ORIGINAL

Indicators for blood glucose control in diabetics with end-stage chronic renal disease : GHb vs. glycated albumin (GA)

Keiko Chujo, Kenji Shima, Hiroaki Tada, Teruyo Oohashi, Jun Minakuchi, and Syu Kawashima

Kawashima Hospital, Tokushima, Japan

Abstract : Diabetics with end-stage renal disease (ESRD) exhibit abnormal life span of erythrocytes, and thus, HbAlc is not necessarily a good indicator for blood glucose control. The present study was conducted to reaffirm this point and determine whether glycated albumin (GA) can be used instead of HbAlc.

The following three groups of patients with diabetes served as subjects : 49 predialysis patients with ESRD (predialysis group), 37 patients with ESRD on dialysis (dialysis group), and 40 patients without nephropathy (non-dialysis group). The profile set mean blood glucose was calculated by measuring blood glucose levels seven times a day. The relationship of profile set mean blood glucose with HbAlc and GA levels was then investigated.

Corrected HbAlc levels were calculated by applying the profile set mean blood glucose of each ESRD patient to the regression formula for the HbAlc of non-dialysis patients. The actual and corrected HbAlc levels for the predialysis patients were 5.4±1.1 and 7.9± 1.1%, respectively, while those for the dialysis patients were 5.6±1.0 and 7.5±0.9%, respectively ($p<0.0001$). The changes in GA levels in relation to the blood glucose control in the dialysis patients matched those in non-dialysis patients.

HbAlc levels for diabetics with ESRD were lower than indicated by their blood glucose control. When assessing blood glucose control based solely on HbAlc, erroneous results may be obtained. In such cases, GA may be used instead of HbAlc. J. Med. Invest. 53:223-228, August, 2006

Keywords **:** *glycohemoglobin, glycated albumin, hemodialysis, daily profile of blood glucose, life span of erythrocyte*

INTRODUCTION

Glycohemoglobin (HbAlc) is most often used as an intermediate indicator for blood glucose control in diabetics, and the Diabetes Control and Complications Trial (DCCT) (1), United Kingdom Prospective Diabetes Study (UKPDS) (2) and Kumamoto Study (3) have greatly valued HbAlc as an indicator for blood glucose control.

However, HbAlc levels are influenced by other factors in addition to blood glucose. Of these other factors, the life span of erythrocytes is particularly important. Therefore, it appears reasonable to assume that HbAlc levels fluctuate in patients with chronic renal failure, particularly those on hemodialysis (4, 5), because the life span of erythro-

Received for publication December 22, 2005; accepted February 28, 2006.

Address correspondence and reprint requests to Kenji Shima, Kawashima Hospital, 1-39 Kitasako Ichiban-cho, Tokushima 770-0011, Japan and Fax : +81-88-631-5500

cytes changes due to periodic blood sampling, residual blood in the dialysis circuit, mechanical hemolysis, erythropoietin administration and blood transfusion (6).

In fact, it has been reported that HbAlc levels tend to be low among hemodialysis patients, and this tendency is particularly marked in patients on erythropoietin therapy (7).

When assessing HbAlc, it is important to examine its relationship to past blood glucose levels and to determine whether absolute HbAlc levels correctly represent diabetic control.

In each patient, a one-day seven-sample glucose profile set (hereinafter referred to as profile set mean blood glucose) was calculated by measuring blood glucose levels on a total of seven occasions : before and at 2 hours after each meal and at bedtime. Profile set mean blood glucose was also used in the DCCT (1), and when compared with one-point blood glucose, it provides a more accurate assessment of blood glucose control. Therefore, we used profile set mean blood glucose as the main indicator for blood glucose control and compared HbAlc levels in diabetics with end-stage renal disease (ESRD) with those in patients without renal failure in an attempt to elucidate the accuracy of HbAlc as an indicator for blood glucose control in diabetics with ESRD. Furthermore, we investigated the relationship between profile set mean blood glucose and glycated albumin (GA), which is unaffected by the life span of erythrocytes (8), in diabetics with ESRD, and then compared absolute GA levels between diabetics with ESRD and those with normal renal function.

MATERIALS AND METHODS

Subjects

A total of 86 diabetes patients with ESRD who were admitted to our institution were divided into two groups : 49 predialysis patients and 37 dialysis patients. These 86 patients were compared to 40 diabetics with normal renal function (non-dialysis patients). The 49 predialysis patients were patients who would soon begin dialysis, while the 37 dialysis patients were already on dialysis. Table 1 shows the patient backgrounds, and while there were no significant differences in average age among the three groups, the average blood glucose levels in the non-dialysis patients were higher than in the predialysis or dialysis patients. In addition, except for five predialysis patients, erythropoietin was used in all ESRD patients.

Methods

Blood glucose levels were measured using a quick blood glucose analyzer (GluTestAce : Sanwa Kagaku K.K.) seven times a day (before and at 2 hours after each meal and at bedtime) to calculate the profile set mean blood glucose. On the day when the profile set mean blood glucose was de-

Table 1. Patient background

Cases (n)	M/F (n)	Mean age (years)	Mean blood glucose (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	Albumin (g/dl)	ChE (IU/dl)	Treatment (Diet/Insulin/OHA) (n)
Predialysis patients with end-stage renal disease (n = 49)	36/13	63.9 ± 13.1 (37-90)	165.8± 47.8 (80-313)	84.4 ± 29.8 (19.2-139.3)	8.2 ± 3.5 (2.1-20.8)	3.2 ± 0.6 (1.9-4.4)	3419± 1185 (1257-6209)	18/19/12
Dialysis patients with end-stage renal disease (n = 37)	25/12	64.4 ± 11.1 (46-86)	147.4 ± 38.8 (83-233)	69.5 ± 23.8 (31.4-129.0)	9.7 ± 2.5 (5.6-16.3)	3.5 ± 0.4 (2.4-4.3)	3698 ± 1363 (1442-8163)	15/17/5
DM patients with normal renal function (n = 40)	28/12	57.7 ± 14.4 (23-83)	228.9 ± 58.8 (140-367)	17.5 ± 6.6 (8.3-42.0)	0.9 ± 0.4 (0.3-2.6)	4.2 ± 0.3 (3.6-4.8)	5762 ± 1336 (3495-10373)	6/11/23

Mean ± SD
(min - max)

OHA : oral hypoglycemic agent

termined, a blood sample was collected to measure HbAlc and GA by either the enzyme or HPLC method using an automatic glycohemoglobin analyzer, an HLC-723 GHbV (Toso, Tokyo) and a boronic acid column (8). At the same time, reticulocyte count (Ret) was determined using an ADVIA 120 (Bayer Medical, Tokyo) and erythrocyte creatine level was measured using the method of Jiao *et al*. (9). Three regression lines were calculated for each patient group by simple regression where HbA1c or GA was the response variable, and the profile set mean blood glucose was the regressor variable. Test for homogeneity of the three regression slopes was conducted with a general linear model using the profile set mean blood glucose, each patient group, and the interaction of the profile set mean blood glucose with each patient group. With regard to statistical analyses, Mann-Whitney U test and Fisher transformation were used, and p values of <0.05 were considered significant.

RESULTS

Relationship between blood glucose control and HbAlc in ESRD patients

Figure 1 shows the relationship between blood glucose control and HbAlc in the predialysis, dialysis and non-dialysis patients. The profile set mean blood glucose was plotted against the horizontal axis, and HbAlc was plotted against the vertical axis. The coefficients of correlation(r) between blood glucose control and HbA1c in the predialysis, dialysis and non-dialysis patients were 0.47, 0.42 and 0.67, respectively. While there were no marked differences in the y-intercept of the regression line among the three groups, the slope of the regression line for the ESRD (predialysis and dialysis) patients was shallower when compared with that for the non-dialysis patients. A significant difference (p=0.045) among the three regression slopes was observed under analysis of variance.

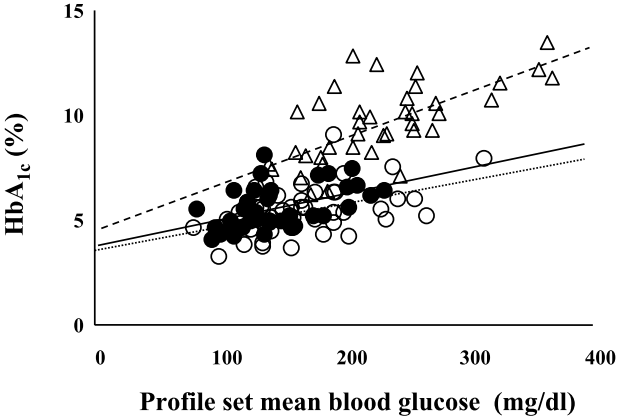

Figure 1: Relationship between blood glucose control and HbA1c in diabetes patients with end-stage renal disease : Comparison to diabetes patients with normal renal function. (white circles, dotted line=predialysis patients (r=0.47, p<0.0005); black circles, solid line=dialysis patients (r=0.42, p<0.01) ; white triangles, broken line=DM patients with normal renal function (r= 0.67, p<0.0001).

This clearly shows that, in the ESRD patients, the level of HbAlc was lower than indicated by their profile set mean blood glucose.

The mean actual and corrected HbA1c levels for the predialysis patients were 5.4±1.1 and 7.9± 1.1%, respectively, while those for the dialysis patients were 5.6±1.0 and 7.5±0.9% respectively (p< 0.0001). The corrected HbA1c levels were calculated by applying the profile set mean blood glucose of each ESRD patient to the regression formula for the HbA1c of non-dialysis patients.The mean actual and corrected HbA1c levels were the mean of an individual value of each patient in the group. There were significant differences between the mean actual and corrected HbAlc levels for the predialysis and dialysis patients.

Comparison of erythrocyte life span between the ESRD and non-dialysis patients

Table 2 compares the reticulocyte count (Ret) and erythrocyte creatine (Cr) between the ESRD and non-dialysis patients. Cr and Ret, which indicate the levels of immature erythrocytes, in the ESRD (predialysis and dialysis) patients were higher than those in the non-dialysis group.

Relationship between blood glucose control and GA levels in the ESRD patients

Figure 2 shows the relationship between GA levels, which are unaffected by the life span of erythrocytes, and blood glucose control in the ESRD (predialysis and dialysis) patients. In each patient, the profile set mean blood glucose was plotted against the horizontal axis, while GA was plotted against the vertical axis. The coefficients of correlation(r) between blood glucose control and GA in the predialysis, dialysis and non-dialysis patients were 0.56, 0.50 and 0.68, respectively. There was no significant difference among the three regression slopes under analysis of variance.

There was no significant difference between the actual and corrected GA levels for the dialysis

Table 2. Comparison of reticulocyte count (Ret) and erythrocyte creatine (Cr) in patients with end-stage renal disease and DM patients with normal renal function

Patients (n)	Hematocrit (%)	Reticulocyte (%)	Creatine in erythrocyte (μmol/g.Hb)
Predialysis patients (n = 49)	24.7 ± 4.9 †	2.35 ± 1.05	1.64 ± 0.66*
Dialysis patients (n = 37)	28.5 ± 5.0 †	2.17 ± 1.25	2.17 ± 0.95 †
DM patients with normal renal function (n = 40)	42.4 ± 4.4	1.83 ± 0.66	1.29 ± 0.32

*: vs. DM patients with normal renal function, p< 0.05
†: vs. DM patients with normal renal function, p < 0.0001
Mean±SD

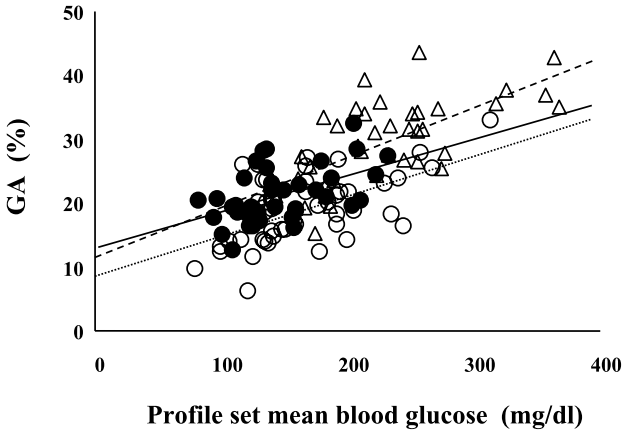

Figure 2: Relationship between blood glucose control and GA in diabetes patients with end-stage renal disease: Comparison to diabetes patients with normal renal function. (white circles, dotted line=predialysis patients (r=0.56, p<0.0001); black circles, solid line=dialysis patients (r=0.50, p<0.0005); white triangles, broken line=DM patients with normal renal function (r=0.68, p< 0.0001).

patients (21.3±4.4 vs. 23.0±3.0%), while the actual GA levels were lower than the corrected GA levels for the predialysis patients (19.0±5.3 vs. 24.4± 3.7%).

DISCUSSION

The results of the present study confirm that HbAlc levels in ESRD patients are lower than indicated by blood glucose control and are lower than those of diabetes patients with normal renal function. This phenomenon was seen in ESRD patients who would soon begin dialysis and those who were already on dialysis. The differences between the actual and corrected HbAlc levels (difference from values in non-dialysis patients under the same blood glucose control) for the predialysis and dialysis patients were comparable, thus suggesting that there is no marked difference in the degree of decrease in HbAlc between these two groups of patients.

Carbamylated hemoglobin levels increase in the erythrocytes of ESRD patients, and in the ion-exchange column method, it coelutes with HbAlc. As a result, it has been reported that HbAlc levels are high in ESRD patients (10,11). However, with a more recent ion-exchange column method, it is possible to separate carbamylated hemoglobin from HbAlc. In the present study, HbAlc levels were measured using the latest ion-exchange column method, and they did not include any carbamylated hemoglobin.

Needless to say, blood glucose is one of the main determining factors of HbAlc, but the life span of erythrocytes can also play a role. As shown in Table 2, the immature erythrocyte ratio for the ESRD patients was higher than in the non-dialysis patients with normal renal function. While there was no statistically significant difference in reticulocyte count, the erythrocyte creatine levels in the ESRD patients were significantly higher. Jiao *et al*. (9) and Takemoto *et al*. (12) reported high levels of erythrocyte creatine and low HbAlc levels in immature erythrocytes (9). Therefore, increased immature erythrocyte ratio appears to be involved in the low HbAlc levels seen in ESRD patients.

Increased immature erythrocyte ratio involves increased erythrocyte destruction and hematopoiesis. In dialysis patients, erythrocytes are physically destroyed during dialysis, and this can stimu-

late hematopoiesis, thus increasing the immature erythrocyte ratio. However, the increased immature erythrocyte ratio in the dialysis patients may not be the main factor mainly due to loss of erythrocyte during dialysis procedure; even in predialysis patients who had not been on dialysis, the immature erythrocyte ratio was high, while HbAlc levels were low.

Subsequently, the cause of the increased immature erythrocyte ratio and decreased HbAlc levels in ESRD patients may be factors that are common to the predialysis and dialysis patients, i.e., periodic blood sampling, erythropoietin administration and blood transfusion. In any case, when compared with diabetes patients without renal dysfunction, levels of HbAlc in the patients with ESRD were lower than indicated by their blood glucose control.

How much do HbAlc levels decrease in patients with ESRD? The average decrease for the predialysis and dialysis patients was 2.5 and 1.9%, respectively. If HbAlc levels are low in all diabetics with ESRD, then the levels of HbAlc can be corrected using a correction formula. However, because there are individual differences in the immature erythrocyte ratio and various factors are involved in low HbAlc levels, we believe that HbAlc levels cannot be accurately corrected using a formula.

In such cases, a blood glucose control indicator that is unaffected by the life span of erythrocytes to replace HbAlc is required. GA is an indicator of blood glucose control that is unaffected by the life span of erythrocytes.

The coefficients of correlation between blood glucose control and HbA1c in the predialysis, dialysis and non-dialysis patients were not significantly different from the corresponding values between blood glucose control and GA in the respective patients groups. We cannot determine which is better than the other only on the basis of these coefficients of correlation as an parameter for blood glucose control. Another important character of the parameter is the similarity of the regression lines plotted against blood glucose control and HbA1c or GA among the groups on the y-intercept and the slope. The slope of the regression lines plotted against blood glucose control and HbA1c for the ESRD was shallower than that for the non-dialysis patients, while the changes in GA levels in relation to the profile set mean blood glucose in the patients with ESRD matched those in non-dialysis patients with normal renal function as shown in Figure 2. Based on these findings, it can be said that GA is a better indicator for blood glucose control than HbA1c in diabetics with ESRD.

However, in the predialysis patients, GA levels were lower, probably because serum albumin levels were low in some patients as a result of nephrosis. Among the patients with serum albumin levels of $\geq$3.5 g/dl, the GA levels for ESRD patients were comparable to those of the non-dialysis patients with normal renal function. Therefore, the level of GA is low in ESRD patients with nephrosis or ESRD patients on peritoneal dialysis because albumin leaks into the peritoneal dialysis solution, and as a result, GA is not a good indicator for blood glucose control for these patients.

Assessing the blood glucose control of dialysis patients based solely on HbAlc can lead to erroneous results, and in such cases, GA is a good substitute for HbAlc.

ACKNOWLEDGMENTS

This study has been published in the abstract volume of the 18th Congress of International Diabetes Federation, Paris, 24-29 August 2003.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group : The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin -dependent diabetes mellitus. N Engl J Med 329 : 977-986, 1993
2. UK Prospective Diabetes Group : Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352 : 837-853, 1998
3. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M : Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus-a randomized prospective 6-year study-. Diab Res Clin Pract 28 : 103-117, 1995

4. Dandona P, Freedman D, Moorhead JF : Glycosylated haemoglobin in chronic renal failure. Br Med J 1 : 1183-1184, 1979
5. Boer MJ, Miedema K, Casparie AF : Glycosylated haemoglobin in renal failure. Diabetologia 18 : 437-440, 1980
6. Eschbach JW Jr, Funk D, Adamson J, Kuhn I, Scribner BH, Finch CA : Erythropoiesis in patients with renal failure undergoing chronic dialysis. N Engl J Med 276 : 653-658, 1967
7. Nakao T, Matsumoto H, Okada T, Han M, Hidaka H, Yoshino M, Shino T, Yamada C, Nagaoka Y: Influence of erythropoietin treatment on hemoglobinA1c levels in patients with chronic renal failure on hemodialysis. Intern Med 37 : 826-830, 1998
8. Shima K, Ito N, Abe F, Hirota M, Yano M, Yamamoto Y, Uchida T, Noguchi K : High-performance liquid chromatographic assay of serum glycated albumin. Diabetologia 31:627-631, 1988
9. Jiao Y, Okumiya T, Tsubosaki E, Matsumura H, Park K, Sugimoto K, Kageoka T, Sasaki M: An enzymatic assay for erythrocyte creatine as an index of the erythrocyte life time. Clin Biochem 31 : 59-65, 1998
10. Fluckiger R, Harmon W, Meier W, Loo S, Gabby H : Hemoglobin carbamylation in uremia. N Engl J Med 304 : 823-827, 1981
11. Smith WG, Holder M, Benton M, Brown CB : Glycosylated and carbamylated haemoglobin in uremia. Nephrol Dial Transplant 4 : 96-100, 1989
12. Takemoto Y, Okumiya T, Tsuchida K, Nakatani T, Yamamoto K : Erythrocyte creatine as an index of the erythrocyte life span and erythropoiesis. Nephron 86 : 513-514, 2000