

EDITORIALS

Targeting Proteinuria as a Valid Surrogate for Individualized Kidney Protective Therapy

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The presence of protein in the urine is a strong indicator that a patient is likely to experience progressive kidney function decline. A patient with proteinuria, even in the setting of a relatively normal glomerular filtration rate (GFR), has a high chance of showing a steep progressive slope of GFR loss compared to a patient with low or no urinary protein excretion. Importantly, treatment of patients with medications that reduce proteinuria appears to be associated with protection against GFR decline.¹⁻⁵ Therefore, proteinuria has been advocated not only as a renal risk marker, but also as a target for treatment.⁶

That proteinuria is a risk marker for renal outcome, independent of other risk factors, is widely accepted. However, the question of whether proteinuria truly is an independent therapeutic target for reducing progressive kidney function loss remains under debate. Clearly, therapy that reduces proteinuria is associated with renal protection, and, interestingly, the more one lowers proteinuria in an individual patient the better the patient is protected against further kidney function loss and eventual kidney failure.^{7,8} However, currently used renoprotective therapies were not designed to be antiproteinuric; rather they were developed to address other kidney disease risk factors—most notably hypertension—and the ability of these medications to reduce proteinuria was discovered as a “side effect”. Of all the antihypertensive medications, drugs that intervene in the renin-angiotensin-

aldosterone system are best known for their antiproteinuric effect; these include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and renin inhibitors.⁹⁻¹² Several large clinical trials using hard end points that include substantial kidney function decline and development of kidney failure have shown that intervention in the renin-angiotensin system subsequently protects kidney function.¹⁻⁵ Interestingly, this protection was associated with reduction in proteinuria, and, importantly, the reduction in proteinuria observed in the first months of treatment was associated with long-term kidney function protection.¹³⁻¹⁵ These findings are supported by Eijkelkamp et al, who recently showed that the initial antiproteinuric effect of an ARB is associated with kidney protection completely independently from the effect of the ARB on blood pressure. Even in individuals in whom use of an ARB was associated with a rise in blood pressure, ARB use remained renoprotective as long as proteinuria was reduced.¹⁶ However, since these studies were not prospectively designed to isolate the antiproteinuric renoprotective effect from the antihypertensive renoprotective effect, there is still no hard evidence that proteinuria should be targeted for treatment.

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For proteinuria to become a target of treatment, one needs to establish that proteinuria is an independent cause of progressive kidney function loss. In addition, one needs to find a therapy that reduces proteinuria without affecting any other risk factor for kidney function decline. In this respect Szeto et al describe a very interesting finding in their article in this issue of *AJKD*.¹⁷ They show that oral calcitriol reduces proteinuria in patients with IgA nephropathy in the absence of a significant change in blood pressure or kidney function. There was a simultaneous reduction in serum transforming growth factor β (TGF- β) levels, correlating with the reduction in proteinuria. Although the study was performed in only 10 patients, this finding may be of marked importance for the future treatment of patients with progressive kidney function loss.

The current renoprotective treatment of patients with diabetic and nondiabetic nephropathy has reduced the risk of developing end-stage renal disease (ESRD); however, the residual risk remains high. Although studies using ACE inhibitors and ARBs in individuals at high risk for kidney failure, including the Collaborative Study Group, the Ramipril Efficacy in Nephropathy (REIN) study, the Reduction of End Points in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and the African American Study of Kidney Disease and Hypertension (AASK) have all shown a significant risk reduction in hard kidney outcomes (50% decline in GFR or doubling of serum creatinine, development of ESRD), the remaining absolute risk of these end points in these high-risk individuals remained between 25% and 50% within 3 years.¹⁻⁵ In all of these trials, high blood pressure was the target of treatment, and thus blood pressure control had a marked emphasis in the planned treatment regimens. Most (if not all) methods for blood pressure lowering were used to achieve preestablished blood pressure targets; accordingly, chances of further renal risk reduction by further decrease of blood pressure appear to be slim. On the other hand, proteinuria was never a target in any of these trials, and, when examined, these trials show that the degree of proteinuria reduction was associated with renoprotection. Thus, optimization of the antiproteinuric effect

might be a means to obtain further kidney protection.

What are the current possibilities to further reduce proteinuria? ACE inhibitors, followed by ARBs, have proven antiproteinuric effects, which are enhanced with dose escalation. Notably, administering ACE inhibitors and ARBs at doses far beyond their blood pressure lowering effect still offers increasing proteinuria reduction.^{18,19} Furthermore, the antiproteinuric effect of these medications may be enhanced by adding a diuretic to the medication regimen.²⁰ Restriction of dietary sodium intake has a similar effect,²¹ and, interestingly, combining low sodium intake and diuretic use with ACE inhibition further reduces proteinuria.²² Finally, the combination of an ACE inhibitor and an ARB not only further lowers proteinuria²³ but also appears to protect the kidneys in patients with nondiabetic renal disease,²⁴ although the latter study still requires confirmation.

Notably, all the measures described above not only improve proteinuria but also reduce blood pressure. Are there any antiproteinuric measures that have no impact on blood pressure? Agarwal et al showed that paricalcitol has an antiproteinuric effect.²⁵ Although this study was not prospectively designed to evaluate proteinuria, it was the first to show a clinical effect of a vitamin D analogue on proteinuria; this has now been confirmed in a prospective study by Szeto et al,¹⁷ where the antiproteinuric effect of the vitamin D analog calcitriol was demonstrated in the setting of concurrent ACE inhibitor or ARB treatment. However, as Szeto et al only evaluated 10 individuals in this study, larger studies will need to confirm their finding. The Selective Vitamin D Receptor Activator (Paricalcitol) for Albuminuria Lowering Study (VITAL) is such a larger ongoing study.²⁶ Of note, there are several other antiproteinuric measures that demonstrate no blood pressure lowering effect; these include low-protein diets, nonsteroidal anti-inflammatory drugs like indomethacin, and sulodexide, a glycosaminoglycan that may reduce proteinuria through effects on the glomerular basement membrane. These measures have an antiproteinuric effect by themselves and in conjunction with ACE inhibitor or ARB treatment.²⁷⁻²⁹

The unanswered question remains: Are any of the above additive measures to lower protein-

uria, in particular the ones that have no effect on blood pressure, of substantial use in further lowering the risk of progressive kidney disease? If this is true, we will have a breakthrough in the treatment of renal disease. In fact, if a treatment directed to only lower the proteinuria renders additional kidney protection to currently recommended therapies, this will imply that proteinuria should be a target of treatment for optimal kidney protection. However, there are only limited prospects at this time for trials to demonstrate efficacy of these interventions. Further trials evaluating low-protein diets promise to be interesting; however, a repeat of the Modification of Diet in Renal Disease (MDRD) Study is not expected. Trials using nonsteroidal anti-inflammatory drugs are not expected either, given the adverse effects of this class of medications on kidney function. The first large hard end point study that may give an answer is the Sulodexide Trial in Diabetic Nephropathy.³⁰ However, evidence from Agarwal et al and Szeto et al suggest that it should not be long before somebody will take the initiative to start a large, hard end point trial using a vitamin D analogue.

Finally, a major challenge for the future is not only to test which drugs synergize in their antiproteinuric effect, but also to assess the best combination of drugs in individual patients. From treatment of high blood pressure we should have learned that each person has an individual response to different antihypertensive drugs and their combinations. For proteinuria reduction one observes something similar, as not every patient responds equally well to ACE inhibitor or ARB therapy. The response may vary from a nearly 100% fall in proteinuria to a rise in proteinuria, with the average being a 50% decrease.³¹ The same holds true for non-blood-pressure-lowering antiproteinuric therapies such as a low-protein diet, nonsteroidal anti-inflammatory drugs, and sulodexide. Szeto et al showed that oral calcitriol is similar in this respect; some patients show a rise, some a modest drop, and some a distinct fall in proteinuria. This pattern is supported by Eijkelkamp et al, who showed that the antiproteinuric response variation to ARB treatment differs from the antihypertensive variation as some individuals without a blood pressure response experienced a marked lowering of proteinuria and vice versa.¹⁶ Given the fact that

some individuals show a good antiproteinuric response to a drug whereas others show no effect at all, we must ask if it is possible to turn a nonresponder into a responder? Bos et al showed that a nonresponder to ACE inhibitor therapy remains a nonresponder to ARB therapy.³¹ However, will a nonresponder to ACE inhibitor or ARB therapy have reduced proteinuria with sulodexide or vitamin D analogues? And what will happen if we combine sulodexide with vitamin D analogs? These are several of the major questions and challenges for the coming decade(s). While it will take some time before we can answer these questions with hard end point studies, if we could come to an understanding that proteinuria, like hypertension, is a valid surrogate for hard kidney outcomes, we will be able to considerably reduce the time before we develop optimal individual renoprotective treatment strategies.

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