Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration

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Abstract

***Objective*—To investigate the predictive value of microalbuminuria (albumin excretion rate 30-300 mg/24 h) as a risk factor for overt diabetic nephropathy in patients with longstanding insulin dependent diabetes.**

***Design*—10 year follow up of patients with normoalbuminuria (albumin excretion rate <30 mg/24 h), microalbuminuria (30-300 mg/24 h), and macroalbuminuria (>300 mg/24 h) based on two out of three timed overnight urine samples.**

***Setting*—Outpatient clinic of Helsinki University Hospital.**

***Subjects*—72 consecutive patients who had had insulin dependent diabetes for over 15 years.**

***Main outcome measures*—Urinary albumin excretion rate, mortality, and prevalence of diabetic complications after 10 years.**

***Results*—56 patients were re-examined at 10 year follow up, 10 had died, five were lost to follow up, and one was excluded because of non-diabetic kidney disease. At initial screening 22 patients had macroalbuminuria, 18 had microalbuminuria, and 26 had normal albumin excretion. Only five (28%, 95% confidence interval 10% to 54%) of the microalbuminuric patients developed macroalbuminuria during the 10 year follow up and none developed end stage renal failure. Two (8%, 1% to 25%) normoalbuminuric patients developed macroalbuminuria and four (15%, 4% to 35%) became microalbuminuric. Seven (32%, 14% to 55%) of the macroalbuminuric patients developed end stage renal failure and six (27%, 11% to 50%) died of cardiovascular complications.**

***Conclusion*—Microalbuminuria is not a good predictor of progression to overt nephropathy in patients with longstanding insulin dependent diabetes.**

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Introduction

About 40% of patients with insulin dependent diabetes will develop overt nephropathy, defined as an urinary albumin concentration above 300 mg/l.[1,2] Progression to end stage renal failure occurs shortly after, indicating that macroalbuminuria (albumin excretion rate >300 mg/24 h reflects an advanced stage of diabetic kidney disease. The finding that microalbuminuria (albumin excretion rate 30-300 mg/24 h) indicates early diabetic nephropathy and predicts progression to overt nephropathy has allowed early diagnosis and preventive interventions at an early stage.[3,4] But most studies of microalbuminuria in diabetic nephropathy have included patients with a mean duration of diabetes of 12 to 14 years.[3,4] It is not known whether microalbuminuria has the same predictive value in patients with longstanding (more than 15 years) insulin dependent diabetes. This information is urgently needed in order to define appropriate screening and follow up programmes for diabetic patients.

TABLE I—*Characteristics of patients with insulin dependent diabetes at initial investigation. Values are mean (SE; range) unless stated otherwise*

	Normoalbuminuria (<30 mg/24 h)	Microalbuminuria (30-300 mg/24 h)	Macroalbuminuria (>300 mg/24 h)
No of patients (F/M)	29 (18/11)	20 (11/9)	22 (14/8)
Albumin excretion rate (mg/24 h)	13 (2; 3-28)	92 (15; 30-265)	2327 (364; 328-7800)
Age (years)	35 (2; 19-52)	37 (2; 27-50)	33 (1; 22-48)
Body mass index (kg/m^2)	22·7 (0·5; 18·0-28·3)	23·2 (0·6; 19·2-28·5)	24·1 (1·0; 18·3-39·9)
Age at onset of diabetes (years)	13 (1; 2-33)	11 (1; 1-24)	12 (1; 4-26)
Mean duration of diabetes (years)	22 (1; 15-38)	26 (1; 16-36)	21 (1; 15-28)
Glycated haemoglobin (%)	9·9 (0·3; 5·8-13·3)	10·4 (0·3; 7·6-13·1)	11·2 (0·5; 7·3-16·6)
Insulin dose (IU/kg)	0·64 (0·03; 0·36-1·03)	0·74 (0·05; 0·45-1·24)	0·73 (0·04; 0·38-1·13)
No (%) with proliferative retinopathy	6 (21)	10 (50)	22 (100)
No (%) with hypertension		6 (30)	16 (73)

Patients and methods

In 1980 we recruited from our outpatient clinic 72 consecutive patients with longstanding (over 15 years), insulin dependent diabetes who were negative for C peptide. All had urinary albumin excretion rates measured (table I). Patients were considered negative for C peptide if peptide concentration six minutes after an intravenous injection of 1 mg glucagon was less than 0·2 nmol/l. One patient was later excluded from the follow up study because of coexisting renal disease (proteinuria and haematuria were present at onset of diabetes). Ten patients died during the 10 year follow up period. The remaining patients were invited to participate in a second study in 1990. Five patients had moved from the region and were lost to follow up. The study protocol was approved by the ethics committee of the Fourth Department of Medicine, Helsinki University Hospital.

Information on patient survival and causes of death was obtained from medical records. Metabolic control had been followed by measuring concentrations of glycated haemoglobin, serum total cholesterol, high density lipoprotein cholesterol, and triglyceride. Urinary albumin excretion was measured in one 24 hour and two timed overnight urine samples, at the beginning and end of the follow up period. Normoalbuminuria was classified as an albumin excretion rate below 20 μg/min (<30 mg/24 h), microalbuminuria as a rate of 20-200 μg/min (30-300 mg/24 h), and macroalbuminuria as a rate over 200 μg/min (>300 mg/24 h) in two out of three consecutive timed overnight urine samples (table I). However, in the tables and text albumin excretion rate is presented as mg/24 h. Blood pressure was measured in the supine position after 10 minutes' rest with a mercury sphygmomanometer. Patients were defined as having hypertension if their systolic blood pressure was >160 mm Hg, their diastolic pressure was >95 mm Hg, or they were taking antihypertensive drugs.

Plasma glucose concentration was measured with a hexokinase method (Boehringer Mannheim, Mannheim, Germany) and glycated haemoglobin by microcolumn chromatography (Isolab, Akron, Ohio, United States). The reference level for the haemoglobin assay was 5-7%. Plasma triglyceride and serum cholesterol concentrations were measured by commercially available methods (Boehringer Mannheim, Mannheim, Germany) and high density lipoprotein cholesterol after ultracentrifugation of plasma. Urine concentrations of albumin were determined immunoturbidimetrically.[5] The sensitivity of the albumin assay was 5 mg/l and the coefficient of variation 7·5%.

All results are expressed as the mean (SE) with 95% confidence intervals. The Mann-Whitney test was used to test the equality of group means and χ^2 test to test the significance of frequency differences.

Results

Twenty nine of the patients examined in 1980 were normoalbuminuric and 26 were available for re-examination in 1990 (figure). By 1990 two patients (8%; 95% confidence interval 1% to 25%) had developed macroalbuminuria and four (15%; 4% to 35%) had progressed to microalbuminuria, 20 patients still remained normoalbuminuric. Two patients died: one who remained normoalbuminuric died of malignancy and one who became microalbuminuric died of myocardial infarction. None of the normoalbuminuric patients had hypertension at the start of the study. Normoalbuminuric patients who progressed to microalbuminuria or macroalbuminuria had higher glycated haemoglobin concentrations during the follow up period ($p<0·02$), lower high density lipoprotein cholesterol concentration ($p<0·05$), required a higher insulin dose ($p<0·01$), and had a shorter duration of diabetes ($p<0·02$) than patients who remained normoalbuminuric (table II).

In 1980 20 patients with insulin dependent diabetes were considered microalbuminuric, 18 of whom could be re-examined in 1990. Five patients (28%; 10% to 54%) had developed macroalbuminuria, six (33%; 13% to 59%) had remained microalbuminuric, and seven (39%; 17% to 64%) had urinary albumin excretion which varied between normal and the microalbuminuric range. One macroalbuminuric and one microalbuminuric patient had died of myocardial infarction (figure). Apart from higher body mass index ($p<0·02$), the patients who progressed to overt nephropathy could not be clinically distinguished from those who remained microalbuminuric (table III). None of the patients who progressed to macroalbuminuria had developed end stage renal failure.

Twenty two patients had macroalbuminuria in 1980. By 1990 seven had developed end stage renal failure, 12 remained macroalbuminuric, while three had become microalbuminuric. Six patients died of cardiovascular disease during the follow up period (figure).

TABLE II—*Initial characteristics of normoalbuminuric patients who did and did not progress to microalbuminuria or macroalbuminuria. Values are mean (SE; 95% confidence interval) unless stated otherwise*

	Progression	No progression	p Value
No of patients (F/M)	6 (4/2)	20 (11/9)	
Albumin excretion rate (mg/24 h)	16 (4; 7 to 25)	12 (2; 8 to 16)	
Age (years)	28 (3; 20 to 36)	38 (2; 34 to 42)	<0·02
Body mass index (kg/m²)	23·1 (0·9; 20·8 to 25·4)	22·7 (0·6; 21·4 to 24·0)	
Age at onset of diabetes (years)	11 (3; 4 to 18)	15 (2; 11 to 19)	
Duration of diabetes (years)	18 (1; 15 to 21)	23 (1; 20 to 26)	<0·02
Insulin dose (IU/kg)	0·81 (0·06; 0·65 to 0·97)	0·59 (0·04; 0·51 to 0·67)	<0·01
Glycated haemoglobin (%)	10·2 (0·6; 8·5 to 11·9)	9·7 (0·4; 8·8 to 10·6)	
Mean glycated haemoglobin (%)*	11·1 (0·5; 9·9 to 12·3)	9·3 (0·4; 8·5 to 9·9)	<0·02
Cholesterol (mmol/l)	6·2 (0·8; 4·3 to 8·1)	5·6 (0·2; 5·1 to 6·1)	
High density lipoprotein cholesterol (mmol/l)	1·4 (0·1; 1·3 to 1·5)	1·7 (0·1; 1·5 to 1·9)	<0·05
Triglyceride (mmol/l)	1·4 (0·3; 0·7 to 2·1)	1·0 (0·1; 0·8 to 1·2)	
Creatinine clearance (ml/s 1·73 m²)	1·52 (0·28; 0·81 to 2·23)	1·77 (0·07; 1·61 to 1·93)	
No (%; 95% confidence interval) with retinopathy	2 (33; 4% to 78%)	2 (10; 1% to 32%)	

* Mean value of all measurements during the follow up period.

TABLE III—*Initial characteristics of microalbuminuric patients who did and did not progress to macroalbuminuria. Values are mean (SE; 95% confidence interval) unless stated otherwise*

	Progression	No progression
No of patients (F/M)	5 (3/2)	13 (7/6)
Albumin excretion rate (mg/24 h)	144 (39; 36 to 252)	79 (16; 45 to 113)
Age (years)	42 (3; 35 to 50)	35 (2; 31 to 39)
Body mass index (kg/m²)	25·8 (0·9; 23.3 to 28·3)*	22·3 (0·7; 20·8 to 23·8)
Age at onset of diabetes (years)	16 (2; 10 to 22)	10 (2; 6 to 14)
Duration of diabetes (years)	26 (1; 22 to 30)	25 (2; 21 to 29)
Insulin dose (IU/kg)	0·66 (0·10; 0·39 to 0·93)	0·78 (0·07; 0·63 to 0·93)
Glycated haemoglobin (%)	11·1 (0·7; 9·3 to 12·9)	10·1 (0·5; 9·2 to 11·1)
Mean glycated haemoglobin (%)†	10·5 (0·8; 8·8 to 12·2)	9·5 (0·3; 8·8 to 10·1)
Cholesterol (mmol/l)	6·6 (0·6; 5·0 to 8·2)	6·0 (0·3; 5·3 to 6·7)
High density lipoprotein cholesterol (mmol/l)	1·4 (0·2; 0·8 to 2·0)	1·7 (0·2; 1·4 to 2·0)
Triglyceride (mmol/l)	1·1 (0·1; 0·7 to 1·5)	1·1 (0·2; 0·7 to 1·5)
Creatinine clearance (ml/s 1·73 m²)	1·56 (0·19; 1·03 to 2·09)	2·00 (0·20; 1·88 to 2·12)
No (%; 95% confidence interval) with retinopathy	3 (60; 15% to 95%)	3 (23; 5% to 54%)
No (%; 95% confidence interval) with hypertension	3 (60; 15% to 95%)	3 (23; 5% to 54%)

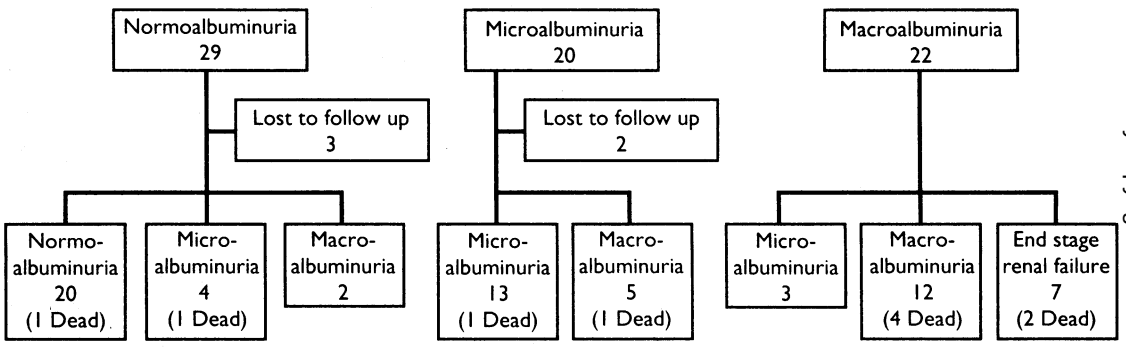
* $p<0·02$ for difference between groups.

† Mean value of all measurements during the follow up period.

Discussion

Our results challenge the view that microalbuminuria is a strong predictor of overt diabetic nephropathy in all patients with insulin dependent diabetes. Our patients had had insulin dependent diabetes for more than 15 years. The prevalence of overt diabetic nephropathy was 31% after a mean duration of diabetes of 22·7 years, which is consistent with prevalence data reported from Denmark.[1,2] The mortality in the proteinuric group was increased threefold compared with that in patients with normal albumin excretion rates (27% *v* 7%). No increase in mortality was seen in patients with microalbuminuria (10%).

Only five of the 18 patients with microalbuminuria progressed to overt diabetic nephropathy compared with seven of eight in the study by Viberti *et al*[3] and 12 out of 14 in the study by Mogensen and Christensen.[4] Although our follow up period was slightly shorter than in these two papers, mean duration of diabetes at initial examination was much longer in our study (26 years *v* 10-14 years). As 22 (31%) of our patients had already developed overt nephropathy at initial examination, the microalbuminuric patients may



Outcome of insulin dependent diabetic patients with normoalbuminuria, microalbuminuria, and macroalbuminuria

represent a subgroup of patients with a low risk of progression to overt nephropathy. In support of this, the incidence of overt diabetic nephropathy increases steeply 10 years after onset of insulin dependent diabetes mellitus and decreases after 30 years.[1] In addition, the prevalence of diabetic nephropathy clearly falls after 40 years.[1]

PREDICTIVE FACTORS

Were there some clinical signs or symptoms to distinguish those patients who developed overt nephropathy from those who did not? In the study by Viberti *et al*, patients who developed overt nephropathy had a slightly longer duration of diabetes than those who did not. Among our initially normoalbuminuric patients, those who developed microalbuminuria or macroalbuminuria had a shorter duration of diabetes than those who remained normoalbuminuric, suggesting that long duration decreases rather than increases the risk of developing nephropathy in these patients. In addition, patients who developed microalbuminuria or macroalbuminuria had higher glycated haemoglobin concentrations during follow up than those who did not progress, indicating that poor glycaemic control contributed to the development of diabetic nephropathy. The patients who progressed to nephropathy also required a greater daily insulin dose and had lower high density lipoprotein cholesterol concentrations than the patients who remained normoalbuminuric. An increased insulin requirement suggests reduced insulin sensitivity, and low high density lipoprotein cholesterol concentrations have been attributed to insulin resistance.[6] In line with the insulin resistance hypothesis, microalbuminuric patients who progressed to nephropathy had a higher body mass index than those who did not. An association between daily requirement of insulin and incidence of nephropathy has been reported.[1]

SUMMARY

In conclusion, in patients with insulin dependent diabetes mellitus of long duration microalbuminuria is no longer an important predictor of progression to overt diabetic nephropathy. The data also suggest that signs and symptoms of insulin resistance are common in patients who progress to overt nephropathy. Since the predictive value of microalbuminuria is different in patients with insulin dependent diabetes mellitus of over 15 years' duration, such patients should be excluded from trials aiming at preventing progression from microalbuminuria to overt proteinuria.

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Use of oral contraceptives by adolescents and its consequences in Finland 1981-91

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Abstract

***Objectives*—To study use of oral contraceptives among Finnish teenagers during 1981-91 and how abortions, childbirths, sexually transmitted diseases, and cardiovascular diseases changed during this period.**

***Design*—Biannual cross sectional surveys with mailed questionnaires from 1981 onwards and analysis of national statistics.**

***Setting*—Finland.**

***Subjects*—A nationwide sample of 14, 16, and 18 year olds. Sample size varied from 1249 to 3887 and response rate from 85% to 94%.**

***Main outcome measures*—Proportion taking oral contraceptive, fertility and abortion rates, hospital discharge rates, rates of sexually transmitted diseases.**

***Results*—The proportion of teenagers taking oral contraceptives increased steadily. In 1991 the percentages among 14, 16, and 18 year olds were 2%, 18%, and 41% compared with 0·2%, 7% and 22% in 1981. Most users had a steady partner (80% of 16 year olds and 85% of 18 year olds). By 1989 rates of abortion had fallen from 12/1000 to 9·3/1000 in 16 year olds and from 25/1000 to 19·2/1000 in 18 year olds; fertility rates had fallen from 4·5/1000 to 2·3/1000 and from 23·5/1000 to 15·3/1000 respectively. Rates in 14 year olds fell only slightly. Gonorrhoea infection fell and HIV infection remained rare. Rates of hospital discharge after thromboembolic venous disease rose slightly.**

***Conclusions*—The increased use of oral contraceptives is the most likely explanation for decreasing abortion and fertility rates among teenagers. Increased reliance on the condom because of the threat of AIDS may increase unwanted pregnancies.**

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Introduction

The need for contraception among adolescents in developed countries is today undoubtable since sexual experience by late adolescence has become so common as to be normal.[1] However, fertility and abortion rates in teenagers suggest that the need for contraception is still not satisfied.[2]

The first oral contraceptives introduced in the 1960s were not suitable for adolescents because of their adverse effects on the growth and maturation of the menstrual cycle. The new low dose and microdose oral contraceptives overcame these problems and they were recommended for teenagers as well.[3-5] As oral contraceptives offer a high degree of protection and are well tolerated among adolescents,[5] increased use could be expected to reduce the rate of unwanted pregnancies.

Although oral contraceptives seem to reduce the risk of pelvic inflammatory disease,[6] they do not protect against sexually transmitted diseases. In the 1980s the HIV epidemic brought a new element into the discus-