Microalbuminuria and Mortality in Long-Duration Type 1 Diabetes

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OBJECTIVE — Microalbuminuria is a recognized risk factor for increased mortality and renal failure in type 1 diabetes. Whether it remains a powerful predictor in patients with a long duration of type 1 diabetes is not known. We ascertained the prognostic significance of abnormal urinary albumin excretion in a cohort of patients with at least 30 years of type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 190 patients with a disease duration of type 1 diabetes of at least 30 years with baseline and 5 years of follow-up.

RESULTS — At baseline 66% were normoalbuminuric, and at 5 years 11% of this cohort had died. Of the 22% who were microalbuminuric at baseline, 26% had died, and of the 8% with persistent proteinuria at baseline, 44% had died. Of the 4% with end-stage renal failure at baseline, 71% had died within 5 years. Death was attributable to a cardiovascular cause in two-thirds of the cases in all groups.

CONCLUSIONS — Even in those with a long duration of type 1 diabetes, the presence of abnormal urinary excretion remains a powerful predictor of increased mortality.

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By 25 years’ duration of type 1 diabetes, 25–40% of patients will have developed renal complications (1–3). The incidence of diabetic nephropathy, however, is not uniform; it increases steeply after 10 years of disease and then declines once again after 30 years (1). While strict glycemic control reduces the risk of developing complications (4), the prevalence of all microvascular complications in long-duration type 1 diabetes is still lower than expected; it is possible that a degree of genetic protection from complications exists in this subgroup (5).

Most studies demonstrating a relationship between microalbuminuria and progression to diabetic nephropathy have included subjects with a mean duration of diabetes <17 years (6–10). One study failed to demonstrate a relationship between duration of diabetes and the progression of microalbuminuria to nephropathy in patients with a mean age of 34 years and duration of diabetes of 17 years (8). In those with a mean disease duration of 26 years, microalbuminuria was found to be a less strong predictor of diabetic nephropathy compared with those with a shorter duration of diabetes (11). The aim of this study was to determine the 5-year clinical outcome in a cohort of patients with a duration of type 1 diabetes exceeding 30 years and variable levels of urinary albumin excretion at baseline.

RESEARCH DESIGN AND METHODS — We identified 204 patients with a clinical diagnosis of type 1 diabetes for >30 years in 1995 from the clinic database. Notes could not be found for three cases, three had longstanding insulin-treated type 2 diabetes that had been misclassified, and eight had no urinary albumin measurement recorded in 1995 and were excluded from further study. Therefore, 190 had complete data available from clinic visits in 1995.

Details of microvascular diabetes complications were obtained by reviewing clinical records along with age, year of diagnosis, BMI, blood pressure, HbA1c, serum creatinine, urine albumin:creatinine ratio, or 24-h urinary protein estimation. Subjects were divided into four groups according to their renal status at baseline: normoalbuminuria (albumin:creatinine ratio <3.5 mg/mmol), microalbuminuria (albumin:creatinine ratio 3.5–30 mg/mmol), proteinuria (albumin:creatinine ratio >30 mg/mmol and/or urine protein concentration >0.3 g/24 h on 24-h collection), or end-stage renal failure due to diabetic nephropathy (requiring dialysis or renal transplantation).

At follow-up in 2000, serum creatinine, urine albumin:creatinine ratio, or 24-h urinary protein estimation were recorded. For those dying before 2000, the cause of death was obtained from death certificates and verified from clinical records review wherever possible. Cardiovascular death was defined as death from ischemic heart disease, heart failure, or cerebrovascular disease. British government actuarial life tables for 1998–2000 for the U.K. were used to determine life expectancy for nondiabetic individuals (12).

Statistical analysis
Statistical analysis was performed using SPSS version 10.0 (SPSS, Chicago, IL). Student’s t tests were used for analysis of parametric data and \( \chi^2 \) test for nonparametric data. Life tables were used to plot survival over time. Values are given as median (range) or mean ± SD, as appropriate.

RESULTS — At baseline in 1995, 125 patients (66%) were normoalbuminuric, 42 (22%) were microalbuminuric, 16 (8%) had persistent proteinuria, and 7 (4%) had developed end-stage renal fail-
ure. All groups were similar in terms of age, age at onset of diabetes, and duration of diabetes (Table 1). At baseline, laser-treated retinopathy was more prevalent with increasing severity of renal dysfunction. After 5 years of follow-up in 2000, 11% with normoalbuminuria at baseline, 26% with microalbuminuria, 44% with persistent proteinuria, and 71% with end-stage renal failure had died (Fig. 1). In an age- and sex-matched nondiabetic cohort, 4% of individuals would have died by 5 years (12). Death was attributable to a cardiovascular cause in approximately two-thirds of cases in total and this proportion was similar within each group (Fig. 1). The predicted median survival from baseline was inversely related to urinary albumin loss (Fig. 2).

A total of 111 subjects with normoalbuminuria at baseline survived until follow-up in 2000 (89%), during which time 5% had progressed to microalbuminuria and none developed proteinuria. Ten percent with microalbuminuria at baseline developed proteinuria, and 30% reverted to normoalbuminuria. One patient with proteinuria at baseline reverted to microalbuminuria. Serum creatinine in the normoalbuminuria and microalbuminuria groups did not rise in the 5 years of follow-up. A significant rise in serum creatinine from baseline to follow-up occurred in the nine patients with persistent proteinuria who survived 5 years from a median (range) value of 115 (95–205) to 157 (94–271) μmol/l (P < 0.05). No patients in any group developed end-stage renal failure during the 5-year follow-up period.

**CONCLUSIONS**—In those with a mean duration of type 1 diabetes of 35 years, abnormal urinary albumin excretion still confers an increase in mortality with a clear gradation of risk across the range of urinary albumin loss. Cardiovascular disease is the most common cause of death in all groups, accounting for two-thirds of deaths. Progression from microalbuminuria to proteinuria still occurs, although the development of end-stage renal failure from proteinuria appears to be uncommon, albeit with a short follow-up of only 5 years. Intriguingly, 30% of patients with microalbuminuria at baseline reverted to normoalbuminuria at 5 years of follow-up. In the microalbuminuric cohort of the Diabetes Control and Complications Trial (DCCT), between 50 and 60% of younger patients with disease duration of 9 years reverted to normoalbuminuria over 6.5 years (13). Our data suggest that reversion to normoalbuminuria may be less common with increasing duration of diabetes. Only 5% of patients with normoalbuminuria at baseline developed microalbuminuria at follow-up, a much lower percentage than in the DCCT (4).

The prevalence of normoalbuminuria and microalbuminuria in our cohort is similar to that described by Mackin et al. (14), although no data on the prevalence of end-stage renal failure in long-duration type 1 diabetes are available from similar studies. It has been proposed that those with a shorter duration of type 1 diabetes progress more rapidly from microalbuminuria to overt nephropathy than people with long disease duration (11). Progression from normoalbuminuria to microalbuminuria and from microalbuminuria to proteinuria still occurs in those with long-duration type 1 diabetes. A study similar in design (15) found a higher rate of progression than observed
in our cohort. We have no explanation for this difference. Although no patients with proteinuria reached end-stage renal failure during the 5-year follow-up period, the significant increase in serum creatinine suggests that end-stage renal failure may still be inevitable in some cases.

The increase in all-cause mortality in type 1 diabetes with and without proteinuria observed relative to the nondiabetic population is also similar to that observed by other groups (8). In the diabetes cohort, even those with normoalbuminuria at baseline had more than double the 5-year mortality of an equivalent British general population (11 vs. 4%) (12).

In the age-group studied, cardiovascular disease would account for approximately one-third of all deaths in a Scottish population (16). The proportion dying of cardiovascular disease was higher than that reported by Rossing et al. (17), who studied a much larger cohort who were younger (mean age 40 years) and with a shorter duration of diabetes (median 20 years), but with a longer follow-up period. In that study, age, smoking, microalbuminuria, persistent proteinuria, and hypertension were found to be predictors of cardiovascular mortality.

In our study, no differences were observed at baseline in terms of blood pressure or HbA1c between those with progressive renal disease compared with those with no change in renal status, or in terms of mortality at 5-year follow-up; however, the numbers in each group were relatively small. It appears that a long duration of diabetes doubles the risk of a cardiovascular death in all categories of urinary albumin loss.

These data reinforce the need to continue to monitor urinary albumin loss in those patients with a long duration of type 1 diabetes to identify those at increased risk of premature mortality, and highlight the need for continued attention to known established cardiovascular risk factors, including smoking, cholesterol, and blood pressure.

References