Proteinuria as a Therapeutic Target in Patients with Chronic Kidney Disease

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I. Introduction

Preserving renal function is of paramount importance in the management of patients with chronic kidney disease. Current guidelines suggest lowering blood pressure to <130/80 mmHg with a regimen containing a renin-angiotensin system blocker is an important part of this strategy. In patients who meet these guidelines, it would be useful to have a readily measurable marker confirming that existing therapy is indeed optimal for long term renal preservation. Should evidence suggest otherwise, this marker could also serve as a guide for the implementation and titration of additional strategies designed to maximize renoprotection. The measurement of urinary protein excretion has emerged as a useful tool for this purpose. Patients excreting large amounts of urinary protein who are otherwise deemed to be optimally treated should still be considered at high risk for renal disease progression. Additional measures that decrease urinary protein excretion will reduce this risk. Maximal reduction in urinary protein excretion should be a therapeutic goal in the overall strategy to preserve renal function in patients with proteinuric chronic kidney disease.

The magnitude of proteinuria is strongly associated with renal outcomes in patients with chronic kidney disease due to a wide variety of causes. Proteinuria can be viewed as a marker of glomerular disease with increasing amounts of urinary protein reflecting a greater degree of glomerular injury. In addition, proteinuria has been shown to play a more direct role in renal disease progression by causing tubular injury as it passes down the lumen [1]. Tubular epithelial cells exposed to plasma proteins release a variety of chemoattractants, pro-inflammatory cytokines, and extracellular matrix proteins all of which can result in interstitial inflammation and fibrosis. Proteinuria may provide a link for development of tubulointerstitial disease in settings where the pathologic process primarily is directed toward the glomerulus [2].

The idea that proteinuria is both a marker and mechanism of renal disease progression is supported by observations demonstrating the degree to which proteinuria is reduced following initiation of therapy is predictive of long term outcome. In the Modification of Diet in Renal Disease (MDRD) study a tight association was found between the decrease in proteinuria and decreased rate of decline in glomerular filtration rate in the low blood pressure group [3]. For every 1 gm/d reduction in proteinuria at 4 months the subsequent decline in glomerular filtration rate was slowed by 1 ml/min/year. Similar results were found in the Ramapril Efficacy In Nephropathy (REIN) study where for every 1.0 gm/d reduction in proteinuria at 3 months of ACE inhibitor treatment the decline in glomerular filtration rate adjusted for the baseline value slowed by 2.0 ml/min/year [4,5]. A reduction in albuminuria was the single most important predictor of preserved renal function in the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study. For each 50% decrease in urinary albumin excretion in the first 6 months the risk for end-stage renal disease was decreased by 45% [6].

While the degree to which proteinuria declines in response to therapy is associated with a favorable effect on renal disease outcomes, the magnitude of proteinuria that remains is

also proportionally associated with renal risk. In a meta-analysis of 1860 patients with non-diabetic renal disease for each 1.0 gm/d of protein remaining after treatment initiation the risk of renal disease progression was increased more than five fold [7]. In the RENAAL trial, the quantity of remaining proteinuria during treatment at 6 months was strongly associated with the subsequent rate of decline in renal function. This relationship was the same whether patients were receiving losartan or placebo suggesting additional suppression of proteinuria through other means could be of benefit [6].

The observation that reductions in urinary protein excretion in a graded fashion over a relatively short period of time correlate with long term preservation of renal function support the idea of using urinary protein excretion as a guide to implementation of renoprotective therapies. The association between residual proteinuria and renal outcomes suggest that minimization of proteinuria is an important therapeutic goal in the management of proteinuric chronic kidney disease patients. In addition to being a marker of renal risk, treatment induced reductions in proteinuria also correlate with a reduction in cardiovascular risk. For each 50% reduction in albuminuria in the RENNAL trial there was an 18% reduction in cardiovascular risk and a 27% reduction in the risk for heart failure [8].

II. Monitoring urine protein excretion

The upper limit of normal for total urinary protein excretion is 150 mg/24 hours. The majority of this protein consists of systemically derived small molecular weight proteins filtered by the glomerulus and proteins derived from the renal tubules and lower urinary tract. The normal amount of albumin excretion is less that 30 mg/d (<20 μg/min). Persistent albumin excretion between 30 and 300 mg/d (20-200 μg/min) is considered microalbuminuria. Values >300 mg/d are considered overt proteinuria or macroalbuminuria. At this level of excretion the standard urinary dipstick is positive and the bulk of urinary protein excretion is composed of albumin.

A variety of collection methods have been utilized for the measurement of urinary albumin excretion (Table 1). Timed collections, either overnight (8-12h) or 24 hours, are the most sensitive assays. Since precisely timed urine collections are often impractical and inconvenient for many patients, the preferred method of measurement is to obtain a spot urine albumin:creatinine ratio. Preferably, this ratio should be measured from values obtained from a first morning urine sample otherwise a random sample may be used. Semiquantitative dipsticks specific for albumin are available, however, are subject to error as a result of variations in urine concentration caused by hydration status. The relatively constant excretion of creatinine throughout the day enables the abumin:creatinine ratio to overcome this limitation.

The total protein:creatinine ratio will give similar results and can be substituted for the albumin:ceatinine ratio in patients with an albumin:creatinine ratio of >500 to 1000 mg/g which corresponds to >500 to 1000 mg/day. However, the albumin:creatinine ratio should be used in the initial quantification of urinary protein excretion because albumin is

a more sensitive marker than total protein in the early stages of chronic kidney disease due to diabetes, hypertension and glomerular diseases. The total protein:creatinine ratio may be within normal limits even though urinary albumin excretion has crossed into the microalbuminuric range.

Table 1. Classification and measurement of urinary protein

	24 hour urine albumin (mg/24)	Timed overnight albumin (μg/min)	Spot albumin to creatinine ratio (mg/g)	Spot total protein to creatinine ratio (mg/mg)
Normal	<30	<20	<30	<0.15 (equivalent to <150 mg/24 hours#)
Microalbuminuria	30-300	20-200	30-300	<0.15 to 0.3*
Macroalbuminuria	>300	>200	>300	>0.3

There is a linear relationship between the total protein:creatinine ratio and 24 hour total protein excretion. For example, a ratio of 1.75 is predictive of 1750 mg total protein/24 h.
*The total protein:creatinine ratio can be normal (<0.15 or <150 mg/d) when albumin excretion is in the microalbuminuric range. Consider a patient with a 24 hour urine total protein excretion of 100 mg of which 10 mg is comprised of albumin. If albumin excretion increases to 50 mg/d the total 24 hour protein excretion will increase to 140 mg which is still within normal limits. Once urine albumin excretion exceeds 300 mg/24 h either the albumin:creatinine or the total protein:creatinine ratio can be used to monitor antiproteinuric therapy

III. Interventions to decrease urinary protein excretion

The antiproteinuric therapies summarized below have proven efficacy and are readily available for clinical use. Table 2 lists other drugs shown to reduce urinary protein excretion that are undergoing investigation in clinical trials.

Table 2. Drugs that reduce urinary protein excretion undergoing clinical trials

Endothelin A selective antagonist
Paricalcitol (vitamin D analog)
Sulodexide (glycosaminoglycan)
Pentoxifylline (Anti-TNF properties)
Ruboxistaurin (PKC β1 isoform inhibitor)
Dipyridamole (adenosine reuptake inhibitor)

A. Stringent blood pressure control

The initial step in reducing urinary protein excretion in chronic kidney disease patients is to establish and maintain stringent blood pressure control. Blood pressure reduction per se will exert an antiproteinuric effect even when accomplished with agents not typically deemed to be renoprotective. In an older study of hypertensive type I diabetics with nephropathy, a regimen of furosemide, hydralazine, and metoprolol reduced urinary protein excretion and provided a progressive reduction in the rate of renal function loss over the course of nine years of therapy [9]. Current guidelines suggest blood pressure should be lowered to <130/80 mmHg in patients with chronic kidney disease [10]. An even lower systolic pressure may be of benefit in slowing progressive renal disease in patients with a spot urine total protein:creatinine ratio of >0.5-1 mg/mg [3,7,11]. Those with lesser amounts of proteinuria derive no additional benefit. Irrespective of urinary protein excretion lowering of systolic blood pressure to <110 mmHg should be avoided as there may be a higher risk of kidney disease progression [12].

Blood pressure control should be centered around a renin-angiotensin system antagonist since these agents consistently demonstrate an antiproteinuric effect that is greater than what can be explained by blood pressure reduction alone. Either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker can be utilized for this purpose as there is no convincing evidence that one drug class exerts a greater antiproteinuric effect compared to the other at comparable doses and similarly controlled blood pressure. When blood pressure is not yet at goal a non-dihydropyridine calcium channel blockers should be considered since these agents will add to the antiproteinuric effect of renin-angiotensin blockers [13,14]. In a subgroup analysis of the Captopril Collaborative Multicenter Study 7/42 patients with nephrotic range proteinuria treated with captopril had remission of proteinuria as compared to 1/66 patients in the control group during the follow up period of 3.5 years [15]. In addition to treatment with the ACE inhibitor, those achieving a remission had a lower mean systolic blood pressure (126 mmHg vs 145 mmHg) suggesting a synergy between stringent blood pressure control and blockade of the renin-angiotensin system. The remission was sustained in most of the patients over a subsequent seven year follow up [16].

B. Restrict dietary sodium and use effective diuretic therapy

A high dietary sodium intake is associated with worsening urinary protein excretion whereas sodium restriction reduces proteinuria [17,18]. This antiproteinuric effect is likely the result of decreases in blood pressure but there is also evidence of favorable effects on renal hemodynamics [19,20]. Restricting dietary salt intake to 80-110 mmol/d is a useful goal. Compliance can be verified by measuring urinary sodium in a 24 hour urine collection.

Sodium restriction is of particular relevance for patients taking ACE inhibitors, angiotensin receptor blockers, and non-dihyropyridine calcium channel blockers since increased sodium intake can abolish the antiproteinuric effect of these drugs. By contrast, sodium restriction augments the antiproteinuric effect of these agents and to an extent

than cannot be accounted for by blood pressure reduction alone [21-23]. Effective diuretic therapy also enhances the antiproteinuric effect of renin-angiotensin blockers and can restore the antiproteinuric effect lost under conditions of high sodium intake [22,24]. Thiazide diuretics are useful for this purpose until the estimated glomerular filtration rate falls to <30 ml/min at which point loop diuretics should be utilized. A combination of salt restriction and effective diuretic therapy will reduce urinary protein excretion to a greater extent that either intervention alone.

C. Avoid high dietary protein intake

Dietary protein restriction exerts an antiproteinuric effect that is greatest in those with high baseline values of urinary protein and is additive to that of an angiotensin converting enzyme inhibitor [25,26]. This effect is associated with a slowing in the progression of chronic kidney disease particularly in those with diabetic nephropathy [27]. Protein intake of 0.8 gm/kg body weight is both effective and usually not accompanied by negative nitrogen balance. Compliance can be verified by measuring urea excretion in a 24 hour urine collection. High dietary protein intake can attenuate the antiproteinuric effect of renin-angiotensin blockade and should be avoided.

D. Use moderate to high doses of renin-angiotensin blockers

The Working Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) recommend that moderate to high doses of ACE inhibitors or angiotensin blockers be used in chronic kidney disease patients [28]. Higher doses of these agents generally exert greater antiproteinuric effects even when there is no further change in systemic blood pressure. Although not yet recommended, small studies have employed supratherapeutic doses of angiotensin receptor blockers in an attempt to determine the ceiling at which no further reductions in urinary protein occur. Doses of up to 900 mg/d of irbesartan and 64 mg/d of candesartan provide further blood pressure independent drops in urinary protein excretion in the absence of significant side effects [29,30]. Supratherapeutic dosing of ACE inhibitors may not be feasible since historically such doses have been associated with toxicicty such as membranous glomerulonephropathy.

E. Combined use of Renin-Angiotensin-Aldosterone blockers

There are numerous small trials demonstrating an additive antiproteinuric effect of ACE inhibitors and angiotensin receptor blockers used together [31]. In many of these studies blood pressure is lower in the combination groups making it difficult to establish whether the benefit is due to the drug combination per se or simply better blood pressure control. In one long term study a combination of trandolapril and losartan reduced urinary protein excretion to a greater extent than either drug used alone and in a setting where reduction in blood pressure was similar [32]. Importantly renal function was better preserved in the combination group. It is not clear whether the combination of an ACE inhibitor and angiotensin receptor blocker is more renoprotective as compared to either of the individual agents used alone but at high doses. In patients with inadequate blood

pressure control the combination may be preferred so as to capitalize on the blood pressure lowering effect of the drugs. Limited evidence suggests the addition of spironolactone or eplerenone to either an ACE inhibitor or an angiotensin receptor blocker can further reduce urinary protein excretion and by an amount not accounted for by blood pressure reduction alone [33].

F. Statin therapy

Lipid lowering therapy with statins exerts an antiproteinuric effect. In a meta-analysis of 15 randomized trials involving 1384 patients statins reduced albuminuria by 48% and 47% in those with baseline albuminuria of between 30-299 mg/d and >300 mg/d respectively [34]. A previously published meta-analysis suggests this effect is accompanied by a significant decrease in the rate of renal function loss [35]. The antiproteinuric effect of statins is additive to that seen with renin-angiotensin blockers. The optimal dose for antiproteinuric therapy and whether or not there is a class effect has not been well studied.

G. Discontinue cigarette smoking

Smoking is associated with a worsening of urinary protein excretion and faster progression of chronic kidney disease of all types [36]. Epidemiologic studies have identified smoking as a risk factor for the development of microalbuminuria in otherwise healthy individuals.

H. Weight loss

Increase body mass index is an independent risk factor for the development of chronic kidney disease [37]. Obesity is accompanied by changes in renal hemodynamics that give rise to increased intraglomerular pressure possibly accounting for the higher risk of focal and segmental glomerulosclerosis. Weight reduction leads to improvements in renal hemodynamics and is accompanied by a decrease in urinary protein excretion [38].

IV. Implementation of Antiproteinuric Therapy

The K/DOQI working group recommends reducing proteinuria as a goal of therapy in both diabetic and nondiabetic chronic kidney disease patients with a spot urine total protein/creatinine >0.5-1 mg/mg [28]. It is reasonable to monitor urinary protein excretion on a three to six month basis after having established a baseline value. The initial value allows one to determine the current risk for renal disease progression and the need for implementation of antiproteinuric therapies. Subsequent measurements gauge the effectiveness of the therapy employed as well as guide further titration when needed (Table 3).

While a reasonable goal of therapy is a total protein:creatinine ratio of <0.5 mg/mg, remission of proteinuria is achievable even in patients otherwise considered to have irreversible and progressive chronic kidney disease. In prospective cohort studies from

the Steno Diabetes Center, remission of nephrotic range proteinuria was induced in 28 of 126 (22%) type I diabetics and 20/79 (25%) type II diabetics with nephropathy (defined as albuminuria <600 mg/24h for at least 1 year) [41,42]. Most of these patients received ACE inhibitor therapy and those achieving remission had a significantly lower mean arterial blood pressure as compared to those without remission. The serum cholesterol was also lower in those achieving remission likely secondary to the reduction in proteinuria since use of lipid lowering drugs was similar to that in the non-remission group. Remission was associated with a risk reduction of 67% for reaching the composite end point of end-stage renal disease and death and of 69% for death alone. In both studies there was no effort to restrict dietary sodium or protein and only a minority of subjects received statins. In addition, >50% of subjects were smokers [43]. It is possible that an even greater remission rate may have been achieved had greater attention been paid to these other antiproteinuric strategies.

Therapies titrated to urinary protein excretion can be a useful adjunct in patients with readily treated conditions such as lupus nephritis and various other glomerular diseases [44,45]. In the absence of active immunologic injury this strategy has been shown to cause remission and in some instances normalization of what was initially nephrotic range proteinuria.

Table 3. Clinically available strategies to lower urinary protein excretion*

- Lower systolic blood pressure to between 110-130 mmHg systolic (avoid systolic pressures <110 mmHg)#
- Pharmacologic therapy should be centered around use of ACE inhibitor or angiotensin receptor blocker
- Restrict dietary dietary sodium to <5 gm/d
- Restrict dietary protein to 0.8 gm/kg body weight
- Use effective diuretic therapy (loop diuretics required when estimated glomerular filtration rate <30 ml/min)
- Add non-dihydropyridine calcium channel blocker as a third agent after renin-angiotensin blocker and diuretic when blood pressure is not at goal
- Maximize dose of renin-angiotensin blocker
- Use a combination of ACE inhibitor and angiotensin receptor blocker **
- Add an aldosterone antagonist to either ACE inhibitor or angiotensin receptor blocker but not both**
- Statin therapy: titrate dose to control LDL cholesterol according to guidelines. If not dyslipidemic use starting dose of preferred statin
- Discontinue smoking
- Weight loss

* The sequence in which various strategies are instituted will vary according to the medications the patient is taking at the time antiproteinuric therapy is initiated.
# Stringent blood pressure control can be associated with an increase in the serum creatinine concentration. A 30% increase over the baseline value that is stable thereafter does not reflect structural injury to the kidney but rather is a functional change reflecting

favorable effects on renal hemodynamics and in particular a lowering of intraglomerular pressure [39].

** The serum potassium should be checked within 1-2 weeks of starting an ACE inhibitor or an angiotensin receptor blocker or when using these drugs in combination in chronic kidney disease patients. The risk of hyperkalemia is low when adding an aldosterone receptor blocker when renal function is normal but markedly increases with reductions in eGFR and should be avoided at an eGFR <30 ml/min. Steps to reduce the likelihood of hyperkalemia in the setting of renin-angiotensin-aldosterone blockade have been the subject of a recent review [40].

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