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CKD Series: Delaying the Progression of Chronic Kidney Disease

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Data from the USRDS 2000 Annual Report¹ projects that the end-stage renal disease (ESRD) population in the United States and its territories will continue to increase. Incident counts are projected to rise to 172,667 by 2010. The prevalence of ESRD in the United States, which is influenced by increased rates of disease, better dialysis therapy, anemia control, improved graft survival, and lower death rates, is projected to rise approximately 77% to exceed 660,000 cases in 2010. This increase will have a large cost in both human and financial terms. Although a variety of strategies can be proposed to reduce this burden, the strategy most accessible to the internist is to slow the rate of progression of chronic kidney disease (CKD) and reduce the number of patients joining the ranks of the ESRD population. Although this task may seem daunting, it is a goal that is amenable to attention to detail in the care of the CKD patient. Small changes in the rate of renal function loss, measured as changes in glomerular filtration rate (GFR) per year, result in a benefit to patients. **Figure 1** demonstrates the apparent magnitude of this benefit. For example, a change in the annual decline of GFR from 5.0 mL/min/1.73 m² to 2.0 mL/min/1.73 m² theoretically adds nearly 30 years of life off dialysis to a 25-year-old patient with CKD. This magnitude of change is achievable with the interventions described in this article.

This article will approach the subject of delaying the progression of CKD from this perspective. Although the long-term goal ultimately is to cure CKD, currently most available strategies focus on a reduction in the slope of the rate of decline of GFR.

TIGHT GLUCOSE CONTROL

Diabetes mellitus is a growing public health threat. The prevalence of diabetes in the United States rose from 4.9% in 1990 to 6.5% in 1998, an increase of 33%. This increase was observed in males and females of all ages, ethnic groups, and education levels and in

nearly all states.²⁻⁴ It is a major cause of morbidity and mortality and contributes significantly to the ESRD population in the United States. During the 12-year period from 1984 to 1996, there was a 5-fold increase in the number of persons initiating dialysis or undergoing renal transplantation for ESRD related to diabetes mellitus.⁴ Perhaps more alarming is the fact that the incidence of ESRD among diabetic patients in the United States tripled between 1989 and 1998, as compared with the stable ESRD incidence rates observed among patients with hypertension.¹ Because diabetes mellitus contributes a large proportion of patients to the ESRD population, the role of blood glucose control in the progression to ESRD is highly relevant.

Type 1 Diabetes Mellitus

The data supporting glucose control in patients with type 1 diabetes mellitus is compelling. The landmark Diabetes Control and Complications Trial (DCCT) randomized patients with type 1 diabetes mellitus to intensive glucose control and conventional therapy.⁵ The intensive therapy group received insulin 3 or more times per day via injection or pump to maintain the hemoglobin A_{1c} (Hb A_{1c}) level within the normal range. The conventional treatment group received insulin 1 or 2 times daily in an attempt to diminish symptoms of hyperglycemia and glycosuria. The intensive therapy group achieved a Hb A_{1c} level of 7.5%, and the conventional therapy group maintained a level of 9%. Primary prevention and secondary intervention cohorts were created based on the absence of retinopathy at enrollment (primary prevention cohort) or its presence

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(secondary intervention cohort). Based on this distinction (as a surrogate marker of nephropathy), the DCCT compared the effects of the 2 interventions on prevention of de novo disease and reduction in progression of established disease. As seen in **Figure 2**, the results are unambiguous but must be carefully interpreted. The development of de novo or progression of established albuminuria was employed as a marker of nephropathy; however, it did not answer the question of whether intensive insulin therapy prevents or slows progression to ESRD. After an average follow-up time of 6.5 years, intensive therapy reduced the risk for developing microalbuminuria (> 40 mg and < 300 mg/24 hours) by 34% in the primary prevention group. In the secondary intervention group, intensive therapy reduced the risk for both microalbuminuria and albuminuria by 43% and 56%, respectively.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus presents a more complicated picture. Three prospective, randomized controlled trials have examined outcomes in patients with type 2 diabetes mellitus who were treated conventionally or intensively. All three examined multiple end points, of which progression of nephropathy (as defined by albuminuria) was one.

A Japanese study compared intensive insulin therapy with conventional insulin therapy in patients with type 2 diabetes mellitus.⁶ Patients (N = 110) were divided into a primary prevention group (no retinopathy and urinary albumin excretion < 30 mg/24 h) and a secondary intervention group (simple retinopathy and urinary albumin excretion > 30 mg/24 h and < 300 mg/24 h) and then randomized to either therapy. Over a 6-year period of follow-up, the Hb A_{1c} level in the intensive therapy group averaged 7.1% and that of the conventional therapy group averaged 9.4%. In the primary prevention group, only 2 patients in the intensive therapy arm developed microalbuminuria, whereas in the conventional therapy group, 5 patients developed microalbuminuria and 2 patients developed albuminuria. In the secondary intervention group, 2 patients in the intensive therapy group and 6 patients in the conventional therapy group developed progression of microalbuminuria; 2 patients in the conventional therapy group also developed albuminuria.

The United Kingdom Prospective Diabetes Study (UKPDS) randomized 3867 newly diagnosed type 2 diabetes mellitus patients to either conventional therapy (dietary counseling) or intensive therapy (sulfonylureas or insulin).⁷ Over a 10-year period of observation, the Hb A_{1c} level in the intensive therapy group

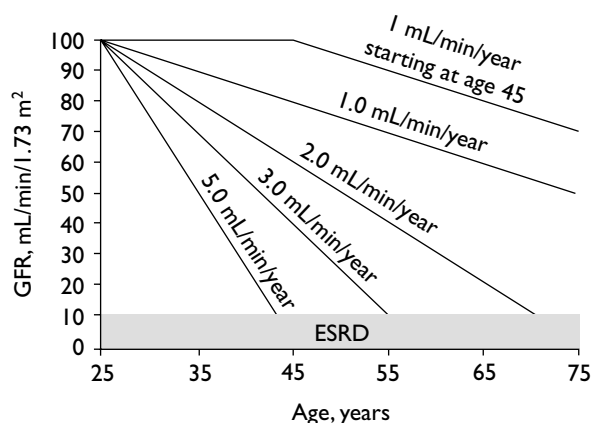


Figure 1. Theoretic curves demonstrating the large beneficial effect, measured in years off dialysis, that can be achieved by incrementally slowing the annual rate of decline of the glomerular filtration rate. ESRD = end-stage renal disease; GFR = glomerular filtration rate. (Adapted with permission from Hebert LA, Wilmer WA, Falkenhain ME, et al. Renoprotection: one or many therapies? *Kidney Int* 2001;59:1212. © 2000 by Annual Reviews. www.annualreviews.org)

averaged 7.0% and that of the conventional therapy group averaged 7.9%. A strong trend towards less microalbuminuria and less proteinuria was noted in the intensively treated group.

In the Steno Type 2 Study, 160 diabetic patients with a 24-hour urine collection containing 30 mg to 300 mg of albumin were randomized to either conventional therapy (usual care provided by a general practitioner) or an intensive step-wise approach to care.⁸ Intensive therapy included access to a full team of diabetes care specialists, dietary and exercise counseling, oral hypoglycemic agents, and insulin.⁸ Patients in the intensive therapy cohort also received 50 mg of captopril twice daily regardless of blood pressure. Patients in the intensively treated group reached a Hb A_{1c} level of 7.6%, whereas the standard therapy group maintained a Hb A_{1c} level of 9.0%. After nearly 4 years of follow-up, 8 patients in the intensively treated group and 19 in the standard therapy group reached the primary end point (progression of albuminuria to > 300 mg/24 h). However, this study was not structured to allow the distinction between the various interventions studied, and the reduction in albuminuria may have resulted from captopril rather than tight glucose control.

Despite the differences in the various studies, the data are compelling. Patients with either type 1 or 2 diabetes mellitus should seek to achieve tight glucose control, as defined by a Hb A_{1c} percentage of 7.0% to 7.5%. However, tight glycemic control may be associated with

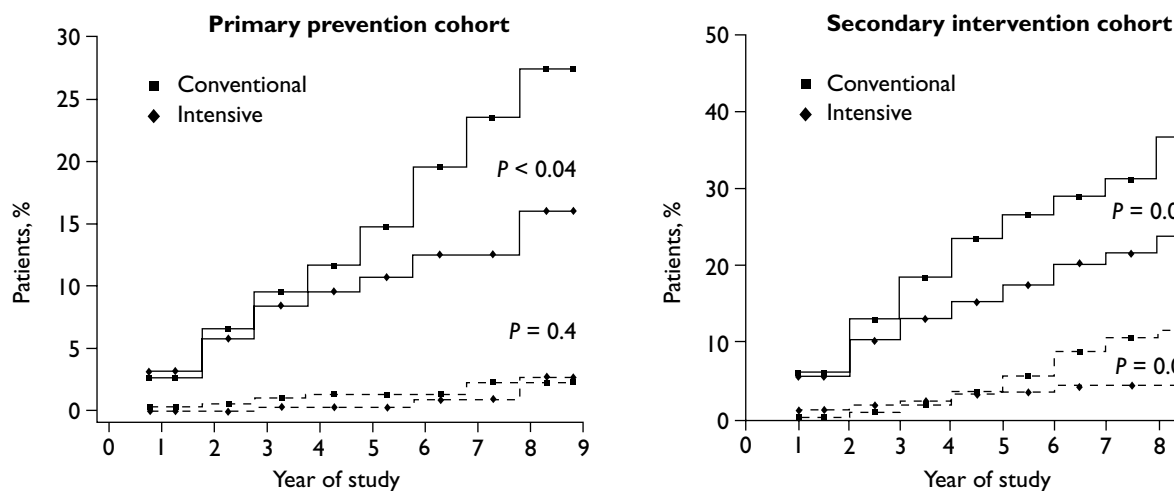


Figure 2. Cumulative incidence of urinary albumin excretion ≥ 300 mg per 24 hours (dashed line) and ≥ 40 mg per 24 hours (solid line) in patients with insulin-dependent diabetes mellitus receiving intensive or conventional therapy. (Adapted with permission from The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329:977–86. Copyright 2003 Massachusetts Medical Society. All rights reserved.)

a higher rate of hypoglycemic episodes.^{5–7} It is therefore prudent that physicians work with patients to achieve blood glucose levels as close to normal, bearing in mind safety issues.

ADEQUATE BLOOD PRESSURE CONTROL Patients Without Diabetes Mellitus

The relationship between elevated blood pressure and the risk for progression of established CKD has been demonstrated to a high degree of certainty.⁹ Additionally, adequate control of hypertension is believed to limit the rate of progression of CKD. **Table 1** lists blood pressure goals and various therapies recommended by the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease for the different stages of CKD.

Whereas the role of blood pressure control in patients with diabetic nephropathy is not disputed, the Modification of Diet in Renal Disease (MDRD) Study has documented the benefit in nondiabetic patients as well.¹⁰ The MDRD was a large trial. It consisted of 2 independent studies, one that evaluated patients with a GFR ranging from 25 mL/min/1.73 m² to 55 mL/min/1.73 m², and one that included patients with a GFR ranging from 13 mL/min/1.73 m² to 24 mL/min/1.73 m². Both study groups were randomly assigned to 1 of 4 study arms that included a low protein diet, a very low protein diet, usual blood pressure control, or tight blood pressure control.

The MDRD study demonstrated that lowering the

mean arterial blood pressure (MAP) to approximately 92 mm Hg (corresponding to systolic/diastolic 125/75 mm Hg) significantly slowed the rate of progression of CKD for patients who had proteinuria in excess of 1.0 g of protein daily. For patients with less than 1.0 g of urinary protein daily, the beneficial effect did not achieve significance, likely due to a short duration of follow-up. It can be argued that a longer duration of follow-up would have demonstrated a positive effect because although the initial difference between the 2 groups was not statistically significant, the groups were diverging at the 2.2 years of follow up, with a benefit favoring the tight control group. This argument rests on the fact that the tight blood pressure control initially decreases renal perfusion pressure by lowering MAP. However, after this initial period of decline, the slope of the rate of the decline in GFR of the tight-control patients was actually less than that of the usual-control patients. To date, the MDRD study stands as the largest and best designed trial to be published on effects of blood pressure control on progression of CKD in nondiabetic patients.

A second large trial, the African American Study of Kidney Disease in Hypertension, has not yet been fully reported. This study randomized patients to usual blood pressure (target MAP of 107 mm Hg [140/90 mm Hg]) and low blood pressure (target MAP of 92 mm Hg [125/75 mm Hg]) groups using either amlodipine or ramipril. The amlodipine arm was terminated early

Table 1. Blood Pressure Goals and Nonpharmacologic and Pharmacologic Therapy Recommended by the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease

Population	Blood Pressure goal (mm Hg)	Nonpharmacologic Therapy	Pharmacologic Therapy
General population	< 140/90	↓ in dietary salt, exercise	β-blockers, diuretics
CKD stages 1–4* with proteinuria (> 1 g/d) or diabetic kidney disease	< 125/75	↓ in dietary salt	ACEi, ARB, or CCB in kidney transplant recipients
CKD stages 1–4* without proteinuria	< 135/85	↓ in dietary salt	ACEi, ARB, or CCB in kidney transplant recipients
CKD stage 5*	< 140/90	↓ in dietary salt ↓ in fluid intake UF in dialysis patients	Any, except diuretics in dialysis patients

Adapted with permission from National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Kidney Disease Outcome Quality Initiative. Am J Kidney Dis* 2002;39(2 Suppl 2):S1–246 [Table 125]. Also available at http://www.kidney.org/professionals/doqi/kdoqi/Gif_file/kck_t125.gif. Accessed 11 Mar 2003.

ACEi = angiotensin II converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; UF = ultrafiltration.

*CKD stages: stage 1, kidney damage with GFR \geq 90 mL/min/1.73 m²; stage 2, kidney damage with GFR 60–89 mL/min/1.73 m²; stage 3, GFR 30–59 mL/min/1.73 m²; stage 4, GFR 15–29 mL/min/1.73 m²; stage 5, GFR < 15 mL/min/1.73 m² or on dialysis.

because of worse outcomes noted in the amlodipine arm compared with the ramipril arm.¹¹ Ramipril, in contrast, appears to be effective in this patient population. The final results are pending; however, published information documents that this blood pressure goal is achievable. At 30 months of follow-up, 59% of those assigned to the low blood pressure group achieved the target blood pressure and 81% were below a blood pressure of 140/99 mm Hg. An average of 3.4 antihypertensive medications was required to reach this target.¹² Thus, preliminary data suggest that blood pressure control can reduce progression of CKD in nondiabetic patients; however, some medications may be less effective or potentially detrimental.

Patients With Diabetes Mellitus

Small case series initially demonstrated the utility of blood pressure control in modulating and reducing the progression of renal disease for patients with diabetic nephropathy. The most convincing data regarding the efficacy of adequate blood pressure control in slowing the progression of diabetic renal disease is intertwined with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in this population. Solid data exist documenting that interruption of the renin-angiotensin-aldosterone system

(RAAS) in normotensive type 1 diabetic patients with an ACE inhibitor slows the progression of CKD.^{13,14} A 48% to 50% reduction in doubling of serum creatinine levels, death, and development of ESRD was garnered by this class of medication.¹³ Data also exist demonstrating that use of an ARB in hypertensive patients with type 2 diabetes mellitus slows the progression of CKD.^{15,16} Finally, studies in diabetic patients without CKD suggest that ACE inhibitors have a beneficial effect on both total mortality and cardiovascular outcome.^{17–19}

The target blood pressure in hypertensive patients with diabetes mellitus should be less than 140/80 mm Hg to more fully reduce the progression of CKD. The UKPDS study, which compared diabetic patients with usual blood pressure control (154/87 mm Hg) with those with tight blood pressure control (144/82 mm Hg), is the source of this recommendation.²⁰ The renoprotective effect is inferred from the statistically significant decrease in microvascular disease, defined as a 34% reduction in the worsening of retinopathy. In addition, the risk for death due to diabetes mellitus and the risk for cerebral vascular accident were also significantly reduced in the tight-control group.

It is currently unclear whether a progressive lowering of blood pressure to low levels is beneficial in hypertensive diabetic patients. A subgroup analysis of

diabetic patients in the Hypertension Optimal Treatment trial demonstrated that the risk for major cardiovascular events, myocardial infarction, and stroke successively declined with decreasing diastolic blood pressure from less than 90 mm Hg to less than 85 mm Hg to less than 80 mm Hg.²¹ This trial was not designed to assess renal end points, but it suggests potential benefit to lowering blood pressure maximally to reduce progression of CKD.

A reasonable approach to treatment of the hypertensive patient with type 1 or type 2 diabetes mellitus, with or without CKD, is to target blood pressure in the range of 120–130/70–80 mm Hg. The best available data support this approach as protective to the kidney as well as to the cardiovascular system. If tolerated, the prescribed medical regimen should include either an ACE inhibitor or an ARB.

Renin-Angiotensin-Aldosterone System Blockade

The development of medications that interrupt the RAAS, in particular by blocking the formation or binding of angiotensin II (AII), has allowed physicians to begin to treat CKD patients with the goal of preserving renal function and perhaps putting renal disease into “remission.” The beneficial effects of these medications—ACE inhibitors and ARBs—are 3-fold. They include blood pressure reduction, antiproteinuric effects, and inhibition of direct and indirect AII-mediated effects in the kidney. Although the first two generate little debate, the last is the most difficult to prove in humans.

Animal studies demonstrate the direct renal toxicity of AII. Exposure of cultured mesangial cells from Sprague-Dawley rats to AII produced a significantly greater amount of messenger ribonucleic acid (mRNA) for transforming growth factor beta (TGF- β), a known profibrotic agent in the kidney.²² The activity of TGF- β in the supernatant was assayed and found to be greater in AII-treated cell cultures than in controls. In the presence of saralasin, a competitive inhibitor of the AII receptor, the amount of mRNA produced in response to AII was no different than in controls. Incubation of mesangial cells with AII increased the amount of fibronectin and collagen type I produced. Finally, infusing AII into live rats for 1 week increased TGF- β mRNA and collagen type I in the kidneys of treated rats. In addition to this study, data exist demonstrating that AII stimulates increased production of plasminogen activator inhibitor,²³ which may prevent the degradation of injury-induced fibrosis, promoting renal fibrosis and irreversible kidney damage.²⁴ These observations provide clues to explain why, when compared with other antihypertensive agents, drugs that modulate the effect

of AII appear to confer a benefit beyond that of their antihypertensive and antiproteinuric effects.^{13,25}

ACE inhibitors clearly slow the progression of CKD in hypertensive and normotensive patients with type 1 diabetes mellitus¹³ and normotensive, normoalbuminuric patients with type 2 diabetes mellitus.¹⁴ Also, a variety of nonnephrotic CKD patients without diabetes mellitus²⁶ as well as patients with various causes of CKD,²⁷ as described in a recent meta-analysis, have benefited from a reduction in progression to ESRD associated with ACE inhibitor therapy. Recently published studies have also documented benefit in this regard for the ARBs. Losartan and irbesatan both have been shown to reduce the increases in serum creatinine over time and slow the progression of CKD in hypertensive patients who have type 2 diabetes mellitus and established nephropathy.^{15,16} Losartan also delayed progression to ESRD, whereas irbesartan reduced the increase in albuminuria in hypertensive patients with type 2 diabetes mellitus with microalbuminuria.²⁸

Although the choice of agent for specific settings may continue to be debated, the point remains that hypertensive patients with CKD caused by either diabetes mellitus or by non-diabetes-associated renal disease, with or without nephrotic range proteinuria, should receive therapy with an agent that effectively blocks the RAAS system. Strictly following the available literature would lead to the conclusion that ACE inhibitors are recommended for patients with type-1 diabetes, whereas ARBs are the drug of choice for those with type-2 diabetes. However, it is the opinion of this author that a therapy that blocks the RAAS is the primary objective, and the actual agent employed is a secondary concern. A more provocative question is whether or not to treat non-hypertensive CKD patients with one of these agents. There is certainly evidence that a benefit may be derived in patients with type 2 diabetes mellitus,¹⁴ and given the fact that therapy is generally well tolerated, one should consider treatment of normotensive CKD patients with an ACE inhibitor or an ARB. These patients should be closely followed to ensure blood pressure stability and to avoid severe hypotension.

Finally, it should be stressed that these agents are safe in patients with mild to moderate renal insufficiency, and may be even more effective in this group.^{13,15,16,26,27} Rather than employing a serum creatinine cut-off value to exclude therapy in CKD patients, it is more reasonable to attempt monitored therapy with an ACE inhibitor or an ARB. This would identify a group of patients who would otherwise not gain the benefit of RAAS inhibition. Patients who develop uncontrollable

hyperkalemia or a serum creatinine level that increases more than 30% above baseline values and does not stabilize should have therapy terminated and undergo evaluation for correctable problems. Obviously, patients with advanced CKD need to be more carefully considered for this type of therapy.

DIETARY PROTEIN RESTRICTION

Restriction of dietary protein as a therapy to slow the rate of GFR loss in CKD patients remains controversial. Clinical experience tells us that the protein restriction may delay the need for dialysis by a few months but at the cost of the development of significant malnutrition.

The effect of dietary modification has been thoroughly studied in the MDRD trial.¹⁰ As discussed previously, this large trial was divided into 2 studies based on level of kidney function (mild versus advanced). Patients with mild renal insufficiency were randomized to receive a regular protein diet consisting of 1.3 g protein/kg body weight or a low-protein diet of 0.58 g/kg. Patients with advanced renal insufficiency were randomized to either the low-protein diet or a very-low-protein diet (0.28 g/kg) plus a supplement of ketoacid–amino acid mixture.¹⁰ No significant difference was noted in renal function at 2.2 years; however, the slope of loss of renal function leveled out and was diverging in favor of the low-protein diet. The rapid decline in renal function over the first 4 months of the study in the low-protein diet groups was likely caused by hemodynamically mediated changes in renal function caused by protein restriction; these changes were not considered to equate to a loss of actual renal mass. Although the low-protein diets were generally well tolerated, weight loss occurred in some of these patients. The study authors report that there were “small but significant” changes in weight and serum albumin, transferrin, and cholesterol levels between the diet groups. Despite the above noted caveats, there does not appear to be a major benefit in renal protection from dietary protein restriction.

CONTROLLING SERUM LIPID LEVELS

Observational studies suggest that controlling serum lipid levels may retard the progression of CKD.^{29–33} However, these studies were unable to determine whether hyperlipidemia actually caused the kidney failure, whether the kidney failure promoted the development of hyperlipidemia, or whether the hyperlipidemia is an epiphenomenon of associated high-grade proteinuria. As such, the cause-and-effect relationship between hyperlipidemia and kidney failure is not understood.

Human mesangial cell culture studies suggest that a pathologic response of mesangial cells occurs in response to low-density lipoprotein. The pathologic response is blocked by the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor lovastatin.^{34,35} Additionally, the inhibition of HMG CoA reductase led to decreased production of monocyte chemoattractant protein-1, which may prevent or reduce the inflammatory response and associated cellular injury.

Small patient numbers plague individual studies that have examined the effects of lipid reduction on slowing the progression of CKD. As a result, nearly all of the studies have confidence intervals that cross zero. Recently, a high-quality meta-analysis examining 13 studies that were prospectively randomized and controlled trials with parallel or cross-over design was performed.³⁶ The studies examined included at least 3 months of follow up, and all employed lipid-lowering therapy that included either HMG CoA reductase inhibitors (n = 11) or triglyceride-lowering agents (n = 2). Lipid-lowering therapy demonstrated a non-significant trend toward reducing albuminuria or proteinuria. A statistically significant but clinically small decrease in the rate of GFR lost per month was also noted. **Figure 3** summarizes the results of 11 of the studies included in the meta-analysis. Nine of the 11 studies either demonstrated a benefit or showed a trend toward benefit of lipid-lowering agents. When analyzed together, however, although there is a trend toward benefit, the confidence interval crosses zero.

Currently, the available data do not conclusively confirm that the addition of an HMG CoA reductase inhibitor to a CKD patient’s medical regimen will slow progression to ESRD. However, from a practical perspective, many CKD patients would derive benefit from these agents for other related health issues, such as atherosclerotic heart disease. Furthermore, these agents appear to be safe in the CKD population. Therefore, it is reasonable to prescribe these agents to CKD patients, with the hope of an additive effect to other therapies in the delay of progression of CKD to ESRD.

CORRECTION OF ANEMIA

Anemia due to progressive renal insufficiency and the resultant decrease in erythropoietin production by the kidney is a major clinical problem for patients with CKD. Undoubtedly, correction of anemia with exogenous erythropoietin significantly improves quality of life, exercise tolerance, and cognitive function in CKD patients.^{37–39} In addition, correction of anemia with erythropoietin may reduce cardiac hypertrophy.⁴⁰ However, it is unclear

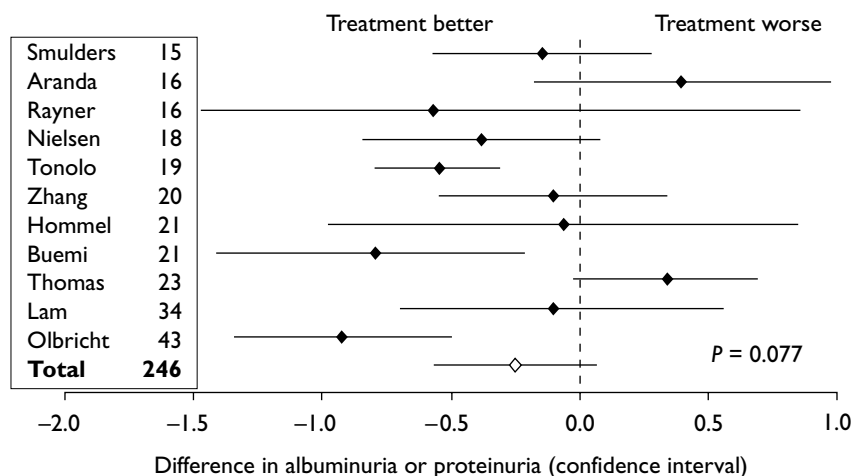


Figure 3. Meta-analysis of studies performed to assess the use of lipid-lowering agents in slowing the progression of chronic kidney disease. (Adapted with permission from Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001;59:266.)

whether the correction of anemia retards the progression of CKD to ESRD. Moreover, there is a lingering concern that the use of erythropoietin to correct anemia may accelerate the loss of renal function, an observation that was first made in animal studies.^{41,42} Unfortunately, most clinical studies have been plagued by 2 problems. First, cited studies expounding benefit were not intended primarily to address this question; second, most studies have not controlled for differences in the use of ACE inhibitors or for the level of blood pressure control achieved between treated and untreated patients.

In regard to safety of anemia correction, pediatric and adult renal transplantation literature suggests that correction of anemia for patients with chronic allograft nephropathy does not accelerate graft loss.^{43,44} Additionally, a well-done randomized trial in CKD patients designed specifically to address the question of the safety of anemia correction in this population was published.⁴⁵ Anemic CKD patients with hematocrit levels lower than 30% were randomized to receive either exogenous erythropoietin to correct their anemia (target range, 33% to 35%) or no therapy. A group of nonanemic CKD patients (hematocrit > 30%) were recruited to serve as an additional control population.⁴⁵ Blood pressure and serum cholesterol were equivalent in all groups. Anemia correction significantly increased renal survival, defined as a doubling of serum creatinine level at 36 months, compared with the untreated group. There was no significant difference between the treated group and the nonanemic controls (**Figure 4**). It is noteworthy that patients with CKD who were not anemic had a similar rate of disease progression as the treated patients. This suggests something intrinsic to a higher hematocrit, such as oxygen delivery, as opposed to a direct erythropoietin effect.

When one considers all of the available data, the proved beneficial effects of correcting anemia in CKD patients and the strong suggestion that correction of anemia may retard the progression to dialysis outweigh the concern of accelerating the pathologic process. Therefore, it is recommended that anemic CKD patients have their anemia corrected to a hematocrit of 33% to 35%. Meticulous attention to blood pressure control is important to avoid the induction of hypertension with the correction of anemia.

SMOKING CESSATION

Smoking cessation should be a goal for all patients, regardless of their specific health concerns. As such, physicians should be unambiguous in the position that all patients should not abuse tobacco. This section, however, will address whether a physician can use the prospect of delaying the progression of CKD as an additional justification.

As outlined by Orth et al,⁴⁶ several mechanisms exist by which smoking may damage the kidney. Similar to other potential contributors to renal disease, tobacco smoking increases GFR. An increase in GFR (hyperfiltration) induced by smoking may injure the nephrons in a manner similar to that observed with diabetes mellitus and remnant kidney models. Another mechanism by which smoking injures the kidney includes an elevation in blood pressure with loss of the nocturnal blood pressure dip. Increased plasma aldosterone levels also occur with smoking. Aldosterone may promote renal injury through increases in blood pressure and direct profibrotic effects. Finally, enhanced platelet aggregation from tobacco may injure renal endothelial cells and promote further kidney damage.

Several studies have attempted to assess the

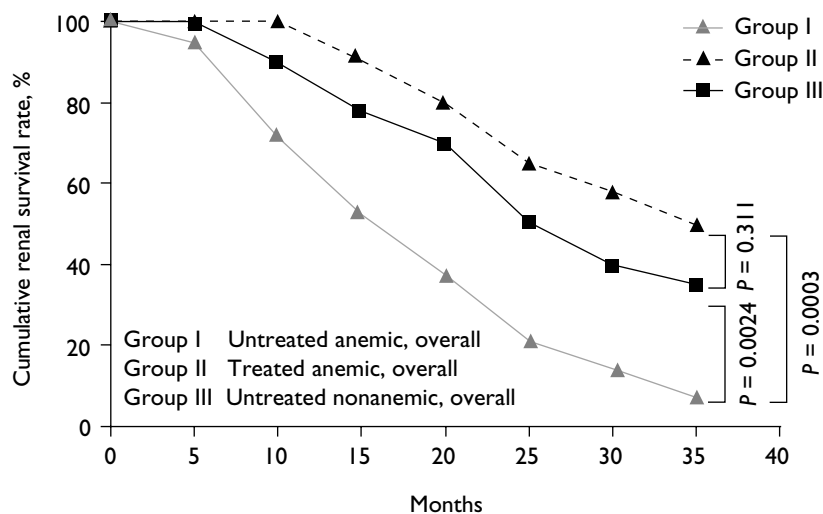


Figure 4. Effect of the correction of anemia on the progression of chronic kidney disease. (Adapted from Kuriyama S, Tomonari H, Yoshida H, et al. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997;77:180, with permission from S. Karger AG, Basel.)

relationship between smoking and the progression of CKD.^{29,47–55} The results are variable—only 4 of 10 studies found an association after evaluation of all potential factors with multivariate analysis.^{47,48,54,55} In 2 large studies examining the risk of development of albuminuria in hypertensive and nonhypertensive males, smoking emerged as an independent risk factor.^{56,57} Insulin-dependent and non-insulin-dependent diabetic patients who smoke have a higher risk for developing albuminuria.^{58,59} In addition, the rate of progression of diabetic nephropathy to ESRD in patients with type 1 diabetes and progression to gross albuminuria in patients with type 2 diabetes is greatly increased in smokers as compared with nonsmokers.^{60,61} In non-diabetic kidney disease (specifically IgA nephropathy and autosomal dominant polycystic kidney disease), smokers had a dose-dependent increase in the risk for developing ESRD as defined by need for dialysis or kidney transplantation.⁶² Increased risk, however, was attenuated by the use of ACE inhibitors in smokers.

Finally, data suggest that the cessation of smoking can slow the rate of progression of diabetic nephropathy.⁵⁸ Insulin-dependent diabetic patients had a significant decrease in albuminuria with smoking cessation.⁵⁸ In another study of patients with insulin-dependent diabetes who were treated with intensive blood glucose and blood pressure control, the progression of diabetic nephropathy was 53% in smokers, 33% in former smokers, and 11% in nonsmokers.⁶³

Although no randomized trials have documented that smoking accelerates progression of CKD, there is ample information on the negative effects of tobacco on the kidney. Associative data regarding patients with hypertension, diabetic kidney disease, or nondiabetic

kidney disease suggest that smoking hastens renal death and that cessation of smoking may ameliorate this effect. Therefore, given the other negative health consequences associated with smoking, it is the opinion of this author that the current data justify telling CKD patients who are actively smoking that continuation of the habit may hasten progression to ESRD and requirement for dialysis.

CONCLUSION

CKD is very likely one of the most challenging medical conditions that confronts the primary care provider. The multitude of organ systems involved often seems overwhelming. However, attention to detail and conscientious care carries with them the potential for large benefits to patients. Knowledge of the detrimental factors that can be modulated to reduce progression of renal disease is key to altering the clinical course of CKD patients. In diabetic patients, tight glucose control is important. Adequate blood pressure control is paramount, and medications that modulate the RAAS appear to reduce progression of CKD beyond their blood pressure-lowering effects. Lipid-lowering therapy, correction of anemia, and smoking cessation probably add to these interventions to reduce progression of CKD. The role of protein restriction is less clear and may be potentially harmful if malnutrition develops. The next article in this series will examine mineral metabolism disturbances in patients with CKD. **HP**

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