Diabetic nephropathy in type 2 diabetes mellitus: prevention and treatment

David N CHURCHILL
Faculty of Health Sciences, Father Sean O'Sullivan Research Centre, St Joseph's Hospital-McMaster University, Hamilton, Ontario, Canada.

INTRODUCTION

Patients with end-stage renal disease (ESRD) secondary to diabetes mellitus have a much higher dialysis-associated mortality rate than similar non-diabetic patients (1). They also have higher morbidity rates, particularly with respect to vascular complications. These results have been described as abysmal for patients with type 2 diabetes mellitus (2) and have focused attention on interventions that might decrease the development and progression of nephropathy.

Diabetes mellitus has become an increasingly important cause for ESRD requiring renal replacement therapy. It was responsible for 22% of cases of ESRD in Canada in 1990, with an increase to 30% in 1998 (1). A similar trend was reported in Europe with an increase from 11% to 17% between 1984 and 1992 (3).

Most of this increase is due to type 2 diabetes mellitus, the prevalence of which increases with advancing age. In 1993, in the United States, the prevalence of diabetes was about 4%, 8% and 11% in those aged 45 to 54 years, 55 to 64 years and over 64 years, respectively (4). A cross-sectional Hong Kong study revealed a standardized prevalence of 9.5% in men and 10.2% in women aged 35 to 64 years (5).

The prevalence has also increased over time. In the United States (4), the incidence of diabetes increased, among those aged 55 to 64 years, from 3% in 1958 to 8% in 1993 while for those aged over 64 years the increase was from 4 to 11%. This increased prevalence with time may be related to improved diagnosis and to better cardiovascular care with some of the survivors developing diabetic nephropathy. The increased prevalence of type 2 diabetes mellitus is greater among African Americans and Mexican Americans than European Americans (6). Among First Nations (aboriginal) people in Canada in 1997, the prevalence of diabetes mellitus in those aged over 64 years was 30% among men and 35% among women (7). This higher prevalence in aging populations over the past 40 years has resulted in an increased population at risk of nephropathy and ESRD.

There is also an increased tendency for these patients to be referred for dialysis care and there are fewer restrictions on their dialysis programs. However, the 5-year survival for patients with ESRD secondary to diabetes mellitus is only 20 to 23% in Canada (1). Earlier intervention to prevent the development and progression of diabetic nephropathy may be more effective.

PREVENTION AND TREATMENT OF DIABETIC NEPHROPATHY (TYPE 1 DIABETES MELLITUS)

There is strong evidence that excellent glycemic control (8) and the use of angiotensin converting enzyme inhibitors (9) will decrease the probability of developing diabetic nephropathy (8) and of doubling the serum creatinine (9). There is less agreement about the role of dietary protein restriction. The finding of increased urinary albumin excretion when dietary protein exceeds 20% of energy intake (10) has led to the suggestion that protein restriction be added to the prevention strategies (11). The stages of diabetic nephropathy associated with type 1 diabetes mellitus have traditionally been described as hyperfunction, latency, microalbuminuria, macroalbuminuria and ESRD (12). The interventions that appear to be effective decrease glomerular hyperfiltration and are associated with the first three stages. The evidence that these same interventions will be effective for those with type 2 diabetes mellitus is less clear.
**STAGES OF DIABETIC NEPHROPATHY (TYPE 2 DIABETES MELLITUS)**

The stages of diabetic nephropathy in type 2 diabetes mellitus differ to those described in type 1. These differences have been recently evaluated (6). When type 2 diabetes is diagnosed, the rate of hyperfiltration is half than that seen in type 1, microalbuminuria is already present in 15% and hypertension may be present. In stage 2 (latency), in addition to glomerular basement membrane thickening and increased mesangial matrix, vascular and chronic interstitial changes are common. In stage 3, the presence of microalbuminuria is predictive of cardio-vascular disease (in type 1 diabetes mellitus it is more predictive of changes in glomerular filtration rate, GFR). Stage 4 (macroalbuminuria) and stage 5 (ESRD) diabetic nephropathy is similar for type 1 and 2 diabetes. With the appearance of macroalbuminuria, the cumulative incidence of ESRD among Caucasians is about 70% over 15 years follow-up, similar to that reported for Pima Indians with type 2 diabetes mellitus. For Caucasians with type 2 diabetes mellitus, the cumulative incidence of ESRD over 15 years is about 15%. This lower rate of ESRD among type 2 diabetic Caucasians may be explained by the older age of onset and greater cardiovascular mortality for Caucasians compared with Pima Indians (6,13-15).

**RISK FACTORS FOR THE DEVELOPMENT OF DIABETIC NEPHROPATHY**

Studies of type 2 diabetes in the Pima Indian population have yielded strong evidence for genetic risk factors. Proteinuria developed in 14% of diabetic offspring when neither parent had proteinuria, 23% if one parent had proteinuria and 46% if both parents had diabetes and proteinuria (16). Other potentially correctable clinical risk factors include hypertension, poor glycemic control, obesity and smoking habit (6).

**PREVENTION AND TREATMENT OF DIABETIC NEPHROPATHY (TYPE 2 DIABETES MELLITUS)**

**Glycemic control**

The role of glycemic control in preventing complications was evaluated in 3867 patients with newly diagnosed type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) (17). Patients were randomly allocated to either conventional (diet) or intensive (diet plus sulphonylurea or insulin) therapy. Over 10 years, the hemoglobin (Hb) A1c value was 7% in the intensive group compared with 7.9% in the conventional group. There was a significant reduction in the risk of microvascular complications, mostly due to fewer patients requiring photocoagulation. Macrovascular complications were not reduced. However, the relative risk of developing microalbuminuria was lower in the intensive group (0.67; 95% CI 0.53-0.86), and the relative risk of developing macroalbuminuria was decreased, although not by a significant degree (0.66; 95% CI 0.39-1.1). Although the number of affected individuals was small, the relative risk of doubling the serum creatinine was decreased in the intensive group over a 12-year follow-up (0.26; 95% CI 0.07-0.91).

In a prospective observational study of 4585 patients in the UKPDS (18), for each 1% reduction in the mean Hb A1c, the relative risk for death related to diabetes decreased by 21% and for myocardial infarction and microvascular complications by 14% and 37% respectively. The lowest risk was for patients with Hb A1c lesser than 6%. The association of albuminuria and renal function were not reported. These data support the application of interventions that improve glycemic control and normalize Hb A1c levels.

**Treatment of hypertension**

A recent consensus report recommended a target blood pressure (BP) of 130/80 mmHg for patients with diabetes and hypertension (19). The studies reviewed show an association between a higher mean arterial pressure and a greater rate of loss of renal function. For a mean arterial pressure of 119 mmHg, the rate of loss of GFR was 12 mL/minute/year compared with 3 mL/minute/year if the mean arterial pressure was 99 mmHg. However, these studies included patients with both types of diabetes and non-diabetic subjects. Other investigators have specifically studied patients with type 2 diabetes (20-22). The effect of angiotensin converting enzyme inhibition has been studied in normotensive patients with type 2 diabetes mellitus, microalbuminuria and a serum creatinine less than 124 µmol/L (20). Patients were randomly allocated to receive enalapril 10 mg daily or placebo. The enalapril treated patients had no change in urinary albumin excretion or serum creatinine over 5 years while the placebo treated group had an increase in urine protein excretion from 123 to 310 mg per 24 hours and a 13% decline in renal function.

In the UKPDS (21), 758 patients with newly diagnosed type 2 diabetes were randomly allocated to tight blood pressure control, 400 to receive angiotensin converting enzyme inhibitors, 358 to receive beta blockers, and 390 to less aggressive BP control. Mean BP was 144/82 in the tight and 154/87 in the less aggressive control group. Glycemic control was similar. Aggressive blood pressure control was associated with a decrease in the risk of death associated with diabetes, stroke and microvascular
complications. However, there was little effect on diabetic nephropathy. At 6 years follow-up, there was a decreased relative risk for a urinary protein concentration of greater than 50 mg/L in the aggressive control group (RR 0.61; 95% CI 0.51-0.99) but no change in the risk of developing macroalbuminuria or of doubling the serum creatinine. This may have been due to inadequate lowering of BP as 44% of the aggressive control group had an average mean arterial pressure lower than 107 mmHg (23).

The Heart Outcomes Prevention Evaluation (HOPE) Study evaluated the effects of ramipril on cardiovascular and microvascular outcomes in 3577 patients with diabetes mellitus (98% type 2) and at least one cardiovascular risk factor (22). Although the risk reductions for myocardial infarction, stroke and cardiovascular death were significantly reduced, the effect on diabetic nephropathy was less impressive. Over 4 to 5 years of follow-up, there was a 24% risk reduction (95% CI 3-40%) for the development of proteinuria, defined as a urinary albumin to creatinine ratio of over 36 mg/mmol.

In a Danish study (24) patients with type 2 diabetes mellitus and microalbuminuria were randomized to standard treatment or an intensive treatment regimen that targeted hyperglycemia, hypertension, dyslipidemia and behavior modification (smoking cessation and exercise). Over a 4-year follow-up, the intensive therapy group had a decreased risk for the development of macroalbuminuria (odds ratio 0.27; 95% CI 0.1-0.75). The GFR declined 13 and 11 mL/minute/1.73m² over 4 years in the standard and the intensive therapy groups respectively.

These data indicate that strategies that aim to normalize glycemia and control BP level to around 130/80, preferably with angiotensin converting enzyme inhibitors are associated with significant decreases in mortality and microvascular complications associated with diabetes. Behavioral interventions that encourage exercise, weight reduction and smoking cessation appear to be logical. The impact on diabetic nephropathy is less convincing. The UKPDS study (17) suggests a benefit for aggressive glycemic control in the prevention of diabetic nephropathy although other studies have not confirmed this (21,22). Ravid et al (20) demonstrated a beneficial effect of angiotensin converting enzyme inhibition for normotensive patients with microalbuminuria while Gaede and colleagues (24) reported encouraging results with a multifactorial intervention strategy with respect to the development of macroalbuminuria. However, the rate of loss of GFR was no different from that of patients given standard therapy. If current strategies are more effective in preventing macrovascular disease than preventing diabetic nephropathy, the net result may be a continued increase in the rate of ESRD due to diabetes.

**ALTERNATIVE STRATEGIES**

An alternative is to target treatment at an earlier point in the pathophysiologic process that leads to diabetic nephropathy. Impaired endothelium-dependent vascular responses in retinal and renal vessels have been demonstrated in patients with type 2 diabetes mellitus compared with normal controls. This impairment was present in those with normal albumin excretion as well as in those with microalbuminuria, although the impairment was greater in the latter. Hyperhomocysteinemia has been associated with endothelial dysfunction in patients with type 1 diabetes mellitus (26). In type 2 diabetes mellitus it has been associated with diabetic neuropathy and nephropathy (27). Patients with type 2 diabetes mellitus have higher plasma homocysteine concentrations than comparable patients with type 1 diabetes and non-diabetics (28). In addition, the urinary albumin excretion rate has a strong positive association with the plasma homocysteine concentration (29). If increased plasma homocysteine is causally related to endothelial dysfunction that, in turn, is responsible for microalbuminuria and more advanced diabetic nephropathy, then strategies that decrease homocysteine concentrations should be logical.

**CONCLUSIONS AND PERSPECTIVES**

A randomized clinical trial that compares a combination of folic acid, pyridoxine and vitamin B12 with placebo has received funding from the Canadian Institutes for Health Research. It is thought that these vitamins should decrease homocysteine levels because of their key roles in homocysteine metabolism: folic acid is the substrate for methylenetetrahydrofolate reductase, pyridoxine is the co-factor for cystathionine beta synthase and B12 for methionine synthase. The doses chosen, folic acid 2.5 mg, pyridoxine 25 mg and Vitamin B12 1 mg, have been shown to effectively reduce homocysteine levels. It is hoped that a reduced homocysteine levels will decrease endothelial dysfunction and improve clinical outcomes. Three hundred patients with diabetic nephropathy in three centres will be randomly allocated to treatment or placebo groups and followed up for 5 years. If effective, this low cost therapy can become part of the multifactorial approach to preventing progression of diabetic nephropathy.
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REFERENCES


