Relative Clinical Usefulness of Glycosylated Serum Albumin and Fructosamine During Short-Term Changes In Glycemic Control in IDDM

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Serial changes in glycosylated blood proteins and direct measures of glycemia were studied in 100 subjects with insulin-dependent diabetes mellitus (IDDM) over a 6-wk period while attempts were made to improve glycemic control. All measures of glycemic control improved significantly ($P < .001$). Mean ± SE glycosylated hemoglobin (HbA_1) fell from 9.1 ± 0.2 to 8.0 ± 0.1%, glycosylated serum albumin (GSA) from 9.8 ± 0.4 to 7.3 ± 0.3%, and fructosamine from 3.92 ± 0.08 to 3.42 ± 0.07 mM. Fasting blood glucose levels fell from 11.1 ± 0.6 to 8.1 ± 0.7 mM, mean blood glucose levels from 12.5 ± 0.3 to 8.8 ± 0.3 mM, and the M value from 118 ± 7 to 40 ± 3 U. Mean percentage changes in direct measures of glycemia (32–66%) and GSA (29%) were greater than for fructosamine (11%) or HbA_1 (12%) levels ($P < .001$). Furthermore, the correlation between the change in GSA and changes in direct measures of glycemia over the initial 2-wk period was significantly different from the corresponding correlations between direct measures of glycemia and fructosamine over this period ($P < .05$–$.01$). Changes in GSA also correlated more closely than HbA_1 or fructosamine did with direct measures of glycemia after 4 and 6 wk. The Spearman rank-correlation coefficient (r_s) of absolute changes in GSA, fructosamine, and HbA_1 after 2–6 wk ranged from 0.27 to 0.57, confirming that the three measures responded differently to changing glycemic control. Cross-sectional analysis between different measures of glycemia demonstrated considerable variation in the degree of association at different times, with the closest correlations observed after 6 wk when glycemic control was relatively stable. GSA and fructosamine levels correlated with levels of mean blood glucose and M values estimated 2–4 wk earlier. GSA appears to be a more sensitive indicator of short-term improvement in glycemic control and glycemic instability in IDDM than fructosamine or HbA_1. *Diabetes Care* 12:665–72, 1989

Glucose 1 mM = 18 mg/dl

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The effective clinical management of insulin-dependent diabetes mellitus (IDDM) requires an accurate biochemical assessment of glycemic control, but there is no consensus on the most appropriate measures (1). Direct measures of glycemia provide information that is complemented by measures of glycosylated blood proteins. Glycosylated hemoglobin (HbA_1) is the most commonly used integrated measure of glycemic control (1), but measurements of glycosylated serum albumin (GSA) (2–7), glycosylated total serum protein (6,8–13), or fructosamine (13–16) may be more useful than HbA_1 in reflecting alterations in glycemic control over a shorter period.

GSA and fructosamine levels are both said to reflect glycemic control over the preceding 2–4 wk (2–6,13–16). However, many comparative studies of GSA and fructosamine with HbA_1 have been cross sectional in nature (2,3,8,13,17–26), combined healthy control groups with patients with IDDM and non-insulin-dependent diabetes mellitus (NIDDM) in the analysis (2,3,8,13,18–21), or made no reference to direct measures of glycemia or indices of glycemic fluctuations (2,12,13,18–21). In general, methods for measuring GSA have been unsuitable for clinical practice (5–7,17–19), although a simple precise assay is available (20,27). The fructosamine assay has also been the subject of controversy, with debate over the effects of serum albumin or

lipid concentrations and the lack of standardization in general (16,26,28–33).

We prospectively examined the clinical value of GSA and fructosamine in a group of patients with IDDM in whom attempts were made to improve glycemic control over a 6-wk period and compared these with established measures of glycemia, such as HbA_1 and fasting and mean blood glucose, to determine whether GSA and fructosamine were sensitive enough to reflect moderate short-term improvements in glycemic control.

RESEARCH DESIGN AND METHODS

The study was approved by the Salford Area Ethical Committee. One hundred thirteen individuals (68 men, 45 women) with IDDM were studied, 100 of whom provided comprehensive data for analysis. They were aged 40.3 ± 1.1 yr (range 15–69 yr) and had been diabetic for 13.1 ± 0.8 yr (range 4 mo to 57 yr). They had an average body mass index (23.6 ± 0.8 kg/m^2, range 15–35 kg/m^2), had preserved kidney function (urea 5.3 ± 0.1 mM), and were normoalbuminemic (range 37–51 g/L). Forty-nine percent of the subjects had no detectable C-peptide response to a standard meal. None of the subjects were ketotic at any time during the assessment. Initial assessments were made in the hospital and samples were taken for measurement of fasting blood glucose, GSA, fructosamine, HbA_1, and serum albumin after an overnight fast. Thereafter, the usual dose of insulin was administered, followed by breakfast 30 min later. A 10-point capillary whole-blood glucose profile (preprandial, 1- and 2-h postprandial, and bedtime measurements) was conducted during the day from which the mean blood glucose and the M value of Schlichtkrull et al. (34) were derived. Blood glucose control was improved by intensified conventional therapy along with a program of education and self-monitoring of blood

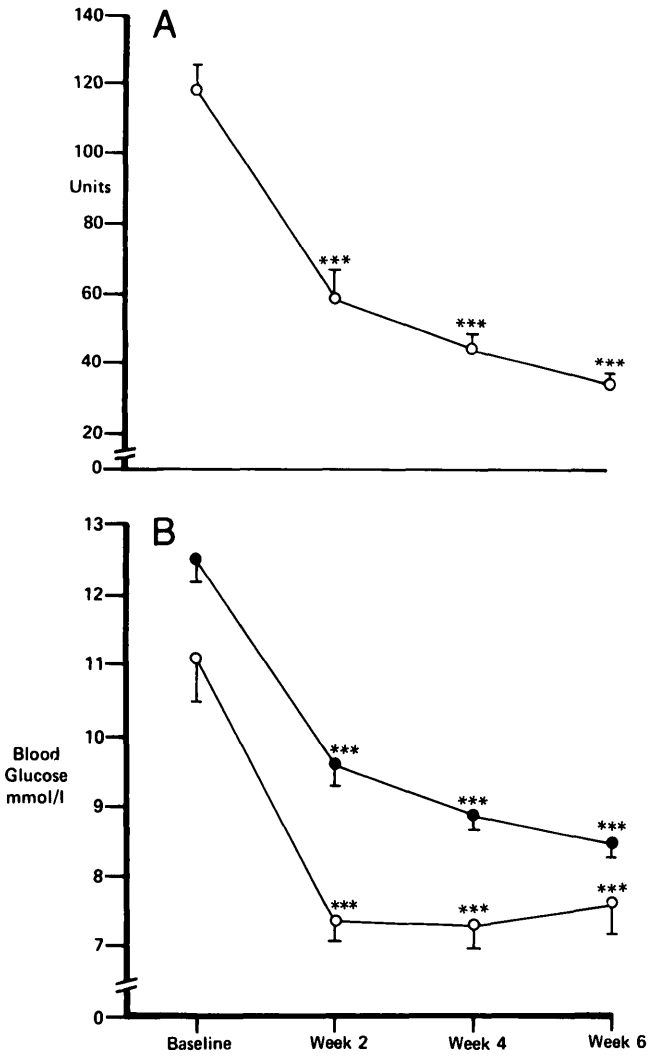

FIG. 1. Serial changes over 6 wk in direct measures of glycemia in 100 subjects with insulin-dependent diabetes mellitus. *A*, M value; *B*, mean blood glucose (●), fasting blood glucose (○). ***$P \leq .001$ vs. baseline values.

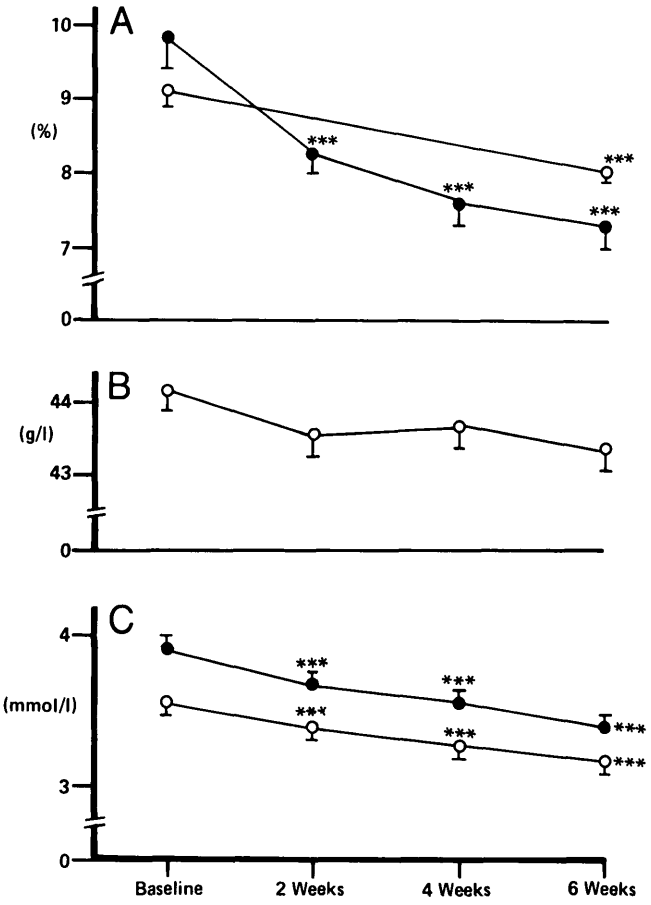

FIG. 2. Serial changes over 6 wk in serum albumin and glycosylated blood proteins in 100 subjects with insulin-dependent diabetes mellitus. *A*, glycosylated hemoglobin (○), glycosylated serum albumin (●); *B*, albumin; *C*, fructosamine (●), corrected fructosamine (○). ***$P \leq .001$ vs. baseline values.

glucose. Patients then returned at 2-wk intervals for fructosamine, GSA, and albumin measurements. Before each 2-wk visit, a 10-point capillary blood glucose profile was conducted with a reflectance meter and on a filter card at home. Patient-generated data were verified by measuring stored blood strips on a hospital meter and by validation with filter card whole-blood glucose measurement as described previously (35). Whole-blood glucose was measured on all occasions by a glucose oxidase technique (between-assay variability 1–3%), HbA_1 by ion-exchange chromatography (Mannheim, FRG; normal range 5.0–8.0%, between-assay variability 3–6%), and GSA by column affinity chromatography and immunoturbidimetry (normal range 1.5–5.4%, between-assay variability 4–7%), as described previously (27). Serum fructosamine was measured with a kit (carbonate buffer pH 10.35) by a Cobas-Fara centrifugal analyzer (Roche, Welwyn Garden City, Herts, UK). Our normal range, based on 56 nondiabetic healthy controls, was 1.87–2.97 mM. Between-assay precision varied from 1 to 3%, and pooled patient serum samples were run in each batch to ensure quality control with a glycosylated albumin solution containing 2.76 mM fructosamine used as a standard. Serum albumin was measured by a turbidimetric method on the Cobas-Fara centrifugal analyzer, and fructosamine values were then corrected to a standard albumin concentration of 40 g/L.

Levels of GSA, fructosamine, and HbA_1 (when appropriate) were compared with the direct measures of glycemia made at 2, 4, and 6 wk. The ability of GSA and fructosamine to reflect improvements in glycemia over periods of 2, 4, and 6 wk was also determined.

Statistical analyses. The relationship between variables and the changes (Δ) over time in measured variables were assessed by the Spearman rank-correlation coefficient (r_s). The Spearman correlation coefficient was chosen because it does not assume a linear relationship between variables and does not require normally distributed variables. One-tailed P values were calculated based on an a priori hypothesis of positive correlation between variables.

The percentage decrease from basal values in glycemic measures over time was calculated for each individual. Mean values are presented because of skewed distribution. The differences in the extent of the decreases were assessed by Wilcoxon's matched-pairs signed-rank test. The Spearman correlation coefficients were compared with Hotelling's t test on the assumption that for a large number of cases they are distributed approximately as Pearson's coefficient (36,37).

RESULTS

Glycemic patterns during 6 wk improved glycemic control. Marked improvements were recorded in all direct measures of glycemia after the initial 2-wk period ($P = .001$; Fig. 1). These were paralleled by significant reductions in GSA, fructosamine ($P = .001$), and corrected fructosamine ($P < .01$) to a lesser degree (Fig. 2). By 4 and 6 wk, further decreases in all measures of glycemic control had occurred compared with initial values ($P < .001$; Figs. 1 and 2). Adjusting fructosamine levels to a standard albumin concentration did not alter the strength of association between fructosamine and other glycemic measures appreciably, and for simplicity, we have only presented data on fructosamine levels without correction for serum albumin levels.

Correlations between glycemic measures and glycosylated blood proteins. Fasting blood glucose was correlated to a greater or lesser extent at the initial, 2-, 4-, and 6-wk time points with levels of GSA (r_s range .22–.44, $P < .05$–.001) and fructosamine (r_s range .22–

TABLE 1
Comparisons of direct measures of glycemia with subsequent glycosylated serum albumin and fructosamine levels after 2–6 wk in 100 subjects with IDDM

	Glycosylated serum albumin (wk)			Fructosamine (wk)		
	2	4	6	2	4	6
Fasting blood glucose levels						
Basal (wk)	.17	.25*	.20†	.25*	.31*	.12
2		.33‡	.38‡		.15	.18
4			.40‡			.36‡
Mean blood glucose levels						
Basal (wk)	.30*	.28*	.20*	.31‡	.26*	.12
2		.42‡	.32‡		.37‡	.30*
4			.39‡			.34‡
M values						
Basal (wk)	.33‡	.33‡	.23*	.33‡	.27*	.12
2		.44‡	.32‡		.36‡	.32‡
4			.36‡			.35‡

Values are correlation coefficients (r_s). IDDM, insulin-dependent diabetes mellitus.
*$P < .01$, †$P < .05$, ‡$P < .001$.

TABLE 2
Extent of changes (Δ) in measures of glycemia over 2-, 4-, and 6-wk periods in 100 subjects with IDDM

Time (wk)	Fasting blood glucose (mM)	Mean blood glucose (mM)	M value (U)	GSA (%)	Fructosamine (mM)	HbA_1 (%)
Δ 0–2	3.9 ± 0.6 (26%)	2.9 ± 0.4 (21%)	58 ± 8 (47%)*	1.5 ± 0.2 (13%)†	0.23 ± 0.08 (8%)‡	
Δ 0–4	3.8 ± 0.6 (29%)	3.6 ± 0.3 (28%)	73 ± 7 (63%)*	2.2 ± 0.4 (24%)	0.35 ± 0.11 (10%)*	
Δ 0–6	3.6 ± 0.5 (32%)	3.7 ± 0.3 (30%)	78 ± 7 (66%)*	2.5 ± 0.3 (29%)	0.50 ± 0.10 (11%)*	1.1 ± 0.1 (12%)*

Figures are absolute decreases expressed as means ± SE and as median percent decrease from initial value. GSA, glycosylated serum albumin; HbA_1, glycosylated hemoglobin; IDDM, insulin-dependent diabetes mellitus.
*$P < .001$ percentage decrease in fructosamine after 4 and 6 wk and in HbA_1 after 6 wk compared with those for GSA and direct measures of glycemia. Percentage decrease in M value compared with other measures after 2, 4, and 6 wk.
†$P < .05$ percentage decrease in fasting and mean blood glucose compared with GSA over 2 wk.
‡$P < .01$ percentage decrease in fasting and mean blood glucose compared with fructosamine over 2 wk.

.39, $P < .05$–.001). Mean blood glucose levels were more closely related to levels of GSA and fructosamine (r_s range .30–.50, $P < .01$–.001) at the same time points. Likewise, M values reflected measures of GSA (r_s range .31–.52, $P < .001$) and fructosamine (r_s range .33–.49, $P < .001$). Cross-sectional correlations were closest after 6 wk.

GSA levels correlated with fructosamine at all time points (r_s range .46–.66, $P < .001$), but there was no suggestion that the measurements closely paralleled one another.

HbA_1 was more highly correlated with GSA than fructosamine both initially (r_s = .68 vs. .44, NS) and after 6 wk (r_s = .47 vs. .22, $P < .05$).

Comparisons of direct measures of glycemia and subsequent GSA and fructosamine levels. Poor correlations were observed when initial fasting blood glucose levels were compared with GSA values at 2 wk and with fructosamine at 6 wk in contrast to values at 4 wk (Table 1). Fasting blood glucose levels at 2 and 4 wk showed improved correlations with GSA levels at 4 and 6 wk and with fructosamine levels at 6 wk.

On the other hand, mean blood glucose levels measured initially and at 2 and 4 wk correlated significantly with subsequent measures of GSA at all time points and with fructosamine at most time points. A similar observation was made with M values and subsequent GSA or fructosamine levels.

Changes in direct measures of glycemia and glycosylated blood proteins. The extent of the decreases in all glycemic measures from baseline are shown in Table 2. Direct glycemic measures fell 30–66% from their original levels after 6 wk; GSA fell 29%, but fructosamine and HbA_1 only fell 11–12%, which is significantly lower when taking the precision of the assays into account ($P < .001$).

The Δ HbA_1, Δ fructosamine, and Δ GSA significantly reflected Δ fasting, Δ mean blood glucose, and Δ M value over 6 wk. However, Δ GSA was more closely related to changes in direct measures of glycemia than

TABLE 3
Comparison of changes (Δ) in direct measures of glycemia and glycosylated blood proteins over 2-, 4-, and 6-wk periods in 100 subjects with IDDM

	Fasting blood glucose	Mean blood glucose	M value	GSA	Fructosamine
Δ HbA_1 (wk)					
0–6	.16*	.22*	.24†	.52‡	.42‡
Δ GSA (wk)					
0–2	.37‡§	.28†‖	.26†‖		.56‡
0–4	.28†	.36‡	.32‡		.53‡
0–6	.38‡	.36‡	.38‡		.27‡
Δ Fructosamine (wk)					
0–2	.18*	.00	.01		
0–4	.13	.19*	.20*		
0–6	.18*	.16*	.18*		

Values are correlation coefficients (r_s). GSA, glycosylated serum albumin; HbA_1, glycosylated hemoglobin; IDDM, insulin-dependent diabetes mellitus. *$P < .05$, †$P < .01$, ‡$P < .001$. Correlation between changes in direct glycemic measures and GSA were significantly greater than with fructosamine. §$P < .05$, ‖$P < .01$.

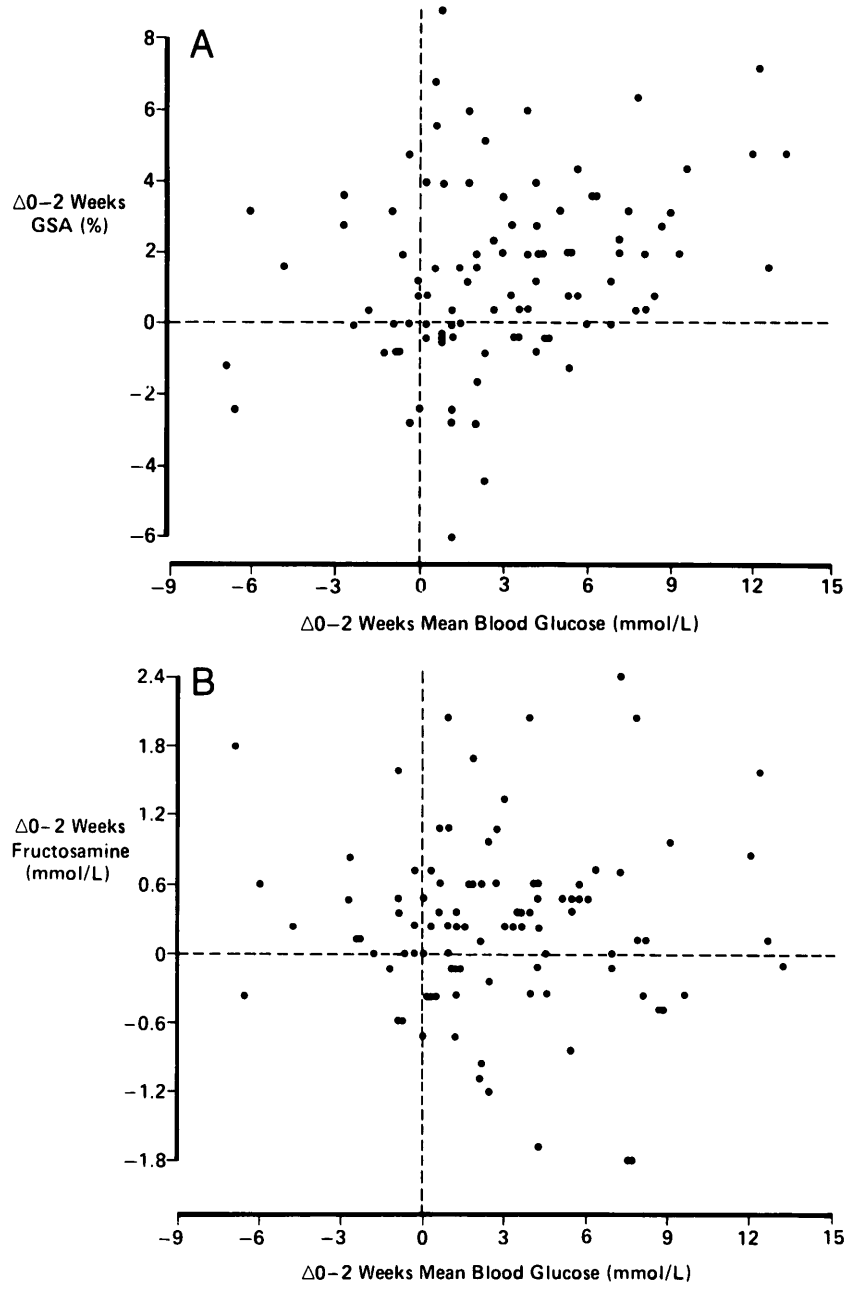

FIG. 3. Comparison of changes (Δ) in mean blood glucose and glycosylated serum albumin (GSA) (*A*; r_s = .28) with changes in mean blood glucose and fructosamine (*B*; r_s = .00) over 2 wk. $P < .01$ difference in r_s between *A* and *B*.

Δ fructosamine, particularly over 2 wk ($P < .05$–$.01$) (Table 3, Figs. 3–4).

Furthermore, although Δ HbA_1 over 6 wk correlated with Δ GSA and Δ fructosamine to a similar extent, changes in GSA and fructosamine over 2–6 wk did not parallel one another (r_s range .27–.56) (Table 3).

DISCUSSION

This is the first study to compare the responses of GSA and fructosamine to short-term changes in glycemic control in IDDM. Direct measures of glycemia and glycosylated blood proteins correlated to a greater or lesser degree at different times, and GSA and fructosamine levels correlated with direct measures of glycemia made cross sectionally and 2–4 wk previously, suggesting that they reflect both ambient and prevailing glycemic control. However, our findings suggest that GSA is more sensitive than fructosamine to improvements in glycemic control over 2 wk. Even after 6 wk, changes in GSA and fructosamine were not parallel, and the magnitude of change in GSA was greater.

Only two of the many reports involving GSA in clinical practice have prospectively evaluated changes in GSA and have documented falls of 50–58% after 4 wk, which paralleled the improvement in glycemia (2–7,13,17–20). One of these reports predominantly involved NIDDM subjects, and the other used an insensitive method to measure GSA (5,6). Anecdotal reports

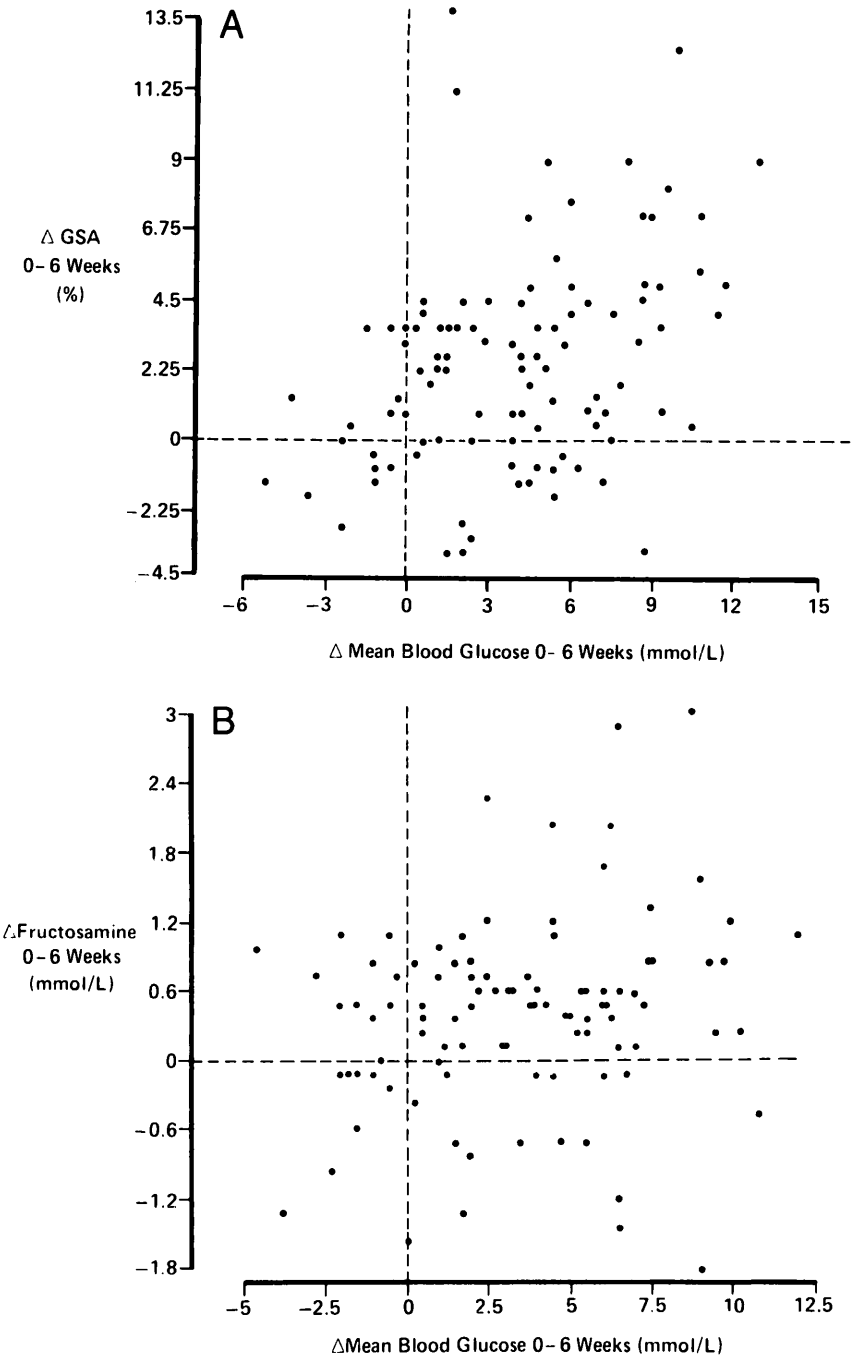

FIG. 4. Comparison of changes (Δ) in mean blood glucose and glycosylated serum albumin (GSA) (*A*; r_s = .36) with changes in mean blood glucose and fructosamine (*B*; r_s = .16) over 6 wk.

(3,4) have suggested that GSA falls 40–50% in IDDM patients after 2–4 wk in response to 50% reductions in mean blood glucose levels. Our study indicates that reductions in mean blood glucose levels of 21–28% (from 12.5 to 9.6 mM after 2 wk, and 8.9 mM after 4 wk) were accompanied by similar reductions in GSA levels. Worsening glycemic control (a rise in blood glucose from 8.3 to 11.1 mM) has been shown to lead to increases in GSA levels after 1 wk (3). Although the affinity chromatography method used to measure GSA in this study is known to be simple, sensitive, and specific (27); the capacity of the affinity columns to extract all glycosylated albumin was exceeded in previous reports (6,7,17–19), and/or insensitive dye-binding techniques were used to measure GSA.

We found that fructosamine was insensitive to short-term improvements in glycemia over 2–4 wk and that levels did not closely parallel those of GSA, confirming our earlier findings (24,26) and those of Mosca et al. (23). In contrast, other groups have suggested in cross-sectional reports that fructosamine levels closely relate not only to HbA_1 but also to measures of GSA and glycosylated total serum proteins (13,16,21,22,25). Most of these reports have combined data from healthy con-

trol subjects and subjects with IDDM and NIDDM. Our study shows that there can be considerable variation in the relationships between the various measures of glycemia in the same group of patients at different points and that the correlations were closest after 6 wk when control was stable. After 2 wk, it is clear that even Δ GSA was limited in reflecting Δ mean blood glucose in many cases.

Despite the apparent advantage of GSA over fructosamine in reflecting short-term improved control in IDDM, we acknowledge that the automated fructosamine assay performed as well as HbA_1 over the 6-wk period and is considerably cheaper and quicker than available HbA_1 or GSA assays.

However, continued controversy remains over standardization of the fructosamine assay (16,28–33). Variation in the pH of the carbonate buffer used in the fructosamine assay can alter reduction of the nitroblue tetrazolium dye and the fructosamine level (16,33), and the use of synthetic and purified secondary standards in different reports makes comparison difficult (16). Moreover, there is evidence suggesting that 50% of the fructosamine level (i.e., 50% of nitroblue tetrazolium reduction) is due to an unidentified serum substrate and not to glycosylated serum proteins (38), which might explain why a particular fructosamine level may estimate a mean blood glucose level that is inaccurate by as much as 4 mM (39). As with GSA, there is little data on the response of fructosamine to improved glycemic control in diabetes. In one report on NIDDM, fructosamine levels did not fall significantly for at least 5 wk when fasting blood glucose levels had fallen almost 50% (from 12.3 to 6.5 mM) (15). One anecdotal report suggested that significant decreases in fructosamine levels were apparent 3 wk after insulin treatment was begun in newly diagnosed IDDM patients (13). Our study demonstrates that fructosamine is less sensitive in reflecting improvements in glycemic control in patients with established IDDM. However, HbA_1, GSA, and fructosamine are all more sensitive to an abrupt deterioration in glycemic control than to a comparable improvement in glycemic control, and significant increases in GSA and fructosamine may develop within 1 wk of sustained hyperglycemia (3,15).

In conclusion, although fructosamine, GSA, and HbA_1 may all give comparable information about preceding hyperglycemia, GSA appears to be the most reliable, sensitive marker of short-term improved glycemic control in IDDM over a 2-wk period.

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