

Theme Issue
Chronic Kidney Disease Revisited



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Chronic Kidney Disease Revisited

The Quest Diagnostics Health Trends™ Report, “An Analysis of Chronic Kidney Disease in the U.S.,” was released on November 6, 2007. Some of the following findings were surprising and frankly alarming:

- **60%** of patients with diabetes and chronic kidney disease (CKD) had not had a widely available and inexpensive urine test (microalbumin) performed in the previous 12 months.
- An astonishing **90%** of patients with hypertension and kidney disease who do not have diabetes also did not have a urine microalbumin test in the same time period.
- **66%** of patients with diabetes and early-stage CKD (the phase when the best chance exists to slow disease progression) had poor glucose control as evidenced by A1c values >7%.
- **53%** of patients with cardiovascular disease (CVD) and early CKD did not meet the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) goal for LDL-cholesterol levels of ≤ 100 mg/dL.

Wow! The National Kidney Foundation (NKF) published its guidelines for classification and management of CKD in 2003. An NKF position paper updated these recommendations in 2007. Where has the medical community been? This is a wake-up call for physicians and patients! As a result of these disappointing findings, I have decided to republish—with

updates—the spring 2006 issue of Quest Diagnostics *Medical News: Physicians Update* on chronic kidney disease detection.

CKD is a major public health problem which threatens to worsen over time. Early CKD affects about 20 million people in the United States. Another 20 million are at risk to develop CKD. In 2000, about 400,000 patients were classified as having end-stage renal disease (ESRD)—that is, requiring renal dialysis or awaiting a kidney transplant. CKD is growing at an alarming rate in the United States as well as worldwide. It is estimated that 8 million people in the United States have significant renal impairment and 10 million have kidney damage indicated by albuminuria. To put it in perspective, when compared to cancer deaths per 1,000, kidney failure incidence is second only to lung cancer deaths.

The number of individuals with ESRD is projected to increase to 2 million by 2030. Imagine the burden on healthcare resources. The cost to the U.S. healthcare system in 2000 was \$19.3 billion, exceeding the total National Institutes of Health’s budget that year by \$1.5 billion! The cost of renal failure represents about 6% of the entire Medicare budget.

The major risk factors for CKD include the following:

- Diabetes
- Hypertension

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- Cardiovascular disease (CVD)
- Obesity
- Age >60 years
- Exposure to certain drugs, including chronic nonsteroidal anti-inflammatory drug (NSAID) use
- U.S. ethnic minority status (African American, American Indian, Hispanic, Asian, or Pacific Islander)
- Family history of CKD

What is CKD? CKD is defined by at least one of two findings: The presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² for 3 or more months, irrespective of cause. Markers of kidney damage include abnormalities in the serum or urine, or on imaging studies. Proteinuria, as manifested by albuminuria, is the earliest marker of kidney damage in diabetes, hypertension, and glomerular diseases; thus it is the most common marker of kidney damage in adults.

The glomerular filtration rate (GFR) is considered the best overall index of renal function in both health and disease. Because the true GFR is difficult and impractical to determine in the clinical setting, many clinicians use the serum creatinine as a surrogate marker to estimate the GFR. The accuracy of this estimate is limited by factors other than creatinine filtration.

A number of estimating equations have been proposed to determine the eGFR. The Modification of Diet in Renal Disease (MDRD) has proven to be the most reliable in predicting the GFR in adults. In fact, using the MDRD formula is more accurate than the traditional laboratory measure of GFR—the creatinine clearance. Eliminating the need for the creatinine clearance in most cases frees the patient, the laboratory, and the physician from the inaccuracies and burden of a 24-hour urine collection.

This discussion will focus on adults, the age group in which CKD typically

develops. Alternative estimating equations are available from the NKF and other sources for calculating the eGFR in children and adolescents.

The reader may recall that the National Institutes of Health (NIH) and the NKF, through their National Kidney Disease Education Program (NKDEP) and Kidney Disease Outcomes Quality Initiative (K/DOQI), advocated that laboratories routinely report eGFR with serum creatinine. At least two states, New Jersey and Tennessee, have passed legislation requiring clinical laboratories to report the eGFR with all serum creatinine results. Others have passed legislation with various modifications of the report-all approach. A recently released report noted that in New Jersey, feedback from physicians has been generally favorable.

To refresh your memory, the table below describes the relationship of eGFR to various stages of CKD, along with notes on a clinical action plan for the various stages of CKD.

The clinical action plan for at-risk patients and those in early-stage CKD consists of screening, evaluating comorbid conditions, and modifying risk factors such as glucose and LDL-cholesterol. This is very important because CKD is largely asymptomatic during its early stages. Patients will not

come forward with symptoms, and physicians will only identify at-risk patients and early-stage CKD by history and screening. By stage 3, management involves treating complications such as anemia, altered bone metabolism, hypertension, CVD, secondary hyperparathyroidism, malnutrition, etc.

We noted in the spring 2006 issue that, in spite of widespread distribution of evidence-based clinical guidelines by many professional societies, there appears to have been a stubborn reluctance to fit these guidelines into daily clinical practice by primary care physicians (PCPs).

Using test data from a large national commercial laboratory, one review of serum creatinine results not ordered with eGFR revealed that many patients with CKD risk factors and abnormal eGFR values were not being identified. Another interview-based review of PCPs revealed five general themes emerging as key findings: (1) lack of awareness of K/DOQI guidelines; (2) desire for more CKD practice guidelines; (3) persistence of traditional, less accurate diagnostic procedure (serum creatinine alone); (4) variability in the treatment of complications; and (5) uncertainty of timing for referral to a nephrologist. The conclusion: Facing a growing CKD incidence, PCPs can have an impact on its progression. The findings of the

Classification of Chronic Kidney Disease and Clinical Action Plans

| eGFR (mL/min/1.73m ²) | Risk/Stage | Description | Clinical Action Plan* |
|-----------------------------------|----------------|--|--|
| ≥90 ⁺ | Increased risk | With CKD risk factors, such as diabetes, metabolic syndrome, hypertension, low income, U.S. minority status [#] , old age | Screening cardiovascular disease risk reduction |
| 60-89 ⁺ | Increased risk | If there is no evidence of kidney damage | Screening cardiovascular disease risk reduction |
| ≥90 ⁺ | 1 | If kidney damage is present, normal or ↑ GFR | Diagnosis and treatment; treatment of comorbid conditions; slow progression; cardiovascular disease risk reduction |
| 60-89 ⁺ | 2 | If kidney damage is present, mild ↓ GFR | Estimating progression |
| 30-59 | 3 | Moderate ↓ GFR | Evaluating and treating complications |
| 15-29 | 4 | Severe ↓ GFR | Preparation for kidney replacement therapy |
| <15 (or dialysis) | 5 | Kidney Failure | Replacement (if uremia present) |

* Includes actions from preceding stages.

⁺ The MDRD equation cannot estimate GFR greater than 59mL/min/1.73m² at this time.

[#] African Americans, Native Americans, and Asians have 4.45, 3.57, and 1.59 times the increased risk of CKD, respectively, when compared to Caucasians.

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Heath Trends Report mentioned earlier suggest that much remains to be done.

Why all the fuss? Why should we routinely adapt the eGFR into our clinical practice? This is not just another burden that the researchers and regulators are trying to force on an already overworked medical community. By using the serum creatinine alone to estimate GFR, many competent physicians may unknowingly be misled. For example, a serum creatinine of 1.2 mg/dL, still within the accepted reference range, represents the following eGFR's, ranging from increased risk to stage 3 CKD:

- 95 ml/min/1.73 m² in a 25-year-old African American male
- 71 ml/min/1.73 m² in a 40-year-old Caucasian male
- 57 ml/min/1.73 m² in a 70-year-old African American female
- 46 ml/min/1.73 m² in a 76-year-old Caucasian female

Many asymptomatic at-risk patients with early CKD can be evaluated and treated with resultant significant delay, stabilization, or even arrest of disease progression. The emphasis by many specialists has been on recognizing CKD and arresting progression to renal insufficiency and failure. This is truly important, but it must be remembered that more patients with CKD die from CVD complications than progress to renal failure.

CVD and hypertension are both risk factors for, and complications of, CKD. In fact, at least one publication has noted that hypertensive patients with an eGFR <60 ml/min/1.73 m² have a better chance of dying from CVD than from ESRD. Good glycemic control and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have been demonstrated to slow the progression of, or stabilize, renal impairment in patients with diabetes and/or hypertension—these drugs are not just for hypertension any more. Patients with CVD risk factors can be managed appropriately using the NCEP ATP III guidelines.

The NKDEP and K/DOQI guidelines recommend creatinine with eGFR and a spot (untimed) urine albumin/creatinine ratio (ACR) for albuminuria to screen for, detect, and monitor CKD. Other organizations have made similar recommendations. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends both eGFR and microalbumin testing. The American Diabetes Association recommends monitoring all type 2 diabetics for the development of CKD by annual estimation of the GFR and quantitation of urine albumin.

Additionally, patients with impaired renal function need to have dosage adjustments made to drugs that are cleared by the kidneys in order to avoid drug toxicity. Some electronic health records already have decision support software built in to recommend drug dosage adjustment based on the eGFR. Many patients with moderate to severe CKD have anemia and can benefit from an erythrocyte-stimulating agent. A significant number also will have secondary hyperparathyroidism.

In addition to the risk factors noted above, the ongoing epidemic of obesity, with its associated metabolic consequences, is resulting in a significant increase in individuals with CVD, impaired fasting glucose, and/or impaired glucose tolerance as well as type 2 diabetes. Chronic NSAID use can also predispose individuals to CKD. Patients with CKD should be advised to avoid chronic NSAID use. These two groups represent a significant portion of the United States population. Furthermore, the risk of kidney failure varies with race. African Americans, Native Americans, and Asians have 4.45, 3.57, and 1.59 times the increased risk of CKD, respectively, when compared to Caucasians.

One concern expressed by some PCPs is that they are uncomfortable managing patients with renal insufficiency and feel that it is

necessary to refer these patients promptly to a nephrologist. As more and more asymptomatic patients with CKD are identified, this approach will not be feasible. By one estimate, referring all patients with a GFR value between 30-59 mL/min/1.73m² (stage 3 CKD) would result in 7 new patients per nephrologist per day—a clearly unsustainable patient load.

PCPs must become more engaged in identifying and managing patients in CKD stages 1 through 3. The guidelines provided by K/DOQI and NKDEP will allow PCPs to more easily identify and manage uncomplicated patients with CKD and continue to maintain the traditional close relationship that is satisfying to both patient and practitioner.

The following are some frequently asked questions about eGFR and CKD:

Who should be screened for CKD using the eGFR?

- Patients with diabetes
- Patients with hypertension
- Relatives of patients with CKD
- Patients with other risk factors such as obesity, CVD, chronic NSAID use, etc.

How should I screen for CKD in adults?

- Order serum creatinine with eGFR using the MDRD equation.
- Order a spot urine microalbumin—persistent albuminuria (>30 mg/gM at least 2 of 3 times over a minimum 90-day period) reveals kidney damage.

*Editor's Note: Quest Diagnostics follows the NKDEP guidelines and reports the eGFR with all serum creatinine results. A 24-hour urine collection is **not** needed. Diabetics should be tested at least once per year. Others require testing less frequently as long as the spot microalbumin remains normal. Gender-specific reference intervals for microalbumin have been proposed but are based only on one study. Some frequency recommendations are opinion*

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based and can be modified at the discretion of the responsible physician.

Who should be treated for CKD?

- Diabetics with a persistent spot urine microalbumin of >30 mg/gM
- Non-diabetics with a spot urine microalbumin of ≥ 300 mg/gM or:
- Anyone with an eGFR of <60 mL/min/1.73m² on repeat measurements taken at least 3 months apart

Editor's Note: If you have an adult patient's serum creatinine result performed 3 or more months earlier, you can use that result as a baseline rather than waiting another 3 months.

If a normal eGFR is >90 mL/min/1.73m², why doesn't your laboratory report an actual value above 60 mL/min/1.73m²?

- The NKDEP presently recommends reporting estimated GFR values above 60 mL/min/1.73m² as >60 mL/min/1.73m² and not as an exact number. For values 60 mL/min/1.73 m² and below, the report should give the actual result rounded to the nearest whole number.

Editor's Note: There are 3 reasons for this recommendation: (1) The MDRD estimating equation has been most extensively evaluated in people with some degree of renal insufficiency; (2) Quantification of the GFR below 60 mL/min/1.73 m² has more clinical implications than above that level; and (3) Inter-laboratory differences in calibration of the creatinine assay and the imprecision of the assay have their greatest impact in the near normal range and therefore lead to greater inaccuracies.

Be aware that the creatinine assay calibrators at Quest Diagnostics are now traceable to the isotope dilution mass spectrometry (IDMS) standard SRM 967, and are therefore compliant with the NKDEP recommendations for laboratories. As recommended by the NKDEP, creatinine assay results at Quest Diagnostics are reported using two decimal places in order to avoid

rounding errors. Additionally, the MDRD estimating equation used is appropriate for an IDMS traceable creatinine assay.

Why can't I get an eGFR for my patients who are younger than 18 years old?

- In adults, age 18 years and older, the MDRD equation has been shown to be the best for estimating the GFR from serum creatinine. The MDRD estimating equation provides the best means currently available for utilizing serum creatinine as a measure of renal function.

Editor's Note: For patients younger than 18 years of age, an eGFR calculator, using the Schwartz and Counahan-Barratt equation, is available on the NKF Web site at http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm. This estimating equation requires patient height. Other equations may require weight and sometimes other biochemical measures.

Why are results reported for African Americans and non-African Americans?

- Clinical scientists have validated the MDRD equation in these two populations. African Americans have results that are 21% higher than for non-African Americans. With more studies ongoing, additional factors are likely to become available for other ethnic groups.

What is the cause of metabolic bone disease in CKD?

- CKD patients frequently develop metabolic bone disease primarily due to a decrease in 1, 25-dihydroxy vitamin D, the biologically active metabolite of vitamin D produced in the kidney. This results from impaired conversion of 25-hydroxy vitamin D to 1, 25-hydroxy vitamin D by the kidney, or to a 25-hydroxy vitamin D deficiency. Lower levels of 1, 25-dihydroxy vitamin D result in decreased absorption of dietary calcium by the small intestine, leading to lower serum calcium concentrations.

As the parathyroid gland detects low serum calcium levels, increased amounts of parathyroid hormone (PTH) are released. Secondary hyperparathyroidism is almost always present by stage 3 CKD. In healthy individuals, PTH promotes the production of 1, 25-dihydroxy vitamin D, increases renal re-absorption of calcium, and mobilizes calcium from the bone. CKD patients are unable to respond appropriately to the renal actions of PTH. As bone mineral metabolism moves farther from homeostasis, patients are at above-average risk for decreased bone mineral density and bone fractures.

When does bone disease occur in CKD?

- Bone disease may occur as early as stage 3 CKD and worsens as the decline in kidney function progresses. In stage 5 CKD or end-stage renal disease, bone disease is common; and by the time dialysis is instituted, nearly all patients are affected.

How are mineral and bone metabolism disorders of CKD monitored?

- Measurements of serum calcium and phosphorous are not sensitive enough to assess mineral metabolism and disturbances in CKD. Serum PTH and vitamin D metabolite levels can detect these disturbances earlier. If serum PTH is elevated above the target range for the corresponding stage of CKD, K/DOQI guidelines recommend measurement of 25-hydroxy vitamin D. K/DOQI testing guidelines and reference ranges for stages 3 and 4 CKD are straightforward and easy to interpret for the non-nephrologist. These reference ranges are presented in the table on page 5.

How is CKD mineral and bone metabolism treated?

- Current therapy involves biologically active 1 alpha-hydroxy vitamin D metabolites as well as various

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phosphate-binding agents, adjustments of dialysate calcium, and anti-bone resorptive agents. Patients being treated with these agents might present with bone disorders associated with low or nearly normal PTH levels.

The K/DOQI guidelines further state, “CKD patients with prolonged exposure to aluminum-based phosphate binders, and those with diabetes mellitus have lower blood levels of PTH than other patients with comparable levels of kidney function. Aluminum deposition in bone, secondary to aluminum overload, interferes with bone mineralization.

Therefore, low-turnover and/or adynamic bone disease may be more prevalent in these patients.

Patients with CKD may also have other factors that are not related to their CKD, but may impact bone and mineral metabolism. Advanced age and deficiency in sex hormones (estrogen and androgens) are associated with osteoporosis and loss of bone mass. Nutritional vitamin D deficiency, medications that affect vitamin D metabolism such as anticonvulsants, and/or hypophosphatemia would also cause defective mineralization of osteoid leading to osteomalacia.”

The reader is referred to the K/DOQI guidelines at <http://www.kidney.org> and cited references for an in-depth review of the subject.

Bottom line: The Quest Diagnostics Health Trends Report shows that we must do a better job with CKD! The medical community and patients need to be more aware of the CKD risk factors and the appropriate steps required to detect, slow, or arrest progression, and to manage the disease.

(*Am J Kidney Dis* 2007; **50**(2):169-180 — Previous references available at <http://www.questdiagnostics.com>)

K/DOQI Recommended Reference Ranges

| CKD Stage | PTH pg/mL | Phosphorus mg/dL | Calcium | Minimum Testing Frequency |
|-----------|--------------|---------------------|---|------------------------------|
| 3 | 35-70 | 2.7 - 4.6 | Within Laboratory Reference Range | Every 12 Months |
| 4 | 70-110 | 2.7 - 4.6 | Within Laboratory Reference Range | Every 3 Months |

Minimum testing frequencies if PTH is above target for the stage

| | Vitamin D, 25-Hydroxy | PTH | Phosphorus | Calcium |
|-----------------------------------|--------------------------|----------------|--|--|
| Vitamin D in range | Annual | Every 3 Months | Every 3 Months | Every 3 Months |
| Vitamin D not in range | Every 6 Months | Every 3 Months | Monthly for 3 Months then Every 3 Months | Monthly for 3 Months then Every 3 Months |

News Credits

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A Happy Flower

Longwood Gardens, Pennsylvania, 2007

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