Slowing progression of chronic kidney disease

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Early identification of chronic kidney disease (CKD) provides an opportunity to implement therapies to improve kidney function and slow progression. The goal of this article is to review established and developing clinical therapies directed at slowing progression. The importance of controlling blood pressure will be discussed along with the target blood pressure that should be achieved in CKD patients. Therapy directed at inhibiting the renin–angiotensin–aldosterone system remains the mainstay of treatment with single-agent inhibition of this system being as good as dual blockade with fewer adverse effects. Other therapies that may be used include correction of metabolic acidosis, dietary protein restriction, and new models for delivering care to patients with CKD. Emerging therapies targeting endothelin, uric acid, kidney fibrosis, and oxidant stress hold promise for the future.

The increasing incidence and prevalence of chronic kidney disease (CKD) is placing significant health burdens on patients and costs on our already stressed health-care system. Screening programs and the reporting of estimated glomerular filtration rate (eGFR) are leading to earlier identification of CKD. This review will focus on what can be done to slow progression of CKD once it is identified. Progression of kidney disease is defined in this review as a loss of GFR over time and includes the need to initiate renal replacement therapy. The mechanisms of kidney disease progression will not be discussed, but all of the therapies derive from what we have learned from the pathophysiology of progression. Translation of preclinical studies to clinical trials has been informative, but has not always yielded consistent results between animals and humans. Advances have been made in defining risk factors and biomarkers to identify patients at highest risk for progression, which allows clinicians to better target the intervention strategies that will be discussed.

Early detection of kidney disease not only allows the clinician an opportunity to impact progression, but also to manage the complications of CKD such as anemia, mineral and bone disorders, hypertension, and cardiovascular disease. In addition, it is important to have enough lead-time to prepare for renal replacement therapy. These topics will not be discussed in the current review but are an integral part of managing the CKD patient.

BLOOD PRESSURE CONTROL

Hypertension and CKD are inextricable. Over 80% of patients with CKD have hypertension and the prevalence increases with more advanced CKD. Elevated blood pressure (BP) is a major risk factor for both progression of nephropathy and incident end-stage renal disease (ESRD) in the general population.[1] As a result of this close link between hypertension and CKD, it has long been assumed that aggressive lowering of BP reduces progression of CKD. National and international guidelines recommend lower BP targets for patients with CKD, especially in the presence of proteinuria.[2]

The evidence supporting these recommendations is based on observational studies and secondary analyses of clinical trials. In observational studies, lower achieved BP during treatment of hypertension is associated with slower decline in eGFR and reductions in renal events and all-cause mortality. However, clinical trials in patients with CKD have failed to

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demonstrate that lower BP targets slow progression. In both the African American Study of Kidney Disease and Hypertension (AASK) and Modification of Diet in Renal Disease study (MDRD), aggressive lowering of BP to a mean arterial pressure of <92 mm Hg did not slow progression of CKD.[3,4] A potential reduction in progression of CKD with the lower target was observed in hypothesis generating subgroup and secondary analyses but the benefit was only observed in the minority of patients with significant proteinuria. Similar lack of benefit with aggressive targeting of BP in CKD was observed in REIN-2 and smaller studies in diabetic and non-diabetic CKD.[5] A systematic review of BP targets in CKD examined 2272 subjects with non-diabetic kidney disease comparing two different levels of BP control.[6] This review included subjects from AASK, MDRD, and REIN-2 and so not surprisingly demonstrated a BP target of 125/75 to 130/80 mm Hg was not better than 140/90 mm Hg. Furthermore, to achieve the lower BP goal required more medications and was associated with more adverse events.

Given the negative results from all of the major target BP trials in CKD, the appropriate goal BP to slow progression of CKD is unknown. A target BP of ≤140/90 mm Hg seems reasonable. This goal is consistent with recent KDIGO guidelines for the BP target in CKD although KDIGO also recommended a BP ≤130/80 if urine albumin excretion was ≥30 mg per 24 h.[2]

Further evidence that aggressive lowering of BP may not slow progression of CKD comes from clinical trials in the general hypertensive population. The incidence of CKD was not reduced in the intense BP arms in multiple large randomized trials including SHEP, UKPDS, HOT, and ACCORD. As with nearly all hypertension trials, the target BP was based on clinic measurements in AASK, MDRD, and the hypertension trials in the general hypertensive population. Other methods for measuring BP may provide more precise estimates of the risk for adverse clinical outcomes associated with hypertension. Night time BP from ambulatory BP monitoring and central BPs may be more appropriate targets as they have been shown to be better predictors of cardiovascular events and all-cause mortality. Further research is needed to evaluate whether targeting lower ambulatory or central BP may reduce progression of CKD.

The Systolic Blood Pressure Intervention Trial (SPRINT) is a 9-year study designed to test the benefits of an intense clinic BP target (systolic BP <120 mm Hg) versus a standard clinic BP target (<140 mm Hg) for adults who are at risk for heart or kidney disease (NCT01206062). This trial is expected to be completed in 2018 and will be important for guiding decisions regarding the BP goal in CKD.

INHIBITION OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The renin–angiotensin–aldosterone system (RAAS) has a pathophysiologic role in the progression of CKD.[7] Mechanisms for these adverse effects include preferential constriction of the efferent arteriole leading to glomerular hypertension, direct effects of angiotensin II on increasing mesangial cell proliferation and matrix expansion, and promotion of inflammation. RAAS can be blocked at multiple steps with a number of different drugs that include angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), renin inhibitors, and aldosterone antagonists.

RAAS blockade has preferential effects on reducing proteinuria and slowing progression of CKD compared with other agents.[8,9] A beneficial effect has been demonstrated in both diabetic and non-diabetic kidney disease, and with ACEI and ARBs. In diabetics, RAAS blockade slows progression from normoalbuminuria to microalbuminuria; from microalbuminuria to overt diabetic nephropathy; as well as the progression of established diabetic nephropathy. However, in a trial of normotensive type 1 diabetics early treatment with ARB or ACEI did not slow nephropathy progression measured as either the fraction of glomerular volume occupied by mesangium or incidence of micro-albuminuria.[10] The magnitude of these beneficial effects of RAAS blockade is estimated to be about a 20% risk reduction. Beneficial effects of ACEI have even been demonstrated in patients with advanced CKD.[11]

Aldosterone antagonists have beneficial effects in many different animal models of kidney disease. In human disease, most studies have only examined the surrogate end point of proteinuria.[12] These have been small studies with short-term follow-up and have not addressed the effects of aldosterone antagonism on progression of CKD.

DUAL BLOCKADE OF THE RAAS

On the basis of preclinical studies, and the reasoning that single agents directed at inhibiting RAAS do not completely block the system, studies combining drugs to inhibit the RAAS pathway at more than one site have been performed. The most common combination has been an ACEI plus an ARB. Initial animal and clinical studies demonstrated a beneficial effect of dual therapy on the surrogate end point of proteinuria. Also, a meta-analysis demonstrated a greater reduction in proteinuria with combination therapy, but did not examine GFR end points.[13] The field was misled by the COOPERATE study that demonstrated a dramatic beneficial effect of dual blockade on long-term renal outcomes, but the study was subsequently retracted because of inconsistencies with the data.[14] Enthusiasm for dual therapy was subsequently reduced by the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial.[15,16] In this study, 25,620 subjects with established atherosclerotic vascular disease or diabetes with end-organ damage were randomized to receive the ACEI ramipril, ARB telmisartan, or both drugs. Combination therapy was associated with a higher occurrence of the composite primary renal outcome of dialysis, doubling of serum creatinine and death. Interestingly, there was dissociation between a greater reduction in proteinuria with combination therapy but worse renal outcomes.

The ALTITUDE trial studied the effects of adding the renin inhibitor aliskiren to ACEI or ARB therapy.[17] This study was terminated early secondary to adverse outcomes including hyperkalemia, hypotension, and stroke. Also the VA multicenter trial in type 2 diabetics with nephropathy examining the effects of combining losartan and lisinopril versus losartan alone (NEPHRON-D) was recently stopped because of a higher incidence of adverse events in the combination group.[18]

In a systematic review and meta-analysis of dual blockade versus monotherapy, 33 randomized controlled trials stratified for patients with and without heart failure were analyzed.[19] This study was not directed at patients with CKD. Dual blockade did not improve all-cause or cardiovascular mortality but was associated with a reduction in hospitalizations for heart failure compared with monotherapy. However, dual therapy was associated with a higher incidence of hypotension, hyperkalemia, renal failure, and withdrawal of treatment because of adverse events. A recent meta-analysis examining the safety of combined versus single RAAS blockade in CKD patients demonstrated a greater reduction in proteinuria and GFR without any benefit on the outcomes of doubling of serum creatinine, hospitalization, or mortality.[20] Similar to other studies, combination therapy was associated with a higher risk of hyperkalemia and hypotension. Based on these studies, dual blockade of RAAS is not recommended.

BICARBONATE SUPPLEMENTATION
Acidosis is a common finding in CKD related to decreased ammoniagenesis secondary to a reduction in renal mass, although ammoniagenesis per single nephron is increased and may have a role in promoting interstitial fibrosis through activation of complement. Bicarbonate therapy has reduced injury in some animal models of kidney disease. Observational studies in humans have demonstrated a relationship between low serum bicarbonate and progression of kidney disease. A trial of 134 subjects with creatinine clearance 15–30 ml/min per 1.73 m^2 and serum bicarbonate concentration 16–20 mmol/l randomized participants to usual care or supplementation with bicarbonate for 2 years. Bicarbonate supplementation resulted in a slower decline in renal function along with a decrease in the number of patients developing ESRD.[21] The effects of sodium bicarbonate, sodium chloride, or placebo on the rate of eGFR decline in 120 subjects with macroalbuminuric hypertensive nephropathy demonstrated that after 5 years the rate of eGFR decline was slower in the bicarbonate group.[22] On the basis of this evidence, it is reasonable to maintain serum bicarbonate concentration > 22 mmol/l in CKD patients.[2]

ENDOTHELIN ANTAGONISTS
Endothelins (ETs) are vasoconstricting peptides with ET-1 being the major isoform in the human kidney. ET-1 has a number of potentially adverse effects on the kidney such as vasoconstriction, glomerular hypertension, proteinuria, and interstitial fibrosis. Elevated circulating and kidney levels of ET-1 have been found in diabetics as enhanced expression of the ET A receptor. Preclinical studies have demonstrated that ET-1 antagonism reduces proteinuria and improves GFR. However, a multicenter randomized trial of the ET antagonist avosentan versus placebo was terminated after 4 months because of excess cardiovascular events in the avosentan group.[23] There was less proteinuria with avosentan but no difference in time to doubling of serum creatinine, ESRD, or death. Atrasentan is another ET antagonist that is more selective for the ET A receptor. Patients with type 2 diabetes, eGFR > 20, and urine albumin-to-creatinine ratio 100 to 3000 mg/g were randomly assigned to placebo or 0.25, 0.75, or 1.75 mg of atrasentan for 8 weeks.[24] Atrasentan significantly reduced albuminuria with the two higher dosages. Edema was most common with the highest dose. Interestingly, the antiproteinuric effect was greater in Hispanic subjects suggesting some ethnic variability in response. Further studies are needed to clarify the role of ET antagonists in slowing the progression of CKD.

OTHER TARGETS AND TREATMENTS
Inflammation and oxidant stress have a role in progressive kidney diseases and have been a target of therapy using bardoxolone, a drug that activates nrf2, a transcription factor that controls 250 different cytoprotective proteins. Bardoxolone improved GFR in type 2 diabetics with nephropathy, an effect that persisted through the 52 weeks of study.[25] However, a follow-up phase III study of bardoxolone that targeted renal events was stopped 'for safety concerns because of excess serious adverse events and mortality in the bardoxolone arm'.[26] No further studies targeting this pathway are currently underway.

Dietary protein restriction is a therapy that improved the course of most experimental renal diseases and was beneficial in many small clinical trials. However, no beneficial effects were seen in the larger randomized controlled MDRD study. Recently, the Cochrane Collaboration examined the effects of low-protein diets in non-diabetic kidney disease and demonstrated a reduction in the incidence of ESRD.[27] A total of 2000 patients were analyzed from 10 different clinical trials. The article concluded that to avoid one renal death, 2–56 patients needed to be treated with a low-protein diet for 1 year. The negative results from the MDRD trial combined with the difficulty of adhering to a low-protein diet have resulted in decreased use of dietary protein restriction as a therapy for slowing progression.

Small studies have demonstrated a beneficial effect of statin therapy on the course of CKD. This issue was definitively addressed in the Study of Heart and Renal Protection (SHARP) study that examined the effects of lowering low-density lipoprotein cholesterol with simvastatin plus ezetimibe in a randomized placebo-controlled trial.[28] The study involved 9270 patients; 3023 were on dialysis. A beneficial effect of therapy on the primary end point of first major atherosclerotic event was seen but there was no effect

on the secondary outcome of renal disease progression defined as development of ESRD, death, or doubling of serum creatinine

Treatment aimed at lowering serum uric acid levels have been based on benefit in preclinical studies and observational studies demonstrating a relationship between hyperuricemia and decline in GFR. Potential pathophysiologic effects of uric acid include promotion of interstitial inflammation, inhibition of endothelial nitric oxide release, and stimulation of the renin–angiotensin system. Early clinical data suggested a similar benefit. In a randomized controlled trial of 113 patients with eGFR < 60, treatment with allopurinol 100 mg/day versus usual therapy for 24 months resulted in lowering of uric acid, less of a decline in eGFR, and decreased cardiovascular events.[29] Confirmatory data are needed before lowering uric acid becomes front-line treatment to reduce progression of CKD.

The Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that patients with type 1 diabetes treated early in the course of their disease with intensive diabetes therapy had a lower risk of developing eGFR < 60 ml/min per 1.73 m^2 than those treated with conventional therapy when followed for median period of 22 years.[30] In addition, they exhibited a slower rate of reduction of GFR and a lower incidence of ESRD. This study provides some of the strongest evidence for the benefit of aggressive diabetes management.

Other therapies are in various stages of assessment for their effects on slowing progression.[31] Targets are renal fibrosis with treatments that include the anti-fibrotic agent pirfenidone, interruption of the transforming growth factor-β pathway, doxycycline through inhibition of matrix metalloproteinases, and an anti-connective tissue growth factor monoclonal antibody FG-3019. Therapies are also targeting advanced glycation end products with B vitamins and their derivatives such as pyridoxamine. Pentoxifylline is a drug being studied for its effects on oxidant stress and inflammation. Ruboxistaurin, a protein kinase C inhibitor has been demonstrated to reduce proteinuria in animal models. These therapies are in early stages of development and the clinical utility and safety await further studies.

DELIVERY OF CKD CARE

The way we deliver care to CKD patients may also affect health outcomes. For example, multidisciplinary CKD programs (CKD clinics) are associated with better adherence to CKD guidelines, a higher incidence of fistula use at initiation of dialysis, and more outpatient dialysis starts (versus emergency inpatient starts).[31] Also, early referral to a nephrologist is associated with improved outcomes once patients initiate dialysis. We are piloting a telehealth-care model at the Minneapolis VA Health Care System that combines home telehealth technology in which patients can be closely monitored and educated about CKD at home, with an interprofessional care team that is implementing CKD guidelines.

CONCLUSION

In conclusion, slowing progression of kidney disease is a critical goal for CKD patients. Lowering BP may be important but the exact target is unclear. RAAS blockade can slow progression and is the most widely studied and used treatment. Single-agent inhibition of the RAAS should be used as dual blockade is not more efficacious and is associated with a higher incidence of adverse events. Serum bicarbonate > 22 mmol/l, low-protein diets (in non-diabetic kidney disease), and lowering uric acid may all be effective at reducing progression although the evidence is not robust. More effective ways of delivering CKD care may also be important in improving CKD outcomes. Future therapies directed at ET-1, fibrosis, oxidant stress, and inflammation are being studied with the hope that our therapeutic armamentarium will increase in the future.

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