Protecting the kidneys in lupus nephritis

Kidney involvement is common in systemic lupus erythematosus. The inciting event in lupus nephritis is immune complex accumulation in the kidneys. While this immune process triggers kidney damage in systemic lupus erythematosus, hemodynamic and metabolic factors activated after this initial event promote chronic, progressive damage to the kidney. Systemic and intraglomerular hypertension, proteinuria, hyperlipidemia, hyperuricemia, uremic acidosis and vitamin D deficiency have all been found to contribute to the progression of kidney disease. The aim of renal protective therapies is to suppress these secondary factors and thereby retard the progression of kidney disease in both active and inactive glomerular disease with residual chronic kidney disease. This can be effectively accomplished through a combination of medications, dietary interventions and lifestyle changes. The aim of this article is to discuss nonimmune therapies that will help retard the progression of kidney disease in lupus nephritis.

KEYWORDS: glomerular disease ■ lupus ■ lupus nephritis ■ nephritis ■ proteinuria ■ renoprotection ■ SLE ■ systemic lupus erythematosus

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Kidney injury is common in systemic lupus erythematosus (SLE). The most common mechanism is immune complex accumulation within the kidneys, followed by infiltration of the kidney by T cells and macrophages, which induce the renal inflammation classified as lupus nephritis (LN) [1]. Unchecked, LN causes progressive kidney damage. This progression, however, is not related only to the immune complex accumulation. Indeed, there are now multiple lines of evidence that hemodynamic and metabolic factors (nonimmune mechanisms) are also important participants in the progression of LN. Furthermore, even when the immune process subsides, these hemodynamic and metabolic factors may continue to cause progressive kidney damage [2].

The aim of this article is to discuss these hemodynamic and metabolic mechanisms of kidney damage and how they can be mitigated. These therapies are often referred to collectively as 'kidney protective therapy'. In general, these therapies are also cardiovascular protective. Specifically, patients with SLE have a five- to six-fold increased risk for significant coronary events compared with the general population [3,4]. So, there are strong reasons to recommend, in LN management, the multiple risk factor interventions that constitute renal and cardioprotective therapy.

All of the recommended protective interventions have been validated in high-quality randomized trials. However, virtually all of these trials have been carried out in chronic kidney disease (CKD) cohorts that did not include LN. Nevertheless, it is widely believed that the outcomes of these CKD trials are relevant to the management of LN. The notion is that combining the anti-inflammatory/immunosuppressive therapies of LN with kidney protective therapies of CKD will result in greater nephron survival and reduce the risk that the LN patients will be left with chronically impaired kidney function (CKD).

There is now compelling evidence that CKD, even when mild, is a strong independent risk factor for increased all-cause mortality, particularly cardiovascular mortality. The need to avoid CKD is particularly strong in LN because generally SLE affects young adults. Thus, even though their LN may eventually be completely suppressed, patients left with CKD will have prolonged exposure to the cardiovascular risks associated with it. We suggest that the use of kidney protective therapies in LN, along with the immunosuppression/anti-inflammatory therapies, is essential to optimizing nephron survival and reducing cardiovascular risk.

CKD & progression

The Kidney Diseases Improving Global Outcomes (KDIGO) initiative defines CKD as kidney damage resulting in a glomerular filtration rate (GFR) less than 60 ml/min/1.73m^2 for 3 months or more regardless of the cause [5]. GFR can be estimated by equations such as the

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Modification of Diet in Renal Diseases (MDRD) or Cockcroft–Gault formula. Many clinical laboratories now include an estimated GFR calculated with MDRD with every creatinine measurement. Progression of renal disease refers to the continuous decline in GFR due to structural damage of the renal vasculature, tubules or interstitium [6].

In normal individuals GFR declines at a rate of 1 ml/min/year after 45 years of age (FIGURE 1) [6]. In patients with CKD, GFR declines progressively. The rate of decline is variable but in those with heavy proteinuria, rates of decline of 4–10 ml/min/year are usually seen [7,8]. Once the kidney has sustained a GFR loss of more than 50%, progression can occur, even if the primary disease is inactive [9]. This is often referred to as 'natural progression'. It is very important to slow natural progression as much as possible because even small improvements in the rate of GFR decline can result in large delays in the time to onset of end-stage renal disease (ESRD) (FIGURE 2). Histologically, the hallmarks of natural progression are glomerulosclerosis with increased glomerular extracellular matrix and obliteration of capillary lumina, and fibrosis of the renal interstitium, usually accompanied by tubular atrophy [10].

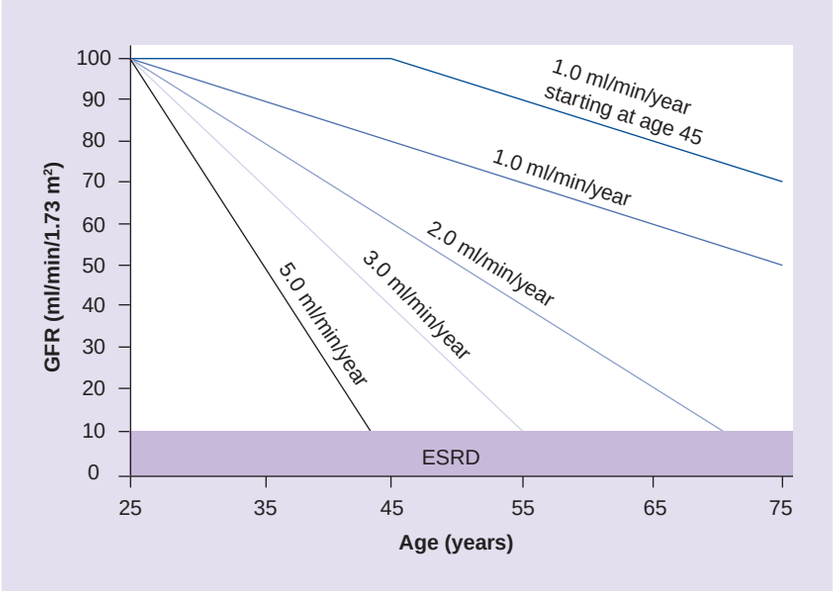

Figure 1. Rate of glomerular filtration rate decline in a normal and a hypothetical patient with onset of progressive renal disease at age 25.
The top curve represents GFR decline with normal aging and is based on a cross-sectional study of true GFR measurements in 357 patients aged 17–70 years old. GFR decline of >1 ml/min/year will lead to ESRD for the 25-year-old over a normal lifespan. Note that only a small difference in rate of GFR decline can result in large differences in time to onset of ESRD.
ESRD: End-stage renal disease; GFR: Glomerular filtration rate.
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Monitoring disease progression

The equations most commonly used to estimate serum creatinine-based GFR are the MDRD and Cockcroft–Gault equations. Both of these formulae are based on the serum creatinine level. They are most useful in alerting clinicians to the possibility of a diminished GFR in patients with a normal appearing serum creatinine value. This may be of particular value in lupus patients who are often young women. Such patients may have a very low serum creatinine at baseline, and with LN the creatinine may increase but remain within the 'normal' range for the clinical laboratory. This can give a misleading impression of preserved kidney function. In patients with an already abnormal serum creatinine, it is usually sufficient to monitor GFR trends by serial measurements of serum creatinine. There are certain circumstances where serum creatinine does not adequately reflect GFR sufficiently. In situations where creatinine production is increased (eating cooked meat, ingesting creatine, increased muscle mass or increased exercise), is decreased (vegetarian diet or muscle wasting) or tubular secretion of creatinine is inhibited (drugs e.g., cimetidine, trimethoprim or dronedarone) serum creatinine measurements will not accurately reflect GFR [11]. In these situations, monitoring can be done with an accurate 24-h urine collection for creatinine clearance.

In the near future it is likely that CKD-EPI will replace MDRD because of its greater accuracy in the GFR range of 60–90 ml/min/1.73 m^2 [12].

Risk factors for CKD progression

Proteinuria & CKD progression (evidence level high)

In chronic glomerular diseases, proteinuria is a major and modifiable risk factor for progression of kidney disease, and cardiovascular morbidity and mortality (FIGURE 3) [13]. Reducing urine protein excretion has been shown to preserve kidney function and decrease cardiovascular events [14,15]. In CKD, for every 1 g/day reduction in proteinuria after 4–6 months of antiproteinuric therapy, subsequent GFR decline was reduced by 1–2 ml/min/year [16].

Proteinuria is not only a biomarker of risk of kidney disease progression, but also a mechanism of progression [17,18]. Urine proteins other than albumin, such as iron transport proteins, lipoproteins and complement, are toxic to the tubules, can initiate inflammatory and redox reactions in the renal interstitium, and

thereby contribute to interstitial fibrosis [19]. Additionally, the proximal tubule catabolizes proteins in the urine, but if overloaded, such as in proteinuric glomerulonephritis, may be injured [20].

Given the importance of proteinuria as a risk factor and mediator of kidney damage, it is necessary to follow urine protein levels in patients with LN. To assess proteinuria we recommend that protein-to-creatinine (PC) ratios be measured in 24-h urine collections that are at least 50% complete based on their urine creatinine content [21,22]. This differs from current National Kidney Foundation-Kidney Disease Outcomes Quality Initiatives (KDOQI) guidelines that recommend random spot urine PC ratios for surveillance [23]. While random spot PC ratios are convenient, recent data suggest that for an individual patient, the concordance between a spot PC and a 24-h urine PC is poor [21,22]. Random spot PC ratios will equally underestimate and overestimate the level of proteinuria [22]. This is important as it may impact treatment decisions in patients with LN. The 24-h urine collection also permits monitoring of sodium and protein intake. Finally, in patients with glomerular disease, once there is overt proteinuria (e.g., 24-h urine PC ratio >0.3) there is no benefit in monitoring albuminuria because at that level of proteinuria, albumin constitutes 60–80% of total proteinuria [24]. The cost of measuring urine albumin is greater than that of total protein in the urine. So in those with overt proteinuria, it is more cost effective to monitor total proteinuria. However, in mild glomerular injury, monitoring albuminuria as microalbuminuria is the preferred method to monitor change. Current recommendations are to measure proteinuria every 2–3 months in patients with nephrotic range proteinuria, and every 6 months for subnephrotic proteinuria [11]. In patients with LN being treated with immunosuppression, proteinuria may need to be measured more frequently.

Blood pressure control (evidence level high)

Hypertension superimposed on kidney disease promotes arteriolar nephrosclerosis and renal disease progression. Progressive kidney disease makes blood pressure more difficult to control, leading to a vicious cycle [13]. Furthermore, hypertension directly affects the level of proteinuria because it raises intraglomerular pressure. As risk factors for progression, hypertension and proteinuria are linked, and control of blood pressure is one of the major tools used to control proteinuria (discussed later).

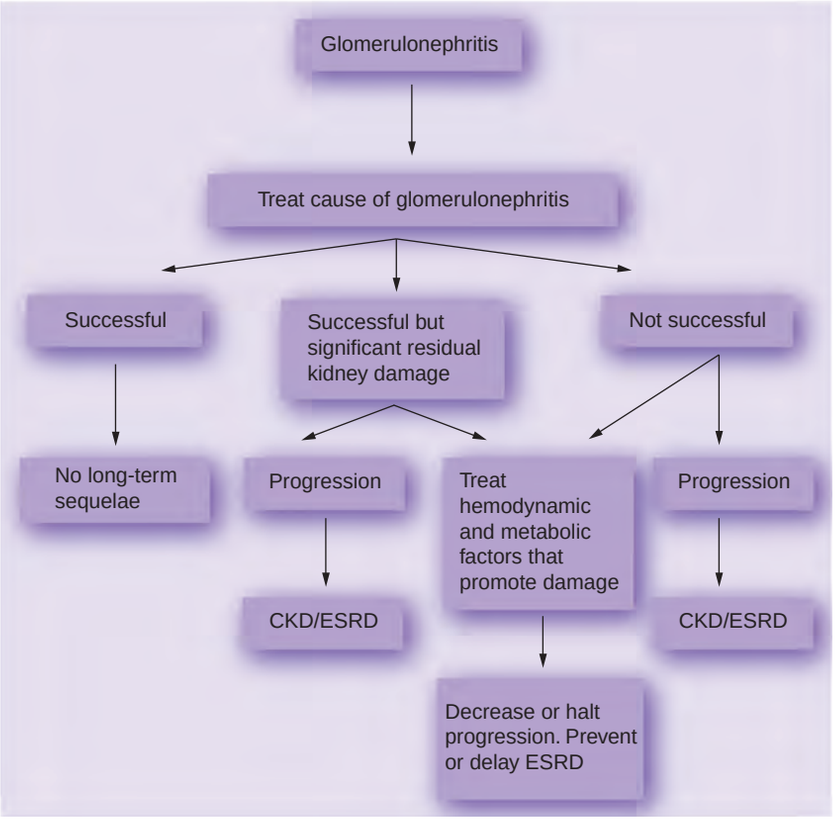

Figure 2. Possible outcomes in glomerular disease such as lupus nephritis.
CKD: Chronic kidney disease; ESRD: End-stage renal disease.

Hypertension is a modifiable risk factor, and several large clinical trials have confirmed the benefit of antihypertensive therapy in

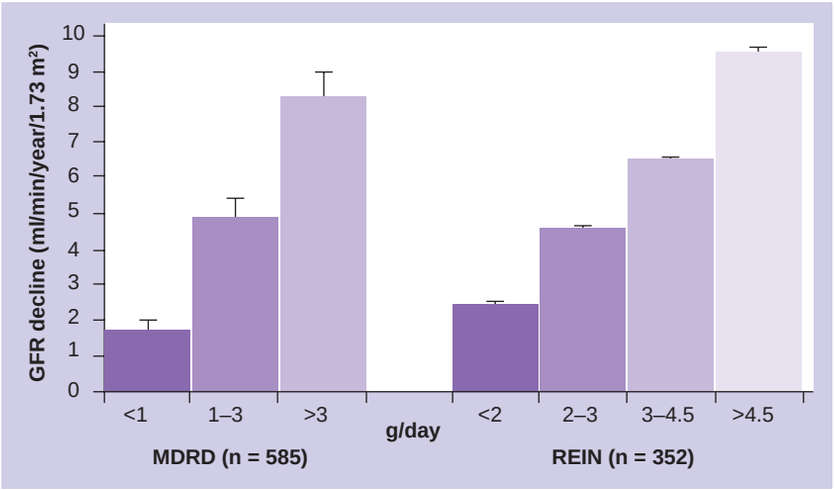

Figure 3. Relationship between baseline 24-h proteinuria and glomerular filtration rate decline during follow-up in the patients of the MDRD and REIN study.
GFR: Glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; REIN: Ramipril Efficacy in Nephropathy.

nondiabetic proteinuric kidney disease. The MDRD study looked at this in two cohorts. In the first cohort 585 patients with a mean GFR of 39 ml/min/1.73 m^2 were randomized to usual or low protein diets (1.3 vs 0.58 mg/kg/day, respectively), and usual or low blood pressure control (mean arterial pressure of 107 vs 92 mmHg, respectively). The benefit of aggressive blood pressure control was most pronounced in patients with greater than 3 g/day of proteinuria. Here, GFR decline was reduced from 10.2 to 6.7 ml/min/year. Preservation of GFR was more modest in patients with 1–3 g/day proteinuria and not seen in patients with less than 1 g/day of proteinuria [24]. MDRD cohort 2 evaluated a lower GFR group (13–24 ml/min/1.73 m^2) and found similar results [24]. The Ramipril Efficacy in Nephropathy (REIN) trial evaluated patients with nondiabetic proteinuric kidney disease with a baseline serum creatinine level of 2.4 mg/dl and mean proteinuria level of 5.3 g/day. Patients were randomized to ramipril or placebo plus another antihypertensive therapy to achieve a diastolic blood pressure of less than 90 mmHg. The trial was stopped prematurely in patients with proteinuria levels greater than 3.0 g/day due to an obvious benefit of angiotensin-converting enzyme (ACE) inhibition in delaying GFR reduction [25]. The benefits of ACE inhibition were also applicable in those with less severe proteinuria and varying levels of kidney dysfunction [25].

Evidence from the MDRD study helped define blood pressure targets for retarding progression of CKD. MDRD showed that control of blood pressure to less than 125/75 mmHg delayed progression to ESRD by 1.24 years [24,26]. This level of blood pressure control is also associated with reduced cardiovascular disease risk [27,28]. Systolic but not diastolic blood pressure was found to correlate with kidney disease progression in several trials [18,29].

Kidney protective therapies

The role of the renin–angiotensin–aldosterone system

The choice of antihypertensive agents to control blood pressure for kidney protection is crucial. The class of drug used to control blood pressure may directly affect the rate of disease progression. Protein excretion varies directly with intraglomerular pressure [30] and blockade of the renin–angiotensin–aldosterone system (RAAS) decreases efferent arteriolar tone, thus decreasing glomerular capillary hydrostatic pressure. The RAAS may also cause proteinuria by direct effects on podocytes [31]. Intrarenal activation of the RAAS mediates podocyte apoptosis via angiotensin receptor 1, and may affect nephrin expression, disrupting slit diaphragm integrity on podocytes causing a loss in the ability to restrict protein filtration [32,33]. Furthermore, angiotensin II has been found to promote glomerular cell proliferation, alter growth factor expression and activate proinflammatory cytokines all of which promote glomerulosclerosis [10,34]. In addition to decreasing proteinuria by decreasing blood pressure, RAAS inhibition mitigates the maladaptive changes triggered by angiotensin II and aldosterone in response to kidney damage. RAAS inhibition restores VEGF-A and angiopoeitin-1 activity, which restores podocyte health [10]. It also inhibits profibrotic factors activated by angiotensin II and aldosterone, such as plasminogen activator inhibitor-1 (PAI-1) and TGF-β (Figure 4) [35].

ACE inhibitor therapy

Because of the effects of RAAS suppression on blood pressure and glomerular structure and function, ACE inhibitors are considered first-line nonimmune therapy in proteinuric kidney diseases like LN. The first study to demonstrate the effect of ACE inhibitors was a prospective, placebo-controlled, randomized trial that evaluated Type 1 diabetics with overt nephropathy (urine albumin >500 mg/day), and showed a 43% reduction in doubling of serum creatinine, a 50% reduction in the combined end point of death, need for dialysis or transplantation, and a 30% reduction in proteinuria in patients treated with captopril versus placebo [36]. The REIN trial showed a 55% reduction in proteinuria and decreased risk of progression of CKD in patients treated with ramipril [25]. After controlling for the effects of blood pressure, the benefit of proteinuria reduction with ACE inhibitors persisted, suggesting that controlling proteinuria alone can slow CKD progression [25]. The African American Study of Kidney Disease (AASK) evaluated African–Americans with hypertensive kidney disease and baseline serum creatinine levels of 2.2 mg/dl with a mean proteinuria level of 600mg/day, and compared ramipril, amlodipine and metoprolol in mitigating progression of CKD. The ramipril-treated group had a 36% reduction in rate of GFR decline compared with the amlodipine-treated group, and a 22% reduction compared with the metoprolol-treated group [37]. Another study evaluated nondiabetics with CKD and

randomized patients to benazepril 20 mg/day or placebo. Patients were then classified as mild (GFR 46–60 ml/min/1.73 m^2) or moderate insufficiency (GFR 30–45 ml/min/1.73 m^2) with a mean proteinuria level of 1.8 g/day. The primary end point was doubling of serum creatinine or need for dialysis. Overall, the benazepril group had a 53% reduction in the primary end point (71% in the mild insufficiency group and 46% in the moderate insufficiency group) after 3 years of follow-up. There was a significant reduction in the rate of GFR decline and proteinuria. The benefits were most profound in patients with baseline proteinuria of greater than 1 g/day. Similar to other trials, the benefit of ACE inhibition could not be explained by blood pressure reduction alone [38].

There are studies suggesting ACE inhibitors do not have a unique benefit in delaying kidney disease progression beyond blood pressure control. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial concluded that lisinopril had no additional benefit compared with chlorthalidone or amlodipine in delaying CKD progression at the same level of blood pressure control [39]. However, in ALLHAT, the control group had lower blood pressure, which could have negated the effects of RAAS inhibition. Additionally, ALLHAT was a cardiovascular study in patients at low risk for CKD progression. A meta-analysis of several studies found no additional benefit of ACE inhibitors or angiotensin receptor blockers (ARBs) in reducing blood pressure or slowing progression of CKD [40]. This meta-analysis included heterogeneous studies that did not all use ACE inhibitor therapy optimally. It is possible that the intrinsic renoprotective effects of ACE inhibitors are not appreciated unless there is significant proteinuria (>1000 mg/day) or at least moderate kidney disease [24,25,36,38]. The data supporting RAAS inhibition with ACE inhibitors are strongest in patients with proteinuria levels greater than 1000 mg/day [24,25,38].

Recommendations

Based on current evidence we recommend using ACE inhibitors as first-line therapy for hypertension in patients with LN and proteinuria greater than 500 mg/day. Given the benefits of proteinuria reduction regardless of blood pressure, we also recommend using ACE inhibitors in normotensive LN patients at or above this level of proteinuria. In both cases the ACE inhibitor should be titrated to the maximum tolerated dose, as there is a dose-dependent increase in the antiproteinuric effect, and this will limit the risk of aldosterone escape (increasing aldosterone levels during ACE inhibitor therapy), which can attenuate the ACE inhibitor effect [41–43]. While there is no evidence to support one ACE inhibitor over another, it is reasonable to consider preferential use of benazepril and ramipril as they have longer half-lives and are strong inhibitors of tissue ACE [11]. Of note, the *ACE* gene is associated with the progression of kidney disease, and the *ACE* gene insertion/deletion polymorphism is thought to partially account for the individual variability in response to ACE inhibitors. Homozygotes for the insertion polymorphism have been found to have slower progression of nondiabetic proteinuric kidney disease and better response to ACE inhibitors when compared with those with the deletion polymorphism [44].

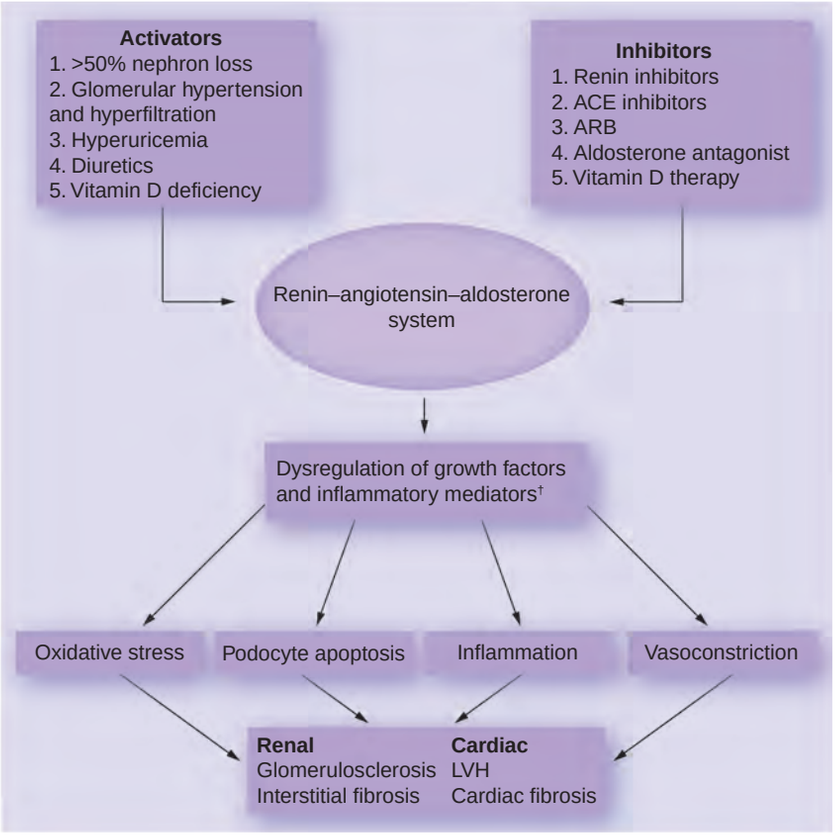

Figure 4. Effect of the renin–anigotensin–aldosterone system: activators and inhibitors. Activation of the renin–anigotensin–aldosterone system promotes renal and cardiac fibrosis. Inhibition of the renin–anigotensin–aldosterone system prevents this process.
†Upregulated factors: TGF-β, CTGF, PAI-1, MCP-1, RANTES, IL-8, IL-6, TNF-α; downregulated factors: nitric oxide, VEGF, angiopoeitin-1.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; LVH: Left ventricular hypertrophy; MCP: Monocyte chemoattractant protein; PAI: Plasminogen activator inhibitor.

A caveat to ACE inhibitor therapy is that the patient must be watched carefully for side effects and progressive rise in serum creatinine [45]. After initiation of ACE inhibitor therapy, an increase in serum creatinine may occur due to reduced filtration pressure from decreased efferent arteriolar tone. Up to a 30% increase in serum creatinine, if not progressive, is tolerable. Patients should be monitored for hyperkalemia, especially if they have advanced CKD. Finally, it is prudent to halt ACE inhibitor or ARB treatment if the patient has developed acute kidney injury for any reason, and 48 h before major surgery or iodinated contrast procedures.

Angiotensin receptor blocker

While the action of ARBs appears to be similar to ACE inhibitors, there are some important differences. First, ARBs act on the angiotensin 1a receptor in the kidney, inhibiting the effects of angiotensin II and thus do not increase bradykinin and have less effect on aldosterone [16,46]. Furthermore, it is not yet clear if ARBs provide equivalent cardioprotection as ACE inhibitors [47]. ARBs have been shown to be renoprotective in patients with Type 2 diabetes and nephropathy [48,49]. Two large, placebo-controlled, randomized clinical trials, the Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trial, demonstrated that ARBs may have renoprotective effects beyond blood pressure control, similar to ACE inhibitors. The RENAAL trial evaluated 1513 patients with Type 2 diabetes, a mean serum creatinine of 1.9 mg/dl and over 1 g of albuminuria who were treated with conventional antihypertensive therapy and placebo or losartan. The losartan group had a 16% reduction in the composite primary end point of doubling of serum creatinine, progression to ESRD or death, a 35% reduction in the urine albumin:creatinine ratio and a 15% decrease in rate of GFR decline [48]. The trial also showed that for every 50% reduction in proteinuria in the first 6 months of therapy, there was a 36% risk reduction in the primary end point. The renoprotective effect of losartan was attributed to its antiproteinuric effect and not the effect of blood pressure control [48]. The IDNT trial evaluated 1715 Type 2 diabetes mellitus patients with a mean serum creatinine level of 1.7 mg/dl and a median of approximately 3 g of proteinuria. Treatment with irbesartan deduced a 20% reduction compared with placebo and a 23% reduction compared with amlodipine in the composite primary end points (doubling of serum creatinine, progression to ESRD or death) [49]. Proteinuria decreased by 33% in the irbesartan group versus 6% in the amlodpine group and 10% in the placebo group. The superior renoprotective effects of irbesartan could not be attributed to blood pressure control alone [49].

Recommendations

Considering this evidence, ARBs may be used as a first alternative to individuals intolerant of ACE inhibitors. Those with the *ACE* gene deletion allele have higher levels of systemic and tissue ACE and therefore higher levels of angiotensin II. Contrary to ACE inhibitors, ARBs have been shown to be more effective in reducing risk of all renal end points in patients homozygous for the deletion polymorphism when compared with the insertion polymorphism [44]. A caveat to the use of ARBs is that the major trials evaluating ARBs were in diabetic but not nondiabetic glomerulopathy. As with ACE inhibitors, patients should be monitored closely for side effects such as hyperkalemia and increases in serum creatinine while on ARB therapy. A nonprogressive increase in serum creatinine of up to 30% is tolerable.

Combination ACE inhibitor plus ARB therapy

The addition of an ARB to a ACE inhibitor may be more antiproteinuric than either agent alone. Several small trials have shown this effect of combination therapy in reducing proteinuria. A recent meta-analysis found a significant 18–25% reduction in proteinuria compared with monotherapy [50]. Several studies have also demonstrated a reduction in the rate of decline in kidney function [51–53]. Of note, the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor on Non-Diabetic Renal Disease (COOPERATE) study, which was the only long-term study favoring combination therapy in slowing progression of CKD and reducing proteinuria, was retracted after publication and its findings, therefore, must be disregarded [54,55]. The more recent Ongoing Temlisartan alone and in Combination with Ramipril Global End point (ON TARGET) study, which evaluated 25,620 individuals with vascular disease or diabetes, found an increased risk of reaching all renal end points with combination therapy despite achieving a lower blood pressure than with either ACE inhibitor

or ARB alone. There were also more adverse events with combination therapy [56]. One possible explanation for this is that the patient population may have had significant underlying vascular disease, and by extension, renovascular disease. If this was the case, it is understandable that lower blood pressures could have led to worse renal outcomes. Additionally, the trial did not demonstrate additional cardiovascular benefit with combination therapy. This finding was similar to the Valsartan in Acute Myocardial Infarction (VALIANT) trial, which evaluated combination therapy immediately postmyocardial infarction and found no benefit and increased adverse events [57]. Two major trials evaluating dual therapy in patients with heart failure have resulted in conflicting results [58,59]. In both trials, combination therapy led to increased adverse events and the combination of a ACE inhibitor, ARB and β-blocker significantly increased mortality risk in one trial [58].

Recommendations

The combination of a ACE inhibitor, ARB and β-blocker should be used with caution. Given the conflicting trial results discussed above, combination therapy with a ACE inhibitor and ARB is no longer recommended [60,61]. Combination therapy may still be warranted in those with heavy proteinuria (>3 g/day) after either drug alone has been maximized. Patients must be closely monitored for side effects and this regimen should generally be avoided in patients with atherosclerotic renal disease.

Renin inhibitors

Aliskiren is an agent that directly inhibits renin activity. The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial evaluated the effect of aliskiren plus losartan in patients with hypertensive and diabetic nephropathy. Combination therapy reduced proteinuria to a greater extent than losartan alone, and this was independent of blood pressure effects [62]. Its role in nondiabetic glomerular disease is untested.

Aldosterone antagonism

In 1996, an experimental model evaluated aldosterone in kidney injury and found intrarenal aldosterone to be significantly elevated. ARBs and ACE inhibitor therapy were found to reduce renal injury. However when aldosterone was given to the experimental animals, ACE inhibitors and ARBs no longer prevented progression of kidney disease. This suggested aldosterone was involved in the pathogenesis of renal injury. Treatment with the aldosterone antagonist spironolactone did not reduce glomerulosclerosis but did reduce proteinuria, arterial pressure and cardiac hypertrophy [63].

Aldosterone is synthesized not only in the adrenal glands, but also in endothelial and vascular smooth muscle cells [64]. Aldosterone's main function in the kidney is to maintain salt and water homeostasis and assist with excretion of potassium. It has now been shown that aldosterone promotes fibroblast and/or myofibroblast growth, and through TGF-β regulates collagen deposition in blood vessels and the heart [65,66]. Within the kidney, aldosterone acts to mediate vascular remodeling, and there is a direct link between the RAAS and the fibrinolytic system. Excess aldosterone expression leads to activation of profibrotic factors including PAI-1 and TGF-β, which can promote tubulointerstitial fibrosis in patients with kidney damage [66,67]. In rat models, aldosterone was found to inhibit nitric oxide synthetase activity, which led to endothelial dysfunction, hypertension and vascular injury [68]. This finding was corroborated in 16 healthy human subjects where aldosterone infusion inhibited endothelium-derived vasodilatation to acetylcholine [69].

Aldosterone antagonists, even in low doses, have antiproteinuric, antihypertensive, antifibrotic and cardioprotective effects [60,61,70,71]. ACE inhibitors provide some blockade of aldosterone action, but work synergistically with aldosterone antagonists [70]. Directly antagonizing aldosterone may therefore be an important adjunctive therapy to primary RAAS inhibition in patients with kidney disease.

Recommendations

While there are no strong clinical trial data with hard end points like ESRD, the available data support the use of aldosterone antagonists in patients with CKD who have not met blood pressure or proteinuria goals with ACE inhibitors/ARBs. Patients with CKD on aldosterone antagonists must be monitored closely for hyperkalemia, especially if on concomitant ACE inhibitor/ARB therapy. Further, aldosterone blockers should not be used in patients with a GFR of <30 ml/min/1.73 m^2.

Other antihypertensive agents

Diuretics

Diuretic therapy synergizes with RAAS inhibition to improve blood pressure and reduce

proteinuria (FIGURE 5) [72]. Diuretics alone have not been shown to reduce proteinuria beyond what is achieved by blood pressure control. Diuretics such as the thiazides may induce significant metabolic side effects such as hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, hyponatremia and stimulation of the RAAS. Most of these side effects are known to increase cardiovascular risk. However, if diuretics are used in conjunction with an ACE inhibitor or ARB, these metabolic effects are mitigated [73]. In addition, in the Avoiding Cardiovascular Events through Combination therapy in Patient's Living with Systolic Hypertension (ACCOMPLISH) trial, combination therapy with benazepril/amlodipine was superior to benazepril/hydrochlorothiazide in reducing cardiovascular morbidity and mortality despite similar blood pressure control [74]. The current NKF-KDOQI guidelines recommend using diuretics as a second agent for uncontrolled hypertension in patients with CKD. For patients with LN and nephrotic syndrome, who are prone to volume retention, diuretic therapy should be beneficial, especially in combination with RAAS blockade [73]. If the patient's GFR is less than 30 ml/min/1.73 m^2 then a loop diuretic is preferred over thiazides. If loop diuretics are used they should be dosed at least twice daily to mitigate salt and water retention late in the day after early volume depletion. Combination loop plus thiazide diuretic may be used in cases where adequate diuresis is not achieved with loop diuretics alone. In this situation a thiazide diuretic should be given 30 min prior to the loop diuretic to provide synergy with blockade of the distal convoluted tubule to achieve more aggressive diuresis. Electrolytes must be monitored closely.

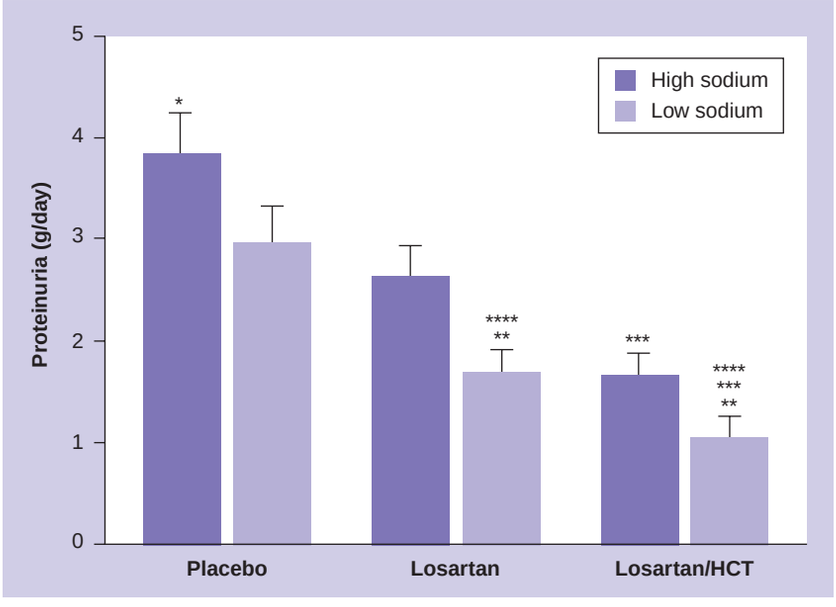

Figure 5. Effect of salt intake on proteinuria in patients treated with placebo, angiotensin receptor blockers or angiotensin receptor blockers plus diuretic. Addition of a diuretic was of particular benefit in patients of African decent, and those with uncontrolled high salt intake and cardiac dysfunction.
*p < 0.05 versus all periods.
**p < 0.05 versus same treatment on high sodium diet (effect of low sodium).
***p < 0.05 versus losartan treatment alone (effect of HCT).
****p < 0.05 versus placebo on same diet.
HCT: Hydrochlorothiazide.
Reproduced with permission from [72].

Nondihydropyridine calcium channel antagonists

The nondihydropyridine calcium channel antagonists (NDCAs), including verapamil and diltiazem, have been found to be antiproteinuric. They have also been found to slow decline in kidney function [75,76]. In a study of patients with overt diabetic nephropathy, NDCAs had antiproteinuric and antiprogression effects similar to lisinopril and superior to atenolol [77]. We recommend use of NDCAs in individuals who have persistent proteinuria and remain hypertensive despite adequate RAAS inhibition, and in patients with a GFR of <30 ml/min.

Dihydropyridine calcium channel antagonists

As opposed to NDCAs, dihydropyridine calcium channel antagonists (DCAs), while extremely effective antihypertensive agents, decrease glomerular afferent arteriolar resistance and thus tend to increase glomerular capillary hydrostatic pressure. This can worsen proteinuria and accelerate loss of renal function (FIGURE 6) [76,78–80]. Several other multicenter trials (IDNT [37] and AASK [49]) also demonstrated this effect. In patients with proteinuric kidney disease these agents should only be used for those with refractory hypertension. The undesirable effect of DCAs may be mitigated if they are used with RAAS inhibitors.

β-blockers

There is no evidence to suggest that β-blockers slow progression of CKD. β-blockers are typically reserved for patients with underlying cardiac disease but have been found to have some antiproteinuric effect. The AASK trial showed that β-blockers were more antiproteinuric then DCAs [37]. Another

small randomized trial compared atenolol and enalapril and found both lowered blood pressure similarly. Proteinuria, however, was only slightly reduced in the atenolol group compared with a significant reduction in the enalapril group [81]. β-blockers may increase the risk for developing diabetes when used as a monotherapy [73,82]. By contrast, carvedilol, a nonselective β-1 and α-1 blocker, was shown in a recent large randomized controlled trial of hypertensive patients with Type 2 diabetes to have no effect on hemoglobin A1c and reduced rate of progression to microalbuminuria when compared with metoprolol [83]. There are no data on the effect of carvedilol in kidney disease. We recommend β-blocker use in patients with cardiac disease and LN, but not as a first-line agent for blood pressure control.

Protein restriction (evidence level high)

A modest reduction in dietary protein may help retard CKD progression and reduce proteinuria [6]. There have been multiple meta-analyses and secondary analyses of randomized controlled trials that have evaluated the effect of protein restriction on kidney disease progression. The MDRD study examined CKD patients given a usual protein diet (1.3 g/kg/day), a low protein diet (0.6 g/kg/day) and a very low protein diet (0.3 g/kg/day). The low protein diet group had a modest delay in kidney disease progression without deleterious nutritional effects. The very low protein group was more likely to suffer from malnutrition [24].

Recommendations

Based on available evidence we suggest a dietary protein restriction from the usual American diet of 1.0–1.5 g/kg/day to 0.7–0.8 g/kg/day in stable LN patients. This mild-to-moderate protein restriction does not seem to impact nutritional status and may help slow kidney disease progression [84], especially in those patients with proteinuria levels greater than 1 g/day [11]. Maintaining a low protein diet, even if there is minimal reduction in GFR, will help slow the rate of increase in proteinuria over time [85].

To avoid malnutrition the diet must have adequate calories and the protein intake must be of high biologic value. A dietician who specializes in kidney diseases should work closely with patients and the patients should be assessed routinely for protein malnutrition. Monitoring dietary protein intake by 24-h urine collection for urea excretion is recommended [6].

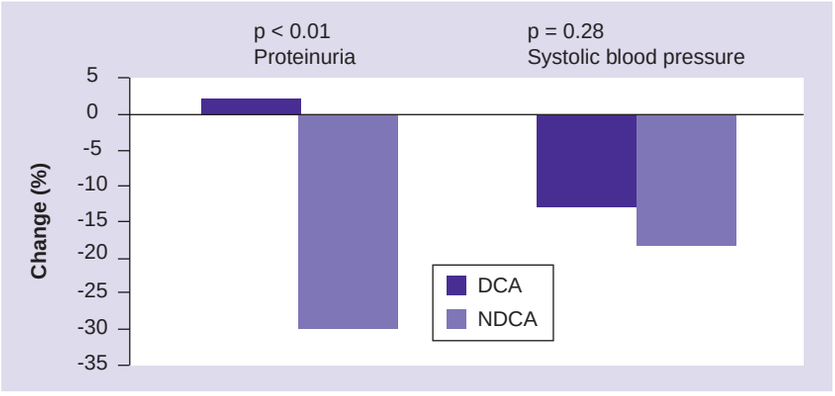

Figure 6. Comparison of nondihydropyridine calcium channel antagonists to dihydropyridine calcium channel antagonists on proteinuria reduction and blood pressure control. Blood pressure reduction was similar between the two groups but proteinuria was significantly reduced in nondihydropyridine calcium channel antagonists compared with dihydropyridine calcium channel antagonists. DCA: Dihydropyridine calcium channel antagonist; NDCA: Nondihydropyridine calcium channel antagonist.
Reproduced with permission from [76].

Sodium restriction (evidence level moderate for CKD & high for hypertension)

Increased salt intake worsens hypertension and proteinuria in patients with CKD [86]. A high salt diet can also override the effects of ACE inhibitors, ARBs and NDCAs [87–89]. The effect of lisinopril on reduction in proteinuria was found to be strongly dependent on dietary sodium intake [87]. Similarly, the addition of salt restriction and diuretics to ARB therapy reduced proteinuria 25% more than ARB alone, and patients who did not initially respond to losartan monotherapy for proteinuria did so after the addition of salt restriction (Figure 5) [72].

Recommendations

The average adult American diet contains approximately 170 mmol/day or 3.9 g/day of sodium. In individuals with LN and proteinuria/hypertension, sodium intake should be restricted to 80–120 mmol/day (2–3 g/day). Salt intake can be monitored by measuring sodium in 24-h urine collection or chloride if a patient is receiving sodium bicarbonate therapy.

Fluid intake (evidence level moderate)

Both the concentrating and diluting mechanisms of the kidney are impaired in CKD. Excessive fluid intake (>2–3 l/day) can cause significant sequealae including volume overload, worsening hypertension and hyponatremia. A retrospective analysis of the MDRD study showed a significant association between high urine volume and

decline in GFR. Urine volumes exceeding 2 l/day were associated with a faster decline in GFR [6]. The higher urine volumes were associated with higher blood pressure and lower serum sodium concentration. In the AASK trial, urine volume was the seventh strongest predictor of GFR decline out of 35 variables assessed [90]. It predicted GFR decline to the same level as baseline systolic blood pressure. Given this evidence, our recommendation would be to allow LN patients to drink to thirst, and to avoid pushing fluids.

■ Lipid control (evidence level high for heart & moderate for kidney)

In kidney disease the effect of lipid control on progression is unclear. In animal models, hyperlipidemia was shown to cause formation of glomerular foam cells and glomerulosclerosis, which was ameliorated by statin therapy [91]. Low-density lipoprotein (LDL) receptors are located on mesangial cells of the kidney, and activation of these receptors by hyperlipidemia stimulates mesangial cell proliferation and recruitment of inflammatory cells, such as macrophages, reactive oxygen species and PAI-1, to the glomerulus [91]. Elevated LDL has been associated with increased rate of progression of CKD in both diabetic and nondiabetic kidney disease [92]. The RENAAL study found baseline total cholesterol and LDL to be predictors of progression to ESRD [48]. A recent meta-analysis found a modest effect of statins on reduction of kidney disease progression of 1.2 ml/min/year [93]. Two randomized, controlled studies in individuals with overt proteinuria showed the addition of statins decreased proteinuria beyond that of ACE inhibition alone [94,95]. The most recent study, the Study of Heart and Renal Protection (SHARP) trial, which was a placebo-controlled, randomized, double-blinded trial, evaluated 9000 patients with CKD and found that the combination of simvastatin 20 mg and ezetimibe 10 mg significantly reduced the incidence of major cardiovascular events in patients with varying levels of CKD [96]. By contrast, the Renal and Vascular End-stage disease Intervention trial (PREVEND-IT) in patients with microalbuminuria showed no additional benefit of statins in reducing proteinuria beyond that achieved by a ACE inhibitor alone [97].

In nephrotic syndrome, hyperlipidemia can promote nephrosclerosis and sustained hyperlipidemia will accelerate atherosclerosis. Statins have proven benefit in reducing atherosclerotic risk and are considered anti-inflammatory. Statins have pleotrophic effects that inhibit macrophage/monocyte infiltration into the glomerulus and thus prevent mesangial proliferation, decrease inflammation and oxidative stress, and reduce podocyte damage [91].

Recommendations

In summary, hyperlipidemia may promote kidney disease progression and treatment with statins may ameliorate this process. The current recommendation for lipid control in patients with kidney disease is to treat hyperlipidemia with a statin to achieve a LDL of <100 mg/dl to reduce cardiovascular risk. These recommendations, combined with the increased risk of atherosclerotic disease in SLE, suggest lipid control in LN is of reasonable [98].

■ Control of uremic acidosis (evidence level moderate)

Uremic acidosis occurs in the setting of advanced CKD and reflects an inability to excrete acid, predominantly due to accumulation of anions (phosphate, sulfate and organic acids) [99]. In animal models there is accumulation of ammonia in the nephron, which can directly activate the alternative complement pathway, leading to tubulointerstitial damage [100]. In addition, chronic uremic acidosis promotes increased protein metabolism as well as bone loss, which occurs due to increased osteoclastic activity to enhance carbonate resorption from bone. Treatment of acidosis with alkali inhibits these processes. Bicarbonate therapy has not been shown to reduce proteinuria but has been shown to slow progression of CKD (Figure 7) [101]. It reduces protein catabolism, which may be beneficial in proteinuric kidney disease and slows bone resorption, limiting bone loss. A recent randomized, controlled trial evaluated CKD patients with low serum bicarbonate levels. These patients were randomized to receive bicarbonate therapy or placebo and were followed for 2 years for the primary end point of rate of GFR decline or ESRD. Patients treated with sodium bicarbonate had better outcomes [101]. Bicarbonate therapy slowed the rate of GFR decline from 2.5 to 1 ml/min/year.

Recommendations

Treatment with sodium bicarbonate in LN patients with advanced CKD and acidosis is recommended with goal serum bicarbonate levels of greater than 20 mg/dl.

Control of phosphorus (evidence level low)

Phosphate retention occurs soon after a fall in GFR. Excess phosphate promotes bone disease and is known to be an independent risk factor for all-cause and cardiovascular mortality [102]. Hyperphosphatemia has also been associated with kidney disease progression [103]. Hyperphosphatemia and elevated calcium/phosphorous product were shown to cause more rapid progression of kidney disease in an observational study of 985 patients with a median follow-up of 2 years [104]. The adjusted hazard ratio was 1.3 for every 1 mg/dl increase in serum phosphorous above normal. While a cause–effect relationship for phosphate-induced kidney injury has not been established, a plausible explanation is increased precipitation of calcium phosphate in the renal interstitium and subsequent activation of inflammation, leading to fibrosis and tubular atrophy [104]. Dietary phosphate restriction and the use of phosphate binders may thus be advantageous in LN patients with hyperphosphatemia, especially given the risk of bone disease in women on long-term corticosteroids.

Supplementation of vitamin D in CKD (evidence level moderate)

Vitamin D deficiency is common in patients with SLE. The endocrine effects of vitamin D are widely recognized, however, the paracrine effects mediated through local 1-α hydroxylase are less appreciated. It has been postulated that in the kidney vitamin D may be important for maintaining podocyte health, suppressing renin gene expression, and preventing inflammation and fibrosis [105]. In experimental models, vitamin D has been shown to be a potent inhibitor of RAAS, primarily by suppressing renin synthesis [105]. An observational study of 15,068 patients who participated in the NHANES III study reported a stepwise increase in albuminuria with decreasing quartiles of 25-hydroxy vitamin D [106]. Low 25-hydroxy vitamin D levels have also been independently associated with hypertension, obesity, insulin resistance, diabetes, hypertriglyceridemia and increased inflammation [107–109]. These data suggest that reduced 25-hydroxy vitamin D is associated with factors that are known to facilitate progression of kidney disease. Treatment with active vitamin D (calcitriol) has been demonstrated to be effective in reducing mortality in patients with CKD [110,111]. The benefit of vitamin D receptor agonists in CKD has been less convincing as the three randomized, controlled studies conducted had significant limitations and inconsistent findings [109].

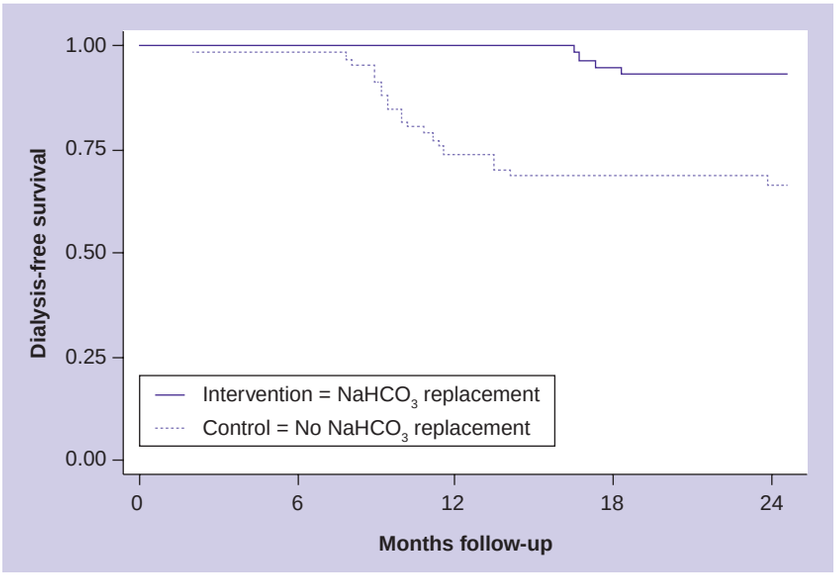

Figure 7. Effect of sodium bicarbonate therapy on chronic kidney disease progression and development of end-stage renal disease. Bicarbonate therapy slows chronic kidney disease progression and development of end-stage renal disease.
Reproduced with permission from [101].

Recommendation

Thus, while it is too soon to say that treatment with vitamin D analogs will reduce proteinuria and progression of CKD, evidence that it mitigates risk factors associated with cardiovascular disease, and acts as an immune modulator provide a compelling reason to treat vitamin D deficiency in LN. We recommend treatment to reach a goal 25-hydroxy vitamin D level of greater than 30 ng/ml.

Control of hyperuricemia in CKD (evidence level moderate)

Hyperuricemia occurs in kidney disease primarily due to decreased excretion of uric acid, and is associated with hypertension, cardiovascular disease and progression of CKD. Experimental data suggest that uric acid stimulates afferent arteriolar vascular smooth muscle proliferation and intraglomerular hypertension, which leads to glomerulosclerosis and interstitial fibrosis [112]. Furthermore, uric acid activates the RAAS, and inhibits endothelial nitric oxide production, leading to vasoconstriction and systemic hypertension [112]. Epidemiologic studies found serum uric acid levels to be an independent risk factor for the development and progression of kidney disease [113].

Table 1. Summary of recommendations.

Intervention	Level of evidence	Goals/comments
Control blood pressure	High	Goal systolic blood pressure in the 120s if tolerated. Greater the proteinuria, the greater the benefit of this blood pressure goal
Reduce proteinuria	High	Reduction of proteinuria with recommended therapies to <500 mg/day will slow progression of CKD
ACE inhibitor therapy	High	Use ACE inhibitor even if normotensive. First choice antihypertensive. Use maximum dose tolerated. 30% rise in serum creatinine is acceptable
ARB therapy	High	First choice if ACE inhibitor intolerance. Use maximum dose tolerated. 30% rise in serum creatinine is acceptable
Avoid DCAs	High	Excellent antihypertensive effects, but not antiproteinuric and may worsen proteinuria and promote kidney disease progression. RAAS blockers may mitigate this
Control protein intake	High	Goal 0.7–0.8 g/kg/day. Effect similar to low blood pressure goal
Restrict NaCl intake	Moderate for kidney, high for hypertension	Goal 80–120 mmol/day (2–3 g/day). Controls blood pressure and will optimize antiproteinuric effect of ACE inhibitor, ARB and NDCA
Control lipids	Moderate for kidney, high for cardiac disease	Goal LDL <100 mg/dl. May be antiproteinuric and prevent kidney disease progression
Aldosterone blockade	Moderate	Growing evidence of antiproteinuric effect at low doses. May slow progression of CKD
Diuretics	Moderate	Recommended use in conjunction with RAAS inhibition for salt-sensitive hypertension and in those with refractory high salt diet or nephrotic syndrome
β-blockers	Moderate	Some antiproteinuric effect but less than ACE inhibitor. Concern for diabetic risk. Recommended in patients with cardiovascular disease
Sodium bicarbonate for uremic acidosis	Moderate	Goal HCO_3 >20 mmol/l. $NaHCO_3$ therapy is not antiproteinuric but blocks complement activation locally preventing tubular damage. Reduces protein catabolism
Correct vitamin D deficiency	Moderate	Goal 25-(OH) vitamin D >30 ng/ml. If low GFR, may consider treating with both ergocalciferol and active vitamin D. Low vitamin D is associated with multiple cardiovascular risk factors and vitamin D inhibits renin, reduces inflammation, may reduce proteinuria and prevents CKD progression
Correct hyperuricemia	Moderate	Goal uric acid is 6.0 mg/dl. Uric acid activates RAAS and inhibits nitric oxide causing vasoconstriction, hypertension and has been associated with increased cardiovascular morbidity. Treat with low purine diet and allopurinol to reduce CKD progression
Combination ACE inhibitor + ARB	Low	Significant adverse events and no long-term prospective studies identifying benefit. May still be appropriate in patients with persistent proteinuria >3 g/day. More clear benefit with combination ACE inhibitor and aldosterone antagonist in CHF
Control hyperphosphatemia	Low	Goal phosphorous is 3.5–5.5 mg/dl. No casual relationship identified but has been associated with CKD progression. Control phosphorous to avoid bone effects and PTH dysregulation in advanced CKD
Reduce obesity	Low	Obesity causes glomerulopathy and proteinuria. Weight reduction decreases proteinuria and is recommended
Smoking cessation	Low	Cigarette smoking increases albuminuria and has been associated with hypertension, cardiovascular disease and CKD progression. Smoking cessation is recommended

25-(OH) vitamin D: 25-hydroxy vitamin D; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CHF: Congestive heart failure; CKD: Chronic kidney disease; DCA: Dihydropyridine calcium channel antagonist; GFR: Glomerular filtration rate; LDL: Low-density lipoprotein; NDCA: Nondihydropyridine calcium channel antagonist; PTH: Parathyroid hormone; RAAS: Renin–angiotensin–aldosterone system.

Several prospective trials have been conducted and demonstrated the benefit of allopurinol therapy in delaying CKD progression [114,115]. A recent prospective, randomized controlled trial of 113 patients with a GFR of less than 60 ml/min/1.73 m^2 compared allopurinol (100 mg/day) or usual therapy. After 2 years the allopurinol group had a significant decrease in uric acid levels and C-reactive protein. This group also had a slower decline in GFR of 1.3 ml/min/year compared with 3.3 ml/min/year in the standard care group [115]. The mechanism of the allopurinol effect is not clear, but may be related to inhibition of xanthine oxidase rather than lowering uric acid.

Recommendations

Hyperuricemia increases the risk for developing hypertension, cardiovascular disease and promotes CKD progression. Control of serum urate may reduce this risk and recent randomized controlled trials suggest allopurinol reduces the rate of GFR decline. Thus, in patients with CKD, we recommend treatment of hyperuricemia with a low purine diet and allopurinol therapy to achieve a goal serum urate of less than 6 mg/dl. It should be noted that close monitoring for side effects, such as Stevens–Johnson syndrome, is necessary for those

Executive summary

Chronic kidney disease & progression

- In normal individuals glomerular filtration rate (GFR) declines at 1 ml/min/year after 45 years of age but in chronic kidney disease (CKD) GFR declines more rapidly, often in the range of 4–10 ml/min/year.
- Progressive worsening of kidney function continues after the kidney has sustained a GFR loss of more than 50%, even if the primary disease is inactive.

Proteinuria & CKD progression

- Proteinuria is a major and modifiable risk factor for progression of kidney disease, and cardiovascular morbidity and mortality.
- Monitor proteinuria in lupus nephritis patients using a urine protein-to-creatinine ratio based on 24-h urine collection because spot protein-to-creatinine ratios are inaccurate.
- The goal for proteinuria management is to achieve a level of less than 500 mg/day.

Blood pressure control

- Hypertension is a major and modifiable risk factor for progression of kidney disease, and cardiovascular morbidity and mortality.
- Strict control of blood pressure to a level of 125/75 mmHg or less, if tolerated, attenuates proteinuria, CKD progression and cardiovascular risk.

Role of the renin–anigotensin–aldosterone system

- Renin–anigotensin–aldosterone system (RAAS) activation due to kidney damage incites inflammation, oxidative stress, vasoconstriction, and podocyte apoptosis leading to glomerulosclerosis and interstitial fibrosis.
- RAAS inhibition mitigates the maladaptive changes triggered by angiotensin II and aldosterone in response to kidney damage.

RAAS inhibition

- Angiotensin-converting enzyme (ACE) inhibitors are the first-line therapy for proteinuric kidney diseases such as lupus nephritis.
- Angiotensin receptor blockers (ARBs) should be used in those intolerant of ACE inhibitors.
- ACE inhibitors (or ARBs) should be considered when proteinuria exceeds 500 mg/day even in normotensive individuals and titrated to maximum dose tolerated.
- Aldosterone antagonists are antihypertensive, antiproteinuric, antifibrotic and cardioprotective, and can be added to CKD patients who have not reached proteinuria and/or blood pressure goals with ACE inhibitor/ARB therapy.
- Combination therapy with ACE inhibitors and ARBs should be restricted to patients with refractory proteinuria >3 g/day. This combination may be more harmful than beneficial at lower levels of proteinuria.

Dietary factors

- A modest reduction in dietary protein intake reduces proteinuria and attenuates CKD progression. Dietary protein intake should be restricted to 0.7 g/kg/day in proteinuric CKD.
- Excessive salt intake worsens hypertension and proteinuria in patients with CKD and can override the antiproteinuric effects of RAAS inhibitors.
- Dietary salt intake should be restricted to 2–3 g/day in patients with lupus nephritis. Salt intake should be monitored with 24-h urine collections for sodium with a goal of less than 100 mmol/24 h.
- Fluid intake should not exceed 2–3 l/day to avoid volume overload and worsening hypertension.

Lipid control

- Hyperlipidemia promotes inflammation and activates reactive oxygen species in the kidney, thus increasing the rate of CKD progression.
- Statin therapy has been shown to mitigate renal injury in those with hyperlipidemia.

Uremic acidosis

- Acidosis activates the alternative complement pathway and may cause tubulointerstital damage.
- Correcting acidosis with sodium bicarbonate may slow CKD progression.
- The goal for acidosis management is to achieve a serum bicarbonate level of >20 mg/dl.

Vitamin D deficiency

- Vitamin D deficiency is common in systemic lupus erythematosus and is associated with cardiovascular risk.
- Vitamin D is thought to be a potent inhibitor of the RAAS and may reduce proteinuria. It is also an immune modulator.
- Correcting vitamin D deficiency reduces proteinuria, CKD progression and cardiovascular risk.

Hyperuricemia

- Hyperuricemia is associated with hypertension, cardiovascular disease and CKD progression.
- Uric acid activates the RAAS and inhibits nitric oxide production causing vasoconstriction.
- Treatment with allopurinol may slow CKD progression and is recommended for those with persistent hyperuricemia despite a low purine diet. Patients should be monitored closely for side effects.

on allopurinol. Furthermore, the combination of allopurinol and azathioprine should be used with caution due to the increased risk for myelosuppression when used in combination.

■ Control of body weight (evidence level low)

Weight reduction may reduce proteinuria and progression of CKD. Diabetic and nondiabetic patients with a BMI of >27 were randomized to a low calorie diet or their usual diet. Patients in the diet group had a significant weight loss while the usual diet group had significant weight gain. Proteinuria decreased by 31% in the diet group and increased in the control group. Renal function was stable in the protein reduction group but worsened in the usual diet group [116]. Patients with obesity and LN should be counseled on importance of weight reduction.

■ Smoking & CKD (evidence level low)

Smoking has vasoconstrictor, thrombotic and direct toxic effects on the vascular endothelium. It is a major risk factor for cardiovascular disease. Based on ambulatory blood pressure monitoring, smokers have higher blood pressures than nonsmokers. A recent observational trial evaluated 40,619 patients and found that even in nondiabetic and nonhypertensive patients, smoking was an independent risk factor for microalbuminuria [117]. Several retrospective studies have demonstrated an association between cigarette smoking and kidney disease progression in patients with glomerulonephritis [118,119]. In patients with LN, smoking cessation is essential for cardiovascular and possibly renal protection.

Conclusion

Renal involvement in LN is common and often associated with poor outcomes. While immunosuppressive therapy may be necessary to treat the primary processes of LN, several additional factors play a role in the progression of kidney disease once renal injury has occurred. These factors are not unique to LN, but are seen in all forms of kidney disease. Based on the best available evidence described above, Table 1 shows a recommended renoprotective algorithm to retard the progression of kidney damage in LN.

Future perspective

Given our present therapeutic tools, we are limited to slowing the progressive nature of CKD. In glomerular diseases like LN, the most important goal is to improve primary immunotherapy, or to enhance early detection of LN flares and make better use of current immunosuppressives to increase the complete remission rates and prevent the development of CKD. The former will be accomplished through the new targeted biologic therapies that are being developed and tested in LN, and the latter will be accomplished through the identification of LN flare biomarkers that can be monitored in at-risk patients. If CKD is prevented than the inexorable decline in renal function toward end-stage kidney disease should not be an issue.

It is also likely that over the next several years we will see trials for medications that can reverse CKD, and thereby eliminate the nature progression toward kidney failure. These drugs will target glomerulosclerosis and interstitial fibrosis, essentially kidney 'scars' that currently cannot be reversed. If fibrosis can be made to regress, and importantly, be replaced by functional kidney epithelia, patients who do not achieve complete remission after treating their LN with specific immunosuppression, could be rescued from CKD.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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