Kinetics of HbA_{1c}, Glycated Albumin, and Fructosamine and Analysis of Their Weight Functions Against Preceding Plasma Glucose Level

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OBJECTIVE — To examine the kinetics of HbA_{1c}, glycated albumin (GA), and fructosamine (FA) levels in response to plasma glucose change and their relationship with the preceding plasma glucose level.

RESEARCH DESIGN AND METHODS — The time courses of HbA_{1c}, GA, and FA after acute glycemic normalization were observed in nine patients with newly diagnosed non-insulin-dependent diabetes mellitus and compared with theoretical ones. Their weight functions against preceding plasma glucose level were analyzed assuming a stepwise plasma glucose change and compared with the theoretical prediction.

RESULTS — The fasting plasma glucose level was acutely normalized after admission with a half-time of 6.3 ± 2.4 days (mean ± SD). The HbA_{1c} level decreased linearly during the initial 2 months with a half-time of 34.6 ± 10.1 days, followed by a gradual decrease thereafter. GA and FA levels decreased very rapidly during the initial 2–3 weeks with half-times of 17.1 ± 2.8 and 12.2 ± 4.8 days, respectively, followed by a gradual decrease thereafter. The time courses of HbA_{1c}, GA, and FA agreed well with theoretically estimated decay curves. Experimental values of weight functions against the preceding plasma glucose level agreed well with the theoretical prediction. The weight functions for glycated proteins had maximum values on the days just before the measurement of glycated proteins and gradually decreased with an increasing time interval. The lengths of the periods over which the weight functions for HbA_{1c}, GA, and FA extend back were estimated to be roughly 100, 40, and 30 days, respectively.

CONCLUSIONS — The levels of HbA_{1c}, GA, and FA do not reflect the simple mean but reflect the weighted mean of the preceding plasma glucose level over a considerably longer period than was previously speculated.

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ANOVA, analysis of variance; CI, confidence interval; FA, fructosamine; FPG, fasting plasma glucose; GA, glycated albumin; HPLC, high-performance liquid chromatography.

Measurement of the levels of glycated proteins, such as HbA_{1c}, glycated albumin (GA), and fructosamine (FA), is the most reliable method for assessing long-term glycemic control in diabetic patients (1–4). Since glycation takes place throughout the life span of hemoglobin and serum proteins, the levels of glycated proteins reflect the degree of hyperglycemia during their life span. From clinical observations, the HbA_{1c} level has been thought to reflect the mean plasma glucose level during the preceding 1–3 months (5–9), whereas GA and FA levels have been thought to reflect the mean plasma glucose level during the preceding 1–2 weeks (10–17). However, there are few reports addressing the question of exactly how the preceding plasma glucose level contributes to the level of glycated proteins.

The traditional idea that the glycated proteins reflect the simple mean plasma glucose level during a certain preceding period raises the following questions. First, if the HbA_{1c} level reflects the simple mean plasma glucose level in the preceding period, the HbA_{1c} level should fall linearly to a new steady-state level after a stepwise plasma glucose change. However, theoretical and experimental examination indicates that the HbA_{1c} level rapidly decreases during the initial 1–2 months, followed by a gradual decrease and a final approach to a new steady-state level 4 months later (2,18–21). Why are the actual time courses different from those derived from the traditional idea? Second, considering the erythrocyte life span, glycated hemoglobin is thought to be accumulated in erythrocytes over 120 days (22). Why does the HbA_{1c} level reflect the plasma glucose level only in the preceding 1–3 months? In other words, why does it not reflect the plasma glucose level in the preceding 4 months? Third, why can we not determine more strictly the length of the period over which plasma glucose is integrated in the glycated protein level?

These conflicting results seem to

arise from the idea that the glycated proteins reflect the simple mean plasma glucose level in the preceding period. Note that this idea has not yet been verified by theoretical and clinical investigations. Recently, we have analyzed theoretically the relationships between the level of glycated proteins and the preceding plasma glucose level using a linear kinetic model (23). We have shown that the rate of contribution of the preceding plasma glucose level to the glycated protein level depends on their time interval. In other words, the level of glycated protein should be considered to reflect the weighted mean plasma glucose level in the preceding period. To test the clinical validity of this idea, we examined HbA_{1c} level responses to stepwise plasma glucose normalization in diabetic patients (21). The results showed that 50% of the HbA_{1c} level was determined by the plasma glucose level during the preceding 1-month period, while 25% of its level was determined by the plasma glucose level during the 1-month period before this month, and the remaining 25% was determined by the plasma glucose level during the 2-month period before these 2 months. These data support the idea that the HbA_{1c} level reflects the weighted mean plasma glucose level over the preceding 4 months.

Such consideration has promoted further examination of the relationship between the level of glycated protein and the preceding plasma glucose level. We have found that the rate of contribution of the preceding plasma glucose level to the glycated protein level can be analyzed from the time course in response to a stepwise plasma glucose change. In this study, we report the kinetics of HbA_{1c}, GA, and FA and the results of analysis of the relationship between the level of glycated proteins and the preceding plasma glucose level.

RESEARCH DESIGN AND METHODS

— Time courses of HbA_{1c}, GA, and FA levels were examined in nine patients with newly diagnosed non-insulin-dependent diabetes mellitus (seven men and two women, aged 30–62 years) who were hospitalized for diabetes education and treatment for 3–4 weeks. Selection criteria for the patients were as follows: fasting plasma glucose (FPG) level and HbA_{1c} on admission were >11 mmol/l and >10%, respectively; FPG level was rapidly reduced to <8 mmol/l within 3 weeks; and FPG level measured at the outpatient clinic was always <8 mmol/l over 4 months. Five patients were treated with insulin, three with oral hypoglycemic agents, and one with diet alone. FPG was measured every weekday during admission and at each visit to the outpatient clinic (~2- to 4-week intervals). HbA_{1c} was measured at intervals of ~2 weeks during admission and at each visit to the outpatient clinic. GA and FA were measured at intervals of ~1 week during admission and at each visit to the outpatient clinic. FPG was measured by the glucose oxidase method. HbA_{1c} was measured by the high-performance liquid chromatography (HPLC) method using an HLC-723GHb (Tosoh, Tokyo, Japan). Serum GA was measured by the HPLC method described previously (24). Serum FA was measured by the reduction of nitro blue tetrazolium using a kit provided by Roche and a Hitachi-7150 analyzer (Hitachi, Tokyo, Japan).

Analytical methods

Time courses of FPG, HbA_{1c}, GA, and FA were analyzed by linearly connecting the measured points. The level of glycated protein was considered to reflect the weighted mean of the preceding plasma glucose level. To describe this idea, the rate of contribution of the preceding plasma glucose to the level of glycated protein was assumed to depend on the time interval. Let the rate of contribution of the plasma glucose s days before the measurement of glycated protein be $W(s)$, the plasma glucose at time t be $G(t)$, and the level of glycated protein measured at time m be $H(m)$. As shown in Fig. 1, the rate of contribution of $G(t)$ to $H(m)$ is

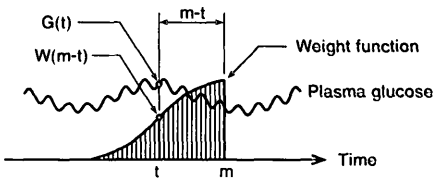

Figure 1—*Schematic presentation of the weight function against preceding plasma glucose level. The level of glycated protein is given by the weighted mean of the preceding plasma glucose level.*

given by $W(m - t)$. $H(m)$ can therefore be written as

$$H(m) = K \int_{-\infty}^{m} W(m - t)G(t)dt$$

where K is a proportional constant. If $W(s)$ fulfills the following condition

$$\int_{0}^{\infty} W(s)ds = 1$$

$H(m)$ reflects the weighted mean of the preceding plasma glucose level. Theoretical responses to ramp and stepwise plasma glucose changes were calculated using the weight functions obtained from the linear kinetic model (23) (see APPENDIX). Experimental analysis of the weight function $W(s)$ was performed assuming that the plasma glucose level changed in a stepwise fashion at time 0 (see APPENDIX).

Statistical analysis

Data are given as means ± SD unless otherwise stated. Normality of the data distribution was tested by Kolmogorov-Smirnov's one-sample test. When the normal distribution was not discarded by this test, statistical analysis was done by Student's t test for paired data or analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS — Figure 2 shows changes in FPG, HbA_{1c}, GA, and FA levels after admission in the subjects studied. FPG level was 12.8 ± 1.5 mmol/l on admission and rapidly decreased to 8.9 ± 1.2,

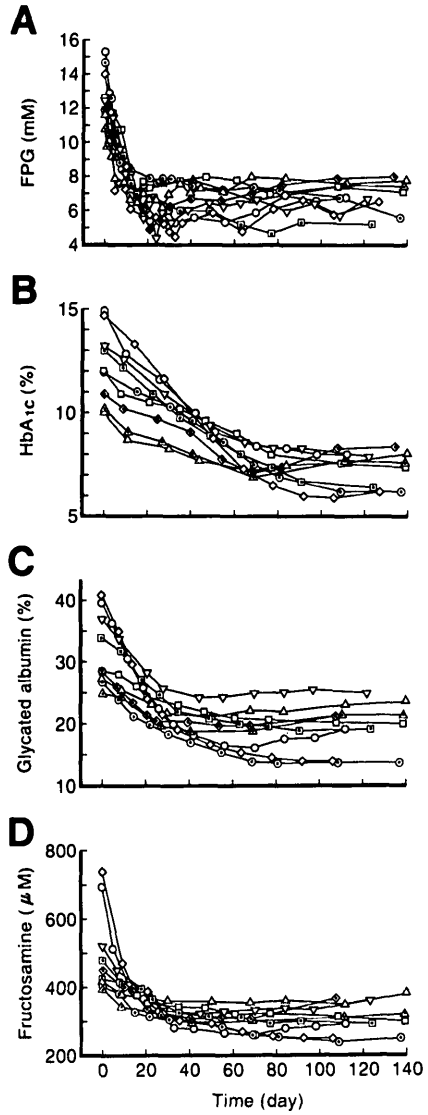

Figure 2—*Changes in the levels of FPG (A), HbA_{1c} (B), GA (C), and FA (D) after admission in diabetic patients studied. Each symbol designates an individual patient.*

7.1 ± 0.8, 6.5 ± 1.0, 6.5 ± 0.9, 6.5 ± 0.9, 6.8 ± 0.9, and 6.8 ± 0.9 mmol/l after 1, 2, 3, 4, 8, 12, and 16 weeks, respectively. Although mean FPG level was nearly constant after 3 weeks (NS by ANOVA), FPG level in each patient fluctuated considerably below 8 mmol/l. Thus, the steady-state level of FPG after diabetes treatment was taken as the mean of the measured points after 3 weeks in individual patients. The half-time of the FPG change from the initial to the steady-state level was 6.3 ± 2.4 days (4.1–10.7 days).

The HbA_{1c} level was 12.3 ± 1.8% on admission and gradually decreased to 10.2 ± 1.1, 8.4 ± 0.7, 7.5 ± 0.7, and 7.4 ± 0.9% after 4, 8, 12, and 16 weeks, respectively. The mean HbA_{1c} level decreased rapidly during the initial 2 months, followed by a gradual decrease and an approach to a new steady-state level 3 months later. The half-time of HbA_{1c} change from the initial to the lowest level was 34.6 ± 10.1 days (19.5–48.7 days), and the time required for 90% change was 70.9 ± 12.9 days (54.6–87.9 days). The time course of the HbA_{1c} change was very similar to those reported in previous studies (19,21). However, the individual time courses differed from that of the mean value. The HbA_{1c} level in six patients continued to decrease for 3–4 months, while the HbA_{1c} level in three patients showed a monotonic decrease for up to 70 days and gradually increased thereafter. Since GA and FA levels in these three patients also showed a small increase thereafter, the glycemic control in these patients is considered to have worsened to some extent.

The GA level was 32.0 ± 6.0% on admission and fell to 26.4 ± 3.4, 22.0 ± 2.3, 20.2 ± 2.5, 19.4 ± 3.1, 19.3 ± 3.7, and 20.3 ± 3.7% after 2, 4, 6, 8, 12, and 16 weeks, respectively. The GA level fell more rapidly than did that of HbA_{1c} with a nearly constant rate during the initial 3 weeks, followed by a gradual decrease thereafter. The half-time of GA change from the initial to the lowest level was 17.1 ± 2.8 days (11.9–20.3 days), and the time required for 90% change was 42.1 ± 13.9 days (24.2–58.5 days).

The FA level was 503 ± 127 μmol/l on admission and fell to 380 ± 29, 333 ± 18, 315 ± 25, 307 ± 39, 303 ± 46, and 309 ± 39 μmol/l after 2, 4, 6, 8, 12, and 16 weeks, respectively. The FA level fell more rapidly than did GA during the initial 2 weeks, followed by a gradual decrease thereafter. The half-time of FA change from the initial to the lowest level

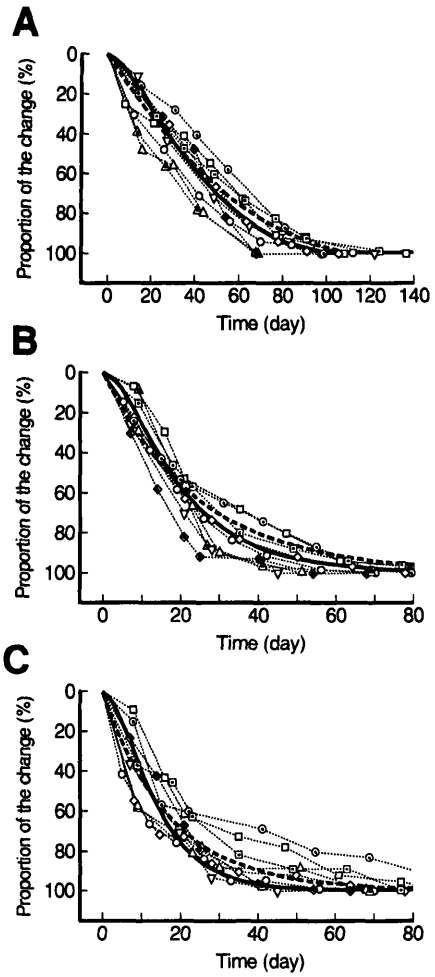

Figure 3—*Relative changes in the levels of HbA_{1c} (A), GA (B), and FA (C) in diabetic patients (dotted lines) compared with theoretically estimated changes in response to ramp (solid curves) and stepwise (broken curves) plasma glucose changes. Each symbol designates the same patient as in Fig. 2.*

was 12.2 ± 4.8 days (7.3–19.3 days), and the time required for 90% change was 46.6 ± 17.8 days (26.9–78.2 days). The half-time of FA was significantly shorter than that of GA ($P < 0.05$).

Since HbA_{1c}, GA, and FA levels did not achieve complete steady-state conditions, the data from the initial to the lowest levels were used in the analysis of time course and weight function. Figure 3 shows the time courses of the proportion of the change in HbA_{1c}, GA, and FA levels. The time courses were compared with

Table 1—*Time constants of changes in HbA_{1c}, GA, and FA*

	Mean ± SD (days)	Min–Max (days)	95% CI of mean (days)	Theoretical value (days)	
				Ramp	Stepwise
HbA_{1c}					
Quarter-time	15.9 ± 6.7	8.6 – 27.0	10.7–20.9	19.1	16.1
Half-time	34.6 ± 10.1	19.5 – 48.7	27.0–41.7	34.8	35.1
Three-quarter-time	53.6 ± 11.0	38.7 – 68.2	45.7–61.9	55.0	60.0
GA					
Quarter-time	9.8 ± 3.0	5.8 – 14.4	7.1–11.7	9.8	7.1
Half-time	17.1 ± 2.8	11.9 – 20.3	15.0–19.2	17.5	17.1
Three-quarter-time	29.5 ± 8.1	18.9 – 41.9	23.4–35.6	29.1	34.2
FA					
Quarter-time	6.1 ± 3.1*	3.0 – 11.7	3.8–8.4	7.0	5.1
Half-time	12.2 ± 4.8†	7.3 – 19.3	8.6–15.8	12.3	12.2
Three-quarter-time	27.6 ± 11.3	17.5 – 51.5	19.1–36.1	19.8	24.4

* $P < 0.05$ vs. quarter-time of GA. † $P < 0.05$ vs. half-time of GA.

two types of theoretical estimation: responses to ramp and stepwise plasma glucose changes. The solid curves show the theoretical time courses in response to a ramp plasma glucose change with a half-time of 6.3 days. In calculating these curves, the real half-times of HbA_{1c}, GA, and FA were assumed to be 28.3, 10.8, and 5.9 days, respectively, which were obtained by subtracting the half-time of FPG from their observed values. The broken curves are those in response to a stepwise plasma glucose change, where the erythrocyte life span was assumed to be 120 days and the half-times of GA and FA were assumed to be 17.1 and 12.2 days, respectively. To examine the agreement between the experimental and theoretical time courses, the values for quarter-time, half-time, and three-quarter-time were calculated as the times required for 25, 50, and 75% changes from the initial to the lowest levels in individual patients. The means ± SD of the time constants and the 95% confidence intervals (CIs) of the mean are given in Table 1. All of the time constants for both theoretical curves fell within the 95% CI.

Experimental analyses of the weight functions were done assuming that the plasma glucose level changed in a stepwise fashion. The results are shown in Fig. 4. Theoretical curves of the weight functions are also shown in the figure, where the erythrocyte life span was assumed to be 120 days and the half-times of GA and FA were assumed to be 17.1 and 12.2 days, respectively. The experimental data were scattered around these curves. The values of the weight functions were maximal on the days just before the measurement of glycated proteins and decreased gradually with increasing time intervals. To estimate the length of the period over which the weight function has a significant level, we applied a straight line to these data and calculated the intercept of the best-fit line with the horizontal axis. In calculation of the best-fit lines for GA and FA, only the data in the region of <50 and <40 days were used, respectively, because the data for GA and FA had a long tail, and analysis using all the data yielded too long a time period. The calculated best-fit lines are shown in Fig. 3 by broken lines. The intercept of the line with the horizontal axis was 112, 53, and 42 days (95% CI 92–155, 44–73, and 34–66 days) for HbA_{1c}, GA, and FA, respectively.

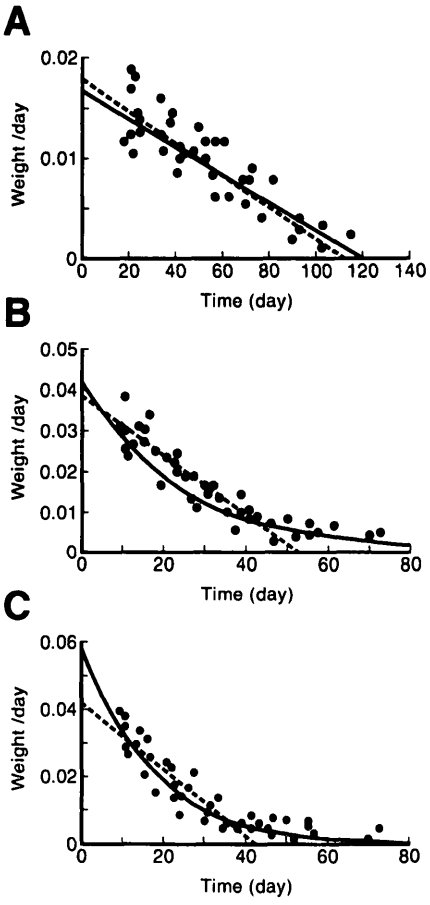

Figure 4—*Weight functions for HbA_{1c} (A), GA (B), and FA (C) against preceding plasma glucose level as a function of time interval (dots, experimental values; solid curves, theoretically estimated values; broken lines, best-fit linear lines).*

CONCLUSIONS— To examine the relationship between the level of glycated protein and the preceding plasma glucose

level, many authors have investigated the responses of glycated proteins to various plasma glucose changes experimentally (5–15) and theoretically (2,18–20,26, 27). However, it has not been well understood how the preceding plasma glucose level contributes to the level of glycated protein. Although the level of glycated protein has been thought to reflect the simple mean plasma glucose level in the preceding period, there are many findings conflicting with this idea. In the present study, we assumed that the level of glycated protein reflects the weighted mean of the preceding plasma glucose levels and analyzed the time courses after acute plasma glucose normalization and the weight functions against the preceding plasma glucose level.

The time courses of glycated proteins after acute plasma glucose normalization were compared with two types of theoretical estimation. One is the response to a ramp plasma glucose change, and the other is the response to a stepwise plasma glucose change. In the calculation of the response to a ramp plasma glucose change, the half-times of glycated proteins were given by subtracting the half-time of FPG from their observed values. On the contrary, the responses of glycated proteins to a stepwise plasma glucose change were calculated assuming that their half-times were equal to the observed values. The theoretical simulation showed that both curves agreed with the experimental results. Considering the lag of plasma glucose normalization, the model of a ramp plasma glucose change seems to apply better to the present data. However, the theoretically expected half-time of HbA_{1c} is 35.1 days when the erythrocyte life span is assumed to be 120 days (19) and that of GA is 17–20 days because it should be equal to the half-life of serum albumin (25). These half-time values seem to be in better agreement with the model of a stepwise plasma glucose change.

At present, we cannot determine which model is more appropriate to the current data, because there are several problems in the theoretical estimation. First, although the time course of glycated protein is influenced by the plasma glucose fluctuation before admission, there were no data indicating whether the plasma glucose level before admission could be regarded as a steady-state condition. Second, the glycemic control level after diabetic treatment could not be regarded as a steady-state condition, because the FPG level after 3 weeks showed considerable fluctuation. Particularly, the change in the glycemic control level before glycated protein normalization strongly influences the time course of glycated protein recovery. If the level of glycemic control is further improved before the level of glycated protein reaches a steady-state level, the half-time of the change in the glycated protein level will apparently become longer, whereas if the glycemic control level is worsened, the half-time will apparently become shorter. Third, the glycemic control level was monitored only by FPG in the present examination. Although the FPG level usually reflects the glycemic control level in diabetic patients, whether the kinetics of the daily glycemic level were the same as those of FPG in the present examination is not clear.

Considering these points, there are many problems in the analysis of the time course, assuming a simple plasma glucose change in a ramp or stepwise fashion. If an ideal ramp or stepwise plasma glucose change had actually been realized, more accurate analysis could be performed. However, it is not easy to realize an ideal plasma glucose change. It is impossible to obtain a steady-state condition before a patient's admission, and it is very difficult to regulate the glycemic level in a complete, steady-state condition over 4 months after admission, even when frequent plasma glucose monitoring is done. A more appropriate way of accurate analysis may be to calculate the time courses using actual glycemic excursion. For this purpose, precise glycemic excursion must be examined throughout the observation period. Considering these points, the present examination cannot provide enough data to assess the accuracy of the agreement between experimental and theoretical time courses of glycated proteins.

Note that the half-time of FA was significantly less than that of GA. The FA level was reported to reflect the level of glycated serum protein (16,17). Since more than half of serum protein consists of serum albumin, FA and GA have been thought to provide similar information about the preceding plasma glucose level (28). However, the FA level was reported to behave differently from GA (29). One of the possible reasons for this discrepancy is that various glycated proteins other than GA also contribute to FA (17), and another is that the reducing activities caused by unknown factors other than glycated proteins contribute to the FA level (30). Therefore, we cannot consider that FA has the same meaning as GA for assessing glycemic control levels in diabetic patients. To establish the clinical significance of FA, the factors that contribute to the FA level should be further examined in detail.

In this study, we have tried to demonstrate the shapes of weight functions for glycated proteins against the preceding plasma glucose level. The results showed that the rate of contribution of the preceding plasma glucose level to the glycated protein level is not constant but decreases gradually with an increasing time interval. Although many authors have tried to analyze the relationship between the level of glycated protein and the preceding plasma glucose level, none has succeeded in demonstrating the relationship between them. In a previous study (23), we analyzed the relationship theoretically using a linear kinetic model. The assumptions used were as follows: the glycation process is irreversible, the fraction of glycated protein is low, and the erythrocyte life span and disappearance constant of serum albumin are unchanged throughout the observation period. This model was similar to those of previous studies (2,18–20). Under such

assumptions, we have shown that the weight functions for HbA_{1c} and GA are maximal on the days just before their measurement and gradually decrease with an increasing time interval.

Contrary to these reports, we assumed in this study that the level of glycated protein can be expressed by the weighted mean of the preceding plasma glucose level. From the mathematical point of view, this assumption indicates a linear relationship between the level of glycated protein and the preceding plasma glucose level. In other words, the level of glycated protein should be proportional to the preceding plasma glucose level under steady-state conditions. As shown in the APPENDIX, we could derive a simple formula that allows us to analyze the weight functions experimentally using data in response to a stepwise plasma glucose change. Using this formula, we analyzed the values of weight functions for HbA_{1c}, GA, and FA and showed that the experimental results agree with the theoretical predictions. The weight functions extended back over 112, 53, and 42 days, respectively.

The largest problem in this analysis is that the plasma glucose level did not change in a stepwise fashion. As discussed in the analysis of the time courses, the lag of plasma glucose normalization delays the time courses of glycated proteins and therefore elongates apparent lengths of the periods over which the weight functions extend back. Although we cannot strictly evaluate the effect of the lag of plasma glucose normalization, the time lengths may be able to be roughly estimated by subtracting twice the half-time of FPG from their observed values. If this is the case, the lengths of the periods over which the weight functions for HbA_{1c}, GA, and FA extend back can be estimated to be about 100, 40, and 30 days, respectively.

To understand the clinical meaning of the weight function, it is useful to consider the response of glycated protein to a stepwise plasma glucose change. As shown in the APPENDIX, the change of glycated protein level m days after a stepwise plasma glucose change is given just by the area under the curve of the weight function between 0 and m. This means that 50% of the level of glycated protein is determined by the plasma glucose level during the preceding period equal to the half-time length. Considering such a simple relationship between the time course and weight function, the responses of glycated proteins to a stepwise plasma glucose change must be examined more accurately.

Finally, let us consider the physiological meaning of the idea that the level of glycated protein reflects the weighted mean of the preceding plasma glucose level. For this purpose, we consider the relationship between the level of glycated hemoglobin in an erythrocyte and the age of the erythrocyte. Hemoglobin in an erythrocyte aged 1 day has been glycated in the preceding 1 day, whereas hemoglobin in an erythrocyte aged 10 days has been glycated over the preceding 10 days, and hemoglobin in an erythrocyte aged 120 days has been glycated throughout the preceding 120 days. Considering the reverse, the plasma glucose level 1 day before the measurement of HbA_{1c} has glycated the hemoglobin in all the erythrocytes aged 1–120 days, whereas the plasma glucose level 10 days before has glycated the hemoglobin in the erythrocytes aged 10–120 days, and the plasma glucose level 120 days before has glycated the hemoglobin in the erythrocyte aged 120 days only. Thus, the amount of glycated hemoglobin in an erythrocyte increases with increasing erythrocyte age, and the plasma glucose in the earlier period has glycated the hemoglobin in fewer erythrocytes. These facts suggest that the rate of contribution of the plasma glucose to the HbA_{1c} level becomes smaller with an increasing time interval. Similar explanations apply to GA and FA by dividing serum albumin and proteins into cohorts with the same elapsed times after their production.

We conclude that the level of glycated protein does not reflect the simple mean plasma glucose level but reflects the weighted mean plasma glucose level in the preceding period, which is considerably longer than was previously speculated.

APPENDIX

Calculation of the time course of glycated protein

Let us assume that the plasma glucose was at a constant level before time 0 and its incremental level at time t ($t \geq 0$) is $\Delta G(t)$. Then, the incremental level of glycated protein at time m ($m \geq 0$) is given by

$$\Delta H(m) = K \int_0^m W(m - t)\Delta G(t)dt \quad \text{(A1)}$$

The theoretical weight function for HbA_{1c} derived from a linear kinetic model (23) is given by

$$W(s) = \begin{cases} 2(T - s)/T^2 & (0 \leq s \leq T) \\ 0 & (s > T) \end{cases} \quad \text{(A2)}$$

where T is the erythrocyte life span. The theoretical weight function for GA derived from a linear kinetic model (23) is given by

$$W(s) = (1/\tau) \exp(-s/\tau) \quad \text{(A3)}$$

where τ is the disappearance constant of GA. Using these equations, we can calculate the time courses of HbA_{1c} and GA in response to any plasma glucose change.

If the plasma glucose changed in a stepwise fashion, the response of HbA_{1c} becomes

$$\Delta H(m) = \begin{cases} \Delta H_0 m(2T\text{-}m)/T^2 & (0 \leq m \leq T) \\ \Delta H_0 & (m > T) \end{cases} \quad \text{(A4)}$$

where $\Delta H_0 = K\Delta G_0$. The half-time of HbA_{1c} change is then given by

$$T_{1/2} = 0.293T \quad \text{(A5)}$$

The response of GA to a stepwise plasma glucose change is given by

$$\Delta H(m) = \Delta H_0 \{1 - \exp(-m/\tau)\} \quad \text{(A6)}$$

The half-time of GA is then given by

$$T_{1/2} = 0.693\ \tau \quad \text{(A7)}$$

Experimental analysis of the weight function

If the plasma glucose level changed by ΔG_0 in a stepwise fashion at time 0, $\Delta H(m)$ can generally be written as

$$\Delta H(m) = K \int_0^m W(m - t)\Delta G_0 dt \quad \text{(A8)}$$

$$= \Delta H_0 \int_0^m W(t)dt$$

Differentiating $\Delta H(m)$ by m, we can obtain the following equation

$$\frac{d\Delta H(m)}{dm} = \Delta H_0\, W(m) \quad \text{(A9)}$$

Thus, $W(s)$ is given by

$$W(s) = \frac{1}{\Delta H_0} \cdot \frac{d\Delta H(s)}{ds} \quad \text{(A10)}$$

This equation indicates that the weight function $W(s)$ can be analyzed experimentally from the time course of $\Delta H(m)$ in response to a stepwise plasma glucose change.

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