Therapeutic measures in proteinuric nephropathy

MANUEL PRAGA

Department of Nephrology, Hospital Universitario 12 de Octubre, Madrid, Spain

Therapeutic measures in proteinuric nephropathy. The level of proteinuria is one of the most important risk factors for progressive renal function loss in renal diseases. Any therapeutic measure that reduces proteinuria will slow or halt the progression of proteinuric nephropathies. Blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors or AT1-receptor antagonists (ARA) is currently the most powerful available antiproteinuric treatment. Recent investigations point out that blockade of RAAS at other levels (e.g., aldosterone or renin antagonists) could also induce a significant decrease in proteinuria. Because angiotensin II is also generated from angiotensin I by enzymes other than ACE, ARA would provide a more effective blockade of angiotensin II; however, ACE inhibition increases plasma levels of substances such as bradykinin and N-acetylseryl-aspartyl-lysyl-proline, which have strong antifibrotic properties. These differential effects of ACE inhibitors and ARA are the rationale for combined administration of both agents, which in clinical studies has demonstrated a significantly higher antiproteinuric and renoprotective effect than by either drug alone. Salt and protein restriction, as well as cautious use of diuretics, can also increase the antiproteinuric effect of RAAS blockade. Treatment with statins or other lipid-lowering agents leads to reduction in proteinuria levels, as some meta-analyses have demonstrated. Smoking is associated with an increased risk for the appearance of proteinuria, so cessation of smoking should be mandatory in proteinuric renal diseases. Recent studies have highlighted an epidemic increase of obesity-related proteinuric glomerulopathies; weight loss is effective not only in this condition, but also in overweight patients with proteinuric nephropathies of other etiologies.

In the past decade, an important number of clinical studies have clearly established that the level of proteinuria or albuminuria is one of the most important risk factors for progressive renal function loss in both diabetic and nondiabetic renal diseases [1–4]. Any therapeutic measure that reduces the level of proteinuria will slow or halt the rate of renal function loss and, conversely, those individual patients in whom proteinuria does not decrease after the introduction of well-known beneficial therapies, such as angiotensin-converting enzyme (ACE) inhibitors, will not obtain the expected benefits of these therapies [5]. The main reason for this relationship between proteinuria and renal failure progression relies on the tubulointerstitial damage induced by proteinuria.

Many experimental studies have demonstrated that proteins abnormally filtered by the glomerulus in the setting of diabetic nephropathy or other renal diseases are actively reabsorbed by proximal tubular cells through a receptor-mediated endocytosis, and degraded by lysosomes [6]. Proximal tubular cells show an intense proliferation when protein concentration increases in the tubular lumen, and synthesize a large number of vasoactive and proinflammatory substances including angiotensin, endothelin-1, transforming growth factor beta, RANTES (regulated upon activation normal T-cell expressed and secreted) monocyte chemoattractant protein-1, and osteopontin [7, 8]. These substances activate the migration of macrophages and T lymphocytes into the renal interstitium; the presence of cellular infiltrates is a classical observation in renal biopsies of patients with proteinuric renal diseases. These interstitial infiltrates, in turn, are a continuous source of proinflammatory and profibrotic factors that gradually transform the infiltrative appearance of interstitium into a diffuse and irreversible fibrosis. Because of the initial histological descriptions of many glomerular diseases, it is well known that the severity of tubulointerstitial changes portends a more ominous prognosis than the glomerular lesions [9]: the level of glomerular proteinuria, continuously inducing the tubulointerstitial damage summarized above, appears to be the most important pathogenic link between glomerular disorders and tubulointerstitial fibrosis.

The role of those specific receptors and transcription factors that promote the proliferation of tubular cells and upregulate the synthesis of proinflammatory and profibrotic mediators has been partially clarified in recent years [6–8, 10, 11]. Nuclear transcription factor κB appears to play a fundamental pathogenic role. Thus, in experimental models of nephrotic syndrome (adriamycin-induced nephrosis), treatment with an antioxidant drug (pyrrolidine dithiocarbamate), which specifically blocks nuclear transcription factor κB, prevented the development of tubulointerstitial damage in spite of the persistence of massive proteinuria [12].

Key words: proteinuric nephropathy, proteinuria reduction, ACE inhibitors, AT1-receptor antagonists, aldosterone antagonists, combined RAAS blockade, obesity-related proteinuria.

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In this review, we summarize those antiproteinuric therapeutic measures that have consistently demonstrated their efficacy in the clinical practice, as well as those therapeutic agents that have shown promising beneficial effects in experimental studies and preliminary clinical investigations.

BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM WITH ACE INHIBITORS OR AT1-RECEPTOR ANTAGONISTS

Blockade of the renin-angiotensin-aldosterone system (RAAS) by ACE inhibitors or AT1-receptor antagonists (ARA) remains the most powerful antiproteinuric treatment currently available. Shortly after their introduction as antihypertensive drugs, ACE inhibitors showed a striking antiproteinuric efficacy, which was largely independent of their blood pressure-lowering effect [13]. Confirming preliminary observations [5], large, prospective, multicenter studies demonstrated that these drugs significantly reduce the risk for renal function loss in diabetic and nondiabetic nephropathies [14–17]. The subsequent introduction of ARA showed that these agents share the antiproteinuric properties of ACE inhibitors [18]. Recent landmark studies have demonstrated a renoprotective effect of losartan and irbesartan in patients with type 2 diabetic nephropathy [19–21], which significantly reduces the risk of end-stage renal failure and progression from microalbuminuria to overt nephropathy. More recently, trandolapril, an ACE inhibitor, has demonstrated its effectiveness to reduce the risk for progression from normoalbuminuria to microalbuminuria in hypertensive type 2 diabetic patients, thus affording primary prevention for diabetic nephropathy with ACE inhibition [22].

A detailed description of all large studies that have firmly established the antiproteinuric and renoprotective effects of ACE inhibitors and ARA in proteinuric diabetic and nondiabetic nephropathies is beyond the scope of this review, but the following remarks, shared by all these studies, are worth underlining, given their importance for clinical practice. (1) The renoprotection induced by these drugs is closely related to their antiproteinuric effect. (2) The reduction in proteinuria induced by ACE inhibitors and ARA is already observed in the first weeks of treatment. (3) Their antiproteinuric effect is largely independent of their blood pressure-lowering action. (4) Reduction in proteinuria is a dose-dependent effect of both ACE inhibitors and ARA. (5) The antiproteinuric and renoprotective properties of these drugs appear to be shared by all ACE inhibitors and ARA so far tested. (6) Although there are very few comparative studies [23], the antiproteinuric and renoprotective efficacy of ACE inhibitors and ARA appear to be similar.

These common properties indicate that, when an ACE inhibitor or an ARA is prescribed for patients with proteinuric nephropathies, the level of proteinuria or albuminuria is the most appropriate marker of their therapeutic effectiveness. In the case of poor reductions in proteinuria, the dose of the selected agent should be progressively increased; if proteinuria remains unacceptable high after reaching the highest therapeutic doses, clinical factors that can reduce the antiproteinuric properties of ACE inhibitors and ARA (see later in this article) should be investigated and treated. The following step, according to recent studies, should probably be the combined blockade of RAAS at different levels (see later in this article).

Another fundamental concept, raised by several landmark studies in recent years, consists of the significant decrease of cardiovascular events among high-risk patients (diabetic patients, patients with ischemic heart disease or peripheral vascular disease) treated with ACE inhibitors [24]. Considering that recent investigations have clearly concluded that the presence of renal insufficiency is a significant risk factor for the development of cardiovascular events [25], the cardiovascular protection given by RAAS blockade is of paramount importance for patients receiving these drugs in the setting of proteinuric renal diseases.

OTHER RAAS BLOCKADE: ALDOSTERONE AND RENIN ANTAGONISTS

Several experimental studies have shown that aldosterone, the final step in the process of RAAS activation, is a potent inducer of endothelial dysfunction and stimulates inflammation and fibrosis in the renal and cardiac interstitium. Aldosterone antagonists counteract renal damage in several experimental models of renal disease, and spironolactone has demonstrated a significant beneficial effect in patients with congestive heart failure already treated with ACE inhibitors [26]. Some clinical studies have shown that spironolactone reduces proteinuria in diabetic and nondiabetic nephropathies, and in a recent comparative study, reduction in proteinuria by spironolactone was higher than the reduction by enalapril [27]. Similar preliminary results have been obtained with eplerenone, another aldosterone antagonist, which induces an important reduction in microalbuminuria in diabetic patients [28].

The possibility to block RAAS at its initial steps has emerged with a renewed interest after the synthesis of renin inhibitors available for oral administration [29]. Although these drugs offer a powerful antihypertensive efficacy, future research must address whether they share the antiproteinuric and renoprotective properties of other RAAS blockers.
COMBINED RAAS BLOCKADE

The possibility that combined RAAS blockade, mainly through the simultaneous administration of an ACE inhibitor and an ARA, would offer a stronger antiproteinuric and renoprotective effect than either drug alone was first suggested by experimental studies and clinical trials involving a small number of patients. However, the growing number of these studies, almost all confirming the superiority of combined therapy, prompted the design and performance of large trials. One of them enrolled 263 patients with nondiabetic renal diseases. These patients were randomly assigned to treatment with losartan, trandolapril, or a combination of both drugs at half doses. Reduction in proteinuria was significantly higher in patients receiving the combination therapy, and the number of patients in this group who reached the primary end point (doubling of serum creatinine or end-stage renal disease) was significantly lower than in the other two groups: 11% versus 23% and 23%. No differences in blood pressure that could have influenced these striking results were observed between the groups [30]. Other clinical studies have shown that combination therapy with an ACE inhibitor and ARA also offers increased proteinuria reduction in diabetic nephropathy [31], and large multicenter studies are currently in progress to confirm these findings and answer the crucial question of a possible better renoprotection afforded by combination ACE inhibitors and ARA in diabetic patients.

In a theoretical point of view, there are several physiologic reasons to explain the superiority of combined ACE inhibition and ARA therapy over either drug alone [32]. ACE inhibitors block the conversion of angiotensin I to angiotensin II, but ACE inhibition alone does not provide a complete blockade of the RAAS. Angiotensin II can be generated from angiotensin I by enzymes other than ACE, such as chymase and other serine proteases. Some studies have estimated that almost 40% of angiotensin I is converted to angiotensin II by enzymes other than ACE, particularly in pathological conditions. Considering these ACE-independent pathways of angiotensin II generation, ARA should be more effective than ACE to counteract the deleterious effects of angiotensin II, directly inhibiting the binding of angiotensin II to AT1 receptors. In addition, ARA can lead to an augmented stimulation of AT2 receptors that induce vasodilatation and decrease cellular proliferation. Nevertheless, ACE inhibition has several specific beneficial effects not shared by ARA. It increases the plasma levels of bradykinin and other substances catabolized by ACE, such as N-acetyl-seryl-aspartyl-lysyl-proline, which possesses strong antifibrotic properties [33].

The complex structure of the RAAS offers the possibility of combined blockade at other levels. Thus, some investigators have shown that the combination of an ACE inhibitor and an aldosterone antagonist offers a stronger antiproteinuric effect than either drug alone [27]. However, in contrast with the remarkable high tolerance to the combination ACE inhibitor and ARA [30], the combined use of ACE inhibitors and aldosterone antagonist carries a very serious risk of hyperkalemia [27, 34].

THERAPEUTIC MEASURES THAT ENHANCE THE ANTIPROTEINURIC AND RENOPROTECTIVE EFFECT OF RAAS BLOCKADE

Since publication of the results of the Modification of Diet in Renal Disease study [35], it is generally agreed that blood pressure control should be targeted to values lower than 130/80 mm Hg in patients with proteinuric renal diseases. For the reasons summarized above, the basis of antihypertensive treatment should consist of drugs that block the RAAS. However, many patients will need the addition of more antihypertensive drugs, which should be selected according to individual patient characteristics. It is generally agreed that antihypertensive drugs other than ACE inhibitors and ARA do not possess specific antiproteinuric properties, but lowering of blood pressure by itself decreases proteinuria in a nonspecific manner. Some authors have suggested that nondihydropyridine calcium-channel blockers could have a specific antiproteinuric effect, mainly in patients with hypertension associated with type 2 diabetes [36]. However, other studies have contradicted these results [37]. Another therapeutic measure that would enhance the antiproteinuric properties of RAAS blockade is protein restriction [38], although this measure is usually restricted to patients with moderate-to-severe degrees of chronic renal insufficiency. The Modification of Diet in Renal Disease study also demonstrated the antiproteinuric effect of protein restriction [35]. Salt restriction and diuretics could also potentiate the reduction in proteinuria induced by ACE inhibitors and ARA [39].

TREATMENT OF HYPERLIPIDEMIA

Despite the compelling experimental studies that have shown an important role of hyperlipidemia in the progression of renal diseases, most clinical studies failed to demonstrate a significant antiproteinuric effect of statins or other lipid-lowering agents. However, a meta-analysis of previously published trials concluded that treatment of hyperlipidemia induces a significant reduction in proteinuria and slows the progression of renal diseases in comparison with nontreated patients [40]. A recent study has shown that treatment with atorvastatin in addition to a regimen of ACE inhibitors or ARA may reduce
proteinuria and the rate of progression of kidney disease in patients with hypercholesterolemia [41].

SMOKING
Given the obvious ethical implications precluding the performance of prospective, controlled studies, retrospective data are of enormous importance, because they show that smoking causes devastating effects in patients with chronic proteinuric renal diseases [42]. Epidemiologic studies have shown that smoking is a significant risk factor for the detection of proteinuria and microalbuminuria in otherwise healthy people [43].

WEIGHT LOSS: IMPROVEMENT OF INSULIN SENSITIVITY
Obesity is a recognized cause of proteinuria and focal glomerulosclerosis [44], and recent studies have shown a worrying growth of obesity-related glomerulopathies, in parallel with the global epidemic of obesity affecting modern societies [45]. Our group showed that both weight loss induced by low-calorie diets and ACE inhibition drastically decrease the level of proteinuria in patients with obesity-related proteinuria [46]. In addition, we have shown that weight loss induces a significant proteinuria decrease in patients with chronic proteinuric nephropathies of different causes (including diabetic nephropathy and chronic glomerulonephritis), where patients who are considered overweight have a body mass index > 27 kg/m². In this study, weight loss was moderate (averaging 4.1% ± 3% at the end of the 5-month study), but the effect on the level of proteinuria was striking: a 31% ± 37% reduction in baseline values was found. Furthermore, decrease in proteinuria and weight loss exhibited a significant correlation: restricting the analysis to those patients who lost more than 3% of baseline weight, a proteinuria reduction of 50% ± 21% from baseline values was observed [47]. All these data indicate that weight loss is a strong antiproteinuric measure, not only in patients with obesity-induced proteinuria, but also in overweight patients with any type of diabetic or nondiabetic proteinuric renal disease. The fact that most patients with type 2 diabetic nephropathy are obese reinforces the significance of these observations.

Abdominal fat expresses higher levels of RAAS components and is the main component of the metabolic syndrome; in turn, patients with metabolic syndrome are at a high risk of developing albuminuria, proteinuria, and chronic renal insufficiency [48]. Insulin resistance is a crucial pathogenic event in the metabolic syndrome; in this setting, clinical observation showing a significant reduction in microalbuminuria with peroxisome proliferator-activated receptor γ agonists, drugs that improve sensitivity to insulin, are particularly interesting [49].

FUTURE PERSPECTIVES
A milestone in the investigation of proteinuric renal diseases has been the cloning and localization of several proteins (nephrin, podocin, CD2AP, and others) that are essential constituents of podocyte slit diaphragms [50]. Mutations in the genes coding for these proteins cause different types of childhood nephrotic syndrome. Moreover, recent investigations have demonstrated that the expression of these podocyte proteins is markedly reduced in any type of proteinuric renal disease, whatever the cause [51]. Interestingly, blockade of RAAS with both ACE inhibitors and ARA restores the expression of these proteins, almost to normality, in experimental models of proteinuria [52]. It is likely that the discovery of these slit-diaphragm proteins will deepen our understanding of the pathogenesis of proteinuric nephropathies and of the mechanisms of many current antiproteinuric measures, as well as inspire future therapeutic avenues.

Reprint requests to Dr. Manuel Praga, Servicio de Nefrología, Avda de Córdoba s/n, Hospital 12 de Octubre, 28041 Madrid, Spain. E-mail: mpragaf@senefro.org

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