Kidney Diseases Beyond Nephrology

Kidney disease in diabetology: lessons from 2007

Guntram Schernthaner

Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria

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**Introduction**

Diabetic nephropathy (DNP) is a devastating disorder and is now worldwide the leading cause of end-stage renal failure. This diabetic complication is a complex disease, whereby various genetic and environmental factors determine susceptibility and progression to end-stage renal disease (ESRD). DNP seems to occur as a result of an interaction between metabolic and haemodynamic factors, which activate common pathways that lead to renal damage. In addition, the renin–angiotensin system (RAS) is also an important target for both metabolic and haemodynamic derangements in DNP. High glucose, via various mechanisms such as increased production of oxidative stress and advanced glycation end products, activation of the RAS and protein kinase C and stimulation of the polyol pathway, elicits vascular inflammation and alters gene expression of growth.

Despite the rapid research progress, ideal predictors to assess prospectively, and with high precision, the risk for DNP in individuals with diabetes are still lacking. Unfortunately, currently available therapies are usually initiated at more advanced stages of DNP characterized by clinically overt manifestations, including increased urinary albumin excretion and decreased glomerular filtration. Although these interventions have proven efficacy in slowing the progression of DNP, they cannot prevent ESRD. It is hoped that new insights into the molecular mechanisms that underlie the origin and progression of DNP are emerging from large-scale genetic and molecular studies in experimental models and humans, and will finally improve the therapeutic options for DNP. Until that, the available treatment strategies have to be used in a more aggressive way, in order to improve the prognosis of patients with DNP as outlined in the review of some papers published in 2007.

**Prevention of diabetic nephropathy by ACE inhibition of ARBs**

Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. Previous studies have indicated that the use of ACE inhibitors or ARBs is beneficial in the prevention or progression of diabetic nephropathy [1]. New studies, confirming that the blockade of the RAS is important when diabetic nephropathy is in the focus, were recently published [2,3].

The ADVANCE study [2] was designed to assess the effects of the routine administration of a fixed combination of the ACE inhibitor, perindopril, and the diuretic, indapamide, versus placebo on vascular disease in a large group of 11 140 type 2 diabetic patients. The ‘active treatment’ was used irrespective of initial blood pressure levels or the use of other blood pressure (BP)-lowering drugs. After a mean follow-up of 4.3 years, patients on active therapy had a mean reduction in systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg compared to patients assigned placebo. The modest BP lowering reduced the relative risk (RR) of a major macrovascular or microvascular event by 9% (P = 0.04) and the RR of death from cardiovascular disease (CVD) by 18% (P = 0.03). Remarkably, the modest BP lowering was also associated with a 21% reduction in all renal events (P < 0.0001), and a 21% reduction in the development of microalbuminuria (19.6% versus 23.6%; P < 0.0001).

In the INNOVATION study [3] the effect of the ARB telmisartan on the prevention of transition from incipient to overt nephropathy was studied in Japanese type 2 diabetic patients presenting with microalbuminuria. A total of 527 patients (mean age: 61.7 years) were randomized to 80 mg or 40 mg telmisartan or placebo; the mean duration of the follow-up was 1.3 years. Regarding the decrease of blood pressure, systolic BP/diastolic BP fell from 138/78 mmHg to 128/72 mmHg with 80 mg telmisartan, from 137/78 mmHg to 128/72 mmHg with 40 mg telmisartan and from 137/77 mmHg to 132/74 mmHg with placebo. Transition rates to overt nephropathy were significantly different in patients randomized to 80 mg telmisartan, 40 mg telmisartan or placebo in both the hypertensive patients (P < 0.0001) (16.7% versus 22.6% versus 49.9%), as well as in...
normotensive patients \( P < 0.01 \) (11.0\% versus 21.0\% versus 44.2\%). Microalbuminuria remission at final observation occurred in 21.2\% with 80 mg telmisartan, 12.8\% with 40 mg telmisartan and 1.2\% with placebo (both telmisartan doses versus placebo, \( P < 0.001 \)). The fact that telmisartan also reduced transition to overt nephropathy in normoten- sive patients could be interpreted that telmisartan had a blood pressure-independent effect.

All previously published BP-lowering studies in type 2 diabetic patients clearly indicate that aggressive BP lowering by using antihypertensive combination therapy is mandatory to reduce serious cardiovascular and renal events [4]. There is an urgent need for the guidelines to be more strictly followed, since diabetes and hypertension (or many times the ill-fated alliance of both) are the key players in increasing continuously the prevalence of ESRD and chronic kidney disease (CKD). An alarming paper appeared recently in *JAMA* [5], indicating that the prevalence of CKD in the United States in 1999–2004 had increased further by 31\% compared to that in 1988–1994; the prevalence of CKD stages 1 to 4 increased from 10.0 to 13.1\%. The increasing prevalence of diabetes and hypertension has substantially contributed to this increase, which may propagate to higher rates of complications and kidney failure requiring dialysis or transplantation [5].

**A low-protein diet reduces proteinuria and inflammation in diabetic patients with macroalbuminuria**

The course of DNP can be ameliorated by optimal glucose control, intensive blood pressure treatment with RAS blockade and reduction of plasma lipids. When CKD occurs, additional therapeutic strategies, such as low-protein-diet regimen, are indicated. DNP is often associated with low-grade inflammation, coagulation abnormalities and dyslipidaemia, which may contribute to the high incidence of cardiovascular morbidity and mortality seen in these patients. In a previous study [6] significant positive correlations were found between urinary albumin excretion rate and plasma fibrinogen, factor VII activity, protein C, von Willebrand factor and lipid peroxides in diabetic patients. In addition, an abnormal albumin and fibrinogen synthesis has been reported in type 2 diabetes [7]. Recently, Giordano et al. [8] have shown that a moderate low-protein (0.8 g/kg/day) diet (LPD) may be useful in the management of type 2 diabetic patients with macroalbuminuria. In fact, LPD induced a significant reduction in proteinuria and low-grade inflammation, while ameliorating albumin synthesis with an increase in plasma albumin level. In addition, these changes were associated with a decrease in protein oxidation and breakdown, suggesting an adaptive response to LPD, which probably prevents diabetic patients from developing protein malnutrition. Due to the small number of patients included in that study additional data are needed to confirm their findings.

**Good glycaemic control lowers mortality in diabetic patients on haemodialysis**

Previous studies have shown that more than half of all diabetic patients on haemodialysis will die within 5 years and that optimal glycaemic control may reduce this high mortality [9]. However the latter information was comes from only very small studies. Hayashino et al. [10] have recently reported data from the Japan Dialysis Outcomes and Practice Pattern Study on haemodialysis (1569 patients with and 3342 patients without diabetes) indicating that the mortality risk in diabetic patients may be low when glycaemic control was relatively good. As expected, diabetic patients on haemodialysis had a higher mortality risk than those without (multivariable hazard ratio 1.37). Compared with those in the bottom quintile of the HbA1c level, the multivariable-adjusted hazard ratio for mortality was not increased in the bottom second to fourth quintiles of HbA1c (HbA1c 5.0–5.5\% to 6.2–7.2\%), but was significantly increased to 2.36 in the fifth quintile (HbA1c ≥ 7.3\%). In conclusion, among dialysis patients, poorer glycaemic control in those with diabetes was associated with higher mortality risk. This suggests a strong effect of poor glycaemic control above an HbA1c level of ∼7.3\% on mortality risk, and that this effect does not appear to be influenced by baseline comorbidity status.

**Improved survival rate in diabetic patients with ESRD**

Good news is coming from colleagues in Denmark, who reported that the survival rate in patients with diabetes and ESRD has improved during the last 15 years [11]. Data were obtained from the Danish National Register on Dialysis and Transplantation and from the Scandiatransplant database. During the study period (1990–1994), 8421 patients (13\% type 1 diabetic, 9\% type 2 diabetic and 78\% non-diabetic) started renal replacement therapy. In a multivariate Cox regression model the mortality risk was 67\% higher in type 1 diabetic patients than in non-diabetic patients. The survival rate in type 1 and type 2 diabetic patients was comparable and the overall survival rate improved by 18\% from time period 1 (1990–1994) to time period 2 (1995–2000) and by 14\% from time period 2 to time period 3 (2000–2004). Notably, the survival rate in diabetic patients treated with dialysis improved by 19 and 17\% for each time period, respectively, whereas the survival rate among diabetic transplanted patients improved by 53 and 58\%; thus, the corresponding 5-year survival rates were 80 versus 85\% for transplanted patients and 18 versus 30\% for dialysis patients. In this study, a similar fraction of incident type 1 diabetic (26\%) and incident non-diabetic patients (24\%) received a renal transplantation, whereas few type 2 diabetic patients received transplantation (5\%). However, the patient survival rate after transplantation was significantly poorer in diabetic than in non-diabetic patients, whereas the graft survival rate was similar in the two groups. The survival rate of transplanted patients with diabetes mellitus (types 1 and 2) compared with non-diabetic patients at 1 year was 95 versus 93\%; at 5 years, 80 versus 85\% and at 10 years, 52 versus 71\%. Among diabetic patients the survival rate was better in transplanted than in waiting-list patients (HR = 0.21). Based on their observations, the authors concluded that renal transplantation should therefore be offered to diabetic patients with ESRD whenever possible.
Recent studies have documented that CKD, commonly defined as GFR of <60 ml/min/1.73 m², is associated with substantially increased risk for CVD morbidity and mortality, independent of traditional cardiovascular risk factors [12]. Using pooled data from population-based studies, the adjusted relative risk for cardiovascular outcomes and all-cause mortality increased by ~30% in patients with CKD compared to subjects with preserved renal function [13,14]. Surprisingly, the impact of CKD on recurrent cardiovascular events among patients with diabetes and established macrovascular disease had not been studied previously. In the post hoc analysis of PROActive, a large group of type 2 diabetic patients with macrovascular disease, CKD was present in 597 (11.6%) of the 5154 patients [15]. The incidence of all-cause mortality, myocardial infarction, and stroke was significantly higher in CKD patients (18.3% versus 11.5%; HR = 1.65; P < 0.0001). For this endpoint, treatment with pioglitazone in CKD patients was associated with a 14.6% incidence (HR = 0.66; versus 21.4% with placebo), whereas in patients with more normal renal function these rates were 10.9 and 12.2%, respectively (HR = 0.89). In conclusion, CKD is an independent risk factor for major adverse cardiovascular events and death, even among a very high-risk population of patients with diabetes and pre-existing macrovascular disease. In these patients with CKD, pioglitazone reduced all-cause death, MI, and stroke, independent of renal function.

Abnormal lipid profiles in type 1 diabetes with impaired renal function

The relationship between the lipid profile, estimated GFR (eGFR) and AER was studied [16] in 2927 type 1 diabetic patients participating in the nationwide, multicentre Finnish Diabetic Nephropathy Study (FinnDiane). Patients with impaired renal function (eGFR <60 ml/min/1.73 m²) had higher total cholesterol, triacylglycerol and apolipoprotein B and lower HDL-cholesterol concentrations (P < 0.001 for all associations) than patients with normal renal function (eGFR >90 ml/min/1.73 m² or mildly impaired renal function (eGFR 60–90 ml/min/1.73 m²). These data indicate that multiple lipid abnormalities are not only present in type 1 diabetic patients with an abnormal AER, but also in those with impaired renal function. The observed lipid abnormalities may be relevant for the increased risk of diabetic patients with impaired renal function.

ADMA predicts cardiovascular events, ESRD and mortality in diabetic patients

Increased urinary albumin excretion rate (AER) is an important risk factor for cardiovascular morbidity and mortality in diabetic patients. However, the mechanisms leading to CVD in patients with T2DM and albuminuria require further exploration. The endogenous competitive nitric oxide synthase inhibitor, asymmetrical dimethylarginine (ADMA), is increased in patients with increased cardiovascular risk. ADMA was significantly increased in T2DM patients with micro- and macroalbuminuria compared to those with normoalbuminuria [17]. A recent prospective follow-up study [18] identified ADMA as new cardiovascular-risk marker in patients with type 2 diabetes and a high cardiovascular risk. ADMA significantly enhanced the predictive role of CRP for incident CVD and was independent of traditional risk predictors. The predictive role of ADMA for fatal and non-fatal cardiovascular events was recently confirmed in the large follow-up study of type 1 diabetic patients in the STENO Diabetes Center [19]. Type 1 diabetic patients with overt diabetic nephropathy (n = 397) and a control group of 175 patients with longstanding type 1 and persistent normoalbuminuria (n = 175) were followed for 11.3 years. In diabetic nephropathy, only 19.4% patients with ADMA levels below the median compared to 43.4% patients above the median suffered a major cardiovascular event during the follow-up period (P = 0.001). This effect persisted after the adjustment for conventional CVD risk factors including baseline GFR. Furthermore, elevated ADMA levels predicted an increased rate of decline in GFR, development of ESRD and all-cause mortality (P < 0.001).

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References


G. Schernthaner


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