

## **Hypertension and nephropathy in diabetes mellitus: what is inherited and what is acquired?**

V. Djordjević

Institute of Nephrology and Hemodialysis, Clinical Center, Niš, Yugoslavia

### **Introduction**

Diabetic nephropathy (DN) is a clinical syndrome characterized by persistent albuminuria ( $>300$  mg/24 h), a relentless decline in glomerular filtration rate (GFR) and raised arterial blood pressure but without other renal disease or heart failure [1,2]. Microalbuminuria indicates a urinary albumin excretion of 30–300 mg/24 h or 20–200  $\mu$ g/min. Microalbuminuria as a marker of glomerular damage predicts the development of overt nephropathy without specific interventions in approximately 80% of IDDM, and 20–40% of patients with NIDDM. Microalbuminuria is also a marker of increased cardiovascular morbidity and mortality in patients with either type 1 or type 2 diabetes. Some evidence also indicates that microalbuminuria may predict cardiovascular events and perhaps early renal damage in patients with essential hypertension [3].

Characteristic structural and functional changes in DN include hyperfiltration, renal and glomerular hypertrophy, mesangial cell hypertrophy and matrix accumulation, glomerular basal membrane thickening, and functional alteration in glomerular filtration barriers. Factors responsible for these typical changes are hyperglycaemia, advanced glycosylation end-products (AGEs), growth factors, cytokines, and glomerular hypertension [2].

Hypertension in diabetes mellitus may be due to one of the following reasons: the metabolic syndrome (hypertension, obesity, atherosclerosis, dyslipidaemia), it may be secondary to complications of diabetes mellitus, due to endocrine disorders and drugs and coincidental (essential arterial hypertension, isolated systolic hypertension). The natural history of hypertension differs markedly between type 1 and type 2 diabetes mellitus. In IDDM patients the blood pressure is usually normal at presentation and remains

normal for the first 5–10 years, but increases with appearance of diabetic nephropathy. In contrast, in NIDDM patients, elevated blood pressure is usually present at diagnosis of diabetes, or may develop thereafter [4]. Systemic hypertension is an early phenomenon in DN. Furthermore, nocturnal blood pressure elevation ('non-dippers') occurs more frequently in IDDM and NIDDM patients with nephropathy. Also, exaggerated blood pressure response to exercise has been reported in long-standing IDDM patients with microangiopathy. Finally, the increase in glomerular pressure consequent to nephron adaptation may be accentuated with concomitant diabetes [2].

### **Aetiology and pathogenesis**

Systemic blood pressure elevation, albuminuria, hyperglycaemia and hyperlipidaemia play important and critical roles in the initiation and progression of kidney dysfunction in IDDM and NIDDM patients with nephropathy. Hypertension in the albuminuric stage is a risk for subsequent development of persistent proteinuria [2,5].

### **Genetic susceptibility to DN**

Recently, attention has focused on genetic susceptibility to renal injury from elevated blood pressure. According to Churchill *et al.* [6], an experimental animal model of renal injury caused by hypertension suggests that nephropathy susceptible genes exist, but these genes have not yet been identified. In humans, the familial clustering of hypertensive renal disease and the identification of polymorphism in the renin–angiotensin–aldosterone system gene components support the idea of genetic susceptibility to hypertensive renal injury in DN [7]. Krolewski *et al.* [8] identified a region on the long arm of chromosome 3 in the vicinity of the angiotensin II type-1 receptor gene that harbours a locus with major effects. In addition, they have demonstrated minor effects of the insertion allele

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Correspondence and offprint requests to: V. Djordjević, Medical Faculty, Clinical Center, Institute of Nephrology and Hemodialysis, B. Taskovica 48, 1800, Nis, Yugoslavia.

in the ACE gene and the T-allele at position 235 in the angiotensinogen gene on the development on DN. This finding must be confirmed in other family-based studies. Is susceptibility to diabetic nephropathy the same as susceptibility to essential hypertension? According to Krolewski *et al.* [8] there is some overlap. Essential hypertension has a significant genetic component with minor gene effects and these authors postulated that the expression and penetrance of one of these minor genes for essential hypertension is changed in the presence of hyperglycaemia in such a way that carriers of that disease allele, which must be a common one, would develop DN together with their hypertension. Overactivity of the  $\text{Na}^+/\text{H}^+$  exchanger in the pathogenesis of DN remains uncertain. Demaine *et al.* [9] presented the results of an analysis of polymorphism in two areas of the aldose reductase gene in normal healthy controls and in IDDM patients with nephropathy. This finding is not confirmed by others [8].

The kidney also plays a critical role in the development of systemic hypertension. The major alterations are sodium retention and increased peripheral vascular resistance [7]. The molecular aspect of this phenomenon in patients with DN is not completely understood.

In conclusion, hypertension and microalbuminuria play a critical role in initiation and progression of DN. The ACE genes (which allele?) may predict DN in some groups. Insulin resistance contributes to DN but mostly indirectly. Also, ACE genes may predict the rate of progression and the antiproteinuric response

to ACE inhibitors. DN does not develop in the absence of hyperglycaemia but other factors exist that interact with poor glycaemic control to produce nephropathy and hypertension. Genetic susceptibility is one of the most important factors.

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