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