concentrations of factor VII and protein C decrease rapidly because of their short half lives. The further decrease in the already low protein C activity leads to thrombosis in the microvasculature, which appears to be the site of protein C activation.[15] The microthrombosis is followed by infarction and haemorrhage, enhanced by the lowered factor VII concentration. As haemorrhagic infarction of the chorioid plexus with intraventricular haemorrhage is not a rare finding in intracranial venous thrombosis[16 17] this mechanism may have started the intraventricular bleeding, and the subsequent excessive coumarin effect may have contributed to its profuse nature.

We conclude that cerebral venous infarction due to protein C deficiency should be considered if spontaneous cerebral symptoms occur in young patients, especially if they have a family history of venous thromboembolism.

Critical comments by Professor E A Loeliger are gratefully acknowledged.

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Serum fructosamine concentration as measure of blood glucose control in type I (insulin dependent) diabetes mellitus

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Abstract

Serum fructosamine activity was studied in 42 patients with type I (insulin dependent) diabetes mellitus and 30 non-diabetic volunteers as an index of blood glucose control. There was a significant correlation both between fructosamine and glycosylated haemoglobin values ($r=0.82$) and between fructosamine and the fasting C peptide concentration ($r=-0.81$). Test results in 14 of the diabetics reflected the mean plasma glucose concentration calculated from 25 serial estimations in a single 24 hour period ($r=0.75$; $p<0.01$) but not the mean amplitude of glycaemic excursion ($r=0.23$; $p>0.05$). Fructosamine concentrations measured in these multiple blood specimens did not change significantly throughout the day (mean coefficient of variation 4·1%) despite wide variability of the respective plasma glucose concentrations (mean coefficient of variation 36·2%).

It is concluded that a single random serum sample analysed for fructosamine concentration provides a simple and reliable assessment of glucose homoeostasis in patients with type I diabetes mellitus.

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Introduction

Blood glucose control is difficult to assess in patients with unstable type I (insulin dependent) diabetes mellitus. Glucose concentrations may fluctuate widely during the day, and multiple daily blood glucose estimations are necessary to characterise the glycaemic state accurately.[1 2] Glycosylated haemoglobin (HbA_{1c}), which reflects integrated blood glucose concentrations over weeks to months, provides a useful alternative measure of diabetic control.[2 3] When the test is properly performed HbA_{1c} concentrations do not vary from day to day,[4 5] offering the convenience of random blood sampling.

We recently described the measurement of serum fructosamine as an index of diabetic control.[6] Fructosamine concentrations correlated with HbA_{1c} and other measures of glycaemia[5] and appeared more useful than HbA_{1c} for monitoring short term (three-six weeks) changes after alterations in the treatment of patients with type II diabetes mellitus.[7] The present study was performed to investigate whether fructosamine provides a reliable index of metabolic control in patients with type I diabetes mellitus.

Subjects and methods

The reference intervals for serum fructosamine, fasting plasma glucose, and HbA_{1c} concentrations were determined in 30 healthy non-diabetic volunteers from the hospital laboratory. Insulin dependent diabetics treated with twice daily injections of short and intermediate acting insulin were from the Auckland Hospital diabetic

TABLE I—*Clinical particulars of non-diabetic and diabetic subjects. Results expressed as range of values (medians in parentheses)*

	Age (years)	Sex	Duration of diabetes (years)	Fasting plasma C peptide (nmol/l)	Body mass index (kg/m²)
Non-diabetics (n = 30)	18-55 (28)	12 M, 18 F		0·20-0·90 (0·35)	18·4-28·0 (21·6)
Insulin dependent diabetics (n = 42)	12-75 (22)	21 M, 21 F	0-38 (10)	0·01-0·30 (0·05)	16·7-27·4 (22·5)
Insulin dependent diabetics (serially sampled; n = 14)	14-46 (22)	4 M, 10 F	2-25 (10)	0·01-0·18 (0·04)	18·3-26·8 (22·6)

Conversion: SI to traditional units—C peptide: 1 nmol/l ≈ 3·02 ng/ml.

clinic. Endogenous insulin secretion for all subjects was assessed by measurement of fasting plasma C peptide concentrations and the C peptide response to intravenous glucagon.[8] All patients had normal liver and renal function and normal haematological profiles. Fourteen diabetic patients were further investigated with 25 serial blood specimens collected over a single 24 hour period. The mean plasma glucose concentration and mean amplitude of glycaemic excursion[1] were derived for each patient from these measurements. Table I summarises the clinical details of all the subjects. Informed consent was obtained from all participants at the outset, and the study was approved by the Auckland Hospital's human ethics committee.

TABLE II—*Correlation of fructosamine and glycosylated haemoglobin (HbA_{1c}) with tests of glycaemic control in patients with type I diabetes mellitus*

Test	Pearson's correlation coefficient	
	Fructosamine	HbA_{1c}
Fasting glucose (n = 42)	0·38*	0·24*
Mean plasma glucose (n = 14)	0·75*	0·79**
Mean amplitude of glycaemic excursion[1] (n = 14)	0·23	0·50

*p < 0·01. **p < 0·001.

TABLE III—*Mean (SEM) preprandial and postprandial glucose, fructosamine, and glycosylated haemoglobin (HbA_{1c}) concentrations in 14 insulin dependent diabetic patients*

Test time*	Glucose (mmol/l)	Fructosamine (mmol/l)	HbA_{1c} (%)
8 am	12·3 (1·2)	2·17 (0·12)	8·2 (0·6)
9 am	17·9 (1·2)†	2·19 (0·08)	8·5 (0·7)
10 am	19·4 (1·3)†	2·21 (0·07)	8·8 (0·7)

*Breakfast served between 8 and 8 30 am. Blood collection at 8 am was fasted specimen.
†p < 0·001 compared with preprandial value.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Fructosamine: 1 mmol/l ≈ 25 mg/100 ml.

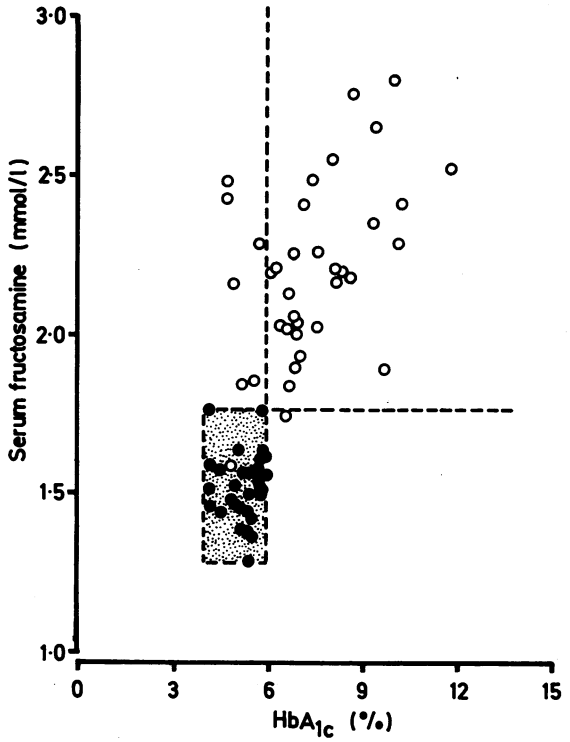

FIG 1—Correlation between fructosamine and glycosylated haemoglobin (HbA_{1c}) concentrations (r = 0·82; p < 0·001) in 42 patients with type I diabetes mellitus (○) and 30 non-diabetic volunteers (●). Hatched area represents non-diabetic values.
Conversion: SI to traditional units—Fructosamine: 1 mmol/l ≈ 25 mg/100 ml.

Blood specimens were obtained from all subjects after an eight hour overnight fast and before the administration of insulin in the diabetic group. Serum or plasma samples were stored at −20°C for glucose, insulin, and fructosamine estimation, and at −70°C for C peptide analysis. Haemolysates were prepared without dialysis and stored in liquid nitrogen for HbA_{1c} analysis. All samples were tested within 24 hours of being thawed.

Fructosamine assay—Serum fructosamine[4] was assayed with an automated discrete analyser (Abbott Laboratories, Chicago). The reagent was carbonate buffer pH 10·35 (0·1M) containing nitro blue tetrazolium chloride (0·25mM), and the standards were 1-deoxy, 1-morpholinofructose[9] in human albumin (40 g/l) (Commonwealth Serum Laboratories). The within batch assay imprecision was 2·9% and between batch assay imprecision 2·9%.

Other tests—Glucose concentrations were determined using a hexokinase and glucose-6-phosphate dehydrogenase technique.[10] Within batch imprecision of the assay was 3·0% and between batch imprecision 1·5%. HbA_{1c} concentrations were determined by isoelectric focusing[11] using commercial polyacrylamide gels and a laser densitometer (LKB, Bromma, Sweden). Within batch imprecision was 4% and between batch imprecision 7%. Plasma C peptide value was measured using a commercial radioimmunoassay kit (Novo, Copenhagen). Plasma free insulin concentrations were measured by radioimmunoassay using antisera against purified porcine insulin[12] after extraction with polyethylene glycol.[13]

Statistical significance was measured by Student's *t* test for paired or unpaired data, as appropriate.

Results

Normal and diabetic values—The range of fructosamine concentrations in 30 healthy non-diabetic volunteers was 1·28-1·76 (median 1·52) mmol/l (32-44 (38) mg/100 ml). Fasting glucose values in the same subjects were 4·1-5·8 (median 5·0) mmol/l (74-105 (90) mg/100 ml) and HbA_{1c} concentrations 4·2-6·0 (median 5·4)%. Fructosamine concentrations in the 42 insulin treated diabetic patients ranged from 1·62 to 2·79 (median 2·28) mmol/l (41 to 70 (57) mg/100 ml). HbA_{1c} values in these patients ranged from 4·8 to 11·8 (median 8·1)%. Figure 1 compares these values in the diabetic and non-diabetic subjects.

Comparison with other indices of diabetic control—Fasting serum fructosamine concentrations in diabetic patients correlated significantly with mean plasma glucose values obtained from multiple blood samples over 24 hours, fasting plasma glucose values, but not mean amplitude of glycaemic excursion. The latter is a measure of within day glucose instability and emphasises the major meal related glucose swings by eliminating minor glucose excursions—that is, those within one standard deviation of the daily mean blood glucose concentration.[1] Table II shows the correlation of these indices of control with HbA_{1c} values in the same patients.

Effect of short term variations in plasma glucose—There was no statistically significant change in mean postprandial fructosamine value (increased 1·8% compared with mean fasting concentration) and mean postprandial HbA_{1c} concentration (increased 7·3% compared with mean fasting value) for the 14 diabetics, despite a highly significant increase of 58% in mean blood glucose concentration after breakfast (table III). The mean intraindividual coefficients of

variation for glucose, fructosamine, and HbA_{1c} values calculated from 25 blood samples collected within a single day were 36·2%, 4·1%, and 6·0% respectively. Figure 2 shows the 24 hour plasma glucose, serum fructosamine, and HbA_{1c} profiles in two of the 14 patients, whose values were near the extremes of the patients' range.

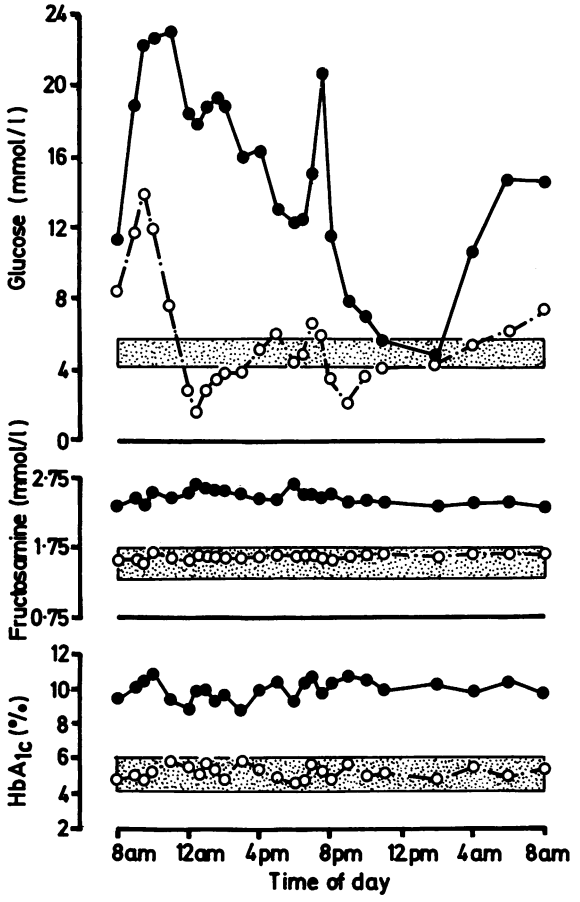

FIG 2—Plasma glucose, serum fructosamine, and glycosylated haemoglobin (HbA_{1c}) values during single 24 hour period in two patients with type I diabetes mellitus. Insulin injected at 7 40 am and 5 40 pm, breakfast served at 8 am, lunch at 12 noon, dinner at 6 pm. Hatched areas are range of values in 30 non-diabetic volunteers. (○=Same subject as case 2 in fig 3.)

Conversion: SI to traditional units—Fructosamine: 1 mmol/l≈25 mg/100 ml. Glucose: 1 mmol/l≈18 mg/100 ml.

Relation to plasma C peptide concentrations—There was a highly significant negative correlation between serum fructosamine and fasting plasma C peptide concentrations ($r=-0·81$; $p<0·001$) in the 42 diabetic and 30 non-diabetic subjects (fig 3). Two outliers were identified in the statistical analysis.[14] Case 1 was a 17 year old youth with needle phobia who tended to neglect his daily injections, and case 2 was a 22 year old woman who frequently suffered mild subclinical hypoglycaemia (see figure 2) and subsequently collapsed, requiring resuscitation in the hospital casualty department. The correlation between fructosamine and fasting plasma free insulin concentrations in the same subjects was not significant ($r=0·12$; $p>0·10$) (not shown).

Discussion

Critical appraisal discloses problems with most of the traditional methods of monitoring blood glucose control in young insulin dependent diabetic patients.[3] Thus major metabolic derangements commonly occur before patients complain of symptoms, urine analysis may give a misleading picture in diabetics with labile control or an abnormal renal threshold for glucose, and isolated blood glucose measurements in the fasting or postprandial state may give an inaccurate impression of mean daily blood glucose concentrations. Many physicians now rely on home blood glucose monitoring by the patient to generate 24 hour (0800-0800 test) glucose profiles on an intermittent basis, complemented by HbA_{1c} estimation in the clinic.[2-4]

Evidence presented here suggests that fructosamine may be used interchangeably with HbA_{1c} estimation as an index of diabetic control in insulin dependent diabetics. Both fructosamine and HbA_{1c} correlated significantly with daily mean plasma glucose concentrations (table II), which reflect the overall adequacy of insulin treatment. Within day individual variability was minimal (coefficient of variation 4·1% for fructosamine, 6·0% for HbA_{1c}) with no significant effect from postprandial fluctuations in blood glucose concentration (table III), indicating that random sampling is justified. Neither variable discriminated diabetics with brittle glucose control,[1] as evidenced by the non-significant correlation with mean amplitude of glycaemic excursion (table II).

The correlation between fructosamine and basal C peptide concentration (fig 3) suggested that fructosamine is strongly influenced by residual endogenous insulin secretion in patients receiving twice daily insulin injection regimens. Conventional insulin treatment is primarily designed to control postprandial hyperglycaemia and often fails to maintain appropriate basal insulin concentrations, particularly at night.[14] Possibly improved insulin delivery by multiple injections or continuous infusion would return the serum fructosamine concentration to normal in this group of patients and eliminate its dependence on endogenous insulin production.

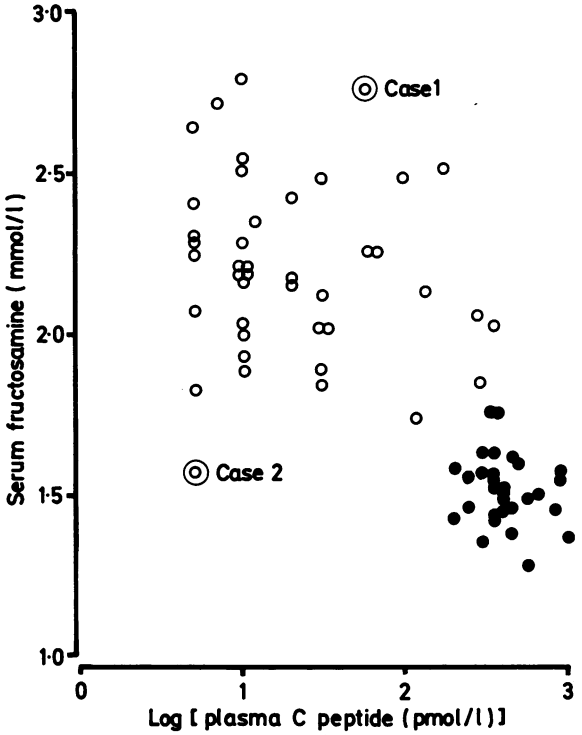

FIG 3—Relation between fructosamine and fasting plasma C peptide concentrations ($r=-0·81$; $p<0·001$) in 42 insulin dependent diabetics (○) and 30 non-diabetic subjects (●). Two outliers[14] (cases 1 and 2) excluded from calculation of correlation coefficient.

Conversion: SI to traditional units—Fructosamine: 1 mmol/l≈25 mg/100 ml. C peptide: 1 pmol/l≈3·02 pg/ml.

We find that the main practical advantages of the fructosamine assay compared with HbA_{1c} estimation are the use of unmodified serum samples, the ease of analysis and precision achieved with automated laboratory equipment, and the suitability of commercial quality control sera to control the method. By contrast, the accurate measurement of HbA_{1c} is technically

demanding and requires special precautions to ensure stability of specimens.[15 16] The assay is also difficult to standardise and control[16] and is commonly unavailable to practising physicians outside the major centres. Similar criticisms may be levelled at alternative glycosylated protein assays,[4] which may be of considerable academic interest but are still unsuitable for widespread application in modern service laboratories.[6 11]

We present the fructosamine assay as a practical alternative measure of overall blood glucose control and the efficacy of insulin treatment in insulin dependent diabetics. The test is cheap and simple to perform using equipment available in most routine service laboratories.[5 6]

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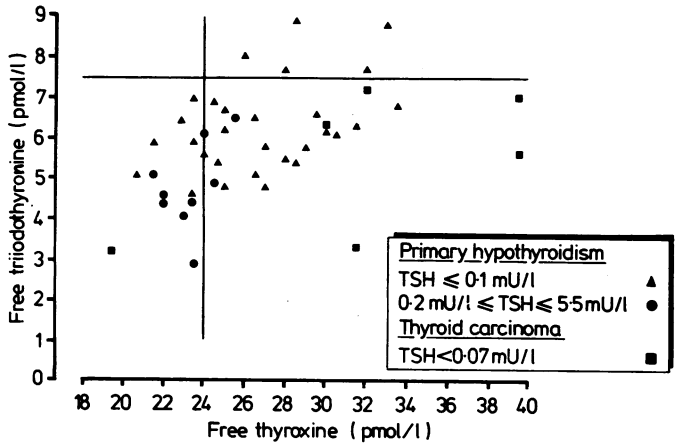
SHORT REPORTS

High sensitivity assay of thyroid stimulating hormone in patients receiving thyroxine for primary hypothyroidism and thyroid carcinoma

As thyroxine treatment often produces raised serum free thyroxine concentrations[1] we measured free thyroxine and thyroid stimulating hormone concentration in patients taking thyroxine for primary hypothyroidism and after ablative radioiodine treatment for thyroid carcinoma. We used an immunoradiometric assay for thyroid stimulating hormone that detects values below the lower limit of normal.

Patients, methods, and results

We studied 38 patients with primary hypothyroidism who were clinically euthyroid (34 women, four men; mean (SD) ages 60 (15) and 70 (3) years, respectively). Two had been treated with thyroxine for two months and the remainder for over a year. We also studied six patients with thyroid carcinoma (five women, one man, aged 45-77). They had received thyroxine for over a year.



Serum concentrations of free thyroxine, free triiodothyronine, and thyroid stimulating hormone (TSH) in 38 patients with primary hypothyroidism and six patients with thyroid carcinoma receiving thyroxine treatment. Horizontal and vertical lines indicate upper limits of normal.

Conversion: SI to traditional units—Thyroxine: 1 pmol/l ≈ 77·7 pg/100 ml. Triiodothyronine: 1 pmol/l ≈ 0·65 pg/ml.

We used Amerlex assays (Amersham International) to measure free thyroxine (normal range 8·0-24·0 pmol/l (0·6-1·9 ng/100 ml)) and free triiodothyronine (normal range 3·0-7·5 pmol/l (2·0-4·9 pg/ml)) and Sucrosep immunoradiometric assay (Boots Celltech Diagnostics) to measure thyroid stimulating hormone (normal range 0·20-5·45 mU/l; typical limit of detection 0·07 mU/l).

Patients with hypothyroidism (figure)—Seven patients were taking 100 μg thyroxine daily and one 75 μg daily. Their mean (SD) free thyroxine and free triiodothyronine concentrations were 24·2 (2·3) and 5·3 (0·95) pmol (1·9 (0·2) ng/100 ml and 3·4 (0·6) pg/ml), respectively. Thyroid stimulating hormone was undetectable in four patients, concentrations in the other four being 0·5, 0·7, 2·9, and 4·2 mU/l. Eleven patients were taking 150 μg thyroxine daily. Their mean free thyroxine and free triiodothyronine concentrations were 26·7 (3·3) and 5·7 (1·0) pmol/l (2·1 (0·3) ng/100 ml and 3·7 (0·7) pg/ml), respectively. Thyroid stimulating hormone concentrations were undetectable in eight patients and 0·1, 0·2, and 0·9 mU/l in the remainder. Nineteen patients were taking 200 μg thyroxine daily. Their mean free thyroxine and free triiodothyronine concentrations were 26·3 (3·4) and 6·4 (1·2) pmol/l (2·0 (0·3) ng/100 ml and 4·2 (0·8) pg/ml), respectively. Thyroid stimulating hormone concentrations were undetectable in 16 patients and 0·2, 0·3, and 1·2 mU/l in the remainder.

Patients with thyroid carcinoma (figure)—Five patients were receiving 200 μg and one 100 μg thyroxine daily. Their mean free thyroxine and free triiodothyronine concentrations were 32·1 (7·5) and 5·4 (1·8) pmol/l (2·5 (0·6) ng/100 ml and 3·5 (1·2) pg/ml), respectively. Thyroid stimulating hormone was undetectable in all patients.

Comment

These results confirm that thyroxine treatment in patients with hypothyroidism may result in raised free thyroxine and normal free triiodothyronine concentrations[1] and that most patients with primary hypothyroidism or thyroid carcinoma have subnormal thyroid stimulating hormone concentrations. The raised free thyroxine and subnormal thyroid stimulating hormone concentrations suggest that these patients had received too much replacement thyroxine and were subclinically hyperthyroid. It might be argued that because triiodothyronine is the hormone active at the level of the tissue the free triiodothyronine concentrations reflect the clinical state accurately.[1] Patients receiving replacement thyroxine lack the thyroidal component of triiodothyronine in the plasma of normal subjects, so that their peripheral tissues must deiodinate enough plasma thyroxine into triiodothyronine to maintain euthyroidism. The pituitary, however, derives more of its nuclear triiodothyronine (which suppresses thyroid stimulating hormone) from circulating thyroxine than peripheral tissues do.[2] The raised circulating thyroxine con-