PAPERS AND SHORT REPORTS

Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus

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Abstract

Fructosamine, a putative measure of serum glycosylated proteins, was measured in 74 subjects referred for oral glucose tolerance tests. A normal range (mean (2 SD)) of 1·6 (0·4) mmol/l (40(10) mg/100 ml) derive from results obtained in 83 healthy non-diabetic volunteers permitted the detection of 15 out of 17 (88%) subjects with proved diabetes and yielded only five (9%) false positive diagnoses. Fructosamine concentrations correlated significantly ($p < 0.001$) with fasting plasma glucose concentrations ($r = 0.76$) and glycosylated haemoglobin concentrations ($r = 0.70$). A longitudinal study suggested that fructosamine concentration was an index of intermediate term (one to three weeks) blood glucose control. Fructosamine concentration was not related to uraemia and did not depend on albumin or total protein concentrations, provided that serum albumin concentrations remained above 30 g/l.

Estimation of fructosamine concentrations is a fully automated procedure and may provide a simple means of screening for diabetes mellitus.

Introduction

Diabetes mellitus is a universal health problem and may occur at any age.[1] The traditional biochemical measurements for initially detecting patients with diabetes mellitus are random estimations of blood and urine glucose concentrations. Despite their common use both tests are fairly non-specific, being influenced by a wide variety of drugs and conditions,[2-4] and have proved to be unsuitable for large population surveys because of the high incidence of misdiagnosis. Accurate detection requires careful standardisation of both the time of day that the sample is collected and the time after carbohydrate ingestion.

Measurement of the glycosylated haemoglobin concentration in a random blood specimen is a more simple screening test for diabetes[6,7] and has the advantage that it reflects blood glucose control under physiological conditions.[8] Unfortunately, its widespread clinical application has been hampered by difficulties with methodology[9]: reliable estimation of glycosylated haemoglobin concentration remains a technically exacting procedure that is ill suited to routine laboratory performance.

We recently described a new colorimetric assay designed to measure serum glycosylated protein concentration.[10] The test, called the fructosamine test in recognition of the Amadori rearrangement product formed by the condensation of glucose and proteins,[11] has the advantage of technical simplicity, low cost, and ease of automation using standard laboratory equipment.

We designed this study to assess the ability of the fructosamine test to detect diabetes mellitus in a mixed group of subjects referred for oral glucose tolerance tests and to determine the rate of change of fructosamine concentrations after changes in diabetic management in patients with established diabetes. We also investigated the effect on fructosamine concentrations of disordered serum protein metabolism by studying non-diabetic subjects with chronic renal disease, including a group with the nephrotic syndrome.

Subjects and methods

SUBJECTS

Non-diabetic controls comprised 33 male and 50 female healthy volunteers aged 15-75 (mean 48) who attended a hospital open day and had no personal or family history of diabetes and a normal random

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blood glucose concentration. Fructosamine concentrations were measured in these subjects to establish a normal range.

Comparison of fructosamine concentrations with other variables of blood glucose control—Fasting serum was obtained from 74 subjects aged 10-83 (mean 45) referred for an oral glucose tolerance test. On the basis of the results of the test the 25 male and 49 non-pregnant female subjects were divided into three groups—namely, those without diabetes, those with inpaired glucose tolerance, and those with diabetes. Fructosamine concentrations were measured in all 74 subjects and compared between the three groups. In addition, we measured fructosamine and glycosylated haemoglobin concentrations in 96 subjects referred to the diabetic clinic, some of whom had diabetes; the correlation between these two variables was assessed.

A longitudinal study was carried out on three male and three female patients aged 14-66 (mean 46) admitted for stabilisation of insulin treatment. Table I gives the clinical details of these patients.

TABLE I—*Clinical details of patients in longitudinal study*

Case No	Sex and age (years)	Duration of diabetes (years)	Complications	Treatment
1	F57	5	Proliferative retinopathy	Glibenclamide 10 mg, metformin 2 g
2	F66	6	Ischaemic heart disease	Insulin 56 U
3	M58	5	Cataracts, background retinopathy	Glibenclamide 20 mg, metformin 1 g
4	M54	4	Ischaemic heart disease	Glibenclamide 15 mg, metformin 1 g
5	M46	0		
6	F14	11	Short stature	Insulin 65 U daily (given in two doses)

Fructosamine concentrations in chronic renal disease were studied in 67 non-diabetic patients with chronic renal disease including 16 patients with the nephrotic syndrome and hypoalbuminaemia (serum albumin concentration < 30 g/l). These patients comprised 38 men and 29 women aged 16-83 (mean 41).

METHODS

Standard two hour oral 75 g glucose tolerance tests were performed after an overnight fast. Results were interpreted using criteria of the World Health Organisation to distinguish subjects without diabetes, those with impaired glucose tolerance, and those with diabetes.[1] Insulin was administered to diabetics with a modified Mill Hill infusion pump (Harvard Apparatus, Massachusetts, USA). Blood glucose control was assessed by a single daily measurement of fasting venous plasma glucose concentration, a daily measurement of serum fructosamine concentration, and the mean blood glucose concentration derived from four daily estimations of capillary blood glucose concentrations using glucose oxidase test strips (Boehringer Mannheim, Federal Republic of Germany).

Analytical techniques and statistical analyses—Glucose concentrations were determined using a hexokinase/glucose-6-phosphate dehydrogenase method[12] adapted to an autoanalyser, and glycosylated haemoglobin concentrations were measured by high pressure liquid chromatography.[13] The fructosamine assay[10] was performed with an Abbott bichromatic discrete analyser (Abbott Laboratories, Chicago, Illinois, USA) using the filter combination 550-650 nm to approximate to the maximum absorbance of the nitro-blue tetrazolium formazan. Serum albumin, total protein, urea, creatinine, and uric acid concentrations were determined with an SMA 12/60 multichannel autoanalyser (Technicon Instruments, Tarrytown, New York, USA). Statistical analyses were performed using a paired or unpaired Student's *t* test as appropriate and least squares regression analysis, deriving the partial correlation coefficient when necessary for interdependent variables.[14]

Results

COMPARISON OF FRUCTOSAMINE CONCENTRATIONS WITH OTHER VARIABLES OF BLOOD GLUCOSE CONTROL

Comparison of fructosamine concentrations with the results of oral glucose tolerance tests in selected individuals in whom diabetes mellitus was suspected clinically yielded a significant difference ($p < 0.001$) between subjects without diabetes (mean 1·69 (SD 0·23) mmol/l) (42(6) mg/100 ml)) and subjects with diabetes (2·42 (0·36) mmol/l) (61(9) mg/100 ml) (fig 1). The normal range (mean (2 SD) 1·60 (0·40) mmol/l (40(10) mg/100 ml)) derived from the non-diabetic volunteers who attended the hospital open day detected 15 of the 17 diabetics (88%) and yielded five (9%) false positive diagnoses. Only one (8%) of the 13 patients with impaired glucose tolerance, however, yielded an abnormal result.

Fructosamine concentration was correlated equally with the fasting ($r = 0.76$) and the two hour ($r = 0.73$) blood glucose concentrations

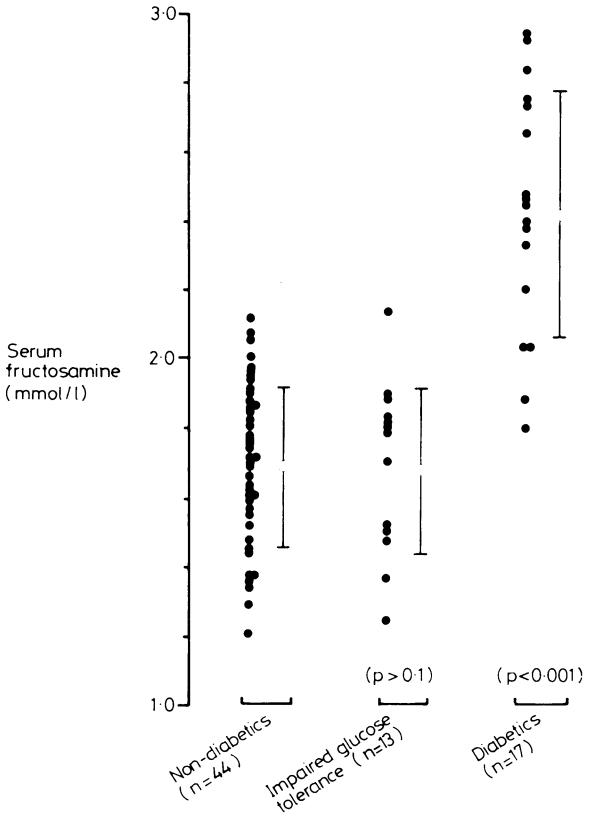

FIG 1—Scattergram of fructosamine concentrations after 75 g oral glucose tolerance tests. Criteria of the World Health Organisation were used to distinguish subjects without diabetes, those with impaired glucose tolerance, and those with diabetes. Bars represent means ± SD.

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

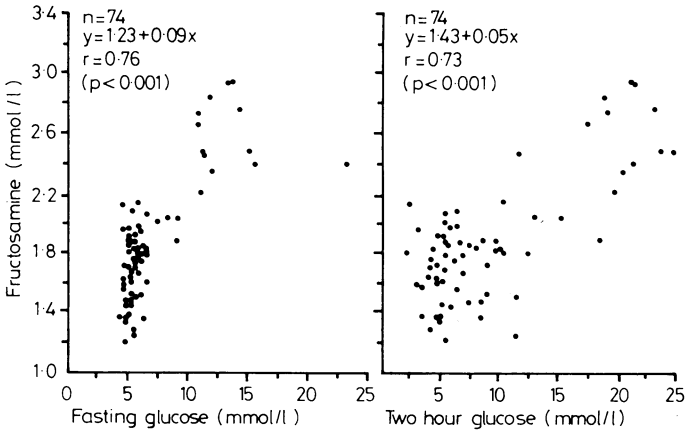

FIG 2—Relation between fructosamine concentration and both fasting plasma glucose concentration and plasma glucose concentration two hours after glucose loading.

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

($p < 0.001$) obtained during the glucose tolerance test (fig 2). The two hour glucose concentration, however, is partly dependent on the preceding fasting glucose concentration. When this interdependence was eliminated statistically by calculating the partial correlation coefficient[14] there was no significant relation between the glucose concentration at two hours and the fructosamine concentration ($r = 0.12$, $p > 0.1$). When the glucose concentration at two hours was partialled out instead a significant relation remained between fasting blood glucose concentration and fructosamine concentration ($r = 0.33$, $p < 0.01$).

Serum fructosamine concentration also correlated significantly with glycosylated haemoglobin concentrations ($r = 0.70$, $p < 0.001$) (fig 3).

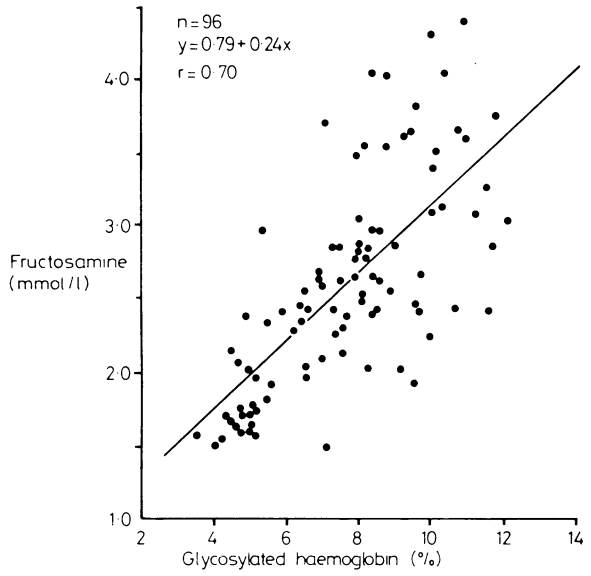

FIG 3—Relation between fructosamine and glycosylated haemoglobin concentrations (normal range for glycosylated haemoglobin is 4-6%). Patients were predominantly insulin dependent diabetics attending the diabetic clinic.

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

LONGITUDINAL STUDY

Figures 4 and 5 show the rate of change of the fructosamine concentration relative to blood glucose control in the six patients with insulin dependent diabetes mellitus studied longitudinally. Despite a profound reduction in fasting plasma glucose concentration of 48% and a 38% fall in mean capillary blood glucose concentration during the first week (fig 4) there was only a marginal decline (8%) in serum fructosamine concentration over the same period. Fructosamine concentrations in the single patient monitored for 48 days after the start of insulin treatment showed roughly an exponential decay, approaching the non-diabetic range by day 20, 16 days after normoglycaemia was established (fig 5).

FRUCTOSAMINE CONCENTRATIONS IN CHRONIC RENAL DISEASE

Table II shows the effects of uraemia and disordered serum protein metabolism on fructosamine concentrations. A significant relation between fructosamine concentration and both total serum protein ($r = 0.79$, $p < 0.001$) and serum albumin ($r = 0.63$, $p < 0.001$) concentrations was found in patients with uncompensated nephrotic syndrome (serum albumin concentration < 30 g/l). Otherwise there was no significant correlation between serum fructosamine concentration and serum urea, creatinine, uric acid, total protein, or albumin concentrations in any of the three groups studied.

Discussion

Awareness that the vascular complications of diabetes have a metabolic basis[15] and are related to blood glucose control[16] has

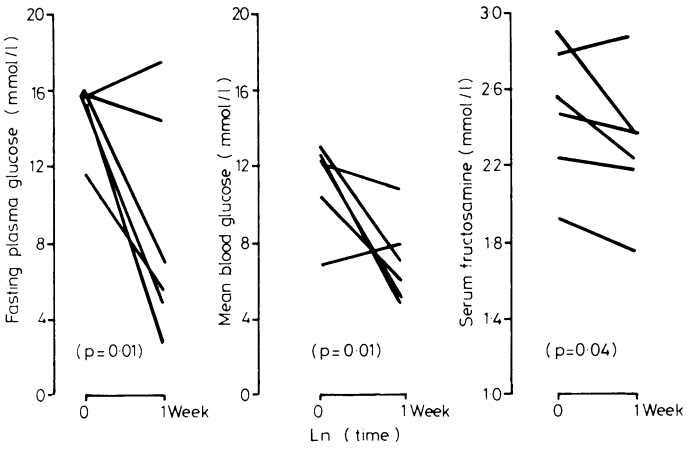

FIG 4—Rate of change of fasting venous plasma glucose, mean capillary blood glucose, and serum fructosamine concentrations over one week in six patients with insulin dependent diabetes mellitus. Logarithmic regression analysis of daily test results with time were performed for each patient and the slopes of the regression equation plotted. Significance levels for the hypothesis of zero slope were obtained using an (unpaired) Student's *t* test on the six independent slopes.

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

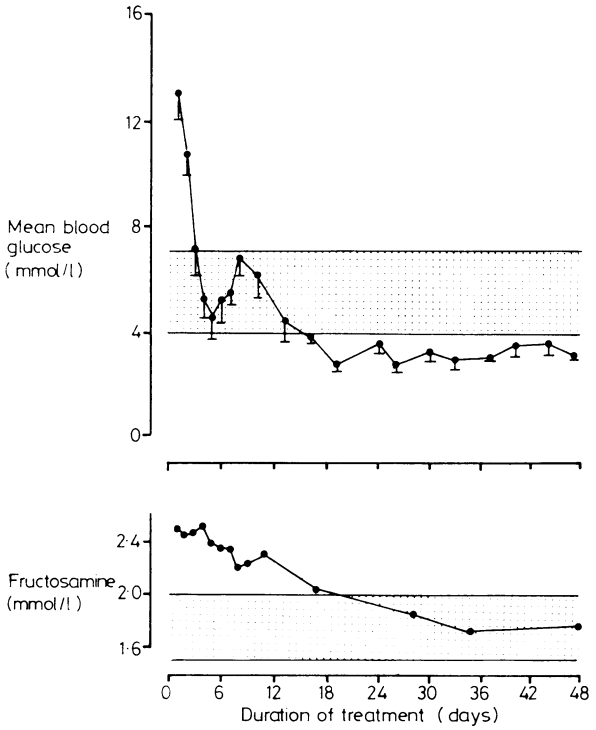

FIG 5—Temporal relation between mean (SD) daily capillary blood glucose concentrations and serum fructosamine concentrations in a patient with newly diagnosed diabetes starting insulin treatment. Stippled areas indicate normal ranges.

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

prompted physicians to adopt a more aggressive approach to diagnosis and clinical management. This change in attitude requires more reliable tests of blood glucose control to permit mass screening for undiagnosed diabetes and frequent monitoring of established cases. It should be emphasised that a positive screening result indicates only that the probability of diabetes is sufficient to warrant a confirmatory diagnostic procedure.[1]

The efficacy of screening tests is customarily determined with Bayesian statistics.[17] Applying Bayes's formula to the

TABLE II—*Mean (1 SD) fructosamine concentrations in patients with uraemia and the nephrotic syndrome*

	Normal controls (n = 83)	Patients with uraemia (n = 51)	Patients with the nephrotic syndrome (n = 16)
Fructosamine (mmol/l)	1·60 (0·20)	1·52 (0·35)*	1·04 (0·24)†
Urea (mmol/l)	5·7 (1·7)	17·5 (11·6)	10·5 (5·7)
Creatinine (mmol/l)	0·08 (0·02)	0·55 (0·46)	0·35 (0·30)
Uric acid (mmol/l)	0·32 (0·10)	0·51 (0·16)	0·45 (0·16)
Albumin (g/l)	43 (3)	39 (4)	24 (4)
Total protein (g/l)	76 (5)	71 (9)	51 (7)

Significance of difference compared with controls: *$p < 0.05$; †$p < 0.001$.
Conversion: SI to traditional units—Fructosamine: 1 mmol/l ≈ 25 mg/100 ml. Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 mmol/l ≈ 11·3 mg/100 ml. Uric acid: 1 mmol/l ≈ 16·8 mg/100 ml.

results of the current study, the probability of a true diagnosis of diabetes mellitus, given a serum fructosamine concentration greater than 2·00 mmol/l (50 mg/100 ml), was 0·75. By comparison, screening of the same 74 patients for glycosuria (not reported), and a blood glucose concentration greater than 8·00 mmol/l (144 mg/100 ml) two hours after a glucose load (World Health Organisation criteria), yielded probabilities of a true diagnosis of diabetes of 0·58 and 0·56, respectively. A major advantage over the other tests, however, may be the high reproducibility of measurements of fructosamine concentration. The mean day to day variation (2·8%) was less than that of random measurements of glucose (10%) or even glycosylated haemoglobin concentrations (4·8%) (table III).

TABLE III—*Mean (SD) values of variables of blood glucose control in five patients with newly diagnosed non-insulin dependent diabetes treated by diet alone.* Percentages are coefficients of variation*

Case No	Sex	Age (years)	Body mass index (kg/m²)	Glucose (mmol/l) (normal < 8·0 mmol/l)	Fructosamine (mmol/l) (normal < 2·0 mmol/l)	Glycosylated haemoglobin (%) (normal < 6·0%)
7	M	42	28·9	11·3 (0·2) 16·8%	2·04 (0·07) 3·4%	6·5 (0·3) 4·8%
8	F	40	33·6	7·8 (1·6) 20·0%	1·21 (0·07) 5·4%	4·8 (0·3) 6·9%
9	M	38	37·1	20·7 (1·0) 4·9%	2·44 (0·02) 1·0%	12·9 (0·1) 0·6%
10	F	69	30·4	6·4 (0·3) 4·2%	1·43 (0·05) 3·8%	5·9 (0·02) 4·3%
11	M	48	28·1	6·1 (0·3) 5·4%	1·51 (0·01) 0·7%	4·7 (0·3) 7·4%

*Tests were performed on random (non-fasting) blood specimens weekly for four weeks.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Fructosamine: 1 mmol/l ≈ 25 mg/100 ml.

Fructosamine concentrations were related primarily to fasting or basal glucose concentrations, as noted previously[10]; postprandial hyperglycaemia probably had little effect as there was no correlation between the fructosamine concentration and glycaemia two hours after a glucose load. This finding is clinically important since it accounts for the almost total failure of the test to identify people with impaired glucose tolerance, many of whom had normal fasting glucose concentrations at the time of testing. A positive result on fructosamine screening is therefore consistent with a conservative diagnosis of diabetes. The discriminatory value (2·00 mmol/l (50 mg/100 ml)) derived from results in healthy volunteers equates with a fasting blood glucose concentration of 8·5 mmol/l (153 mg/100 ml) and a two hour blood glucose concentration of 11·4 mmol/l (205 mg/100 ml) in the current study (fig 2).

The strong correlation of fructosamine concentration with glycosylated haemoglobin concentration compares favourably with the results of others using the thiobarbituric acid reaction to measure glycosylated serum proteins.[18,19] The decay characteristics of fructosamine (figs 4 and 5) were also similar to those in previous reports on serum glycosylated protein or glycosylalbumin metabolism.[19,20] Since fructosamine concentration appears to be an index of intermediate term diabetic control, tests performed at intervals of one to three weeks might give a continuous assessment of integrated blood glucose concentrations.

The other important consideration in the clinical interpretation of fructosamine concentration is the effect of variations in serum protein concentrations. There was no demonstrable linear relation between fructosamine and serum protein concentrations in normal subjects and those with uraemia. Serum protein concentrations became important only in patients with the nephrotic syndrome and severe hypoalbuminaemia (serum albumin concentration <30 g/l). This implies that a serum fructosamine concentration uncorrected for serum protein concentration is valid provided that there is not coexisting severe hypoproteinaemia.

Fructosamine concentrations were not affected in vitro by raised uric acid or creatinine concentrations,[10] which excludes any direct interference of these with the method. The slightly lower fructosamine concentration in patients with uraemia, despite an almost normal albumin concentration, may presumably be explained by the accelerated protein catabolism characteristic of this disorder.[21] The test therefore remains valid in diabetics with renal failure since, in contrast to glycosylated haemoglobin, results are not modified by uraemia.[22]

TABLE IV—*Comparison of costs incurred with tests of blood glucose control, calculated for one analytical batch (25-30 specimens) and including labour. (Interbatch imprecision was estimated using commercial quality control sera, and intrabatch imprecision using paired patient specimens)*

Method	Fructosamine test (nitroblue tetrazolium, automated)	Glucose test (hexokinase, automated)	Glucose test (peroxide electrode, manual)
Cost per test ($)	24c	30c	34c
Coefficient of variation:			
Intrabatch	2·9	3·0	2·0
Interbatch	2·9	1·5	3·4
Instrument used	ABA-VP*	ABA-VP*	YSI†

*Abbott Laboratories, Chicago, Illinois.
†Yellow Spring's Instruments, Denver, Colorado.

The evidence presented here indicates that measurement of the fructosamine concentration is a suitable screening test for diabetes. The cost of the test is less than that of a single measurement of glucose concentration (table IV), and up to 90 samples may be analysed in an hour. Use of the test in patients with uraemia or other conditions such as pregnancy in which serum protein metabolism is altered would require use of a group specific reference range. Further clinical studies are in progress to confirm these preliminary observations.

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Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study

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Abstract

In the Whitehall study of 18 403 male civil servants aged 40-64 years the 10 year mortality rates from coronary heart disease and stroke showed a non-linear relation to two hour blood glucose values, with a significantly increased risk for glucose intolerant subjects with concentrations above the 95th centile point (5·4-11·0 mmol/l; 96-199 mg/100 ml) and for diabetics (blood glucose ⩾ 11·1 mmol/l; ⩾200 mg/100 ml). Multiple logistic analysis showed that between one half and three quarters of the relative risks for deaths from coronary heart disease and stroke were "unexplained" by between group differences in risk factors such as age, blood pressure, obesity, smoking, cholesterol concentration, and electrocardiographic abnormalities. Within the glucose intolerant and diabetic groups the risk factors most strongly related to subsequent death from coronary heart disease were age and blood pressure, with less consistent relations for smoking, cholesterol concentration, and obesity.

This study confirms the importance of hypertension as a cardiovascular risk factor in groups with glucose intolerance and diabetes, and this may have important preventive implications.

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Introduction

Mortality statistics for England and Wales[1] and other countries[2 3] support the findings of several large cohort studies[3-6] in showing increased mortality from coronary heart disease and stroke associated with diabetes mellitus. The Whitehall study[7] and several other studies[8-10] have also shown an increased mortality from coronary heart disease in subjects with raised blood glucose concentrations indicative of glucose intolerance but below those diagnostic of diabetes mellitus.[11] Nevertheless, the relation of asymptomatic hyperglycaemia to other forms of occlusive vascular disease such as stroke remains unclear. Only limited data are available from prospective studies of the relative importance of established risk factors for coronary heart disease—hypertension, hypercholesterolaemia, cigarette smoking—in the aetiology of the vascular disease associated with glucose intolerance and diabetes.[12 13] We have therefore examined the relation of various degrees of glycaemia and other possible risk factors to mortality from coronary heart disease and stroke using 10 year mortality data from the Whitehall study.

Subjects and methods

In the Whitehall study 18 403 male civil servants aged 40 to 64 were examined between 1967 and 1969 and their records tagged at the Central Registry of the National Health Service. A virtually complete 10 year mortality follow up was therefore available for the group.

At the screening examination a resting electrocardiogram (limb leads only) was recorded and classified according to the Minnesota code.[14] Abnormal tracings were defined as those with the following Minnesota code items (Whitehall criteria): Q/QS waves (1·1-1·3); S-T depressions (4·1-4·4); T wave inversion or flattening (5·1-5·3); or left bundle branch block (7·1). Arterial blood pressure was measured using the London School of Hygiene sphygmomanometer with the subjects sitting. Body mass index was calculated as weight (kg)/height $(m)^2$.

Subjects attended on the morning after an overnight fast and capil-