Treatment of chronic kidney disease

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Treatment of chronic kidney disease (CKD) can slow its progression to end-stage renal disease (ESRD). However, the therapies remain limited. Blood pressure control using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) has the greatest weight of evidence. Glycemic control in diabetes seems likely to retard progression. Several metabolic disturbances of CKD may prove to be useful therapeutic targets but have been insufficiently tested. These include acidosis, hyperphosphatemia, and vitamin D deficiency. Drugs aimed at other potentially damaging systems and processes, including endothelin, fibrosis, oxidation, and advanced glycation end products, are at various stages of development. In addition to the paucity of proven effective therapies, the incomplete application of existing treatments, the education of patients about their disease, and the transition to ESRD care remain major practical barriers to better outcomes.

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Treatment of chronic kidney disease (CKD) aims to slow progression to end-stage renal disease (ESRD) and to prepare for ESRD. Because the symptoms of chronically progressive renal failure develop slowly, therapy of CKD is usually directed at an asymptomatic condition detected only by laboratory testing. The task is also made more difficult as it usually represents a late attempt at prevention. That is, the major causes of ESRD, hypertension, and type 2 diabetes can themselves be avoided to some degree by primary preventive measures such as diet, weight control, and exercise. Furthermore, once hypertension or diabetes are manifest, their renal complications can be mitigated by secondary prevention efforts aimed at blood pressure and glycemic control. Thus, treatment of CKD often represents an example of tertiary prevention in populations who have failed the first lines of prevention but who are still relatively asymptomatic. These features make CKD therapy a formidable task in practice. However, over the past 20 years, some effective treatments of CKD have developed. These can delay and, in some cases, prevent ESRD.

The notion of CKD as a single entity with generic therapy is a simplification but a useful one. Admittedly, some forms of CKD, especially inflammatory and autoimmune ones, require special treatments. However, even these approaches are usually applied in addition to those used for the most common hypertensive and diabetic causes. Viewing CKD as a single process rests both on the effectiveness of therapy across a range of primary diseases and on the data, suggesting that final common physiological pathways underlie the progression of CKD irrespective of initiating insult.[1–3]

Cardiovascular disease (CVD) is now well known to be common and often fatal in people with CKD.[4,5] Hence, careful attention to reducing traditional CVD risk factors in CKD is of great importance. Nevertheless, delay of ESRD remains a primary goal of CKD therapy simply because specific treatments to avoid CVD in this population do not currently exist. Standard methods of CVD prevention should be assiduously applied in CKD. Similarly, people with CKD should receive health maintenance applicable to the general population such as cancer screening and vaccinations.

The definition of CKD has itself received considerable attention. The most important consequence of the definition is its implications for therapy of an individual patient. Current treatment options are broadly initiated across CKD populations because they are relatively inexpensive and safe.

Given the low potential risk for individuals treated with these medications, and the absence of sophisticated prognostic tools, extended debate of CKD definitions is largely unimportant for clinical practice. If more toxic or expensive therapies are forthcoming, or when better markers of progression develop, then the definition may need refinement. At present, we regard the simple definition of CKD as an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2 and/or persistent albuminuria >30 mg of urinary albumin per gram of urinary creatinine as adequate.

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Angiotensin-converting enzyme (ACE) inhibitors were the first treatment shown to be effective in slowing the progression of diabetic nephropathy in 1993 by Lewis *et al.*[6] The work followed on animal studies by several laboratories, most notably that of Barry Brenner in the 1980s.[7] ACE inhibitors and angiotensin II receptor blockers (ARBs) are standard drugs for primary hypertension. However, they are each especially effective in slowing the progressive decay of GFR in CKD.[6,8–11] Diabetic nephropathy has been the disease state most studied with these agents. In both diabetes mellitus type 1 and type 2, slowing the rate of progressive renal injury with renin–angiotensin–aldosterone system (RAAS) inhibition has been intimately associated with the stabilization or reduction of proteinuria.[6,11] These findings have been demonstrated in patients with microalbuminura and macroalbuminuria.[6,12,13] In nondiabetic renal diseases, the data for the benefits of RAAS inhibition on progression of CKD are strongest in those patients with proteinuria >1000 mg/day according to a recent meta-analysis.[14] The AASK trial further supports this in African Americans with hypertensive nephropathy.[15] The benefit of RAAS inhibition in subjects with nondiabetic kidney disease without proteinuria is less clear. In certain disease states such as autosomal dominant polycystic kidney disease, there may be little to no benefit from ACE inhibitors and ARBs despite measurable reductions in proteinuria.[16] This is a current topic of investigation in the HALT PKD trial.[17] The exact nature of the relationship between proteinuria and progressive renal injury remains a topic of debate.[18] It may be misleading to interpret reductions in albuminuria as a surrogate for improved renal function. Although some authors argue that experimental evidence suggests that proteinuria has direct toxic effects, currently there is no consensus that the available evidence clearly establishes a cause and effect role.[19,20] For this reason, the significance of the antiproteinuric properties of ACE inhibitors and ARBs is unclear.

On the contrary, there are two widely accepted mechanisms by which ACE inhibitors and ARBs are understood to be beneficial agents in CKD: hemodynamic/antihypertensive actions and anti-inflammatory/antifibrotic actions. Their reduction of angiotensin II (AngII) levels (and subsequent reduction in aldosterone levels) is central to both of these pathways. In many animal models of CKD, glomerular capillary pressures are elevated. ACE inhibitors and ARBs reduce this capillary hypertension by both reducing arterial perfusion pressure and relaxation of the efferent arteriole, the dominant site of AngII action.[1,7] Relief from this excessive capillary pressure likely prevents mesangial cell proliferation and matrix production, as well as podocyte loss.[1]

Subsequent to the description of beneficial hemodynamic effects, investigators began to describe the RAAS as a proinflammatory and profibrotic mediator. AngII activates NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), upregulates adhesion molecules, and may directly stimulate proliferation of lymphocytes.[21,22] The net result of these actions is a local inflammatory environment in areas where AngII is in high concentration, namely the kidney. AngII may also foster fibrosis via interactions with transforming growth factor-β (TGF-β) and the induction of extracellular matrix proteins such as type I procollagen, fibronectin, and collagen type IV.[23] In addition, animal models have implicated aldosterone to be directly involved with mechanisms of endothelial dysfunction, inflammation, and fibrosis.[24] Table 1 gives a more complete list of the proposed inflammatory mechanisms mediated by the RAAS. Using ACE inhibitors and ARBs to quell these hostile attacks in the kidney is likely an important factor in slowing the progression of CKD.

As ACE inhibitors and ARBs each slow progression individually, the question has arisen as to whether the combination would provide additional advantage. This issue has not been definitively settled. One early report of the COOPERATE trial claimed that the combination was superior to the individual drugs.[25] However, these results and their analyses have been brought into question and retracted.[26,27] These events make any conclusions drawn from the COOPERATE trial invalid. An analysis of a study designed to examine cardiovascular end points in subjects with cardiovascular disease but generally good renal function (the ONTARGET study) found lesser proteinuria with combination ACE inhibitor and ARB therapy, but no benefit in terms of preventing a decline in GFR.[28] This study raises a couple of interesting findings. First, the relationship between improved proteinuria and worsening GFR contributes further reason to question the significance of reduced albumin excretion as a meaningful clinical outcome. Second, the lack of improved renal end points in those receiving dual therapy questions the validity of this treatment strategy for slowing CKD progression. A high burden of renal vascular atherosclerosis in the participating subjects may have contributed to these results, and it remains unclear whether these findings can be directly applied to broader populations with renal dysfunction. Currently, several trials are underway to address this, but at present there are no firm data to support the use of combination therapy.[17,29]

Aldosterone contributes along with AngII to the adverse actions of the RAAS in progressive CKD. Recognition of the deleterious effects of aldosterone has led to attempts to selectively block it by using the mineralocorticoid receptor blockers.[30] A large number of studies in experimental animals have supported this approach. Several trials in human

Table 1 | Reported nonhemodynamic effects of renin–angiotensin–aldosterone system

Mechanism	Comment	Mediator
Stimulation of NF-κB	A transcription factor resulting in a cascade of cytokines and other proinflammatory factors	AngII, AngIII, AngIV
Stimulation of ETs-1	A mediator of vascular inflammation with T-cell and macrophage/monocyte recruitment	AngII
Adhesion molecules Vascular cellular adhesion molecule 1 Intracellular adhesion molecule 1 Integrins	Facilitates adhesion of inflammatory cells to capillary walls	AngII
Cell proliferation Mesangial cells Glomerular endothelial cells Fibroblasts	Enhances structural renal damage and fibrosis	AngII/Aldo
Apoptosis	As opposed to cellular proliferation, under certain circumstances, AngII instead induces apoptosis; how this is regulated is unclear	AngII
Increased TGF-β expression	An important protein that results in cascading effects central to inflammation and fibrosis	AngII/Renin
Increased connective tissue growth factor	Can occur by direct stimulation by AngII or via TGF-β upregulation	AngII
Increased ECM products Type I procollagen Fibronectin Collagen type IV	Result in ECM accumulation and are pivotal factors that contribute to fibrosis	AngII
Increased metalloproteinase inhibitors Plasminogen activator inhibitor-1 Tissue inhibitor of matrix metalloproteinases	Also results in ECM accumulation due to decreased turnover	AngII
Ac-SDKP hydrolysis	Increases fibrosis and inflammatory cell infiltration	ACE
Reactive oxygen species	Leads to cellular damage	Aldo
MAPK activation	Contributes to mesangial injury and renal fibrosis	AngII/Aldo

Abbreviations: ACE, angiotensin-converting enzyme; Ac-SDKP, N-acetyl-seryl-aspartyl-lysyl-proline; Aldo, aldosterone; Ang, angiotensin; ECM, extracellular matrix; ETs-1, endothelins-1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; TGF-β, transforming growth factor-β.

subjects with CKD have shown a reduction in proteinuria when aldosterone blockade was added to an ACE inhibitor or ARB.[30–33] However, there is not yet a large enough trial to assess the effects on decline in GFR. Moreover, hyperkalemia is more frequent. Thus, there are no sufficient data to recommend the addition of aldosterone blockade to standard therapy in CKD.

Inhibition of renin is yet another means of interrupting the RAAS. Addition of a renin inhibitor to an ARB reduced proteinuria in diabetic nephropathy.[34] The diminution of proteinuria was with little if any further reduction in blood pressure, and no additional side effects were noted with the combination. A larger and longer trial is underway to test the value of renin inhibitor addition to ACE inhibitors or ARBs using cardiovascular and renal end points.[35]

In summary, blockade of the RAAS with ACE inhibitors or ARBs has proven effective in retarding progression of CKD. Studies are ongoing to assess the value of interrupting the pathway simultaneously at multiple sites, but such approaches have, at this time, not been proven more effective than the use of ACE inhibitors or ARBs and have not been adequately assessed for safety.

BLOOD PRESSURE

Although there is a considerable amount of overlap when considering the beneficial effects of RAAS inhibition and blood pressure control, it is important to appreciate them as two separate treatment targets. The reductions in arterial and glomerular capillary pressure affected by antihypertensive medications dictate their beneficial effects. However, the optimal target arterial pressure in CKD is largely a matter of opinion. Current guidelines suggest a target of $<130/80$ mm Hg for patients with CKD, a more stringent control than the 140/90 mm Hg recommended for the general population. A recent meta-analysis was performed to specifically address this question.[36] The study included results from 2272 subjects with nondiabetic renal disease involved in the MDRD, AASK, and REIN-2 trials. Overall, no benefits in renal outcomes, cardiovascular outcomes, or death were obtained in patients with CKD who were treated to a goal blood pressure of 125–130/75–80 mm Hg as compared with 140/90 mm Hg. From subgroup analysis, proteinuria did appear to be an effect modifier. Participants with daily proteinuria >300 mg in the AASK trial and >1000 mg in the MDRD trial did show a benefit. The ACCORD trial in type 2 diabetes compared a goal systolic blood pressure of 140 mm Hg with one of 120 mm Hg and found no overall benefit to the lower goal.[37] Albuminuria was less with the lower pressure but eGFR was also lower at the end of the study in this group. However, the trial did not target people with CKD, and on average the starting eGFRs were >90 ml/min per 1.73 m^2 and albumin excretion less than the microalbumuria level. Whether a goal of 120 mm Hg systolic pressure is desirable in the CKD population is unknown but is a question to be addressed by the SPRINT trial, which will recruit a large fraction of subjects with CKD.

Until we have these results, the present guideline of 130/80 mm Hg seems reasonable, especially for those patients with higher amounts of proteinuria.

If first-line therapy with an ACE inhibitor or ARB fails to achieve the target of 130/80, and often it will not, the choice of the second agent is also largely a matter of opinion. Addition of a diuretic has physiological appeal. In short-term studies, the addition of a thiazide diuretic to an ARB showed additional reduction of proteinuria in CKD, possibly suggesting further renal protection.[38] Often it is said that thiazide diuretics lose potency in later stages of CKD compared with loop diuretics. There is little evidence for this contention.[39] Many people with CKD will require more than the combination of a diuretic and ACE inhibitor or ARB to reach target blood pressures. Further choices are similarly not based on long-term studies of progression, but β-blockers, calcium channel blockers, and/or central sympatholytic agents are satisfactory.

Targeting blood pressure $<130/80$ mm Hg is recommended, but will often require two or more drugs.

GLYCEMIC CONTROL IN DIABETES

Glycemic control reduces the progression of renal disease as judged by the mitigation of increasing albuminuria in both type 1 and type 2 diabetes.[40–43] For example, in the DCCT, in type 1 diabetes, strict glycemic control compared with usual control lessened the progression from microalbuminuria (30–299 mg albumin per g creatinine) to macroalbuminuria (>300 mg albumin per g creatinine). Similarly, in the ACCORD trial, transitions to microalbuminuria and macroalbuminuria were diminished by stringent glycemic control. However, the incidence of ESRD was not different between levels of glycemic control in ACCORD or ADVANCE, another study of glycemic control in type 2 diabetes, and the incidence of ESRD has been low in follow-ups to DCCT.[42–44]

No large-scale studies have specifically tested the benefits of glycemic control in diabetic CKD with GFR of <60 ml/min per 1.73 m^2 or macroalbuminuria. Thus, although attention to glucose control seems to afford renal protection, this has been gauged largely by changes in albuminuria. Evidence that glucose control can forestall ESRD in people with established diabetic CKD is lacking. The exact best level of glycemic control is uncertain. Because of overall mortality risks with very stringent glycemic control, current guidelines call for hemoglobin A1c levels of $<7.0\%$. At present, maintaining hemoglobin A1c of $\leqslant 7.0\%$ remains reasonable for people with established diabetic CKD.

METABOLIC DERANGEMENTS OF CKD

Acid base

Although the acidosis of CKD results from decreased renal ammoniagenesis, ammonia production per residual GFR in patients and per residual nephron in animals actually rises as CKD progresses.[45–48] Data in rat models of renal disease have suggested that excess ammoniagenesis per residual nephron causes tubulointerstitial injury because of the interaction of ammonia with complement component, C3.[49,50] Bicarbonate supplementation reduced injury in some but not all rat models tested.[51–53]

An analysis of the relation of serum bicarbonate to progression of renal disease in a data set including over 5000 outpatients found that low serum bicarbonate level was strongly associated with subsequent progression of kidney disease.[54] Obviously, this strong association does not prove a causal relationship, and a clinical trial is needed to determine whether amelioration of acidosis would lessen progression. Kovesdy *et al.*[55] have recently reported that lower serum bicarbonate was associated with mortality in a cohort with CKD.

Several relatively small trials of the effects of bicarbonate supplementation on renal disease progression have been recently reported. The first trial was randomized, but not blinded or placebo controlled, and studied people with advanced CKD.[56] It comprised 129 subjects with estimated creatinine clearance (CrCl) of <30 ml/min who were randomized to receive either sodium bicarbonate or continuation of usual care. The treated group received an average of 14 mEq/day of bicarbonate. The most striking result was a 6.5% vs. 33% incidence in ESRD over a 2-year follow-up, treated vs. control, respectively. Another trial studied subjects with relatively high eGFR (~ 75 ml/min) and assigned 40 subjects each to sodium bicarbonate supplementation, sodium chloride supplementation, or nothing.[57] Sodium bicarbonate at a dose of 0.5 mEq per kg body weight per day was associated with fewer subjects developing more advanced disease over 5 years (<60 ml/min). The rate of decline in eGFR was significantly less in those receiving sodium bicarbonate as compared with those receiving sodium chloride or placebo. Interestingly, urinary endothelin excretion declined with bicarbonate treatment. In an uncontrolled trial comparing 30 patients with eGFR <60 ml/min given sodium citrate for 24 months with 29 CKD patients not treated with alkali, eGFR was higher at the end of the study in the treated group.[58] An effect of alkali on progression of kidney disease in these patients may have been mediated by a reduction in endothelin secretion. More recent data suggest that treatment with alkali in CKD patients reduces both endothelin and aldosterone secretion.[59]

Thus, the effects of alkali supplementation on the progression of renal disease have been tested only in small studies with less than optimal design but with encouraging results. Present guidelines suggest treating patients with alkali when serum bicarbonate level decreases to <22 mEq/l. Although this is opinion based, the available human data and the prior animal studies raise the possibility that such treatment could retard progression.

Phosphate

Recent evidence suggests that fibroblast growth factor-23, a phosphaturic hormone, increases early in CKD to maintain phosphorous balance.[60] Regardless of this, without intervention, hyperphosphatemia regularly appears as CKD progresses. Control of hyperphosphatemia with dietary restriction and phosphate binders have long been mainstays

of therapy directed at preventing bone disease. However, animal studies more than 30 years ago also suggested that hyperphosphatemia hastened progression to ESRD by causing calcium–phosphate crystal deposition within the renal interstitium.[61] More recent observational studies have found that elevated phosphate associates with more rapid decline in eGFR, and also that separately it associates with CVD in CKD as well as the general population.[62–67] In parallel to this, additional studies have also linked elevated serum fibroblast growth factor-23 with a greater risk for progression of CKD.[68,69]

In recent years, the proposed pathogenetic mechanisms for extraosseous toxicity have grown to suggest a role for hyperphosphatemia in vascular and cardiac calcifications, both of which are common in advanced CKD. These calcifications may be mediated through hormonal reactions to phosphate such as the phosphatonins and cellular transformations of vascular smooth muscle cells to those with more bone phenotypes.[70] In any case, interventional trials to test the efficacy of phosphate-lowering strategies for either slowing CKD progression or preventing CVD are lacking. Thus, phosphate control when used in CKD must be based on data for ameliorating bone outcomes, which are themselves modest, or at best opinion based on animal and epidemiologic work. Further trials are needed.

Vitamin D

Deficiency of 1,25-dihydroxyvitamin D may be expected with advancing CKD, as the kidney is the site of its synthesis. However, low levels of its precursor 25-hydroxyvitamin D have been linked epidemiologically to more rapid progression of CKD.[71] The physiological actions of vitamin D are multiple and extend well beyond its classic effects on calcium, phosphate, and bone.[72] For example, vitamin D suppresses renin secretion, and this action has been proposed as beneficial in CKD.[73] There are no long-term trials of vitamin D supplementation in progressive renal disease using the strongest outcomes such as reduction of GFR or incidence of ESRD. However, in the VITAL study, a synthetic vitamin D analog, paricalcitol, did lower albuminuria in subjects with diabetic nephropathy.[74] In this study, reduced albuminuria was associated with a decrease in blood pressure and an increase in eGFR, suggesting that vitamin D–mediated renin suppression may have been the major contributing mechanism. Clearly, clinical trials are needed to test the effect of vitamin D on hard outcomes, and especially to test inexpensive forms such as nutritional vitamin D, cholecalciferol.

Parathyroid hormone

Secondary hyperparathyroidism also regularly attends progressive CKD and is at least partly a consequence of hyperphosphatemia and vitamin D deficiency. Elevated PTH levels have also been suggested as toxic even beyond their capacity to induce bone loss.[75] However, an analysis of published literature found that the evidence for links between parathyroid hormone (PTH) and CVD or mortality was poor.[66] The usual recommendations for phosphate and vitamin D should mitigate secondary hyperparathyroidism, but whether this slows progression of CKD or lessens CVD is uncertain. In principle, targeted suppression of PTH with a calcimimetic would be an attractive means of testing the role of PTH in extraosseous sequelae of CKD. However, to date, the role of PTH in such events is untested.

Uric acid

Epidemiological studies have often found an association between hyperuricemia and CVD.[76–78] The basis for this association is uncertain. However, over the past several years, hypertension has been ascribed to hyperuricemia based largely on animal studies, but human studies are few.[76] One study of newly diagnosed hypertensive adolescents found that lowering uric acid with allopurinol reduced blood pressure.[79]

With regard to CKD, hyperuricemia predictably appears as GFR declines. Furthermore, uric acid is clearly toxic to the kidney in very high concentrations as in tumor lysis. Whether more modest elevations of uric acid are detrimental is more controversial. Observational studies have found modest associations of hyperuricemia with decline in renal function.[80] One small randomized but unblinded trial involved 25 patients with mixed causes of CKD. Subjects were assigned to receive either allopurinol or conventional treatment.[81] The investigators succeeded in lowering uric acid, but in this study blood pressure was not affected. The serum creatinine tended to remain lower in the allopurinol-treated group, but was not statistically different from that in the control group. A combined end point of incident ESRD and 40% rise in creatinine was significantly greater in the untreated group. A second randomized control study involving 113 patients, again with mixed causes of CKD, also showed a favorable effect induced by allopurinol.[82] In this study, those receiving allopurinol had a mean eGFR increase of 1.3 ml/min per 1.73 m^2 over a period of 24 months. This was a statistically significant difference when compared with the mean eGFR decrease of 3.3 ml/min per 1.73 m^2 observed in the control group. These findings occurred independent of any differences in blood pressure between the two groups. These studies, although suggestive, are not sufficiently robust to recommend allopurinol as a means of slowing progression. Larger studies might be warranted except that allopurinol has a rather high risk for allergic reactions that can be severe. If better alternatives for uric acid–lowering drugs were available, then larger trials would be attractive.

Anemia

Several studies have tested the efficacy and safety of therapy of anemia with erythropoietin congeners in CKD before dialysis.[83] The largest and most persuasive study TREAT randomized 4038 subjects with CKD due to type 2 diabetes to a target hemoglobin of 13 g/dl, or placebo with darbepoieten rescue if the level dropped below 9 g/dl.[84] The baseline eGFR was $\sim$35 ml/min per 1.73 m^2 for each of the two groups. Except for more strokes in the higher

hemoglobin group, there were no differences in cardiovascular or renal outcomes between the two groups. Approximately 16% of the subjects in each group developed ESRD over the 4 years of study. Thus, maintaining hemoglobin levels at 13 g/dl is unwarranted. The lower hemoglobin group had an average level of 10.6 g/dl but received more transfusions. The optimal level is not clear. Current guidelines call for levels between 10 and 12 g/dl in ESRD, and this also seems reasonable for patients with CKD predialysis. However, lower levels might be equally good, but in practice a small percentage of CKD patients require treatment for severe anemia before ESRD.

Dietary protein

Dietary protein restriction was one of the earliest therapeutic maneuvers used in CKD. In addition to contributing to alterations in phosphorous, metabolic acidosis, and uric acid as described previously, other proposed mechanisms for renal injury from increased dietary intake include altered hemodynamics, leading to glomerular hyperfiltration, and reduced cytokine-mediated fibrosis.[85,86] Protein restriction does seem to ameliorate some of the symptoms of advanced CKD, and many animal studies showed that it reduced renal injury.[87] However, clinical trials have been less clear as to its efficacy in slowing progression. A large analysis of the available clinical trial literature concluded that low-protein diets reduced the incidence of ESRD in nondiabetic patients.[88] Because of varying study designs, this review could not define an optimal level of intake. Properly constructed and monitored protein restriction can be safe.[87] Probably because successful and safe protein restriction requires much effort for physicians, dieticians, and patients, it is not sedulously practiced. Provided that malnutrition is avoided and the burden is acceptable to the individual patient, a target of 0.8 g of protein per kg body weight per day seems reasonable. However, careful monitoring of nutritional status and attentive dietary care is needed if protein restriction is attempted.

LIPID-LOWERING THERAPY

Abnormal lipid metabolism often accompanies renal dysfunction. Although hyperlipidemia does not in itself seem to cause primary renal disease, it may contribute to the progression of CKD. The hypothesis of lipid nephrotoxicity was first generated by Moorhead *et al.*[89] in 1982. The proposed mechanisms parallel the injury events that lead to atherosclerosis in other vascular beds. In the presence of lipids, mesangial cells are stimulated to recruit macrophages through the production of chemokines.[90] Activated mesangial cells and accumulated macrophages subsequently release oxygen radical species that lead to oxidized low-density lipoproteins. These oxidized low-density lipoproteins have been shown to stimulate proinflammatory and profibrotic cytokines.[91] A likely integral component to this process is the phagocytosis of lipoproteins by macrophages and mesangial cells to produce foam cells. As evidence for this, foam cells are frequently found in sclerotic regions of glomeruli, as well as areas of interstitial fibrosis.[92] In addition, mesangial cell proliferation may also be directly stimulated by low-density lipoproteins and triglyceride-rich lipoproteins.[93]

Experimental studies in animals and observational data in humans support the hypothesis that lipids contribute directly to renal injury and progression of CKD. Rats fed high-cholesterol diets were found to have greater amounts of glomerulosclerosis and tubulointerstitial damage compared with those fed standard diets.[94,95]

In humans, a number of epidemiological studies have suggested that elevated cholesterol and triglyceride levels are associated with a more rapid progression of renal dysfunction.[96–98]

Given this, lipid-lowering therapy to slow the progression of CKD has generated a great deal of interest in the nephrology community. Although a number of different classes of these medications have been studied, the pertinent data revolve around HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins). This class of medication seems to offer a potential benefit not just by way of decreasing the lipoprotein burden within tissues, but also by way of their additional anti-inflammatory affects. In animal studies, statin therapy has been shown to reduce macrophage recruitment into the glomerulus, limit expression of inflammatory factors including chemokines, cytokines, and adhesion molecules, and decrease fibrosis and mesangial cell expansion.[99] These beneficial effects have been seen across a number of disease models including diabetic nephropathy, focal glomerulosclerosis, cyclosporine nephrotoxicity, and chronic allograft dysfunction.[100–103]

Data in human trials supporting the benefits of statin therapy for slowing the progression of CKD have been less convincing. In a meta-analysis of 39,704 patients from 27 randomized, controlled, and crossover studies, treatment with statins resulted in a small but statistically significant favorable effect on yearly decline in eGFR (1.22 ml/min/year slower in statin recipients as compared with placebo).[104] In a subgroup analysis, those patients with cardiovascular disease were the most likely to benefit, whereas those with diabetes or hypertensive nephropathy or glomerulonephritis were not found to have a statistically significant benefit. The GREACE study evaluated the effects of a structured care algorithm for titrating atorvastatin to reach the low-density lipoprotein level of <100 mg/dl vs. usual care in the secondary prevention of major cardiac events. A *post hoc* analysis evaluated the effects of statin therapy on change in renal function. For those patients who received atorvastatin as part of the structured care group the CrCl increased by 12%, and for those who received various statins as part of the usual care group the CrCl increased by 4.9%. In contrast, those who did not receive any statins had a decrease in CrCl of 5.2%. These results represent the largest benefit of any trial to date; however, it is important to keep in mind that the study design and the fact that this was a *post hoc* analysis invites certain bias. Another meta-analysis of 15 studies including

1384 subjects found that those treated with statins were more likely to have reductions in albuminuria or proteinuria; however, no hard clinical outcomes were reported.[105]

The recently completed Study of Heart and Renal Protection (SHARP) is the largest randomized controlled trial to date to study the effects of statin therapy on progression of CKD.[106] The study involved over 9438 participants, 6382 of whom had CKD and were not on hemodialysis. Comparing those who received simvastain 20 mg plus ezetimibe 10 mg with those who received placebo, there was no difference in the risk of those with CKD to progress to ESRD. Although the study did suggest that lipid-lowering medications are beneficial in predialysis CKD patients to prevent major cardiovascular events, this is the strongest evidence to date to demonstrate a lack of benefit in slowing CKD progression with these agents. Thus, despite a reasonably conceived hypothesis, and supporting experimental evidence in animal studies, current human data do not convincingly show a significant benefit from statins for altering the disease course of CKD.

SELECTED NEW THERAPIES

Pirfenidone

Pirfenidone is a synthetic molecule with antifibrotic properties that has emerged as a promising oral treatment for CKD. Although the exact mechanism of action is unknown, the effects of pirfenidone seem to be mediated through interruptions in the TGF-β pathway.[107] Mesangial cell cultures treated with pirfenidone have shown a reduction of TGF-β production, antagonism of TGF-β signaling, inhibition of TGF-β-induced reactive oxygen species generation, and a reduction of TGF-β-mediated matrix production. In a murine model of diabetic nephropathy, pirfenidone significantly reduced mesangial matrix expansion independent of alterations in albuminuria or blood glucose levels.[107] Similar findings have been found in rat models of post-adaptive focal segmental glomerulosclerosis.[108]

Clinical trials have shown encouraging results for the use of pirfenidone in the treatment of various nonrenal fibrotic diseases including cirrhosis, multiple sclerosis, and pulmonary fibrosis.[109–111] Specific to kidney disease, an open-label, observational study of 18 subjects with focal segmental glomerulosclerosis and a mean baseline GFR of 26 ml/min per 1.73 m^2 compared the change in GFR during a 12-month baseline period with a subsequent 12-month treatment period with pirfenidone.[112] Although the GFR declined throughout both periods in all patients, the median monthly GFR decline rate was significantly less during the treatment period as compared with the baseline period (−0.45 vs. −0.61 ml/min per 1.73 m^2; $P<0.01$). A phase II randomized controlled trial involving 77 participants with diabetic nephropathy (eGFR 20 to 75 ml/min per 1.73 m^2) was recently completed.[113] The subjects receiving a 1200 mg dose of pirfenidone not only had a significant benefit with regard to change in eGFR as compared with placebo, but also actually had a mean increase in eGFR of 3.8 ml/min per 1.73 m^2 over 54 weeks. A 2400 mg dose group was also included; however, a significant dropout rate occurred in these subjects and no significant change in eGFR as compared with placebo was found. Interestingly, inflammatory biomarker levels were highly correlated with baseline eGFR in this study. No significant changes in biomarker levels occurred as a result of treatment with pirfenidone. Overall, these results are promising, and it will be interesting to see whether larger studies continue to show a benefit for using this medication to treat diabetic nephropathy.

Bardoxolone methyl

Bardoxolone methyl is the first member of a new antioxidant inflammation modulator drug class. Bardoxolone methyl and other antioxidant inflammation modulators activate nuclear factor-erythroid 2-related factor 2, a transcription factor that controls over 250 cytoprotective proteins.[114] The net result is an inhibition of immune-mediated inflammation at the tissue level, which may protect against end-organ damage.

Results from a recently completed phase IIb clinical trial reported that bardoxolone methyl has a positive effect on the progression of diabetic nephropathy.[115] In this multicenter, randomized, controlled trial sponsored by the manufacturer of the drug, 227 adults with diabetes mellitus type 2 and moderate-to-severe CKD (eGFR 20–45 ml/min per 1.73 m^2) were randomized to receive either bardoxolone methyl or placebo. Almost all of the patients were receiving either an ACE inhibitor or an ARB and had well-controlled serum glucose and blood pressure levels. Over the course of 24 weeks, patients receiving 25, 75, or 150 mg of bardoxolone methyl all had statistically significant increases in mean eGFR as compared with those receiving placebo (between-group differences in eGFR were 8.2, 11.4, and 10.4 ml/min per 1.73 m^2, respectively). Continued follow-up found that these benefits persisted over 52 weeks. Surprisingly, improvements in GFR were seen as early as 4 weeks, and this suggests some skepticism about whether the improved GFR was truly a result of reduced inflammation and sustainable changes in kidney structure or was a more temporary change resulting in improved GFR due to altered hemodynamics. Also raising concern was the increase in frequency of adverse events such as muscle spasms, nausea, hypomagnesemia, and decreased appetite seen in those receiving bardoxolone methyl. The suggestion that this drug may actually improve GFR in patients with diabetic nephropathy is intriguing; however, more long-term studies with larger groups are needed to validate its effects.

Endothelin-1 antagonism

Endothelins are a group of related peptides with powerful vasoconstrictor properties. Endothelin-1 (ET-1) is the predominant isoform in the human kidney and acts on a wide distribution of receptors throughout the renal vasculature and collecting system.[116] ET-1 contributes to renal dysfunction through multiple mechanisms including arterial

vasoconstriction, glomerular hypertension, increased proteinuria, and interstitial fibrosis.

ET-1 blockade has been studied as a potential treatment strategy for CKD. Animal studies have demonstrated elevations of ET-1 after subtotal nephrectomy.[117] Treatment with ET-1 antagonist in these models has shown not only reductions in proteinuria, but also improvements in CrCl.[117,118] These promising findings provided proof of concept and have led to human trials. In one study, antagonism of the endothelin type A receptor (ET_a) improved renal blood flow and reduced renal vascular resistance in subjects with CKD.[119] However, results from a large, multicenter, randomized, controlled trial have raised serious questions about the safety of these agents. The study compared the efficacy of avosentan with placebo for treatment of CKD progression in subjects with diabetic nephropathy.[120] After a median follow-up of only 4 months, the trial was prematurely terminated owing to an excess of cardiovascular events in the avosentan-treated group. It is noteworthy that those in the treatment group did have significantly less proteinuria, but there was no difference in the primary composite end point of time to doubling of serum creatinine, ESRD, or death. A more recent trial tested another ET_a antagonist, atrasentan, in 89 subjects with diabetic nephropathy.[121] Reported to be more selective for the ET_a receptor than the ET_b receptor as compared with the previously mentioned avosentan, it was felt that atrasentan would result in fewer safety concerns. In this study, all patients were already receiving a RAAS blocking agent. No difference in albumin excretion was found with a 0.25 mg dose group; however, 0.75 and 1.75 mg dose groups did result in a significant reduction. The most common side effect was peripheral edema, and this was only significantly more frequent in the 1.75 mg dose group. This study provides some suggestion that both ET_a receptor selectivity and dose may be important with regard to the safety profile of these medications. Whether reductions in albumin excretion will translate into improvements in more robust renal outcomes is unclear. Until additional studies address this, and more evidence becomes available to clearly support the safety of endothelin antagonists, it remains questionable whether these agents will become a viable treatment option for CKD.

INHIBITORS OF ADVANCED GLYCATION END PRODUCTS

Advanced glycation end products (AGEs) form from the nonenzymatic glycation of proteins by glucose and its metabolites. AGEs facilitate cellular damage by directly modifying cellular proteins and altering their function or by binding to specific AGE receptors that induce a broad range of cellular responses leading to injury. While implicated as a major pathogenic mechanism in diabetic nephropathy, AGEs also contribute to kidney injury in other forms of nondiabetic renal disease and aging.[122] The use of direct therapeutics that disrupt the AGE/AGE receptor axis is a developing treatment strategy.[123] In addition to common therapies such as RAAS inhibitors, statins, aspirin, and metformin, more specific agents for inhibition of AGE formation or AGE receptor blockade have been developed and studied. A number of these agents have shown potential to treat CKD in animal studies.[124–129] Aminoguanidine was the first AGE inhibitor to be studied in humans. Although proteinuria was decreased in type 1 diabetics during a phase III trial, no significant improvement on the progression to overt nephropathy was found.[130] This study was terminated early because of safety concerns and apparent lack of efficacy. Pyridoxamine is a vitamin B_6 derivative. Phase II studies in subjects with diabetes mellitus type 1 and type 2 demonstrated it to be well tolerated and showed a statistically significant slower decrease in creatinine over 24 weeks.[131] Other agents in this class have been used in human studies as well; however, their specific benefit on renal outcomes has not yet been evaluated.[132,133] These medications have not yet proven clear efficacy for treatment of CKD, but given the promising experimental data, there are likely to be more clinical trials to come in the near future.

DELIVERY OF CKD CARE

Patients with CKD have many challenges including management of multiple medications, major changes in diet, and surgery for dialysis access months before any symptoms of kidney failure occur. Multidisciplinary CKD programs use patient education, nutrition resources, and guideline-driven nephrology care to achieve the goals of decreasing cardiovascular morbidity, slowing the progression of renal disease, and improving the transition to dialysis or transplant. These programs are heterogeneous between different practices but often include a subset of nephrologists, physician assistants or nurse practitioners, nurses, social workers, dieticians, and pharmacists. Many of the services that are included in these programs such as social workers, nutrition counseling, nursing care, and pharmacist interventions are not paid for by standard fee-for-service payments; therefore, there is a large need to prove that these interventions are clinically effective as well as cost effective. There is growing literature that shows that multidisciplinary programs can decrease hospitalizations, improve arterial–venous access placement before hemodialysis, and decrease mortality both before and after the initiation of dialysis.

Using evidence-based guidelines has been shown to improve outcomes of patients with CKD. One study by Snyder and Collins[134] demonstrated that adherence to the Kidney Disease Outcomes Quality Initiative preventive health-care guidelines decreased atherosclerotic heart disease. These authors found that the more preventive measures used per year, including two creatinine measurements, lipid measurement, calcium–phosphorus measurement, PTH measurement, HbA1c measurement, and influenza vaccine, decreased the risk of atherosclerotic heart disease in a high-risk Medicare cohort with CKD. Guideline-driven care in a multidisciplinary program is often implemented by a physician extender. Lee *et al.*[135] showed that a nurse practitioner using guideline-directed care was more effective

in decreasing hospitalizations after initiation of dialysis. They also had a substantial increase in patients starting dialysis with an arterial–venous access in 5 years; 62% had arterial–venous access in the nurse practitioner group compared with 20% in a renal hypertension clinic.[135]

Several other studies also showed decreased hospitalization rates and improved arterial–venous access using a multidisciplinary model. Cohorts of patients who had attended multidisciplinary programs in California, Canada, and Taiwan showed dialysis starts with increased number of functioning arterial–venous accesses, and with either decreased number of inpatient days or decreased number of hospitalizations.[136–138] Decreased hospitalizations by outpatient dialysis starts and the use of arterial–venous access achieved by multidisciplinary programs also result in health-care savings. According to the USRDS (United States Renal Data System) database, the inpatient cost per member per month for dialysis initiation ranges from $9846 for Medicare recipients up to $22,841 for patients with commercial insurance; this could be greatly reduced by increasing outpatient dialysis starts.[139] A functional arterial–venous fistula is associated with a difference of approximately $3000 dollars per patient per year compared with a hemocatheter, and the total yearly dialysis expenditure for a patient with a hemocatheter averages $90,110 compared with $64,701 for a patient with a fistula.[139] Proponents of multidisciplinary programs maintain that the cost savings of these programs outweigh the personnel and increased health-care utilization costs. A study in Taiwan found that the patients in the interdisciplinary program studied for 6 months before dialysis initiation had a mean cost of $1200 per patient less than those patients who had seen a nephrologist only.[138]

Patient education and multidisciplinary care through different models have decreased both the rate of kidney disease progression and the rate of reaching ESRD. A randomized controlled trial demonstrated that one 90-min educational session with a follow-up phone call every 3 weeks significantly decreased the time to dialysis by $\sim$3 months in patients expected to start dialysis within 6–18 months.[140] Richards *et al.*[141] studied a cohort of patients with eGFRs <30 ml/min in a primary care program in England who had access to a nurse, patient education, medication management, and dietary advice. They found that the program significantly decreased the rate of fall of eGFR, and the impact was greatest in those patients whose eGFR was falling the fastest, >5 ml/min in the 9 months before the study. The positive impact of multidisciplinary programs has also been demonstrated in patients with higher eGFRs, those between 30 and 59 ml/min. A study in a health maintenance organization population found that the rate of eGFR decline was less in patients who enrolled in an interdisciplinary care model compared with historical controls.[142] Given that the average cost per patient per year for hemodialysis, peritoneal dialysis, and transplant is $77,506, $57,639, and $26,668, respectively, delaying ESRD would likely result in a considerable cost savings.[139]

Access to a nephrologist for >1 year before dialysis initiation has been shown to decrease mortality for patients with CKD.[143,144] Multidisciplinary care has also been shown to decrease mortality both before and after the initiation of dialysis. Two studies compared outcomes of patients who initiated hemodialysis and found that those patients who had been followed up in a multidisciplinary program before dialysis starts had lower mortality rates.[145,146] Hemmelgarn *et al.*[147] compared a predialysis cohort of patients who had multidisciplinary care to a cohort of propensity-matched controls and found significantly decreased mortality rates in the patients exposed to the multidisciplinary intervention.

Multidisciplinary care has been shown to improve outcomes in patients with CKD and is likely cost effective. However, most of the evidence is from small cohorts and not randomized controlled trials. In addition, there is likely a publication bias with only centers that have positive outcomes publishing their data. These programs likely improve care in this patient population, and more rigorous study is needed to demonstrate their benefit and ability to decrease costs.

CONCLUSIONS

The increasing use of treatments to attenuate progressive CKD, most notably glycemic control in diabetic CKD and blood pressure treatment with ACE inhibitors and ARBs in almost all forms of CKD, have coincided with a plateau in the incidence of ESRD in the United States over the past few years.[139] This is a very welcome change after decades of increasing incidence and is likely related to the use of these treatment options. However, a stable rate of incidence at over 100,000 people per year is not good enough, and the field has not seen a truly new therapy for slowing progression in over a decade.

Organized multidisciplinary clinics seem to be an effective means to apply the tools we have. However, these tools are far from perfect. One can consider a clinical trial as something akin to such a clinic, and subjects in the trials taking ACE inhibitors or ARBs still progressed, although more slowly than subjects on the comparators. If a better result than a stable incidence of ESRD is to be achieved, then new therapies are needed. Obviously, basic research will be critical. Although beyond the scope of this review, recent findings such as the deleterious reactivation of the role of NOTCH pathway in CKD and the discovery of *APOL 1* (*apolipoprotein L, 1*) polymorphisms conferring risk for focal segmental sclerosis are strong examples of such basic research with potential drug targets.[148,149] New reliable markers of renal disease that would allow faster, smaller, and therefore less expensive trials are highly desirable. Finally, testing of relatively simple and cheap approaches such as bicarbonate and nutritional vitamin D that will not be supported by the pharmaceutical industry seems overdue.

DISCLOSURE

All the authors declared no competing interests.

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