Progression of Chronic Renal Failure

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Chronic renal failure is characterized by a persistently abnormal glomerular filtration rate. The rate of progression varies substantially. Several morphologic features are prominent: fibrosis, loss of native renal cells, and infiltration by monocytes and/or macrophages. Mediators of the process include abnormal glomerular hemodynamics, hypoxia, proteinuria, hypertension, and several vasoactive substances (ie, cytokines and growth factors). Several predisposing host factors may also contribute to the process. Treatments to delay progression are aimed at treating the primary disease and at strictly controlling the systemic blood pressure and proteinuria. The role of antihypertensive agents, statins, and use of other maneuvers such as protein restriction and novel approaches are also discussed herein.

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Chronic renal failure is characterized by a persistently abnormal glomerular filtration rate (GFR). It represents an evolving process that is initiated by various causes, all with the common end result of persistent and usually progressive damage of varying severity to the kidneys. However, the rate of decline, often referred to as progression, can vary substantially. The present article will discuss processes that affect progression after the initial renal insult has occurred.

Chronic renal failure is a common problem. In the third National Health and Nutrition Examination Survey done from 1988 to 1994, 3% of the US adult population was found to have elevated serum creatinine values. Once the renal failure is well established, the rate of progression can be estimated, although limitations exist.

Many features are common to progression of renal failure of various causes, and the final histologic appearance is one of glomerulosclerosis, interstitial fibrosis, and loss of native renal cells. Nevertheless, the causes of chronic renal failure are heterogeneous, and the mechanisms and locations of the initial injury may vary. Different animal models emphasize different aspects of the pathophysiologic characteristics and only incompletely replicate clinical disease.

MORPHOLOGIC CHANGES

Several morphologic features are prominent: fibrosis; loss of normal renal cells, mainly by apoptosis; and infiltration by monocytes and/or macrophages. These represent the end result of the constant interplay between vasoactive substances (ie, cytokines and growth factors).

Impairment of renal function correlates better with the extent of tubulointerstitial injury than with histologic glomerular injury. Interstitial fibrosis results from increased synthesis and decreased breakdown of extracellular matrix (ECM). The abnormal ECM contains an excess of normal components such as fibronectin, laminin, proteoglycans, and type IV collagen. Apart from the evident histologic changes, alterations in the ECM composition also change the ways the cells interact with the ECM, and these in turn affect gene regulation in response to specific growth factors. The details remain an active area of inquiry.

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Myofibroblasts (cells containing features of smooth muscle cells and of fibroblasts) are involved in the fibrogenic process and can secrete alpha 2(1) and alpha 2(III) collagens and fibronectin. Their origins vary because several types of intrarenal cells can transdifferentiate into myofibroblasts. Moreover, in animal models, injured tubular cells also contribute to the development of interstitial fibrosis.14

Physiologic cell death is a normal event in tissue homeostasis and is important for removal of unnecessary or damaged cells. In the context of renal disease, the balance between cell proliferation and apoptosis plays a critical role in maintaining an optimal number of cells after an insult. In chronic renal failure, there is a loss of normal resident cell population thought to be caused by a combination of abundant profibrotic stimuli and diminished antiapoptotic stimuli. Examples of the former are transforming growth factor β (TGF-β), tumor necrosis factor (TNF), Fas ligand (FasL), and interferon α. At the same time, the normal ECM, probably through interaction with cell-surface β-integrin receptors, inhibits apoptosis. Because the normal ECM becomes replaced by an abnormal one, its antiapoptotic effect is lost. The end result is a decreased population of the normal glomerular and tubular epithelial cells.

The Fas apoptosis pathway is initiated by the binding of FasL to Fas, which triggers a cascade of intracellular signals that results in apoptotic deletion of Fas-bearing target cells. Fas and FasL are constitutively expressed in renal tubular cells. Animal studies suggest that up-regulation of Fas in the tubules in response to cytokines favors its binding to FasL located on adjacent cells and thus leads to apoptosis. Tissue hypoxia from decreased perfusion of the microvasculature in chronic renal failure also stimulates Fas-mediated apoptosis. In addition, podocyte apoptosis may play an early role in progression of diabetic nephropathy and in focal segmental glomerulosclerosis.

Monocytes and/or macrophages are recruited by cytokines, which are overexpressed in chronic renal failure. As a response to injury, overexpression of macrophage colony stimulating factor by the tubules drives local macrophage proliferation in the kidney. Plasma levels of neopterin, a marker of monoocyte activation, increase progressively with worsening clinical renal function. Macrophage infiltration in the interstitium correlates with the degree of renal dysfunction. These cells amplify the response by producing more cytokines, which promote further fibrosis and apoptosis. Treatment modalities that decrease chemotaxis ameliorate renal failure. Experimentally, macrophage-derived cytokines, including interleukin (IL) 1β, IL-6, and TNF-α, inhibit expression of vascular endothelial growth factor (VEGF); this is probably partly responsible for impaired angiogenesis and capillary loss. Recently, mast cells in the interstitium have been found to correlate with severity of interstitial fibrosis in patients with various glomerulonephritides. There is also association with its growth factor and myofibroblasts suggests that these cells may be involved in progression of interstitial fibrosis as well.

MEDIATORS OF INJURY

For purposes of the present discussion, mediators are factors and processes that perpetuate renal dysfunction after an initial insult of sufficient severity has occurred. They usually occur as a consequence, no matter how remote, of the initial renal damage (Figure).

Hemodynamics

In rats subjected to subtotal nephrectomy, compensatory hyperfiltration of the spared nephrons helps to maintain overall GFR. However, this adaptation also leads to glomerular hypertension, proteinuria, and progressive chronic renal failure. The stretching of the capillary tuft also stretches the adjacent mesangial cells, which induces mesangial cell proliferation and glomerulosclerosis at least partly by overexpression of cytokines such as platelet-derived growth factor (PDGF) and monococyte chemoattractant protein 1.

Early diabetic nephropathy is well known to be associated with an elevated GFR. Experimentally, increased glomerular capillary hydraulic pressure and hyperfiltration occur (despite normal systemic pressures) due to a proportionally greater reduction in the afferent relative to efferent arteriolar resistance. Indirect measurements suggest that glomerular capillary hypertension is present in human patients with diabetes as well, and there is also a correlation between urine albumin excretion and the glomerular pressure but not systemic pressure. Thus, as in the remnant kidney model, the glomerular hypertension in diabetic nephropathy itself propagates chronic GFR decline, at least partly by increasing protein leakage across the glomerular capillaries into the Bowman space. Apart from increased glomerular capillary hydraulic pressure, cytokines activated by injury may counteract tonic mesangial cell contraction and also contribute to hyperfiltration.

Hyperfiltration has not been well studied in nondiabetic human
renal disease, and the extent to which this occurs in humans is not known for certain. Keller et al \(^4\) recently found that white hypertensive patients have fewer but larger glomeruli, suggesting compensatory hyperfiltration. Modeling of human lupus nephritis also suggests that hyperfiltration occurs and is indeed beneficial, at least in the short term. \(^8\) Studies of patients who have undergone unilateral nephrectomy have shown no deterioration in renal function. \(^45-47\) However, there may be a critical renal mass below which hyperfiltration becomes detrimental. Patients with greater than 50% loss of renal mass have been shown to have a long-term increased risk for proteinuria and renal insufficiency. \(^58\)

**Hypoxia**

Hypoxia has been regarded as a potential cause as well as effect of progression. There is loss of the postglomerular intertubular capillaries in chronic renal failure of various causes. \(^49\) Glomerular sclerosis is thought to contribute to this by decreasing downstream tubular blood flow. Expansion of the interstitial space may also diminish capillary perfusion of the tubules. \(^50\) The resultant hypoxia favors release of proinflammatory and profibrotic cytokines. Experimentally, this is associated with increased expression of the antiangiogenic factor thrombospondin 1 and decreased expression of the proangiogenic factor VEGF, which may impair angiogenesis and further propagate the hypoxia. \(^33\)

Cellular hypoxia prevents degradation of the transcription factor hypoxia-inducible factor 1, which then becomes available to bind to hypoxia-response elements in genes that are switched on by hypoxia. \(^21\) One such hypoxia-response element has been found in the tissue inhibitor of metalloproteinase 1 promoter. \(^32\) Apart from this, hypoxia has been found to increase expression of endothelin (ET) \(^1\) \(^3\) and collagen alphal (1) and to decrease expression of collagenase. \(^22\) Tubular hypoxia also favors expression of Fas in the tubular cell membrane and apoptosis. \(^23\)

**Proteinuria**

Proteinuria occurs as a result of glomerular capillary hypertension and damage to the permeability barrier in the glomerulus. Protein leaking across the glomerulus is taken up by the proximal tubule cells by endocytosis. This causes protein overload on the proximal tubular cells, leading to increased activation of the intrarenal angiotensin-converting enzyme (ACE) \(^34\) and also, either directly or via activation of transcription factors, \(^55\) to abnormal production of the following cytokines: ET-1, monocyte chemoattractant protein 1, and RANTES (regulated on activation, normal T-cell expressed and secreted). \(^36\) The cytokines favor fibrosis, apoptosis, and monocytic infiltration, further propagating the process.

In proteinuric animals, there is also direct translocation of growth factors such as TGF-\(\beta\) and hepatocyte growth factor directly from plasma into tubular fluid. These then interact with receptors located at the apical membrane of tubular cells to promote interstitial fibrosis. \(^37,38\)

Specific protein metabolites may also be involved in the progression of chronic renal failure. Indoxyl sulfate, one such metabolite, has been shown to increase glomerulosclerosis in animals \(^59\) by increasing renal TGF-\(\beta\) synthesis, both directly and by promoting the expression of intercellular adhesion molecule 1, the latter leading to monocyte infiltration. \(^60\) Elevated urinary levels of this metabolite also correlate with a more rapid progression in humans. \(^61\) Animal and human studies have shown decreased serum and urinary indoxyl sulfate levels by using AST-120, an oral adsorbent. \(^62,63\)

In the presence of impaired glomerular permeability, transferrin in association with iron also enters the tubular lumen and is taken up by the proximal tubule cells. Such accumulation has been demonstrated in human chronic renal disease. \(^64\) In vitro evidence using human proximal tubular epithelial cells indicates that iron-mediated lipid peroxidation \(^65\) and complement activation by the apotransferrin component \(^66\) contribute to toxic effects.

Consistent with its role in pathophysiology, proteinuria is a strong predictor of clinical progression of renal disease. The rapidity of GFR decline is proportional to the severity of proteinuria. \(^67\)

**Systemic Hypertension**

Systemic hypertension is a frequent accompaniment to chronic renal disease. Sodium, volume excess, and activation of the renin-angiotensin-aldosterone system in patients with chronic renal failure all cause hypertension. In addition, afferent stimuli from the kidneys may activate the sympathetic nervous system and contribute to the elevated pressure. \(^68\) Hypertension itself accelerates decline in renal function, \(^69\) \(^71\) likely due to the associated increased glomerular capillary hypertension.

**Complement Activation**

There is at least 1 animal model in which proteinuria is ameliorated by inhibition of complements. \(^72\) Clinically, patients with proteinuria have been shown to excrete complement degradation products into the urine. \(^73\) Because of abnormal glomerular permeability, complement can enter the tubular lumen and initiate formation of the C5b-9 membrane attack complex. \(^74\) Exposure of tubular cells to an unidentified component of serum protein have also been shown to cause increased synthesis and release of complements by the cells themselves, predominantly toward the basolateral component. \(^75\) It has also been suggested that hyperammoniagenesis resulting from intratubular catabolism of excessive protein load also leads to complement activation and consequent interstitial scarring. \(^75\)

**Angiotensin II**

Angiotensin II (AII) is formed by progressive cleavage of angiotensinogen. The kidneys contain all the machinery necessary to generate AII locally. \(^76\) This local intrarenal renin-angiotensin system is regulated independently of the systemic one and plays a critical role in renal auto-regulation and pathophysiologic de-
development. Enhanced sensitivity to effects of locally produced AII is present in diabetic rats and has been postulated in an animal model of non-diabetic renal failure.

Apart from its hemodynamic effects, AII also stimulates expression of fibronectin and several other downstream cytokines and growth factors that favor fibrogenesis and recruitment of macrophages. Examples are TGF-β, plasminogen activator inhibitor 1 (PAI-1), aldosterone, ET, and osteopontin, as well as possibly the transcription factor nuclear factor κB.

Other Chemical Mediators

As noted above, a growing list of vasoactive substances (ie, cytokines and growth factors) have been shown to be involved in progression of renal disease (Table 1). Cytokines and growth factors gain access to the kidneys by multiple pathways. They can be synthesized elsewhere and be ultrafiltered across the glomeruli and act on tubular cells through apical receptors. They can be synthesized in the renal tubules and by infiltrating monocytes. More importantly, they can be synthesized elsewhere and be ultrafiltered across the glomeruli and act on tubular cells by infiltrating monocytes. Inducible nitric oxide synthase catalyzes this reaction: constitutive endothelial nitric oxide synthase, neuronal nitric oxide synthase, and inducible nitric oxide synthase. Nitric oxide inhibits mesangial cell proliferation and ECM synthesis and may limit capillary permeability. In rat models, nitric oxide inhibition results in proteinuria, increased blood pressure, and decreased GFR independent of renal AII levels. Collagen I expression is also increased, independent of systemic hemodynamics. It has been suggested that nitric oxide inhibits collagen I expression in the renal vasculature, and the detrimental effects of endogenous AII are increased in states of low nitric oxide availability. A polymorphism of the endothelial nitric oxide synthase gene has been described and found to be associated with development of diabetic nephropathy, suggesting that the associated lower mean plasma nitric oxide level may translate into decreased suppression of ECM synthesis.

Total nitric oxide production has been shown to be low in chronic renal failure in most, but not all, studies. The major source of endogenous arginine is normally the proximal tubules. Whole-body L-arginine synthesis of arginine remains normal in hemodialysis patients and may reflect compensatory extrarenal synthesis. The extent to which local arginine availability may affect nitric oxide production locally is unclear. Parathyroid hormone, which is elevated in chronic renal failure, down-regulates nitric oxide synthase expression. Various substances overexpressed in renal failure (PAI-1, asymmetric dimethylarginine, PDGF, TGF-β, and ET-1) can inhibit nitric oxide synthase, thereby diminishing conversion of L-arginine to nitric oxide. In patients with diabetes, scavenging of formed nitric oxide by advanced glycosylation end products may also contribute to the decreased nitric oxide levels.

Table 1. Selected Cytokines and Growth Factors Involved in Progression of Chronic Renal Failure

<table>
<thead>
<tr>
<th>Cytokine/Protein</th>
<th>Source</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 4</td>
<td>Resident cells</td>
<td>Antinflammatory</td>
</tr>
<tr>
<td>Macrophage-colony stimulating factor</td>
<td>Resident cells</td>
<td>Promotes proliferation</td>
</tr>
<tr>
<td>Insulinlike growth factor 1</td>
<td>Resident cells</td>
<td>Growth promoting</td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>Resident cells</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Renal tubular cells</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Thrombospondin 1</td>
<td>Renal mesangial cells</td>
<td>ECM stabilization</td>
</tr>
<tr>
<td>Stem cell factor</td>
<td>Renal mesangial cells</td>
<td>Stem cell proliferation</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
<td>Renal mesangial cells</td>
<td>ECM stabilization</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
<td>Renal mesangial cells</td>
<td>ECM stabilization</td>
</tr>
<tr>
<td>RANTES (regulated on activation, normal T cell expressed and secreted)</td>
<td>Renal tubular cells</td>
<td>Chemotaxis</td>
</tr>
<tr>
<td>Connective tissue growth factor</td>
<td>Renal mesangial cells</td>
<td>ECM stabilization</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Renal mesangial cells</td>
<td>ECM stabilization</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Endothelial cells</td>
<td>Vasoactive</td>
</tr>
</tbody>
</table>

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On the other hand, cytokines activated by injury may inappropriately activate inductive nitric oxide synthase. It has been proposed that the resultant relaxation of tonic mesangial cell contraction leads to hyperfiltration and contributes to progression of renal failure.

Aldosterone. Aldosterone levels are often elevated in normokalemic patients with chronic renal failure. Animal studies suggest that aldosterone may mediate progression of chronic renal failure. Subtotal nephrectomy in rats results in adrenal hypertrophy and elevation of plasma aldosterone level. ARB and an ACE inhibitor. Infusion of exogenous aldosterone restores the deleterious effects of subtotal nephrectomy, despite the concomitant administration of the ARB and the ACE inhibitor. These can be prevented by adrenalectomy.

Aldosterone has also been shown to up-regulate ACE messenger RNA expression in cultured neonatal rat cardiocytes, thus completing a positive feedback mechanism. Aldosterone increases PAI-1 expression and may induce renal injury through this mechanism. Alternatively, there is experimental evidence that aldosterone may mediate renal vascular damage independent of its effects on blood pressure. It has been hypothesized that fibrosis may then be a secondary effect of the vascular damage.

Endothelin. The ET system consists of 2 receptors, 3 ligands, and 2 activating peptidases. The 2 mammalian receptors are labeled ET-A and ET-B. The 3 ligands are ET-1, ET-2, and ET-3. All are constitutively synthesized and released by glomerular and tubular cells. Endothelin expression is favored by AII, IL-1, TGF-β, glucose, and hyperoxia, among others. Several actions mediated by ET may play a role in the progression of renal failure: blockage of inducible nitric oxide synthase transcription via the ET receptor; increased expression of the collagen 1 gene; vascular remodeling; mediation of proteinuria; macrophage chemotaxis; and stimulation of interstitial fibroblast proliferation and ECM synthesis. Endothelin may also mediate renal activation of nuclear factor κB, which in turn regulates the transcription of other genes involved in renal injury. Experimentally, the use of an ET receptor antagonist in combination with an ACE inhibitor improves proteinuria and histologic changes beyond what occurs with either agent alone. This suggests that ETs play a role in at least some animal models. In the rat subnephrectomy model, blockade of the ET receptor reduces proteinuria more than does nonselective blockade. It has also been shown that the ET receptor, but not the ET receptor, mediates salt sensitivity of AII-induced hypertension in the rat.

Platelet-Derived Growth Factor BB. Platelet-derived growth factor has been implicated in the progression of renal injury. It stimulates mesangial proliferation and increases ECM synthesis. Furthermore, overexpression of this cytokine, as well as its receptor, in the glomeruli and tubular and interstitial compartments has been demonstrated experimentally. Levels of PDGF are increased in response to AII, lipoproteins, ET, and other cytokines. Two chains, PDGF-A and PDGF-B, form the active homodimers or heterodimers. Experimentally, PDGF-BB, but not PDGF-AA, induces renal myofibroblast transdifferentiation and tubulointerstitial fibrosis.

ACE Gene Polymorphism

A 287-base-pair fragment in intron 16 in the ACE gene can either be present (the I allele) or absent (the D allele). Presence of the D allele is associated with elevated systemic ACE levels while the I allele is associated with the opposite effect. Both alleles are codominant such that the 3 resulting genotypes (II, ID, and DD) are associated with low, intermediate, and high amounts of circulating ACE, respectively. This relationship holds true for intrarenal ACE as well.

The D allele has been found in numerous studies to be either different or deleterious to the progression of renal failure, as noted in a recent review. A study in patients with IgA nephropathy indicated that the risk associated with the D allele was most apparent in patients without proteinuria or hypertension, suggesting a weaker effect compared with these 2 risk factors.

There remains controversy as to whether the presence of the D allele affects response to antiproteinuric therapy with ACE inhibitors. Conclusions from retrospective studies on nondiabetic nephropathy are divided, with some finding a poorer response with the I allele, and others with the DD genotype. A prospective study on type 1 diabetes mellitus has shown better response of albuminuria to ACE inhibitor treatment among those with the II genotype.

Other polymorphisms have also been studied, albeit to a lesser extent than that involving the ACE gene. Examples include the angiotensinogen M235T polymorphism, the chymase gene CM A/B polymorphism, and the angiotensin receptor A1166C polymorphism. Of these, the M235T polymorphism is thought to contribute to risk of developing chronic renal failure, though this remains undefined.

Smoking

Smoking has been found to be associated with progression in diabetic nephropathy, primary renal disease, and severe hypertension. Smoking is a risk factor for proteinuria independent of the presence of
diabetes and blood pressure\textsuperscript{145} and may contribute to progression because of the associated proteinuria. Elevation of ET-1 levels\textsuperscript{146} and acceleration of atherosclerosis and ischemic nephropathy\textsuperscript{147} may also be contributory. There are no prospective studies addressing whether smoking cessation ameliorates progression of renal failure.

**African American Descent**

In a prospective cohort study of previously untreated nondiabetic men with hypertension enrolled in the Multiple Risk Factor Intervention Trial (MRFIT), effective blood pressure control was associated with stable or improving renal function in nonblacks but not in blacks.\textsuperscript{148} A subsequent article\textsuperscript{149} involving all participants of the above MRFIT study found an increased risk of end-stage renal disease among blacks independent of several other factors. Analysis of the baseline characteristics of the Modification of Diet in Renal Disease study also identified black race as an independent predictor of a faster GFR decline.\textsuperscript{150}

Socioenvironmental factors and genetic background have been proposed to account for the tendency toward excessive disease progression in African Americans. Part of the greater susceptibility may be from increased cytokine activation: ET-1\textsuperscript{151} and TGF-\(\beta\)\textsuperscript{152} levels have been found to be more elevated in African Americans with hypertension than in their white counterparts.

**Diabetes Mellitus**

Men with diabetes have been found to have a higher incidence of end-stage renal disease ascribed to non-diabetic causes, even after accounting for age, ethnicity, income, blood pressure, cholesterol, and history of coronary artery disease.\textsuperscript{153}

**Male Sex**

Various studies have suggested that nondiabetic renal diseases progress more rapidly in men.\textsuperscript{154-158} However, the studies vary widely in design and methodology. Not all studies have clearly shown the effect of sex to be independent of other factors such as proteinuria, severity of hypertension, and smoking history. Various mechanisms have been reviewed elsewhere\textsuperscript{159,160} and include increased response to AII in men\textsuperscript{161} and estradiol's ability to reverse TGF-\(\beta\)1-mediated fibrogenesis.\textsuperscript{162}

**Hyperlipidemia**

Chronic renal failure is associated with elevation of triglyceride levels, oxidized low-density lipoprotein, lipoprotein (a), and decreased apolipoprotein (a). Renal failure itself may also promote hyperlipidemia by down-regulating the expression of the enzyme lecithin:cholesterol acyltransferase in the liver and its activity in the plasma.\textsuperscript{163}

Experimentally, hypercholesterolemia and hypertriglyceridemia can each promote proteinuria and tubulointerstitial injury,\textsuperscript{164} while treatment aimed at decreasing lipid levels ameliorates the rate of progression.\textsuperscript{165} Putative mechanisms of damage include stimulation of reactive oxygen species, inhibition of nitric oxide, modulation of mesangial growth and proliferation, monocyte infiltration,\textsuperscript{166} and stimulation of growth factor and cytokine release.\textsuperscript{166-168}

In humans, various lipid abnormalities have been associated with the development of new renal insufficiency\textsuperscript{169} and progression of established renal disease.\textsuperscript{150,170} However, a definite causal relationship is equivocal. Moreover, the component(s) of the dyslipidemic milieu most responsible for progression is not clearly defined.\textsuperscript{169,171} Elevation of total cholesterol levels, low high-density lipoprotein, elevated triglyceride levels, and apolipoprotein B–containing lipoproteins have all been implicated.\textsuperscript{169,172,173}

**Recreational Drug Use**

The use of heroin and other opiates\textsuperscript{174} and of cocaine has been found to be associated with increased risk for development of end-stage renal disease.\textsuperscript{175} Cocaine use may exacerbate hypertensive nephrosclerosis through progression of renal ischemia. It is unclear whether heroin and opiate use is causally related to the increased risk or represent only a surrogate marker.

**Prenatal Factors**

Animal studies have shown a decrease in glomerular number with induced intrauterine malnutrition\textsuperscript{176} but not with spontaneous low birth weight.\textsuperscript{177} In humans, the number of glomeruli correlates directly with the birth weight.\textsuperscript{178} There is also a direct correlation between low birth weight and chronic renal disease, which appears to hold true across races.\textsuperscript{179-181} While a resultant lowered renal reserve and any possibly compensatory glomerular capillary hypertension might theoretically accelerate progression to end-stage renal disease, it is not yet clear if the low birth weight itself is directly responsible for the increased incidence of chronic renal failure because hypertension\textsuperscript{182,183} and diabetes\textsuperscript{183,184} are also associated with retardation of intrauterine growth.\textsuperscript{185}

**TREATMENT**

The major steps involved in slowing the progression of renal failure are outlined in Table 2. More detail is provided below.

**Treatment of Underlying Disease**

Treatment of some causes retards progression to chronic renal failure. Experimentally, antagonism of PDGF during the acute phase of an animal model of mesangioproliferative nephritis prevented functional and morphologic changes of chronic renal failure from developing.\textsuperscript{133} Clinically, this may involve treatment of acute disease, although this is not invariable. For example, even in established chronic diabetic nephropathy, euglycemia of 10 years' duration following pancreatic transplantation has been shown to reverse histologic renal lesions.\textsuperscript{186}

At the other extreme, there is encouraging if early evidence that at least in some animal models, more specific downstream therapy may be useful for well-established chronic disease. Examples include use of relaxin (which decreases macrophage infiltration and interstitial fibrosis independent of hemodynamic effects\textsuperscript{187}), VEGF,\textsuperscript{188} and aldosterone antagonists.\textsuperscript{189}
Treatment of Hypertension

The renal benefit of treatment depends to a significant extent on the underlying proteinuria. This was borne out in the Modification of Diet in Renal Disease study, which consisted of 2 randomized clinical trials. Study 1 evaluated patients with GFRs of 25 to 55 mL/min, while study 2 evaluated patients with GFRs of 13 to 24 mL/min. In both studies, patients were randomized to groups with mean arterial pressure (MAP) goals of either 92 mm Hg or 107 mm Hg. The decline in GFR was found to be slower in the more aggressively treated group overall, and the benefit was in direct proportion to the severity of the baseline proteinuria.190

In renal disease from type 1 diabetes mellitus, tighter blood pressure control, independent of use of ACE inhibitors, decreases proteinuria.191 A recent study from the Steno Diabetes Center showed that tight blood pressure control (MAP goal of 93 mm Hg) in this population can decrease the GFR decline to that found with normal aging.192

The UK Prospective Diabetes Study (UKPDS) and the Hypertension Optimal Treatment (HOT) study suggest that blood pressure can be aggressively yet safely lowered. The UKPDS showed a linear relationship between blood pressure and microvascular disease in patients with type 2 diabetes mellitus. This held true for average systolic blood pressures at least as low as 114 mm Hg.193 The HOT study showed that treating the blood pressure control (MAP goal of 93 mm Hg) in this population can decrease the GFR decline to that found with normal aging.192

ACE Inhibitors. As many of the pathophysiologic changes associated with chronic renal disease are driven by AII, ACE inhibitors have become the logical and accepted choice for treatment. ACE inhibitors block the rate-limiting step in the formation of AII. Benefits have been shown in experimental and clinical settings. These drugs preferentially dilate the efferent arteriole, thereby hemodynamically decreasing glomerular hypertension and proteinuria.196,197 They also decrease proteinuria by preserving the integrity of component proteins of the slit diaphragm198,199 and by ameliorating podocyte foot process broadening.200

Numerous other salutary effects have been found. Experimentally, ACE inhibitors ameliorate monocyte/macrophage infiltration, TGF-β expression, fibroblast proliferation, differentiation into myofibroblasts,201 and development of interstitial fibrosis.202 Inhibition of at least some of these AII-mediated cytokine releases is probably due to decreased TGF-B1, which has been shown in patients treated with ACE inhibitors.203,204

Clinical benefits have been found for diabetic and nondiabetic renal disease.67,205-207 In patients with diabetes, ACE inhibitors prevent progression of microalbuminuria, even in patients with controlled blood pressure. In a European study on type 1 diabetes mellitus, mean baseline systolic and diastolic blood pressure in the group randomized to receive lisinopril were 122 and 79 mm Hg, respectively. Adjustment for effects of systolic and diastolic blood pressure reduced, but did not eliminate, this benefit.206 A meta-analysis of 12 studies involving type 1 diabetes mellitus also came to the same conclusion.208

Even in the presence of chronic renal insufficiency, ACE inhibitors can be used.207,209,210 The benefits are proportional to the extent of proteinuria.67,210 Improvement in proteinuria is evident within the first 2 months.57,211 The preservation of GFR is directly proportional to the extent of lowering of proteinuria, which thus serves as a useful prognostic indicator.67,212

Angiotensin Receptor Blockers (ARBs). Because ACE can be formed by non–ACE-dependent pathways and because of intolerance to ACE inhibitors in many patients, ARBs have been increasingly used to delay progression of renal damage. Experimentally, ARBs have been shown to block fibroblast proliferation and synthesis of TGF-β.203 As in the case of ACE inhibitors, multiple mechanisms are responsible for the antiproteinuric effect. Angiotensin receptor blockers block expressions of cytokines like VEGF.213 They also have been found to normalize the glomerular nephron deficiency214 and podocyte foot process broadening in diabetic animals.200,214 Animal studies suggest that the benefits are similar to those of ACE inhibitors.198,214

Recent clinical trials have shown that these agents diminish proteinuria215-217 and protect against renal function decline among patients with type 2 diabetes mellitus and nephropathy.215,216 The 2 largest studies have been done on patients with relatively mild azotemia. However, results from studies using ACE inhibitors suggest that ARBs may be beneficial even in patients with more advanced chronic renal failure.

No large-scale comparative studies have been published comparing ARBs and ACE inhibitors regarding progression of chronic renal failure. However, small studies suggest comparable benefits in antiproteinuric effects,218,219 and no differences in rate of progression were found in a study of diabetes mellitus at 1 year.220 Animal data indicate that the combination results in
better reduction of renal AII levels than either agent alone. Clinical studies have been conflicting as to whether a combination of both agents has additive antiproteinuric effects. However, the addition of ARBs to maximal ACE inhibition may reduce renal TGF-β1 production despite the lack of salutary effects on proteinuria. Unfortunately, no large prospective studies on rate of progression using combination therapy are currently available.

Calcium-Channel Blockers. Dihydropyridines do not have antiproteinuric effects. Nondihydropyridines, in contrast, appear to have some role, at least in diabetic nephropathy. There are no good data on its usage in nondiabetic nephropathies for retarding progression of renal disease, although plans for a multicenter study were recently published to investigate combined treatment with an ACE inhibitor and either a dihydropyridine or a nondihydropyridine calcium channel blocker, using proteinuria as an end point.

β-Blockers. Though smaller studies had suggested that β-blockers may worsen the decline of GFR in patients with diabetes, the larger UKPDS-39 study found atenolol and captopril to be equivalent in limiting progression of albuminuria and azotemia over 4 years. Interestingly, a recent animal study found that blocking the sympathetic nervous system may be beneficial independent of antihypertensive effects. In a multicenter prospective study of nondiabetic African Americans with hypertensive renal disease, metoprolol was comparable with ramipril in reduction of proteinuria and in progression to end-stage renal disease. However, a composite end point and the overall rate of GFR decline was worse with metoprolol, suggesting that ACE inhibitors should still be the preferred agents in this population.

Protein Restriction

The role of protein restriction remains controversial. The largest prospective study to evaluate the role of protein restriction in retarding progression of renal disease failed to show a significant benefit. Subsequent secondary analysis of the data revealed a correlation between decreased protein intake and slower progression.

Two relatively recent meta-analyses of low-protein studies have been performed. In both, non-diabetic patients with chronic renal failure were shown to benefit from protein restriction. However, it appears that the difference in rate of decline of GFR is small. Pooling the results of 13 randomized control trials, Kasiske et al estimated a difference of only 0.53 mL/min per year among those assigned to protein restriction, which may not be clinically meaningful. For diabetic chronic renal disease, the benefits seemed greater, but the pooled number of patients was small, totaling only slightly over 100 in both meta-analyses.

A caveat has to be noted. It has been shown that a low-protein diet decreases the filtered urine creatinine as well as urine creatinine secretion and affects the latter more than the former. Such changes can occur independent of changes in the GFR.

In the clinical trial setting, at least, low-protein diets have been shown to be safe and have not been associated with hypalbuminemia or other evidence of worsening malnutrition. Whether this is replicable outside of a research environment remains to be seen. It also remains unclear whether there is benefit in combining a low-protein diet with use of ACE inhibitors.

For patients with advanced renal failure (GFR <25) who are not undergoing dialysis, the K/DOQI guidelines currently recommend protein restriction to 0.6 g/kg per day, but allowing for a maximum of 0.75 g/kg per day. While this avoids generation of nitrogenous metabolites and ameliorates uremic manifestations, an outright benefit in delaying progression remains unproven.

Aldosterone Antagonism

In vitro, in the presence of AII, aldosterone further increases PAl-1 expression. This raises the possibility that aldosterone antagonism may have additional benefits beyond those of AII antagonism. Moreover, aldosterone suppression by ACE inhibitors alone may not be sustained. In different models of renal failure, however, aldosterone antagonism only partially reverses some, but not all, of the deleterious effects. Whether this is replicable outside of a research environment remains to be seen. It also remains unclear whether there is benefit in combining a low-protein diet with use of ACE inhibitors.

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Erythropoietin

Erythropoietin receptors are present in the human kidney. It has thus been speculated that erythropoietin can exert cytokine effects on the kidneys and regulate their survival and proliferation. Apart from amelioration of hypoxia, this may have a salutary effect in progression of renal failure. Prospective clinical studies have been contradictory as to whether renal function is better preserved with erythropoietin.

Binding Protein Metabolites

Indoxyl sulfate is a protein metabolite that promotes the progression of glomerulosclerosis in animal studies. It was recently shown in a small study that AST-120, an oral adsorbent that binds indole (the precursor for indoxyl sulfate in the gut), decreases serum and urinary levels of
Early Nephrology Referral

Studies on the effect of timing of nephrology referral on mortality have yielded conflicting results. However, late referral is associated with an increase in early morbidity. Specifically, early nephrology referral is associated with better predialysis care and more appropriate choice of angioaccess for eventual hemodialysis. It has also been found to be cost-effective.

Other Modalities

Experimental Pharmacologic Agents. Endogenous atrial natriuretic peptide and brain natriuretic peptide cause vasodilation and natriuresis. A short study has also shown benefit in nondiabetic glomerulosclerosis. Soy protein produced encouraging results. A ten beneficial effects have been reported by blocking harmful cytokines and proteinuria. Alternative treatment in decreasing proteinuria and glomerulosclerosis has been found to be cost-effective.

SUMMARY

Chronic renal failure is a common problem affecting a large number of people in the US population. Hemodynamic factors and various chemical mediators contribute to progression of chronic renal failure. Aggressive control of blood pressure and proteinuria, preferably with a regimen containing ACE inhibitors, remains the cornerstone of therapy. The role of protein restriction remains poorly defined but it does not appear to be generally useful. Statins may be useful. Novel agents and other modalities are at varying stages of development.

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REFERENCES


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