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Summary

Background To evaluate prospectively the clinical value of measuring serum concentrations of 1,5-anhydroglucitol (1,5AG) in monitoring glycaemia in patients with newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM), we measured serum 1,5AG in 56 such patients.

Methods 28 patients (group A) were started on, and continuously received, an oral hypoglycaemic agent for at least 6 weeks. The other 28 patients (group B) were given such agents for 4 weeks, and then stopped taking them for at least 2 weeks. All patients were then followed for an additional 10 weeks. Serum 1,5AG, fructosamine, glycated haemoglobin (HbA_1c), and self-monitoring of blood glucose were monitored every 14 days for 16 weeks.

Findings When sudden worsening of glycaemia occurred within 2 weeks, entailing withdrawal of oral treatment, 1,5AG accurately detected the slight change in glycaemia whereas HbA_1c and fructosamine both failed to detect it. Although the change was detected by measurement of fasting plasma glucose (FPG) concentrations, FPG was less sensitive than 1,5AG. In patients with "near-normoglycaemia" (HbA_1c about 6·5%) in the preceding 8 weeks, those who showed a lower concentration of 1,5AG (<10·0 μg/mL) manifested a higher mean daily plasma glucose concentration even though HbA_1c measurement suggested good control of glycaemia. Results of 1,5AG were correlated more strongly with the FPG (r=0·790) and mean daily plasma glucose (r=−0·835) estimated on the same day than those estimated in the preceding 2, 4 and 8 weeks, and with a fall in the Spearman correlation coefficient at any preceding time interval.

Interpretation Because 1,5AG accurately detected a slight change in glycaemia without delay, it is suitable for use in monitoring for strict control of glycaemia, an important clinical goal.

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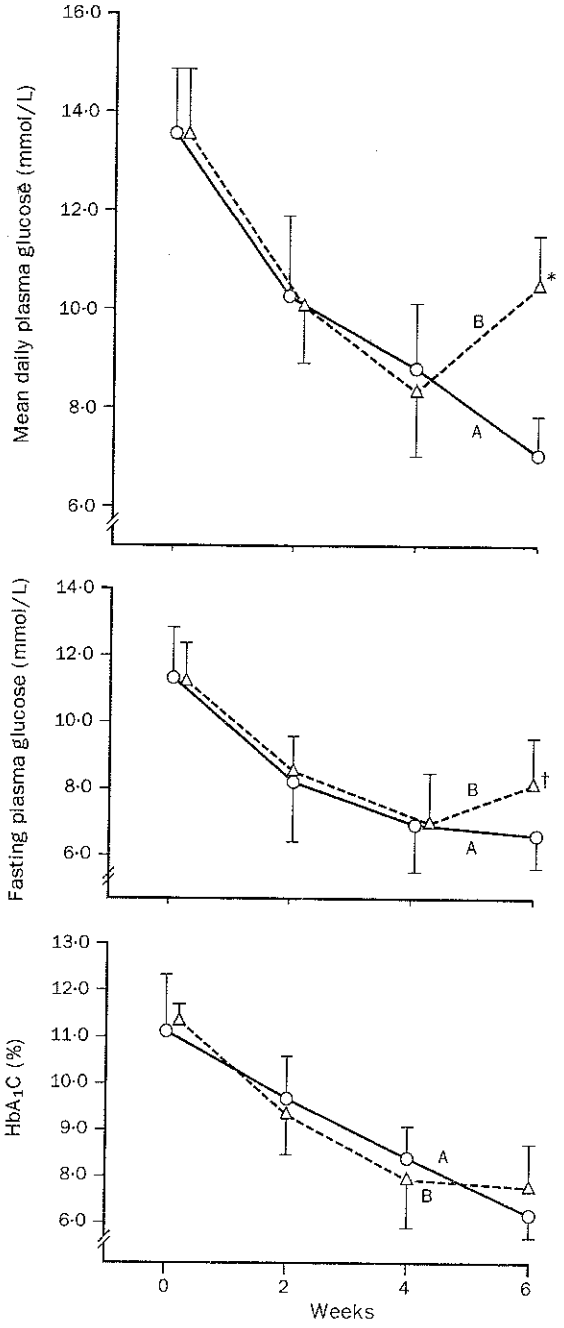
Introduction

The Diabetes Control and Complications Trial (DCCT)[1] established that control of glycaemia helps to prevent the complications of diabetes mellitus. Thus, monitoring of 24 h blood glucose concentrations by a simple method is mandatory for the management of diabetes. While the monitoring of glycaemia became easier following the introduction of a test for glycated haemoglobin (HbA_1c),[2] this test has at least three problems:[3-5] (1) there is wide variation between different methods in the measured values of HbA_1c that leads to large interlaboratory variations in results; (2) the narrow range of HbA_1c values, corresponding to changes in glycaemic control, indicate that the HbA_1c value may be influenced by variations in the assay; and (3) HbA_1c includes a component of information on glycaemic control that occurred 1 to 2 months earlier, thus the change in HbA_1c is often observed after the true change in glycaemia has occurred.

The polyol 1,5-anhydro-D-glucitol (1,5AG) is a six-



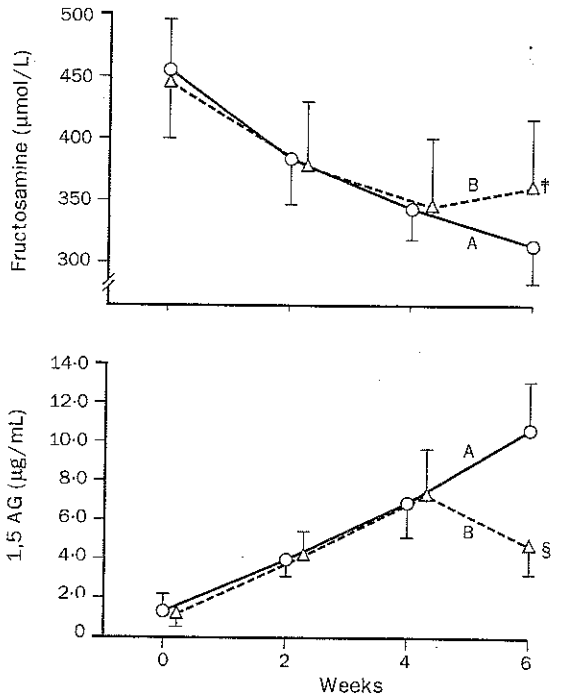


Figure 1: **Serial changes in glycaemic markers in 56 newly diagnosed NIDDM patients over 6 weeks**
Mean daily plasma glucose, fasting plasma glucose, HbA_1c, fructosamine, and 1,5AG are shown at 2-week intervals. A=28 patients who continued treatment for 6 weeks, and B=28 patients who discontinued treatment 4 to 6 weeks after its start. *p<0·001, †p<0·01, ‡p<0·05, §p<0·0001 *vs* group A at week 6.

carbon monosaccharide that is the 1-deoxy form of glucopyranose. Because the serum concentration of 1,5AG shows a sensitive[6,7] and specific change[8-11] in patients with diabetes mellitus, this polyol is being used in Japan as a new marker for monitoring the control of hyperglycaemia.[12] Determination of 1,5AG in a multicentre study proved superior to measurements of HbA_1c and of fructosamine in detecting diabetes mellitus.[13] We studied the utility of serum measurements of 1,5AG in assessing the control of plasma glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM).

Patients and methods

Patients and protocol

56 newly diagnosed Japanese patients with NIDDM and a fasting plasma glucose (FGP) concentration of about 11·0 mmol/L were studied for 16 weeks after the initiation of an oral hypoglycaemic agent. Excluded from study were patients with concomitant diseases or with severe diabetic complications, particularly nephropathy (plasma creatinine >0·2 mmol/L), anaemia (haemoglobin <10·0 g/dL), or hypoalbuminaemia (serum albumin <3·0 g/dL), as well as patients taking drugs that might affect the measurement of HbA_1c such as ascorbic acid and aspirin. Informed consent for participation was obtained from each patient before starting the study. Serum concentrations of HbA_1c, fructosamine, and 1,5AG, and the daily plasma concentration of glucose were monitored every 2 weeks for 16 weeks.

Patients were randomised to one of two groups, each of which initially received daily oral glibenclamide (0·625–5·0 mg) or gliclazide (20–40 mg). In group A were 28 patients who continued their hypoglycaemic drug treatment for at least 6 weeks, and in group B were 28 patients who received such treatment for 4 to 6 weeks then discontinued it for 2 weeks. Glycaemia deteriorated in group B after withdrawal of treatment; the oral hypoglycaemic agents were then reinstituted after week 6 as indicated. The daily dose of glibenclamide at week 4 averaged 1·25 mg. The clinical characteristics of these patients are shown in table 1. Patients were encouraged to exercise and/or to follow a diet during the study.

Every patient provided home-glucose-monitoring records at least once a week for 16 weeks. Blood was sampled at least seven times daily (preprandial, postprandial, and bedtime).

Assays

Patients fasted for 12 h before blood was sampled for

	Number	Sex (male/female)	Mean (SD) age (years)	Mean (SD) body-mass index (kg/m²)
Group A	28	13/15	51·3 (7·2)	23·3 (2·5)
Group B	28	12/16	50·5 (6·9)	23·6 (2·4)

Table 1: **Characteristics of patients in groups A and B**

Parameter	Week 4	Week 6	Parameter change	Δ parameter index	p
Mean (SD) daily plasma glucose (mmol/L)	8·39 (1·33)	10·50 (1·00)	2·11 (1·35)	1·560 (1·001)	
Mean (SD) fasting plasma glucose (mmol/L)	7·00 (1·50)	8·17 (1·39)	1·19 (1·11)	1·070 (0·973)	0·2287
Mean (SD) HbA_1c (%)	8·0 (1·2)	7·8 (0·9)	−0·2 (0·9)	−0·264 (0·997)	0·0001
Mean (SD) fructosamine (μmol/L)	347 (55)	362 (55)	15 (29)	0·512 (0·999)	0·01
Mean (SD) 1,5AG (μg/mL)	7·4 (2·2)	4·8 (1·5)	2·6 (1·8)	1·375 (0·996)	0·6273

Parameter change refers to the difference in values for each parameter between weeks 4 and 6 in the individual. A false-negative change is calculated as a minus value. Δ parameter index refers to the result of the parameter change divided by the within-group SD of the differences. p value indicates the significance of the difference between a change in test and the change in mean daily plasma glucose.

Table 2: **Sensitivity of four markers to a worsening of hyperglycaemia in 28 patients**

determination of serum 1,5AG and other markers. Self-monitoring of blood glucose (SMBG) was determined with the Glutest E system (Kyoto Daiichi Kagaku, Kyoto, Japan). To ensure the accuracy of the self determination of blood glucose, we made frequent comparisons between the glucose concentrations of samples obtained by each patient and those obtained in blood collected at our outpatient clinic and analysed by the hospital laboratory. A good agreement was demonstrated between the two methods (r=0·941).

HbA_1c (normal range 4·9–5·9%) was assayed by high-pressure liquid chromatography (Auto A_1c, Kyoto Daiichi Kagaku). Serum fructosamine (normal range 205–285 μmol/L) was measured by the fructosamine test (Roche, Nutley, NJ, USA). The interassay coefficient of variation (CV) was less than 3·0% for HbA_1c and less than 5·0% for fructosamine. Serum 1,5AG concentration (normal range 14·0–39·0 μg/mL) was determined with a autoanalyser (HLC-727AG, Tosoh, Tokyo, Japan).[14] The interassay CV was 3·1% and the intra-assay CV was 2·2%. All of the above measurements were done at our hospital laboratory.

Statistical analyses

Data are reported as mean (SD). For normally distributed data, statistical analysis was done with the unpaired t test. Differences between groups were estimated by Scheffe's test for single subgroups. To eliminate a skewed distribution, serum 1,5AG values were log-transformed for statistical analyses and transformed back into their real units for presentation. Analysis of mixed multiple observations from different subjects was done according to the method described by Bland and Altman.[15] Statistical significance was set at a p value of less than 0·05.

Results

The mean daily plasma glucose concentration was improved on drug treatment by week 4 in both groups: in group A from 13·56 (1·33) to 8·83 (1·28) mmol/L, and in group B from 13·61 (1·28) to 8·39 (1·33) mmol/L (figure 1). Concomitantly, the FPG, HbA_1c, fructosamine, and 1,5AG concentrations also improved. After administration of an oral hypoglycaemic agent was discontinued in group B, mean daily plasma glucose rose to 10·5 (1·0) mmol/L within 2 weeks, becoming significantly higher ($p<0·001$) than the value in group A. The HbA_1c did not rise during this period, and failed to identify the difference in glycaemic states between the two groups. FPG and fructosamine both significantly discriminated group B from group A; however, the p values were higher than that of 1,5AG. Table 2 shows the results based on the comparison of the calculated value of the relative magnitudes of the differences between week 4 and 6 for the same parameter. The changes in 1,5AG paralleled the deterioration of glycaemic control indicated by mean daily plasma glucose and FPG concentrations. Inconsistent responses were observed for HbA_1c and fructosamine, indicating that these tests did not accurately detect a short-term deterioration in glycaemia.

All 28 patients in group A monitored their glycaemic markers for 16 weeks to evaluate any advantage of 1,5AG compared with the conventional markers for detecting a change in glycaemia in the range of "near-normoglycaemia". Of these 28 patients, 20 showed a low HbA_1c concentration of about 6·5% during the 8 weeks preceding the 1,5AG measurement. When these patients were subdivided into those with a mean serum 1,5AG concentration above or below 10·0 μg/mL, the mean daily plasma glucose concentration was significantly higher in the former (8·83 [1·17] mmol/L) than in the latter (6·83 [1·44] mmol/L) (table 3).

The 28 patients in group B again received a hypoglycaemic agent after week 6 as needed. Of the 28 patients, 23 showed a decrease of 10–15% in the mean daily plasma glucose concentration 2 weeks after such drug treatment was reinstituted. We compared the sensitivity of HbA_1c, fructosamine, and 1,5AG in detecting minimal changes in glycaemia in the 2 week period. Mean daily plasma glucose concentration changed from 11·00 (3·06) to 9·72 (3·89) mmol/L, HbA_1c from 8·2 (2·0) to 7·9 (2·1)%, fructosamine from 355 (65) to 338 (67) μmol/L, and 1,5AG from 4·4 (3·9) to 7·9 (4·4) μg/mL. Mean differences were −1·29 (3·87) mmol/L for mean daily plasma glucose, −0·3 (1·8)% for HbA_1c, −17 (36) μmol/L for fructosamine, and 3·5 (2·0) μg/mL for 1,5AG. Calculation of the Δ parameter index (see table 2) showed that the changes in 1,5AG paralleled the improvement of glycaemia during this short period. By contrast, the changes in HbA_1c and in fructosamine showed a significant difference at that time.

Table 4 summarises the correlations between 1,5AG values and the mean fasting and daily plasma glucose concentrations during the preceding 2, 4, and 8 weeks in all 56 patients. Correlations between the fasting concentrations of plasma glucose and of 1,5AG resembled those between the mean daily plasma glucose

Parameter	1,5AG<10·0 μg/mL (n=7)	1,5AG≥10·0 μg/mL (n=13)
Mean (SD) HbA_1c (%)	6·5 (0·3)	6·4 (0·3)
Mean (SD) daily plasma glucose (mmol/L)	8·83 (1·17)	6·83 (1·44)*

Patients whose glycaemic control had been maintained at an HbA_1c concentration of about 6·5% for at least the 8 weeks before 1,5AG measurement, were monitored for 1,5AG and for mean daily plasma glucose. Individual data were calculated as the mean of three samples collected at 2 week intervals during the latter period. *p<0·005.

Table 3: **Glycaemic status of patients with low versus high serum concentration of 1,5AG in near-normoglycaemia as indicted by HbA_1c concentration**

Parameter	Week preceding 1,5AG measurement			
	0	2	4	8
Fasting plasma glucose	−0·790*	−0·713*	−0·436*	−0·387
Mean daily plasma glucose	−0·835*	−0·807*	−0·565*	−0·429*

Zero point is at the last day of study (week 16). *p<0·05.

Table 4: **Correlation between fasting or mean daily plasma glucose concentrations and 1,5AG (Spearman analysis) in 56 patients**

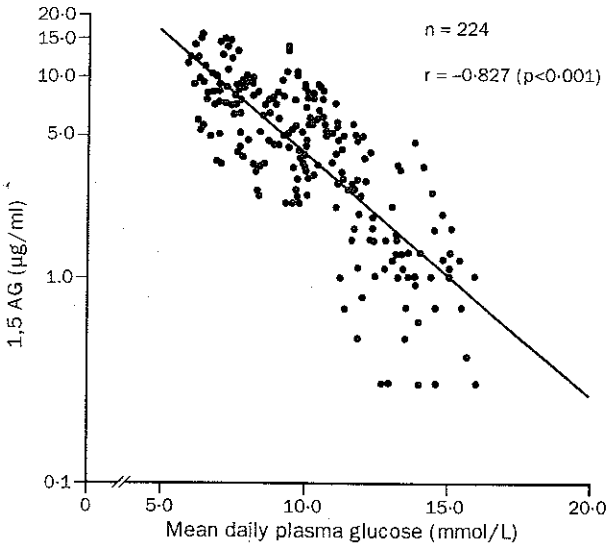


Figure 2: **Relation between serum 1,5AG and mean daily plasma glucose pairs**
Data were obtained from paired samples collected at weeks 0, 2, 4, 6 in 56 patients.

concentrations and those of 1,5AG. The highest r value was observed at zero point, defined as the last day of study (week 16). The r values showed a fall at any contiguous time intervals. Figure 2 shows the relation ($r=-0{\cdot}827$) between 1,5AG and mean daily plasma glucose values (all pairs) obtained within 6 weeks of initiating treatment.

Discussion

The present study supports the clinical usefulness of 1,5AG in monitoring for changes in glycaemia. This substance originates in the diet and exists in a large pool in the body,[16] being minimally degraded and metabolised.[16–20] The renal reabsorption of 1,5AG is competitively inhibited by the glucosuria induced by hyperglycaemia, and its concentration in serum decreases.[7,8,11] The daily recovery (increase) rate of serum 1,5AG is constant (0·3 μg/mL per day) in and between those individuals with excellent glycaemic control.[7] Because of its large body pool, serum 1,5AG concentration is little influenced by food intake.[6] There is a close correlation between the reduction in serum 1,5AG and the amount of glucose excreted in urine,[7,21] which allows 1,5AG to be used in Japan as an accurate indicator of glycaemia.[12]

An automated, highly accurate analyser of 1,5AG[14] can measure 1,5AG in 20 samples per hour. We used this autoanalyser in evaluating the usefulness of the 1,5AG measurement. During the subacute alteration in glycaemia, 1,5AG detected the change in glycaemia within a short period of 2 weeks with a higher level of statistical significance than either HbA_1c or fructosamine. The value of 1,5AG varies so widely, especially in the range of near-normoglycaemia that, compared with HbA_1c or fructosamine, its change is highly objective, and is little affected by assay variations. Although HbA_1c is usually adequate for rough estimate of the severity of glycaemia, it has been reported that, in the interpretation of HbA_1c levels, only changes that exceed 0·65% points in the HbA_1c level are significant.[22] These points are important for evaluating data on glycaemic change in an individual, not for the statistical analysis of the glycaemic state of a population. It has been suggested that 1,5AG can change significantly in 1 to 2 days according to the change in glucosuria.[12] The present study measured this serum marker every 2 weeks. Results confirmed its clinical utility. Because 1,5AG proved to be superior to HbA_1c in identifying the current status of glycaemia, this marker should be useful in preventing the hypoglycaemia caused by the prolonged administration of a hypoglycaemic agent. The test for 1,5AG is suitable for use in monitoring changes in glycaemia 2 to 4 weeks after the start of, or after a change in, oral hypoglycaemic treatment.

The reasons that the same degree of near-normoglycaemia with a similar level of HbA_1c could be further subdivided by 1,5AG may be as follows. First, the broad range of 1,5AG values that corresponds to a change in glycaemic control indicates that the 1,5AG value is less influenced by assay variations than is the HbA_1c. Second, the effect of individual variation in the sensitivity to glycation/deglycation cannot be ignored around the normal range of HbA_1c.[4] Although some reports have demonstrated a superiority of 1,5AG to HbA_1c, as well as to fructosamine, in screening a hospital population for diabetes,[13,23] conflicting results were obtained in a community-based population study.[24] There may exist a bias in selecting for study those patients with more severe glucosuria.[25] Additional long-term prospective studies are required to resolve this issue.

Are other glycaemic markers needed in addition to glycated haemoglobin and fructosamine? Because 1,5AG is influenced by intermittent excretion of urinary glucose, a discrepancy between the values for 1,5AG and HbA_1c usually indicates the presence of fluctuations in glycaemia and/or the frequent occurrence of hypoglycaemia in patients with IDDM[21] as well as in those with NIDDM.[26] Thus, the estimation of glycaemic control by a combination of HbA_1c and 1,5AG would provide more complete information for patient management. In the future, markers such as HbA_1c, whose changes depend on glycation, will not serve as a marker of glycaemia but rather of glycation, in that antiglycation drugs are currently being developed to prevent diabetic complications.[27] Such drugs will mean the end of glycated markers as markers of glycaemia. The use of glycated and non-glycated glycaemic markers in combination would make it easier to assess the effect of an antiglycation drug. Because of its closed chemical structure, 1,5AG is not involved in the glycation phenomenon. Methodological differences have little effect on the 1,5AG value, unlike that of HbA_1c. We therefore anticipate that this new marker will help in the effective maintenance of glycaemic homeostasis.

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