Glycemic Instability Estimated By 1,5-Anhydroglucitol Persists Even After Normalization of A1C By Treatment in Patients With Type 2 Diabetes

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OBJECTIVE

The purpose of this study was to compare the extent of glycemic instability over the long term in patients with type 2 diabetes who had achieved normoglycemia after treatment with that in normal subjects.

BACKGROUND

Postprandial hyperglycemia often occurs in subjects with apparently good metabolic control (ie, A1c <7.0 %). However, it is not clear whether postprandial hyperglycemia or glycemic excusions still occur after normalization of mean glycemia levels has been achieved with treatment.
Glycemic excursions occur commonly in everyday life not only due to the variety of food eaten, but also to irregular meal times, extent of exercise, mental stress, sleep duration, adherence to lifestyle improvements, compliance with drugs, etc. Continuous glucose monitoring systems (CGMS) reveal that glucose excursions occur, extensively on a day-to-day basis even in diabetic patients who maintain near-normoglycemia.
1,5-AG is a novel marker for glycemia, developed in Japan, and recently also used commercially in the United States. 1,5-AG can easily detect slight changes in the glycemic state, and is well suited to monitoring postprandial hyperglycemia and/or excursions of glycemia.

Table 1 Study sample Characteristics

	Non-diabetic subjects	mean A1c (%)		
		< 5.8	5.8-6.4	6.5-6.9
n	82	21	52	66
Sex (male/female)	(48/34)	(13/8)	(30/22)	(35/31)
Age (year)	57.1±6.3	56.6±8.1	58.7±6.9	60.4±6.5
BMI (kg/m2)	23.5±1.6	24.1±1.1	24.5±1.3	23.6±3.0
Treatment (diet/oral hypoglycemic agent/ insulin)*	-	17/4/0	0/52/0	0/61/5

Data are means ± SD *Statistically significant

RESEARCH DESIGN AND METHODS

Data were sampled from medical records since 1998. For our analyses, we made screenings approximately 1300 subjects who had complete monthly data for at least consecutive 12 months for fasting plasma glucose (FPG), 1,5-AG, and A1c levels.
Subjects with an FPG <110 mg/dl (5.6 mmol/l) and a non-fasting glucose level <140 mg/dl (7.8 mmol/l) were considered non-diabetic. Subjects that fit only one of the glucose level defined above were excluded from the study. Non-diabetic subjects consisted mainly of subjects with essential hypertension, familial mild hypercholesterolemia, and non-obese hyperuricemia and/or gout. Subjects with a body mass index (BMI) ?30 kg/m2, nephropathy (serum creatine ≧120 μmol/l), severe liver dysfunction, or anemia were excluded, as were pregnant woman.
Glycemic levels of diabetic patients were classified by A1c level using Japanese guidelines*. Inclusion criteria of this study was that mean value of A1c of 12 consecutive monthly for 1 year measurements was entered into one of these ranges. Glycemic excursions** were estimated by 1,5-anhydroglucitol (1,5-AG) levels calculated from 12 consecutive monthly measurements and were compared with that of non-diabetic subjects.

* Japanese guidelines for the A1c in glycemic control		
< 5.8	5.8-6.4	6.5-6.9
excellent	good	fairly good control

** The calculating formula of excursion index

$$\frac{\text{SD of each parameter}}{\text{average of the same parameter}} \times 100(\%)$$

In this study, we called this the 1,5-AG excursion index or mean A1c excursion, respectively. In this formula, SD and average were calculated from the data of 12 points of 1,5-AG or A1c in a year in each subjects.
Example: Figure 1.
A1c (normal range, 4.3% - 5.8%) was assayed by high-performance liquid chromotography (Auto A1c; Kyoto Daiichi Kagaku, Japan), with a CV of 2.4%. 1,5-AG (normal range, 14.0 - 39.0 μg/ml) was measured with an autoanalyzer system (Automatic Clinical Analyzer, Model 7150; Hitachi, Tokyo, Japan), with an interassay CV of 4.5% and an intra-assay CV of 1.0%.

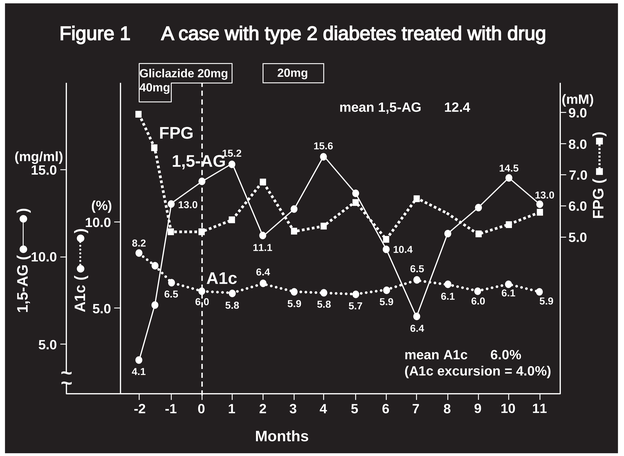
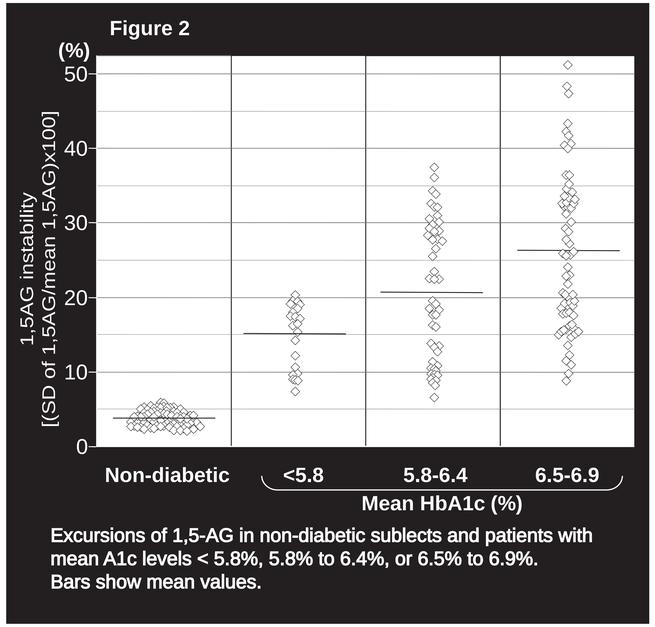


Table 2 Mean and extent of excursion of glycemic parameters during the monitor period for 12 months

	Non-diabetic subjects	mean A1c		
		< 5.8	5.8-6.4	6.5-6.9
mean 1,5-AG (mg/ml) (range)	25.1±8.7 (14.8-40.2)	15.6±4.3* (7.4-25.3)	9.6±4.3* (3.0-16.2)	7.8±3.3** (2.6-12.8)
mean FPG (mmol/l) (range)	5.2±0.3 (4.4-5.6)	5.4±0.4 (5.1-5.7)	6.2±1.5* (5.8-6.4)	6.7±1.3* (6.5-6.9)
mean 1,5-AG excursion (%) † (1,5-AG excursion index)	3.8±1.0	15.1±4.3***	20.6±9.1***	26.2±12.0***
mean A1c excursion (%) †	4.5±0.7	4.3±0.5	4.6±2.2	5.2±2.0

Data are means ± SD. *P<0.01, ***P<0.0001 vs non-diabetic.

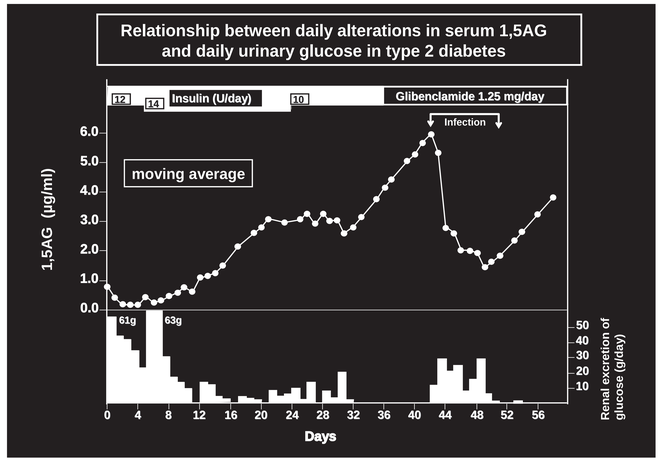


DISCUSSION

1,5-AG, a 1-deoxyglucopyranose, is a new glycemic marker. It is excreted quickly into urine by glucosuria when glycemia increases. If a patient has postprandial hyperglycemia or glycemic excursions with glucose spikes, 1,5-AG levels easily decrease, induced by repeated glucosuria. Unlike 1,5-AG levels, A1c levels cannot sufficiently detect these short-term incidences of hyperglycemia, because the time required for complete formation of glycation is much longer than the duration of the glucose spike. This is the main mechanism that contributes to the d iscrepancy between 1,5-AG and A1c values.
Even after normalization of A1c levels, glycemia was far from stable compared with normal subjects. These results are consistent with the relatively short observation reported by Dungan et al.
The pathophysiology of diabetes mellitus must include not only hyperglycemia but a deterioration in glycemic-excursion control as well.
Can we normalize the excursions of glycemia in diabetic or previously diabetic patients?
One possibility may arise from a longer maintenance of good glycemic control, at least more than several years. Another is to recover the patients' own absolute normal glycemic level.
Usually, we aim to reach the normal level of A1c defined by the population study. However, recent studies reveal that A1c levels vary individually. Perhaps we need to aim not for e pidemiological normal ranges, but rather for individual normal A1c levels when treating d iabetes mellitus.

CONCLUSIONS

Glycemic stability in diabetic patients is not easily restored for long periods even with treatment that maintains normoglycemia, as estimated by A1c levels.



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