctuation compared to HbA1c. In patients with type 1 diabetes, the plasma glucose levels are generally unstable with greater amplitude of glycemic fluctuation. For that reason, GA levels in patients with type 1 diabetes were significantly higher than HbA1c values comparing with type 2 diabetes. According to our results, the GA/HbA1c were shown to be significantly higher in patients treated with insulin compared to those on diet therapy or treated

 

with oral hypoglycemic drugs (82). The insulin secretory function was significantly impaired in patients treated with insulin compared to those without insulin; HOMA-%β, an insulin secretory function index, showed a significant negative correlation with the GA/HbA1c. The findings above suggested that glycemic fluctuation caused by the impairment of insulin secretory function may lead to higher GA/HbA1c. Recently, similar results have been reported, and supported our speculation (83-86).

Plasma glucose measurements have come to be feasible using a CGM system. According to a study in diabetic patients with poor glycemic control status, GA was a marker with a stronger relationship to the glycemic fluctuation compared to HbA1c and 1,5-AG (87).

Postprandial hyperglycemia has been shown to be closely associated with the development of diabetic complications, especially for retinopathy (88). From such a viewpoint, it is interesting to note whether a diabetic complication related to postprandial hyperglycemia is more closely associated with GA compared to HbA1c. We investigated cross-sectional studies; no significant difference in HbA1c values was observed between the presence and absence of DR, while GA values were significantly higher in the DR group. Moreover, GA was shown to be a significant explanatory variable for DR by multivariate analysis (89). Pu *et al.* showed that GA values could be an index for predicting the onset and severity of a coronary artery disease (CAD) (90). In the meantime, no significant differences in HbA1c values were observed between the CAD and non-CAD groups. Recently, Song *et al.* performed a longitudinal study with follow-up for 1.5 to 2 years regarding changes in increased intima-media thickness (IMT) in patients with type 2 diabetes. As a result, it was shown that HbA1c was not a significant factor in the increase in IMT, and GA was the significant factor (91).

In a Japanese study (n=1,575) without diabetes, GA was associated with IMT (69). The appearance of evidence from a prospective study indicating that GA might be a more useful glycemic control index as an index for prognostic factors of diabetic macroangiopathy compared to HbA1c could be expected in the future.

Although diabetes conventionally had a poor prognosis due to frequent complications above, the progress of treatment for diabetes has decreased the frequency of diabetic complications and led to improvements in the prognosis. With longevity in diabetic patients, new complications that had not been known have developed. New complications that have attracted attention include dementia and cancer. In this article, we focus on dementia for an explanation.

In recent years, the development of dementia has rapidly increased, and Alzheimer's disease mainly accounts for the conditions (92). The onset of diabetes has also increased in recent years; research from the Hisayama study showed that diabetes and impaired glucose tolerance might be significant risk factors in Alzheimer's disease (92). Mean amplitude of glycemic excursion (MAGE), which is a glycemic fluctuation index obtained by CGM, had a significant negative correlation with cognitive function, and the relationship of glycemic fluctuation with dementia was therefore suggested (93). All subjects underwent a glucose tolerance test for medical checkups in Hisayama study; the factor that was significantly responsible for Alzheimer's disease was two-hour post-load plasma glucose but not fasting plasma glucose (92). Furthermore, the significant factor responsible for the extent of hippocampal atrophy on MRI scan (94) and senile plaque of the brain indicating amyloid beta deposition observed during autopsy (95) was also two-hour post-load plasma glucose but not fasting glucose. The findings above suggested the association of a glycemic control markers that reflected the glycemic fluctuation. The analysis results of the Hisayama study have been reported for glycemic control markers and the onset of Alzheimer's disease (96). In a five-year prospective study, follow-up was performed in 1,187 residents aged at least 65 years without dementia for an average of 4.8 years; 116 residents developed Alzheimer's disease. The incidence of Alzheimer's disease had a significant positive relationship with the GA/HbA1c (P for trend: <0.01), and a weak positive relationship with the GA levels (P for trend: 0.06), but no apparent relationship with HbA1c and 1,5-anhydroglucitol levels was observed. Even after multivariate adjustment with other risk factors, a significant positive relationship of the GA/HbA1c with the onset of Alzheimer's disease was observed (P for trend: 0.01). Those results showed that Alzheimer's disease was more associated with the glycemic fluctuation (postprandial hyperglycemia) than mean plasma glucose. Prevention for onset and suppression of the progression of diabetic complications that target glycemic fluctuation may become important issues in the future.

## Conclusions

The utility of GA is now gaining popularity as an intermediate glycemic control marker in the monthly management of diabetes and diabetes-associated pathologies,

 

such as hemolytic anemia, hemoglobinopathy, ESRD, and iron deficiency, as well as pregnancy. Moreover, there are many studies regarding the reference range of GA that also develop cutoff values to diagnose diabetes and screen diabetes using GA. In conclusion, GA appears to have potential as a glycation index in diagnosing and screening diabetes, guiding parameters after intensified medication, evaluating glycemic control status especially for patients with ESRD and pregnant women, and as a predictor of diabetic complications.

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## Footnote

*Conflicts of Interest:* T Kohzuma is an employee of Asahi Kasei Pharma, Tokyo, Japan. The authors have no other conflicts of interest to declare.

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