Progression of renal failure in diabetic nephropathy

C. Marcantoni, V. Ortalda, A. Lupo and G. Maschio
Division of Nephrology, University of Verona, Verona, Italy

Abstract. The onset of renal damage in diabetes mellitus may be influenced by several factors which largely result from genetic predisposition, hereditary factors and the early appearance of microalbuminuria and/or systemic hypertension. Most of these factors are also implicated in the progression of nephropathy from microalbuminuria to overt proteinuria and to end-stage renal failure (ESRF). Over the last few years, the role of hyperglycaemia has emerged as critical in mediating the progressive renal damage in diabetes. However, hyperglycaemia leads to increased formation of glycated proteins which may act as promoters of progression by localizing in renal tissue. In addition, hyperglycaemia may have a synergistic effect with some other risk factors, such as growth factors and the renin–angiotensin system, in accelerating renal deterioration.

Key words: diabetic nephropathy; hyperglycaemia; hypertension; progression of renal failure; proteinuria; renin–angiotensin system

Introduction

The progression of renal damage in diabetic nephropathy is most likely multifactorial, for example genetic predisposition, systemic hypertension, microalbuminuria, proteinuria, hyperglycaemia and smoking playing roles of varying importance (Table 1).

Table 1. Factors affecting progression of renal damage in diabetic nephropathy

1. Genetic predisposition
2. Systemic hypertension
3. Microalbuminuria
4. Proteinuria
5. Hyperglycaemia
6. Activation of the renin–angiotensin system
7. Smoking

Genetics

Many channels of evidence suggest a genetic predisposition, not only in the development but also in the progression of diabetic nephropathy. This topic is reviewed in detail by R. Trevisan in this supplement.

Systemic hypertension

Systemic hypertension is known to accompany overt nephropathy in both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), and may also precede the development of renal damage in this disease [1]. In IDDM, some retrospective studies have clearly shown that, at the time of diagnosis, patients who eventually developed nephropathy had significantly greater mean arterial pressure (MAP) than those who never presented with evidence of renal damage [2]. On the other hand, MAP values are correlated directly with albuminuria, both parameters being important factors in the progression to overt diabetic nephropathy [3].

In NIDDM, hypertension is a frequent finding, and again it may precede or follow overt diabetic nephropathy. In this disease, many additional factors (including macrovascular complications, insulin resistance and dyslipidaemia) may contribute to explaining the development of renal damage [4]. The blood pressure (BP) values recorded before the onset of persistent hyperglycaemia are important predictors of albuminuria in NIDDM of Pima Indians. Prevalence of albuminuria was 9% in individuals whose BP was in the lowest tertile 1 year before the diagnosis, and was 23% in those who were in the highest tertile at the same time [5].

In addition, hypertension seems to confer a graded risk for the development of overt diabetic nephropathy, the fastest rate of progression being observed when BP values are consistently >160/95 mmHg [5]. A quantitative relationship has been reported between BP values and loss of renal function. In a retrospective analysis of 59 patients with established diabetic nephropathy [7], a more rapid decline in glomerular filtration rate (GFR) correlated most strongly with higher diastolic...
BP: for each mmHg of diastolic BP >80, GFR decreased by 0.69 ml/min/year.

Therefore, elevated BP is an important determinant of progression of renal damage both in early and late stages of diabetic nephropathy. Many studies [4,8] have shown a more rapid decline in GFR in diabetic patients with systemic hypertension than in those with normal or near-normal BP values.

**Microalbuminuria and proteinuria**

Microalbuminuria has long been regarded as a predictor of clinical proteinuria and a progression to overt nephropathy in diabetic patients [2]. Prospective studies have shown a lower risk of such advancement in NIDDM patients (22%) than in those with IDDM (80%) after a 10 year follow-up [9].

The onset of microalbuminuria can be explained, at least in part, by the typical haemodynamic (hyperfiltration, systemic hypertension) and metabolic (hyperglycaemia) alterations found in the early stages of diabetes mellitus. However, partial reversal of microalbuminuria has been obtained with several therapeutic measures, including dietary protein restriction, glycaemic control and antihypertensive treatment [10]. Persistent microalbuminuria, however, may have a structural basis and is now regarded as incipient diabetic nephropathy, a view confirmed by several morphological studies [11].

Statistically significant associations were observed between microalbuminuria, systemic hypertension and poor glycaemic control [12] and, in addition, microalbuminuria is associated with increased risk for cardiovascular morbidity and mortality in NIDDM patients [13].

Once established, persistent proteinuria is the most important predictor of progression of diabetic nephropathy to end-stage renal failure (ESRF). There is a considerable variability in the average interval between onset of proteinuria and ESRF: many additional factors (age, race, gender, genetic predisposition, severity of systemic hypertension, glycaemic control, quality and duration of dietary and non-dietary intervention) may play important roles in mediating progression.

It is interesting that, for similar baseline levels of proteinuria, the progression rate is comparable in IDDM and NIDDM patients [14]. Similarly to non-diabetic renal disease, proteinuria reflects, to some extent, the degree of glomerular sclerosis and hence the severity of renal damage. In addition, proteinuria *per se* may exert a toxic effect on the kidney by damaging proximal tubular cells and hence triggering severe tubulo-interstitial changes [15].

**Hyperglycaemia**

Several lines of evidence suggest that poor glycaemic control is an independent predictor of the progression rate of diabetic nephropathy. One likely consequence of persistent hyperglycaemia could be the non-enzymatic reaction between glucose and the amino groups of various matrix proteins, the early stage of the Maillard reaction. The generated Schiff base is then converted to stable Amadori products, which subsequently are rearranged to form 3-deoxyglucosone (3-DG). This compound reacts with the amino groups of proteins to form the advanced glycation end-products (AGEs), the late stage of the Maillard reaction.

AGEs have been implicated in pathological processes associated with ageing, diabetes mellitus, dialysis-related amyloidosis and Alzheimer’s disease [16]. Elevated serum AGEs and their precursors have been observed both in diabetic and in non-diabetic patients with chronic renal failure [17]. In addition, accumulation of AGEs in renal tissue has recently been associated with progressive renal damage in diabetic nephropathy.

Nishino et al. [18] observed the localization of AGEs in ~30% of glomeruli in renal biopsies obtained from patients with diabetic nephropathy. AGEs were also detected in expanded mesangial matrix, in nodular lesions, in Bowman’s capsule and in arteriolar walls of patients with diabetic nephropathy [19–21].

Sakai et al. [22] succeeded in staining, by specific monoclonal antibodies, both Amadori products and AGEs in renal biopsy specimens. The mRNA expression of these compounds was also evaluated by *in situ* hybridization. The localization of both Amadori products and AGEs paralleled the severity of glomerular damage in diabetic patients. In addition, Amadori products have been shown to modulate renal haemodynamics, by enhancing NO activity in endothelial cells [23]. These studies suggest an important role for glycated proteins in the progression from early to late stages of diabetic nephropathy, not only in experimental animals but also in humans [24].

Both hyperglycaemia and AGE-modified proteins may generate reactive oxygen species and stimulate the synthesis of several growth factors, including transforming growth factor-β1 (TGF-β1), insulin-like growth factor I (IGF1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and tumour necrosis factor-α (TNF-α). Hyperglycaemia was found to induce intraglomerular TGF-β1 mRNA expression *in vivo*. The expression of this cytokine in renal biopsy specimens was correlated with HbA1c in NIDDM patients and with various degrees of renal functional impairment [25]. The hyperactivity of TGF-β1 may promote renal tubular growth and hypertrophy, eventually resulting in severe tubulo-interstitial changes [26,27]. Interestingly, hyperglycaemia *per se* may promote collagen biosynthesis, thus adding its effect to that of TGF-β1 [26]. Hyperglycaemia has also been shown to activate protein kinase C (PKC) through an elevation of diacylglycerol. This activation produces several consequences, including, increased production of vasodilatory prostaglandins, leading to hypertension; cellular proliferation; and increased synthesis of type IV collagen and fibronectin, leading to base-
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15. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of not only exerts its strong haemodynamic effect on renal microcirculation, but also increases proteinuria and stimulates the synthesis of several cytokines and growth factors [31]. It is of interest that angiotensin II and hyperglycaemia may act synergistically in promoting the activity of some important mediators of renal damage in diabetic nephropathy, such as TGF-β and PDGF [32]. The protective effect of ACE inhibitors might be related to their ability to suppress the intrarenal RAS preferentially, thus counteracting the injurious effect of tissue angiotensin II [31].

Renin–angiotensin system (RAS)

The role of the RAS has long been regarded as unimportant in the pathogenesis of progressive renal damage in diabetic nephropathy. However, the beneficial effects of both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists in reducing proteinuria and protecting the residual renal function have led to a reconsideration of this system among the factors affecting progression of diabetic nephropathy. In this disease, angiotensin II not only exerts its strong haemodynamic effect on renal microcirculation, but also increases proteinuria and stimulates the synthesis of several cytokines and growth factors [31]. It is of interest that angiotensin II and hyperglycaemia may act synergistically in promoting the activity of some important mediators of renal damage in diabetic nephropathy, such as TGF-β and PDGF [32]. The protective effect of ACE inhibitors might be related to their ability to suppress the intrarenal RAS preferentially, thus counteracting the injurious effect of tissue angiotensin II [31].

Smoking

The only exogenous component in the constellation of factors affecting progression of diabetic nephropathy is achieving increasing importance. Smoking has been shown to increase the risk of microalbuminuria and of its progression to proteinuria both in IDDM and NIDDM patients [12,33]. In addition, the progression rate of diabetic nephropathy seems faster in smokers than in non-smokers [8]. Finally, smoking has been reported to increase the mortality rate in patients with diabetic nephropathy [34].

Table 2. Potential mechanisms by which hyperglycaemia can affect progression of diabetic nephropathy

| 1. Activation of protein kinase C |
| 2. Non-enzymatic glycation of various matrix proteins and their accumulation in the kidney |
| 3. Stimulation of several growth factors (TGF-β, IGF1, PDGF, TNF-α, FGF) |
| 4. Generation of reactive oxygen species |
| 5. Stimulation of collagen biosynthesis |

ment membrane thickening and extracellular matrix expansion [28,29] (Table 2). Long-term clinical studies now agree with the view that a poor glycaemic control is associated with a faster rate of decline of GFR even when BP is finally controlled [30].