1,5-Anhydro-D-glucitol Evaluates Daily Glycemic Excursions in Well-Controlled NIDDM

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OBJECTIVE — To evaluate the usefulness of plasma 1,5-anhydro-D-glucitol (1,5-AG) as a possible marker for daily glycemic excursion, we measured plasma 1,5-AG, HbA_{1c}, fasting plasma glucose (FPG) level, and daily excursion of glycemia, from which the M-value (after Schlichtkrull) was calculated as an index of daily glycemic excursion.

RESEARCH DESIGN AND METHODS — The subjects were 76 patients with well-controlled non-insulin-dependent diabetes mellitus (NIDDM) treated with diet therapy only (diet, $n = 17$), oral hypoglycemic agents (OHA, $n = 28$), conventional insulin therapy (CIT, $n = 16$), or multiple insulin injection therapy (MIT, $n = 15$).

RESULTS — HbA_{1c} values were similar among all the groups (diet, 6.9 ± 0.6; OHA, 7.2 ± 0.5; CIT, 7.1 ± 0.6; MIT, 7.2 ± 0.5%). The MIT group showed a significantly higher 1,5-AG concentration (11.5 ± 5.3 μg/ml), a significantly lower M-value (9.2 ± 5.2), and little risk of hypoglycemia (<4 mmol/l) and hyperglycemia (>10 mmol/l) (1.3 ± 1.1 times/24 h) compared with the CIT group (6.9 ± 3.3 μg/ml, 15.7 ± 8.9, 2.2 ± 1.6 times/24 h, respectively). Insulin doses (22.4 ± 4.5 vs. 22.0 ± 8.9 U/day), FPG (6.6 ± 2.2 vs. 7.4 ± 2.4 mmol/l), and HbA_{1c} concentrations were not significantly different between the CIT and MIT groups. M-values significantly correlated with 1,5-AG concentrations ($r = 0.414$, $P < 0.05$), but not with HbA_{1c} concentrations.

CONCLUSIONS — The findings suggest that the plasma 1,5-AG concentration can be a useful index of the daily excursion of blood glucose, especially in patients with well-controlled NIDDM.

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1,5-AG, 1,5-anhydro-D-glucitol; CIT, conventional insulin therapy; FPG, fasting plasma glucose; IDDM, insulin-dependent diabetes mellitus; MIT, multiple insulin injection therapy; NIDDM, non-insulin-dependent diabetes mellitus; OHA, oral hypoglycemic agents; SMBG, self-monitoring of blood glucose.

One of the main sugar alcohols in human cerebrospinal fluid and serum, 1,5-anhydro-D-glucitol (1,5-AG), is a six-carbon chain monosaccharide in C-1 chain conformation with an oxygen ring in the pyran position (1). The plasma 1,5-AG concentration is considered to be a useful indicator of glycemic control, because 1,5-AG significantly correlates with fasting plasma glucose (FPG) and HbA_{1c} (2–4). HbA_{1c} and fructosamine are affected by the plasma glucose concentration during both hypoglycemia and hyperglycemia periods (5,6). Plasma 1,5-AG concentration can also be considered to be a marker of hyperglycemia, because 1,5-AG concentration decreases only when blood glucose concentrations exceed the threshold for urinary glucose excretion (3,4,7).

In the previous reports, a marked difference in 1,5-AG concentration was seen among patients indicated to be under similar glycemic control by traditional tests (8,9). To analyze the mechanism resulting in different 1,5-AG concentrations among the patients with well-controlled diabetes, judged from their low HbA_{1c} concentrations, we measured several markers for glycemic control in patients with non-insulin-dependent diabetes mellitus (NIDDM) controlled by diet, oral hypoglycemic agents (OHA), conventional insulin therapy (CIT), or multiple insulin injection therapy (MIT).

RESEARCH DESIGN AND METHODS

— Participants in this study were 76 nonobese NIDDM outpatients to Osaka University Hospital. The patients were treated with diet alone (diet, $n = 17$), OHA ($n = 28$), CIT ($n = 16$), or MIT ($n = 15$) (10). The patients with good control of diabetes were selected using a marker of previous glycemic control, HbA_{1c}. Their HbA_{1c} had been lower than 8.0% with <0.2% variation for the previous 2 months. Insulin doses in the CIT and MIT groups were 22.4 ± 4.5 and 22.0 ± 8.9 U, respectively (NS) (Table 1). The duration of di-

Table 1—*Patient characteristics*

	CIT	MIT	*P* value
Sex (M/F)	8/7	6/10	—
Age (years)	55.1 ± 7.3	57.6 ± 6.6	—
Duration of diabetes (years)	10.8 ± 5.7	13.1 ± 5.2	—
Duration of insulin therapy (years)	6.4 ± 3.3	4.4 ± 3.8	—
Insulin dose (U/day)	22.4 ± 4.5	22.0 ± 8.9	—
FPG (mmol/l)	6.6 ± 2.2	7.4 ± 2.4	—
HbA_{1c} (%)	7.1 ± 0.6	7.2 ± 0.5	—
1,5-AG (μg/ml)	6.9 ± 3.3	11.5 ± 5.3	<0.05
M-value	15.7 ± 8.9	9.2 ± 5.2	<0.05
Rate of hyperglycemia (>10.0 mmol/l) (per 24 h)	1.2 ± 0.9	1.1 ± 0.9	—
Rate of hypoglycemia (<4.0 mmol/l) (per 24 h)	1.0 ± 0.9	0.1 ± 0.3	—

Data are means ± SD.

abetes in the CIT and MIT groups was 10.8 ± 5.7 and 13.1 ± 5.2 years, respectively (NS). The durations of insulin therapy in the CIT and MIT groups were 6.4 ± 3.3 and 4.4 ± 3.8 years, respectively (NS). They did not have severe diabetic complications or other diseases independent of diabetes.

Plasma 1,5-AG concentration, HbA_{1c}, and FPG were measured after overnight fasting. Daily excursions of glycemia (self-monitoring of blood glucose [SMBG]) were assessed with 35 subjects (2 diet, 2 OHA, 16 CIT, 15 MIT). On the day of SMBG, glucose concentrations were determined before each meal (breakfast, lunch, and supper), 2 h after each meal, just before sleeping for the night, and before breakfast the next morning. From these determinations, M-values were calculated by the method of Schlichtkrull et al. (11). FPG was determined by the glucose oxidase method. SMBG was conducted using a non-wiping–type glucose meter (12). The blood glucose concentrations determined by the sensor (Y) were compatible with the plasma glucose concentrations (X) determined by the glucose oxidase method ($Y = 1.06X - 0.91$, $r = 0.99$) (12). The HbA_{1c} concentration was determined by high-performance liquid chromatography. Plasma 1,5-AG concentration was determined by an enzymatic method (Nippon Kayaku, Tokyo, Japan) (13).

All values were expressed as means ± SD. Data of two groups were compared with Student's t test. Regression analysis was performed to account for the interaction between 1,5-AG concentrations and M-values. $P < 0.05$ was considered significant.

RESULTS — HbA_{1c} concentrations showed no significant differences among the diet, OHA, CIT, and MIT groups (6.9 ± 0.6, 7.2 ± 0.5, 7.1 ± 0.6, and 7.2 ± 0.5%, respectively) (Fig. 1). FPG values showed no significant differences among the diet, OHA, CIT, and MIT groups (6.4 ± 2.3, 6.7 ± 1.4, 6.6 ± 2.2, and 7.4 ± 2.4 mmol/l, respectively). 1,5-AG concentrations in the diet, OHA, CIT, and MIT groups were 17.3 ± 6.9, 10.7 ± 6.3, 6.9 ± 3.3, and 11.5 ± 5.3 μg/ml, respectively. Plasma 1,5-AG concentrations in CIT were significantly lower than those in the diet, OHA, and MIT groups ($P < 0.05$). Plasma 1,5-AG concentrations in the OHA and MIT groups were significantly lower than those in the diet group ($P < 0.05$). M-values calculated by the daily excursions of glycemia were 15.7 ± 8.9 for the CIT group and 9.2 ± 5.2 for the MIT group. During the investigation, the rates of hyperglycemia (<10 mmol/l) in the CIT and MIT groups were 1.2 ± 0.9 and 1.1 ± 0.9 times/24 h, respectively. The rates of hypoglycemia (<4 mmol/l) in the CIT and MIT groups were 1.0 ± 0.9 and 0.1 ± 0.3 times/24 h, respectively. Plasma 1,5-AG concentrations significantly correlated with M-values ($r = 0.414$, $P < 0.05$), although there was no correlation between HbA_{1c} concentrations and M-values (Fig. 2).

CONCLUSIONS — Plasma 1,5-AG concentration has been reported to correlate significantly with the FPG value and

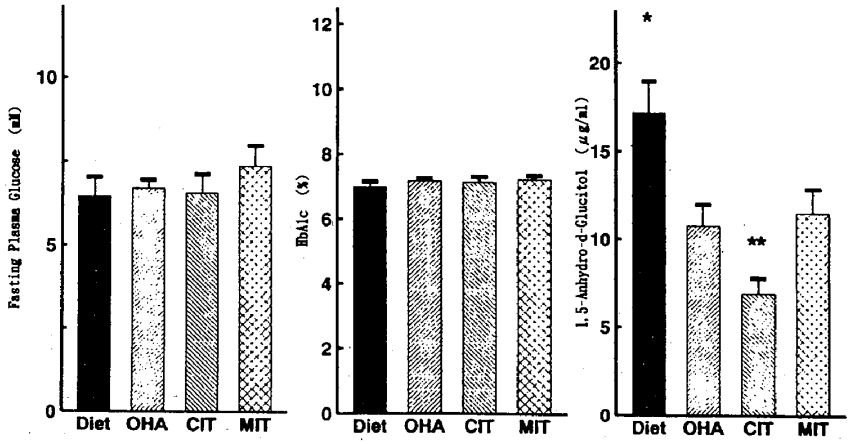

Figure 1—*Plasma 1,5-AG, HbA_{1c}, and FPG levels in NIDDM patients, well controlled with diet, OHA, CIT, or MIT (mean ± SE). *Plasma 1,5-AG concentrations in the diet group significantly higher than those in the OHA and MIT groups ($P < 0.05$). **Plasma 1,5-AG concentrations in CIT significantly lower than those in diet, OHA, and MIT groups ($P < 0.05$).*

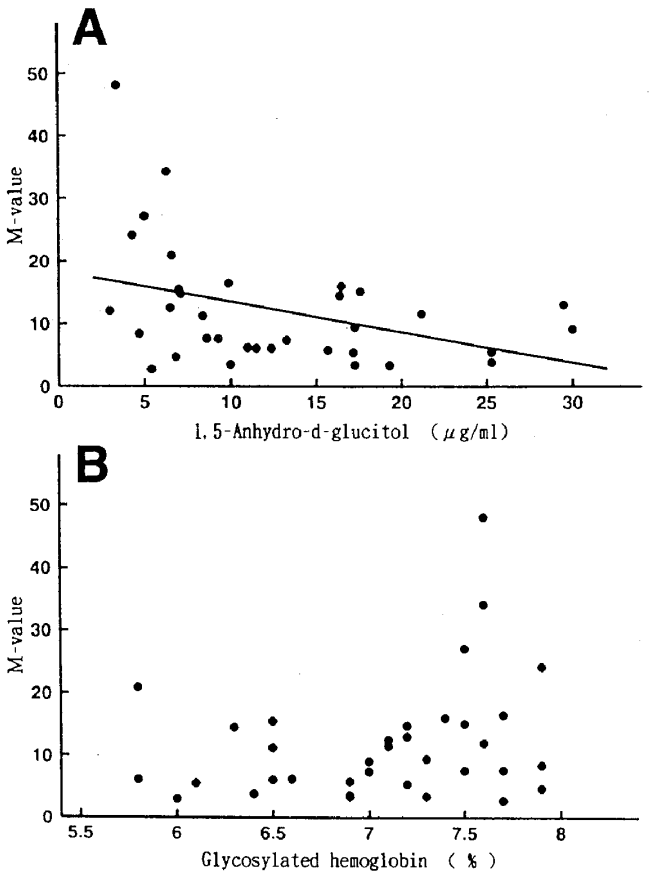

Figure 2—*Correlation between M-values (after Schlichtkrull) and plasma 1,5-AG concentrations (A) and glycosylated hemoglobin concentrations (B) in 35 NIDDM patients. Plasma 1,5-AG concentrations significantly correlated with M-values. There was no correlation between HbA_{1c} concentrations and M-values.* $Y = -0.4830X$. $r = 0.41487$ ($P < 0.05$). $n = 35$.

the HbA_{1c} concentration and is thus considered to be a useful indicator of glycemic control (2–4). However, some patients exhibit a marked discrepancy between plasma 1,5-AG concentration and glycosylated markers; the reason for this discrepancy remains to be clarified (8,9).

1,5-AG originates from orally ingested food, and plasma 1,5-AG concentration increases slowly (14). The daily intake of 1,5-AG is ~4.4 mg, which is independent of kinds of food (0.22 mg/100 kcal). 1,5-AG is filtered out by the glomeruli and largely reabsorbed by the renal tubules (14). The average 1,5-AG concentration in nondiabetic subjects is reported to be 21–26 μg/ml, whereas the origin of 1,5-AG is balanced with 1,5-AG urinary excretion (3,4,14,15). Because 1,5-AG has a structure similar to that of glucose, its absorption meets with competition from glucose in the renal tubules. When the blood glucose concentration exceeds the threshold for urinary glucose excretion, 1,5-AG reabsorption is reduced, and plasma 1,5-AG concentration is decreased (3,4,7,16). Moreover, it has been reported that a change in the plasma 1,5-AG concentration is correlated with the amount of urinary glucose (16). This suggests that the plasma 1,5-AG concentration might be considered as a marker of hyperglycemia.

HbA_{1c} and fructosamine are affected by plasma glucose concentrations during both hypoglycemic and hyperglycemic periods and thus show averaged glycemic excursion. Therefore, a diabetic patient who has a low plasma 1,5-AG concentration as well as a good HbA_{1c} concentration may have fluctuating daily glycemic excursion. To evaluate this hypothesis, we measured plasma 1,5-AG, HbA_{1c}, and the daily excursion of glycemia in patients with well-controlled NIDDM of different treatment groups. We found no significant difference in HbA_{1c} concentrations and FPG values among the groups. Also, insulin doses and diabetic durations were not significantly different in the CIT and MIT groups. However, 1,5-AG concentrations in the CIT group were significantly lower than those in the other treatment groups. In the CIT group, M-values calculated by daily excursions of glycemia and rates of hyperglycemia and hypoglycemia were larger than those in the MIT group. The M-value significantly correlated with plasma 1,5-AG concentration but not with the HbA_{1c} concentration. These results suggest that the plasma 1,5-AG concentration is a useful index for daily excursion of glycemia when averaged daily glycemia is well controlled.

CIT or intermediate insulin therapy cannot completely control postprandial hyperglycemia due to lack of bolus insulin and might cause hypoglycemia before a meal. Therefore, plasma 1,5-AG concentrations in the CIT group were less than those in the MIT group. IDDM patients showed lower 1,5-AG concentrations than NIDDM patients (8,9). It was thus considered that plasma 1,5-AG concentration might depend on pancreatic β-cell–secretory activity. However, in our study, there was no significant difference in plasma 1,5-AG concentration between the OHA and MIT groups. These data suggest that plasma 1,5-AG concentration depends on glycemic control rather than on pancreatic β-cell–secretory activ-

ity. Furthermore, because IDDM patients more frequently have hypoglycemia and hyperglycemia than NIDDM patients, IDDM patients might have lower plasma 1,5-AG concentrations than NIDDM patients whose glycemic control subjects were indicated to be similar, based on HbA_{1c} concentrations as reported previously (8,9).

The mechanism regulating plasma 1,5-AG concentration in diabetic patients is mainly the competition of glucosuria, and other mechanisms may cooperate, such as dietary change and renal disease (1,17). Recently, it was reported that nondiabetic patients with end-stage renal disease not receiving dialysis had markedly lower plasma 1,5-AG concentrations (18). We did not consider the effect of diabetic complications and other diseases, because the patients who participated in this study did not have those diseases. Diabetic patients with both low plasma 1,5-AG concentrations and low HbA_{1c} concentrations should be examined, however, to rule out postprandial hyperglycemia or other diseases such as severe renal complications.

In conclusion, plasma 1,5-AG concentration can serve as a marker for the daily excursion of glycemia, especially in patients who seem to have well-controlled diabetes, as judged from low HbA_{1c} concentrations.

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