Genetics of diabetic nephropathy

M. Merta, J. Reiterova, R. Ryšavá, D. Kmentová and V. Tesař

First Medical Department, First Medical Faculty, Charles University, Prague, Czech Republic

Abstract

Diabetic nephropathy (DN) develops in ~40% of type 1 diabetic patients and is a leading cause of end-stage renal failure. Its rate of progression varies greatly among individuals. Several factors, including genetic predisposition, metabolic and haemodynamic alterations and various growth factors, may contribute to the initiation and progression of DN. The genetic background of DN is believed to be polygenic. Polymorphisms of different genes, mainly from the renin–angiotensin system, have been studied extensively, and some of them have been suggested to contribute to the development of DN. A search for genes and combinations of genes which could influence the development and progression of DN is in progress.

Keywords: diabetes; diabetic nephropathy; genes; gene polymorphism; IDDM; NIDDM

Diabetic nephropathy (DN) is an important cause of morbidity in subjects with both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). Moreover, it is associated with increased cardiovascular mortality. DN is the most common cause of end-stage renal failure (ESRF) in developed countries, and it follows a well-defined clinical course, starting with microalbuminuria through proteinuria and azotaemia, and culminating in ESRF. Before the onset of overt proteinuria, various renal functional changes occur including renal hyperfiltration, hyperperfusion and increased capillary permeability to macromolecules. Basement membrane thickening and mesangial expansion are histological changes typical of DN. It is believed that DN occurs as a result of the interplay of metabolic and haemodynamic factors in the renal microcirculation. The duration of diabetes mellitus (DM), tightness of glycaemic control and blood pressure (BP) are undoubtedly implicated. Hyperglycaemia damages tissue via the accumulation of advanced glycation end-products (AGEs), the activation of isoform(s) of protein kinase C (PKC) and the activation of aldose reductase. The balance between extracellular matrix production and degradation is of crucial importance; transforming growth factor-β (TGF-β) appears to play a pivotal role in the accumulation of the extracellular matrix in the diabetic kidney. Haemodynamic disturbances are presumed to be responsible for the development of glomerulosclerosis and its attendant proteinuria. PKC is one of the key signalling molecules in the induction of the vascular pathology of diabetes [1].

All these factors are insufficient on their own to predict which patients will develop DN. Newer evidence suggests that an interaction with genetically determined susceptibility to hyperglycaemia-induced glomerular injury is very likely. The prevalence of DN associated with IDDM increases with longer duration of DM, but levels out at ~15 years, when a cumulative prevalence of ~50% is reached; this is less easily demonstrable in DN associated with NIDDM, where the time of onset of the disease is less clearly defined. Only a subset of diabetic patients are at risk of developing renal disease, which is in contrast to retinopathy, whose prevalence continues to rise with increased duration of DM, so that most patients will develop this complication if they live long enough.

There is familial clustering of diabetic kidney disease. The familial aggregation of DN in IDDM was observed by the Diabetes Control and Complications Trial (DCCT) Research Group [2]. An increased risk of nephropathy in relatives of nephropathy-positive vs nephropathy-negative DCCT subjects has been demonstrated. The familial aggregation of DN and NIDDM was studied extensively in Pima Indians, who exhibit one of the highest rates of NIDDM and also of DN in the world (associated...
with slower metabolic rate, combined with high fat diet and tendency to obesity). A familial predisposition to DN in two generations of NIDDM Pima subjects has been found [3].

Is the onset and development of DN associated with some biochemical or clinical parameters typical of DM, such as arterial hypertension (AH) or insulin resistance syndrome (IRS)? Is DN inherited separately from DM? These issues have been discussed intensively recently; however, clear conclusions are still lacking. It could be hypothesized that a number of genes predispose to DN and to renal disease. Some of these genes, but not all, might predispose to both the renal disease and to DN and other manifestations of IRS. Consistency in the findings of familial aggregation of DN and of its co-aggregation with other features of the IRS, particularly AH, makes a genetic component likely. Evidence of familial aggregation alone is not sufficient to prove genetic influences (sharing of many environmental factors in families). The ultimate proof, i.e. identifying the responsible genes, should be performed (positional cloning based on linkage analysis or by the candidate gene approach). So far, the genetic model of inheritance of DN could be proposed as a multifactorial one. This model could involve, on the genetic side, the genes affecting or encoding the development of AH, type 2 DM, other manifestations of the IRS and different components typical for the morphology of DN (intra-glomerular pressure independent of AH, glomerular permeability, basement membrane thickening, matrix expansion). In terms of the environment, genes affecting glycaemic control, BP control and possibly intra-uterine malnutrition could be involved [4,5].

A number of gene loci have been investigated to explain the genetic susceptibility to DN. The genes encoding components of the renin-angiotensin system have received special attention, due to the central role that this system plays in the regulation of BP, sodium metabolism and renal haemodynamics. A meta-analysis by Tarnow in 1998 suggested that angiotensin-converting enzyme (ACE) insertion/deletion polymorphism contributes to the genetic susceptibility to DN in Japanese NIDDM patients, but does not play a major role in the initiation of DN in Caucasian NIDDM patients. In Caucasian IDDM patients, a trend towards a protective effect of the II genotype on the development of DN was observed [6]. Endothelial dysfunction is closely associated with the development of diabetic retinopathy, nephropathy and atherosclerosis in both IDDM and NIDDM. A hypothesis that DNA sequence differences in the endothelial NO synthase gene (eNOS) could contribute to endothelial dysfunction and, indirectly, to development of DN seems to be supported by some recent findings [7].

A contradictory conclusion could be drawn from studies focusing on the role of an amino acid variant (K121Q) in glycoprotein PC-1 (associated with insulin resistance) and its effect on DN.

Other gene polymorphisms that possibly affect the onset and/or course of DN are being studied, including polymorphisms of genes encoding angiotensinogen, angiotensin II type-1 receptor, G-protein B3 subunit, apolipoprotein E and TGF-β.

In conclusion, the hunt for genes contributing to the development of DN has begun recently. In order to uncover its genetic background, it is indispensable to identify gene loci and to test specific candidate genes and possibly their interaction. The employment of new and more sensitive genetic approaches (transmission disequilibrium test, sib-pair method) is also needed. The rationale of gene identification remains clear—to improve the prevention and treatment of DN.

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References