Progression of Chronic Kidney Disease: Diagnosis, Management and Prevention

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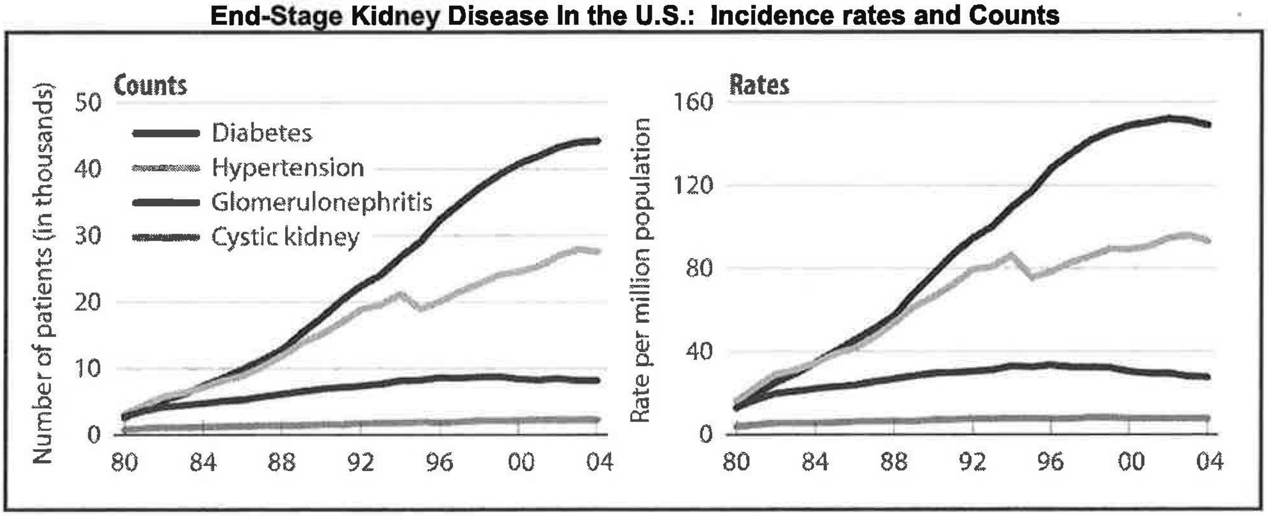
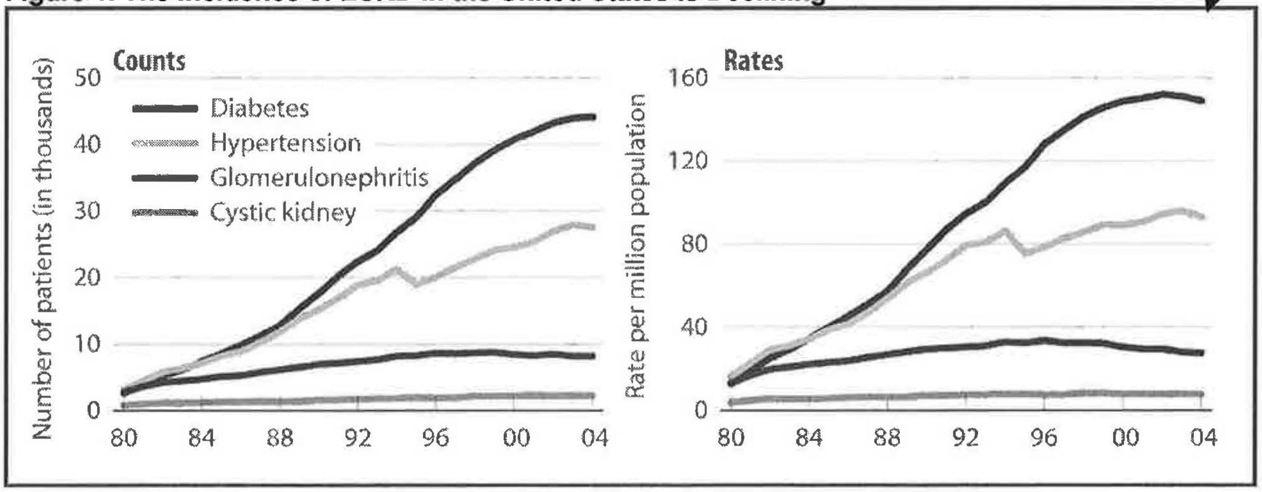
End-Stage Kidney Disease In the U.S.: Incidence rates and Counts



Introduction

Chronic kidney disease (CKD) is a major public health problem and more common than previously recognized. National Health and Nutrition Examination Survey III data estimate that 11% of adults in the US have some degree of chronic kidney disease[1]. CKD is characterized by: 1) abnormalities of kidney structure and function; 2) high prevalence of comorbidity (e.g. hypertension, anemia, etc); 3) increased risk for cardiovascular morbidity and mortality; and 4) progression of kidney disease to end-stage. Among care-givers, it is generally believed that most, if not all, CKD is progressive, and in the absence of a fatal CV event, will culminate in end-stage renal disease (ESRD). ESRD is a catastrophic illness that necessitates dialysis or transplantation, and nationwide medical costs to manage ESRD are in excess of $30 billion annually. While effective therapeutic approaches to slow progression of kidney disease have emerged over the past 10 years, halting the progression of disease in most individuals has not become a reality. However, for the first time in the past 24 years, the incidence of end-stage kidney disease in the US is decreasing (**Figure 1 arrow**)[2]. At the same time, cumulating evidence from both animal and human studies indicates that it is possible to halt progression of kidney disease and even improve kidney function and structure. This remarkable finding forms the basis for this review.

Figure 1. The Incidence of ESRD in the United States is Declining



Case Presentation - No Progression of Diabetic Nephropathy for 4 years:

A 45 year old white female presented in 2003 with an 8 year history of type 2 diabetes mellitus and hypertension. She has a past history of aortic stenosis, but no stroke or myocardial infarction, and is a non-smoker. Medications at the time included quinapril10 mg once daily, thiazide 25 mg once daily, insulin, atorvastatin 20 mg once daily. On exam: BMI 34.7 kg/m2, blood pressure 180/85, pulse 78, diabetic retinopathy, S4, 2+ edema, diminished pulses, mild peripheral neuropathy. Laboratory data included a serum creatinine of 2.4 mg/dl, K 4.1 mEq/L, A1 c 8.8%, Hb 11.3 g/d, TG 220 mg/dl, HDL 33 mg/dl, LDL 137 mg/dl, and urine albumin/creatinine ratio 875 mg/g. Renal sonogram revealed 11 cm kidneys and no obstruction. Her therapeutic plan was changed to focusing on to the following: 1) increasing insulin and prescribing exercise and weight reducing diet to improve glycemic control; 2) increasing quinapril to 40 mg once daily, substituting furosemide 40 mg BID for HCTZ, adding metoprolol XL 100 mg once daily and amlodipine

10 mg once daily and a 2 gm per day sodium intake in order to achieve BP goal of 130/80 mmHg and reduce albuminuria to < 300 mg/g; 3) adding aspirin 81 mg once daily. Four years later in 2007 despite no change in BMI her laboratory now reveals: A1c 6.4%, BP 125/72, K 5.2 mEq/L, LDL 77 mg/dl, urine albumin/creatinine ratio 220 mg/g. Most importantly for this discussion her serum creatinine level remains at 2.4 mg/dl. She has had no stroke or myocardial infarction during this time interval. These observations raise important questions:

- Has kidney disease progression ceased in this patient?
- Is she still at risk for kidney disease progression?
- What is the mechanism of lack of progression?
- Is lack of progression attributable to rigorous control of risk factors including blood pressure, proteinuria, renin-angiotensin system and dyslipidemia?
- Can progression of kidney disease be halted in all patients like her?

DIAGNOSIS

Table 1. Definition of Chronic Kidney Disease

- Kidney damage (≥ 3 months) defined by structural or functional abnormalities of the kidney, with or without decreased GFR manifest by either
  - Pathological abnormalities; or
  - Markers of kidney damage including abnormalities in composition of blood or urine, or abnormalities in imaging tests
- Glomerular filtration rate ≤ 60 ml/min/1.73 m^2

Clinical Practice Guidelines for Chronic Kidney Disease

Definition: Chronic kidney disease (National Kidney Foundation) is defined as kidney disease of greater than 3 month duration or an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2 (**Table 1**). Kidney disease may be manifested as abnormalities in the urine analysis, imaging studies, or blood measurements of kidney function[3]. For example, one may have autosomal dominant polycystic kidney disease with a normal GFR and multiple cysts, or one may have CKD with an estimated of glomerular filtration rate of 50 ml/min/1.73 m^2 and no other manifestation (e.g. proteinuria, hematuria, etc.). This definition is a practical way to help physicians to speak the same language when characterizing patients with chronic kidney disease. However, it is based on the limited biomarkers available for detection of disease and in the future will evolve as improved methods for gauging of abnormal kidney function and structure are discovered. Studies indicate that CKD is an independent predictor of cardiovascular morbidity and mortality, and in fact, patients with CKD are more likely to die of a cardiovascular event than they are to progress to end-stage kidney disease. Much emphasis has been placed on management of risk factors that may cause fatal cardiovascular events among those with CKD[3, 4].

Patients at Risk for Chronic Kidney Disease: Patients with risk factors for chronic kidney disease should undergo screening by measuring serum creatinine, urine albumin/creatinine ratio and urine analysis. Risk factors in the medical history include older age, male gender, race, genetic predisposition/family history of kidney disease, hypertension, diabetes, proteinuria and exposure to nephrotoxic drugs or chemicals.

Table 2: Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m2)
	At increased risk	≥90 (with CKD risk factors)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialysis)

Staging of Chronic Kidney Disease: Chronic kidney disease is staged by estimating glomerular filtration rate using serum creatinine-based equations such as the MDRD equation. This method uses age, gender, serum creatinine and race (black or non-black) to estimate GFR and CKD is then staged as follows: 1) GFR > 90; 2) 60-89; 3) 30-59; 4) 15-29; 5) < 15 ml/min/1.73 m^2 (**Table 2**). CKD staging is based on GFR because it is thought that filtration rate is the best overall measure of kidney function. In addition, an abnormally low GFR is a predictor of future decline in GFR, for example in some studies GFR declines faster in those with lower as compared to higher levels of GFR[5, 6]. Moreover, it is known that as GFR declines the number of complications and comorbidities associated with CKD increases. Since most of the data relating CKD to CV events is observational and the observations show that the lower the GFR the higher the death rate, slowing or halting progression of kidney disease should also decrease cardiovascular mortality.

Problems with Current Markers of Chronic Kidney Disease

Glomerular filtration rate is widely accepted as the gold standard of measuring kidney function and for diagnosing progression of kidney disease (see Medical Grand Rounds on GFR by Henry Quinones, M.D., 2006). However, there are several shortcomings of using GFR or an estimate of GFR for detecting and monitoring disease progression. First, it is well established that in most patients, proteinuria is a major modifier of the rate of decline in glomerular filtration rate and may be a better and more robust predictor of end-stage kidney disease than GFR[7]. Second, precision and accuracy of estimating GFR using creatinine based methods far from optimal. For example, a patient with an estimated GFR of 50 ml/min/1.73 m^2 using MDRD may have a true GFR in the range of 30-70 ml/min/1.73 m2[8]. Third, it is well known that kidney function and structure may deteriorate despite little or no detectable change in serum creatinine. This can occur as a result of compensatory hyperfiltration (see below) in remnant nephrons as single nephron GFR increases in these nephrons as filtration ceases in other nephrons.

Whereas GFR measured by clearance of inulin is an accurate marker of filtration function of the kidney, filtration does not correlate strongly with a number of other functions of the kidney. This is especially the case in patients with chronic kidney disease and normal glomerular filtration rate. Moreover, filtration does not measure or indicate how well the renal tubules function. Remember, the renal tubules and interstitium, while dependent on kidney blood flow and glomerular filtration rate, perform a wide variety of kidney functions beyond filtration and excretion of wastes. These functions include endocrine (vitamin D synthesis, metabolism of insulin, production of glucose, etc.), secretion of renin, protein metabolism, water and ion transport, drug metabolism, lipid metabolism, and erythropoietin production.

The importance of tubular function can be seen by comparing a patient with chronic kidney disease caused by reduced kidney blood flow, chronic heart failure, with that of a patient with intrinsic kidney disease: the heart failure patient with high BUN and creatinine has low filtration but tubules function normally so the patient has few or no uremic symptoms. In contrast the patient with intrinsic renal disease has many or all the symptoms and signs of uremia. Clearly filtration markers are not the whole story in characterizing kidney function.

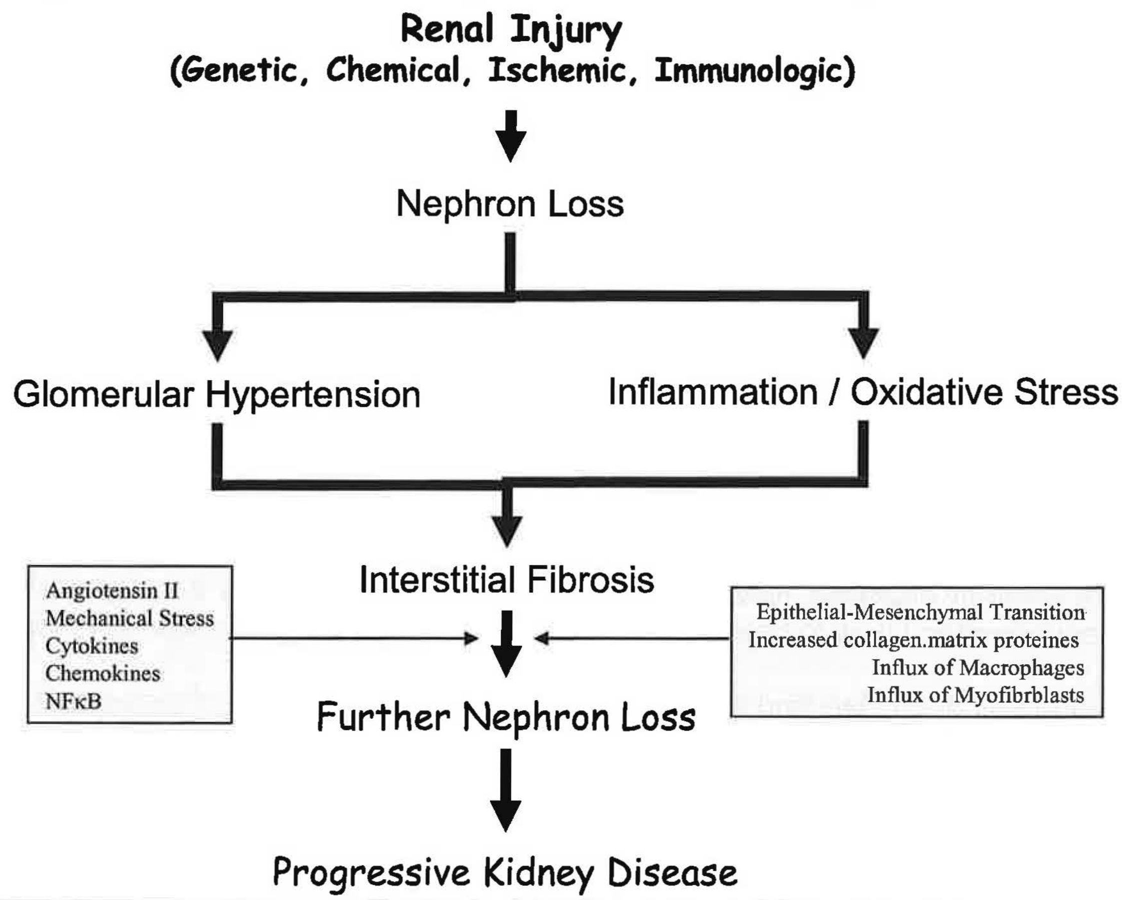
Furthermore, severe kidney disease can be present in the presence of a normal glomerular filtration rate in diabetes, lupus and other glomerular diseases, cystic kidney disease and hypertension. In the clinic, it is often difficult and confusing to explain to a patient with nephrotic syndrome that despite the fact that the patient's kidneys are filtering normally, they are severely diseased. New clinically relevant markers of kidney function are needed to better understand how to detect and monitor progressive decline in kidney function.

Proteinuria has been identified as a marker for progression of kidney disease as well as a nephrotoxin itself. Although the latter effect may be mediated through activation of multiple inflammatory mediators, experimental proof of this concept is lacking. Evidence for the latter has not been forthcoming[9]. Moreover, the amount and type of protein in the urine does not translate into a specific rate of progression. Some studies in glomerular disease suggest that non-albumin in urine predicts progression, but thus far no clinically relevant marker of tubular kidney function has emerged as a reliable predictor of kidney disease progression. Furthermore, the origin of proteinuria is not always certain, i.e. it can be from glomerular leakage, tubular damage or both. Finally, the term is confusing because of the non-specificity and the literature continues to confuse physicians by using terms proteinuria and albuminuria sometimes interchangeably and by publishing different values for normal and abnormal depending on whether one measures total protein or albumin.

What is known is about proteinuria and seems to be a consistent finding is that abnormal albumin excretion rate is associated with increased risk for progression of chronic kidney disease and cardiovascular morbidity and mortality. To date, no clinical trials specifically targeting proteinuria has demonstrated that this prevents ESRD. Still, in many but not all cases, proteinuria is a powerful predictor of likelihood of progressive kidney disease. There is a need to improve quantitative relationship between proteinuria progression of kidney disease.

Summary: Chronic kidney disease is more common than previously thought, and is associated with increased risk for progression of disease to end-stage and to increased risk for cardiovascular morbidity and mortality. Identifying those at risk for kidney disease and staging the disease by GFR assist clinicians in helping to reduce the risk for progression and CV events. While both GFR and proteinuria are markers for kidney disease progression, identifying novel markers is a high priority for future research.

Figure 2. Mechanisms of Progression of Chronic Kidney Disease



Kidney Injury and Mechanisms of Progression in Chronic Kidney Disease

Hemodynamic Injury: As illustrated in **Figure 2,** many mechanisms of injury can lead to progressive kidney disease. Acute injury to the kidney (e.g. ischemia) may be completely reversible with no significant loss of nephrons. However, permanent loss of nephrons, whether from an acute reversible injury (e.g., glomerulonephritis) or a chronic persistent injury, may result in progressive deterioration in kidney structure and function. In both of these situations, partially damaged or undamaged nephrons undergo compensatory hypertrophy leading to glomerular capillary hypertension, hyperfiltration and progressive nephron scarring. This "two-hit" mechanism (injury causing loss in nephrons and subsequent maladaptation with glomerular hypertensive injury) of progressive kidney damage is a major pathogenetic factor underlying progression of chronic kidney disease in both experimental animal models and in humans with chronic kidney disease.

Most modern interventions designed to slow or halt progression of chronic kidney disease have focused on reducing glomerular hypertension, especially drugs that block the intrarenal effects of angiotensin II on the glomerular capillary circulation. And indeed such intervention works to slow progression of kidney disease and reduce proteinuria. However, drugs that block the renin-angiotensin-aldosterone system also modify a variety of other mechanisms known to exacerbate glomerular, tubular and interstitial scarring. These include inhibition of oxidative stress, secretion of profibrotic cytokines such as transforming growth factor beta, plasminogen activator inhibitor 1, macrophage chemotactic factor, NFκB activation, tissue metalloproteinases, proliferation of smooth muscle cells, and enhancement of epithelial mesenchymal transition.

Oxidative Stress: Patients with chronic kidney disease exhibit evidence for low levels of inflammation and oxidative stress markers, particularly in those with stages 3-5. These include elevated levels of CRP, IL-6, increases in lipid peroxidation and advanced oxidation protein products[10]. The cellular and molecular mechanisms responsible for oxidative injury in the kidney include activation of transcription factors that upregulate proinflammatory and profibrotic cytokines and induction of apoptosis of glomerular podocytes and mesangial cells[11]. Behaviors (e.g. diet, exercise, nephrotoxin exposure) and interventions (e.g. novel anti-fibrotic drugs, see below) that reduce oxidative stress may be useful new strategies for slowing or halting kidney disease progression.

Fibrosis: The mechanisms of renal fibrosis are complex and probably include a variety of interacting cell types within the kidney and circulating inflammatory cells, including bone-marrow derived leukocytes and macrophages that secrete proinflammatory and profibrotic cytokines, among which transforming growth factor-beta is prominent. These cells and molecules participate in a final common pathway resulting in progressive interstitial fibrosis and peritubular capillary destruction leading to further destruction of functioning nephrons. TGF-beta and engender pro-fibrotic phenotypes and increase synthesis of fibrogenic molecules such as connective tissue growth factor (CTGF) and plasminogen activator inhibitor-1[12, 13]. In addition, reduced levels of antifibrotic factors that are normally produced in the kidney, such as hepatocyte growth factor and bone morphogenic protein-7, may accelerate fibrosis and its destructive consequences. Development of new therapeutic agents for CKD looks promising, but several agents that target different components of the fibrogenic cascade will almost certainly be necessary.

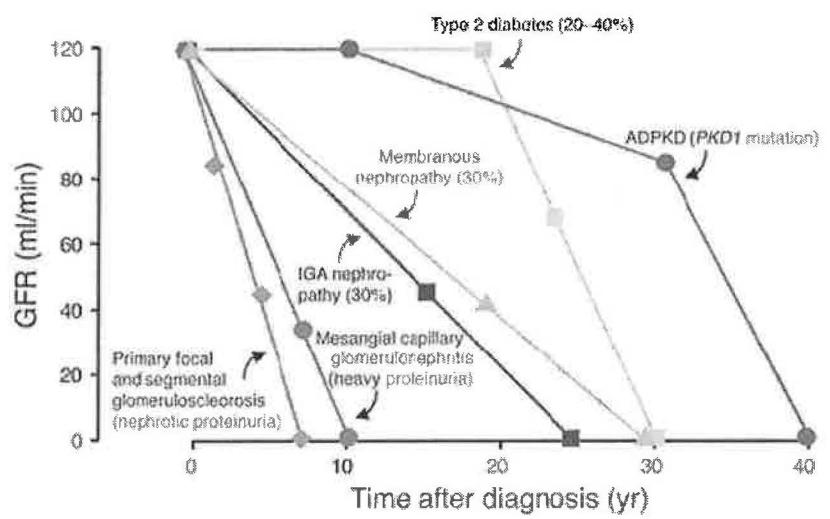
Epithelial mesenchymal transition is believed to play an important role in the progression of chronic kidney disease by accelerating interstitial fibrosis, a well known histologic marker of increased risk for progression of kidney disease and poor clinical outcomes[14]. The molecular mechanisms by which renal injury induces the transition of epithelial cells to fibroblasts are under investigation. These mechanisms are likely present in a variety of kidney diseases, including hypertensive diseases, diabetes, glomerulonephritis, interstitial nephritis, nephrotoxic injury (e.g. cyclosporine, asitolochic acid, analgesic agents (phenacetin, acetaminophen, aspirin, lead, etc.) and genetic diseases including autosomal polycystic kidney disease, Fabry's disease and sickle cell disease, resulting in a final common pathway of nephron scarring culminating in end-stage kidney disease.

Summary: The pathogenesis of progressive kidney disease is complex, involving hemodynamic and inflammatory processes that conspire to cause progressive scarring of the renal vasculature, tubules and interstitium. Recent studies, especially epithelial-mesenchymal transition, have shed new light on the progression of kidney disease and highlight novel therapeutic targets for halting disease progression [14]. Identification and validation of non-invasive markers of renal fibrosis are an important area of ongoing laboratory and clinical investigation.

Progression of Kidney Disease

Definition: Progression of kidney disease is usually defined as a progressive decline in kidney function over time. It is generally detected as an increasing serum creatinine concentration (or by estimation of glomerular filtration rate), but the precise rate of decline that differentiates progressive from non-progressive kidney disease has not been determined. In order to establish that chronic kidney disease is progressive, it is essential to measure kidney function over time to establish progression and estimate the rate of progression. Aging is associated with a decline in estimated glomerular filtration rate of about 0.75 ml/min/year in upper middle class white men, but the "normal" decline in GFR for other populations has not been carefully studied[15]. This problem is compounded by the fact that the rate of progression of chronic kidney disease is highly variable not only among different kidney diseases but also among patients with the same kidney disease (**Figure 3).** Because the rates of decline in glomerular filtration rate are not only heterogeneous within a population with a particular kidney disease (e.g. diabetic nephropathy) but also between populations of different kidney disease (e.g. polycystic kidney disease vs hypertensive nephrosclerosis), it is difficult, if not impossible, to define the minimal rate of decline in GFR that defines a progressive form of kidney disease. In fact, using GFR as an estimate of declining kidney function, the precision with which we can now define progressive kidney disease boils down to "I know it when I see it". Today, with the relatively large number of potential patients with stage 3 kidney disease, the natural history of progression of kidney disease is masked by the aforementioned risk for death amongst this group of patients. In one prospective study that selected individuals based on low GFR and compared to those with normal GFR, no difference in rate of decline in GFR was observed over a 4 year interval. In the same study, those with albuminuria and low GFR had a rapid decline in GFR as compared to the background population[16]. This example supports the view that proteinuria is a better predictor of kidney function decline in the general population than estimated GFR and underscores the need for more sophisticated methods to establish the likelihood of progression.

Figure 3. Time of Onset and Rates of Progression of Some Proteinuric Kidney Diseases (ref 49)



Any patient with established CKD is theoretically at risk for kidney disease progression regardless of the etiology, but the rates of progression may differ, not only because of the underlying cause of kidney disease but also because of the mechanisms of progression.

In general proteinuric kidney diseases (glomerulonephritis, diabetes, polycystic kidney disease) have faster progression than non-proteinuric kidney diseases. The exact level of proteinuria that defines progressive kidney disease is also not established, and recent evidence suggests that there is a continuum rather than a threshold for protein excretion that identifies those whose kidney disease is destined to progress.

The dogma is that proteinuria represents glomerular damage, and that it in turn is tubulotoxic, activating inflammatory cascades that cause further renal damage[17]. Recent studies in rats have challenged this view. Under normal circumstances filtered albumin is reabsorbed across the apical membrane of the proximal tubule by a process of receptor-mediated endocytosis. The reabsorbed albumin may be: a) degraded by the tubular cell and its fragments digested by the cell or excreted in the urine, or b) transported into the blood across the basolateral membrane. In rat models using fluorescent labeled albumin and intravital 2-photon microscopy it was shown that albumin filtration in non-proteinuric rats is more than 50 times greater than previously measured and is followed by rapid endocytosis into proximal tubule cells. The endocytosed albumin appears to undergo transcytosis in large vesicles and was returned to peritubular capillaries across the basolateral membrane. Moreover, in nephrotic rats the uptake of albumin by the proximal tubule was decreased. These findings suggest that normally the kidney filters larger amounts of albumin than previously thought and the cause of proteinuria is impaired tubular uptake of filtered albumin[18, 19]. This heretical view, if substantiated, would suggest that markers of tubular structure and function may be important in refining our ability to detect kidney disease and its progressive nature. These new findings raise the possibility that a new definition of progression of kidney disease may be in the near future as new biomarkers of tubular function and handling of filtered proteins are discovered.

Importance of Diagnosing Progression of Chronic Kidney Disease: From a clinician's point of view, the significance of progressive kidney disease is that not only is it associated with an outcome of ESRD with its attendant disease burden, but also, as kidney disease progresses, both the prevalence of comorbidity and the likelihood of death increase[20]. From a public health point of view, the costs of progressive kidney disease are enormous. The incalculable loss of productivity resulting from the progressing morbidity associated with failing kidneys takes a toll on the patient, their family and society. Moreover, the financial cost of care progressively increases and skyrockets at the onset of ESRD.

Predicting Progression: The ability and precision for predicting progression of chronic kidney disease is limited by incomplete understanding of the stage of disease, the mechanisms of progression of disease and the accuracy and precision of markers of disease progression. So far, the goal of developing a practical risk score for predicting risk for ESRD similar to the Framingham Risk Score for cardiovascular disease has not been achieved. **Table 3** illustrates risk factors for progression of chronic kidney disease. These factors have been gleaned from data obtained in observational cohort studies and long term clinical trials in patients with chronic kidney disease[21-44].

Several studies have attempted to develop risk scores as a means of improving predictive power of readily available clinical and laboratory characteristics in diabetics and non-diabetic nephropathies[45]. For example, Keane developed a risk score in type 2 diabetics with nephropathy followed for an average of 3.5 years in the Reduction in Endpoints in NIDDM with the Angiotensin Antagonist Losartan (RENAAL) trial. They found that baseline

Table 3. Risk Factors for Progression of Chronic Kidney Disease	
Non-modifiable	**Modifiable**
Age	Blood pressure
Gender	Proteinuria
Race	Glycemia
Genetic Predisposition	Anemia
	Obesity
	Smoking
	Serum albumin
	Serum creatinine (nephron number)
	Dyslipidemia
	Nephrotoxin exposure
	Cardiovascular disease

albuminuria, serum creatinine, hemoglobin level and serum albumin were independently associated with development of end-stage kidney disease. And although albuminuria was a strong risk factor for ESRD, the contribution of serum albumin, serum creatinine, and hemoglobin level further enhanced the prediction of ESRD in this patient population. Future trials with a similar patient population and outcomes measures should consider adjusting analyses for baseline risk factor[25, 46]. Similarly, Dimitrov determined that urine albumin, serum creatinine and calcium-phosphorus product were independently associated with progression to end-stage kidney disease[47].

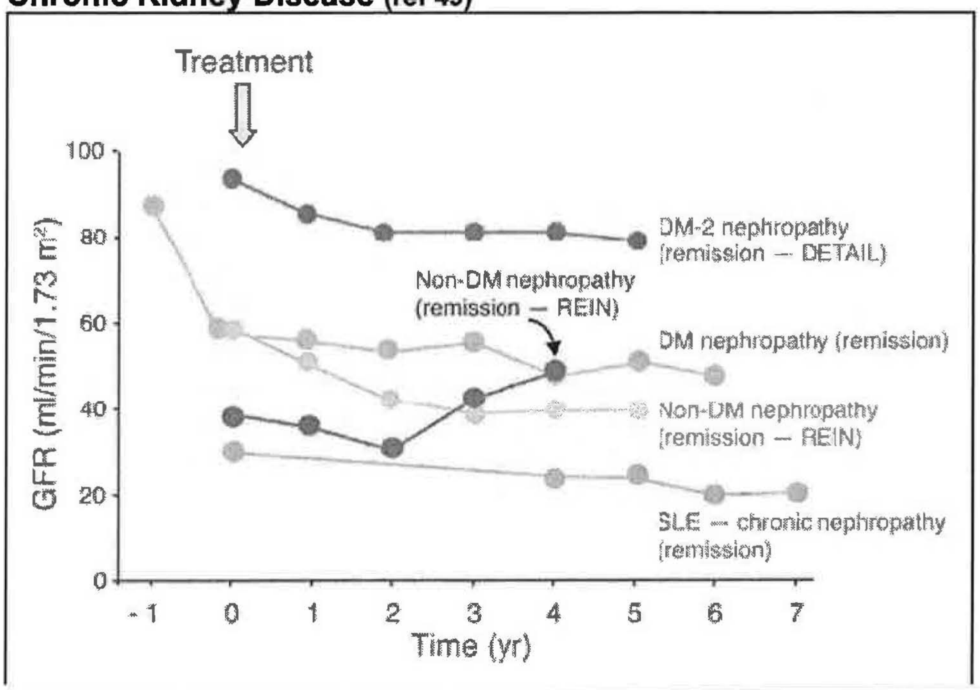
Novel Biomarkers for predicting progression: Examples of novel protein biomarkers of kidney disease severity and progression under investigation include plasma concentrations of tissue metalloproteinases and smooth muscle actin alpha, which have been shown to correlate with serum creatinine and rate of decline in GFR. In addition, TGF-beta in blood and urine, urinary collagen II and III levels and resistin have been shown to correlate with disease activity in various kidney diseases. Urinary fatty acid binding protein and serum prostaglandin D synthase have also been investigated as potential markers of kidney disease progression. However, none of these has been studied in prospective longitudinal studies to validate their potential as superior markers of kidney disease progression. There are no standards for these markers in the experimental or clinical setting thus far. Expression profiling in tissue and blood have provided evidence for dysregulation of a number of gene products involved in progression of kidney disease, but again no specific profile has successfully predicted kidney disease presence or progression[48].

Predicting Response to Intervention: The single most well identified predictor of response to treatment in patients with chronic kidney disease is a reduction in urine protein excretion in those with proteinuric nephropathies. Unfortunately, baseline proteinuria does not necessarily predict response to treatment. Studies to identify pharmacogenomic predictors of outcome are underway. In addition, we have recently begun to evaluate whether urine proteomic profiling may be helpful for predicting antiproteinuric response to adding spironolactone or losartan onto the background of high dose (80 mg/ day) lisinopril. In collaboration with Dr. Kevin Rosenblatt in the Department of Pathology and Dr. Skip Garner in Translational Medicine Division, we are investigating whether novel protein biomarkers detected by novel separation methods coupled to high resolution mass spectrometry can identify novel markers of treatment response to combination RAAS blockade in diabetics with nephropathy enrolled in an ongoing clinical trial at UT Southwestern. These studies may provide insight into disease mechanisms and lead to new methods for detecting and monitoring progression of kidney disease.|

Halting Progression of Chronic Kidney Disease: Yes, it's possible!
It is widely believed that all chronic kidney disease is progressive once it reaches a critical turning point. The problem with this dogma is that the critical point for a given patient is not well defined. For example, it has been estimated that, at the point where kidney function (estimated by GFR) is 20-25% of normal, one can expect an inexorable decline in kidney function to end-stage (GFR ~ 10% normal). However, numerous cases in the literature and in our own practices provide examples of patients with GFR in this range but demonstrate no decline in glomerular filtration rate after years of follow up. Stopping progression of kidney disease is defined clinically as stabilization of kidney function with no evidence of decline in GFR above normal, i.e. $\leq$ 0.75 ml/min/year.

As illustrated in **Figure 4**, treatment can halt progression of chronic kidney disease in diabetics and non-diabetics with proteinuric kidney diseases. Several reports in the literature including both animal and human experiments have documented cessation or reversal of glomerulosclerosis and interstitial inflammation with regeneration of kidney disease occurred. In Munich-Wistar Fromter rats, a genetic model of progressive proteinuric kidney disease, high dose administration of ACE inhibitor lisinopril was demonstrated to halt progression, as evidenced by stable creatinine, amelioration or abrogation of proteinuria and by reversal of glomerulosclerosis by histologic measurement[49]. Long-term (10 years) normalization of glycemia by pancreas transplantation in type 1 diabetes has been reported to reverse glomerulosclerosis and reduce proteinuria[50]. In some patients with non-diabetic proteinuric nephropathies, long-term treatment with ACE inhibition can abolish proteinuria and stabilize or increase glomerular filtration rate [51]. In patients with diabetic nephropathy and nephrotic syndrome ACE inhibition may abolish proteinuria and stabilize GFR for up to 8 years[52]. In one case of lupus nephritis, long-term administration of ACE inhibitor combined with an ARB and a statin resulted in cessation of kidney disease progression[53]. Aggressive blood pressure control combined with drugs that inhibit RAAS (and statins in the lupus case) were employed in all of these studies, except the pancreas transplantation example. In the human studies, the authors of these reports believe that

Figure 4. Examples of Interventions that Halt Progression of Chronic Kidney Disease (ref 49)

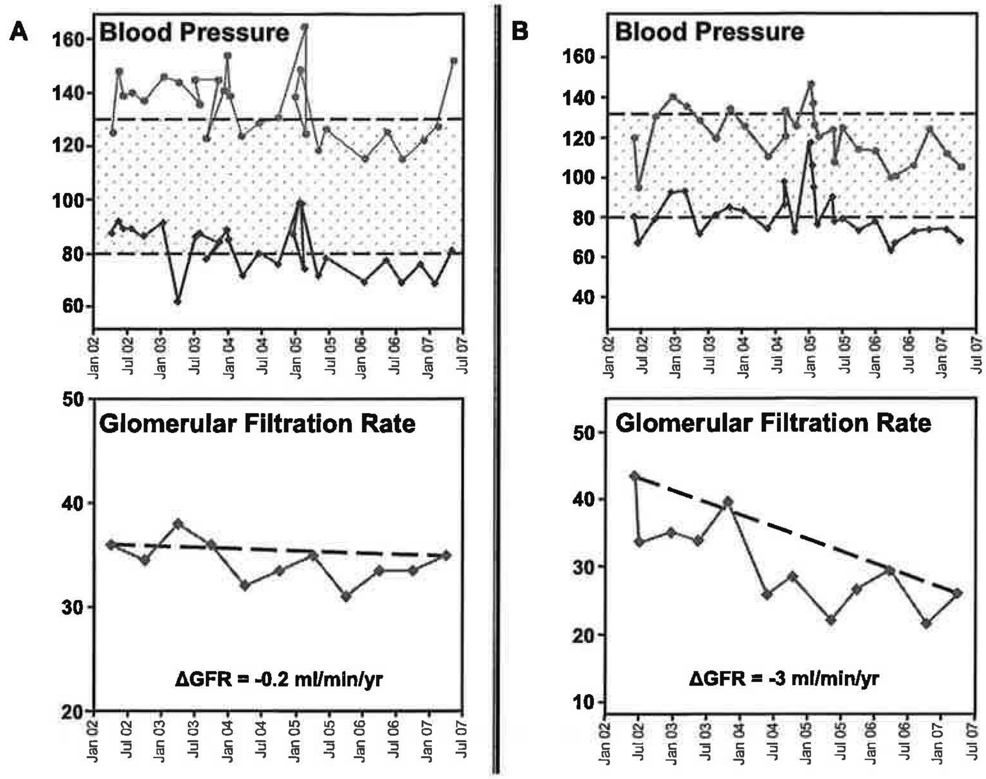


ACE inhibition and BP lowering are critical and responsible for these remarkable observations.

These promising findings indicate that, at least in some patients, either stabilization of kidney function or regeneration of normal kidney structure may occur with aggressive BP control combined with RAAS in proteinuric nephropathies. However, with the exception of the pancreas transplanted patients, none of there reports included repeated kidney biopsy specimens to assess kidney structure. Moreover, it is not clear why these individuals responded while others did not. We do not know if these individuals were more compliant than others, or whether there are pharmacogenetic factors at play in their response to these agents. At the present time genetic or molecular markers of those most likely to respond to treatment with cessation of progression of kidney disease remain undefined or unknown.

New insights from studies in hypertension, diabetes and glomerulonephritis: As already noted, clinical trials have in general demonstrated that lower blood pressure is associated with slower rate of decline in glomerular filtration rate. The African-American Study of Kidney Disease and Hypertension was a controlled trial in which 1089 **non-diabetic** African-Americans with longstanding hypertension and a baseline GFR in the range of 20-65 ml/min/1.73 m2 were randomized to strict (BP ~ 120/80 or usual (BP ~ 140/90 mmHg) blood pressure control and different antihypertensive agents. Despite achieving, on average, a 13 mmHg lower systolic and 8 mmHg lower diastolic blood pressure in the strict group, neither the rate of decline in GFR nor the risk for ESRD were decreased.[5] Moreover, during an additional 5 year AASK cohort follow-up during which blood pressure control was strictly maintained and ACE inhibition was employed, the on average kidney disease progressed toward end-stage[54]. However, careful analysis of this trend revealed the surprising finding that many of these patients experienced little or no decline in GFR. Therefore, despite the overall trend for continued progression of kidney disease, in fact some patients progress while others do not. **Figure 5** illustrates blood pressure control and rate of decline in estimated GFR in two participants in the AASK cohort followed for 5 years. During this 5 year study, participants were evaluated every 4 months and standard of care including strict BP control regimen (< 130/80 mmHg) and the treatment with the ACE inhibitor ramipril was administered. As shown in the figure, despite similar level of blood pressure control **patient A had no decline in GFR** whereas **patient B had a significant decline in GFR** that was on average 15 times greater than patient A. These two examples provide an opportunity to identify markers of disease activity and progression that explain causes of progression of kidney disease beyond blood pressure in this at risk patient population. This is important since 25% of all new cases of ESRD in the United States are attributed to hypertension. The findings from the AASK study raise the following important questions: 1) what is the actual disease process causing kidney disease progression in this populations?; 2) why is antihypertensive therapy associated with absence of progression in some and not others?; 3) what are the molecular mechanisms of causing progression of kidney disease?; 4) what markers (e.g. genetic, biochemical) are predict disease progression despite blood pressure control?; 5) what are the factors beyond blood pressure that should be targets for future intervention?; 6) are the differences in outcome due to differential responses to blood pressure lowering and/or specific drug therapy?. These questions also apply to studies in diabetics and to those with glomerulonephritis (see above). Datasets like the AASK study compel the search for new and better markers of disease and response to intervention.

Figure 5



Summary: Chronic kidney disease is often progressive and any patient with CKD is considered at risk for progression to end-stage kidney disease. However, clinical experience and increasing reports in the literature suggest that kidney disease can be halted at least in some patients by aggressive multifactorial interventions currently available. Studies are needed to predict who is likely to progress to end-stage kidney disease.

MANAGEMENT: How you can halt progression of Kidney Disease in Your Patient

Identify those at risk

As illustrated in **Table 4** many modifiable risk factors for progression of chronic kidney disease are amenable to currently available therapies. In this section we review some modifiable risk factors shown to be associated with development and progression of human diabetic renal disease. For the purposes of this discussion, microalbuminuria is defined as a urine albumin/creatinine ratio ≥ 30 and < 300 mg/g and macroalbuminuria (also referred to as overt nephropathy) as ≥ 300 mg/g[55]. Renal function is usually within the normal range in microalbuminuric subjects and remains in normal range. In contrast, although renal function, measured as glomerular filtration rate (GFR), may be normal at initial evaluation in macroalbuminuric subjects, it is the harbinger of rapidly declining renal function that often leads to ESRD.

Blood Pressure: Achieving blood pressure control in CKD patients can be difficult. Compliance with diet and medication is the greatest obstacle to achieving BP goal of < 130/80 mmHg. Still, it is possible to do this even in those with stage 2 hypertension and an

Table 4. Office Practice Guideline for Halting Progression of Chronic Kidney Disease

Parameter	Goal	How to Get to Goal
Estimated GFR	Stable	Cockcroft-Gault or MDRD
Blood pressure	< 130/<80 mmHg	Combine diet and drugs
Urine albumin/creatinine	< 300 mg/g	Uptitrate BP drugs + RAAS blockers
RAAS blockade	ACEi, ARB, MRA, combination	Use max dose ACEi first
A1c	< 6.5%	Insulin/oral agents as needed
Hemoglobin	> 11 and < 13 g/dl	Iron and ESPs
LDL cholesterol	< 100 mg/dl (<70, very high risk)	Statins, ezetimibe, others
Parathyroid Hormone	55-70 stage 3, 71-110 stage 4	Vitamin D, Phosphate, binders
25-OH vitamin D3 level	> 30 ng/dl	If < 30 ng/dl; Rx: ergocalciferol
Smoking	Cessation	Cessation programs/medication
Weight Loss	Ideal body weight	Patient education
Exercise	45 minutes aerobic 3-4/week	Patient education

MDRD = Modification of Diet in Renal Disease; RAAS = renin-angiotensin-aldosterone system; ACEi = angiotensin converting enzyme inhibitor; ESP = erythrocyte stimulating protein

estimated GFR below 50 ml/min, as illustrated in the cases presented earlier. Maximizing doses of ACEi or ARB followed by a diuretic (thiazide for eGFR > 50 and loop for eGFR ≤ 50), followed by a calcium channel blocker or beta blocker then an alpha blocker or Clonidine, will work in most patients. This drug regimen should be built upon a foundation of a 2 gram sodium diet, and for obese patients a weight loss/exercise regimen.

Angiotensin II: Blockade of RAAS with either an ACEi or an ARB at maximum dose for lowering BP is reasonable. Combining ACEi with either an ARB or a mineralocorticoid antagonist can reduce proteinuria and the ACEi + ARB combination has been shown to reduce risk for ESRD. My preference is to use doses of lisinopril up to 80 mg once daily combined with either 100 mg losartan or 25 mg of spironolactone in diabetics with nephropathy. I have also found combining ramipril 20 mg once daily with losartan 100 mg (or equivalent dose of other ARB such as irbesartan) to be effective for stabilizing chronic kidney disease progression. Most patients tolerate the combinations of these drugs quite well. Although this has not been proven to halt progression of kidney disease, this level is associated with slower progression and may lead to stabilization of serum creatinine.

Proteinuria: The minimal level of proteinuria to halt progression of kidney disease in patients with hypertension, diabetes and glomerulonephritis is unknown (see Grand Rounds by Biff Palmer, 2007). Based on data from clinical trials, a reasonable target for albuminuria is < 300 mg/g creatinine. A 24 hour urine is not necessary; instead a morning urine specimen for albumin and creatinine is adequate[56]. There are no long-term studies in large trials that document a specific effective regimen for achieving this target. As already noted, combining lower blood pressure with drugs that block the RAAS at multiple sites is an effective approach. Further precision for titration of this marker of kidney disease progression and development of a more robust and quantitative marker of kidney disease progression is the subject of ongoing genomic, proteomic and metabolomic research.

Dyslipidemia: The goal is to lower LDL cholesterol to < 100 mg for most and to < 70 mg/dl in those at very high risk for a coronary event[57]. Lowering cholesterol with statins is associated with slowing decline in GFR in those with heavy proteinuria[58]. Statins are very effective for lowering LDL cholesterol in patients with CKD, including those on hemodialysis. Treatment should include dietary interventions and weight loss in obese patients. Also, patients should be monitored for development of myositis. The incidence of rhabdomyolysis in patients with CKD on statins is low, and the benefits of these drugs outweigh the potential risk of this rare complication. Post-hoc analyses of clinical trials that included patients with chronic kidney disease demonstrate that lowering cholesterol reduced cardiovascular death risk and subgroup analyses from hemodialysis patients suggest that statins may reduce cardiac morbidity and mortality[59]. Caution should be used when combining fibric acid derivatives with statins for managing dyslipidemia in those with CKD because of an increased risk for rhabdomyolysis.

Smoking: Chronic cigarette smoking is a major risk factor for cardiovascular and cancer morbidity and mortality[60]. Smoking accelerates decline in renal function in patients with overt nephropathy and is associated with increasing albuminuria in microalbuminuric patients[23, 61]. The mechanism of accelerated decline in renal function is not known, but renal vasoconstriction and glomerular endothelial injury are factors that may be involved [62-65]. Increased production of superoxide and other free radicals as well as activation of endothelin release, sympathetic activation and suppression of nitric oxide in the kidney may also play a role[66]. All patients should be advised to stop smoking regardless of associated kidney disease[61, 62].

Anemia: Anemia is associated with increased risk for progression of chronic kidney disease in type 2 diabetics[26, 67]. Whereas small studies hint that treatment of anemia with erythropoietin stimulating proteins may slow progression of kidney disease[68], more recent larger-scale trials provide no evidence of renal benefit of anemia treatment with these agents[69, 70]. The Trial to Reduce Endpoints with Aranesp Therapy is the largest ever clinical trial in nephrology. This study will test the hypothesis that treatment of anemia in a population of 4000 type 2 diabetics with CKD reduces cardiovascular morbidity and mortality[71]. The trial has a prespecified endpoint of ESRD and should provide a definitive answer to the question of whether anemia treatment slows or halts kidney disease progression in this population.

Obesity: It is not known whether weight loss in obese patients with CKD is associated with slowing of progression of kidney disease. Several studies have shown strong associations between obesity and metabolic syndrome and its components and chronic kidney disease. In a preliminary report from the AASK cohort, metabolic syndrome was found to be associated with progression to ESRD[72]. This finding has yet to be confirmed. Obesity is strongly associated with hypertension and sleep apnea, which may in turn exacerbate hypertension and is associated with proteinuria. Prospective studies are needed on effects of weight loss on risk of kidney disease onset and progression.

Nephrotoxins: What is and what is not?: Avoiding nephrotoxic drugs or chemicals whenever possible is advisable for patients with CKD. For example limiting exposure to radiocontrast, NSAIDs and other nephrotoxins for prolonged periods, including calcineurin inhibitors, is wise. It should be noted that reversible increases in serum creatinine are common with use of ACEi and angiotensin, but these agents are not generally toxic. Short-term withdrawal or dose adjustment of these agents usually returns the creatinine to baseline. These drugs should not be avoided in patients with chronic kidney disease unless serum potassium is > 5.5 mEq/L. In addition, once daily aspirin (81-325 mg) is not nephrotoxic and may provide benefit to patients with chronic kidney disease.

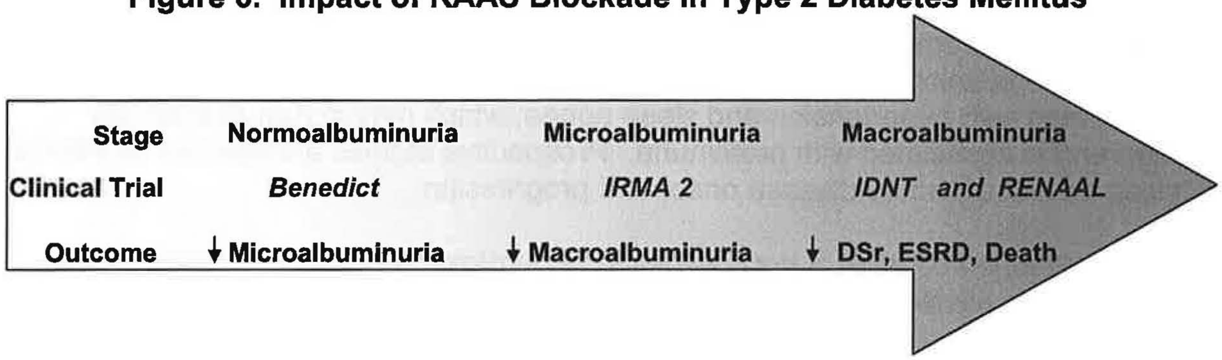
PREVENTION

It is not known how many cases of chronic kidney disease are prevented by either detection early intervention for risk factors (see above) or intervening cardiovascular death.

Diabetic Nephropathy: The most compelling evidence for prevention of progression of kidney disease comes from studies performed in type 2 diabetes with RAAS blockade. One of the hallmarks of diabetic kidney disease in the clinic is the presence of proteinuria, which carries the risk for kidney disease progression and cardiovascular catastrophes (stroke, myocardial infarction). Type 2 diabetes is the leading cause of end-stage kidney disease in the United States and throughout the world. Based on the assumption that albuminuria is a marker of early kidney disease in diabetes and that as the kidney disease progresses so does the albuminuria, a series of clinical trials intervening at earlier and earlier stages of the disease process indicate that it may be possible to prevent kidney disease in susceptible individuals.

Studies in normoalbuminuric, microalbuminuric and macroalbuminuric type 2 diabetics have confirmed that intervention with either an ACEi or an angiotensin receptor blocker may halt disease progression[73-77]. As illustrated in **Figure 6**, interventions at each level of albuminuria have been successful in slowing progression of kidney disease. This is promising data and provides hope that kidney disease from diabetes can one day be prevented. Aggressive treatment of type 2 diabetics with ACEi even in the absence of albuminuria as a way to prevent future kidney disease is recommended by some, but this has not been embraced as a new clinical practice guideline by the American Diabetes Association or the National Kidney Foundation yet. Some patients with diabetes and reduced GFR do not have evident proteinuria but do have progressive kidney disease. Do these patients have another kidney disease? Is there disease caused by atherosclerosis with vascular injury but lack of albuminuria? Since most patients with diabetes and kidney disease do not undergo kidney biopsy, the answers to these questions are not known. In addition, there is no other kidney disease that has been as well studied at different stages

Figure 6. Impact of RAAS Blockade in Type 2 Diabetes Mellitus



of the disease; therefore, it is not known whether this strategy would be as effective in clinical trials.

Novel Interventions

Anti-fibrotic agents: Antibodies to transforming growth factor beta and to connective tissue growth factor are under development for treating fibrotic diseases, including the lung and kidney. Urinary connective tissue growth factor (CTGF) and urinary TGF-beta levels correlate with proteinuria in chronic kidney disease and novel therapies targeting these proteins may ameliorate or arrest fibrogenic mechanisms in the kidney that are regulated by TGF-beta and CTGF[78, 79]. Pilot studies to test the safety and efficacy of antibodies to reduce proteinuria are ongoing. Surrogate markers of renal inflammation and fibrosis in blood and urine including macrophage chemotactic factor-1 are being utilized to monitor the effects on fibrosis.

Bone Morphogenic Protein (BMP)-7 is a member of the transforming growth factor superfamily is known to inhibit renal scarring in animal models of chronic kidney disease. Studies indicate that BMP7 can reduce epithelial mesangial transformation and renal fibrosis in animal models[80-82]. BMP-7 acts to inhibit activation of TGF-beta secretion in the kidney and reduces renal scarring [83]. Clinical trials of BMP-7 are under design to determine its efficacy and safety in humans with progressive kidney diseases.

Vitamin D Receptor Agonists among a small group of type 2 diabetics. The pleiotropic effects of vitamin D receptor agonists such as paricalcitol include reduction in smooth cell proliferation, altered endothelial cell function, anti-inflammatory effects and effects on epithelial and endothelial cell growth characteristics[84]. To the extent that these effects may reduce glomerular and tubular injury and proliferation this class of drugs may be renoprotective in those with progressive kidney diseases*:* In an observational study the oral vitamin D receptor agonist paricalcitol was recently shown to reduce dipstick positive proteinuria in patients with CKD[85]. A large-scale double-blind randomized placebo-controlled trial is now underway to determine whether paricalcitol reduces proteinuria and to what magnitude.

Thiazolidinediones: Several small studies indicate that thiazolidinediones can reduce proteinuria, and the potential mechanisms of this class of drugs on renal function has been reviewed recently[86, 87]. Still, to date there are no studies demonstrating the effects of TZDs on renal outcomes such as doubling serum creatinine or ESRD. A clinical trial in type 1 diabetics with albuminuria and supported by the Juvenile Diabetes Foundation is now underway to assess the benefit of this drug not on glycemic control but on kidney outcomes.

Sulodexide: Glycosaminoglycans comprise a group of glomerular basement membrane proteins that function in part as a barrier to trafficking of plasma proteins into Bowman's space. Loss of GAG have been demonstrated in human glomerular diseases, including diabetes and focal glomerular sclerosis. Sulodexide, or glucuronylglycosaminoglycan sulfate, is an orally available glycosaminoglycan (GAG) in the same GAG family as low-molecular weight heparin that does not cause anticoagulation at usual doses. Several small, short-term human studies indicate that oral administration of sulodexide reduces proteinuria studies in mice and indicate that it can reduce glomerulosclerosis and proteinuria[88-93]. The precise mechanisms by which this GAG reduces proteinuria are unknown. Restoration of anionic charge on GBM, alteration in mesangial cell matrix production and decreased heparanase activity have been proposed as possible protective effects of sulodexide. This agent is under investigation in diabetic nephropathy and focal sclerosis.

Protein Kinase C Beta-1 Inhibition in diabetic nephropathy: Protein kinase C beta-1 isoform is activated in diabetic kidneys by increased cytosolic glucose. Inhibition of PKC-beta-1 in animal models of diabetic nephropathy retards kidney disease progression and mitigates proteinuria. In a multi-center double-blind, randomized placebo controlled pilot study conducted at UT Southwestern and 11 other centers, long-term administration of the orally active PKC-beta-1 inhibitor ruboxistaurin reduced albuminuria by 25% and was associated with stable creatinine clearance in type 2 diabetics with persistent proteinuria despite treatment with an ACEi or ARB. In this study, urinary excretion of TGF-beta was also reduced by 25% as compared to by ruboxistaurin. These effects occurred independent of blood pressure, ACEi or ARB administration and glycemic control, suggesting that this agent may be a promising therapy for halting progression of established diabetic nephropathy.

FUTURE RESEARCH

Future research in progression of kidney disease is likely to focus on further understanding the molecular pathogenesis of glomerular and tubular scarring because of the compelling evidence that renal scarring may be stoppable if not someday reversible. At the cellular and molecular level, genetic and biochemical mechanisms responsible for kidney disease progression are being worked out in diabetic nephropathy, polycystic kidney disease and lupus nephritis. These mechanisms will be coupled with the discovery of novel biomarkers that better predict the onset and progression of kidney disease and provide insight into the mechanisms of disease.

While searching for better methods to estimate glomerular filtration rate as means of screening for and following patients with chronic kidney disease, it is the discovery of these new markers of kidney function beyond serum levels of creatinine and blood urea nitrogen that will lead to a better understanding of the disease and a more effective and efficient therapeutic approach to patients with chronic kidney disease. New biomarkers should be sought for to distinguish those who progress from those who do not. Whether these markers are biochemical measures in blood and urine or genetic and proteomic markers or metabolomics is uncertain. But these approaches are likely to occur in the next decade, bringing forth a new set of solutions to the rising tide of chronic kidney disease and its attendant human and economic costs.

Summary: We have a framework for detecting and monitoring kidney disease built around filtration function of the kidney that has helped us to improve recognition of patients with kidney disease who are at high risk for progression of kidney disease and fatal cardiovascular events. Careful application of currently available strategies to diagnose and manage progressive chronic kidney disease can halt progression and likely reduce will reduce cardiovascular morbidity and mortality as well. Physicians can therefore improve the outcomes in patients with CKD while research into disease mechanism, diagnosis and prevention continue. Standard methods for detecting and monitoring kidney disease lack sensitivity and specificity. Therefore, we need to discover and validate novel non-filtration markers in order to: 1) diagnose kidney disease; 2) identify progressors; 3) provide alternative quantitative measures of disease progression; and 4) identify new molecular targets for intervention. Possible methods for detecting onset and progression of kidney disease include blood and urine markers of tubular or interstitial metabolic function or inflammation in the kidneys. The NIH seeks to fund projects to identify new markers for detecting and monitoring chronic kidney disease and both basic and clinical scientists must work hard to discover and validate new approaches. If they do, the future for patients with chronic kidney disease will improve.

Reference List

(1) Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003 January;41(1):1-12.

(2) USRDS. United States Renal Data Systems Annual Data Report. *Am J Kid Dis* 2007 January 1;49(Suppl. 1):S10-S294.

(3) Levey AS, Coresh J, Balk E et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003 July 15;139(2):137-47.

(4) National Kidney Foundation. Clinical Practice Guidlines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disase. Tuttle K, editor. American Journal of Kidney Diseases 49[2, Supplement 2], S1-S123. 2007.

(5) Wright JT, Jr., Bakris G, Greene T et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002 November 20;288(19):2421-31.

(6) Keane WF, Brenner BM, de ZD et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int* 2003 April;63(4):1499-507.

(7) Lea J, Greene T, Hebert L et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005 April 25;165(8):947-53.

(8) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine* 1999;130(6):461-70.

(9) Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol* 2006 November;17(11):2974-84.

(10) Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg? *Semin Dial* 2004 November;17(6):449-54.

(11) Shah SV, Baliga R, Rajapurkar M, Fonseca VA. Oxidants in chronic kidney disease. *J Am Soc Nephrol* 2007 January;18(1):16-28.

(12) Eddy AA. Progression in chronic kidney disease. *Adv Chronic Kidney Dis* 2005 October;12(4):353-65.

(13) Brosius FC, III. Trophic factors and cytokines in early diabetic glomerulopathy. *Exp Diabesity Res* 2003 October;4(4):225-33.

(14) Iwano M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. *Curr Opin Nephrol Hypertens* 2004 May;13(3):279-84.

(15) Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney International* 1984;26:861-8.

(16) Halbesma N KDBAeal. Macroalbuminuria is a better risk marker than low GFR to identify subjects at risk for accelerated GFR loss in a general population. J.Am.Soc.Neph 16, 3A27. 2005.

(17) Ruggenenti P, Remuzzi G. The role of protein traffic in the progression of renal diseases. *Annu Rev Med* 2000;51:315-27.

(18) Russo LM, Bakris GL, Comper WD. Renal handling of albumin: a critical review of basic concepts and perspective. *Am J Kidney Dis* 2002 May;39(5):899-919.

(19) Russo LM, Sandoval RM, McKee M et al. The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: retrieval is disrupted in nephrotic states. *Kidney Int* 2007 March;71(6):504-13.

(20) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004 September 23;351(13):1296-305.

(21) de ZD, Remuzzi G, Parving HH et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 2004 June;65(6):2309-20.

(22) Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000 July;58(1):293-301.

(23) Wesson DE, Chaurihan T. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am J Kid Dis* 2002;39(2):376-82.

(24) Wesson DE. The relationship of cigarette smoking to end-stage renal disease. *Semin Nephrol* 2003 May;23(3):317-22.

(25) Keane W, Brenner B, deZeeuw D et al. The Risk of DevelThe Risk of Developing End-Stage Renal Disease in Patients with Type 2 Diabetes and Nephropathy: The RENAAL Study. *Clin J Am Soc Neph* 2006;in press:761-7.

(26) Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. *Kidney Int* 2004 September;66(3):1131-8.

(27) Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs* 2006;66(17):2213-34.

(28) Kramer H. Obesity and chronic kidney disease. *Contrib Nephrol* 2006;151:1-18.

(29) Praga M, Morales E. Obesity, proteinuria and progression of renal failure. *Curr Opin Nephrol Hypertens* 2006 September;15(5):481-6.

(30) Chow KM, Wong TY, Li PK. Genetics of common progressive renal disease. *Kidney Int Suppl* 2005 April;(94):S41-S45.

(31) Barzilay JI, Davis BR, Bettencourt J et al. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens (Greenwich)* 2004 March;6(3):116-25.

(32) Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 1995 June;47(6):1703-20.

(33) Ruggenenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal diseases. *Lancet* 2001 May 19;357(9268):1601-8.

(34) Jafar TH, Stark PC, Schmid CH et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 2001 September;60(3): 1131-40.

(35) Ruggenenti P, Perna A, Zoccali C et al. Chronic proteinuric nephropathies. II. Outcomes and response to treatment in a prospective cohort of 352 patients: differences between women and men in relation to the ACE gene polymorphism. Gruppo Italiano di Studi Epidemologici in Nefrologia (Gisen). *Journal of the American Society of Nephrology* 2000;11(1):88-96.

(36) Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 2000 June;35(6):1155-65.

(37) Ruggenenti P, Perna A, Benini R et al. In chronic nephropathies prolonged ACE inhibition can induce remission: dynamics of time-dependent changes in GFR. Investigators of the GISEN Group. Gruppo Italiano Studi Epidemiologici in Nefrologia. *J Am Soc Nephrol* 1999 May;10(5):997-1006.

(38) Ruggenenti P, Gambara V, Perna A, Bertani T, Remuzzi G. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol* 1998 December;9(12):2336-43.

(39) Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006 January;69(2):375-82.

(40) Appel LJ, Middleton J, Miller ER, III et al. The rationale and design of the AASK cohort study. *J Am Soc Nephrol* 2003 July;14(7 Suppl 2):S166-S172.

(41) Benabe JE, Rios EV. Kidney disease in the Hispanic population: facing the growing challenge. *J Natl Med Assoc* 2004 June;96(6):789-98.

(42) Lopes AA. Relationships of race and ethnicity to progression of kidney dysfunction and clinical outcomes in patients with chronic kidney failure. *Adv Ren Replace Ther* 2004 January;11(1):14-23.

(43) Chiapella AP, Feldman HI. Renal failure among male Hispanics in the United States. *Am J Public Health* 1995 July;85(7):1001-4.

(44) Pugh JA, Medina RA, Cornell JC, Basu S. NIDDM is the major cause of diabetic end-stage renal disease. More evidence from a tri-ethnic community. *Diabetes* 1995 December;44(12):1375-80.

(45) Taal MW, Brenner BM. Predicting initiation and progression of chronic kidney disease: Developing renal risk scores. *Kidney Int* 2006 November;70(10):1694-705.

(46) Dimitrov BD, Perna A, Ruggenenti P, Remuzzi G. Predicting end-stage renal disease: Bayesian perspective of information transfer in the clinical decision-making process at the individual level. *Kidney Int* 2003 May;63(5):1924-33.

(47) Dimitrov BD, Ruggenenti P, Stefanov R, Perna A, Remuzzi G. Chronic nephropathies: individual risk for progression to end-stage renal failure as predicted by an integrated probabilistic model. *Nephron Clin Pract* 2003;95(2):c47-c59.

(48) Perco P, Pleban C, Kainz A et al. Protein biomarkers associated with acute renal failure and chronic kidney disease. *Eur J Clin Invest* 2006 November;36(11):753-63.

(49) Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *J Clin Invest* 2006 February;116(2):288-96.

(50) Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998 July 9;339(2):69-75.

(51) Ruggenenti P, Perna A, Benini R et al. In chronic nephropathies prolonged ACE inhibition can induce remission: dynamics of time-dependent changes in GFR. Investigators of the GISEN Group. Gruppo Italiano Studi Epidemiologici in Nefrologia. *J Am Soc Nephrol* 1999 May;10(5):997-1006.

(52) Wilmer WA, Hebert LA, Lewis EJ et al. Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the Captopril Study. *Am J Kidney Dis* 1999 August;34(2):308-14.

(53) Ruggenenti P, Brenner BM, Remuzzi G. Remission achieved in chronic nephropathy by a multidrug approach targeted at urinary protein excretion. *Nephron* 2001 July;88(3):254-9.

(54) L.Appel. Relentless Progression of Hypertensive Chronic Kidney Disease (CKD) Despite Excellent Blood Pressure (BP) Control and Use of Angiotensin Converting Enzyme Inhibitor (ACEI) Therapy: Results from the African-American Study of Kidney Disease and Hypertension (AASK) Cohort Study. Journal of American Soc.Neph. September 2006. 2006.

(55) Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis* 1999 May;33(5):1004-10.

(56) Gansevoort RT, Verhave JC, Hillege HL et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney Int Suppl* 2005 April;(94):S28-S35.

(57) Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004 July 13;110(2):227-39.

(58) Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta- analysis. *Kidney Int* 2001 January;59(1):260-9.

(59) Baber U, Toto RD, de Lemos JA. Statins and cardiovascular risk reduction in patients with chronic kidney disease and end-stage renal failure. *Am Heart J* 2007 April;153(4):471-7.

(60) Howard G, Wagenknecht LE, Burke GL et al. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study [see comments]. *JAMA* 1998 January 14;279(2):119-24.

(61) Chuahirun T, Wesson DE. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am J Kid Dis* 2003;41(1):13-21.

(62) Mehler PS, Jeffers B, Beggerstaff S, Schrier R. Smoking as a risk factor for nephropathy in non-insulin-dependent diabetics. *J Gen Med* 1998;13(12):842-5.

(63) Ritz E, Ogata H, Orth SR. Smoking: a factor promoting onset and progression of diabetic nephropathy. *Diab Med* 2000;26(4):54-63.

(64) Sawicki PT, Didjurgeit U, Muhlhauser I. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 1994;17:126-31.

(65) Hansen HP, Rossing K, Jacobsen P, Jensen BR, Parving HH. The acute effect of smoking on systemic haemodynamics, kidney and endothelial functions in insulin-dependent diabetic patients with microalbuminuria. *Scand J Clin Lab Invest* 1996 August;56(5):393-9.

(66) Benck U, Clorius J, Ritz E. Renal hemodynamic changes during smoking: effects of adrenoreceptor blockade. *Eur J Clin Invest* 1999;29(12):1010-5.

(67) Keane WF, Brenner BM, de ZD et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int* 2003 April;63(4):1499-507.

(68) Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997;77(2):176-85.

(69) Singh AK, Szczech L, Tang KL et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006 November 16;355(20):2085-98.

(70) Drueke TB, Locatelli F, Clyne N et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006 November 16;355(20):2071-84.

(71) Mix TC, Brenner RM, Cooper ME et al. Rationale--Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. *Am Heart J* 2005 March;149(3):408-13.

(72) J.P.Lea. Metabolic Syndrome Predicts the Progression of Chronic Kidney Disease in Hypertensive African-Americans. J.Am.Soc.Neph September 2006. 2006.

(73) Ruggenenti P, Fassi A, Ilieva AP et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004 November 4;351(19):1941-51.

(74) Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003 January 30;348(5):383-93.

(75) Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001 September 20;345(12):861-9.

(76) Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001 September 20;345(12):851-60.

(77) Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. [Effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes]. *Ugeskr Laeger* 2001 October 1;163(40):5519-24.

(78) Nguyen TQ, Tarnow L, Andersen S et al. Urinary connective tissue growth factor excretion correlates with clinical markers of renal disease in a large population of type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 2006 January;29(1):83-8.

(79) Inigo P, Campistol JM, Lario S et al. Effects of losartan and amlodipine on intrarenal hemodynamics and TGF- beta(1) plasma levels in a crossover trial in renal transplant recipients. *J Am Soc Nephrol* 2001 April;12(4):822-7.

(80) Zeisberg M. Bone morphogenic protein-7 and the kidney: current concepts and open questions. *Nephrol Dial Transplant* 2006 March;21(3):568-73.

(81) Zeisberg M, Shah AA, Kalluri R. Bone morphogenic protein-7 induces mesenchymal to epithelial transition in adult renal fibroblasts and facilitates regeneration of injured kidney. *J Biol Chem* 2005 March 4;280(9):8094-100.

(82) Zeisberg M, Kalluri R. Experimental strategies to reverse chronic renal disease. *Blood Purif* 2004;22(5):440-5.

(83) Kalluri R, Zeisberg M. Exploring the connection between chronic renal fibrosis and bone morphogenic protein-7. *Histol Histopathol* 2003 January;18(1):217-24.

(84) Tan X, Li Y, Liu Y. Therapeutic role and potential mechanisms of active Vitamin D in renal interstitial fibrosis. *J Steroid Biochem Mol Biol* 2007 March;103(3-5):491-6.

(85) Agarwal R, Acharya M, Tian J et al. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. *Kidney Int* 2005 December;68(6):2823-8.

(86) Bakris GL, Ruilope LM, McMorn SO et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. *J Hypertens* 2006 October;24(10):2047-55.

(87) Sarafidis PA, Bakris GL. Protection of the kidney by thiazolidinediones: an assessment from bench to bedside. *Kidney Int* 2006 October;70(7):1223-33.

(88) Dedov I, Shestakova M, Vorontzov A, Palazzini E. A randomized, controlled study of sulodexide therapy for the treatment of diabetic nephropathy. *Nephrol Dial Transplant* 1997 November;12(11):2295-300.

(89) Gambaro G, Kinalska I, Oksa A et al. Oral sulodexide reduces albuminuria in microalbuminuric and macroalbuminuric type 1 and type 2 diabetic patients: the Di.N.A.S. randomized trial. *J Am Soc Nephrol* 2002 June;13(6):1615-25.

(90) Skrha J, Perusicova J, Pont'uch P, Oksa A. Glycosaminoglycan sulodexide decreases albuminuria in diabetic patients. *Diabetes Res Clin Pract* 1997 October;38(1):25-31.

(91) Solini A, Vergnani L, Ricci F, Crepaldi G. Glycosaminoglycans delay the progression of nephropathy in NIDDM. *Diabetes Care* 1997 May;20(5):819-23.

(92) Sorrenti G, Grimaldi M, Canova N, Palazzini E, Melchionda N. Glycosaminoglycans as a possible tool for micro- and macroalbuminuria in diabetic patients. A pilot study. *J Int Med Res* 1997 March;25(2):81-6.

(93) Szelachowska M, Poplawska A, Topolska J, Kinalska I, Grimaldi M. A pilot study of the effect of the glycosaminoglycan sulodexide on microalbuminuria in type I diabetic patients. *Curr Med Res Opin* 1997;13(9):539-45.