Possible discrepancy of HbA1c values and its assessment among patients with chronic renal failure, hemodialysis and other diseases

Kaori Inoue1,3 • Atsushi Goto2,3 • Miyako Kishimoto1 • Tetsuro Tsujimoto1 • Ritsuko Yamamoto-Honda1 • Hiroshi Noto1 • Hiroshi Kajio1 • Yasuo Terauchi3 • Mitsuhiko Noda2

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Abstract

Background Glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. However, these markers are influenced by alterations in hemoglobin and albumin metabolism. Thus, conditions such as anemia, chronic renal failure, hypersplenism, chronic liver diseases, hyperthyroidism, hypoalbuminemia, and pregnancy need to be considered when interpreting HbA1c or GA values. Using data from patients with normal albumin and hemoglobin metabolism, we previously established a linear regression equation describing the GA value versus the HbA1c value to calculate an extrapolated HbA1c (eHbA1c) value for the accurate evaluation of glycemic control. In this study, we investigated the difference between the measured HbA1c and the eHbA1c values for patients with various conditions.

Methods Data sets for a total of 2461 occasions were obtained from 731 patients whose HbA1c and GA values were simultaneously measured. We excluded patients with missing data or changeable HbA1c levels, and patients who had received transfusions or steroids within the previous 3 months. Finally, we included 44 patients with chronic renal failure (CRF), 10 patients who were undergoing hemodialysis (HD), 7 patients with hematological malignancies and a hemoglobin level of less than 10 g/dL (HM), and 12 patients with chronic liver diseases (CLD).

Results In all the groups, the eHbA1c values were significantly higher than the measured HbA1c values. The median difference was 0.75 % (95 % CI 0.40–1.10 %, P for the difference is <0.001) in the CRF group, 0.80 % (95 % CI 0.30–1.65 %, P for the difference is 0.041) in the HD group, 0.90 % (95 % CI 0.90–1.30 %, P for the difference is 0.028) in the HM group, and 0.85 % (95 % CI 0.40–1.50 %, P for the difference is 0.009) in the CLD group.

Conclusions We found that the measured HbA1c values were lower than the eHbA1c values in each of the groups.

Keywords Glycated hemoglobin • Glycated albumin • Chronic renal failure

Introduction

Glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. HbA1c is used as the gold standard index of glycemic control in clinical practice for diabetes treatment [1]. Since the lifespan of erythrocytes is approximately 120 days, HbA1c reflects the plasma glucose levels over the past few months. The metabolic turnover of albumin is faster than hemoglobin, with a lifespan of approximately 17–23 days. Accordingly, GA is used as an index of short-term glycemic control [2].

Although these glycemic control markers are well correlated with blood glucose levels, HbA1c is influenced by alterations in hemoglobin metabolism and GA is influenced by alterations in albumin metabolism. In clinical practice,
conditions such as anemia, chronic renal failure, hyper-
splenism, chronic liver diseases, hyperthyroidism, hypoal-
buminemia, and pregnancy need to be considered when 
interpreting HbA1c or GA values.

In a previous study, we developed a linear regression 
equation describing the GA value versus the HbA1c value 
among participants without altered albumin metabolism or 
hemoglobin metabolism, to calculate an extrapolated 
HbA1c (eHbA1c) value for the accurate evaluation of 
glycemic control [3].

We often encounter patients with conditions affecting 
the turnover of either HbA1c or GA. In such patients, the 
measured HbA1c and GA values are likely to diverge from 
the equation. Earlier studies have evaluated the associ- 
ations between mean blood glucose levels, HbA1c val-
ues, and GA values in patients on dialysis or patients with 
chronic liver diseases or hemolytic anemia [4–6]. How-
ever, the impact of each condition affecting the turnover of 
either HbA1c or GA on the direction and magnitude of the 
discrepancy between the measured HbA1c and eHbA1c, 
which is the equation developed in patients who were free 
of such conditions is not well understood. In this study, we 
investigated the differences between the measured HbA1c 
and the eHbA1c values in patients with various conditions.

Materials and methods

A flow diagram depicting this study is shown in Fig. 1. We 
retrospectively analyzed the medical charts of patients at-
tending the National Center for Global Health and Medi-
cine (Tokyo, Japan) during 2011, and selected data sets for 
a total of 2461 occasions from 731 patients (including non-
diabetes patients) whose HbA1c and GA values were si-
multaneously measured. If these values were measured in 
a single patient on more than one occasion, we selected the 
data set containing the smallest HbA1c value.

We excluded patients whose previous HbA1c values 
were missing or whose HbA1c levels were changeable and 
selected 550 patients. We then excluded patients without 
albumin, hemoglobin or eGFR data, and patients who had 
been treated with transfusions or steroids within the pre-
vious 3 months. Finally, we included 44 predialysis pa-
ients with an eGFR of less than 30 mL/min/1.73 m^2 
proteinuria and require erythropoietin or iron preparations.

In our previous study, we established the following 
equation: eHbA1c = 0.216 × GA + 2.978 [3]. Figure 2 
shows scatter plots for the HbA1c values versus the GA 
values for each group with a line for the equation.

In all the groups, the eHbA1c values (i.e., the line for the 
equation in Fig. 2) tended to be higher than the measured 
HbA1c levels. We further analyzed the medians of the 
differences between the eHbA1c and measured HbA1c 
values, and calculated the corresponding 95 % CI and 
P values for each group (Table 2). In all the groups, the
eHbA1c values were significantly higher than the measured HbA1c levels. The median of the difference was 0.75 % (95 % CI 0.40–1.10 %, \( P \) for the difference is <0.001) in the CRF group, 0.80 % (95 % CI 0.30–1.65 %, \( P \) for the difference is 0.041) in the HD group, 0.90 % (95 % CI 0.90–1.30 %, \( P \) for the difference is 0.028) in the HM group, 0.85 % (95 % CI 0.40–1.50 %, \( P \) for the difference is 0.009) in the CLD group.

**Discussion**

In this study, we calculated the eHbA1c value using an equation for each of the several groups of patients suffering from various diseases, and investigated the difference from the measured HbA1c values. Few studies have investigated the difference between estimated values and actual measurements of HbA1c.

The patients were classified into 4 groups as follows: 44 patients with chronic renal failure, 10 patients undergoing hemodialysis, 7 patients suffering from hematological malignancies and who had a hemoglobin level of less than 10 g/dL, and 12 patients who were suffering from chronic liver diseases. In all of the groups, the eHbA1c values were significantly higher than the measured HbA1c values. These results suggested that the measured HbA1c values in these groups may be underestimated in clinical practice.

In cases with chronic renal failure, renal anemia lowers the HbA1c values because the lifespan of the erythrocytes is shortened. The HbA1c and eGFR values are reportedly correlated with the lifespan of the erythrocytes in patients with diabetic nephropathy [8]. It has also been reported that the values of HbA1c are underestimated in patients with diabetic nephropathy undergoing peritoneal dialysis or hemodialysis [9]. Furthermore, the HbA1c values in patients who were treated with erythropoietin were lower than those patients who were not treated, since the life span of the erythrocytes is shortened [10]. Because renal anemia is unlikely to affect the GA value, GA may be useful in patients with renal anemia. Although HbA1c has been commonly measured, several professional societies (e.g., the Japanese Society for Dialysis Therapy [11]) now recommend GA measurements for such patients. Our findings further suggest that eHbA1c may be a useful marker for the
evaluation of glycemic control in patients with CRF or HD. However, a careful consideration is required in patients with diabetic nephropathy with marked proteinuria. The GA values are affected by the increased turnover of albumin metabolism and tend to decrease independent of glycemic state in patients with marked proteinuria [12], indicating their possible limited ability to evaluate glycemic control in such patients. Because the number of patients with marked proteinuria was relatively small in the present study, further studies are needed to clarify whether eHbA1c or GA is more useful than HbA1c in such patients.

In this study, we investigated 7 patients who were suffering from hematological malignancies and who had a hemoglobin level of less than 10 g/dL. Both the measured HbA1c and the eHbA1c levels in the HM group were lower than those in the other groups. The lower frequency of patients with diabetes in the HM group may explain the lower GA and eHbA1c levels. HbA1c values are known to be low, relative to the glucose levels in patients with hemolytic anemia because the lifespan of the erythrocytes is shortened in patients with this condition [6]. Moreover, in patients with iron deficiency anemia, the HbA1c values tend to be higher than in healthy individuals but decrease after iron treatment [13]. Although the mechanisms remain to be investigated, the altered lifespan of erythrocytes may partially explain the difference between the measured HbA1c and eHbA1c levels in the HM group observed in this study.

In chronic liver diseases, such as chronic hepatitis and liver cirrhosis, hypersplenism lowers the HbA1c values because of the shortened lifespan of the erythrocytes.

| Table 1 | Clinical characteristics in each groups |
|---------|---------------------------------------|
| Predialysis with an eGFR <30 mL/min/1.73 m² (n = 44) | Hemodialysis (n = 10) | Hematological malignancies and Hb <10 g/dL (n = 7) | Chronic liver diseases (n = 12) |
| Men (n) | 35 | 8 | 5 | 6 |
| Age (years) | 66.8 ± 12.0 | 67.8 ± 11.7 | 69.3 ± 18.2 | 71.5 ± 10.3 |
| HbA1c (%) | 6.8 ± 1.3 | 6.4 ± 0.9 | 5.7 ± 0.5 | 7.1 ± 0.8 |
| GA (%) | 20.8 ± 5.7 | 19.7 ± 4.5 | 16.1 ± 2.0 | 22.9 ± 4.4 |
| Hb (g/dL) | 11.3 ± 1.8 | 10.9 ± 1.6 | 8.7 ± 0.8 | 12.1 ± 1.6 |
| Alb (g/dL) | 3.7 ± 0.5 | 3.6 ± 0.9 | 2.9 ± 0.7 | 3.7 ± 0.4 |
| eHbA1c (%) | 7.5 ± 1.2 | 7.3 ± 1.0 | 6.4 ± 0.4 | 7.9 ± 1.0 |
| cGFR (mL/min/1.73 m²) | 16.6 ± 7.8 | – | 123.3 ± 104.1 | 69.0 ± 14.4 |
| Diabetes (n) | 43 | 9 | 2 | 11 |
| Urinary protein3+ (n) | 13 | 4 | 0 | 0 |
| Using erythropoietin (n) | 19 | 6 | 0 | 0 |
| Using iron preparation (n) | 7 | 2 | 0 | 1 |

Table 2 The medians of the difference between eHbA1c and measured HbA1c values in each group

| The median of the difference between eHbA1c and measured HbA1c values (%) | 95 % CI | P values |
|---------------------------------------------------------------------------|--------|---------|
| Predialysis with an eGFR <30 mL/min/1.73 m² (n = 44)                       | 0.75   | 0.40–1.10 | <0.001 |
| Hemodialysis (n = 10)                                                     | 0.80   | 0.30–1.65 | 0.041 |
| Hematological malignancies and Hb <10 g/dL (n = 7)                        | 0.90   | 0.90–1.30 | 0.028 |
| Chronic liver diseases (n = 12)                                           | 0.85   | 0.40–1.50 | 0.009 |

![Fig. 2 Scatter plots for HbA1c values versus GA values in each group.](image)

In our previous study, we established the following equation: eHbA1c = 0.216 × GA + 2.978. Scatter plots for the HbA1c values versus the GA values are shown for each group with a line for the equation. In all the groups, the eHbA1c values tended to be higher values than the measured HbA1c levels.

![Image with equation: eHbA1c = 0.216 × GA + 2.978](image)
whereas, it raises the GA values because of reduced albumin synthesis and the prolonged half-life of serum albumin [5, 14]. Although neither marker reflects the plasma glucose control status accurately, we found the eHbA1c values were significantly higher than the measured HbA1c values in the CLD group.

Our study had several limitations. First, we retrospectively selected patients in whom simultaneous HbA1c and GA measurements had been obtained. Thus, a selection bias may exist. We excluded the patients, whose previous HbA1c values were missing or their HbA1c levels were changeable, but we couldn’t exclude the patients who had become good control over past few weeks. Second, as the data were collected from a single hospital and the GA values were not standardized, the present results might not be directly applicable to other hospitals. Third, the small sample size might limit the applicability of the findings. In clinical situation, patients with various conditions affect the GA values, so we should take consideration to use the equation of the eHbA1c.

In conclusion, we found that the measured HbA1c values were lower than the eHbA1c values in groups of patients with chronic renal failure, who were undergoing hemodialysis, suffering from hematological malignancies and had a hemoglobin level of less than 10 g/dL, and who had chronic liver diseases.

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Conflict of interest None of the authors have any potential conflicts of interest associated with this research.

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