Glycated proteins are created by non-enzymatic reactions between various tissue proteins and glucose. Such proteins have been used clinically as long or short-term indices of glycemic control in diabetic patients. At present, these are some essential tests for the monitoring of glycemic control in diabetic patients. Hemoglobin A1C (HbA1C) is a typical glycated protein and is the most common index used. It reflects the weighted mean blood glucose level over the previous 1-2 months based on the lifespan of red blood cells1–4). On the other hand, glycated albumin (GA)5,6), another glycated protein, and the polyol 1,5-anhydroglycitol (1,5-AG)7) have been reported to be useful short-term indices of the weighted mean blood glucose level. However, it is difficult to use these tests in Japan because the cost is not covered by the National Health Scheme. The assays for GA and 1,5-AG also have problems with respect to standardization, linearity with the mean blood glucose level, and speed of determination.

In the present study, we calculated the corrected HbA1C value on the basis of HbA1C data obtained over 4 months in 19 patients with type 2 diabetes. The usefulness of cHbA1C as a short-term glycemic control index was compared with that of glycated albumin. Both the HbA1C value (measured by immunoassay) and the calculated cHbA1C value showed significant positive correlations with glycated albumin. However, cHbA1C showed a stronger correlation with glycated albumin. In each patient, the variation of cHbA1C values was also more marked than that of HbA1C.

However, neither HbA1C nor cHbA1C was able to closely reflect blood glucose changes in patients with unstable glycemic change. In conclusion, cHbA1C may be a useful measure of the weighted mean blood glucose over the preceding one month in patients with comparatively slow changes of blood glucose level.

**Materials and methods**

The subjects were 19 patients with type 2 diabetes who attended the outpatient clinic of Kazama Medical Hospital. There were 10 men and 9 women with a mean age of 59.6 ± 13.7 years (mean ± S.D.), a mean duration of diabetes of 14.6 ± 8.6 years, and a mean HbA1C of...
GA and corrected \( HbA_{1c} \) (\( cHbA_{1c} \)) were compared. \( cHbA_{1c} \) was calculated from \( HbA_{1c} \) data obtained over a maximum of 120 days before the previous monthly determination of \( HbA_{1c} \). It was defined as corresponding to the mean blood glucose level in the 1-month period before the present month and was calculated as described below.

Glycation of hemoglobin (HbA\(_{0}\)) occurs via two reactions. In the first reaction, unstable \( HbA_{1c} \) is formed by Schiff base binding between the amino groups of valine and glucose. In the second reaction, unstable \( HbA_{1c} \) is converted to stable \( HbA_{1c} \) by Amadori rearrangement. Thus, stable \( HbA_{1c} \) formed by the second reaction reflects the mean blood glucose level in the past. The first reaction is reversible, and it usually exists in equilibrium because it occurs rapidly. On the other hand, the second reaction is irreversible, and it is a rate-limiting reaction for the glycation process because it is very slow. Therefore, the reaction producing stable \( HbA_{1c} \) (subsequently referred to simply as \( HbA_{1c} \)) can be approximated by the following linear expression\(^\text{8-10}\):

\[
\text{Hemoglobin (HbA\(_0\)) + Glucose} \rightarrow \text{HbA}\(_{1c}\)
\]

When glycation is expressed in the above manner, the glycation rate determined at time \( m \) [\( HbA_{1c} (m) \)] is given by the following expression, if the glycation rate of hemoglobin is low\(^\text{11}\):

\[
HbA_{1c}(m) = \int_{-\infty}^{\infty} kF(m-t)G(t)\,dt (1)
\]

where, \( F(s) \) is the percent contribution of blood glucose at \( s \) hours before, \( k \) is the glycation rate constant, and \( G(t) \) is the blood glucose level at time \( t \). \( F(s) \) is the weighting function, which is calculated as shown below, and \( T \) is the lifespan of erythrocytes\(^\text{11}\).

\[
F(s) = \begin{cases} 1 - s/T & (0 < s < T) \\ 0 & (s > T) \end{cases}
\]

Based on these assumptions, an expression can be derived for calculating \( cHbA_{1c} \) from the \( HbA_{1c} \) data obtained over the previous 4 months. Its derivation is described in detail in Results. GA was determined using high performance liquid chromatography (Sumikin Bioscience, Inc., Amagasaki, Japan). \( HbA_{1c} \) was determined by an immunoassay using DCA2000 (Miles-Sankyo, Tokyo, Japan).

Relationships between the variables were tested by calculating Pearson’s correlation coefficients.

**RESULTS**

In equation (1),

\[
HbA_{1c}(m) = \int_{-\infty}^{\infty} kF(m-t)G(t)\,dt.
\]

If \( F(m-t) = 1 - \frac{m-t}{T_0} \), \( m = T_0 \) (= 120 days), the \( HbA_{1c} \) at \( T_0 \) is calculated as follows:

\[
HbA_{1c}(T_0) = k\int_{T_1}^{T_0} \left[1 - \frac{T_0-t}{T_0}\right]G(t)\,dt,
\]

where \( T_1 \) represents the period of 120 days before this month and is expressed as \( T_1 = 0 \).

Since \( G(t) \) cannot be determined in real time, it is removed from the function by dividing the interval from \( T_1 \) to \( T_0 \) into 4 periods and approximating \( G(t) \) in each period by the mean blood glucose level between \( T_i \) and \( T_{i+1} \).

Accordingly,
Then, and integration is performed, this yields

\[
HbA_{1c}(T_0) = k \int_{T_1}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt \\
+ k \int_{T_2}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt \\
+ k \int_{T_3}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt \\
= k \left[ G \right]_{T_1}^{T_0} \int_{T_1}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] \, dt \\
+ k \left[ G \right]_{T_2}^{T_0} \int_{T_2}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] \, dt \\
+ k \left[ G \right]_{T_3}^{T_0} \int_{T_3}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] \, dt
\]

[\left[ G \right]_{T_j}^{T_0}] is the mean blood glucose level between \( T_j \) and \( T_0 \), and it can be expressed as \([HbA_{1c}]_{T_j}^{T_0}\). Then,

\[
HbA_{1c}(T_0) = \frac{[HbA_{1c}]_{T_1}^{T_0}}{T_0} \int_{T_1}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt \\
+ \frac{[HbA_{1c}]_{T_2}^{T_0}}{T_0} \int_{T_2}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt \\
+ \frac{[HbA_{1c}]_{T_3}^{T_0}}{T_0} \int_{T_3}^{T_0} \left[ 1 - \frac{T_0 - t}{T_0} \right] G(t) \, dt
\]

If the glycation constant is defined as \( k = \frac{2}{T_0} \), and integration is performed, this yields

\[
= \frac{[HbA_{1c}]_{T_1}^{T_0}}{T_0} \left( T_0^2 - (T_1)^2 \right) \\
+ \frac{[HbA_{1c}]_{T_2}^{T_0}}{T_0} \left( T_0^2 - (T_2)^2 \right) \\
+ \frac{[HbA_{1c}]_{T_3}^{T_0}}{T_0} \left( T_0^2 - (T_3)^2 \right)
\]

If the value of \( k \) is as described above and the mean glucose level shows no difference between months,

\[
[HbA_{1c}]_{T_1}^{T_0} = \frac{[HbA_{1c}]_{T_2}^{T_0}}{T_2} \\
= \frac{[HbA_{1c}]_{T_3}^{T_0}}{T_3} \\
[HbA_{1c}(T_0) = \frac{[HbA_{1c}]_{T_2}^{T_0}}{T_2} = \frac{[HbA_{1c}]_{T_3}^{T_0}}{T_3}
\]

Thus, the mean monthly blood glucose level is equal to the value of \( HbA_{1c} \).

If,

\[
a_g = k \int_{T_j}^{T_{j+1}} \left[ 1 - \frac{T_0 - t}{T_0} \right] \, dt \\
= \frac{2}{(T_0)^2} (T_0 - T_j) (T_0 - T_{j+1}) \\
+ \frac{2}{(T_0)^2} ((T_j)^2 - (T_{j+1})^2), \quad k = \frac{2}{T_0}
\]

in equation (2)

The value of \( HbA_{1c} \) for this month \((T_0)\), i.e., \( HbA_{1c}(T_0) \), is given by

\[
a_g = k \int_{T_j}^{T_{j+1}} \left[ 1 - \frac{T_0 - t}{T_0} \right] \, dt \\
= \frac{2}{(T_0)^2} (T_0 - T_j) (T_0 - T_{j+1}) \\
+ \frac{2}{(T_0)^2} ((T_j)^2 - (T_{j+1})^2), \quad k = \frac{2}{T_0}
\]

If \( T_0 = 120 \), \( T_1 = 90 \), \( T_2 = 60 \), and \( T_3 = 30 \) (days), then \( a_{00} = 0.4375 \), \( a_{01} = 0.3125 \), \( a_{02} = \)
0.1875, and \( a_{05} = 0.0625 \)

\[
HbA_{1C}(T_0) = 0.4375 [HbA_{1C}]_{T_1}^0 + 0.3125 [HbA_{1C}]_{T_2}^0 + 0.1875 [HbA_{1C}]_{T_3}^0 + 0.0625 [HbA_{1C}]_{T_4}^0
\]

Similarly, \( HbA_{1C}(T_1), HbA_{1C}(T_2) \) and \( HbA_{1C}(T_3) \) can be calculated as follows:

\[
HbA_{1C}(T_1) = a_{11} [HbA_{1C}]_{T_1}^{T_1} + a_{12} [HbA_{1C}]_{T_2}^{T_1}
+ a_{13} [HbA_{1C}]_{T_3}^{T_1} + a_{14} [HbA_{1C}]_{T_4}^{T_1}
\]

\[
HbA_{1C}(T_2) = a_{21} [HbA_{1C}]_{T_1}^{T_2} + a_{22} [HbA_{1C}]_{T_2}^{T_2}
+ a_{23} [HbA_{1C}]_{T_3}^{T_2} + a_{24} [HbA_{1C}]_{T_4}^{T_2}
\]

\[
HbA_{1C}(T_3) = a_{31} [HbA_{1C}]_{T_1}^{T_3} + a_{32} [HbA_{1C}]_{T_2}^{T_3}
+ a_{33} [HbA_{1C}]_{T_3}^{T_3} + a_{34} [HbA_{1C}]_{T_4}^{T_3}
\]

Thus, each \( HbA_{1C}(T) \) value is given by the expression \([HbA_{1C}]_{T,T-1}^{T}\).

If this equation is solved inversely under an approximation (see appendix) and each \([HbA_{1C}]_{T,T-1}^{T}\) is expressed as \( HbA_{1C}(T) \), the result is as follows:

\[
[HbA_{1C}]_{T_1}^{T_0} = b_{00} HbA_{1C}(T_0) + b_{01} HbA_{1C}(T_1)
+ b_{02} HbA_{1C}(T_2) + b_{03} HbA_{1C}(T_3)
\]

\[
[HbA_{1C}]_{T_2}^{T_1} = b_{11} HbA_{1C}(T_1) + b_{12} HbA_{1C}(T_2)
+ b_{13} HbA_{1C}(T_3)
\]

\[
[HbA_{1C}]_{T_3}^{T_1} = b_{21} HbA_{1C}(T_1) + b_{22} HbA_{1C}(T_2)
+ b_{23} HbA_{1C}(T_3)
\]

\[
[HbA_{1C}]_{T_4}^{T_1} = b_{31} HbA_{1C}(T_1) + b_{32} HbA_{1C}(T_2)
+ b_{33} HbA_{1C}(T_3)
\]

Each \( b_i \) is represented in the appendix.

Since \([HbA_{1C}]_{T_i}^{T_0}\) is the mean blood glucose level in the present month, the corrected \( HbA_{1C}\) is obtained as \( cHbA_{1C} = [HbA_{1C}]_{T_i}^{T_0}\).

If \( T_0 = 120, T_1 = 90, T_2 = 60, \) and \( T_3 = 30 \)
(days), then \( b_{00} = 2.29, b_{01} = -1.63, b_{02} = 0.19, \)
\( b_{03} = 0.24 \).

\[
cHbA_{1C} = 2.29 HbA_{1C}(T_0) - 1.63 HbA_{1C}(T_1) + 0.19 HbA_{1C}(T_2) + 0.24 HbA_{1C}(T_3)
\]

In this equation, \( HbA_{1C}(T_0) \) is the value of \( HbA_{1C} \) for this month and \( HbA_{1C}(T_1) \) is the value for the previous month. \( HbA_{1C}(T_2) \) and \( HbA_{1C}(T_3) \) represent the \( HbA_{1C} \) values for 2 months and 3 month before the present month, respectively.

We made a nomogram table to show \( cHbA_{1C} \) values based on \( HbA_{1C} \) values of this month and the previous three months (Table 1). The table was made on the assumption that the \( HbA_{1C} \) values in the previous three months were identical.

The mean GA value was 20.6 ± 2.5 % and the mean \( cHbA_{1C} \) value 7.30 ± 1.0 %. Both \( HbA_{1C} \) and \( cHbA_{1C} \) showed a significant positive correlation with GA, but \( cHbA_{1C} \) (Fig. 1, \( n = 19, r = 0.83, p < 0.05 \)) showed a closer correlation than \( HbA_{1C} \) (Fig. 2, \( n = 19, r = 0.61, p < 0.05 \)).

In the patients with a small difference (<0.4) between \( HbA_{1C} \) and \( cHbA_{1C} \), both parameters were strongly and equally correlated with GA (Fig. 3, \( n = 11, r = 0.80, p < 0.05 \)). However, in patients with a larger difference (< 0.4) between \( HbA_{1C} \) and \( cHbA_{1C} \), the latter was still closely correlated with GA (Fig. 4, \( n = 8, r = 0.86, p < 0.05 \)), but \( HbA_{1C} \) only showed a weak correlation with GA (Fig. 5, \( n = 8, r = 0.31, p < 0.05 \)).

We observed changes in \( cHbA_{1C}, HbA_{1C} \) and blood glucose in two representative patients for more than six months. In each patient, the time course of \( cHbA_{1C} \) showed a tendency to parallel more closely that of blood glucose (Fig. 6) or mean blood glucose (Fig. 7) than \( HbA_{1C} \).
Table 1. Nomogram table of cHbAIC values obtained from HbAIC values of this month and previous three months. cHbAIC was calculated on the assumption that HbAIC values during previous three months were identical. Values in the 1st row show HbAIC values for previous month, values in the 1st column show HbAIC values for this month.

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Fig. 1. Correlation between corrected HbA1c (cHbA1c) and glycated albumin in diabetic subjects. (r = 0.83, p < 0.05, n = 19)

Fig. 2. Correlation between HbA1c and glycated albumin in the diabetic subjects. (r = 0.61, p < 0.05, n = 19)

Fig. 3. Correlation between HbA1c and glycated albumin in subjects for whom the difference between HbA1c and cHbA1c was less than 0.4. (r = 0.80, p < 0.05, n = 11)

Fig. 4. Correlation between corrected HbA1c (cHbA1c) and glycated albumin in subjects for whom the difference between HbA1c and cHbA1c was more than 0.4. (r = 0.86, p < 0.05, n = 8)
DISCUSSION

It has been considered that HbA\textsubscript{1C} generally reflects the weighted mean blood glucose level over the previous 1-2 months and that it more closely reflects a weighted mean value than a simple mean\textsuperscript{10–12}. It has been reported that 50\% of HbA\textsubscript{1C} is accounted for by the weighted mean blood glucose level over the previous 1 month, while 25\% is contributed by the weighted mean blood glucose levels for each of the two months before that (the 3rd and 4th months before the present month)\textsuperscript{12}. There is little literature regarding the theoretical basis for these percentages, but the weightings can be calculated according to equation (2) shown in Results. If patients return to the outpatient clinic at regular intervals (30 days), equation (4) is established, and the weightings for these months can be calculated as 44\%, 31\%, 19\%, and 6\%, respectively. This indicates that the influence of the blood glucose level around 2 months before the present month is also very important.

HbA\textsubscript{1C} is an index of medium- to long-term glycemic control. Unlike GA, it does not reflect short-term changes of the blood glucose level. Since the half-life of albumin is only about 17 days, GA is thought to reflect the mean blood glucose level over the previous 2 weeks and GA is an excellent index of short-term glycemic control\textsuperscript{5,6,13}. However, apart from evaluating the initial response to drug therapy for diabetes and the control of unstable patients, GA is only used for patients with nephrotic syndrome or pregnant women and is not determined routinely in Japan. In the present study, we calculated cHbA\textsubscript{1C} to assess short-term glycemic control on the basis of monthly HbA\textsubscript{1C} data, and we compared both cHbA\textsubscript{1C} and HbA\textsubscript{1C} with GA. We found that HbA\textsubscript{1C} itself showed a significant pos-
itive correlation with GA, but cHbA1C was more strongly correlated with GA. As GA is generally considered to reflect the mean blood glucose level over the past 2 weeks, the usefulness of cHbA1C as a short-term index was also suggested. In addition, relatively slight changes of HbA1C corresponded to larger changes of cHbA1C (Fig. 6, Fig. 7), suggesting that the latter is more useful for assessing recent glycemic control.

For example, if HbA1C decreases from sustained 8% to 7%, cHbA1C can be calculated as 5.7%, showing a larger change than HbA1C itself (Table 1). Moreover, even when HbA1C decreases gradually from 9% to 6%, cHbA1C will fall to 5.2%. In contrast, if HbA1C shows no appreciable difference from month to month, there is very little difference between HbA1C and cHbA1C, with both parameters showing a strong correlation with GA. In this case, HbA1C also shows a close positive correlation with GA (r = 0.8, Fig. 3). Similar results have been reported by Yamamoto and others14.

We found that both HbA1C and cHbA1C showed weak correlation with GA at the start of insulin therapy or in patients with unstable glycemic control, although statistical analysis could not be performed because of the small number of such patients. This was presumably because HbA1C itself does not closely reflect short-term blood glucose changes10,15 and cHbA1C may therefore show a similar trend. Accordingly, parameters like GA and 1,5-AG need to be determined to assess the more recent trend of blood glucose levels in such patients. These results indicate that cHbA1C may be useful for assessing mean blood glucose levels over the last 1 month in patients showing relatively slow changes of blood glucose.

Finally, equation (6), rather than equation (7), has to be used if the intervals between blood tests are relatively irregular. However, it is easy to employ this equation if calculation software is available.

[APPENDIX]

Each \(b_j\) in equation (6) can be derived from equation (3) and (5).

\[
HbA_{1C}(T_0) = a_0 + a_2 [HbA_{1C}]_{T_1}^2 + a_3 [HbA_{1C}]_{T_2}^3 + a_5 [HbA_{1C}]_{T_3}^4 \\
HbA_{1C}(T_1) = a_1 [HbA_{1C}]_{T_2}^2 + a_2 [HbA_{1C}]_{T_3}^3 + a_3 [HbA_{1C}]_{T_4}^4 + a_5 [HbA_{1C}]_{T_5}^5 \\
HbA_{1C}(T_2) = a_2 [HbA_{1C}]_{T_3}^3 + a_3 [HbA_{1C}]_{T_4}^4 + a_4 [HbA_{1C}]_{T_5}^5 + a_5 [HbA_{1C}]_{T_6}^6 \\
HbA_{1C}(T_3) = a_3 [HbA_{1C}]_{T_4}^4 + a_4 [HbA_{1C}]_{T_5}^5 + a_5 [HbA_{1C}]_{T_6}^6 + a_6 [HbA_{1C}]_{T_7}^7 \\ (3)
\]

Since the time before \(T_i\) exceeds 0 days, further approximation can be performed based on the assumption that all \([HbA_{1C}]_{T_i}^j\) (j \(\geq 4\)) are identical with \([HbA_{1C}]_{T_i}^j\). Then,

\[
HbA_{1C}(T_0) = a_0 + a_2 [HbA_{1C}]_{T_1}^2 + a_3 [HbA_{1C}]_{T_2}^3 + a_5 [HbA_{1C}]_{T_3}^4 \\
HbA_{1C}(T_1) = a_1 [HbA_{1C}]_{T_2}^2 + a_2 [HbA_{1C}]_{T_3}^3 + a_4 [HbA_{1C}]_{T_4}^4 + a_5 [HbA_{1C}]_{T_5}^5 \\
HbA_{1C}(T_2) = a_2 [HbA_{1C}]_{T_3}^3 + a_3 [HbA_{1C}]_{T_4}^4 + a_4 [HbA_{1C}]_{T_5}^5 + a_6 [HbA_{1C}]_{T_6}^6 \\
HbA_{1C}(T_3) = a_3 [HbA_{1C}]_{T_4}^4 + a_4 [HbA_{1C}]_{T_5}^5 + a_5 [HbA_{1C}]_{T_6}^6 + a_6 [HbA_{1C}]_{T_7}^7 \\
HbA_{1C}(T_i) = a_{ij} [HbA_{1C}]_{T_{i-1}}^j + a_{j} [HbA_{1C}]_{T_i}^j \\
a_{00} + a_{02} + a_{03} = 1 \\
a'_{13} = a_{13} + a_{14}, a_{11} + a_{12} + a'_{13} = 1 \\
a'_{23} = a_{23} + a_{24} + a_{25} + a_{26} = 1 \\
(8)
\]

If this equation is solved inversely and each \([HbA_{1C}]_{T_i}^j\) is expressed as \(HbA_{1C}(T_i)\), the result is as follows:
\[ [HbA_{1C}]_{i}^{T_{n}} = \frac{1}{a_{i0}} HbA_{1C}(T_{i}) - \frac{a_{i1}}{a_{i0}} HbA_{1C}(T_{i}) + \frac{a_{i2}}{a_{i1}} a_{i2} - \frac{a_{i2}}{a_{i1}} a_{i2} \]

Hence in equation (6),

\[
\begin{align*}
 b_{00} &= \frac{1}{a_{00}}, \\
 b_{01} &= -\frac{a_{01}}{a_{00} a_{11}}, \\
 b_{02} &= -\frac{a_{02}}{a_{00} a_{11}} - \frac{a_{10}}{a_{00} a_{11}}, \\
 b_{11} &= \frac{1}{a_{11}}, \\
 b_{12} &= -\frac{a_{12}}{a_{11} a_{22}}, \\
 b_{21} &= \frac{a_{12} a_{23} - a_{22} a_{13}}{a_{11} a_{23}}, \\
 b_{22} &= \frac{1}{a_{22}}, \\
 b_{23} &= -\frac{a_{23}}{a_{22}} \\
 b_{33} &= 1
\end{align*}
\]

REFERENCES