Outpatient Management of Chronic Kidney Disease: Proteinuria, Anemia and Bone Disease as Therapeutic Targets

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There is increasing emphasis on chronic kidney disease (CKD), owing to its prevalence and its association with cardiovascular risk. Important issues concerning treatment of CKD are delaying its progression, improving patients’ quality of life, and decreasing related mortality. These issues can be addressed with certain therapeutic options, targeting proteinuria, anemia, and secondary hyperparathyroidism. The management options and possible benefits related to treatment of these complications of CKD are reviewed.

Introduction

Kidney disease has been classified into 5 stages by the National Kidney Foundation (NKF). Chronic kidney disease (CKD) is defined as kidney damage demonstrated by either structural or functional abnormalities of the kidneys persisting for >3 months. Examples of structural damage to kidneys can range from specific findings on kidney biopsy, such as fibrosis or scarring, to asymptomatic abnormalities of the urine sediment, such as proteinuria and hematuria. A functional abnormality of the kidneys refers to a decreased glomerular filtration rate (GFR). GFR represents kidney function more accurately than the serum creatinine level, because a single serum creatinine value can represent very different GFRs depending on the individual patient. For example, a creatinine value of 1.1 mg/dL can represent a GFR of 95 mL/min in a healthy 31-year-old African American male, whereas it represents a GFR of 48 mL/min in a 75-year-old Caucasian woman. GFR is now estimated via several formulas. The formula favored by the NKF is called the MDRD
equation, after the study (Modification of Diet in Renal Disease) on which it was based. This formula uses demographic data (age, ethnicity, and gender) and blood test results (creatinine, blood urea nitrogen, and albumin values) as variables. Modified versions are available to calculate the GFR when some variables are missing. The MDRD equation better estimates GFR in patients with a GFR <60 mL/min because it was developed on a patient population with CKD.

Recognizing the lack of standard terminology for different degrees of renal insufficiency, the NKF presented a classification system for CKD in 2002 (Table 1). Stages of CKD are determined by evidence of kidney damage (eg, proteinuria, hematuria, or anatomic abnormalities such as cysts) or the functional level of the kidneys, as measured by the GFR. The staging system allows better recognition of compromised renal function and better management, as certain complications are more prevalent at different stages of kidney disease. CKD was defined by a GFR <60 mL/min because this is the level at which the complications of CKD are more frequent. Besides providing a useful tool that allows more precise communication of patients’ renal function between clinicians, the stages of CKD allow for management suggestions, as complications of CKD can be anticipated and treated.

CKD is garnering more attention. The prevalence of CKD (estimated at approximately 10% of the adult United States population) and the association of CKD with cardiovascular risk are two important reasons for this emphasis on CKD. Key issues across all stages of kidney disease are delaying progression of kidney disease, decreasing mortality, and improving quality of life. Certain therapeutic options are available to address these issues in CKD. This article reviews the evidence behind treating three therapeutic targets associated with CKD: proteinuria, anemia, and secondary hyperparathyroidism (SHPT). Medical evidence supports treating proteinuria to both delay the progression of CKD as well as reduce cardiovascular disease. Treating anemia can improve the patient’s quality of life and may have some added benefits of delaying progression of kidney disease and improving cardiovascular outcomes.

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Treating the SHPT found in CKD may also improve mortality and quality of life. Here we review the evidence for treating these complications, suggesting some management options and delineating the possible benefits for patients.

**Proteinuria**

*Background*

Proteinuria is a hallmark of renal disease. Healthy adults excrete up to 150 mg of protein in the urine in 24 hours, the composition of which includes albumin, renal tubular epithelial cell proteins, and low-molecular-weight globulins. Proteinuria is defined as urinary protein excretion of >150 mg/d. Proteinuria is often classified as either low-grade (or tubular) proteinuria (<1 to 2 g/d) or nephrotic-range (or glomerular) proteinuria (>3 to 3.5 g/d). This division helps isolate the source of the proteinuria: whereas <2 g of protein in the urine may come from a glomerular or interstitial (tubular) process, >2 g of protein a day usually reflects a glomerular process.

Proteinuria can be detected on urine dipstick or urinalysis, which are sensitive to urinary albumin. Although convenient, the dipstick is not accurate for quantifying proteinuria, as the concentration of the urine sample will affect the measurement of proteinuria on dipstick. To accurately quantify proteinuria, a 24-hour urine protein collection or a random urine protein-to-creatinine ratio can be used (Table 2). The 24-hour urine test measures the total amount of protein in a 24-hour period. If done correctly, this yields the most accurate measure of proteinuria. However, mistakes in following the collection protocol and the inconvenience of the collection make this a less-than-ideal method. Measuring the amount of protein and creatinine on a spot (random) sample of urine has been shown to estimate 24-hour proteinuria in the range of 500 mg to 4000 mg fairly accurately.² The spot protein–to-creatinine ratio is much easier to
determine and thus is easier to follow. In our practice, we often follow the spot protein–to-creatinine ratio, and if the results do not seem consistent with the clinical presentation we also send a 24-hour specimen for urine protein testing.

Management of proteinuria is important in caring for the patient with CKD, particularly because proteinuria is associated with significant morbidity and mortality. Multiple studies have demonstrated the long-term effects of proteinuria, and it is well established that proteinuria is an independent risk factor for progressive renal failure and end-stage kidney disease as well as both cardiovascular- and noncardiovascular-disease-related mortality.2-7 Furthermore, clinical trials have shown that treatment of proteinuria results in a significant reduction in the progression of renal failure.8 Thus, reduction of proteinuria is a desirable goal in the treatment of CKD.

Nonpharmacologic therapy

There are a number of nonpharmacologic strategies that are beneficial to the management of proteinuria. Patients, particularly those who are hypertensive, should be counseled about restricting salt intake and losing weight if overweight or obese. Reducing dietary protein intake from the usual intake of 1.0 to 1.5 g/kg ideal body weight per day to about 0.7 g/kg ideal body weight per day decreases proteinuria.9 Dietary protein restriction may also slow the progression of renal disease, though the magnitude of the benefit is not clear and may be small. Smoking cessation is strongly recommended, because cigarette smoking has been associated with proteinuria and faster progression of CKD and cardiovascular disease.10

Pharmacologic therapy: Control of blood pressure

The benefits of blood pressure (BP) control on proteinuria are evident from large trials, such as the MDRD (Modification of Diet in Renal Disease),11 ABCD (Appropriate Blood Pressure Control in Diabetes),12 and AASK (African American Study of Kidney Disease and Hypertension)13 investigations. These trials selected patients with CKD and compared the effects of maintaining a usual BP goal (140/85 mm Hg) to maintaining a low BP goal (125/75 mm Hg) with regard to proteinuria and the progression of renal disease. The MDRD study demonstrated that a lower BP goal resulted in a 50% decrease in proteinuria and a slower rate of decline of renal function. The patients with a greater baseline level of proteinuria benefited more from a greater percent reduction in proteinuria. In the AASK trial, there was a significant decrease in proteinuria compared to baseline in patients randomized to the low BP
goal, although there was no difference in retarding the progression of renal disease. Similarly, a reduction in the increase of proteinuria seen in the usual BP goal group was observed in low BP goal patients in the ABCD trial. The AASK trial also assessed differences in antihypertensive agents and revealed that the angiotensin converting enzyme (ACE) inhibitor ramipril had the most antiproteinuric effects, although a reduction in proteinuria was also seen with metoprolol; amlodipine was associated with an increase in proteinuria. On the basis of these trials, aggressive BP control with an ideal BP goal of 125/75 mm Hg or lower results in slower decline of GFR and is a recommended strategy in the treatment of CKD.

ACE inhibitor and angiotensin receptor blocker therapy

Suppression of the renin-angiotensin system with ACE inhibitors and/or angiotensin receptor blockers (ARBs) is currently the most effective therapy for proteinuria. Several large randomized, controlled trials have demonstrated significant benefits of these medication classes in patients with proteinuria and renal disease. Two important trials examined the effects of ACE inhibition in patients with type 1 diabetes mellitus with evidence of proteinuria or microalbuminuria. Both showed that after 2 to 3 years of follow-up, treatment with captopril decreased the risk of worsening renal function, as evidenced by a doubling of serum creatinine values. Treatment also reduced the progression from microalbuminuria to overt proteinuria and led to a decrease in the combined risk of death, dialysis, and kidney transplantation.14,15 Following these two studies, three other trials showed that the benefits of ACE inhibitors could be extended beyond patients with diabetic kidney disease to patients with CKDs from various causes, including glomerulonephritis, tubulointerstitial disease, nephrosclerosis, and polycystic kidney disease.16-18 Similarly, these studies demonstrated that patients who received ACE inhibitors when compared to those who received placebo and conventional antihypertensive treatment had a significant reduction in the risk for progression of renal failure. Notably, the renoprotective effects of ACE inhibitors are independent of their BP control. The medications used in the aforementioned trials included captopril, enalapril, benazepril, and ramipril; however, the benefits of these medications are likely a drug-class effect, and other ACE inhibitors should provide similar benefits. The ACE inhibitor should be started at a low dose and titrated to the maximum dose tolerated. Patients should always be monitored for the development of hypotension, hyperkalemia, or worsening renal function.
For patients who cannot tolerate ACE inhibitors because of cough, angioedema, or allergy, ARBs are recommended as an alternative. Two major studies, the RENAAL Study\textsuperscript{19} and the IDNT study,\textsuperscript{20} showed that in patients with type 2 diabetes mellitus, losartan and irbesartan, in comparison with placebo and conventional antihypertensive treatment, were able to decrease not only the progression of proteinuria and renal failure but also the development of end-stage kidney disease, thus conferring renoprotective effects similar to those of ACE inhibitors. For patients whose BP goals are not reached with an ACE inhibitor alone, addition of an ARB is appropriate. Randomized, controlled trials have demonstrated that a combination of an ACE inhibitor and an ARB can be more antiproteinuric and more renoprotective than monotherapy.\textsuperscript{21}

**Aldosterone antagonism therapy**

There are now data that suggest a role for aldosterone antagonists in the treatment of proteinuria. One small randomized, controlled study compared the antiproteinuric effects of spironolactone to the ACE inhibitor cilazapril in postmenopausal women with type 2 diabetes, hypertension, and nephropathy.\textsuperscript{22} Treatment with spironolactone resulted in a significantly greater reduction in albuminuria than did that with cilazapril (52.2% vs 33.8%) after 24 weeks, independent of its antihypertensive effects. Addition of spironolactone to the ACE inhibitor cilazapril resulted in greater antiproteinuric effects than with treatment with cilazapril alone; however, the combination of an aldosterone antagonist with an ACE inhibitor may result in hyperkalemia. These initial findings will need to be corroborated by larger randomized, controlled trials.

**Summary**

Given that proteinuria is an independent risk factor for the progression of renal disease and is associated with increased cardiovascular and all-cause mortality, treatment of proteinuria is a vital component in the management of CKD. Patients should be advised to restrict salt intake, lose excess weight, stop smoking, and monitor their dietary protein intake. Aggressive BP control is recommended, and patients should be started on ACE inhibitors as first-line agents. Those who cannot tolerate ACE inhibitors can be alternatively treated with ARBs. Effectively using these therapeutic modalities can lead to a reduction in proteinuria and cardiovascular risk and retard the progression of renal disease. Combination therapy with ACE inhibitors, ARBs, and/or spironolactone antagonists may be recommended in the future.
Anemia

Background

Anemia is typically defined as a hemoglobin value of <13.5 g/dL in males and <12 g/dL in females. However, recent NKF guidelines indicate that a workup should be initiated for patients with CKD when the hemoglobin is <12 g/dL in adult males and post-menopausal females and when the hemoglobin is <11 g/dL in premenopausal females. These values have been chosen to approximate 80% of the mean hemoglobin, a ‘lower end of normal range,’ in healthy subgroups, at which the consequences of anemia might begin to occur according to NKF guidelines. The United States Renal Data Service and several independent follow-up studies have identified that at the time of initiation of dialysis, approximately two thirds of patients with CKD have a hemoglobin of 11 g/dL or less; thus, it stands that anemia is one of the most common and treatable complications of CKD. The importance of anemia in patients with CKD is now supported by numerous studies which demonstrate that effective treatment of anemia can improve ischemic and structural heart disease, improve cognitive function, improve quality of life, and decrease overall morbidity in these patients.

Anemia caused by CKD usually results from insufficient erythropoietin production, shortened red blood cell survival, and iron deficiency. In the absence of features to suggest an alternate cause for anemia, a minimal workup should include measurement of hemoglobin of hematocrit, red blood cell indices, reticulocyte count, and iron studies, including serum iron, total iron binding capacity, transferrin saturation, and serum ferritin. The workup for anemia in these patients is always prefaced by the rule that other causes of anemia should be excluded; thus, if iron deficiency is present, the possibility of occult gastrointestinal loss must be evaluated prior to initiating therapy (with erythropoietin). The hemoglobin concentration is currently viewed as the best measure of anemia and its response to treatment; furthermore, it is the index most commonly used internationally to manage anemia in CKD. As above, a workup should be initiated when the hemoglobin is <12 g/dL in a male and <11 g/dL in a female, with the goal being to correct the hemoglobin to 11 to 13 g/dL, irrespective of gender.

Pharmacologic therapy

The principal treatments of renal anemia are to replete iron stores and supplement erythropoietin. Recombinant human erythropoietin (rHuEPO) has been used with success for several years as an agent that mimics
natural erythropoietin-driven hematopoietic precursor cell proliferation and maturation.\textsuperscript{30} NKF guidelines suggest that rHuEPO should be given initially at a dose of 80 to 120 units/kg/week, administered subcutaneously.\textsuperscript{23} Rarely, this dose is divided into two to three doses over each week. The benefits of subcutaneous administration over intravenous are better pharmacodynamics; a lower average rHuEPO dose required to achieve the same hemoglobin concentration; and preservation of veins in patients who may potentially require dialysis. The goal is then to achieve target hemoglobin over 2 to 4 months, with weekly hemoglobin monitoring until a stable and adequate response is achieved. In the case of patients who require large doses of rHuEPO, some may find weekly subcutaneous administration intolerable due to the volume delivered. In that unusual circumstance, intravenous administration at a dose 50% greater than the subcutaneous dose may be considered. Although rHuEPO is generally tolerated well, significant hypertension may occur in as many as 65\% of patients receiving it.\textsuperscript{31} This is thought to result from increased peripheral vascular resistance following relief of hypoxic vasodilation and increased blood viscosity.\textsuperscript{32} Slower correction of anemia and more aggressive antihypertensive regimens may be required.

A newer alternative to rHuEPO is darbepoetin-alpha, a long-acting agent that binds to the same receptor as erythropoietin, has the same mechanism of action, and uses similar intracellular signaling.\textsuperscript{33} Because of differences in the structure of the molecule, darbepoetin-alpha has a longer half-life and therefore can have a more extended dosing interval.\textsuperscript{34,35} The extended dosing interval is a convenient feature for patients who have to travel to a clinic to receive their injections. The most common adverse events attributed to darbepoetin-alpha are hypertension and injection site pain, both occurring at a frequency similar to that with rHuEPO.

In order for rHuEPO or darbepoetin-alpha to be effective, iron stores must be adequate. NKF guidelines recommend that the transferrin saturation be kept at \( \geq 20\% \) and the serum ferritin level at \( \geq 100 \text{ ng/mL} \).\textsuperscript{23} A trial of 200 mg oral elemental iron daily may be attempted, although as CKD advances there is an increased need for parenteral iron to maintain adequate iron stores. Intravenous iron dextran is no longer used as standard parenteral therapy because of the risk of allergic/anaphylactoid reactions\textsuperscript{23} as well as myalgias, arthralgias, flushing, hypotension, and fever.\textsuperscript{31} Iron dextran has largely been replaced by ferric sodium gluconate and iron sucrose preparations, which have markedly improved tolerance and safety profiles, as well as more flexible dosing options.
Target hemoglobin

One of the most debated aspects in the correction of renal anemia is the target hemoglobin. A recent update in NKF guidelines has broadened the target hemoglobin to 11 to 13 g/dL, with the lower limit set as an evidence-based recommendation and the upper limit set as a clinical practice recommendation (based on potential improvement in quality of life with higher hemoglobin). However, 2 recent large multicenter trials demonstrated no improvement in quality of life or risk of cardiovascular events in subgroups of patients assigned to higher target hemoglobin values. In fact, Singh et al demonstrated an increased risk of adverse events, including death, myocardial infarction, congestive heart failure, and stroke, in the subgroup with a target hemoglobin of 13.5 g/dL as compared to a target of 11.3 g/dL. Given the adverse effects associated with higher doses of rHuEPO, discordance of results in outcomes trials, and cost of therapy, the choice of hemoglobin target within the range of 11 to 13 g/dL should be made on a case-by-case basis until sufficient evidence supports the higher or lower ends of this range.

Conclusion

Anemia is a serious and widely prevalent consequence of CKD, with implications regarding quality of life, cardiovascular morbidity, cognitive function, other short- and long-term morbidity, and frequency of hospitalization. Raising the hemoglobin to target range has been associated with regression of left ventricular hypertrophy in several trials, with improved perceptual and motor functioning, and with improved energy, physical functioning, home management, and social activity. Aggressive monitoring of hemoglobin and iron indices provides an opportunity to identify renal anemia early and correct it with the agents discussed above. Darbepoetin-alpha may be of particular benefit to patients with CKD because of less-frequent dosing and thus more independence from the health care setting. Newer-generation parenteral iron therapies have proven to be tolerable and safe for those with recalcitrant iron deficiency. In order to optimize therapy, further studies need to be done to better characterize the risks and benefits of the higher and lower ends of the target hemoglobin range.

Bone disease

Background

Patients with CKD have altered regulation of calcium and phosphorus metabolism and subsequently can develop abnormal parathyroid hormone
(PTH) levels. The mineral and hormonal abnormalities affect the skeletal system and cause bone disease. The bone disease with CKD is called renal osteodystrophy (ROD), a collection of abnormalities in bone turnover, bone density, and bone architecture. Based on histological degree of bone turnover and matrix mineralization, there are four types of bone disease associated with CKD: osteitis fibrosa (SHPT with high bone turnover), osteomalacia (low turnover with a mineralization defect), mixed uremic bone disease (both high and low turnover with increased osteoid volume), and adynamic bone disease (decreased turnover without mineralization defects). A single patient may have a combination of the four types of bone disease histologically evident at any given time, making treatment decisions difficult. A recent position statement\textsuperscript{39} has proposed a new classification system for CKD-mineral and bone disorder (CKD-MBD). CKD-MBD would replace the nebulous term renal osteodystrophy. The classification of CKD-MBD would be based on the presence or absence of abnormalities in calcification, laboratory values (calcium, phosphate, PTH, alkaline phosphatase), and bone biopsy. The classification system is intended to clarify the extent of involvement of CKD-MBD in the individual patient as well as to direct future research efforts.

In CKD, particularly in stages 4 and 5, reduced renal function can result in inadequate excretion of the daily phosphorus load. The kidneys also are responsible for converting the less-active 25-hydroxy vitamin D to the active 1,25-dihydroxy vitamin D. Therefore, as CKD progresses, less 1,25-dihydroxy vitamin D may be available. Decreased 1,25-dihydroxy vitamin D can cause both a low serum calcium level and a high PTH value, because 1,25-dihydroxy vitamin D normally suppresses PTH. Also, the retention of phosphorus can lead to abnormal complexes and possibly precipitation of calcium and phosphorus, causing a low serum calcium level. The low serum calcium level, low 1,25-dihydroxy vitamin D level, and high serum phosphorus level all contribute to increased PTH levels. The high PTH, low serum calcium, and high serum phosphorus levels create the milieu for abnormal bone metabolism. Treatment of ROD has focused on controlling phosphorus, calcium, and PTH levels, with some recent focus on vitamin D levels.

\textit{Nonpharmacologic treatment}

A critical component of controlling ROD is controlling the serum phosphorus level. Phosphorus is abundant in many foods. Initial treatment in CKD focuses on dietary education with regard to avoiding high-phosphorus foods. Chocolate, colas, and dairy products are three common
high-phosphorus culprits, although it is best to have patients meet with a dietician to review the overall diet, including high-phosphorus foods, to come up with a safe dietary plan ensuring adequate calories and nutrition, especially when CKD patients can develop a loss of appetite. With dwindling renal function, diet alone may not be able to control the phosphorus levels.

Pharmacologic treatment

The complex interplay between the mineral and hormonal factors that account for renal bone disease are still not fully understood. At this time, pharmacologic treatment centers on controlling the phosphorus level, evaluation and replacement of vitamin D, and controlling the PTH level.

Phosphorus control

The target phosphorus level in CKD stages 3 and 4 is 2.7 to 4.6 mg/dL. If dietary modification alone does not control the serum phosphorus level, agents that bind dietary phosphorus are prescribed. These agents, taken with food, bind the phosphorus in food and prevent the absorption of phosphorus from the gastrointestinal tract. The agents can be divided into those that contain calcium and those that do not contain calcium.

The calcium containing binders are calcium carbonate (Tums) and calcium acetate (PhosLo). Calcium-containing binders have been shown to be effective at binding dietary phosphorus. Depending on the serum phosphorus level, patients are instructed to take from 1 to 3 pills with each meal. Because these binders contain calcium, the serum calcium level as well as phosphorus level must be followed. Especially because of its easy availability and low cost, calcium carbonate is an excellent choice of binder if the calcium level is not high and the calcium and phosphorus product (that is, the serum calcium multiplied by the serum phosphorus) is <55.

Soft-tissue calcification has begun to receive much attention. Dramatic pictures of the calcification of blood vessels in patients with kidney disease and the high cardiovascular event rate found in kidney disease have brought attention to this topic. The abnormal physiology in CKD may foster abnormal deposition of calcium into soft tissues rather than bones. Therefore, the calcium “burden,” or total calcium intake, should be monitored carefully in CKD. In response to this concern, there are now two phosphorus binders that do not contain calcium. Sevelamer hydrochloride (Renagel) and Lanthanum carbonate (Fosrenol) both bind phosphorus and do not contain calcium. These agents are primarily designed
for patients on dialysis, and as such their use in CKD stages 3 and 4 is not yet supported with strong evidence.

It should also be noted that aluminum in the form of aluminum hydroxide (Amphogel, Basalgel) is a potent phosphorus binder that does not contain calcium. Unfortunately, aluminum toxicity resulting in anemia, dementia, and/or osteomalacia is possible in patients with CKD, and therefore aluminum-containing agents should not be used as a chronic treatment.

**Vitamin D levels and PTH levels**

Guidelines have been formulated regarding the management of renal bone disease. These guidelines include recommendations for vitamin D levels and PTH levels. Although it is important to have some guidance in the treatment of these parameters, the limited evidence in this relatively new area of study has resulted in treatment guidelines that, at least at this time, are frequently based on opinion rather than definitive evidence.

In patients with CKD stages 3 and 4, the goal PTH levels are 35 to 70 pg/mL and 70 to 110 pg/mL, respectively. Guidelines recommend checking the 25-hydroxy vitamin D level if the PTH level is out of range and if the phosphorus value is <4.6 mg/dL and the serum calcium value is <9.5 mg/dL. If the 25-hydroxy vitamin D level is <30 ng/mL, then supplementation with ergocalciferol is recommended. Because ergocalciferol is currently available only as a 400-IU over-the-counter pill or as a 50,000-IU prescription pill, replacement of vitamin D is usually done with 50,000-IU pills weekly to monthly, depending on the level of deficiency. Calcium, phosphorus, and 25-hydroxy vitamin D levels should be followed during vitamin supplementation.

If patients with CKD have a serum calcium level <9.5 mg/dL, serum phosphorus level <4.6 mg/dL, and serum 25-hydroxy vitamin D level >30 ng/mL, then treatment with active vitamin D is considered if the PTH level is >70 pg/mL in stage 3 or >110 pg/mL in stage 4. The choices for active vitamin D sterols are calcitriol (Rocaltrol), doxercalciferol (Hectorol), and paricalcitol (Zemplar). All three of these agents are available in an oral pill form. Once administration is started, the serum calcium, phosphorus, and PTH levels need to be monitored closely.

An agent that activates the calcium receptor, called a calcimimetic because it mimics the effect of calcium at the calcium receptor, is now available. This agent [cinacalcet (Sensipar)] will suppress PTH by activating the calcium receptor. It therefore has a different mechanism of action than the vitamin D analogues. It is currently indicated for stage 5 DM, April 2010
(dialysis) CKD, and its role in stages 3 and 4 CKD has not yet been defined.

**Conclusion**

ROD is receiving more attention as a complication of CKD. Although symptoms of bone pain, fractures, and tendon rupture are typically associated with advanced CKD, skeletal changes begin years earlier. Therefore, it is important to detect patients at risk and begin treatment early. General guidelines are available to assist in management, but at this point they consist largely of opinion-based recommendations. Until further information dictates otherwise, the essence of ROD management involves controlling the serum phosphorus level first with dietary modifications and then with binders if needed. Vitamin D levels and PTH levels should be followed and corrected on the basis of current guidelines. Because serum calcium, phosphorus, vitamin D, and PTH levels are physiologically interlinked, all levels should be followed closely when the patient is under treatment. A future consideration is the involvement of vitamin D receptors in the cardiovascular system. Vitamin D/PTH management may also incorporate modifying cardiovascular risk in the future.

**Summary**

Whether due to modern lifestyles, better management of chronic conditions, an aging population, or a combination of these and other factors, CKD prevalence is increasing. An estimated 10 to 20 million Americans have CKD, so familiarity with the common complications, rationale for treatment, and treatment options is beneficial for practitioners. The ultimate goal in managing a disease state is to improve survival and improve quality of life. Treatments that decrease proteinuria have been shown to delay progression to end-stage renal disease (a dramatic improvement in quality of life) and also are known to reduce cardiovascular risk. Anemia correction has been shown to improve quality of life, an important goal in patients with a chronic disease. Although the data regarding specific treatment recommendations in ROD are not firmly established, there is enough evidence for guidelines to help improve bone health and quite possibly decrease cardiovascular risk through decreased calcification or other (eg, vitamin D receptor) pathways. The ability to recognize the complications, institute appropriate therapy, and provide close follow-up when treatments are instituted is the cornerstone of CKD management.
Addendum

We would like to report on several new developments since the original publication of our article. We are excited that new studies in our field have answered some questions and, inevitably, raised more questions. Here we review some interesting recent articles of high impact that relate to our original paper.

Proteinuria

A large cohort study was recently published in the Journal of the American Medical Association\cite{41} that reviewed the clinical outcomes of over 900,000 patients in their database who had a serum creatinine and a measure of urine protein. The authors found that proteinuria, when divided into normal, mild, and heavy, was associated with a graded and increased risk of 4 different outcomes: mortality, myocardial infarction, doubling of serum creatinine, and end stage renal disease. The association of proteinuria with worse outcomes occurred at all levels of GFR from stage 2 to stage 4 and was independent of GFR. The ONTARGET\cite{42} study evaluated treating patients with atherosclerotic vascular disease or diabetes with end organ damage with an ace-inhibitor alone, an angiotensin receptor blocker alone, or both medications in combination. The primary outcome was the first occurrence of dialysis, doubling of serum creatinine, renal transplantation, or death. The secondary outcomes included composites of the primary outcomes as well as changes in eGFR and progression of proteinuria. The study, which recruited over 25,000 patients from around the world, showed that ace-inhibitor and angiotensin receptor blocker treatment alone resulted in similar outcomes, but combination therapy with the ace-inhibitor and angiotensin receptor blocker showed no benefit in high renal risk groups (e.g. overt diabetic nephropathy), and was associated with worse renal outcomes in the low risk renal groups (more dialysis needed, particularly more acute dialysis). Combination therapy did result in more effective reduction of proteinuria. While there was reduction of proteinuria, the lack of definitive benefit of improved renal outcomes suggests that using a combination of ace-inhibitor and angiotensin receptor blocker should be considered on an individual patient basis, particularly until further studies looking at patients with high risk of kidney disease progression are reported. We also would like to note that the COOPERATE study (which supported angiotensin receptor blocker and ace-inhibitor use in combination) has been retracted by the editors of the Lancet.\cite{43}
Anemia

The recently published TREAT study evaluated treating patients with type 2 diabetes mellitus and chronic kidney disease with an erythropoietic stimulating agent (ESA) targeting a hemoglobin level of 13 g/dL versus a placebo group that only received an ESA if the hemoglobin fell below 9 g/dL. The primary outcomes of the TREAT study consisted of a composite outcome of death or a cardiovascular event or death or end stage renal disease. Treatment with an ESA did not improve any of the primary outcomes. This study has raised questions about the utility of ESAs in the chronic kidney disease population. ESAs do reduce the need for transfusion, an important feature particularly when many of the patients who are a target population for ESAs may also be on the transplant list. Further commentary from the Food and Drug Administration has speculated about dose of ESA, rate of rise of hemoglobin, and target level of hemoglobin value (a target less than 12 may be more optimal) as being possible contributors to the lack of mortality benefit with ESAs. Until further studies delineate an appropriate target hemoglobin or dosing regimen, ESAs should be used cautiously (if at all) in patients with chronic kidney disease. In a chronic kidney disease patient on the transplant list, particularly if the patient has a low hemoglobin or need for transfusion, an ESA may be helpful. The target hemoglobin is uncertain but should be less than 12 g/dL. Rather than a specific target, the goal of treatment may simply be keeping the hemoglobin from drifting too low to avoid the need of transfusions. High doses of ESAs and rapid changes of hemoglobin level should be avoided.

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42. Mann J, Schmieder R, McQueen M, et al. Renal Outcomes with telmisartan, ramipril, or both in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. The Lancet 2008;372:547-543.

