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Nephropathy of type 1 and type 2 diabetes: diverse pathophysiology, same treatment?

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Introduction

Diabetic nephropathy is a syndrome of albuminuria, declining glomerular filtration rate (GFR), arterial hypertension, and increased cardiovascular risk that affects 20–40% of type 1 (insulin-dependent) and type 2 (non insulin dependent) diabetic patients [1–3]. Diabetics, mostly type 2, account for about one third of all patients requiring chronic renal replacement therapy in western countries. Indeed, type 2 diabetics with end-stage renal disease (ESRD) are rapidly increasing because of the continuing increase in the prevalence of type 2 diabetes and the progressively declining mortality rate from cardiovascular causes. The costs associated with management of the disease (in 1996, $4.6 billion in the United States alone) are increasing in proportion and will soon become unbearable for most western countries. High mortality, costs, and decreased quality of life associated with chronic renal replacement therapy, have motivated the search for the causes and the possible treatments that might effectively delay or even completely prevent the progression of diabetic nephropathy to ESRD.

In both types of diabetes, chronic hyperglycaemia is the primary cause of the disease. In type 1 diabetes hyperglycaemia starts in the first decades of life and is usually the only recognized cause of nephropathy. On the contrary, in type 2 diabetes hyperglycaemia starts after the forties, usually when the kidneys have already suffered the long-term consequences of ageing and of other recognized promoters of chronic renal injury such as arterial hypertension, obesity, dyslipidaemia, and smoking. Ageing is *per se* a cause of progressive glomerulosclerosis and combined with the above risk factors may contribute to the aspecific changes of arteriolosclerotic type that so often coexist with, and occasionally overwhelm, the typical features of diabetic glomerulopathy, in particular in type 2 diabetes [2]. Due to the high prevalence of accelerated atherosclerosis involving the renal macrovasculature, ischaemic changes are also frequently observed in type 2 diabetics. Thus, the term diabetic nephropathy describes a syndrome that is common to type 1 and type 2 diabetes. Especially in type 2 diabetics, however, it reflects a heterogeneous mixture of different diseases that are sustained by different mechanisms and may coexist in different combinations. Notably, such a combination of different structural changes is also a function of time. Pure diabetic glomerulopathy is more frequently observed in patients with earlier onset of diabetes and evaluated at the stage of microalbuminuria (incipient nephropathy) [4], whereas aspecific, vascular and tubulo-interstitial changes are more prominent in older patients with macroalbuminuria, renal insufficiency (overt nephropathy) and long lasting history of arterial hypertension [5]. Regardless of the involved mechanisms, this heterogeneous pattern of renal diseases may explain why, unlike in type 1, in type 2 diabetes the outcome and response to treatment, in particular at the stage of overt nephropathy, is so poorly characterized. Since, at least in theory, different underlying diseases might account for different responses to treatment, the effects of potentially renoprotective treatments should be explored in homogeneous populations of diabetics with well-characterized patterns of renal involvement. Thus, type 1 diabetics should be considered separately from type 2 diabetics and those with incipient nephropathy separately from those with overt nephropathy. Ideally, among type 2 diabetics with overt nephropathy, those with typical glomerulopathy resembling the pattern of nephropathy of type 1 diabetes should be considered separately from those with predominant, aspecific changes and from those with recognized renal vascular disease.

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Overt nephropathy: the role of tertiary prevention

Unfortunately, although type 2 diabetics represent the large majority of macroalbuminuric diabetics at risk of ESRD [2,3], most trials in overt nephropathy have been so far restricted to type 1 diabetics. Thus, in type 1 diabetes [6], as well as in all the other chronic proteinuric nephropathies of non-diabetic type, ACE inhibitors ameliorate glomerular barrier size-selective dysfunction, and concomitantly reduce proteinuria. This, among other factors, conceivably translates into less renal toxicity of proteins and explains the long-term amelioration in GFR decline documented by various studies (for review see [7]). In contrast, clear-cut evidence of a similar effect in type 2 overt nephropathy is, so far, unavailable. Notably, ACE inhibitors failed to ameliorate glomerular barrier dysfunction—as documented by their negligible effect on the sieving profiles of test macromolecules (neutral dextrans)—and to limit proteinuria even in type 2 diabetics with biopsy proven diabetic glomerulopathy [8]. Actually, in harmony with experimental findings that ACE inhibitors are poorly effective when started at advanced stages of diabetic nephropathy [9], it was argued that too advanced and diffuse renal changes accounted for the poor responsiveness of these patients. However, regardless of the mechanisms involved, the failure to limit protein traffic may explain why ACE inhibitors failed to confer to macroalbuminuric type 2 diabetics the same renoprotective effect as to type 1 diabetics [10].

Clearly, these data do not justify a generalized use of ACE inhibitors in proteinuric type 2 diabetics just because they are beneficial in type 1 diabetes, especially if one considers the high prevalence of renovascular disease and the potential risk of ACE inhibitor-associated acute renal failure and life-threatening hyperkalaemia in this setting. Thus, tight blood pressure control with any drug remains the cornerstone to limit progression of type 2 nephropathy. The Modification of Diet in Renal Disease study [11] clearly showed that in proteinuric nephropathies antihypertensive agents should be targeted to achieve and maintain systolic/diastolic blood pressure values below 130/80 mmHg. This approach is safe even in older patients and may substantially limit cardiovascular events, including fatal and non-fatal myocardial infarction and stroke [12]. Among the available antihypertensive drugs, ACE inhibitors are those with the best cardiovascular profile, whereas dihydropyridine calcium channel blockers (CCBs) have been reported to increase the risk of acute cardiovascular events, in particular in type-2 diabetes [2]. Thus, the use of the latter should be restricted to those selected cases in which other drugs are either contraindicated or ineffective.

Available data show that, in both types of diabetes, tight metabolic control and restricted protein intake add no further renoprotection to the above treatments.

Incipient nephropathy: the role of secondary prevention

In incipient nephropathy, unlike overt nephropathy, the potential renoprotective effect of ACE inhibitors has been extensively explored and clearly demonstrated in both type 1 and type 2 diabetes (for review see [13]). In the above studies, ACE inhibitors uniformly decreased albuminuria, which translated into slower GFR decline or delayed progression to overt nephropathy. Overall, available data show that at the stage of incipient nephropathy the specific renoprotective effect of ACE inhibition is independent not only of the type of diabetes but also of the degree of arterial blood pressure, urinary albumin excretion rate or GFR, and of the type of ACE inhibitor employed [13].

In contrast, data on the effects of intensified metabolic control have been discouraging. No reliable information is available in type 2 diabetics and preliminary positive findings from some Scandinavian studies in type 1 microalbuminuric diabetics [13] were not confirmed by the Diabetes Chronic Complication Trial (DCCT) [14] or by the Microalbuminuria Collaborative Study [15] which failed to detect any beneficial effect of improved metabolic control on progression to macroalbuminuria. A possible interpretation of these negative findings is that when intensified insulin treatment is needed to optimize metabolic control, the potential benefits of near normal glycaemia are counterbalanced, or even overwhelmed, by the drawbacks of chronic hyperinsulinism, including increased blood pressure and body weight. In this regard, the use of human insulin analogues, such as insulin lispro, appears quite promising and may improve metabolic control due to their favourable pharmakokinetic profile, without the need of increased insulin doses in both types of diabetes [16].

Primary prevention of diabetic nephropathy: a target for the third millennium

Notably, available data on the possibility of preventing progression from normo- to micro-albuminuria (primary prevention) are more consistent in type 2 than in type 1 diabetes (for review see [2]). In line with experimental evidence that early ACE inhibition therapy—i.e. at the stage of diabetes induction—may completely prevent the onset of nephropathy, a preliminary study in a small group of hypertensive type 2 normoalbuminuric diabetics found that 3-year ACE inhibitor therapy slightly ameliorated GFR and decreased the risk of progression to microalbuminuria [2]. Similarly, a recent study in normotensive, normoalbuminuric type 2 diabetics found that enalapril treatment over 6 years decreased urinary albumin excretion rate and progression to microalbuminuria more effectively than placebo [17]. A large scale, prospective, randomized trial is currently exploring whether ACE inhibition can effectively prevent or delay the onset of

nephropathy in type 2 hypertensive, normoalbuminuric diabetics and whether this effect can be maximized by a combined therapy with non-dihydropyridine CCBs [18].

The DCCT found that primary prevention of nephropathy could be achieved even with intensified metabolic control [14]. Whether this applies to type 2 diabetes is unclear, since the UK Prospective Diabetes Study (UKPDS) showed a trend to a lower incidence of microalbuminuria in normoalbuminuric diabetics on intensified metabolic control as compared to diabetics on conventional treatment, but the effect was not statistically significant [19]. However, it is worth mentioning that a much smaller study, with a design similar to the DCCT, in Japanese type 2 diabetics also showed a beneficial effect on progression from normoalbuminuria to micro- and macro-albuminuria [2,3]. Whether these contrasting results reflect differences in study design or in racial susceptibility to the benefits of improved metabolic control is still unclear.

Conclusions

Efforts aimed at early detection of renal involvement (incipient nephropathy) seem worthwhile. ACE inhibitor therapy appears to be maximally cost-effective in both types of diabetes when treatment is started at the stage of incipient nephropathy. Later intervention at the stage of overt nephropathy is poorly effective in type 2 diabetics. On the other hand, the effectiveness of earlier intervention at the stage of normoalbuminuria is still under investigation. As for the renal effects of intensified metabolic control, data are discouraging when treatment is started at the stage of incipient or overt nephropathy, but they clearly show that when near normal glycaemia is obtained in normoalbuminuric patients, primary prevention of nephropathy is feasible, at least in type 1 diabetes. However, regardless of the type of diabetes and the stage of renal involvement, achievement of systolic/diastolic blood pressure values of 130/80 mmHg or less and of HbA1C levels of 7.5% or less are of paramount importance for the beneficial effect which optimal blood pressure and metabolic control may have on all the other macro- and micro-vascular chronic complications of diabetes [2,3]. Whether improving the lipid profile and limiting oxidative stress by decreased dietary fat intake, in particular fatty acids, increased physical exercise, smoking cessation, vitamin C and vitamin E supplementation, and combined treatment with antiplatelet agents and statins, may add further renal and cardiovascular protection to this high risk patient population is worth investigating [20].

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