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Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes

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Abstract

Objective—To examine whether slightly elevated urinary albumin excretion precedes development of atherosclerotic vascular disease in patients with insulin dependent diabetes independently of conventional atherogenic risk factors and of diabetic nephropathy.

Design—Cohort study with 11 year follow up.

Setting—Diabetes centre in Denmark.

Subjects—259 patients aged 19-51 with insulin dependent diabetes of 6-34 years' duration and without atherosclerotic vascular disease or diabetic nephropathy at baseline.

Main outcome measures—Baseline variables: urinary albumin excretion, blood pressure, smoking habits, and serum concentrations of total cholesterol, high density lipoprotein cholesterol, sialic acid, and von Willebrand factor. End point: atherosclerotic vascular disease assessed by death certificates, mailed questionnaires, and hospital records.

Results—Thirty patients developed atherosclerotic vascular disease during follow up of 2457 person years. Elevated urinary albumin excretion was significantly predictive of atherosclerotic vascular disease (hazard ratio 1.06 (95% confidence interval 1.02 to 1.18) per 5 mg increase in 24 hour urinary albumin excretion, $P=0.002$). Predictive effect was independent of age; sex; blood pressure; smoking; serum concentrations of total cholesterol, high density lipoprotein cholesterol, sialic acid, and von Willebrand factor; level of haemoglobin A_{1c}; insulin dose; duration of diabetes; and diabetic nephropathy (hazard ratio 1.04 (1.01 to 1.08) per 5 mg increase in 24 hour urinary albumin excretion, $P=0.03$).

Conclusion—Slightly elevated urinary albumin excretion independently predicted atherosclerotic vascular disease in patients with insulin dependent diabetes.

Introduction

Macrovascular complications—that is, atherosclerotic vascular diseases—are the commonest causes of early death in patients with insulin dependent diabetes mellitus.¹ In particular, patients with clinical diabetic nephropathy have an extremely high morbidity from macrovascular disease.^{2,3} However, even patients who remain free from diabetic nephropathy have a mortality from macrovascular diseases that is four times higher than that of the general population.³ Preliminary studies have suggested that this excess mortality in people with insulin dependent diabetes might particularly occur among those with slightly elevated urinary albumin

excretion,^{4,5} as is seen in patients with non-insulin dependent diabetes and non-diabetic people.⁶⁻¹² It is, however, not known whether clinical vascular disease in these patients develops before the start of diabetic nephropathy (that is, during the course of slightly elevated urinary albumin excretion) or whether elevated urinary albumin excretion precedes atherosclerotic vascular disease independently of the conventional atherogenic risk factors that are often increased in these patients.¹³⁻¹⁸ The aim of this study was to clarify these points.

Subjects and methods

PATIENTS

Between 1983 and 1986 we recruited a cohort of 288 patients with insulin dependent diabetes mellitus,^{15 19-24} making up about 40% of all the patients with similar age and duration of diabetes attending the outpatient clinic of the Steno Diabetes Center. Patients were excluded if they had atherosclerotic vascular disease (subjective symptoms or changes on a 12 lead resting or exercise electrocardiogram compatible with ischaemic heart disease) or clinical nephropathy (urinary albumin excretion > 300 mg/24 h), if they took any drugs apart from insulin, and if they were not white. By the autumn of 1994 nine patients had died and five had emigrated, leaving 274 for follow up evaluation of their vascular status by means of a mailed questionnaire. After two mailings 250 of the patients had responded, and we obtained the hospital records and death certificates of the patients who had died. Thus, the overall ascertainment was 259/288 (90%).

The participants gave their informed consent. The study was in accordance with the Declaration of Helsinki and approved by the regional ethics committee.

BASELINE MEASUREMENTS

Patients' blood pressure was measured with a standard sphygmomanometer and an appropriately sized cuff after they had rested lying down for 10 minutes. The average of two measurements was recorded. Hypertension was defined as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg (World Health Organisation criteria). Body mass index was calculated as weight (kg)/(height (m)²). Urinary albumin excretion was measured with a radial immunodiffusion technique²⁵ (intra-assay coefficient of variation, 5%; intra-individual coefficient of variation, 47-50%²⁶). The value recorded was an average of two or three 24 hour sterile urine samples that gave negative results on urine analysis. Micro-albuminuria was defined as a urinary albumin excretion of 30-300 mg/24 h in two sterile urine collections.

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Serum total cholesterol and high density lipoprotein cholesterol concentrations were measured by enzymatic colorimetric methods (Chol Chod-pap and high density lipoprotein cholesterol precipitant, Boehringer-Mannheim GmbH, Mannheim, Germany).^{15,27} Serum sialic acid concentration was measured with an enzymatic colorimetric method (Biochemica test combination, Boehringer-Mannheim).²⁸ Serum von Willebrand factor concentration was measured by enzyme linked immunosorbent assay (ELISA) (reagents from Dako A/S, Glostrup, Denmark; calibrator from WHO International Laboratory for Biological Standards, London).²⁹ Haemoglobin A_{1c} in blood was measured by high performance liquid chromatography (Bio Rad, Diamat, Richmond CA, USA).³⁰ The interassay coefficients of variation were 5-8% in all assays.

Patients' smoking habits were recorded and categorised as ever smoked or never smoked. The retina was examined through the dilated pupil, and retinopathy status was categorised as none, background, or proliferative.

FOLLOW UP EVALUATION OF VASCULAR STATUS

The mailed questionnaire was in accordance with the Rose questionnaire.³¹ Classification of whether a subject has cardiovascular disease based on the

questionnaire has been shown to be concordant with the classification based on exercise electrocardiography in the Copenhagen community.^{32,33} Patients were asked in detail (including year of onset) about any history of ischaemic heart disease (chest pain on effort, acute myocardial infarction, coronary artery bypass surgery), stroke (acute cerebral infarction or haemorrhage, transient cerebral attack), or peripheral arterial insufficiency (intermittent claudication, peripheral artery bypass surgery, lower limb amputation). The presence and onset of diabetic nephropathy were identified from the questionnaires and by examining hospital records. The answers to the questionnaires were interpreted by two researchers who were unaware of patients' atherogenic risk profiles and urinary albumin excretion rates. All positive answers were verified from hospital records. For the nine patients who had died, vascular status, nephropathy status, and year of onset were obtained from hospital records and death certificates.

STATISTICAL ANALYSIS

The predictive effect of baseline variables on development of atherosclerotic vascular disease was explored by the Cox proportional hazards regression analysis. Univariate and multivariate analyses with conditional forward selection of the baseline variables (selection criterion: $P < 0.05$) were performed. Time of follow up was calculated from the year of entry into the study (baseline) until the year of start of atherosclerotic vascular disease, start of diabetic nephropathy, death, or until the autumn of 1994. Patients who developed diabetic nephropathy during the follow up were censored at the start of nephropathy, irrespective of later development of atherosclerotic vascular disease. Hazard ratios and 95% confidence intervals are given.

Differences between relevant groups in baseline variables were tested by means of Student's unpaired t test for continuous variables (with non-normally distributed variables first being logarithmically transformed) and the χ^2 test for dichotomised variables. P values below 0.05 (two tailed) were taken to indicate statistic significance. All analyses were performed with the statistical package SPSS for Windows version 6.0.

Results

Table 1 shows the patients' clinical and biochemical baseline characteristics. The 24 non-responders had similar parameters except for level of haemoglobin A_{1c}, which was higher (9.4% *v* 8.4%, $P = 0.04$).

During a mean follow up of 10 years (2457 person years), 30 patients developed clinical atherosclerotic vascular disease: 16 with ischaemic heart disease, seven with stroke, and seven with peripheral arterial insufficiency. Sixteen patients developed diabetic nephropathy.

Table 2 shows the predictive effect of the baseline variables on development of atherosclerotic vascular disease. Elevated urinary albumin excretion remained significantly predictive of atherosclerotic vascular disease after adjustment for the effects of age; sex; blood pressure; smoking; concentrations of total cholesterol, high density lipoprotein cholesterol, sialic acid, and von Willebrand factor; haemoglobin A_{1c}; insulin dose; and duration of diabetes (hazard ratio 1.04 (95% confidence interval 1.01 to 1.08) per 5 mg/24 h increase, $P = 0.03$).

Discussion

This study is the first to show that slightly elevated urinary albumin excretion preceded the development of atherosclerotic vascular disease in patients with

Table 1—Baseline clinical and biochemical characteristics of the 259 patients with insulin dependent diabetes. Values are means (95% confidence interval; 5th and 95th centiles) unless stated otherwise

Proportion (95% confidence interval) of men (%)	54 (44 to 64)
Age (years)	34.7 (33.7 to 35.7; 21.1 and 48.2)
Duration of diabetes (years)	17.7 (17.1 to 18.7; 10.0 and 27.0)
Insulin dose (IU/kg)*	0.62 (0.60 to 0.64; 0.35 and 1.03)
Level of haemoglobin A _{1c} (%)	8.4 (8.2 to 8.6; 6.4 and 10.7)
Blood pressure (mm Hg):	
Systolic	126 (124 to 128; 103 and 155)
Diastolic	79 (78 to 80; 65 and 93)
Proportion (95% confidence interval) hypertensive (%)	6 (3 to 9)
Body mass index (kg/m ²)	23.3 (23.0 to 23.6; 20.0 and 27.7)
Proportion (95% confidence interval) ever smoked (%)	64 (58 to 70)
Urinary albumin excretion (mg/24 h)*	16 (15 to 18; 6 to 110)
Proportion (95% confidence interval) with microalbuminuria (%)	18 (13 to 22)
Serum concentration:	
Total cholesterol (mmol/l)	5.2 (5.0 to 5.4; 3.7 and 6.8)
High density lipoprotein cholesterol (mmol/l)	1.33 (1.27 to 1.39; 0.71 and 2.26)
Sialic acid (mmol/l)	1.88 (1.84 to 1.92; 1.46 and 2.45)
Von Willebrand factor (U/ml)	1.40 (1.34 to 1.46; 0.73 and 2.26)
Proportion (95% confidence interval) with levels of retinopathy (%):	
None	46 (36 to 56)
Background	48 (38 to 58)
Proliferative	6 (1 to 11)

*Geometric means given because of non-normal distribution.

Table 2—Predictive effect of baseline variables on development of atherosclerotic vascular disease. Values are unadjusted hazard ratios (95% confidence interval) for specified change in variable

Baseline variable	Hazard ratio	P value
Men (<i>v</i> women)	0.97 (0.47 to 1.99)	0.93
Age (by 1 year increase)	1.11 (1.05 to 1.16)	0.0001
Duration of diabetes (by 1 year increase)	1.01 (0.94 to 1.07)	0.87
Insulin dose (by 1 IU/kg increase)	0.52 (0.11 to 2.49)	0.41
Haemoglobin A _{1c} (by 1% increase)	1.03 (0.76 to 1.38)	0.87
Blood pressure (by 5 mm Hg increase):		
Systolic	1.17 (1.04 to 1.32)	0.008
Diastolic	1.38 (1.11 to 1.72)	0.004
Hypertension (<i>v</i> no hypertension)	3.33 (1.15 to 9.65)	0.03
Body mass index (kg/m ²) (by 1 unit increase)	1.06 (0.92 to 1.23)	0.43
Ever smoked (<i>v</i> never smoked)	1.87 (0.80 to 4.37)	0.15
Urinary albumin excretion (by 5 mg/24 h increase)	1.06 (1.02 to 1.18)	0.002
Microalbuminuria (<i>v</i> normoalbuminuria)	2.46 (1.02 to 5.92)	0.04
Serum concentration (by 1 unit increase):		
Total cholesterol (mmol/l)	1.77 (1.23 to 2.54)	0.002
High density lipoprotein cholesterol (mmol/l)	0.86 (0.41 to 1.81)	0.69
Sialic acid (mmol/l)	3.71 (1.49 to 9.22)	0.005
Von Willebrand factor (U/ml)	1.47 (0.74 to 2.91)	0.27

insulin dependent diabetes. The predictive effect was independent of diabetic nephropathy, conventional atherogenic risk factors, and duration and control of diabetes.

Clinical diabetic nephropathy is strongly associated with atherosclerotic vascular disease.³ The 16 patients who developed diabetic nephropathy during follow up were censored as controls regardless of whether they later developed atherosclerotic vascular disease, so that the confounding influence of diabetic nephropathy was controlled. Thus, this study showed that in patients without overt diabetic nephropathy the risk of developing atherosclerotic vascular disease increased with increasing urinary albumin excretion. This suggests that the excess macrovascular mortality seen in insulin dependent diabetic patients without diabetic nephropathy^{3,4} may predominantly occur in those with slightly elevated urinary albumin excretion. Conversely, patients with normal urinary albumin excretion may not be at increased risk of atherosclerotic morbidity despite longstanding diabetes, hyperinsulinaemia, or poor glycaemic control.

Our study cohort was representative of patients with uncomplicated insulin dependent diabetes of similar age in the Copenhagen area. Thus, the ratio of men to women was above one³⁴; diabetes was quite well controlled, with a level of haemoglobin A_{1c} about 8.4%³⁵ (that is, 30% above the upper normal limit); and the prevalence of arterial hypertension and microalbuminuria was 6% and 18% respectively.^{35,36} In addition, body mass index³⁴ and serum concentrations of total cholesterol,^{15,16} high density lipoprotein cholesterol,^{15,16} sialic acid,^{37,38} and von Willebrand factor²² were in the usual range for patients with insulin dependent diabetes. Ninety per cent of the initial cohort could be traced, and the non-responders had baseline parameters similar to those of the responding patients apart from slightly poorer glycaemic control. However, elevated levels of haemoglobin A_{1c} had no predictive effect on atherosclerotic vascular disease. Thus, it is unlikely that there was any important participation bias.

MECHANISM OF ACTION

The pathogenic mechanism linking elevated urinary albumin excretion to atherogenesis is obscure. It is hypothesised that increased urinary albumin excretion reflects a generalised vascular dysfunction caused by structural alterations of the vascular wall, such as reduced content or sulphation of heparan sulphate

within the extracellular matrix.³⁹ Such alterations may potentiate albuminuria and several of the processes involved in atherogenesis.⁴⁰

In subjects without diabetes mellitus an elevated serum concentration of sialic acid is predictive of atherosclerotic vascular disease.⁴¹ Sialic acid is incorporated into carbohydrate chains of glycoproteins and glycolipids in serum and tissues.⁴² The degree of incorporation of sialic acid has been reported to affect several haemorheological factors,⁴³ transvascular permeability,⁴⁴ and accumulation of lipid in the arterial wall.⁴⁵ In our study elevated sialic acid was significantly associated with development of atherosclerotic vascular disease even after adjustment for the effect of conventional atherogenic risk factors (data not shown). However, when urinary albumin excretion was included in the model, sialic acid just lost significance. It therefore seems that the predictive effect of elevated sialic acid on development of vascular disease depends on a concomitant elevation of urinary albumin excretion.

In keeping with some previous reports,^{1,46} neither male sex nor elevated levels of haemoglobin A_{1c} predicted atherosclerotic vascular disease. This was also the case for elevated von Willebrand factor. Surprisingly, however, smoking also failed to show a significant predictive atherogenic effect. This might be due to the rough classification of smoking status in our study.

CONCLUSION

Our study suggests that elevated urinary albumin excretion predicts atherosclerotic vascular disease in people with insulin dependent diabetes independently of the conventional atherogenic risk factors, diabetic nephropathy, and duration and control of diabetes.

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Conflict of interest: None.

Key messages

- Atherosclerotic vascular diseases are commonest causes of early death in patients with insulin dependent diabetes
- Preliminary studies suggested that this mortality might particularly occur among patients with elevated urinary albumin excretion
- We studied predictive effect of slightly elevated urinary albumin excretion in development of atherosclerotic vascular disease in 259 patients with insulin dependent diabetes
- Patients with urinary albumin excretion of 30-300 mg/24 h had 2.5 times higher risk of atherosclerotic vascular disease than those with lower excretion rates
- The predictive effect was independent of conventional atherogenic risk factors and of development of diabetic nephropathy, and duration and control of diabetes

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Sensitivity and specificity of QTc dispersion for identification of risk of cardiac death in patients with peripheral vascular disease

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Abstract

Objective—To determine whether QTc dispersion, which is easily obtained from a standard electrocardiogram, can predict those patients with peripheral vascular disease who will subsequently suffer a cardiac death, despite having no cardiac symptoms or signs.

Design—Patients with peripheral vascular disease were followed up for five years after they had had coronary angiography, radionuclide ventriculography, and their QTc dispersion calculated from their 12 lead electrocardiogram.

Subjects—49 such patients were then divided into three groups: survivors (34), cardiac death (12), and non-cardiac death (3).

Main outcome measure—Survival.

Results—The mean (SD; range) ejection fractions were similar in all three groups: survivors 45.9 (11.0; 27.0-52.0), cardiac death 44.0 (7.90; 28.5-59.0), and non-cardiac death 45.3 (4.55; 39.0-50.0). QTc dispersion was significantly prolonged in the cardiac death group compared with the survivors (86.3 (23.9; 41.0-139) v 56.5 (25.4; 25.0-164); $P=0.002$). A QTc dispersion ≥ 60 ms had a 92% sensitivity and 81% specificity in predicting cardiac death. QTc dispersion in patients with diffuse coronary artery disease was significantly ($P<0.05$) greater than in those with no disease or disease affecting one, two, or three vessels.

Conclusions—There is a strong link between QTc

dispersion and cardiac death in patients with peripheral vascular disease. QTc dispersion may therefore be a cheap and non-invasive way of assessing the risk of cardiac death in patients with peripheral vascular disease.

Introduction

Patients with peripheral vascular disease commonly have coronary artery disease, which is asymptomatic in most cases. Despite being free of symptoms, these patients are at high risk of dying from cardiac causes. It would therefore be worth while to identify patients at most risk of cardiac death so that they could receive appropriate cardiac treatments, in addition to treatment for vascular disease.¹

A fairly new and simple variable currently under investigation in cardiac disease is QT dispersion.² Here the QT interval is calculated for all 12 electrocardiographic leads, and the shortest interval is subtracted from the longest interval to give the QTc dispersion. We have shown recently that QTc dispersion was prolonged in patients with chronic heart failure who died suddenly and unexpectedly as compared with a group of such patients who were matched for severity of disease but who survived.³ Similar data linking QTc dispersion and cardiac death also exist for patients after myocardial infarction and for patients with hypertrophic cardiomyopathy.^{4,5}

We therefore investigated whether in patients with

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