Renal outcome of type 2 diabetes in South Africa — a 12-year follow-up study

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Aims. Previous studies of type 2 diabetes mellitus have indicated a benign renal outcome after long-term follow-up. The aim of this study was to determine how often renal failure due to diabetic nephropathy was a cause of death in patients with type 2 diabetes.

Methods. Prospective observational study of 59 South African patients with type 2 diabetes over a 12-year period. During the study repeated clinical evaluations were accompanied by measurements of serum creatinine, serum cholesterol, random blood sugar, and urine protein/creatinine ratios.

Results. The mean duration of diabetes at the end of the study was 17.8 years. There was a wide variation in the time from clinical diagnosis of diabetes to macroproteinuria (mean 9.7 years, SD 5.9, range 0 - 21) and the rate of deterioration of renal function. This rate correlated with poor control of blood pressure, a glucose level of > 14 mmol/l, heavy proteinuria, a high retinopathy score, a body mass index of < 28 and the number of pack years of smoking.

At the end of the study 47 patients (79.7%) had died. Of these deaths 17 (28.8%) were due to chronic renal failure.

Conclusions. In contrast to other studies we have shown that in a developing country renal failure in type 2 diabetic patients is a major cause of death. Determining the prognosis for an individual patient is difficult as there are wide ranges in the time of onset of proteinuria, the rise in serum creatinine and the time to ultimate progression to end-stage renal failure.

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There are few long-term follow-up studies evaluating renal prognosis in type 2 diabetes. In 1982 Fabré *et al.*[1] reported minimal renal impairment with almost no deaths due to chronic renal failure in type 2 diabetic patients after 0 - 35 years of follow-up.[1] As our experience of type 2 diabetes in a developing country did not match these results we undertook a prospective observational long-term follow-up study to evaluate the natural history of type 2 diabetes.

Methods

Inclusion criteria

Our inclusion criteria were similar to those of other groups who distinguished type 2 from type I diabetics.[2-4] Macroproteinuria at entry was assessed with a reactive test tape (Multistix; Ames, Elkhart, IN) on two consecutive urine samples.[5,6]

Patient recruitment and methods

Patients were recruited sequentially from the Groote Schuur Hospital Outpatients Diabetic Clinic or the Somerset Hospital Outpatients and were evaluated every 2 - 3 years over a period of 12 years. Patients were informed that they would be examined and that their blood and urine would be tested but that routine care would continue under their primary care physicians.

The following were documented at each visit: the age at onset of diabetes; the date and age at which insulin was started; the time from the onset of diabetes to the first recorded macroproteinuria; the time to the rise in serum creatinine (SCr); the time to the doubling of the SCr; and the time from doubling to an SCr level of 400 µmol/l and to end-stage renal failure (ESRF).

A detailed retrospective analysis was made of patient records dating back to 1966. Evidence for ischaemic heart disease (IHD), peripheral vascular disease (PVD), cerebrovascular disease (CVD) and any symptoms relating to cardiac decompensation were noted.

Blood pressure was measured with a mercury sphygmomanometer after a 5-minute rest period. Retinopathy was carefully documented by the primary investigator and virtually all patients were also seen by the specialist Ophthalmology Clinic.[3,5] The patient's height and weight were recorded at entry and at follow-up visits to evaluate the body mass index (BMI).

Criteria

Hypertension was defined by three successive diastolic blood pressure readings of 90 mmHg or greater. IHD was defined by a typical history of angina, ECG evidence of a previous

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myocardial infarction or chest pain associated with an elevated creatine phosphokinase level. PVD was defined by a typical history of claudication and the absence of peripheral pulses.

The final cause of death was established in all but 2 patients by death certificate together with direct contact with the doctor, family member or hospital staff caring for the patient. If death due to renal failure was complicated by a co-morbid condition such as cardiomyopathy or sepsis, an SCr of 500 µmol/l or more was defined as primary renal death.

The grading of adverse factors

Adverse factors were graded as: retinopathy: 1 = no diabetic retinopathy, 2 = mild background changes, 3 = severe background retinopathy; 4 = proliferative retinopathy; IHD: 1 = absent, 2 = angina, 3 = myocardial infarction; vascular disease: 1 = no vascular disease, 2 = CVD, 3 = PVD and 4 = CVD and PVD; alcohol use: 1 = no intake, 2 = occasional social drinking, 3 = moderate regular intake, and 4 = heavy intake affecting and interfering with lifestyle and health; peripheral neuropathy: 1= no peripheral neuropathy, 2 = asymptomatic, 3 = symptomatic with objective findings of absent or reduced ankle reflexes and/or distal sensation.

Patients were divided into four groups according to the SCr level at the end of the study or death. Group 1 had a normal SCr throughout, group 2 levels between 120 and 199 µmol/l, group 3 levels between 200 and 399 µmol/l, and group 4 levels of 400 µmol/l or more.

Laboratory investigations

At each visit urea, SCr, cholesterol and blood glucose were measured and a random urine sample tested for protein/creatinine ratio.[7]

Statistical evaluation

Comparisons were made between males and females; insulin-dependent and non-insulin-dependent patients; smokers and non-smokers; patients alive at the end of the study and those who had died of ESRF by the end of study; patients with an SCr rise soon after the onset of diabetes and those with a later rise; patients with preserved renal function (groups 1 and 2) as against poor renal function (groups 3 and 4, and group 4 alone); group 4 patients who died early and those who died later; and patients with rapid doubling of SCr and those with slow doubling.

Factors that were compared by Student's *t*-tests in all these groups were: age at the onset of clinical diabetes (ONSET); duration of diabetes; age at the end of the study or death; smokers versus non-smokers by 'pack-years' (20 cigarettes/day x 1 year = 1 pack-year); insulin-dependent versus non-insulin-dependent patients; BMI < 28 or > 27; systolic and diastolic blood pressure; blood glucose; serum cholesterol; and the times from onset of diabetes to macroproteinuria, to the initial rise of SCr, to doubling of SCr, and to SCr reaching ≥ 400 µmol/l. Chi-square analysis was applied to the non-continuous graded variables of CVD/PVD, IHD, retinopathy and BMI.

All calculations were made with a commercially available program (Statgraphics; STSC, Rockville, MD, USA).[8]

Results

Of 62 individuals entered into the study, 3 were lost to follow-up. The mean age at entry was 62 years. There were 21 males and 38 females. Of the patients 44 were of mixed ancestry, 9 black, 5 white and 1 Indian. The mean duration of diabetes was 17.8 years. Twenty-seven patients were on diet or oral hypoglycaemic agents and 32 patients required insulin. The mean BMI was 31 (SD 6), the median 31 and the range 19 - 46. Thirty-two patients were non-smokers and 27 smokers. Six patients admitted to substantial intake of alcohol in the past but 5 had stopped many years before the onset of diabetes and only 1 patient continued major alcohol abuse.

The significant differences between patients on insulin and those on oral agents were a longer duration of diabetes (19.5 v. 15.8 years, $p < 0.024$), a longer time before doubling of SCr (17.7 v. 13.7 years, $p < 0.04$) and poorer control of blood glucose (14.1 v. 12.3, $p < 0.005$) in patients on insulin.

Comparing patients with good renal function (groups 1 and 2) and those with poorest renal function (group 4), group 4 had higher diastolic blood pressures (96 v. 90 mmHg, $p < 0.022$), higher protein/Cr ratios (5.9 v. 2.9, $p < 0.0006$) and a higher SCr at entry (115 v. 84.7 µmol/l, $p < 0.0027$) with a shorter time to doubling of SCr (14.4 v. 20.2 years, $p < 0.015$).

Chi-square analysis of the graded risk factors, comparing patients with good renal function (groups 1 and 2) to group 4, showed group 4 to have higher scores for vascular disease (CVA/PVD $p < 0.04$), retinopathy ($p < 0.002$) and glucose > 14 mmol/l ($p < 0.035$).

Table I illustrates the pattern of renal dysfunction and the time to events. There was a wide range for onset of proteinuria with even macroproteinuria at first diagnosis of diabetes. Eighty-three per cent of patients (49/59) had an elevated SCr at the end of the study and in 66.1% (39/59) the SCr level had doubled during the study.

The data for 4 patients listed in Fig. 1 illustrate the wide variability in the duration of proteinuria and the deterioration of renal function. Patient 1 had prolonged proteinuria with a minimal fall-off in renal function, patient 2 had impaired renal function at entry with a slow decline to an SCr of 600 µmol/l, and patients 3 and 4 had macroproteinuria from 14 to 17 years before reaching ESRF.

By the end of study 47 of the 59 patients had died and in

Table I. Pattern of renal functional deterioration to end of study or death

	N	Age (yrs) Mean (SD)	Median	Range
Age at entry to study	59	62 (9.4)	62	46 - 89
Age of onset of diabetes	59	47 (10)	46	28 - 81
Duration of diabetes	59	17.8 (6)	17.0	4 - 33
Duration of diabetes to proteinuria	56	9.7 (5.9)	9.0	0 - 21
Initial rise in SCr	40	13.5 (5.2)	13.5	0 - 25
Creatinine rise to doubling	39	16.4 (5.6)	16.0	3 - 28
Doubling of SCr to level of 400 µmol/l	24	17.0 (6)	18.0	3 - 31
Age at 1995 or death	58	65 (9)	63.0	48 - 91

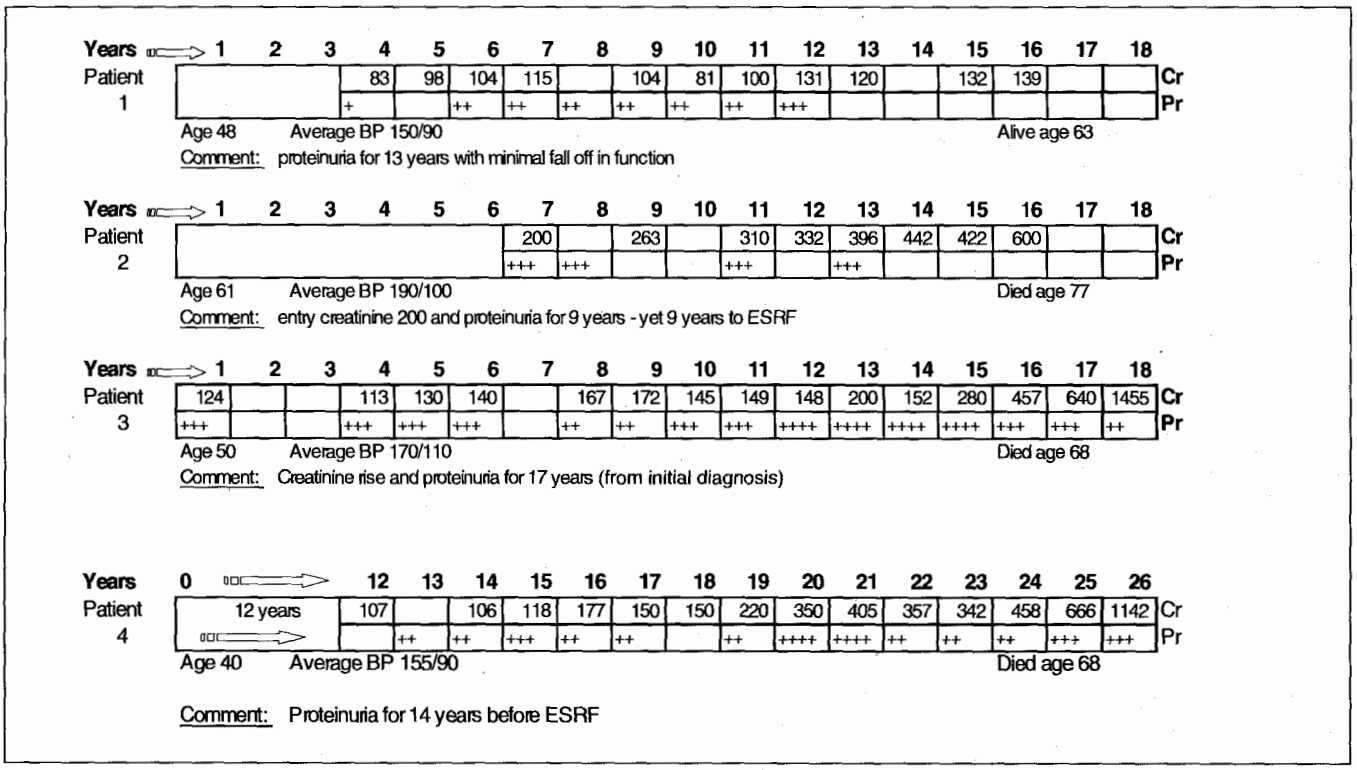

Fig. 1. Variability in duration and magnitude of proteinuria and the rate of deterioration of renal function in 4 patients for comparison with the average shown in Table I.

only 2 patients was the cause of death not established. Death (at a mean age of 65 years) was due to chronic renal failure in 17 cases, myocardial infarction (MI) in 11 and CVA in 7. Patients who had died from chronic renal failure were more likely to have had a high entry SCr ($p < 0.006$), a BMI of < 28 ($p < 0.003$), more severe retinopathy ($p< 0.002$) and a mean glucose level of >14 mmol/l ($p < 0.035$) compared with the patients who were still alive at follow-up. The differences between patients who died at > 73 years of age compared with those who died below the age of 60 years are shown in Table II. The younger age at death is partially explained by the earlier age of onset of diabetes.

Table III shows the differences between smokers and non-smokers with any degree of impaired renal function (groups 2, 3 and 4).

Discussion

When this study was initiated in 1984 there was little documentation of diabetic nephropathy as a cause of ESRF in type 2 diabetics. At the end of the present study we were able to confirm that ESRF was a major cause of death in 29% of our mainly non-Caucasian patients (17/59). In studies of largely Caucasian patients with type 2 diabetes death due to chronic

Table II. Significant differences between patients dying at > 73 years of age compared to those dying < 60 years of age (mean (SD))

	Age at death		
	> 73 years (N = 9)	< 60 years (N = 12)	p-value
Pack-years smoking	3.1 (4)	23.3 (28)	< 0.045
Age at onset of diabetes	59 (11)	42 (7)	< 0.0003
Maximal proteinuria	2.9 (1)	6.1 (4)	< 0.035
Diastolic blood pressure	86 (8)	97 (11)	< 0.03

Table III. Comparison between smokers and non-smokers with impaired renal function (SCr > 119 µmol/l) in 1995*

	Smokers (N = 24)	Non-smokers (N = 25)	p-value
Age at 1995 or death (yrs)	62 (8)	68 (9)	< 0.016
Systolic blood pressure (mmHg)	158 (15)	167 (15)	< 0.049
Retinopathy score	1.87 (0.9)	2.54 (0.9)	< 0.017
Onset of proteinuria (yrs)	8.7 (6)	12.1 (5)	< 0.045

*Five of 24 smokers were alive at a mean age of 63 years and 3 of 25 non-smokers were alive at a mean age of 67 years.

renal failure (CRF) is rare, with reports of no deaths[1,9] and 3 - 8% of deaths due to CRF.[10,11] There is a high incidence of ESRF due to type 2 diabetes in Australian aboriginals (42%) and New Zealand Maoris (61%),[12] and a higher relative risk (4.8) among black Americans.[13]

The reason why our cohort of patients showed a wide variation in the evolution of nephropathy may include some of the following factors: imprecise clinical timing of the onset of type 2 diabetes; vascular and cardiac deaths interrupting the natural progression of renal failure; non-diabetic renal disease (NDRD) in some patients; variations in the incidence and progression of nephropathy in different racial groups; possible effect of male or female gender; and the impact of blood pressure control and appropriate therapy on the rate of progression.

Difficulty in defining the precise time of onset of type 2 diabetes has been documented by Fabré *et al.*,[1] who were uncertain of the time of onset in 20 out of 490 of their patients, and is supported by the presence of macroproteinuria in 5 of our patients at the time of apparent onset of clinical diabetes.

In two large population studies of the prevalence of retinopathy the onset of retinopathy was predicted to be 4 - 7 years before the clinical diagnosis of diabetes,[4] while the chemical diagnosis of diabetes can precede retinopathy by 5 - 40 years.[14] The delay between the biochemical onset of diabetes and its clinical diagnosis can therefore be very difficult to determine with certainty.

Vascular and cardiac death interrupted the natural evolution to renal failure in 6 of our group 3 patients. In three studies of largely Caucasian patients from the UK, Israel and Denmark, the major cause of death was vascular with only 0 - 3% of deaths due to uraemia.[9,10]

In our study neither renal biopsy nor postmortem histology was available to confirm diabetic nephropathy as a cause of the chronic renal failure. In the few studies where renal biopsies were available the percentages of NDRD ranged from 9% to 28%.[1,15,16] The higher figure reflects selective referrals, and in black patients the incidence was only 5.9%. Factors suggesting NDRD were age of onset > 55 years, duration of diabetes < 5 years, no neuropathy and Caucasian race. All these features were minimally represented in our patients.

Various interstitial and vascular changes have been interpreted as NDRD in diabetic patients, yet interstitial and vascular changes as a feature of early diabetic nephropathy are provided from biopsy data of 53 consecutive type 2 diabetic patients with micro-albuminuria.[17]

Cigarette smoking is a well-known adverse factor in diabetic patients, with a higher percentage developing micro-albuminuria[11] and macroproteinuria.[18] In our smokers the onset of proteinuria was earlier and death occured at a younger age (Table III) than non-smokers, who had a higher systolic blood pressure and more severe retinopathy.

While the small number of patients in our study does not allow major conclusions in relation to the effects of hypertension, an elevated diastolic blood pressure was associated with severely impaired renal function and a younger age at death (Table II). Higher systolic blood pressures were found in the non-smokers who lived longer (Table III).

The association of poor glucose control with complications of diabetes is well established.[11,18,19] We only found an association between random blood sugar and poor renal function at a glucose level > 14 mmol/l. In patients with micro-albuminuria and an HbA_{1c} > 8.1% the risk of retinopathy increases logarithmically. Below these levels the relationship is flat.[20]

A strong association of retinopathy with macroproteinuria,[3,5] fatal myocardial infarction,[2] PVD and peripheral neuropathy[5] has been shown. In our patients, retinopathy was associated with poor renal function and death from chronic renal failure (association of retinopathy score and renal function $p < 0.002$).

The association of a BMI < 28 in our patients with impaired renal function is difficult to explain since they do not belong to the late-onset version of type 1 diabetes as only 5 of 10 were on insulin. An adverse factor in these 10 patients was a mean glucose level of > 13.8 mmol/l. An apparent adverse effect of a low BMI on renal function is also suggested by a study on type 2 patients not on insulin, in whom proteinuria was present in 16.8% with a BMI of 25.2 - 28.4 as opposed to 7.9% with a BMI of 32 - 49.3 after 4-year follow-up.[18]

Conclusions

In contrast to other studies, we have shown that renal failure is a major cause of death in type 2 diabetics in a developing country, particularly among non-Caucasians. This study was started before angiotensin-converting enzyme (ACE) inhibitors were commonly used and therefore provides information on the natural progression of diabetic nephropathy.

Determining the prognosis for an individual patient is difficult as there is a wide range for time of onset of proteinuria, rise in SCr and ultimate progression to renal failure. We have shown a strong association between retinopathy, heavy proteinuria and an adverse renal outcome. A further major adverse factor in our study is heavy smoking, which was associated with a younger age at death, earlier onset and heavier proteinuria. The importance of vascular disease as a cause of death in a small number of patients was shown by the interruption of the progression to ESRF by vascular events.

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IN BRIEF

Mitochondrial function deficiency link to type 2 diabetes

The authors of an article recently published in the *New England Journal of Medicine* (2004; **350:** 664-671) state that insulin resistance in the skeletal muscle of insulin-resistant offspring of patients with type 2 diabetes is associated with dysregulation of intramyocellular fatty acid metabolism, possibly because of an inherited defect in mitochondrial oxidative phosphorylation. The presence of similar inherited defects in beta-cell mitochondrial function or content might explain the increased incidence of diabetes in the insulin-resistant offspring of patients with type 2 diabetes. This could lead to answers to a number of questions regarding moderately overweight people who develop type 2 diabetes early in life, and also explain why it does not develop in obese, inactive people. Efficacy of drug therapy may be enhanced with this new knowledge. The study permits us 'to peer into the powerhouse of the cell in order to bring causation and pathogenesis into sharper focus'.