The biologic price of aging includes progressive structural and functional deterioration of the kidney, and these changes are among the most dramatic of any organ system. Understanding the age-related changes in kidney may help to focus future research to identify potential interventions. This article considers the functional and structural changes that occur with normal aging.

Age-Related Changes in Kidney

Functional and Structural Changes

The glomerular filtration rate (GFR) is known to be low at birth, approaches adult levels by the end of the second decade of life, and is maintained at approximately 140 ml/min/1.73m² till the fourth decade. As indicated by the classic inulin clearance studies of Davies and Shock, GFR declines by about 8 ml/min/1.73m² per decade thereafter. Studies using GFR estimates on population-based data suggest that the decline may begin earlier, after the second decade of life. Although clinically important in many older subjects, it should be noted that there is wide variability among individuals in the age-related fall in GFR. There is an ongoing debate as to the distinction between age-related loss of GFR and the presence of chronic kidney disease (CKD) in the elderly population.

Epidemiologic studies suggest that acceleration of age-related loss of renal function may be associated with systemic hypertension, lead exposure, smoking, dyslipidemia, atherosclerotic disease, presence of inflammatory markers, increased levels of advanced glycosylation endproducts, and possibly obesity and male gender. Recently, a history of one or more episodes of acute kidney injury has also been recognized as a risk factor for subsequent development or progression of CKD.

The age-related reduction in creatinine clearance (CrCl) is accompanied by a reduction in the daily urinary creatinine excretion as a result of reduced muscle mass. Accordingly, the relationship between serum creatinine (SCr) and CrCl changes. The net effect is near constancy for SCr whereas true GFR and CrCl decline, and consequently, substantial reductions of GFR occur despite a relatively normal SCr level.

Similar changes in renal blood flow (RBF) occur, so that RBF is well maintained at about 600 ml/min till approximately the fourth decade, and then declines by about 10% per decade. This reduction in RBF is not entirely because of loss of renal mass. Xenon-washout studies demonstrate a progressive reduction in blood flow per unit kidney mass with advancing age. The decrease in RBF is most profound in the renal cortex; redistribution of flow from cortex to medulla may explain the slight increase in filtration fraction seen in the elderly people.

The incidence of glomerular sclerosis increases with advancing age. Sclerotic glomeruli comprise fewer than 5% under the age of 40; thereafter, the incidence increases so that sclerosis involves as much as 30% of the glomerulus by the eighth decade. Thus, both diminished glomerular lobulation and sclerosis of glomeruli tend to reduce the surface area available for filtration, and therefore contribute to the observed age-related decline in kidney function ($K_t$) and GFR. In addition, age-related changes in cardiovascular hemodynamics, such as reduced cardiac output and systemic hypertension, are likely to play a role in the progressive reduction in renal perfusion and filtration.

Physiologic Changes of Mediators

The systemic renin-angiotensin system (RAS) is suppressed in aging, the intrarenal RAS may not be equivalently suppressed, and pharmacologic RAS blockade has been shown to slow the progression of age-related CKD. Total body renin and aldosterone levels fall during aging because of decreased renin production and release. Decreased responsiveness of the RAS leads to decreased renin release in response to appropriate stimuli. Conversely, the prolonged low levels of renin and aldosterone may result in an exaggerated renal response to these components of the RAS when present.
Nitric oxide (NO) plays diverse role affecting renal vasculature and cell growth. Nitric oxide acts as a vasodilator, and also inhibits mesangial cell growth and matrix production. Oxidative stress which increases with age and low availability of the substrate L-Argenine are potential factors for NO reduction with age.

The balance of vasoconstrictor versus vasodilatory responsiveness seems to play an important role in the kidney's response to acute injury. Impaired ability to autoregulate can lead to a fall in GFR even when the magnitude of the acquired renal insult is moderate. In the context of current patterns of therapeutics in older patients—such as administration of RAS blockers and non-steroidal anti-inflammatory drugs—the older kidney is at increased risk for development of acute kidney injury, including normotensive ischemic nephropathy.

Sex hormones are likely to contribute as well. The rate of progression of CKD tends to be slower in women, both experimentally and clinically. Gender affects the age-related changes in the RAS and NO systems, as well as metalloprotease activity. Experimentally, estrogen therapy and androgen deprivation are protective against progression of CKD.

Nitric oxide, as described, has an overall protective effect in kidneys because of decreased mesangial cell and matrix production. With advancing age, endothelial NO synthase abundance decreases and oxidative stress increases, both of which contribute to impaired endothelial NO production and endothelial dysfunction. Gender differences in NO levels are most likely related to the relationship between NO and 17β-estradiol, which stimulates release of NO synthase. Additionally, the age-related increase in asymmetric dimethyl argenine is delayed in premenopausal women as compared with men, which may also result in more available NO synthase in women and subsequently greater NO production. Indeed, the renal vasoconstrictor effect of NO synthase inhibition is considerably more pronounced in aging men than in women.

Discrepancy in the levels of metalloproteases may also affect gender-specific renal dysfunction. Metalloproteases break down matrix, which may help prevent matrix expansion (a key element in CKD progression). Metalloprotease levels increase in aging women as compared with levels seen in aging men.

Although estrogens appear to have a protective effect in terms of renal aging, men may be at increased risk of renal dysfunction because of possible negative effects of androgens. Androgens may also increase fibrosis and mesangial matrix production. This effect may be in part related to androgen-driven inhibition of age-related increases in metalloproteases. Additionally, androgens may stimulate the RAS and thereby increase sodium retention, resulting in worsening hypertension which may adversely affect CKD progression.

Source: Advances in Chronic Kidney Disease, 2010; 17:302-307
Chronic Kidney Disease in Primary Care

The prevention, early detection, and prompt treatment of chronic kidney disease is within the realm of the family physician. It is estimated that 13% of the adult population suffers from chronic kidney disease and the numbers are expected to continue to climb. With this rise in the prevalence of chronic kidney disease, the role of the general physician in improving patient care and disease outcomes has become increasingly evident.

Chronic kidney disease is defined by the National Kidney Foundation of United States of America as either a decline in glomerular filtration rate (GFR) to <60 ml/min/1.73m² or the presence of kidney damage for at least 3 months. Signs of kidney damage classically include proteinuria but other markers of damage, such as persistent glomerulonephritis or structural damage from polycystic kidney disease, can also be present. Chronic kidney disease has been subdivided into 5 stages of increasing severity (Table II).

Previous laboratory evaluations of renal function, such as 24-hour urine collections for creatinine clearance, are generally no longer necessary because of the accuracy and ease of the calculation of the GFR from serum laboratory values. The use of serum creatinine is not sufficient for determining chronic kidney disease because approximately half of the renal function must be lost before the creatinine will be elevated out of the normal range. Glomerular filtration rate calculations should be included routinely by laboratories; however, if needed, it can be easily calculated using the Modification of Diet in Renal Disease study calculator. This is the equation that is recommended by the National Kidney Foundation. The Cockcroft-Gault equation is useful for medications that require renal dosing because it is used to calculate creatinine clearance. Neither of these calculations should be used during acute renal failure because a stable creatinine level is required to ensure their accuracy.

Prevention

Knowledge of the risk factors for the development of chronic kidney disease is crucial to prevention of the disease process. Diabetes mellitus and hypertension are the leading causes of chronic kidney disease; therefore, these risk factors must be tightly controlled in all patients. In addition, medication lists should be reviewed closely with patients to ensure that any potentially nephrotoxic medications are being used appropriately and in correct dosages. In particular, over-the-counter medications should be evaluated for the potential of drug interactions and nephrotoxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) are notoriously nephrotoxic.

Screening

Patients with long-standing diabetes and/or hypertension are at increased risk of chronic kidney disease; these conditions are the primary contributors to kidney disease. The National Kidney Foundation of USA has identified the following additional risk factors for chronic kidney disease: >60 years old, racial or ethnic minorities, exposure to known nephrotoxins, low income or education level, autoimmune diseases, systemic infections, urinary tract infections, nephrolithiasis, neoplasia, family history of kidney disease, recovery from acute renal failure, reduction in kidney mass, and low birth weight. For these patients who are at increased risk for chronic kidney disease, it is recommended that the minimal screening for kidney damage include assessment of GFR and proteinuria. Currently, the guidelines for hypertension from the

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**Table I: Commonly Used Formulas for Estimating Renal Function. MDRD = Modification of Diet in Renal Disease**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Cockcroft and Gault equation</strong></td>
<td>Estimated creatinine clearance (ClCr) = ( \frac{(140 - \text{age}) \times \text{weight} \times 1.2}{\text{SCr} \times (0.85 \text{ if female})} ) x (0.85 if female) x (0.85 if female)</td>
</tr>
</tbody>
</table>
| Where: age is expressed in years, \( \text{SCr} \) in \( \mu \text{mol/l} \), and weight is in kg
| **6-variable MDRD** | \( 170 \times \left( \frac{\text{SCr}}{88.4} \right)^{1.154} \times \text{age}^{-0.176} \times (\text{SU}/0.357)^{0.170} \times (\text{SAlb} \times 10)^{0.318} \) x (0.762 if female) x (1.180 if black) |
| Where: \( \text{SCr} \) = serum creatinine in \( \mu \text{mol/l} \), \( \text{SU} \) = serum urea in mmol/l, \( \text{SAlb} \) = serum albumin in g/l, and age is expressed in years |
| **4-variable MDRD** | \( 186.3 \times \left( \frac{\text{SCr}}{88.4} \right)^{1.154} \times \text{age}^{0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}) \) |
| Where: \( \text{SCr} \) = serum creatinine in \( \mu \text{mol/l} \), and age is expressed in years |
| **Modified 4-variable MDRD (traceable by isotope dilution mass spectrometry)** | \( F \times 175 \times \left( \frac{\text{SCr}}{88.4} \right)^{1.154} \times \text{age}^{0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}) \) |
| Where: \( F \) = correction factor, \( \text{SCr} \) = serum creatinine in \( \mu \text{mol/l} \), and age is expressed in years |

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**Table II: Clinical Relevance of the Five Stages of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Estimated glomerular filtration rate (ml/min)</th>
<th>Clinical significance</th>
<th>Stage of chronic kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>With another abnormality*, otherwise regard as normal</td>
<td>1</td>
</tr>
<tr>
<td>60-89</td>
<td>With another abnormality*, otherwise regard as normal</td>
<td>2</td>
</tr>
<tr>
<td>30-59</td>
<td>Moderate impairment</td>
<td>3</td>
</tr>
<tr>
<td>15-29</td>
<td>Severe impairment</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Advanced renal failure</td>
<td>5</td>
</tr>
</tbody>
</table>

*Patients with estimated glomerular filtration rate >60 ml/min/1.73 m² should be regarded as normal unless they have evidence of kidney disease (persistent proteinuria or hematuria, or both, microalbuminuria in patients with diabetes, structural kidney disease such as polycystic kidney disease in adults or reflux nephropathy)
Seventh Report of the Joint National Committee (JNC 7th Report) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines recommend an annual screening urine analysis to assess proteinuria; however, the National Kidney Foundation of USA and the European Society of Cardiology/European Society of Hypertension recommend screening for microalbuminuria. The European Society of Cardiology/European Society of Hypertension state in their 2007 Guidelines for the Management of Arterial Hypertension: “Microalbuminuria has now been considered an essential component in the assessment of organ damage because its detection is easy and relatively inexpensive.” A routine urinalysis detects only protein unless an albumin-specific dipstick is used. When the glomerular membrane is damaged, the initial protein that is spilled into the urine is albumin because of its molecular size and negative charge. Therefore, screening for the presence of microalbuminuria is the more sensitive test for detection of early kidney damage.

The American Diabetic Association recommends that all diabetic patients have an annual screening for microalbuminuria. Microalbuminuria is considered positive when the level is >30 mg/g; however, there are gender-specific values that have not entered into routine use at this point (>17 mg/g in men and >25 mg/g in women).

### Management: Interventions to Slow the Progression of Kidney Disease

The Modification of Diet in Renal Disease study followed chronic kidney disease patients at all stages for a 2-year period and concluded that 85% of patients had a decline in their GFR, with the average rate of decline 4 ml/min annually regardless of the baseline GFR. There are modifiable and non-modifiable factors that contribute to this decline. These factors have been shown to be significant regardless of the underlying etiology of the chronic kidney disease. In general, the non-modifiable risk factors associated with more rapid decline in kidney disease include increased age, African-American race, and male sex. The modifiable risk factors are the focus of treatment to halt disease progression, and include higher levels of proteinuria, a lower serum albumin level, higher blood pressure, poor glycemic control, and smoking. Currently there is conflicting data regarding the role of dyslipidemia and anemia in the role of kidney disease progression.

### Proteinuria

Because proteinuria contributes to an increase in renal damage, screening and quantification of the presence of proteinuria is critical in the care of chronic kidney disease patients. Random (spot) samples of urine for calculation of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Classical clinical course of microalbuminuria, followed by clinical proteinuria, hypertension, and then declining GFR.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Usually characterized by severely elevated blood pressure readings over a long period, with associated end-organ damage in addition to kidney disease.</td>
</tr>
<tr>
<td>Nephrotoxic medications</td>
<td>Prescribed and over-the-counter medications should be reviewed as well as intravenous contrast dye or gadolinium exposure.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Evaluate for photosensitivity, malar/discoid rashes, oral ulcers, arthritis, serositis, neurological symptoms, hematological findings, ANA/dsDNA positive.</td>
</tr>
<tr>
<td>HIV nephropathy</td>
<td>Signs and symptoms of immunodeficiency; HIV positive on testing.</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Signs and symptoms of heart failure present. Because fluid overload is common in chronic kidney disease, diagnosis is made through echocardiogram to evaluate systolic and diastolic heart function.</td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>Evaluation of family history is suggestive.</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>History or evidence of cirrhosis with resultant portal hypertension, ascites, and renal vasoconstriction. Classically lack significant proteinuria.</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>History of hematuria and symptoms of renal colic should be evaluated. Long-standing obstruction can cause permanent renal impairment.</td>
</tr>
<tr>
<td>Benign prostatic hypertrophy</td>
<td>Male patients for hesitancy, straining, or weak flow during urination and nocturia should be evaluated. Prostate exam should be confirmed.</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Broad category of diseases including postinfectious (streptococcal) as well as various vasculitis diseases. Urinalysis suggestive with presence of red blood cell casts.</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate; ANA: antinuclear antibodies; dsDNA: double-stranded deoxyribonucleic acid; HIV: human immunodeficiency virus.
the urine protein-creatinine ratio eliminate the need for 24-hour urine collections for quantification of proteinuria. Once proteinuria is identified, its control becomes a high priority. The goal of treatment is to decrease the degree of proteinuria; even low levels of proteinuria are associated with progression of chronic kidney disease and cardiovascular disease.

Angiotensin converting enzyme (ACE) inhibitors are considered as first-line medications for proteinuria, regardless of the underlying cause or stage of chronic kidney disease. Because hyperkalemia and slight worsening of renal function can occur with the initiation of ACE inhibitors, these factors should be monitored; however, the medications should not be discontinued without due cause. Mild hyperkalemia can often be controlled by dietary changes, and cessation of NSAIDs and potassium-sparing diuretics, if applicable. In addition, potassium excretion can be enhanced by the addition of a loop diuretic. For hyperkalemia > 5.6 mmol/l, the ACE inhibitor should be immediately discontinued and the patient should be treated appropriately. With regard to the concern of acute renal failure related to the initiation of ACE inhibitors, a modest rise in creatinine level (< 30% increase) within 1 to 2 weeks of initiation of therapy is considered acceptable. The patient should be monitored to ensure that additional rise does not occur because this would be cause for discontinuation of medication and further evaluation. Renal artery stenosis, hypovolemia, or uncompensated heart failure may be associated with a rise in creatinine level of > 30% and, once treated, the ACE inhibitor may be reinstated safely.

An angiotensin receptor blocker (ARB) may be considered for patients who are unable to tolerate ACE inhibitors. In diabetic kidney disease, an ARB may be used as a first-line alternative to ACE inhibitors. In addition, the candesartan and lisinopril microalbuminuria study demonstrated the benefit of the use of the combination of an ACE inhibitor (lisinopril) with an ARB (candesartan) in patients with diabetic-associated microalbuminuria. The addition of a nondihydropyridine calcium channel blocker, such as diltiazem or verapamil, can further decrease the degree of proteinuria, as can the addition of a thiazide or loop diuretic. However, the blockade of the renin-angiotensin system remains the cornerstone of treatment of proteinuria.

**Blood Pressure Control**

Strict blood pressure control is a high priority in the care of the patient with chronic kidney disease. Angiotensin converting enzyme inhibitors or ARBs are commonly used as the initial medications to achieve blood pressure control; however, often a multidrug regimen is needed. Commonly, diuretics are needed for patients with chronic kidney disease because of the hypertensive effect of volume overload. According to Seventh Report of the Joint National Committee (JNC 7th Report) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines, the goal blood pressure is <130/80 mm Hg in patients with chronic kidney disease; however, the National Kidney Foundation suggests a more stringent goal of <125/75 mm Hg for patients with chronic kidney disease and significant proteinuria. With the achievement of these blood pressure goals, further kidney damage can be avoided and the progression of the chronic kidney disease can be slowed.

**Glycemic Control**

Regardless of the cause of chronic kidney disease, tight glycemic control should be achieved for all diabetic patients. The American Diabetic Association recommends a target glycated hemoglobin level of <7.0 for all diabetics, regardless of whether kidney disease is present. Treatment of diabetes in patients with kidney disease can be complicated. Metformin, which is the cornerstone oral medication for diabetic glycemic control, is contraindicated with creatinine >1.5 in men and >1.4 in women because of the concern about lactic acidosis.

**Diet Therapy for Chronic Kidney Disease (CKD) to Maintain Good Nutritional Status, Slow Progression, and to Treat Complications**

The key diet components to slowing progression of CKD are:
- Controlling blood pressure by reducing sodium intake
- Managing diabetes  
- Reducing protein intake, if excessive
- Treating anemia due to impaired erythropoiesis and low iron stores  
- Managing malnutrition  
- Treating mineral imbalance and bone disorder (calcium, phosphorus, and vitamin D)

**Control of Blood Pressure**

Blood pressure control slows progression of CKD and lowers cardiovascular disease (CVD) risk. Dietary Sodium plays a major role in blood pressure control in CKD as a result of alterations in sodium excretion by the kidneys. 

**Ranges/Goal**

Goal <130/80 mm Hg
**Dietary Intervention**
- Limited sodium intake to 2,300 mg a day or less
- Weight reduction may be beneficial
- Serum potassium should be monitored in patients on renin angiotensin system (RAS) antagonists; dietary potassium intake should be limited when serum potassium is >5 mEq/l.

**Albumin Reduction**
Decreased albuminuria is associated with slower progression of CKD, particularly in diabetics. Limiting dietary protein may reduce albuminuria and improve blood glucose control, hyperlipidemia, blood pressure, renal bone disease, and metabolic acidosis. Limiting excessive protein may activate adaptive responses that decrease albuminuria and increase serum albumin, without increasing risk for protein malnutrition. Evidence suggests that further lowering to 0.6g protein/kg/day in non-diabetic patients may be beneficial, but adherence is difficult. Some patients may be able to achieve this level with intensive counselling.

**Ranges/Goal**
To reduce or stabilize the amount of albumin lost in the urine

**Dietary Intervention**
Limited excessive dietary protein as follows:
- Non-diabetic: 0.8 g protein/kg/day
- Diabetic: 0.8-1.0 g protein/kg/day

**Managing Diabetes**
Blood glucose control may help slow progression of CKD

**Ranges/Goal**
HbA1C = 7.0%

**Dietary Intervention**
Less-stringent control should be considered for patients with histories of hypoglycemia, the elderly, and patients with multiple co-morbid conditions. Patients should be instructed to treat hypoglycemia or hyperkalemia.

**Malnutrition**
Malnutrition is common in CKD; as estimated GFR (eGFR) declines, so may appetite. Malnutrition in CKD patients is associated with increased morbidity and mortality. Serum albumin is used to monitor nutritional status. Hypoalbuminemia may result from reduced protein and/or calorie intake, uremia, metabolic acidosis, albuminuria, inflammation or infection. Appetite may improve in renal failure with adequate renal replacement therapy (i.e., dialysis treatment or kidney transplantation).

**Ranges/Goal**
Albumin > 4.0 g/dl
Normal range: 3.4-5.0 g/dl
Serum albumin < 4.0 g/dl, prior to initiation of dialysis, may predict morbidity and mortality
Blood urea nitrogen (BUN) < 20 mg/dl

**Dietary Intervention**
- Patients should be managed with adequate calories and nutrients.
- Water-soluble vitamin supplementation may be indicated due to the restricted protein intake. Vitamin C is typically not supplemented above the Dietary Reference Intake, as it may cause oxalosis. Vitamins A, E, and K can accumulate more rapidly in CKD and are not recommended for supplementation. Specific renal vitamin formulas are available for dialysis patients.

**Metabolic Acidosis**
Patients with CKD are at risk for metabolic acidosis as a result of reduced excretion of acid load. Dietary protein is a source of metabolic acid. Serum bicarbonate levels may increase with dietary protein restriction. Metabolic acidosis is thought to result in loss of bone and muscle mass, negative nitrogen balance, increased protein catabolism, and decreased protein synthesis.

**Ranges/Goal**
Bicarbonate: CO₂ > 22 mEq/l
Normal range: 21-28 mEq/l

**Dietary Intervention**
Sodium bicarbonate supplementation may be prescribed to improve nutritional parameters and slow rate of CKD progression. Blood pressure should be monitored closely when this medication is used, as some patients may experience elevated blood pressure associated with increased sodium load.

**Hyperkalemia**
Patients with CKD are at risk for hyperkalemia as a result of reduced potassium excretion, intake of high-potassium foods, metabolic acidosis, and medications that inhibit potassium excretion, such as RAS antagonists for blood pressure control.

**Ranges/Goal**
Potassium 3.5-5.0 mEq/l
Hyperkalemia is usually not seen until CKD is advanced, but may be seen at higher eGFRs in diabetics.

**Dietary Intervention**

Patients should be counseled to restrict dietary potassium when serum level is 5.0 mEq/l or higher or when adhere to sodium bicarbonate therapy, if prescribed. Patients should be cautioned to avoid potassium-containing salt substitutes and instructing patients with diabetes to treat hypoglycemia. Correction of acidosis may lower potassium. The potassium content of most vegetables can be decreased through a process of leaching. Leaching entails slicing and soaking the vegetable overnight in water, then draining and boiling the vegetable in new water. A recent study, however, shows that white potatoes do not need to be soaked overnight. The potassium content of other tuberous root vegetables commonly eaten in the Caribbean and South America has been shown to be reduced somewhat by double-cooking, however, most still remained higher than 200 mg per serving.

**Calcium**

Control of calcium and phosphorus levels helps control Parathyroid Hormone (PTH).

**Ranges/Goal**

Calcium 8.5-10.2 mg/dl

To maintain within normal range.

**Dietary Intervention**

- Dietary calcium recommendations for CKD have yet to be established.
- Calcium-based phosphate-binding medications can increase total daily intake and elevate calcium.
- Supplementation with active vitamin D increases the risk for hypercalcemia.
- Correction of calcium with hypoalbuminemia by using formula: Corrected calcium (mg/dl) = serum calcium (mg/dl) + 0.8 (4.0 - serum albumin g/dl)

**Phosphorus**

Control of phosphorus and calcium levels helps control PTH. Serum phosphorus levels may be "normal" until CKD is advanced.

**Ranges/Goal**

Phosphorus 2.7-4.6 mg/dl

To maintain within normal range.

**Dietary Intervention**

- If serum phosphorus is elevated, dietary phosphorus restriction may be indicated. The recommended level of restriction has yet to be determined in CKD.
- Dietary protein restriction decreases phosphorus intake. If further restriction is needed, patients should be counseled to reduce intake of foods with added phosphorus.
- Patients should be counseled to read ingredient lists for "phos" to identify foods with phosphate additives, as these additives may be absorbed more efficiently than food sources.
- Limiting whole grains may help if further reduction is needed.
- Phosphorus binders may be prescribed to lower phosphorus levels. Patients should be counseled to take binders with meals to help limit absorption of phosphorus from food and beverages.

**Parathyroid Hormone**

Secondary hyperparathyroidism (elevated PTH) is associated with the most common cause of bone disease in CKD. Parathyroid hormone is the hormone that regulates serum calcium levels. Low levels of 1,25(OH)2D, hypocalcemia, and hyperphosphatemia stimulate PTH secretion. Its metabolic actions include mobilizing calcium and phosphorus from bone; increasing intestinal absorption and renal tubular reabsorption of calcium; and decreasing renal tubular reabsorption of phosphorus. Parathyroid hormone enhances conversion of 25(OH)D to 1,25(OH)2D.

**Ranges/Goal**

Normal PTH <65 pg/ml

Measured as intact PTH

PTH varies by level of kidney function and type of bone disease.

**Dietary Intervention**

Dietary phosphorus restriction and use of active vitamin D or its analogs may help control PTH levels in CKD. Calcium supplementation may help as well.

**Vitamin D**

The kidneys activate 25(OH)D (calcidiol) to 1,25(OH)2D (calcitriol or active vitamin D). Reduction of kidney function results in decreased production and conversion of calcidiol to calcitriol. There may be corresponding imbalances of calcium, phosphorus, and PTH.

**Ranges/Goal**

Vitamin D > 30 ng/ml

Measured as 25(OH)D

To maintain within normal range.

**Dietary Intervention**

- Supplementation may be indicated. Specific requirements in CKD have yet to be determined.
- Ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) may be used in early CKD to replete vitamin D.
- Active vitamin D (calcitriol) or its analogs (doxercalciferol, paricalcitol, or alfacalcidol) may be used as eGFR declines. Hypercalcemia and/or hyperphosphatemia should be monitored when using supplements. Active vitamin D increases calcium and phosphorus absorption.

**Anemia**

Anemia may develop early during the course of CKD due to inadequate synthesis of erythropoietin by the kidneys. Uncomplicated anemia of CKD is usually normocytic and normochromic. Transferrin Saturation (TSAT) is a measure of iron saturation. Transferrin transports iron absorbed by the intestines. Ferritin levels reflect iron stores.

**Ranges/Goal**

Hemoglobin 11-12 g/dl

Without CKD:

Women: 12-16 g/dl

Men: 14-17 g/dl

Transferrin Saturation (TSAT) >20%
Ferritin >100 ng/ml
Without CKD:
Women: 18-160 ng/ml
Men: 18-270 ng/ml

Dietary Intervention
Both iron supplementation and injectable erythropoiesis-stimulating agents (ESAs) have been used to correct anemia. The risks and benefits of these treatments in CKD are not yet defined.

Cardiovascular Disease
Patients with CKD are at high risk for developing CVD; the risk increases as eGFR declines. CVD is the leading cause of mortality in CKD.

Ranges/Goal
Total cholesterol < 200 mg/dl
LDL cholesterol < 100 mg/dl
HDL cholesterol > 40 mg/dl
Triglycerides < 150 mg/dl

Dietary Intervention
Decreasing intake of saturated and trans fats (substituting for monounsaturated and polyunsaturated fats), along with physical activity, can help control hyperlipidemia and reduce inflammation. Controlling dyslipidemia may reduce the rate of decline in eGFR. To further decrease risk of developing CVD, pharmacological therapy may be necessary.

Complications of Chronic Kidney Disease
The prevalence of the complications of chronic kidney disease increases with each stage of the disease. The prevalence of complications for a patient with stage 1 chronic kidney disease is 0.28, and it rises to an average of 1.71 in stage 4. Therefore, it is recommended that screening for anemia, bone metabolism abnormalities, and metabolic acidosis be performed once the GFR is ≤60 ml/min/1.73m² (stage 3). The interval for each screening test varies by the stage of chronic kidney disease. If a complication is identified, the interval shortens to follow the success of treatment interventions.

Anemia of Chronic Kidney Disease
The National Kidney Foundation recommends that patients have at least an annual complete blood count as a screening for anemia. This recommendation leaves room for more frequent assessments in patients who are at higher risk or have had a decline in their hemoglobin but have remained within the normal range. The presence of anemia in a patient with chronic kidney disease requires further evaluation to elucidate the underlying cause of the anemia. Erythropoietin is produced by the kidney and stimulates production of reticulocytes in the bone marrow. As kidney function declines, the production of erythropoietin declines and anemia results. In addition, chronic kidney disease is a pro-inflammatory condition that can result in anemia of chronic disease. Furthermore, nutritional deficiencies may be present and the assessment of iron, folate, and vitamin B₁₂ levels should be made when clinically indicated. The minimal work-up suggested for a patient with anemia includes the complete blood count indices, reticulocyte count, serum ferritin, and TSAT. The reticulocyte count can be used to calculate the reticulocyte index, which provides essential information regarding the capability of the bone marrow to compensate for the anemia. The serum ferritin is a measurement of the total body iron stores and is considered low when <25 ng/ml in men and <12 ng/ml in women. The TSAT is a measurement of the adequacy of iron for erythropoiesis and is considered low when <16%. Classically, the anemia associated with chronic kidney disease is a normocytic, normochromic anemia with a normal ferritin and TSAT.

The target hemoglobin level for patients with anemia from chronic kidney disease is between 11.0 and 12.0 g/l. It is recommended by the National Kidney Foundation that hemoglobin should not be above 13.0 g/l because this has been shown to be associated with increased incidence of cardiovascular mortality. There are several erythropoietin analogs that can be given either subcutaneously or intravenously for the treatment of this anemia. Patients being treated with these agents require monthly assessments of hemoglobin levels because dose adjustments are frequently needed to maintain the hemoglobin at the target of 11.0 to 12.0 g/l. Work-up and treatment of any associated iron deficiency anemia should be done in conjunction with this treatment because the effectiveness of the erythropoietin is dependent on iron as a building block for hemoglobin synthesis.

Metabolic Acidosis
The National Kidney Foundation recommends that patients with chronic kidney disease be screened for metabolic acidosis by an assessment of total CO₂ at varying frequency intervals per their stage of kidney disease. The target total CO₂ is 22 mmol/l. When the level falls below 22 mmol/l, treatment with supplemental alkali salts should be considered.

Cardiovascular Risk
Physicians must be aware that chronic kidney disease has been recognized as an independent risk factor for cardiovascular disease. The modifiable risk factor of hyperlipidemia is of particular importance. Patients with chronic kidney disease frequently have multiple lipid abnormalities; however, low-density lipoproteins should be the primary target, with attention paid to the non-high-density lipoprotein levels if the triglycerides are elevated to >200 mg/dl.

References
2. British Medical Journal, 2006; 333: 733-737
3. Chronic Kidney Disease (CKD) and Diet: An Overview Guide for Dietitians, April 2010, National Kidney Diseases Education Program (USA)