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Measurement of Plasma Fructosamine Evaluated for Monitoring Diabetes

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The mean fructosamine concentration in plasma of diabetics (n = 200) differed significantly (p < 0.001) from those of a hospitalized nondiabetic population (n = 163)—the latter mean being essentially the same for ambulatory subjects (n = 145), expectant mothers (n = 58), and patients with renal failure (n = 31), regardless of sex. In the diabetic group, values for plasma fructosamine correlated with those for glycated hemoglobin (r = 0.767, p < 0.01) and glycated protein (r = 0.817, p < 0.01). Values for plasma fructosamine were stable from day to day in patients with controlled blood glucose, but fluctuated in certain patients receiving only parenteral nutrition, even when their concentrations of glucose were normal and stable. We conclude that measurement of plasma fructosamine is suitable for assessing intermediate-term control of blood glucose when the turnover of plasma proteins is normal.

Additional Keyphrases: comparison with results for glycated hemoglobin and glycated protein · pregnancy · renal failure

A novel approach for measuring glycated proteins, based on the ability of glucose bound to protein with a ketomine linkage (fructosamine) to reduce nitro blue tetrazolium in alkaline conditions, is reportedly inexpensive and reliable for determining intermediate-term (one to three weeks) control of blood glucose (1). The measurement of plasma fructosamine has an interbatch variation of 6.5%, which compares very favorably with the intra-assay variation of 6.2% for the measurement of glycated hemoglobin (2). An advantage of measuring plasma fructosamine is that this can be automated (3, 4), thereby reducing analytical time and imprecision.

The measurement of plasma fructosamine has been used to screen for diabetes mellitus (3) and to monitor the management of non-insulin-dependent diabetes (5). We report here our findings for the normal concentrations of plasma fructosamine determined in a general hospital population, the general public (participants in a diabetic awareness project), and antenatal patients. Because the interpretation of plasma fructosamine relies upon a stable pool of vascular proteins, we also monitored several patients who were receiving only parenteral nutrition, to determine the effects of hypercatabolic states on the concentration of fructosamine in plasma.

Materials and Methods

We measured fructosamine as previously described (1), modifying the procedure for use in a Centrifichem 400 centrifugal analyzer as follows: Mix 30 μL of sample with 40 μL of distilled water, then add to 250 μL of buffered nitro blue tetrazolium reagent. Measure absorbance at 550 nm, 10 and 15 min after starting the reaction, which is performed at 37 °C. We included standards that had been previously calibrated against a 5 mmol/L standard solution of 1-deoxy-1-morpholinofructose containing 40 g of albumin per liter. For day-to-day calibration we used a control serum (QCS Normal Control Serum, lot no. 0831301; Ortho Diagnostic Systems Inc., Westwood, MA 02090) standardized
Glycated hemoglobin was measured with a commercial kit (Bio-Rad Laboratories, Richmond, CA 94804); glucose (6) and albumin (7) were determined by routine methods.

Glycated protein was measured by affinity chromatography (8) with use of boronate affinity gel (Endocrine Sciences Products, Tarzana, CA 91356).

The normal ranges of plasma fructosamine concentrations were determined in capillary blood samples from an ambulatory population (average age 42 years, range 6 to 80 years). For all other patients we used venous blood anticoagulated with heparin. The samples were kept at 4 °C until analysis and plasma fructosamine was measured within 48 h of sample collection.

The imprecision of the method was determined by measuring fructosamine in a human serum-based quality-control material in duplicate each run.

**Results**

Figure 1 illustrates the distribution of fructosamine concentrations in plasma of hospitalized patients, ambulatory patients, nondiabetic antenatal patients, and diabetics with insulin-dependent and non-insulin-dependent diabetes. The mean concentrations (mmol/L) of plasma fructosamine for a nondiabetic ambulatory population (2.00), nondiabetic antenatal patients (1.69), and 31 patients whose mean concentration of plasma creatinine was 295 μmol/L (range 151–809 μmol/L) were not significantly different from that of a nondiabetic hospitalized population (1.97) but differed significantly (p < 0.001) from that of diabetic patients (3.21). The concentration of plasma fructosamine for nondiabetic males (2.02 mmol/L) was not significantly different from that of nondiabetic females (2.01 mmol/L).

Figure 2 shows the day-to-day variation of plasma fructosamine concentrations in non-diabetic patients who were receiving only parenteral nutrition when their blood-glucose concentrations were controlled.

![Figure 1. Distribution (mean ± 2 SD) of plasma fructosamine concentrations in (a) hospitalized nondiabetic patients, 1.96 ± 0.65 mmol/L; (b) ambulatory nondiabetic patients, 2.00 ± 0.47 mmol/L; (c) nondiabetic antenatal patients, 1.74 ± 0.53 mmol/L; (d) insulin-dependent and non-insulin-dependent diabetics, 3.20 ± 1.78 mmol/L.](image)

**Discussion**

Although the demand for measurement of glycated hemoglobin is increasing as an adjunct to home monitoring of blood glucose, it is time consuming and comparatively expensive; the automated measurement of plasma fructosamine, therefore, may offer several advantages.

Baker et al. (3) have reported that concentrations of plasma fructosamine correlate with those of glycated hemoglobin (r = 0.70), as our study substantiates (r = 0.867). Although both correlations are statistically significant, only...
49% and 58% of the respective observations are in close agreement for individual samples. This is not unexpected, because these measurements reflect the integration of blood glucose concentrations over different time periods; about eight weeks for glycated hemoglobin vs one to three weeks for fructosamine (5). Obviously, therefore, results for glycated hemoglobin and plasma fructosamine will not be comparable when the management of diabetes is changed.

In patients with diabetic ketoacidosis, plasma fructosamine concentrations decrease after initiation of treatment (3). Interpretations of changes in fructosamine concentrations, however, depend on the half life of albumin being constant. Although day-to-day concentrations of plasma fructosamine may not change in patients whose plasma glucose is within normal limits (Figure 2A), they may fluctuate in certain patients receiving only parenteral nutrition, even when their blood glucose concentrations are normal and stable (Figure 2, B–D). We speculate that these latter three patients were hypercatabolic for periods of time, thereby increasing the catabolism of the albumin pool. There may also have been an increased exchange with interstitial albumin, which composes 60% of the total body albumin; it is not known whether intravascular and interstitial albumin are glycated at the same rate. Because the concentration of plasma fructosamine reportedly is decreased but stable in nondiabetic patients with severe hypoalbuminaemia (<30 g/L), correction for plasma protein concentration is not required (3). We have found that the mean concentration of fructosamine in plasma is slightly lower in antenatal patients, whose plasma contains less albumin, but the differences were not statistically significant. That the mean concentration of plasma fructosamine in hospitalized nondiabetic patients does not differ from that for an ambulatory nondiabetic group suggests that plasma fructosamine is not influenced by redistribution of body water and albumin, as occurs in supine subjects.

Because plasma fructosamine is considered a measure of glycated protein, we compared the concentrations of fructosamine and glycated plasma proteins by boronate affinity chromatography, which selectively binds free cis-diols. The correlation ($r = 0.817$, Figure 3) was disappointing.

The assumed measurement of glycated albumin as plasma fructosamine has several advantages. The reagents are inexpensive and deoxy-1-morpholino-fructose (which is not satisfactorily stable, even at 4°C) is now commercially available, but we recommend use of a secondary lyophilized protein standard for daily standardization. Plasma fructosamine measurement is automatable, which increases the number of tests that can be measured by one operator and improves precision. In our study the inter-batch imprecision (CV) was 7.4% (for a mean concentration of fructosamine of 2.66 mmol/L) and 4.6% (mean 3.66 mmol/L). The method may not be suitable for all automated instruments because of the 10-min delay required after the working reagent is added; it is inadvisable to reduce the delay time, however, because of significant nonspecific interference.

In conclusion, measurement of plasma fructosamine appears to be a reliable indicator of blood glucose concentrations over the previous seven to 21 days if there is no increase in turnover of the intravascular albumin pool. This short integration period may be advantageous in management of diabetic patients.

References