Circulating 1,5-Anhydroglucitol Levels in Adult Patients With Diabetes Reflect Longitudinal Changes of Glycemia

A U.S. trial of the GlycoMark assay

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OBJECTIVE — 1,5-Anhydroglucitol (1,5AG) is a major circulating polyol arising primarily from ingestion and excreted competitively with glucose. Japanese studies have demonstrated reduced concentrations of 1,5AG in serum in hyperglycemic patients in comparison with euglycemic subjects and a gradual normalization of 1,5AG values for patients responding to antihyperglycemic therapies. In this first U.S. study, we assessed the ability of 1,5AG measurements to monitor glycemic control in a cohort of 77 patients with diabetes (22 with type 1 diabetes, 55 with type 2 diabetes) who presented with suboptimal glycemic control at baseline (defined as $HbA_{1c} \geq 7\%$).

RESEARCH DESIGN AND METHODS — Each patient received therapies consisting of combinations of diabetes education, nutritional counseling, and addition or dose adjustment of various insulins or oral antihyperglycemic medications. Therapy was targeted to reduce mean HbA_{1c} by $\geq 1.0\%$ over the monitoring period. 1,5AG, HbA_{1c}, fructosamine, and random glucose measurements were performed at baseline and at 2, 4, and 8 weeks after the initiation of therapy.

RESULTS — 1,5AG, fructosamine, and glucose values progressed significantly toward euglycemia by week 2 of monitoring (Wilcoxon's signed-rank test, $P < 0.05$), with median changes of 93, −7, and −13% for 1,5AG, fructosamine, and glucose, respectively. In contrast, HbA_{1c} values did not respond significantly to therapy until week 4. On an individual patient basis, 89.6% of patients displayed longitudinal changes of 1,5AG from baseline to week 8 in concordance with HbA_{1c}. 1,5AG was also highly correlated with HbA_{1c} and fructosamine (Spearman $\rho = -0.6459$ and -0.6751, respectively; both $P < 0.0001$).

CONCLUSIONS — We conclude that 1,5AG responds sensitively and rapidly to changes in glycemia and monitors glycemic control in accordance with established markers.

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The incidence of diabetes is clearly a serious health concern. During the period 1991–2000, the incidence in the U.S. increased by 49% (4.9–7.3% of the total population), and this was correlated with a 61% increase in obesity during the same period (1,2). For those afflicted with diabetes, control of their glycemia is of paramount importance because good metabolic control can reduce the incidence of micro- and macrovascular complications (2–5).

In recent years, various biochemical markers have been cleared by the U.S. Food and Drug Administration (FDA) for assessment of glycemia. These include self-monitored blood glucose methods and assays for HbA_{1c} and fructosamine. These tests differ in the time period in which measured values reflect glycemia. Random glucose measurements convey a "snapshot" of ambient circulating glucose but do not report the consistency of glycemic control or excursion thereof. In contrast, HbA_{1c} and fructosamine measurements reflect time-averaged glycemia in the past 2–3 months and in the past 2–3 weeks, respectively. Of these two measures, HbA_{1c} has been identified in multiple studies as the most valid predictor of risk of complications (2–6). However, despite the demonstrated use of HbA_{1c} measurements, the slow rate of change may contribute to delays in modification of therapy. Thus, a marker that responds rapidly and significantly to changes in glycemia, that is metabolically stable, that demonstrates low biological variability, and that can be easily measured would be useful in management of patients with diabetes.

1,5-Anhydroglucitol (1,5AG) has been recently proposed as a marker conforming to these criteria (7). 1,5AG was first discovered in the plant family *Polygala senega* in 1888. The structure was identified in 1943, and the presence of the compound in human blood (8) and cerebrospinal fluid (9) was established in 1972 and 1973, respectively. Research studies have shown that 1,5AG originates mostly from foods with a mean intake of ~4.4 mg/day, that the closed pyran ring structure confers metabolic stability, that the rate of intake is matched by the daily excretion rate, and that a bodily pool of ~500–1,000 mg of 1,5AG is constantly

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Abbreviations: 1,5AG, 1,5-anhydroglucitol; FDA, Food and Drug Administration; PROD, pyranose oxidase.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

maintained (10). The body pool may originate from an accumulation of small amounts of retained dietary 1,5AG or from biosynthesis. There is some evidence to support de novo biosynthesis of 1,5AG in the amount of ~0.5 mg/day (10), but this has neither been extensively investigated nor confirmed.

1,5AG is well absorbed in the intestine and distributes to all organs and tissues (11). Renal reabsorption of 1,5AG is 99.9% and is competitively inhibited by excessive excretion of urinary glucose (glucosuria). With this finding, Japanese research groups demonstrated reduced concentrations of 1,5AG in serum of hyperglycemic patients in comparison with euglycemic subjects (12,13). Additionally, a gradual normalization of 1,5AG values for patients responding to antidiabetic therapies (14) has been demonstrated, and studies have shown that 1,5AG measurements reflect glycemic status over the previous 48 h to 2 weeks. Dietary variation does not appreciably affect the efficacy of such measurements because the content of 1,5AG is similar in various starches (mean, 2.5 ± 1.1 μg/g), meats and seafood (0.9 ± 0.6 μg/g), vegetables (0.4 ± 0.2 μg/g), fruits (0.7 ± 0.6 μg/g), and beverages (0.8 ± 0.7 μg/g) (10). Only raw soybeans have been demonstrated to have significantly enriched levels of 1,5AG, although processed soybeans (e.g., tofu, soy sauce) have 1,5AG content essentially equivalent to all other starches (10). Based on these early analytical and clinical findings, an automated assay using an enzymatic methodology was developed and has been commercially available in Japan since 1991 (15). A domestic version of this assay (GlycoMark) has been under evaluation in clinical trials in the U.S. and has recently been cleared for marketing by the FDA as a tool for intermediate-term monitoring of glycemia.

It is the objective of this study to present the results of the first U.S. clinical study evaluating the ability of the GlycoMark assay to respond to and reflect changes in glycemia in a cohort of type 1 and type 2 diabetic patients with suboptimal glycemic control who are being managed aggressively with antihyperglycemic treatments. Specific attention is given to addressing the question of whether the assay can reflect changes in accordance with the established method of choice, HbA_{1c}.

RESEARCH DESIGN AND METHODS

— The experimental protocol for this study was approved by the Washington University Medical Center Human Studies Committee. Written informed consent was obtained from all patients, and all participants were either previously or newly diagnosed with either type 1 or type 2 diabetes as defined by the American Diabetes Association criteria (16). Patients who were pregnant or lactating or had a history of severe hypoglycemia or liver dysfunction, various hematological abnormalities (including significant anemia), unstable or advanced renal disease or significant proteinuria, unstable retinopathy, or recent retinal procedure were excluded. Hypoproteinemia was not an exclusion criterion. Patients were recruited from the outpatient clinic population of the investigator, clinics associated with the principal investigator's hospital or institution, or from a volunteer database. Each patient presented at baseline with suboptimal glycemic control, defined as HbA_{1c} ≥7.0%. The study cohort was comprised of 38 men and 39 women. The cohort ethnic distribution included 58 Caucasian patients, 18 African-American patients, and 1 patient of Hispanic origin. Mean subject age was 50 ± 11 years (men 53 ± 10, women 47 ± 12). Sex-specific mean body weights were 100 ± 21 kg (men) and 100 ± 7 kg (women). Overall, 22 patients with type 1 diabetes (8 men and 14 women) and 55 patients with type 2 diabetes (30 men and 25 women) were recruited for the study.

This was a longitudinal trial of 8 weeks' duration comparing changes of serum 1,5AG to whole-blood HbA_{1c}, serum fructosamine, and random serum glucose measurements. After screening, each patient received a combination of antihyperglycemic treatments, including diabetes and nutritional education, various insulin therapies, thiazolidenediones, sulfonylureas, glitinides, α-glucosidase inhibitors, and metformin. Therapy was targeted toward reducing HbA_{1c} by at least 1.0% on average over the monitoring period. Blood was drawn for biochemical measurements at baseline and at 2, 4, and 8 weeks. At these time points, individual treatment regimens were adjusted as necessary to achieve progression toward euglycemia. Serum 1,5AG values were not used in patient management.

Biochemical measurements

Serum 1,5AG was measured with the GlycoMark assay (Tomen America, New York, NY) as automated on a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN). The method uses pyranose oxidase (PROD) as an oxidase of 1,5AG to oxidize the second position hydroxyl group of 1,5AG and to detect the generated hydrogen peroxide by colorimetry. Because PROD also reacts with glucose, the sample is pretreated by enzyme reaction using glucokinase, and glucose is changed into a nonreactive substance by phosphorylation. This makes the reaction specific for 1,5AG. The reactions are performed at 37°C. At time zero, 4 μl of standard (50 μg/ml 1,5AG), control, reagent blank, or sample is added to 120 μl of the glucokinase-containing pretreatment reagent. After a 5-min incubation, 50 μl of coloring reagent (containing PROD) is added, and the absorbance is measured at 546 and 700 nm. Absorbance at both wavelengths is again measured after a 10-min incubation. The absorbance at 700 nm is subtracted from that at 546 nm to correct for background. The kinetic difference in corrected absorbance at 546 nm is then calculated. Concentrations of 1,5AG in the reagent blank, control, or sample are determined by comparison with a two-point calibration based on the corrected kinetic absorbance of the reagent blank and standard.

The assay for 1,5AG displayed an analytical sensitivity of 0.2 μg/ml, was linear to 113 μg/ml, and demonstrated intra- and interassay coefficients of variation of <4%. Hemoglobin, triglycerides, and bilirubin did not interfere with the assay at concentrations of up to 125 mg/dl, 1,153 mg/dl, and 53 mg/dl, respectively. Assay results were also unaffected by glucose concentrations up to 1,000 mg/dl. The sex-specific 5th to 95th percentile reference ranges established for the assay, based on analysis of samples from 224 healthy individuals, were 10.7–32.0 μg/ml (men) and 6.8–29.3 μg/ml (women). The reference ranges and associated interindividual biological variation parameters are essentially equivalent to those established for the assay in Japan and reflect an insensitivity to cultural dietary differences.

HbA_{1c} was determined from whole-blood samples via turbidimetric inhibition immunoassay (Tina-Quant; Roche Diagnostics) as automated on the Hitachi

917. The Roche Frucostamine and GlucoQuant tests were used to measure fructosamine and glucose, respectively, in serum samples. Both assays were also automated on the Hitachi 917. Intra- and interassay coefficients of variation were <1.0 and 3.0%, respectively, for the HbA_{1c}, fructosamine, and glucose assays.

All biochemical assays were performed at the Core Laboratory for Clinical Studies at Washington University School of Medicine. The facility is a secondary reference laboratory for the National Glycohemoglobin Standardization Program.

Data analysis

Demographics, baseline characteristics, baseline medical histories, concomitant medications, antihyperglycemic treatments, adverse events, and hypoglycemic events were analyzed descriptively. The Wilk-Shapiro test was used to determine the distribution of values of all biochemical measurements. The Spearman's nonparametric analysis was used to determine association between variables, and Wilcoxon's signed-rank test was used to determine the significance of changes versus baseline values at individual monitoring time points ($P < 0.05$ was considered significant). To determine the degree of concordance between longitudinal changes in 1,5AG and HbA_{1c}, individual patients were scored as to the direction of change in measured values between baseline and week 8. Concordance was defined as either increases in 1,5AG with corresponding decreases of HbA_{1c} or, conversely, decreases in 1,5AG values with corresponding increases in HbA_{1c}. Concordance of 1,5AG and fructosamine and fructosamine and HbA_{1c} were similarly determined.

Software

The JMP version 5.0 software (SAS Institute, Cary, NC) was used for all statistical investigations.

RESULTS

Baseline measures, concomitant medications, and adverse and hypoglycemic events

Baseline physical examinations were performed and medical histories taken. The cohort of 77 patients meeting the entry criteria had no preexisting conditions that would compromise study procedures and/or biochemical measurements. Use of concomitant medications was monitored throughout the study. No patients in the cohort were found to have used any medication that would interact with antihyperglycemic treatments or interfere with the outcome measures. Three serious adverse events occurred during the study. One female patient underwent a discectomy and spinal fusion for a preexisting disc herniation, one male patient underwent catheter ablation for atrial tachycardia, and one female patient was hospitalized for insulin dose adjustment due to chronic hyperglycemia. None of these serious adverse events or any of the minor adverse events impacted the accuracy of any of the biochemical measurements. Forty-three of the cohort of 77 patients reported at least one hypoglycemic event during the study. Of these, only two patients reported hypoglycemic events requiring assistance. Again, none of the events reported impacted the biochemical outcome variables.

Therapeutic regimens

All patients received diabetes education and nutritional counseling at baseline and throughout the study. For those patients with type 1 and type 2 disease already receiving insulin therapy at baseline, the insulin regimen was modified by changing the dosage of insulin, changing the type of insulin, changing the schedule of insulin delivery, or initiating or changing the combination of insulins. Some patients with type 2 diabetes who were not previously receiving insulin initiated insulin therapy under the study protocol. Oral antihyperglycemic regimens were added or modified for patients with type 2 diabetes. Throughout the monitoring period, these regimens were continually optimized to achieve the average HbA_{1c} target decrease of ≥1%. Of the oral antihyperglycemic medications, metformin and various glitinides and sulfonylureas, in combination with insulin therapies, were the most frequently used and were observed to best induce progression toward euglycemia.

Distribution of biochemical marker values, correlation, and longitudinal changes

The distribution of values for 1,5AG, HbA_{1c}, fructosamine, and random glucose measurements was found to be nongaussian, thus supporting the need for nonparametric analyses. Correlations between variables were assessed. 1,5AG was most closely associated with HbA_{1c} and fructosamine, with Spearman ρ values of −0.6459 and −0.6751, respectively (both $P < 0.0001$). HbA_{1c} and fructosamine were also highly associated ($\rho = 0.6955$). Correlations of glucose with 1,5AG ($\rho = -0.3358$), HbA_{1c} ($\rho = 0.3334$), and fructosamine ($\rho = 0.3529$) were lower due to the diurnal and situational variability of random glucose measurements.

Longitudinal changes in 1,5AG, HbA_{1c}, fructosamine, and glucose values were assessed (Table 1). Whole-blood HbA_{1c} was reduced by 1.3% from baseline to week 8, indicating that the therapeutic regimens used had achieved the study design target. However, mean and median absolute percent changes versus baseline are markedly higher for 1,5AG than for HbA_{1c}, fructosamine, and glucose (Fig. 1). By week 2 of treatment, 1,5AG values had already increased by 57.9%, reflecting the sensitive and rapid response of 1,5AG to changes in blood glucose. For HbA_{1c}, significant changes were not observed until 4 weeks. By week 8, 1,5AG mean values had increased by ~160% versus diminution of values of 12.1–35.3% for the established markers of glycemia.

Concordance of longitudinal changes

Longitudinal changes in glycemic control were evaluated on an individual patient basis (Fig. 2). HbA_{1c} and 1,5AG values at baseline and week 8 were assessed individually for indications of progression toward, or away from, euglycemia. The concordance of these indications was then tabulated. In the cohort of 77 patients, the longitudinal changes of 1,5AG were in concordance with changes of HbA_{1c} in 69 (89.6%) of 77 patients. Seventy-five of the 77 patients were classified as responders to therapy based on diminution of HbA_{1c} values with time. The two patients classified as nonresponders were both men with type 2 diabetes. In these patients, 1,5AG values decreased with time and HbA_{1c} values increased, thus indicating 100% concordance in these patients.

Concordance between longitudinal changes of 1,5AG and HbA_{1c} in the intermediate time points of the study was also assessed. Concordance ranged from 58.4 to 76.6%, with earlier time points displaying lower concordance. Concordance

Table 1—*Longitudinal changes of biochemical variables*

Time point/statistic	1,5AG (μg/ml)	HbA_{1c} (%)	Fructosamine (μmol/l)	Glucose (mg/dl)
Baseline				
Mean ± SD	1.9 ± 1.9	9.5 ± 1.7	410.6 ± 108.6	225.0 ± 105.6
Median	1.4	9.1	375.0	218.0
Minimum to maximum	0.0–10.7	7.0–14.2	269.0–908.0	64.0–574.0
Week 2*				
Mean ± SD	3.0 ± 2.2†	9.1 ± 1.5	362.4 ± 76.5†	187.4 ± 91.0†
Median	2.7	8.7	348.5	190.0
Minimum to maximum	0.0–12.6	6.8–14.0	232.0–572.0	27.0–448.0
Mean percent change vs. baseline	57.9	4.2	11.7	16.7
Median percent change vs. baseline	92.9	4.4	7.1	12.8
Week 4				
Mean ± SD	3.7 ± 2.5†	8.8 ± 1.4†	340.0 ± 79.1†	181.4 ± 102.4†
Median	3.5	8.7	321.0	157.0
Minimum to maximum	0.0–13.3	6.6–13.2	206.0–559.0	29.0–701.0
Mean percent change vs. baseline	94.7	7.4	17.2	19.4
Median percent change vs. baseline	150.0	4.4	14.4	28.0
Week 8				
Mean ± SD	5.0 ± 3.6†	8.2 ± 1.2†	317.5 ± 75.4†	172.6 ± 100.5†
Median	4.8	8.0	295.0	141.0
Minimum to maximum	0.0–15.7	6.3–12.3	197.0–575.0	16.0–545.0
Mean percent change vs. baseline	163.2	13.7	22.7	23.3
Median percent change vs. baseline	242.9	12.1	21.3	35.3

Reference ranges: 1,5AG, 10.7–32.0 μg/ml (men) and 6.8–29.3 μg/ml (women); HbA_{1c}, <6.0%; fructosamine, 205–285 μmol/l; glucose, 55–115 mg/dl. *One male patient did not provide a blood sample at week 2, thus the *n* for this time point is 76. †$P < 0.05$ vs. baseline.

from baseline to week 8 between 1,5AG and fructosamine (67 of 77 patients, 87.0%) and HbA_{1c} and fructosamine (75 of 77 patients, 97.4%) was also assessed. Those patients demonstrating discordance between 1,5AG and HbA_{1c} displayed concordance between HbA_{1c} and fructosamine and vice versa (i.e., the two patients found to be discordant by assessments of HbA_{1c} and fructosamine were concordant when comparing changes of 1,5AG with changes of HbA_{1c}).

CONCLUSIONS — The present study has examined the ability of the GlycoMark assay for 1,5AG to reflect changes of glycemia in a cohort of patients with type 1 and type 2 diabetes who are being treated aggressively with various regimens and who are being monitored with established biochemical markers of glycemia. Over the 8-week monitoring period, values for 1,5AG, HbA_{1c}, and fructosamine were highly correlated, and the results were in good agreement with previous Japanese studies (17,18). Furthermore, 1,5AG responded rapidly and significantly to population-based changes in glycemia, with the first significant change appearing at 2 weeks of treatment. In contrast, HbA_{1c} responded more slowly, and both HbA_{1c} and fructosamine displayed more modest changes in value. These results are in agreement with the literature. For instance, in a 1996 study by Yamanouchi et al. (17), 56 patients newly diagnosed with type 2 diabetes were monitored for 4 weeks after initiation of oral antihyperglycemic medications. At the end of the 4-week period, one-half of the patients continued on treatment while the rest discontinued treatment. The results showed that 1,5AG

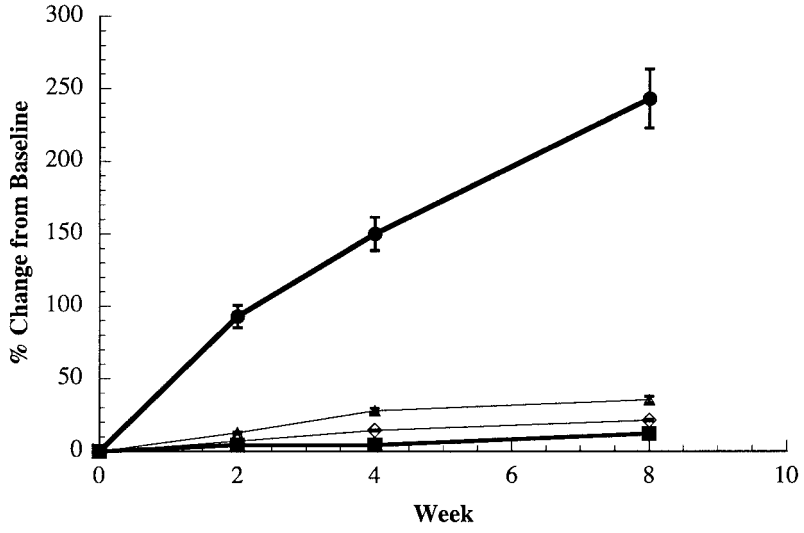

Figure 1—*Percentage change from baseline by time point for serum 1,5AG (●–●), whole-blood HbA_{1c} (■–■), serum fructosamine (◇–◇), or random serum glucose (△–△). Error bars = SE.*

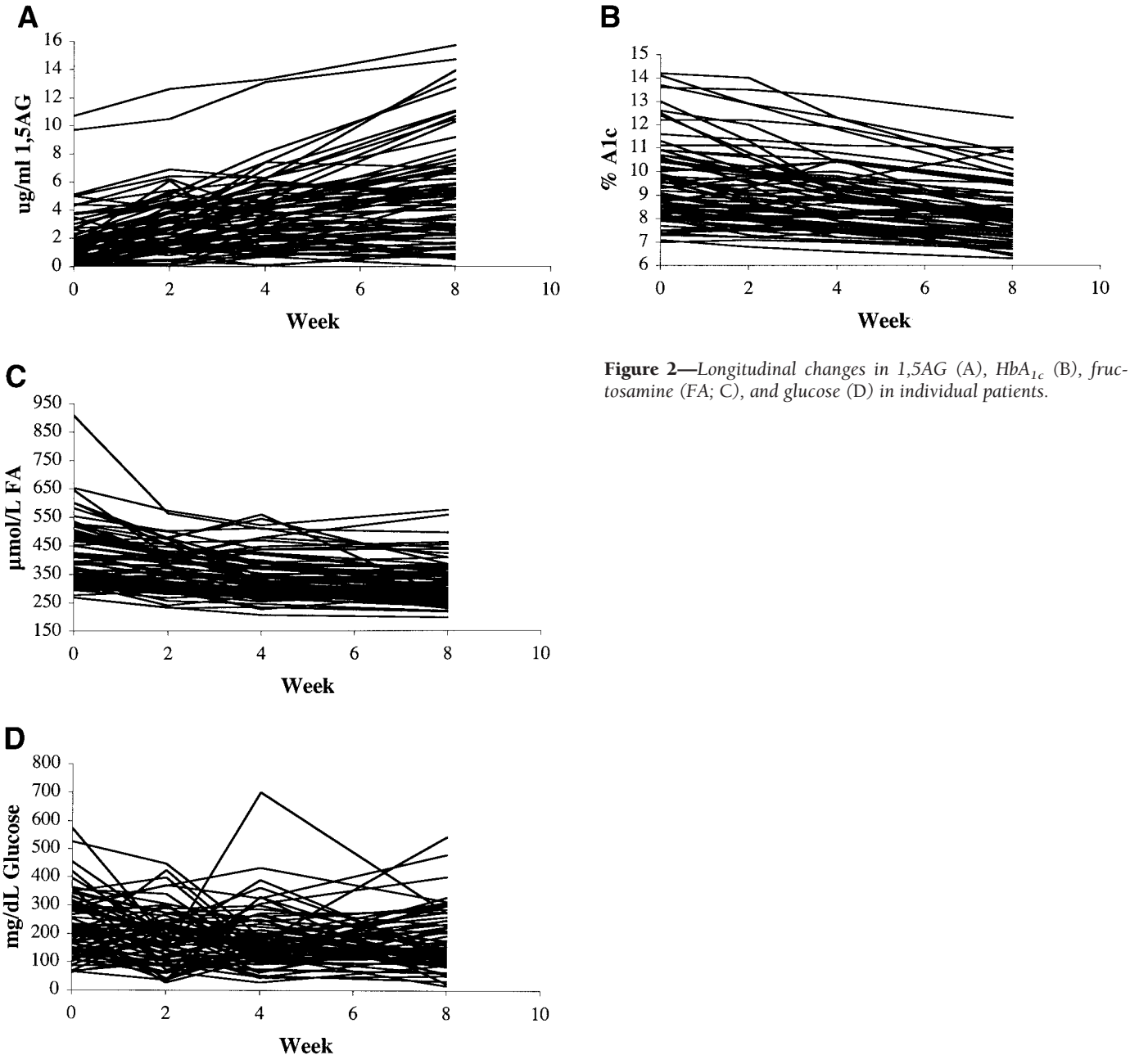

Figure 2—*Longitudinal changes in 1,5AG* (A)*, HbA_{1c}* (B)*, fructosamine (FA; C), and glucose* (D) *in individual patients.*

increased rapidly and demonstrated a significant change versus baseline at 2 weeks of monitoring. After discontinuation of treatment, 1,5AG values sharply decreased, and the values at the 6-week time point were significantly different from those in the subgroup who continued on therapy. Results for fructosamine and HbA_{1c} demonstrated a lesser response to therapy in the initial 4 weeks. Furthermore, whereas fructosamine responded to the discontinuation of therapy between weeks 4 and 6, HbA_{1c} did not. Thus, the present study adds to the body of evidence in Japan that demonstrates a rapid and significant response of 1,5AG to antihyperglycemic treatments.

The present study also demonstrates that changes in 1,5AG values reflect changes in glycemic control in good accord with HbA_{1c} on an individual patient basis. Overall, 89.6% displayed concordant changes of 1,5AG and HbA_{1c} from baseline to week 8. Percent concordance was reduced at intermediate time points due to the relative insensitivity of HbA_{1c} to changes in glycemia at time periods <8 weeks. Examination of the results from the eight patients with discordant 1,5AG and HbA_{1c} changes revealed that 1,5AG values either slightly diminished or remained unchanged over the monitoring period, whereas HbA_{1c} values diminished slightly, indicating some minimal improvement in glycemic control. The relative insensitivity of 1,5AG in these patients may be due to excessive depletion of the body pool of 1,5AG. Such depletion has been observed to occur in severe hyperglycemia as a result of persistent glucosuria (19). Additionally, a dynamic mass balance two-compartment

model has been developed for 1,5AG (20), and it demonstrates that the tissue compartment is two to three times the mass of the plasma compartment. Model estimates suggest that accelerated depletion of 1,5AG is associated with slow recovery upon the initial improvement of glycemia, because the body pool of 1,5AG represents ~5 weeks of normal dietary intake. If the model is accurate, it suggests that the use of 1,5AG is optimal in the range of modest hyperglycemia to near euglycemia. In this range, the GlycoMark assay may represent a valuable means for the maintenance of near-normal glucose levels, as it responds rapidly and sensitively to even transiently ascending glucose concentrations.

Clearly the overall clinical management of diabetes, whether type 1 or type 2 diabetes, requires continual multifactorial evaluation of glycemic status. The GlycoMark assay for 1,5AG may be a useful tool as an adjunct to existing methods. For example, observations of good correlation between circulating 1,5AG and the magnitude of glycemic excursions within a day (21) indicate some potential for 1,5AG to substitute for frequent glucose measurements in type 2 diabetes. Furthermore, circulating 1,5AG concentrations may also reflect transient glycemic excursions due to postprandial hyperglycemia and, as such, may provide significant benefit for improving long-term outcomes. Additionally, 1,5AG as an intermediate-term marker could be evaluated between standard 3-month assessments of HbA_{1c} to indicate worsening of glycemic control and to incite behavioral change before induction of significant vascular damage. There have also been indications of the prognostic capability of 1,5AG measurements. In a study by Sone et al. (22), 1,5AG levels were measured for 5 consecutive days in a cohort of 22 patients with type 2 diabetes. Changes in 1,5AG during the 5 days were significantly correlated ($R = 0.70$, $P < 0.01$) with changes in HbA_{1c} over the subsequent 3 months. The authors concluded that 1,5AG could be used to identify patients at high risk for poor glycemic control in the future.

In conclusion, this first U.S. clinical trial of the GlycoMark assay for the metabolically stable analyte, 1,5AG, has demonstrated the capability of this simple, automated method to report changes in glycemia induced by antihyperglycemic treatment regimens. The results are in excellent accord with Japanese studies over the previous two decades and serve to indicate that the ethnically and culturally diverse population of the U.S. does not negatively impact the perceived use of the marker. Furthermore, the recent clearance granted by the FDA makes the GlycoMark assay available for intermediate-term monitoring, which, it is hoped, will allow patients to seek medical intervention in a timely manner, such as when initiating or altering therapy. This may empower patients to achieve and maintain better control of their disease. Of course, further studies will be useful to better clarify the role of 1,5AG measurements in clinical diabetes management.

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