Diabetic nephropathy in type 1 diabetes: has the outlook improved since the 1980s?

S. M. Marshall

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Abstract This edition of Then and Now discusses three papers published in *Diabetologia* in the 1980s relating to diabetic nephropathy. Two epidemiological papers by Andersen et al (1983; 25:496–501) and Borch-Johnsen et al (1985; 28:590–596) described in graphic detail the ravages of diabetic nephropathy in type 1 diabetes. After 40 years of diabetes, 41% of their cohort had developed persistent proteinuria. The median time from first appearance of proteinuria to death was 7–8 years, the majority dying of uraemia or cardiovascular disease. The third paper, by Mathiesen et al (1984; 26:406–410), identified individuals with microalbuminuria, a much earlier stage of diabetic nephropathy, and analysed the risk of progression to persistent proteinuria at various levels of urine albumin excretion. Since the description of microalbuminuria, clinicians have hoped that earlier identification of individuals at high risk of end-stage kidney disease, coupled with aggressive use of reno-protective therapies, would prevent, or at the very least significantly delay, the development of end-stage renal disease. Recent data suggest that the outlook has indeed improved since the 1980s, at least in some populations. However, we may be delaying rather than preventing the development of microalbuminuria, proteinuria and kidney failure. Whilst a delay of 10 or more years in the appearance of end-stage renal disease is very welcome, further work is needed to understand why rates of chronic kidney disease vary substantially between cohorts and to develop novel therapies.

Keywords Diabetic nephropathy · End-stage renal disease · Microalbuminuria · Persistent proteinuria · Type 1 diabetes

Abbreviations

CVD	Cardiovascular disease
eGFR	Estimated GFR
ESRD	End-stage renal disease
SMR	Standardised mortality rate
UAE	Urine albumin excretion

Introduction

At the beginning of the 1980s, diabetic nephropathy was diagnosed late, at the appearance of dipstick-positive proteinuria, when kidney damage was severe and irreversible. Preliminary data derived from small studies in selected populations suggested that the outlook was grim. Two of the three studies in this edition of Then and Now are large epidemiological studies which highlight this poor prognosis [1, 2]. The third study [3], along with others published immediately beforehand [4–6], brought hope for an earlier diagnosis at a time when end-stage disease might be preventable. These studies have all been quoted extensively, and laid the foundation for much further research and, indeed, change in clinical practice. Has this resulted in an improved outlook for the person with type 1 diabetes?

S. M. Marshall (✉)
Faculty of Clinical Medical Sciences, Institute of Cellular
Medicine, Newcastle University,
Floor 4, Leech Building, Framlington Place,
Newcastle upon Tyne NE2 4HH UK
e-mail: sally.marshall@newcastle.ac.uk

Then

Proteinuria, mortality and end-stage renal disease The study by Andersen et al [1] included a cohort of 1,475 individuals with ‘type 1 diabetes’: onset of diabetes at age

<31 years, diagnosed before 1953, and who were referred to the Steno Memorial Hospital between 1932 and 1977. The median duration of diabetes at referral was 7 years and 73% were referred at <16 years' duration. The main reason for referral was difficulty with glucose control, rather than the presence of complications. Individuals were followed until a diabetes duration of at least 25 years or to death.

During follow-up, 41% developed persistent proteinuria because of diabetic nephropathy, defined as total protein excretion >0.5 g/24 h or Albustix-positive proteinuria in four or more consecutive samples. A further 3% had persistent proteinuria which was due to another cause and 57% remained free of proteinuria. The maximum prevalence of proteinuria was 21% at 20–25 years' duration of diabetes, and ~10% at ≥40 years. Only 4% developed proteinuria within 10 years' duration of diabetes. There were two peaks in the annual incidence, the larger at 16 years' duration (3%) and a smaller second peak at 32 years' duration (2%). For a duration of diabetes of ≥40 years, the annual incidence was ~1%. Those with a very long diabetes duration seemed to be at low risk, with only 4% developing proteinuria after more than 35 years duration. Thus, the cumulative incidence of proteinuria appeared to plateau after 35–40 years of diabetes, suggesting that only a subset of individuals will ever develop nephropathy.

The poor prognosis was illustrated starkly: 83% of those who developed persistent proteinuria died during follow-up compared with 25% of those without proteinuria. Uraemia accounted for 66% of deaths, and ischaemic heart disease and stroke for 19%. Within 7 years of the onset of persistent proteinuria, 49% had died.

The paper by Borch-Johnsen et al [2] included a cohort of patients similar, but not identical, to those in the Andersen et al paper, as individuals diagnosed before 1933 were excluded. Follow-up was until January 1982, death or emigration. Of the 1,001 individuals with full information, 406 had persistent proteinuria at referral or developed it during follow-up. The incidence of proteinuria rose dramatically after 10 years of diabetes, reaching a maximum after 13–18 years of diabetes, after which it decreased. No second peak was observed. The incidence of persistent proteinuria decreased with increasing year of diagnosis from 1933 to 1952. Of those with proteinuria, 350 died. The relative risk of death of those with proteinuria, compared with the background Danish population, increased sharply from age 20 years, reaching almost 100 at age 30–40 years (median duration of diabetes 15–25 years), before declining sharply again. In those without proteinuria, relative mortality was about 2 and remained relatively constant throughout life. Life expectancy was 50% longer in those diagnosed in 1950 compared with those diagnosed in 1935, mainly as a result of the decreasing incidence of persistent proteinuria. Individuals who developed proteinuria after a diabetes duration of 15 years had a better prognosis than those

who developed it earlier. Uraemia accounted for 66% of deaths in those with proteinuria, and cardiovascular disease (CVD) was the cause of 23%. Mortality from CVD was almost tenfold higher in those with proteinuria compared with those without.

Thus, these two papers demonstrated that a subset of approximately 40% of individuals with type 1 diabetes developed persistent proteinuria, with its associated enormous increase in relative mortality and a median survival time of 7–8 years.

Microalbuminuria The generally accepted clinical definition of diabetic nephropathy is persistent urine protein excretion >0.5 g per 24 h, or the presence of dipstick-positive proteinuria. However, normal urine protein excretion is at least tenfold lower. Thus, persistent proteinuria represents relatively advanced urine protein leak. The development of a sensitive radioimmunoassay, specific for albumin, the main urine protein excreted early in diabetic nephropathy, allowed the measurement of urine albumin concentrations in the normal range [7]. This was quickly followed by the demonstration that, in some newly diagnosed individuals with type 2 diabetes, urine albumin excretion (UAE) was higher than in non-diabetic individuals [8]. This observation appears to have been ignored largely until the early 1980s, when three groups demonstrated that type 1 diabetic individuals with a UAE rate greater than normal but without dipstick-positive proteinuria were much more likely to develop persistent proteinuria or to die than their peers with a UAE rate within the normal range [4–6]. Albuminuria in this range was named microalbuminuria and heralded a new era in diabetes research.

The paper by Mathiesen et al [3] quickly followed from these original descriptions of the significance of microalbuminuria. In a longitudinal cohort, UAE had been measured in 71 consecutive, dipstick-negative type 1 diabetic patients in 1974. Sixteen had a UAE rate >20 µg/min initially, the upper limit of the normal range (mean +2 SD), determined in 19 non-diabetic individuals. Five of the 71 developed a UAE rate >200 µg/min and an additional five developed persistent proteinuria during a 6-year follow-up. Those individuals who progressed had a higher baseline UAE and systolic blood pressure and were more likely to have retinopathy at baseline than those who remained normoalbuminuric. All seven individuals who had a baseline UAE rate >70 µg/min progressed, while only three of 64 individuals with an initial UAE rate ≤70 µg/min did so. Those with a UAE rate >70 µg/min initially had a much greater rise in blood pressure and serum creatinine during the 6-year follow-up than those with lesser degrees of albuminuria or normal albumin excretion.

Mathiesen et al also studied a cross-sectional cohort of 227 randomly selected dipstick-negative type 1 diabetic individuals. Of these, 67 had a UAE rate >20 µg/min.

Systolic and diastolic blood pressure were higher in these individuals compared with those with lower levels of albuminuria and normal albumin excretion. They were also more likely to have proliferative retinopathy. GFR was similar; all demonstrated hyperfiltration. Glycaemic control (HbA_{1c} and urine glucose) differed little across UAE groups.

Now

Change in incidence of proteinuria—delay or prevention? The papers by Andersen et al [1] and Borch-Johnsen et al [2] set the yardstick against which our progress in the prevention of nephropathy in type 1 diabetes is judged. Has the incidence declined? Are we preventing nephropathy? The dearth of population-based or large cohort studies reporting such data is testament to the difficulty of performing such epidemiological work. However, relevant studies are summarised in Table 1 [9–14]. There is a striking variation between cohorts. However, in the majority, the cumulative incidences of persistent proteinuria and of ESRD for a duration of diabetes of 25–30 years have declined since the paper by Andersen et al was published. Several studies also suggest that the cumulative incidence of proteinuria is declining with increasing year of calendar diagnosis of diabetes [10, 13]. Aggregated data from the European Dialysis and Transplant Association Registry from 1990 onwards show an unchanged reported rate of ESRD in type 1 diabetes, at a time when the prevalence of type 1 diabetes is increasing, and survival is also improving [15]. In contrast to the large peak in annual incidence of proteinuria at a diabetes duration of about 16 years reported by Andersen et al [1], more recent studies have shown a lower, relatively constant annual incidence for durations between 19 and 30 years [10, 14]. However, when the annual incidence is summated into cumulative incidence and extended to include durations of diabetes >30 years, the cumulative incidence of nephropathy

in the more recent studies appears to at least equal that of the older studies, but with a 5–15 year delay in the appearance of proteinuria (Fig. 1). Thus, rather than prevention, we may only be delaying the onset of proteinuria. It is likely that many factors have contributed to this delay, including improved glycaemic and blood pressure control, increased use of statins and inhibitors of the renin–angiotensin system and a reduction in smoking.

Change in incidence of end-stage renal disease? Recent observations from Finland [13] and Sweden [14] report rates of ESRD in individuals with persistent proteinuria of 2.5–7.8% at 30 years duration of type 1 diabetes, whilst in the DCCT/EDIC cohort the reported rates after 25 years duration were 2% and 1% in the conventionally and intensively managed groups, respectively [9]. In 22 years of follow-up of the DCCT/EDIC cohort, only 24 participants assigned to intensive therapy and 46 to conventional therapy developed an estimated GFR (eGFR) $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ (risk reduction $p=0.006$) [16]. Thus, the incidence of ESRD in type 1 diabetes does appear to be lower than that reported in the 1980s, although again the difference between centres is substantial.

Change in survival and cause of death in proteinuric type 1 diabetic individuals? The paper by Borch-Johnsen et al [2] demonstrated the dismal survival of type 1 diabetic patients with proteinuria compared with those without proteinuria and with the general population, the median survival time following the appearance of proteinuria being 7–8 years. Has this changed? One paper suggests that the median survival time from the onset of proteinuria has improved over the years to 21.7 years [17]. In this recent cohort, 42% of the deaths were attributed to CVD, and 50% died with ESRD. However, CVD mortality and ESRD are competing risks, and sophisticated analyses are required to control for this. Two recent papers performed such analyses and estimated that the current incidence of ESRD in type 1 diabetic

Table 1 Cumulative prevalence of diabetic nephropathy or end stage renal disease after 20–40 years of type 1 diabetes

Study [ref.]	Country	Year of diagnosis of diabetes	Duration of diabetes (years)	Cumulative incidence (%)	
				Proteinuria	ESRD
Andersen [1]	Denmark	Before 1953	40	41	
DCCT/EDIC [9]	USA	~1978–1988	30	Conventional: 25 Intensive: 9	Conventional: 2s Intensive: 1
Pambianco [10]	USA	1965–1980	25	32	
Hovind [11]	Denmark	1979–1984	20	13.7	
Nordwall [12]	Sweden	1971–1975	25	13	
Finne [13]	Finland	1965–1999	30		7.8
Mollsten [14]	Sweden	1977 onwards	30		4.1 (men) 2.5 (women)

Fig. 1 Changing cumulative incidence of persistent proteinuria in type 1 diabetes by duration of diabetes [1, 9, 10]. The horizontal arrow represents the potential delay in appearance of persistent proteinuria. Solid line, Steno cohort, diagnosed before 1953 [1]; long dashed line, Pittsburgh cohort, diagnosed 1950–1980 [10]; short dashed line, intensively managed DCCT cohort, diagnosed ~1978–1988

individuals with persistent proteinuria is 5.1–5.8 per 100 person-years [18, 19]. In one of these studies, 36% developed ESRD and 9% died without ESRD over a 9.9-year follow-up [18], with different baseline factors determining the individual specific outcome. In the second study, despite an increased use of reno-protective therapies, the risk of ESRD did not change from 1993 to 2008 [19]. The 15-year cumulative risk was 52% for ESRD and 11% for pre-ESRD death. Why these figures are poorer than those from other groups [9, 17] remains conjecture. However, in all series, the time from onset of proteinuria to ESRD or death is greatly improved from that reported in the early 1980s, again suggesting delay rather true prevention.

Microalbuminuria Initial studies suggested a lifetime risk of developing microalbuminuria of approximately 50%, generally appearing at a type 1 diabetes duration of between 10 and 20 years. The natural history was believed to be progressive to dipstick-positive proteinuria in most individuals. It was hoped that, with intensified management of glucose, blood pressure and cardiovascular risk factors, microalbuminuria would be prevented, or at the very least progression to proteinuria and ESRD would be halted. Has this hope been fulfilled? In the DCCT/EDIC cohort, the cumulative incidence of persistent microalbuminuria was 38% after 30 years in the conventional group and 25% in the intensive group [20]. The incidence appears to plateau in both groups after 25–30 years. Microalbuminuria developed most frequently in the second decade of diabetes in the conventional group, the incidence being particularly blunted during this time in the intensive group. Of note, in the 10 years following the first appearance of persistent microalbuminuria, regression to normoalbuminuria occurred in 40%, with 28% developing proteinuria and 4% ESRD. Use of intensive insulin therapy and lower HbA_{1c} levels were associated with

better renal outcomes. This confirms reports from other cohorts that, even after persisting for several years, microalbuminuria may revert to normal [21]. Thus, the data suggest that microalbuminuria is being delayed or prevented, particularly by intensive glucose management, and that rates of regression from microalbuminuria to normal albumin excretion are much higher and progression rates to proteinuria lower than first believed.

Is the clinical phenotype of diabetic kidney disease changing? In the 1980s, diabetic nephropathy was envisaged as a continuously progressing process, beginning with microalbuminuria that increased gradually until urine protein excretion became detectable by standard urine dipstick (proteinuria). Proteinuria then progressed gradually towards the nephrotic range. Glomerular filtration began to decline at a relatively late stage, when dipstick-positive proteinuria was present. As described above, we are now aware that microalbuminuria may regress to normal albumin excretion. There is also some evidence that proteinuria may regress to microalbuminuria, at least temporarily, usually with intensification of blood pressure control [22].

It has also become apparent that GFR may decline progressively in individuals with normal albumin excretion or non-progressive low-level microalbuminuria [23, 24]. In the DCCT cohort, 72% of individuals who developed sustained eGFR <60 ml min⁻¹ 1.73 m⁻², 61% had a history of proteinuria and 16% had microalbuminuria, but the other 23% persistently had normal albumin excretion [23]. In a second cohort, the proportions were 72%, 21% and 7%, respectively [24]. Whether this phenotype represents a different form of diabetic nephropathy or another disease process remains to be determined. However, the clinical implication is that screening for kidney disease in diabetes must include measures of both urine albumin excretion and glomerular filtration.

Why is the risk of CVD increased? The demonstration of the huge premature mortality, primarily from CVD, in type 1 diabetic individuals with proteinuria was followed by studies describing the increased risk associated with microalbuminuria [25, 26]. Two more recent studies have confirmed that the all-cause standardised mortality rates (SMR) in type 1 diabetic patients with microalbuminuria is two to three times that of the general population, 9–12 fold for those with proteinuria and 18–30 fold for those with ESRD [27, 28]. Perhaps even more important is the observation that, in those with normal albumin excretion at baseline and who remain normoalbuminuric, the SMR over 10 years [27] and 20 years [28] is similar to that of the general population.

Why CVD mortality is so high in type 1 diabetic individuals with any evidence of renal disease remains unclear. These individuals undoubtedly have an excess of classical

CVD risk factors, and a number of novel factors have also been described. The inherited predisposition to nephropathy appears to encompass CVD risk factors and disease [29, 30]. Insulin resistance, observed in the report by Andersen et al as increased insulin dose/kg body weight [1], but not recognised as such, also seems part of the familial susceptibility [31]. However, genetic testing has so far failed to identify robustly those at risk [32]. A full discussion of the links between albuminuria and CVD is beyond the scope of this article, but the topic has been reviewed recently [33].

Conclusions

The seminal papers by Andersen et al [1] and Borch-Johnsen et al [2] detailed a 40% chance of an individual with type 1 diabetes developing dipstick-positive proteinuria over 40 years duration of diabetes. Median survival from first appearance of proteinuria was 7–8 years, with the majority dying of uraemia and CVD. The discovery of microalbuminuria provided us with the ability to identify those at very high risk of chronic kidney disease and CVD at a much earlier stage, and raised hopes that earlier intervention with aggressive management of glucose, blood pressure and CVD risk factors would improve the outlook. Using the Andersen et al [1] and Borch-Johnsen et al [2] data as our yard-stick, the incidence of proteinuria at a diabetes duration of 30 years has declined, but this almost certainly represents a delay in onset rather than true prevention. Kidney and patient survival once proteinuria has appeared have also improved, but remain much poorer than in the person with type 1 diabetes and normal albumin excretion. The incidence of microalbuminuria is also less than expected, but again this may be a delay in appearance rather than true prevention. One major challenge for the future is identifying reasons why rates of proteinuria and survival times differ so widely between centres. Is this due to differences in standards of care, different genetic susceptibilities or other factors? Novel therapies are also required.

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