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The changing epidemiology of diabetic microangiopathy in type 1 diabetes

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Abstract Diabetic microvascular complications in the kidney and the eye are a major burden for diabetic patients due to increased morbidity and mortality. Furthermore, diabetic nephropathy is the leading cause of end-stage renal disease and diabetic retinopathy is the leading cause of blindness in younger patients, representing a major public health concern. During the past two decades beneficial effects of, in particular, aggressive antihypertensive control and strict glycaemic control have been demonstrated in randomised controlled clinical trials. Technological improvements in diabetes care have made good metabolic control easier to achieve. Has this led to an improved prognosis? In observational studies from dedicated centres, a decrease from 47 to 13% has been reported in the incidence of proliferative diabetic retinopathy after 20–25 years of diabetes, and the incidence of overt diabetic nephropathy after 20 years has decreased from 28 to 5.8%. Even functional and morphological remission of diabetic nephropathy has been reported. Despite this, recent population-based studies have failed to demonstrate a decrease in the incidence of blindness caused by diabetes, and the incidence of end-stage renal disease has progressively increased. This may, in part, be the result of a combination of increasing numbers of diabetic patients and a lag phase between improvement in management and a decline in end-stage complications. It is of concern, however, that the results from specialised centres may not apply to routine diabetes care. It is, therefore, mandatory that the beneficial effects of pharmacological and non-pharmacological interventions demonstrated in clinical trials and recommended by treatment guidelines are translated into clinical practice to ensure a widespread improvement in prognosis.

Keywords Diabetic nephropathy · Diabetic retinopathy · Epidemiology · Microvascular complications · Review · Type 1 diabetes

Introduction

Diabetes predisposes to the development of generalised microangiopathy, with clinical consequences affecting kidney, eye and nerves [1]. Diabetic nephropathy is the leading cause of end-stage renal disease in the Western world, and is responsible for more than 40% of new cases of end-stage renal disease in the USA; the proportion of patients with end-stage renal disease due to diabetes has increased during the last decades [2]. Almost all patients develop background retinopathy with time, and 40–50% progress to proliferative retinopathy within 25 years of diabetes onset [3]. Diabetic retinopathy is the most important cause of visual impairment in the Western world among individuals aged <60. Furthermore, the burden of macrovascular morbidity and mortality is also increased in patients suffering from microvascular disease [4–6].

New techniques for diabetes management have been introduced over the past few decades, including self-monitoring of blood glucose, long-term monitoring of glycaemic control by HbA_{1c}, basal-bolus insulin treatment and the use of insulin pen devices. These advances have been matched by improvements in blood pressure control with aggressive antihypertensive treatment, with particular focus on agents that block the renin–angiotensin system. The prevalence of smoking has also declined. The impact of these developments upon microvascular complications in type 1 diabetes that affect the kidney and eye will be reviewed in this paper.

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The changing course of diabetic kidney disease

Older studies report a cumulative incidence of nephropathy in young patients of 25–40% after 25 years of diabetes; a higher incidence was noted in those diagnosed in the 1930s

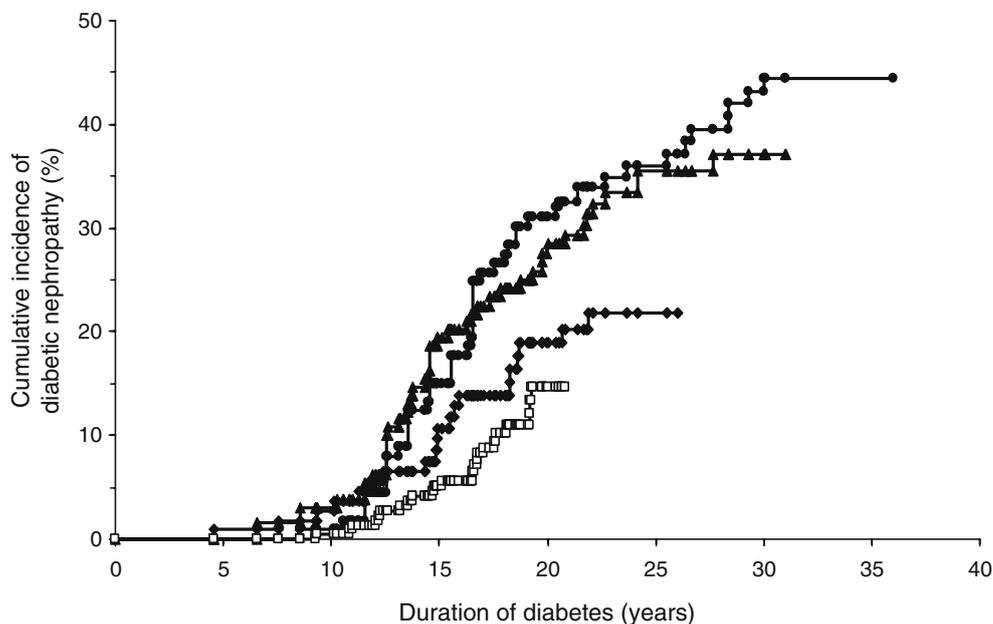
than in those diagnosed in the 1950s [7, 8]. Overt diabetic nephropathy with persistent proteinuria has traditionally had a poor prognosis, characterised by a relentless decline in renal function, development of end-stage renal failure and a median survival time of only 6–7 years after onset of nephropathy [9, 10]. As Kussman et al. remarked in 1976, “once the clinical signs of nephropathy have become manifest, the natural course is inexorably progressive to death” [9]. There was, therefore, considerable interest in a study from Sweden that, in 1994, reported a dramatic decline in the incidence of diabetic nephropathy: the 20-year cumulative incidence fell from 28% in patients with onset of type 1 diabetes from 1961–1965 to only 5.8% in patients with onset of diabetes from 1971–1975 [11]. Furthermore, not one patient diagnosed between 1976 and 1980 developed persistent proteinuria [11]. These excellent results were probably due to the work of a dedicated team that achieved glycaemic control equivalent to that seen in an intensively treated group in the DCCT study [12]. We attempted to replicate these findings at the Steno Diabetes Center, but found no decline in the incidence of diabetic nephropathy. The difference in the results of the two studies can probably be explained by worse glucose control in the Danish cohort [13] in combination with a higher proportion of smokers—smoking is probably a risk factor for the development of diabetic nephropathy as smoking has been related to proteinuria in cross-sectional studies [14–16] and to the progression from normo- to microalbuminuria in prospective studies [17, 18]. In contrast, a subsequent study from our centre found a marked decline in diabetic microangiopathy: the cumulative incidence of diabetic nephropathy after 20 years of diabetes decreased from 31.1% in patients with onset of diabetes from 1965–1969 to only 13.7% in those with onset of diabetes from 1979–1984 [19] (Fig. 1). The improvement was considered to be the result of earlier and more aggressive antihypertensive medication, improved glycaemic control and fewer smokers. These

findings suggested that the falling cumulative incidence of diabetic nephropathy that was first detected in a single study from Sweden might have a more widespread significance.

The natural history of diabetic nephropathy has historically been associated with an inexorable increase in the urinary AER, and a decrease in the GFR of 10–15 ml min⁻¹ year⁻¹ [20]. Two decades ago, it was demonstrated that antihypertensive treatment could delay the development of end-stage renal failure by reducing the rate of decline of the GFR [21, 22], a finding that has subsequently been confirmed in randomised controlled trials (see below). Observational studies indicate a decline in the GFR of 3.7 ml min⁻¹ year⁻¹ in patients on antihypertensive therapy [23]. Poor glucose control and hypercholesterolaemia have also been associated with a more rapid deterioration of kidney function in observational, but not interventional, studies [23, 24].

Similar findings have been reported by Nishimura et al. [25], who assessed the long-term incidence and temporal trends of end-stage renal disease in childhood-onset diabetes using a population based cohort of 1,075 type 1 diabetic patients from Allegheny County (PA, USA). Complication status was assessed in 74.2% of the cohort. These results revealed that the 20-year cumulative incidence of end-stage renal disease fell from 9.1% in children with onset of diabetes from 1965–1969 to 3.6% in those diagnosed from 1975–1979. The authors further reported an increase in the time to development of end-stage renal disease had increased, suggesting that not only is the incidence of end-stage nephropathy declining, but also the progression of nephropathy to chronic renal failure is at least being delayed [25]. Furthermore, median survival from onset of proteinuria has increased from 6–7 years to 14 years [26]. Even so, a recent analysis has shown that the requirement for renal replacement therapy in type 1 diabetes had risen in parallel with the 2.4% annual increase in the incidence

Fig. 1 Cumulative incidence of diabetic nephropathy in 600 type 1 diabetic patients with onset of diabetes from 1965–1969 ($n=113$, ●), 1970–1974 ($n=130$, ▲), 1975–1979 ($n=113$, ◆) and 1979–1984 ($n=244$, □), $p<0.001$, log rank test. Copyright 2003 American Diabetes Association. From *Diabetes Care* (2003) vol. 26:1258–1264. Reprinted with permission from *The American Diabetes Association*



of this condition in Europe from 1991–2000 [27]. The incidence of new cases of end-stage renal failure due to diabetes has, however, plateaued since 2000 in both the USA [2] (Fig. 2) and Denmark [28].

In their paper, Kussman et al. state that diabetic nephropathy is irreversible [9]; however, the observation that morphological lesions of diabetic nephropathy can be reversed by normoglycaemia following pancreas transplantation implies that microvascular lesions in the kidney are potentially reversible [29]. Regression of the earlier stages of microalbuminuria has been demonstrated following antihypertensive treatment, and one prospective observational study reported that, over a 7.5-year follow-up period, regression occurred in 35% of 79 type 1 patients with microalbuminuria (in 39% of patients treated with an ACE inhibitor and in 13% of untreated patients). In another study, a reduction (>50%) in the urinary AER was observed in 58% of 386 microalbuminuric type 1 diabetic patients, but this reduction was transient in many patients, the follow-up period was shorter and the drop-out rate was 47% [30].

Remission of overt diabetic nephropathy has been defined as a sustained (>1 year) reduction in the urinary AER to microalbuminuric levels or less (<200 $\mu\text{g}/\text{min}$), and regression of nephropathy has been defined as a decrease in the GFR of $1 \text{ ml min}^{-1} \text{ year}^{-1}$ (corresponding to normal adult loss of renal function) [31]. An observational study that followed 301 type 1 diabetic subjects with overt diabetic nephropathy for 7 years (range 3–14 years) found remission of nephropathy in 31% of patients and regression of nephropathy in 22%; this was attributed to aggressive antihypertensive treatment [31]. Patients with nephrotic-range proteinuria have the worst prognosis in terms of loss of renal function and survival, but remission of proteinuria has been observed even in this group of patients [32]. In a recent study, the urinary AER of 22% of those with nephrotic-range albuminuria (>2500 mg/24 h) was reduced to less than 600 mg/24 h, with a resultant decrease in the rate of decline of the GFR, and—more importantly—improved survival [33].

These improvements in the prognosis for type 1 diabetic patients with nephropathy are most likely due to develop-

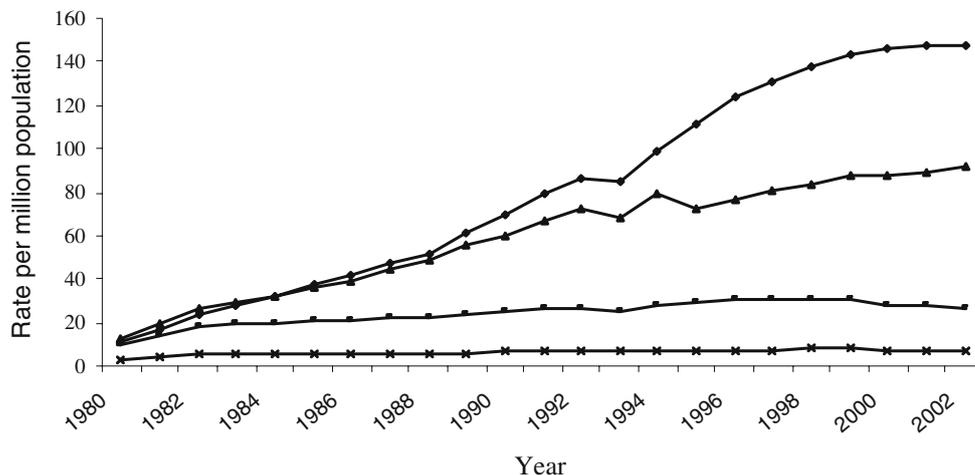
ments in patient management, in particular the use of early and aggressive antihypertensive therapy. Initial studies demonstrated that aggressive antihypertensive treatment delayed the development of end-stage renal failure in type 1 diabetic patients with diabetic kidney disease by reducing the loss of renal function [21, 22]. More recent randomised controlled studies have suggested that intervention targeting the renin–angiotensin system is particularly renoprotective, i.e. preserves renal function above and beyond the effect of lowering blood pressure [34, 35].

ACE inhibition has also been tested at an earlier stage to determine whether it has a protective effect against the development of microalbuminuria in normoalbuminuric patients. This could not be confirmed in the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID), which enrolled 440 normoalbuminuric type 1 diabetic patients [36]. However, this unsuccessful attempt at primary prevention is in contrast with the success in secondary prevention demonstrated in a meta-analysis suggesting that ACE inhibitors reduce progression from microalbuminuria to overt nephropathy by 62%. A three-fold increase in the rate of regression of microalbuminuria to normoalbuminuria was seen in patients treated with ACE inhibitors, as compared with placebo-treated patients [37]. Preservation of GFR for up to 8 years has been demonstrated in microalbuminuric patients receiving an ACE inhibitor [38].

Changes in diabetic retinopathy

The initial Swedish study [11] that reported a marked decline in diabetic kidney disease with time found no effect on retinopathy [39]. Recently, a follow-up study of the same population ($n=269$) found a significant decline in severe retinopathy after 25 years, from 47 to 24%, in cohorts with onset of diabetes from 1961–1965 and 1971–1975, respectively [40]. In patients with onset from 1976–1985, there was a trend for further improvement, but the majority of patients still developed background retinopathy [40]. Another Swedish study found that the incidence of blindness due to diabetes in Stockholm county fell by

Fig. 2 Rates of development of end-stage renal disease in the USA (per million population) from 1992–2002 according to primary diagnosis [2]. ♦, diabetes; ▲, hypertension; ■, glomerulonephritis; x cystic kidney disease. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US



more than 50% over a 15-year period [41]. In contrast, from 1990–1998, there was no significant change in the incidence of blindness due to diabetes in the district of Württemberg-Hohenzollern, a German district with a population of 5 million [42]. A Danish study, meanwhile, found that the cumulative incidence of proliferative diabetic retinopathy after 20 years of diabetes declined from 31.2 to 12.5%, with a decline in maculopathy from 18.6 to 7.4% observed over the same time period [43]. There was a parallel improvement in visual acuity in more recent cohorts [44]. Unfortunately, larger population-based data on changes in the incidence of earlier stages of diabetic retinopathy are lacking.

Prevention of initiation of diabetic retinopathy, i.e. primary prevention of diabetic retinopathy, is most likely achieved through improvements in glycaemic control, as demonstrated in the primary prevention cohort in the DCCT study [12]. It is possible that control of blood pressure is also important in type 1 diabetic patients, as shown for type 2 diabetic patients in the UK Prospective Diabetes Study (UKPDS) [45]. However, as mentioned above, even among patients with good glycaemic control, a substantial number will develop background retinopathy [40].

For secondary prevention, i.e. progression of retinopathy to potentially sight-threatening complications, glycaemic control is also very important, as demonstrated in the secondary intervention cohort of the DCCT study [12]. The declining incidence of proliferative retinopathy, described above, can probably be explained by improved glycaemic control, but it is also likely that improved blood pressure control played an important role. As in the kidney, there has been interest in the potential additive benefit of ACE inhibition upon microvascular lesions in the eye [46]. Randomisation of normotensive patients with type 1 diabetes to ACE inhibition in the EUCLID study reduced the risk of progressing one level on the retinopathy scale by 50%, and reduced the risk of the development of proliferative retinopathy by 82% [47]. This has not yet been confirmed in other studies, but the ongoing Diabetic Retinopathy Candesartan Trial (DIRECT) aims to evaluate what effect blockade of the renin–angiotensin system with an angiotensin II receptor blocker has on the initiation and progression of diabetic retinopathy in type 1 and type 2 diabetes.

For tertiary prevention, i.e. loss of vision or development of blindness, laser treatment has been the cornerstone of treatment designed to prevent or delay loss of vision in those with proliferative diabetic retinopathy [48, 49], preferably in the early stages. Thus, regular screening is mandatory if a reduction in blindness is to be attained. It has also been suggested in some cases of very severe non-proliferative retinopathy [50], and is also successful in the treatment of macular oedema [51]. In the most severe cases with retinal traction, surgery with vitrectomy may improve the visual prognosis [52].

The increasing prevalence of susceptible patients

While studies from specialised centres have demonstrated a decline in the cumulative incidence of microvascular complications, the number of patients presenting with end-stage renal disease in the USA [2] (Fig. 2) and Europe [27] has increased in recent decades. How can this be explained? One note of caution is that results obtained in specialised centres should not be generalised to more routine diabetes care. Another likely reason is the increasing incidence of type 1 diabetes—the reduction in the individual risk of progression may have been counterbalanced by an increase in the total number of individuals at risk.

Conclusion

Observational studies from dedicated centres have shown that the individual risk of developing microvascular complications has fallen in recent years as a consequence of improvements in diabetes management. These improvements include aggressive antihypertensive therapy and improved glycaemic control; the benefits of both interventions have been well demonstrated in randomised clinical trials. Even so, the number of patients suffering from end-stage renal disease has increased. It is, therefore, mandatory that the beneficial effects of pharmacological and non-pharmacological interventions demonstrated in clinical trials and recommended by treatment guidelines are translated into clinical practice to ensure a widespread improvement in prognosis.

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