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Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria

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Abstract

Objective—To determine whether insulin dependent diabetics with microalbuminuria have significant abnormalities in concentrations of lipoproteins, apolipoproteins AI and B, fibrinogen, and clotting factor VII which could result in increased cardiovascular risk.

Design—Case-control study.

Setting—Outpatient department of a metabolic ward.

Patients—Group of 20 insulin dependent diabetics with urinary albumin excretion rates greater than 30 µg/min (microalbuminuria) and 20 individually matched insulin dependent diabetics with normal urinary albumin excretion rates (below 30 µg/min) matched for age, sex, and duration of diabetes.

Interventions—Fasting venous blood samples were taken for determination of concentrations of glucose, glycated haemoglobin, lipoproteins, apolipoproteins AI and B, fibrinogen, and factor VII. Height, weight, arterial pressure, and usual insulin dose were recorded, and each patient was given a dietary questionnaire to be completed at home.

End point—Comparison of blood pressure and concentrations of lipoproteins, apolipoproteins AI and B, and fibrinogen in the diabetics with microalbuminuria and the controls.

Measurements and main results—Patients with microalbuminuria had significantly higher concentrations of low density lipoprotein cholesterol (mean 3.33 (SE 0.20) v 2.84 (0.12) mmol/l) and very low density lipoprotein cholesterol (0.30 (0.05) v 0.17 (0.03) mmol/l) than controls but significantly lower concentrations of high density lipoprotein 2 subfraction cholesterol (0.32 (0.04) v 0.54 (0.04) mmol/l). Concentrations of total triglyceride (1.11 (0.14) v 0.68 (0.08) mmol/l), very low density lipoprotein triglyceride (0.56 (0.10) v 0.30 (0.05) mmol/l), apolipoprotein B (0.88 (0.06) v 0.67 (0.03) g/l) and fibrinogen (2.2 (0.1) v 1.9 (0.1) g/l), and diastolic arterial pressure (80 (2) v 74 (2) mm Hg), were also higher in patients with microalbuminuria.

Conclusions—Cardiovascular risk factors—namely, disturbances in lipoprotein and apolipoprotein concentrations, increased fibrinogen concentration, and increased arterial pressure—are already present in insulin dependent diabetics with microalbuminuria. The increased risk of coronary heart disease in patients with clinical proteinuria may result from prolonged exposure to these risk factors, which are present before any impairment of renal function.

Introduction

Insulin dependent diabetics who develop clinical proteinuria have a much greater risk of premature death from cardiovascular complications than those without proteinuria.^{1,2} A subclinical increase in urinary excretion of albumin (microalbuminuria) predicts the development of persistent clinical proteinuria and renal failure in insulin dependent diabetics.^{3,4} In both prospective and cross sectional studies of non-insulin dependent diabetics microalbuminuria strongly indicated an increased risk of death from cardiovascular complications,^{7,9} and it may also do so in non-diabetics.^{10,11}

At the stage of clinical proteinuria and progressive renal failure changes in plasma lipoprotein concentrations,¹²⁻¹⁴ an increase in systemic blood pressure,¹² and haemorrhological changes^{15,16} have each been proposed as contributing to the increased cardiovascular risk. The situation is less clear in patients with microalbuminuria, in whom renal function is normal or even supranormal. Several workers have shown a raised arterial blood pressure at this stage,^{4,6,17} and control of blood glucose concentration has also been reported to be worse.¹⁷ Reports have suggested that profiles of lipoprotein concentrations are changed in diabetics with microalbuminuria and lie between those in diabetics with normal albuminuria and diabetics with clinical proteinuria.^{13,14} The differences, however, were not significant and could have been accounted for by the poorer glycaemic control in the diabetics with microalbuminuria.¹³

In this case-control study we compared concentrations of lipoproteins, apolipoproteins, fibrinogen, and factor VII in insulin dependent diabetics with microalbuminuria and diabetics with normal albumin excretion rates with similar control of their blood glucose concentration.

Patients and methods

Twenty insulin dependent diabetics with microalbuminuria were matched individually for age, sex, and duration of diabetes with 20 insulin dependent diabetics shown to have normal rates of albumin excretion. All were less than 65 years old and had had diabetes since before the age of 35. All patients were Europeans and received the standard dietary advice given to diabetics. None were taking drugs other than insulin apart from two patients with microalbuminuria, who were receiving long term thyroxine and cortisol replacement treatment. No patient had a history of renal disease or of drug or alcohol abuse.

As part of a collaborative screening programme¹⁸ we

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identified insulin dependent diabetics with microalbuminuria—that is, those with urinary albumin concentrations exceeding 15 mg/l (or a ratio of albumin creatinine concentrations greater than 3.5) in their first morning urine sample and, in confirmatory tests over the next few weeks, overnight albumin excretion rates greater than 30 µg/min (geometric mean (range) 48 (31-210) µg/min). The control patients had urinary albumin concentrations <15 mg/l (and ratios of albumin creatinine concentrations <3.5) and were excreting albumin at rates less than 30 µg/min based on analysis of at least two overnight collections of urine (geometric mean (range) 5 (2-18) µg/min). Patients with arterial blood pressure ≥160/95 mm Hg or receiving treatment for hypertension were excluded from the screening programme. Table I gives the clinical features of the two groups.

The patients attended a metabolic ward at 8.30 am; all food, tea, coffee, alcohol, and tobacco had been prohibited from 10 pm the previous night. The morning dose of insulin was withheld until after the observations were complete. After at least 10 minutes' rest in the supine position arterial pressure (phases I and V) in the right arm was measured on two occasions three minutes apart to the nearest 2 mm Hg by the same observer with a standard mercury sphygmomanometer. The mean of the two measurements was used for analysis. A blood sample was taken without cuffing, a history of smoking was recorded, and a dietary questionnaire was completed at home for assessment of the intake of important macronutrients. Dietary data were analysed by the computerised program adapted for the Medical Research Council Caerphilly and Speedwell collaborative heart disease studies.^{19,20}

The glomerular filtration rate was measured by monitoring the clearance of edetic acid labelled with chromium-51 (given in a single bolus injection)²¹ either on the same day as the other measurements were taken or on a different occasion, but always within six months of the study visit, in all patients with microalbuminuria and in 14 of the controls.

MEASUREMENTS

The following measurements were made: plasma glucose concentration by the glucose oxidase method with a Yellow Springs analyser; haemoglobin A₁ concentration by Corning gel electrophoresis (normal range 5.0-7.6%); plasma concentration of electrolytes,

TABLE I—Clinical features of 20 insulin dependent diabetics with microalbuminuria and 20 matched controls

	Patients with microalbuminuria	Controls
No male	17	17
Mean (range) age (years)	39 (19-59)	39 (21-60)
Mean (range) duration of diabetes (years)	20 (8-32)	20 (9-35)
Mean (range) dose of insulin (U/kg/day)	0.7 (0.4-1.2)	0.7 (0.5-1.5)
Mean (range) body mass index (kg/m ²)	25 (19-32)	24 (20-29)

TABLE II—Geometric mean (SE) concentrations (mmol/l) in 20 insulin dependent diabetics with microalbuminuria and 20 matched controls

Lipoprotein	Patients with microalbuminuria	Controls	Mean difference (95% confidence intervals)	p Value
Cholesterol:				
Total	5.41 (0.25)	4.98 (0.18)	0.26 (-0.30 to 0.94)	
Low density lipoprotein	3.33 (0.20)	2.84 (0.12)	0.44 (0.04 to 0.89)	<0.02
Very low density lipoprotein	0.30 (0.05)	0.17 (0.03)	0.17 (0.02 to 0.33)	<0.025
High density lipoprotein	1.07 (0.06)	1.24 (0.06)	-0.18 (-0.35 to 0.01)	
High density lipoprotein 2	0.32 (0.04)	0.54 (0.04)	-0.22 (-0.33 to -0.09)	<0.002
High density lipoprotein 3	0.76 (0.04)	0.75 (0.04)	-0.01 (-0.14 to 0.12)	
Triglyceride:				
Total	1.11 (0.14)	0.68 (0.08)	0.49 (0.21 to 0.81)	<0.001
Low density lipoprotein	0.35 (0.04)	0.28 (0.01)	0.12 (-0.05 to 0.30)	
Very low density lipoprotein	0.56 (0.10)	0.30 (0.05)	0.36 (0.09 to 0.67)	<0.005
High density lipoprotein	0.19 (0.02)	0.18 (0.02)	0.02 (-0.05 to 0.08)

Concentrations of low density lipoprotein cholesterol and high density lipoprotein 2 cholesterol in 20 insulin dependent diabetics with microalbuminuria and 20 matched controls. Horizontal bars indicate geometric means

urea, and creatinine with a multichannel autoanalyser (Hitachi, Boehringer Corporation, United Kingdom); and urinary albumin concentration by radioimmunoassay.³

Blood for determination of lipoprotein concentrations was collected in plain glass tubes and left for the serum to separate (less than two hours). The serum was stored at 4°C until further analysis, which was always performed within five days. Low density, very low density, and high density lipoproteins were separated by ultracentrifugation²² and high density lipoprotein subfractions by a combination of precipitation²³ and ultracentrifugation. Serum concentrations of cholesterol, triglycerides, and lipoprotein subfractions were assayed by enzymatic colorimetric techniques (cholesterol oxidase/peroxidase-amidopyrine and glycerol phosphate oxidase/peroxidase-amidopyrine, Boehringer Mannheim, Germany), with a Cobas-Bio centrifugal analyser (Roche, United Kingdom). Concentrations of apolipoproteins AI and B were measured by immunoturbidimetry with a Cobas-Bio analyser and Orion Diagnostica antiserum and reagents (Oxoid, United Kingdom). A separate, citrated blood sample was taken for measurement of plasma fibrinogen and clotting factor VII concentrations (Coag-A-Mate/2 analyser, General Diagnostic Products, United States).

STATISTICS

The significance of differences was assessed by paired *t* test unless otherwise stated. Data are expressed as means (SEM) and means of the differences with 95% confidence intervals. Log transformation was applied to data on lipids because of their positively skewed distributions.

Results

Concentrations of low density and very low density lipoprotein cholesterol and total triglycerides and very low density triglycerides were significantly higher in the diabetics with microalbuminuria compared with the controls (table II). The concentration of high density lipoprotein 2 cholesterol was reduced in those with microalbuminuria, but there were no significant differences in the concentrations of total or high density lipoprotein 3 cholesterol. The figure shows the concentrations of low density lipoprotein cholesterol and high density lipoprotein 2 cholesterol in each

TABLE III—Mean (SE) concentrations of apolipoproteins AI and B in 20 insulin dependent diabetics with microalbuminuria and 20 matched controls

	Patients with microalbuminuria	Controls	Mean difference (95% confidence interval)
Apolipoprotein AI (g/l)	1.14 (0.05)	1.16 (0.03)	-0.02 (-0.15 to 0.12)
Apolipoprotein B (g/l)	0.88 (0.06)	0.67 (0.03)	0.21* (0.11 to 0.32)
Apolipoprotein AI:apolipoprotein B	1.36 (0.08)	1.80 (0.08)	-0.44* (-0.65 to -0.22)

*p<0.001.

TABLE IV—Mean (SE) fasting plasma glucose, haemoglobin AI, plasma creatinine, and albumin concentrations in 20 insulin dependent diabetics with microalbuminuria and 20 matched controls

	Patients with microalbuminuria	Controls
Fasting plasma glucose (mmol/l)	13.9 (1.5)	13.0 (1.6)
Haemoglobin AI (%)	8.6 (0.4)	8.3 (0.3)
Plasma creatinine (μmol/l)	98 (4)	92 (2)
Plasma albumin (mmol/l)	47 (1)	45 (1)

TABLE V—Mean (SE) dietary intake (g/day) of important macronutrients in 20 microalbuminuric insulin dependent diabetics with microalbuminuria and 20 matched controls

Macronutrient	Patients with microalbuminuria	Controls
Total fat	73 (6)	78 (5)
Saturated fat	32 (3)	34 (2)
Polyunsaturated fat	11 (1)	13 (2)
Protein	73 (4)	77 (4)
Carbohydrate	205 (15)	209 (12)

patient. Apolipoprotein B concentration was increased in the patients with microalbuminuria, and the ratio of apolipoprotein AI to apolipoprotein B concentration was reduced (table III).

The fibrinogen concentration was significantly higher in those with microalbuminuria (2.2 (0.1) g/l) than in the controls (1.9 (0.1) g/l; mean difference (95% confidence interval) 0.3 (0.0 to 0.6); p<0.05), but this was not so for factor VII concentration (0.9 (0.1) v 1.1 (0.1) g/l). The diabetics with microalbuminuria had higher arterial diastolic pressure (80 (2) v 74 (2) mm Hg; p=0.04); systolic pressure was also higher, but the difference was not significant (132 (4) v 127 (2) mm Hg). Fasting plasma glucose, glycated haemoglobin, and serum albumin and creatinine concentrations were similar in the two groups (table IV), as were body mass index and daily dose of insulin (table I). The mean glomerular filtration rate in the 20 patients with microalbuminuria was 113 (6) ml/min/1.73 m², which was not significantly different from that of the 14 controls in whom it was measured (mean 111 (3) ml/min/1.73 m²; p=0.77 by unpaired *t* test). Dietary intake of total, saturated, and polyunsaturated fats and protein and carbohydrate did not differ significantly between the two groups (table V).

Discussion

Our results show that insulin dependent diabetics with microalbuminuria, a group at risk of clinical nephropathy, have significant alterations in serum lipoprotein and apolipoprotein and plasma fibrinogen concentrations. Several factors could be responsible for the differences in concentrations of lipoprotein sub-fractions. The extent of glycaemic control influences lipoprotein concentrations in young insulin dependent diabetics,²⁴⁻²⁶ and differences in lipid concentrations have been described in diabetics with microalbuminuria with poor glycaemic control compared with concentrations seen in diabetics with normal albumin concentrations with good glycaemic control.¹³ The extent of glycaemic control was, however, similar

in the two groups in our study, as were the intake of important macronutrients, the body mass index, and the insulin dose. Renal function, as measured by serum creatinine concentration and glomerular filtration rate, was comparable between diabetics with microalbuminuria and controls. An increased loss of albumin, however, could contribute to differences in lipoprotein concentrations. Severe proteinuria is associated with disturbances of serum lipid concentrations, and together with loss of albumin, the loss of apolipoproteins and small lipoproteins in urine may lead to increased synthesis of albumin and apolipoproteins with altered ratios of high to low density lipoprotein concentrations.²⁷⁻²⁹ Whether this applies to the patients with microalbuminuria with their considerably smaller loss of albumin is not known.

In addition to absolute concentrations, the relative concentrations of lipoproteins and apolipoproteins are also important in atherogenesis.³⁰⁻³¹ Ratios of high density lipoprotein cholesterol to low density lipoprotein cholesterol concentrations and apolipoprotein AI to apolipoprotein B concentrations were significantly lower in the patients with microalbuminuria, a finding consistent with their higher risk of coronary heart disease.

Both in the general and in the diabetic population plasma fibrinogen concentrations have been associated with an increased prevalence of vascular complications,¹⁵⁻³²⁻³³ although whether this is causal, concomitant, or simply a consequence of the vascular disease has not been determined. The processes in the glomerular and arterial walls responsible for the increased permeability to albumin in the patients with microalbuminuria could conceivably lead to a rise in plasma fibrinogen concentration,³⁴⁻³⁵ even though whether this increase results from a relative over-production of fibrinogen or a reduction in its degradation is not known.³⁶ In both insulin dependent diabetics and experimental diabetic animals microalbuminuria is associated with an increase in whole body escape of albumin through the capillaries³¹ and intravascular permeation of protein.³² Larger vessel walls may also be more readily penetrated by other substances, including lipoproteins, where binding by specific apolipoprotein receptors on macrophages, smooth muscle cells, and fibroblasts could result in acceleration of the atherosclerotic process.³⁷⁻³⁸

In addition to the postulated increased risk of atherosclerosis altered lipoprotein concentrations, increased fibrinogen concentration, and arterial blood pressure could also contribute to progression of the renal changes. Moorhead *et al* suggested that increased circulating low density lipoproteins, by binding to the polyanionic glycoproteins on the glomerular basement membrane, could increase the permeability of the membrane, leading to accumulation of lipoproteins and other substances within the mesangium, and stimulate mesangial cell proliferation.³⁹ In animal models of renal disease high fat diets lead to abnormal plasma lipid concentrations and accelerate renal damage.⁴⁰⁻⁴¹

In conclusion, this study has shown that at least some of the prerequisites for the development of atherosclerosis, such as abnormalities in lipoprotein concentrations, hyperfibrinogenaemia, and raised arterial pressure, are found in insulin dependent diabetics with microalbuminuria, itself a strong predictor of later development of clinical proteinuria and greatly increased risk of coronary heart disease. The preconditions for atherosclerosis thus exist well before the onset of renal failure.

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Transplants from living donors in the United Kingdom and Ireland: a centre survey

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Abstract

A survey was carried out to determine for the first time the extent of transplantation from living donors in the United Kingdom and Republic of Ireland and the views of transplant surgeons regarding future developments. Questionnaires were sent to 32 transplant centres representing 18 health regions and covered their extent of experience of transplantation, sources of donors, ages of donors and recipients, outcome of transplantation, and views on expansion of living donor transplantation services. Replies received from 27 transplant centres representing 17 health regions gave data on more than 1200 transplants from living donors. Transplants from living donors accounted for 0-25% of the total experience of health regions. Two centres had abandoned living donor transplantation. Sixty per cent of transplant surgeons favoured expansion of the living donor programme to meet a shortage of kidneys from

cadavers, and the remainder thought that existing programmes were optimal.

Living donor transplantation promises to be an important factor in the future planning of health care resources.

Introduction

When reviewing kidney transplantation in Leicester during 1987 we found a reduction in the number of transplants (table) consequent on a diminishing supply of donor organs despite vigorous campaigns to encourage organ donation. No transplantations from living donors had been performed in the area since 1984 even though seven of the eight previous recipients had functioning grafts. Possible reasons for the decline in transplantations from living donors were the excellent survival of patients with grafts from cadavers after treatment with cyclosporin, uncertainty over the long