«NEFROPATÍA DIABÉTICA TIPO II: LA EPIDEMIA DEL SIGLO XXI»

New approaches to primary and secondary prevention of diabetic nephropathy

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About 30% of insulin dependent diabetic (IDD) and 15-60% of non-insulin-dependent diabetic (NIDD) patients develop diabetic nephropathy (DN), a syndrome of macroalbuminuria, systemic hypertension and declining glomerular filtration rate (GFR), associated with a 20 to 40-fold increased risk of cardiovascular mortality. DN, the leading cause of end stage renal failure in Western countries, is invariably heralded by the appearance of persistent microalbuminuria (incipient nephropathy: IN). Every year, 4.4% to 6.8% of IDD patients on conventional insulin therapy and 4.6% of NIDD patients progress to micro-albuminuria. A higher rate of progression is reported in smokers and in patients with higher blood pressure. Thus, microalbuminuria is now considered an early marker of renal involvement in diabetes, and its prevention can be taken as to indicate primary prevention of DN.

It is well established that angiotensin converting enzyme (ACE) inhibitors delay the progression of IN to overt DN (secondary prevention) either in IDD and in NIDD and remarkably decrease disease progression to uremia and overall cardiovascular mortality in IDD patients with overt DN. Whether early treatment with ACE inhibitors in normoalbuminuric diabetic patients may effectively prevent progression to microalbuminuria (primary prevention) is not established so far. However, preliminary evidence is available that the incidence of microalbuminuria may be reduced by ACE inhibition therapy in hypertensive NIDD patients.

Calcium channel blockers (CCBs) inhibit the vasoconstrictor as well as both the hypertrophic and hyperplastic effects of angiotensin II and other mytogens on mesangial and vascular smooth muscle cells through blockade of calcium dependent mechanisms. Early studies, however, demonstrate marked differences between the antiproteinuric effects of dihydropyridine CCBs and nondihydropyridine CCBs, such as verapamil and diltiazem. Recent data support the concept that differences in antiproteinuric response subclasses relate to their differential effects on glomerular permeability, that is, dihydropyridine CCBs do not ameliorate glomerular barrier perm-selectivity whereas nondihydropyridine CCBs attenuate it. Failure to restore the sieving properties of the glomerular barrier increases protein ultrafiltration and enhanced protein traffic in the long-term contributes to the progression of renal injury independently of the underlying renal disease. Recent studies found that nondihydropyridine CCBs may have the same reno-protective potential of ACE inhibitors either in experimental models of progressive renal disease and in NIDD patients.

The association of ACE inhibitors with nondihydropyridine CCBs may even more effectively than the two agents alone decrease, at comparable level of blood pressure control, proteinuria and prevent glomerulosclerosis in experimental diabetes and in hypertensive stroke-prone rats. Additionally, recent studies document that the association of ACE inhibitors with nondihydropyridine CCBs reduces urinary albumin excretion rate more effectively than the two agents alone in hypertensive NIDDM patients either with incipient or overt nephropathy. Furthermore, in proteinuric NIDDM patients, the combination of these classes of agents appears to slow GFR decline and to yield the lowest side effect profile over either agent alone in diabetic patients with overt nephropathy. Lastly, the association of a calcium channel blocker to ACE inhibition therapy in hypertensive diabetics may reduce the need for additional diuretic therapy that has been associated with an excess mortality in diabetic mellitus. However, whether the association may more effectively than ACE inhibitors alone prevent the onset of microalbuminuria (primary prevention) or delay the progression from microalbuminuria to macroalbuminuria (secondary prevention) is not established so far.