Quest Diagnostics

Medical News
Physicians Update

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Our Values

Quality

Integrity

Innovation

Accountability

Collaboration

Leadership

Editor's Note:

Winter has been a time of dealing with dark cold days for some, and a time of concern and uncertainty about the economy for all of us. Spring is a period of renewal—a time to look forward, be positive, and get on with life. I hope that all of our readers are entering spring with a renewed sense of hope and optimism as I am.

This edition of Quest Diagnostics *Medical News: Physicians Update* is a potpourri of medical news dealing with a variety of topics, including frequently visited ones, such as chronic kidney disease (CKD), diabetes management, and unusual variables that can affect laboratory test results.

March is National Kidney Month in the United States, and every year World Kidney Day is recognized worldwide in March. In 2009, World Kidney Day occurs on March 12. Last year, this editor, and other members of the team from Quest Diagnostics, had the honor of being invited to participate in World Kidney Day with representatives of the National Kidney Foundation (NKF) at Grand Central Terminal in New York City. Meeting ordinary citizens and explaining the importance of screening for hypertension, diabetes, and CKD, as well as answering their questions, was a gratifying experience for me.

This year, World Kidney Day activities focus on hypertension, which, along with diabetes, is a leading cause of CKD. According to the Centers for Disease Control and Prevention, approximately 26 million persons in the United States had CKD in the year 2000. However, in 1999-2004, only 42% of adults with severe kidney disease (stage 4) and nearly 10% of those with less severe disease (stages 1-3) were aware of their condition. The NKF also noted that in 2000, approximately 400,000 people were receiving kidney dialysis or awaiting transplantation. That number is projected to increase to 2 million by 2030. The NKF also stated that the prevalence of patients with earlier stages of CKD was estimated to be 20 million in 2000.

Screening for and detecting early-stage CKD using serum creatinine along with an estimated glomerular filtration rate (eGFR) and a urine microalbumin or albumin/creatinine ratio (UACR) is still underutilized. In this issue we discuss the article, "Top 10 Things Nephrologists Wish Every Primary Care Physician Knew," which was published in the February 2009 issue of *Mayo Clinic Proceedings*.

A frequently asked question is—what do I tell my patient whose fasting plasma glucose is in the prediabetic range (100-125 mg/dL)? The question assumes more urgency for both patients and clinicians when the glucose result is between 100 and 110 mg/dL. A consensus statement on the subject of prediabetes was issued by the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) in October 2008. The consensus conference examined the current status of prediabetes, facts about related complications and what happens to people who progress to diabetes, available intervention trials, economic

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implications of early intervention, and what additional studies are needed.

In this issue we also describe an unusual preanalytic variable secondary to medication that can affect serum potassium results and impact patient safety. As you may recall, laboratory testing is divided into three phases: **preanalytic** (prior to testing), **analytic** (the testing phase), and **postanalytic** (following testing). Most test results are affected by factors that involve the preanalytic phase.

Finally, we are extremely proud to announce that Quest Diagnostics again has been named to FORTUNE magazine's list of the World's Most Admired Companies. Quest Diagnostics ranked second in the "Health Care" category of "Pharmacy and Other Services." The 2009 ranking is the second consecutive year that the company has been included on FORTUNE's Most Admired Companies list. The company advanced to second place from third in 2008. The new World's Most Admired Companies list is widely considered the definitive report card on corporate reputations.

"This prestigious recognition reflects the dedicated efforts of our 43,000 employees to put patients first and provide superior diagnostic services," said Surya Mohapatra, Chairman and CEO of Quest Diagnostics. "We are particularly gratified to have been ranked number one in our industry category for long-term investment, which demonstrates support for our strategy and vision."

FORTUNE's list of the World's Most Admired Companies is based on surveys of more than 4,000 executives, directors, and securities analysts of companies they admire most in their industry based on nine criteria: innovation, people management, use of corporate assets, quality of management, social responsibility, financial soundness, long-term investment, quality of products and services, and global competitiveness. For 2009, FORTUNE published one list rather than separate World's Most Admired and America's Most Admired lists in order to better represent the competitive landscape faced by today's companies.

CKD Update

An article in *Mayo Clinic Proceedings* carried the provocative title, "The Top 10 Things Nephrologists Wish Every Primary Care Physician Knew." Although the article addressed nephrology issues other than CKD, we will limit this discussion to the portion dealing with CKD. The purpose of the article was to avoid common pitfalls in recognition and treatment, as well as to provide some evidence-based pearls of wisdom for primary care physicians who encounter patients with renal disease in their daily practice. For a complete discussion of CKD and other renal conditions discussed in the article, the reader is referred to the cited reference. This editor has modified some of the pearls, which are noted below:

- ***A "normal" serum creatinine level may not be normal.*** Depending on age, race, and gender, the eGFR associated with a "normal" creatinine may be <60 mL/min per $1.73M^2$. Additionally, an increasing rate of serum creatinine levels may signal CKD. The eGFR should only be interpreted when the serum creatinine value is at a steady state.
- ***Be aware of medications that spuriously elevate the serum creatinine level.*** The serum creatinine level may increase without reflecting a change in the actual GFR. Commonly used medications, such as the antibiotic trimethoprim-sulfamethoxazole and the H_2-blocker cimetidine, can reduce tubular creatinine secretion with a corresponding rise in the serum creatinine level, which is not related to a change in the actual GFR. The antibiotic cefoxitin also can result in increased serum creatinine levels secondary to preanalytic interference with some colorimetric assays.
- ***Positive urine dipstick test results for proteinuria should be followed up with a spot UACR.*** Variations in urine flow and concentration can affect the semiquantitative albumin dipstick result. A quantitative determination of albumin is required for confirmation in adults. A urine protein/creatinine ratio should be used to confirm proteinuria in children.
- ***In patients with early-stage CKD, periodic evaluation and intervention are appropriate to slow progression.*** Follow the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for evaluation, monitoring, and treatment of patients with early-stage CKD. Of note, nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and radiocontrast agents, should be used with caution or avoided. The UACR should be checked periodically to monitor response and to evaluate the likelihood of progression. Since more patients with CKD die from cardiovascular complications than renal failure, it is therefore critical to evaluate

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cardiovascular disease (CVD) risk factors and manage appropriately.

- ***Consider comanagement with a nephrologist in late stage 3 and referral to a nephrologist in stages 4-5***. The increased detection rate of early-stage CKD makes referral to a nephrologist prior to stage 4 problematic because of limited resources. Uncomplicated patients with early-stage CKD can be managed adequately by primary care physicians.

Editor's Note: In this and previous discussions regarding CKD, we indicated that two widely available tests, serum creatinine with eGFR and urine microalbumin, can identify patients with and at risk for progressive CKD. Rapid screening for excessive urinary albumin secretion at the point of care with specialized dipsticks still requires laboratory confirmation and quantitation. These dipsticks can now be replaced by a CLIA-waived, quantitative point-of-care test for microalbumin.

The HemoCue® Albumin 201 system marketed by Quest Diagnostics was compared to both traditional laboratory testing for the UACR and specialized urinary microalbumin dipsticks. In one study, the performance of the HemoCue instrument was described to be as accurate and precise as the laboratory-based UACR determinations.

Additionally, the National Kidney Disease Education Program-International Federation of Clinical Chemistry Working Group on the Standardization of Albumin in Urine is developing standard urine collection methods. The group also will address urine albumin and creatinine measurements based on a complete reference system, test result reporting, and reference intervals for UACR.

(*Mayo Clin Proc* 2009; **84**(2):180-186 — *Am J Nephrol* 2008; **28**:324-329 — *Clin Chem* 2009; **55**(1):24-38 — *MMWR* 2009; **58**:193)

Prediabetes Consensus Statement

As stated in the consensus statement from the ACE and the AACE, "A worldwide pandemic of obesity and diabetes is well advanced." In the United States alone, diabetes now affects an estimated 24.1 million people, representing an increase of 3 million in only 2 years. Alarmingly, 25% of people with diabetes are unaware of their disease. Another 57 million persons in the United States have prediabetes. Prediabetes is defined by the consensus group as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Individuals with prediabetes may already have the microvascular changes seen in frank diabetes. Worldwide, the number of people with prediabetes is estimated to be 314 million and is projected to reach 418 million by 2025. Diabetes is expensive—the associated yearly direct and indirect costs of diabetes in the United States are $174 billion!

Prediabetes raises the short-term risk of type 2 diabetes by 3- to 10-fold, with some populations exhibiting greater risk than others. People with diabetes are vulnerable to multiple and complex medical complications, including heart attack, stroke, peripheral vascular disease, retinopathy, neuropathy, and diabetic kidney disease. Epidemiologic data suggest that the complications of diabetes begin early in the progression from normal glucose metabolism to frank diabetes.

Early identification and treatment of individuals with prediabetes have the potential to reduce or delay the progression to diabetes. Despite the clear indications of diabetes-related complications early in the prediabetic state, few recommendations have been made for the diagnosis and management of persons with prediabetes. No medications are approved for managing either IFG or IGT. Many insurance companies do not cover lifestyle changes as treatment to prevent diabetes. In the medical community, there are also differences of opinion regarding the therapeutic approach to treating individuals with prediabetes.

Questions that need to be addressed by healthcare professionals were noted as follows:

- When do the risks of diabetes begin?
- What can we do to prevent diabetes?
- What strategies are necessary to reduce the vascular complications related to diabetes?
- How does society pay for the preventive costs of diabetes in the large number of people at risk?

The following are some of the questions addressed by the consensus conference:

- ***What is the spectrum between normal glucose tolerance, prediabetes, and diabetes?*** Prediabetes currently refers to people who have IFG (100-125 mg/dL), IGT (2-hour postglucose load, 140-199 mg/dL), or both. The consensus group also added the National Cholesterol Education Program (NCEP) definition of the metabolic syndrome as a prediabetes equivalent. Presently, diabetes is diagnosed somewhat arbitrarily at a fasting plasma glucose level of ≥126 mg/dL or a 2-hour postchallenge glucose concentration of ≥200 mg/dL.

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In the prediabetes gap between normoglycemia and diabetes, data indicate that, for many individuals, these glucose levels are not benign and may be a sign of impending type 2 diabetes and CVD, as well as microvascular complications. Therefore, the ill-defined area in fasting glucose of 100-125 mg/dL and 2-hour postglucose load of 140-199 mg/dL is thought to describe a prediabetic range, where some degree of increased microvascular and macrovascular complications of diabetes has been described.

The risk for progression to diabetes with IGT is 6-10% per year. For persons with both IFG and IGT, the cumulative incidence of diabetes may be as high as 65%. For comparison, the cumulative incidence of diabetes for persons with normal glucose at baseline is on the order of 5%. Additionally, approximately one half of patients with IGT fit the NCEP criteria for the metabolic syndrome. The consensus committee noted that the higher the glucose values, the greater the risk of progression to diabetes and diabetic complications.

- ***What are the clinical risks of not treating prediabetes?*** Most, if not all, diabetic complications become more severe as glycemia progresses. Increases in dyslipidemia, CVD, cardiovascular death, hypertension, microalbuminuria, retinopathy, and peripheral neuropathy have been observed in patients with prediabetes, whether or not prediabetes progresses to diabetes. The consensus committee suggested that patients are at risk when IGT is identified, and when untreated, these patients experience progression in their incidence of diabetes, as well as microvascular and macrovascular risk.

- ***What goals and treatment modalities should be the focus of prediabetes management?*** The management of prediabetes involves a set of global treatment measures designed to address its abnormalities and cardiometabolic disease risks. The cornerstone and preferred treatment approach for all of the abnormalities associated with prediabetes is intensive lifestyle management. This approach has a proven track record for safety and effectiveness.

  However, if prediabetes progresses, therapies directed toward hyperglycemia and the individual CVD risk factors may be essential. The consensus committee proposed a set of treatment goals for CVD, blood pressure, dyslipidemia, and glycemia control either after or together with lifestyle changes. The committee noted that, at present, there are no FDA-approved/cleared pharmacologic therapies for the prevention of diabetes in adults. The decision to use pharmacologic agents is considered off-label and requires careful judgment. The reader is referred to the cited reference for an in-depth discussion of the consensus committee's view on drug therapy use in prediabetes.

- ***What are the appropriate measures to monitor prediabetes and its treatment? Should we measure parameters of glucose and which ones?*** The consensus committee felt that the answers to these questions depended on the risk stratification of the individual, with more monitoring appropriate for those at the highest levels of risk based on many factors, including glucose, lipid, blood pressure abnormalities, and family history, etc. In general, monitoring of patients with prediabetes to assess a deteriorating glycemic status should include fasting glucose and A1C testing, with a 2-hour postglucose load challenge for those in whom progression is suspected and a more sensitive measure is needed. Patients with prediabetes should also have a microalbumin test, fasting lipid, and blood pressure measurement at least annually. Those patients considered at highest risk for progression to diabetes should be monitored more frequently. The consensus committee defined highest risk as more than one of the following: IGT, IFG, or metabolic syndrome.

  Diabetes is one of the few major diseases for which there are no biomarkers. The consensus committee noted that "In the future, biomarkers and genetic markers may also allow more targeted interventions and even lead to suggested therapeutic options in appropriately selected individuals at high risk."

- ***Can society afford the costs of treating or not treating the prediabetic state?*** Prevention of diabetes is a key strategy for reducing patient suffering and the high social costs of the disease. Diabetes costs are driven by vascular complications, which account for more than 50% of total costs largely through the cost of hospitalization. A number of studies have analyzed the cost-effectiveness and effect on quality-adjusted life-years for the various interventions described. The evidence seems clear that preventing the progression of prediabetes to diabetes is cost-effective, even at the present time. Given the current basis of evidence, it is incumbent upon healthcare systems and healthcare providers to develop lifestyle intervention programs that prevent diabetes. The consensus committee concludes, "A restructuring of health care remuneration to reward disease prevention will be necessary to counteract the increasing burden of diabetes. Furthermore, our patients' health depends on built environments in communities that

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Prediabetes Consensus Statement
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provide healthy lifestyles, necessitating collaboration among civic and governmental partners to achieve this goal."

Editor's Note: The American Diabetes Association noted in its publication, "Standards of Medical Care in Diabetes—2009," that A1C will likely be recommended as the preferred diagnostic test for diabetes. Diagnostic cut-points are now being discussed. It is anticipated that the recommendations will occur in 2009. Once that takes place, the definition of prediabetes will need to be revisited. Stay tuned!

It seems clear that the epidemic of obesity and diabetes, occurring worldwide, is threatening the economic health of nations and the physical health of patients. The medical community and third party payors in the United States are shifting from a disease treatment to a disease prevention strategy. This bodes well for our nation's health.

(*Endocr Pract* 2008; **14**(7):933-946 — *Diabetes Care* 2009; **32**(Suppl 1):S13-S61)

Preanalytic Variables

In previous issues we have discussed the preanalytic variables affecting serum and plasma potassium results. Another little known issue that can affect serum potassium results was recently reported. An article in *The American Journal of Medicine* reports a case of hyperkalemia secondary to a commonly used antibiotic.

A 44-year-old diabetic, male patient was admitted with Fournier's gangrene—a potentially fatal necrotizing fasciitis involving the genital and perineal area. Following incision, drainage, and wound debridement, the patient was treated with multiple antibiotics, including ampicillin, followed by penicillin G, and oral penicillin VK. On hospital day 21, the patient's serum potassium was noted to be 6.0 mmol/L. The rest of the electrolytes remained in the normal range. The patient was treated with ion exchange resin, and the surgeon was advised to replace the penicillin VK with amoxicillin. The patient's serum potassium returned to normal levels following treatment and discontinuation of the potassium-containing antibiotic.

The authors note that a review of the literature found four reported cases of cardiac arrest caused by penicillin-induced hyperkalemia. Hyperkalemia is common in diabetics, with an estimated prevalence of 15%. Chronic hyperkalemia in diabetic patients is most often attributable to hyporeninemic hypoaldosteronism and CKD caused by diabetic nephropathy. Conditions including urinary tract obstruction, volume depletion, and drugs can acutely provoke hyperkalemia in susceptible individuals. The risk of dangerous hyperkalemia in diabetic patients is particularly high with the concurrent administration of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

In the case described, the hyperkalemia was most likely due to the potassium load in penicillin G and penicillin VK. The patient received 30.6 mmol of potassium daily in penicillin G and 6.9 mmol of potassium per day in penicillin VK. The authors noted that it is important for physicians to be aware of the potassium as well as sodium load in penicillin preparations administered and to monitor the patient's electrolytes closely, especially if they have diabetes, CKD, or congestive heart failure.

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Bright Spring Colors
Longwood Gardens, Pennsylvania, May 2007

News Credits

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