ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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A Simple Urine Test Detects Rapid Kidney Function Decline

By Tracy Hampton

A simple and inexpensive urine test that can be routinely performed in family physicians' offices can help identify individuals who are silently experiencing rapid kidney function decline (RKFD), according to new research. The test could help save lives because RKFD predicts cardiovascular morbidity and mortality, but serial assessment of kidney function by measuring estimated GFR (eGFR) is not cost effective for the general population.

"Our new strategy using a simple urine dipstick allows clinicians to follow fewer patients with serial eGFR assessments to identify those with rapid kidney function decline," said William Clark, MD, of the University of Western Ontario and London Health Sciences Centre, in London, Ontario, Canada, who was the lead author of the *Journal of the American Society of Nephrology (JASN)* study. "This strategy enables earlier identification of many patients with rapid kidney function decline in the general population and will potentially provide an opportunity to introduce therapy to reduce cardiovascular mortality and end stage kidney failure in this asymptomatic subgroup," he added.

Detecting kidney decline

For the approximately 60 million people globally who have chronic kidney disease, early detection and treatment are crucial for preventing kidney failure and cardiovascular complications. Unfortunately, individuals with chronic kidney disease often do not experience symptoms until later stages of the disease. In particular, patients with RKFD are at increased risk for cardiovascular disease and mortality, even when they have only mildly reduced kidney function at baseline.

Although serial monitoring of kidney function in the general population would likely catch such silently progressing disease early, it is too expensive. Simi-

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New Ways to Diagnose and Treat Diabetic Nephropathy Is Topic of Joint Symposium

By Cathy Yarbrough

With "disturbing news about diabetic nephropathy" as a backdrop, Lori M. Laffel, MD, MPH, co-chaired the first joint symposium of ASN and the American Diabetes Association (ADA) on June 27 as part of ADA's 71st annual meeting in San Diego. "Despite an increase in the use of pharmacological therapies, the prevalence of diabetic nephropathy (DN) has not decreased," said Laffel, of the Joslin Diabetes Center.

Laffel was referring to findings published in the June *Journal of the American Medical Association (JAMA)*, "Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States," based on data from the National Health and Nutrition Examination Survey.

The proportion of diabetic patients taking glucose-lowering medications climbed from 56.2 percent in 1988–1994 to 74.2 percent in 2005–2008, according to the *JAMA* article, and the use of renin-angiotensin-aldosterone system inhibitors soared from 11.2 percent to 40.6 percent during those same time periods. However,

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larly, screening for proteinuria to prevent ESRD is not cost effective unless it is directed at high-risk populations.

To date, no studies have investigated the clinical utility of combining risk-factor assessment with routine screening tests to identify those at highest risk for RKFD who would benefit the most from serial eGFR assessment and early intervention.

To conduct such an investigation, Clark and his colleagues designed a prospective cohort study to identify the risk factors for RKFD and to evaluate the ability of routine screening tests for urine protein to improve the efficiency of detecting the condition across a broad range of eGFR values.

A simple test

The investigators monitored 2574 participants in a community-based clinic for an average of 7 years. They found that dipstick proteinuria (a urinary protein concentration of ≥1 g/L) had better diagnostic utility for identifying patients at risk for RKFD than did albuminuria (albumin:creatinine ratio of >2.0 mg/mmol if male or >2.8 mg/mmol if female). Although more participants were identified with albuminuria (n = 253), fewer developed RKFD (6 percent) in comparison with those identified at various thresholds of dipstick protein. Among the participants who developed RKFD,12 percent had trace or above protein; 33 percent, ≥1 g/L protein; and 40 percent, ≥3 g/L protein.

Overall, 2.5 percent of participants in the study had a urinary protein concentration of ≥1 g/L at the start of the study. If all of them were followed up with serial monitoring of kidney function, one case of RKFD would be identified for every 2.6 patients who were monitored. This decreased to 2.3 among those with cardiovascular disease, diabetes, or hypertension or who were 60 or older.

The test correctly identified whether or not individuals had RKFD in 90.8 percent of participants, mislabeled 1.5 percent as having the condition, and missed 7.7 percent who were later identified as having the condition. Among those with cardiovascular disease, diabetes, or hypertension or who were age 60 or older, the probability of identifying RKFD from serial kidney function measurements increased from 13 percent to 44 percent after the incorporation of a positive dipstick test result. Although albuminuria had greater sensitivity, particularly among persons with diabetes, a higher false-positive rate resulted in a greater number to follow up.

"This novel strategy, although not identifying all with RKFD, addresses the shortcomings of many prior studies by changing the focus from static eGFR assessment among those with eGFR below 60 mL/min per 1.73 m^2 to dynamic assessment of those with eGFR above and below 60 mL/min per 1.73 m^2," Clark said.

He added that strategies that focus on identifying progressive renal disease in individuals with eGFR below 60 mL/min per 1.73 m^2 identify patients later in their disease. This analysis focused on all adults, including those with eGFR above 60 mL/min per 1.73 m^2, whose conditions may otherwise go undetected and yet are likely to experience greater therapeutic benefit if the disorder is identified at an earlier stage. More than 80 percent of those with RKFD in the study cohort had an eGFR above 60 mL/min per 1.73 m^2.

"The paper by Clark et al is a major step forward in the ongoing search for a practical and universal Renal Risk Score that can be used to predict the likelihood of progressive renal failure and eventual end stage renal disease in subjects within the general population, in a fashion similar to the Framingham Risk Score for cardiovascular risk assessment," said Richard Glassock, MD, who was not involved with the research and is professor emeritus at the David Geffen School of Medicine at UCLA in Los Angeles.

Next steps

The techniques described in this study should not be difficult to incorporate into the clinic, but Hiddo Lambers Heerspink, PharmD, PhD, of the University Medical Center Groningen in the Netherlands, noted that confirmation of the approach in other independent cohorts is needed before the strategy can be implemented.

"How and whom to screen for kidney disease remains an unanswered question,"

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said Catherine Clase, MB, FRCPC, of McMaster University in Hamilton, Ontario, Canada. "There is now little doubt that further research into screening strategies for kidney disease should, as the authors suggest, incorporate both measurement of urine protein and dynamic assessment of clearance. Dipstick proteinuria looks very attractive as a metric for assessment of proteinuria."

Early treatment may be warranted for those who are found to have RKFD as determined by the techniques in this study, but future research is needed to assess the impact and cost effectiveness of different follow-up strategies.

"The next and much more difficult step will be show that early intervention in subjects with high Renal Risk Scores but without marked proteinuria or moderately depressed eGFR actually prevents progression and avoids end-stage renal disease," said Glassock.

Joint Symposium

Continued from page 1

during these two periods, the prevalence of impaired GFR increased from 14.9 percent to 17.7 percent. Although impaired albuminuria declined from 27.3 percent to 23.7 percent, this decrease was not statistically significant, according to the authors of the *JAMA* article.

Titled "New Concepts in Diagnosing and Treating Diabetic Nephropathy," the first joint symposium was targeted to endocrinologists and other ADA conference attendees. The second joint symposium is slated to occur at ASN's Kidney Week 2011, Nov. 8–13, in Philadelphia.

"We [nephrologists] spend a lot of time taking care of patients with diabetes, since it is the leading cause of chronic kidney disease and end stage kidney disease," said symposium co-chair and ASN past president Sharon Anderson, MD. "So it behooves us as nephrologists to stay current on diabetes treatments."

ASN president Joseph V. Bonventre, MD, PhD, spoke about the role of renal proximal tubule injury and dysfunction in the pathophysiology of DN. Bonventre, of Harvard Medical School, was one of the four symposium speakers.

"Specific proximal tubular injury leads to interstitial fibrosis and glomerulosclerosis," he said. "It may be that the kidney tubules are the primary place where diabetes has its earliest actions."

A potential sensitive and specific biomarker for early tubular injury is the transmembrane glycoprotein kidney injury molecule-1 (KIM-1), which Bonventre's laboratory cloned and characterized. Expressed only by proximal tubule cells, KIM-1 is undetectable in normal kidneys. With acute kidney injury, the mRNA and the protein are markedly upregulated.

In mice models, long-term expression of KIM-1 leads to kidney failure, and replacement of normal KIM-1 with a mutated form results in a molecule that fails to uptake oxidized lipids and glycation end products, said Bonventre. Citing unpublished research from his laboratory, he noted that high ambient glucose enhances KIM-1 expression in renal epithelial cells.

In a February 2011 *Kidney International* article, Bonventre and colleagues reported that low urinary levels of KIM-1 and the lysosomal enzyme N-acetyl-beta-D-glucosaminidase (NAG) are associated with regression of microalbuminuria (MA) in patients with type 1 diabetes (T1D) who were monitored for two years. MA regression occurred independently of glycemic control, blood pressure, or treatment with angiotensin converting enzyme inhibitors.

Bonventre and colleagues also reported that significantly elevated urinary levels of KIM-1 and NAG characterized patients with T1D and MA in comparison with diabetic patients with normoalbuminuria and with healthy control individuals without diabetes. These and other studies suggest that KIM-1 may serve not only as a therapeutic target for drug development but also as the basis of an early diagnosis test for DN.

Symposium speaker Bruce A. Perkins, MD, MPH, addressed predictive biomarkers of early DN beyond MA.

"Recent studies have shown us that microalbuminuria on its own is not the perfect predictor of who will develop advanced kidney disease, and we need to get beyond the idea of relying so much on microalbuminuria," he said.

In the recent studies, elevated urinary albumin excretion regressed to normoalbuminuria in a majority of T1D patients. In only a minority of T1D patients did MA lead to proteinuria, said Perkins, of the University of Toronto.

"What we and others have learned is that the old notion that people don't start to lose renal function until they have proteinuria appears to have been false," he pointed out. In about one third of T1D patients, GFR loss can begin at the onset of microalbuminuria, well before proteinuria appears. "End stage renal loss can occur before proteinuria," Perkins noted, referring to the Joslin Diabetes Center's findings of renal function decline in T1D patients with normal albumin excretion.

As a potential biomarker for early GFR loss, Bruce proposed serial measurement of serum cystatin C, a cysteine protease inhibitor that is freely filtered by the renal glomeruli and metabolized by the proximal tubule.

In an April 2011 issue of *JAMA*, researchers reported that combining creatinine-based estimated GFR and urine albumin-to-creatinine ratio with cystatin C was associated with improved prediction of end stage kidney disease and all-cause death. Cystatin C and albuminuria were both strongly and independently associated with all-cause death among patients

with or without chronic kidney disease (CKD) defined by creatinine-based estimated GFR. The risk of future end stage renal disease (ESRD) was concentrated within the patient subset with CKD defined by all three markers. The second highest risk group for ESRD was missed by creatinine but was detected by cystatin C and albumin/creatinine ratio.

"If we screen people with new onset microalbuminuria, we now know that about a third of them will lose substantial GFR in subsequent years, so we could measure serum cystatin C levels over time to estimate the rate of decline and identify those people at highest risk of reaching advanced kidney disease," Perkins said.

As another potential biomarker for early GFR loss, Perkins cited tumor necrosis factor-α (TNFα/TNF), a key mediator of inflammation that also plays a role in apoptosis. Joslin researchers have shown that soluble TNF receptors are strong predictors of early GFR loss in T1D. Perkins referred to Joslin scientists' ADA poster reporting that plasma levels of TNF receptors did not increase with renal function loss in T1D patients. The Joslin researchers concluded that because elevation of TNF receptors preceded kidney dysfunction, they could be both predictors of, and risk factors for, early GFR loss in T1D.

Kumar Sharma, MD, spoke about novel treatments for DN, including the investigational antifibrotic and antiinflammatory drug pirfenidone. Sharma, of UC San Diego, headed a randomized, double-blind, placebo-controlled clinical study that evaluated pirfenidone in 77 DN patients with elevated albuminuria and reduced GFR.

"Pirfenidone not only halted decline but actually improved kidney function in these patients," said Sharma, who with his collaborators reported the study findings in an article published in the April 2011 issue of the *Journal of the American Society of Nephrology.*

Sharma also spoke about bardoxolone methyl, first in a new class of antioxidant inflammation modulators. In the June 24, 2011, issue of the *New England Journal of Medicine*, investigators reported the results of a phase 2, double-blind, randomized, placebo-controlled trial in 227 CKD patients. "Bardoxolone improved eGFR as early as four weeks after initiation of treatment," Sharma said. Improved GFR characterized patients at both 24 and 52 weeks.

Marie Pavlakis, MD, of Beth Israel Medical Center, reviewed data supporting the use of preemptive kidney transplantation before the start of dialysis. "The treatment of choice for these diabetics would be a live donor kidney transplant before dialysis treatment," she said. "We have evidence that people who get kidney transplants preemptively live longer and do better, and the kidney lasts longer than in people who get a transplant when they are already on dialysis."

"Research shows the highest mortality risk for type 1 diabetics is for those on dialysis," she added. "We need to get the message out to the endocrinology community on the remarkable mortality benefit that predialysis kidney transplantation offers for type 1 diabetics."

Industry Spotlight

More Dialysis Merger News

Noteworthy mergers continue in the dialysis field. In late 2010, Liberty Dialysis of Mercer Island, Washington, merged with Renal Advantage in Brentwood, Tennessee, to create the number three firm in dialysis. Then in August, Fresenius Medical Care, a global provider of dialysis services and products, agreed to purchase the newly fashioned Liberty Dialysis Holdings for $1.7 billion.

Last November, Renal Advantage and Liberty Dialysis agreed to combine and formed the third largest dialysis provider in the United States after Fresenius and DaVita. The new firm had 5300 employees serving more than 19,000 patients in 260 locations in 32 states. The transactions closed near the year's end. The terms were not disclosed, but revenues have been estimated in the $1 billion range, according to *Bloomberg News*.

At that time, Mark Caputo, chief executive officer of Liberty Dialysis, said, "This merger unites two patient-focused, physician-driven, and employee-oriented companies with the autonomy to build their unique brands while taking advantage of the combined financial strength, purchasing power, and systems investment of two leading companies in the dialysis industry."

That type of power gained the attention of dialysis giant Fresenius, based in Bad Homburg, Germany, which plans to complete the acquisition of Liberty by early 2012 and gain a better position for its North American dialysis services and product sales.

Fresenius further announced that it would acquire American Access Care Holdings for $385 million. That firm, based in Glen Rock, Pennsylvania, dovetails with dialysis business, providing services from vascular clinicians who specialize in fistulas or grafts that allow for a permanent point of access to blood vessels for dialysis.

By eliminating the need for a temporary catheter, the company's products can lower the risk of infections, which can add costs to care, so the acquisition makes "strategic sense," said Lisa Clive, an analyst with Sanford C. Bernstein Ltd in a Bloomberg interview.

She also noted that the acquisition makes sense in this climate because it boosts Fresenius' already considerable economies of scale. The recent application of a bundled rate is easier to absorb in a larger company, Clive said. The dialysis industry is now subject to a completely different incentive because drug costs are rolled into a fixed compensation rate imposed to reduce the overuse of drugs that were previously separately billable.

Guidelines Released for Transitioning Adolescents with Chronic Kidney Disease from Pediatric to Adult Care

By Kurtis Pivert

As more children and adolescents get chronic kidney disease (CKD), more will eventually need to move from pediatric to adult care. Managing the move between the two clinical settings and the issues that arise during the patient's transition—from unique pediatric etiologies to treatment compliance—is the focus of a recent consensus statement from the International Society of Nephrology (ISN) and International Pediatric Nephrology Association (IPNA).

The guidelines address how to ensure a smooth transition and continuity of care for adolescents and young adults 14–24 with CKD stages 3–5 who will require renal care as adults. The transfer to the adult unit is the end result of a lengthy transition process preparing the patient, and the pediatric and adult nephrologists, long before the actual transfer occurs.

Adolescence is a time of physical and developmental changes, and dealing with a chronic disease can be challenging during this period. Noting that multidisciplinary support teams in the pediatric clinic may not exist in adult settings, the consensus statement advocates that preparation for the transition should start early, in an age-appropriate manner, between the ages of 12 and 14. Patient support must continue as the transfer approaches, with peer networks, an individualized transition plan, transition tools, and inclusion of family and friends in the planning all key to a smooth transition.

Addressing care from both sides

The success of the adolescent's transition to adult care lies in good communication between the pediatric and adult nephrology services. Coordinating the transfer of patient records, customizing a transition plan, providing site visits, and appointing a "transition champion" and "transition coordinator" to oversee the transfer are imperative.

The creation of a "transfer clinic in either the adult or the pediatric renal unit with both adult and pediatric nephrologists in attendance is the optimal minimal standard" for the transfer of adolescents to adult care, and the clinic's nephrologists should be familiar with the unique aspects of childhood CKD, the statement said.

To young adults, continuity of care and maintaining stability and trust with their physicians during a time of great change is vital. A young adult unit within the adult nephrology service or a dedicated transfer team can address this issue.

Timing the transfer

The last step in the transition is determining the optimal time for the patient to move to the adult clinic. Meeting milestones in their transition plan, completing their education, having a stable home environment, addressing other specialties treatment plans, and their financial situation all must be considered before the decision to transfer the patient is made.

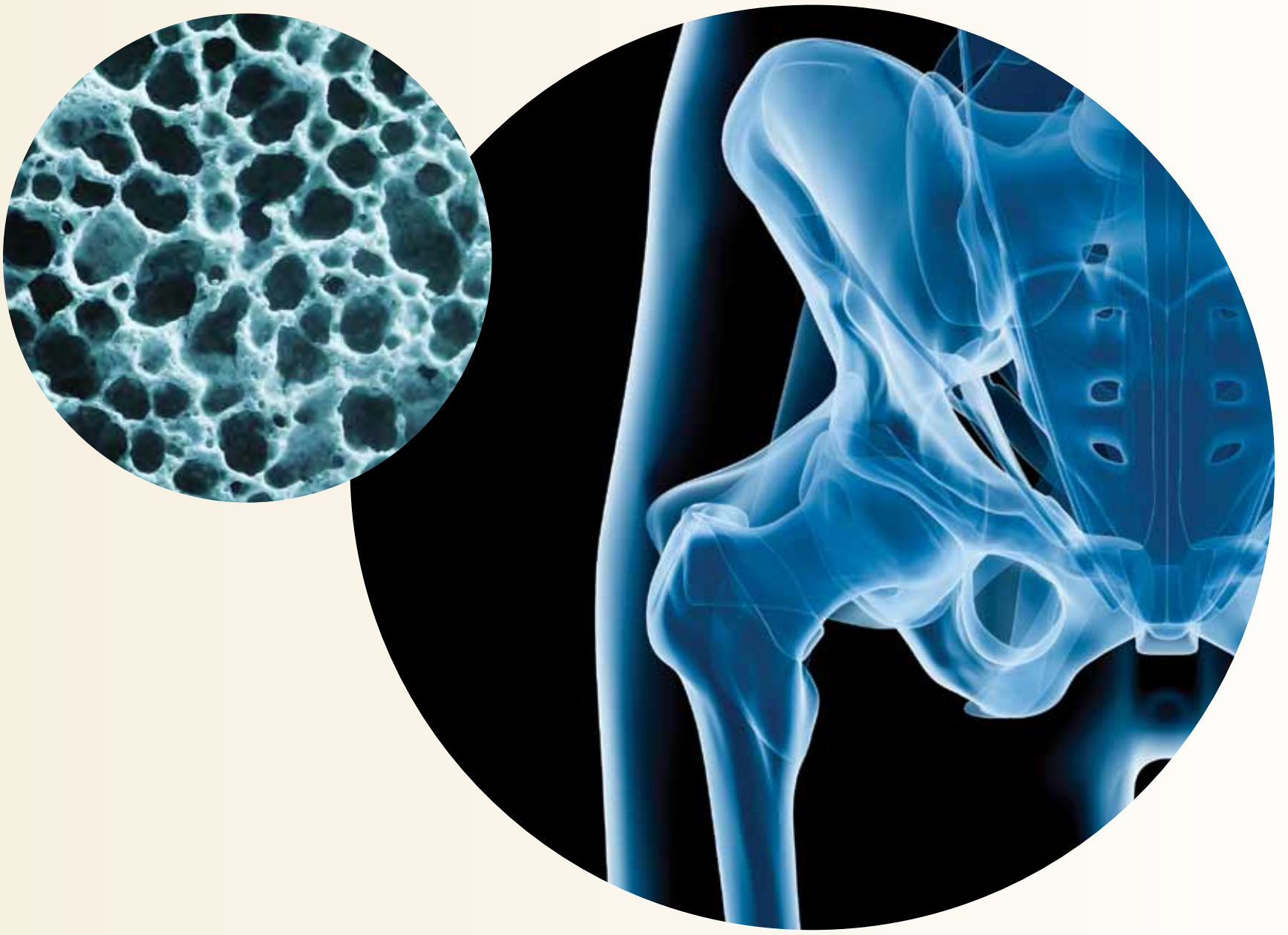
"The ISN/IPNA statement provides an excellent basis upon which to approach transition, but it is important to recognize that it is based on general, international concerns," said William Schnaper, MD, president of the American Society of Pediatric Nephrology (ASPN). "In the United States, local factors such as how CKD care is delivered and compensated will have a significant impact on our solutions. These issues will require continued discussion and study."

The ASPN agrees that "it is important for pediatricians to communicate to the internal medicine nephrologists the special concerns involved in the care of children who have developmental or genetic kidney diseases, and conversely, pediatricians need to learn more from internists about what information and preparations are needed to support effective transition. Also, because many of the diseases affecting pediatric patients are syndromic, patients will require input from multiple specialists, not just nephrologists," Schnaper said.

A major concern for Schnaper and the ASPN is that "our most vulnerable patients risk the loss of their health care coverage just when transition is occurring. We continue to advocate for programs that protect the patient during this critical time, such as extending the duration of Medicare coverage for antirejection drugs and increasing the age at which children may be covered by their parents' health insurance, as supported by the Affordable Care Act."

The ultimate goal is not merely the smooth transfer of adolescents to an adult care setting but, "assuring that the patient enters adulthood as a productive member of society who has access to optimal health care," Schnaper said.

Stones and Bones



Nephrologist to Lead American Society for Bone and Mineral Research

Keith Hruska, MD, chief of pediatric nephrology at Washington University in St. Louis, becomes the new president of the American Society for Bone and Mineral Research (ASBMR) at this month's annual meeting of the ASBMR in San Diego. He will be the first nephrologist to hold this prestigious position in the history of the society.

"The bone–kidney connection has changed with new understanding of the pathophysiology of chronic kidney disease (CKD)-mineral bone disorder (MBD)," said Hruska, a longstanding member of the American Society of Nephrology (ASN). "The nephrology contingent in the ASBMR used to be much stronger. Hopefully we can rebuild the interest of nephrologists in the ASBMR, given the role of the skeleton in the pathogenesis of CKD-MBD and in the increased mortality of CKD patients."

When asked about his goals for his ASBMR presidency, Hruska commented that the ASBMR has developed a five-year strategic plan. "One of the components of that plan is for the ASBMR to strengthen its interactions with sister societies whose focus is other organs that interact with the skeleton including the kidney, and with the ASN," he said. Specific strategies will include increased interactions at scientific meetings, for example, co-sponsored symposia; increased joint advocacy for research and development; and enhanced communication with primary care providers to ensure that patient care is based on scientific rigor that is unbiased and free from potential conflicts.

Hruska said that this year's ASBMR would include a focus on muscle research. Over 50 percent of osteoporotic fractures are due to falls, and falls result from frailty. A major factor contributing to frailty is declining muscle function. This body of research typically focuses on the effect of aging on muscle, but the relationship of muscle and bone has been largely unexplored. Early frailty can be seen in a number of younger populations, including those with kidney disease. The prevalence of frailty has been found to increase with progression of CKD. At next year's ASBMR annual meeting, the hope is to incorporate a muscle interest group to bring together investigators in this area of research to share ideas and enhance collaboration.

Hruska plans to work hard to develop a similar multidisciplinary approach with investigators researching CKD-MBD. His hope is that the ASN will recognize the importance of understanding CKD-MBD, an area that falls outside the interest of the ASN advisory groups as they are currently defined.

"There is a small group of researchers in the pathophysiology of CKD-MBD in the ASN organization," Hruska said. "Yet CKD-MBD presents a huge burden of disease in our patients. Thus, we need to increase awareness and interest among nephrology researchers."

Vitamin D:
How much hope? How much hype?

By Eleanor Lederer

Of longstanding interest to nephrologists, vitamin D has now become a hot topic in the general medical and lay literature. While the beneficial effects of vitamin D on mineral metabolism have been appreciated for a century, a burgeoning body of literature attests to a multitude of other effects including modulation of the immune system, anti-infectious and anti-neoplastic effects, anti-proteinuric effects, antagonism of the renin angiotensin system with attendant cardiovascular benefits, and insulin-sensitizing effects.

Low vitamin D levels have been correlated with a greater incidence of several cancers including prostate and breast; autoimmune diseases such as multiple sclerosis; and metabolic syndrome. The majority of these claims stem from animal studies or epidemiologic association studies in humans. In parallel with these studies, a large number of reports document the very high incidence of low vitamin D levels in multiple populations including the elderly, the chronically ill, African Americans, and even generally healthy young people. Naturally, the intuitive response to these findings is to raise vitamin D levels under the assumption that normalizing the level will diminish the risk of the associated illnesses.

But how strong are the data supporting aggressive vitamin D replacement? Until very recently, vitamin D deficiency was defined as 25-hydroxy vitamin D levels (D2 or D3) less than 10 ng/mL, but an optimal vitamin D level was not established. The methodology for measuring 25-hydroxy vitamin D has only recently been standardized, allowing comparisons between different laboratories. Based on data demonstrating that vitamin D levels lower than 30–32 ng/mL in adults were associated with the development of secondary hyperparathyroidism and less efficient intestinal absorption of calcium, the ADA recommended targeting 32 ng/mL as the optimal vitamin D level with suggestions that higher levels are being considered. The Institute of Medicine (IOM) reviewed this subject and recently presented a concensus statement. The report supports the ingestion of 600 IU cholecalciferol daily for the mineral benefits, but did not find sufficient evidence that vitamin D supplementation can benefit conditions such as cancer, autoimmune diseases, and metabolic syndrome. Furthermore, the institute concluded that levels of 20 ng/mL were sufficient and that there was inadequate evidence to support pushing for higher levels. So who is right? The ADA or the IOM? It is too early to say. Clearly, more well-designed large studies examining the effect of vitamin D in selected populations are needed.

What about the dialysis and chronic kidney disease populations, populations with a high incidence of vitamin D insufficiency/deficiency and a high incidence of cardiovascular disease and insulin resistance? A number of studies suggest that dialysis patients receiving active vitamin D supplementation such as paracalcitol or calcitriol enjoy a survival benefit over dialysis patients who are not receiving calcitriol or its analogs, without differences in biochemical measures of calcium, phosphate, and parathyroid hormone. However, no mechanisms for the survival advantage have been identified—it is only postulated. As these studies have been predominantly observational, the association between vitamin D or calcitriol/analog administration and survival is correlative only. No cause and effect conclusion can be made.

The consensus reached by the committees responsible for the KDOQI and KDIGO guidelines has taken these studies into consideration and recommends the monitoring and maintenance of vitamin D levels throughout the stages of chronic kidney disease. A fall in 1,25 hydroxy vitamin D is the first measurable change in mineral metabolism noted during the course of chronic kidney disease, long before the onset of hyperparathyroidism, hyperphosphatemia, or hypocalcemia. The nearly universal prevalence of bone mineral disorders in this population suggests strongly the need for vitamin D replacement.

One very interesting discovery regarding vitamin D replacement in this population is that administration of the precursor molecule, cholecalciferol, can result in significant increases in active 1,25 dihydroxy-vitamin D, even in patients on dialysis, perhaps owing to autocrine conversion at extra-renal sites. While the hope is that maintenance of normal vitamin D status will result in superior cardiovascular outcomes for our patients, those answers will not come for several years. Questions regarding the effect of vitamin D, calcitriol/analog replacement on bone metabolism, vascular calcification, insulin resistance, and cardiovascular disease will require long-term controlled studies in large numbers of patients. In the meantime, our best approach is to use the data that we have now, embark on the needed studies, and adjust our guidelines as better data emerge.

Eleanor Lederer, MD, is professor of medicine, Robley Rex VA Medical Center and University of Louisville School of Medicine in Louisville, KY.

The Rare **Kidney Stone** Consortium

By David S. Goldfarb

One might think that rare diseases are rare. But if one were to combine all the rare diseases that affect Americans, the overall prevalence is not rare at all. In fact, 30 million Americans, or roughly 10 percent of the population, are affected by a rare disease. Many of these disorders are severe and lead to a significant effect on people's lives and life expectancy. To bring new and concentrated attention to these often poorly studied disorders, 19 collaborative consortia were funded in 2009 by the Rare Disease Clinical Research Network, a project jointly sponsored by the National Institutes of Health and the Office of Rare Disease Research (see http://rarediseasesnetwork.epi.usf.edu). These consortia span a fascinating range, including diseases of the mitochondria, lysosomal storage diseases, and vasculitis.

The Rare Kidney Stone Consortium (RKSC) (see www.rarekidneystones.org) is making progress in the management of four rare genetic kidney stones that are often more severe than the usual stones that affect more than 10 percent of Americans. The consortium is trying to highlight these rare stones and make sure that they are not missed by physicians who may not be aware of diseases associated with them. When the diseases are recognized, they are often not managed optimally because of physicians' lack of experience. The result is more frequent recurrence of stones, more urologic procedures, and a higher prevalence of chronic kidney disease.

The principal investigator of the RKSC is Dawn Milliner, MD, a pediatric nephrologist at the Mayo Clinic in Rochester, MN, and an expert on primary hyperoxaluria. The disease is caused by a mutation of a liver enzyme. Although calcium oxalate stones are common in the general population, patients with primary hyperoxaluria have more frequent stones, and calcium oxalate crystals accumulate and damage the kidneys. If kidney function worsens, calcium oxalate can accumulate and damage the heart, eyes, and other organs. The ultimate treatment may be liver transplantation to replace the abnormal enzyme. Milliner and her group have established an international registry to determine which patients do well and which do not, while pioneering new treatments to safely eliminate oxalate from the blood and urine (1).

A second disorder is studied by our collaborators in Reykjavik, Iceland, headed by Vidar Edvardsson, MD. They are investigating deficiency of adenine phosphoribosyltransferase, a cause of dihydroxyadenine stones. Because these stones are very rare in the United States, we suspect that they are often missed and misidentified. Edvardsson is characterizing the Icelandic population and looking for evidence that Americans with this disorder are being incorrectly diagnosed (2).

The third disorder, Dent disease, is most often caused by a mutation in a chloride channel in the kidney. Too much calcium in the urine results in calcium stones. Many patients with the disease are seen by nephrologists who fail to order appropriate tests. The patients are being characterized by John Lieske, MD, at the Mayo Clinic and Lada Beara-Lasic, MD, at the New York University (NYU) School of Medicine.

The consortium is trying to highlight these rare stones and make sure that they are not missed by physicians who may not be aware of diseases associated with them.

The fourth disorder is cystinuria, a genetic condition in which the kidneys fail to reabsorb filtered cysteine. This amino acid is poorly soluble, appears in the urine in large amounts, and precipitates to form large, recurrent stones. Cystinuria is the most common of the four disorders, affecting as many as 10,000 Americans. I am the principal investigator of this project at the NYU Langone Medical Center (3). Some of my patients helped found the International Cystinuria Foundation (www.cystinuria.org), an organization devoted to providing educational support to people with cystinuria. We also are connected to the Cystinuria Support Network, an e-mail group that allows affected people to connect to one another for support and advice.

Last year, Michael Ward, PhD, of the department of chemistry at NYU, identified new inhibitors of cystine crystallization (4). One potential drug, cystine dimethylester, significantly slowed cystine crystal growth. A mouse model of cystinuria, the result of knocking out one of the mouse genes corresponding to one of the responsible human genes, was developed by Amrik Sahota, PhD, and Jay Tischfield, PhD, at the University of Medicine and Dentistry of New Jersey. The model is now being used to determine whether cystine dimethylester works to prevent stones not only in vitro, as Ward's work demonstrated, but in vivo as well. If it is shown to be effective and safe, we hope to proceed with studies in humans in the coming years.

The RKSC has been a successful consortium, developing registries, pioneering clinical research, and providing some hope to people affected by these rare and debilitating cases of kidney stones.

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David S. Goldfarb, MD, FASN, is chief of the nephrology section at the New York Harbor VA Medical Center, director of the kidney stone prevention program in the endourology section at Lenox Hill Hospital, and professor of medicine and physiology at the New York University School of Medicine.

Phosphate: Time for a Fresh Look at Dietary Control?

By Sharon M. Moe

Phosphate is a true uremic toxin. Cross-sectional studies in patients undergoing dialysis uniformly demonstrate an increased risk of mortality with increasing phosphate levels. The population-attributable risk of mortality in dialysis patients is markedly greater for phosphate than anemia or urea reduction ratio. Additional cross-sectional studies in patients with and without chronic kidney disease (CKD) who are not yet receiving dialysis have demonstrated that phosphate levels in the upper quartile or tertile within this normal range have increased cardiovascular and/or all-cause mortality. In vitro, animal, and some human studies demonstrate that control of extracellular phosphate levels attenuates the process of vascular calcification. Despite recognition of the importance of this uremic toxin, it remains a clinical challenge to control.

The level of blood phosphate is controlled by three hormone systems—parathyroid hormone, fibroblast growth factor 23 (FGF23)/Klotho, and the vitamin D axis—and each of these systems regulates the others. Despite this complex regulation, there is a fairly wide range of "normal" levels: from 3.0 to 4.7 mg/dL in most laboratories. In patients with CKD, the phosphate level rises with progressive kidney disease because of a failure of this homeostatic system leading to decreased ability to excrete a phosphate load. There is also a normal diurnal variation in phosphate levels, with a peak in the middle of the night and a nadir in the morning, even in CKD. This diurnal variation may also lead to the wide range of "normal" phosphate levels, inasmuch as patients do not get their blood drawn at the same time of day. But three other factors likely play a prominent role in this clinical conundrum.

The first is inadequate dialysis. The majority of total body phosphate is not in the extracellular space, so longer or daily dialysis is required to optimize removal. In the Frequent Hemodialysis Study, a randomized trial of daily versus standard dialysis, survival was greatest and the phosphate was lowest in the daily dialysis arm. Although these findings certainly do not constitute proof that removing more phosphate improves mortality, inasmuch as many other factors were also improved, the study was proof that daily dialysis is an effective therapy for phosphate removal.

The second is food additives—a hidden source of dietary phosphate. Unfortunately, nearly every prepackaged food type, whether in a can, a box, or frozen, has a phosphate-based preservative. The quantity is not shown on the food label, but whatever is eaten is highly bioavailable and therefore is rapidly absorbed. One study has shown that just advising dialysis patients to avoid prepackaged foods can lower blood phosphate levels.

The third is the source of dietary protein. Phosphate is a key component of all proteins. However, in grain-based sources of protein such as soy, and in nuts and beans, the protein is bound to phytate. Humans lack the enzyme phytase and thus cannot metabolize phytate, leading to decreased intestinal bioavailability of those protein sources of phosphate. By contrast, in meat and dairy sources of protein (casein), the phosphate is much more bioavailable, and thus a greater percentage of the phosphate will be absorbed.

In rats with CKD, this difference in phosphate levels between those fed with grain and those given casein (synthetically made) diets is substantial, and the differences also lead to worsened hyperparathyroidism, vascular calcification, and progressive kidney disease.

We recently completed a small pilot crossover trial comparing a vegetarian (nearly vegan except for eggs) diet to a meat diet, each containing 3 g sodium, 80 g protein, and 800 mg phosphate in patients with a mean estimated GFR of 32 mL/min. The vegetarian diet led to a decrease in phosphate levels by 0.3 mg/dL and decreased the FGF23 levels by nearly 30 percent. The first lesson learned from this study was that the estimates of phosphate content from vegetarian sources in the available research databases were very inaccurate. This is not terribly surprising, given that the actual phosphate content of grains depends a lot on the type of grain and the soil and water phosphate content where it was grown. The second lesson learned from this study was that it was nearly impossible to develop a diet incorporating all of the renal diet recommendations, even by experienced research dieticians. And yet, we hand our patients individual lists of different things to avoid and call them noncompliant when they cannot put it together in a single meal. The differences in the dietary sources of protein may also explain why hyperphosphatemia appears to be more common (or more severe) in the Western world than in other cultures.

Perhaps we need a fresh approach to kidney nutrition counseling. And perhaps this can be a simple message: Avoid canned and boxed foods, and eat vegetarian sources of protein. The latter will take some education of patients who are not vegetarian or vegan, but it is likely a much easier educational program than separate handouts for phosphorus, potassium, sodium, and protein. Long-term studies are needed to show the sustained efficacy of, and increased compliance with, such an approach, but we shouldn't give up dietary phosphate restriction. We should also push for the reduction of phosphate-based preservatives—or, at the very least, quantitation of those substances on food labels. Unfortunately, we are what we eat!

Sharon M. Moe, MD, is professor of medicine and anatomy & cell biology and director of the division of nephrology at Indiana University. School of Medicine.

Inhibitors: The Key to Controlling Vascular Calcification

By W. Charles O'Neill

Arterial calcification is a common problem in advanced kidney disease and contributes to the high prevalence of cardiovascular disease. There are two forms: neointimal calcification, associated with atherosclerosis, and medial calcification. The former is not exclusive to renal failure and occurs in anyone with atherosclerosis. It is unclear whether this has any clinical significance other than being a convenient marker of atherosclerosis. Medial calcification is independent of atherosclerosis and is strongly linked with chronic kidney disease (CKD). Recent data based on mammography show that there is a more than threefold risk of medial calcification in ESRD and that this risk may begin as early as stage 3 CKD.

Although disordered phosphate metabolism clearly plays a role in medial arterial calcification, it cannot by itself explain this problem, and strategies other than controlling hyperphosphatemia are needed. A large body of data implicates extracellular pyrophosphate (PPi), an endogenous inhibitor of hydroxyapatite formation, in arterial calcification. Humans lacking the ectoenzyme that produces PPi develop severe arterial calcification in childhood, and mice lacking the same enzyme also develop arterial calcification. Extracellular PPi may also be derived from intracellular PPi, and a mutation in the putative transporter (ANK) leads to ectopic calcification in mice, but primarily of joints rather than vessels.

Plasma levels of PPi are reduced in hemodialysis patients and correlate inversely with arterial calcification. This may be related to another key enzyme in extracellular PPi metabolism, tissue-nonspecific alkaline phosphatase (TNAP), which hydrolyzes PPi and induces arterial calcification when genetically overexpressed in vascular smooth muscle in vitro and in vivo. The activity of TNAP is increased in vessels from uremic rats, suggesting a pathologic role. Currently, little is known about the regulation of TNAP in vascular smooth muscle cells and why it is upregulated in renal failure.

Therapies based on pyrophosphate show promise as potential clinical tools. Both PPi and bisphosphonates (nonhydrolyzable analogs of PPi) inhibit arterial calcification in uremic rats, and recently developed small molecule inhibitors of TNAP can prevent arterial calcification *in vitro*. The doses of bisphosphonates required to inhibit vascular calcification *in vitro* are far greater than those used to inhibit bone resorption in humans. One potential drawback to this approach (and any potential therapy for ectopic calcification) is inhibition of bone mineralization, which requires a high local activity of TNAP to remove inhibitory PPi. Consequently, the nonhydrolyzable bisphosphonates, but not PPi, inhibit bone formation at doses required to prevent arterial calcification in rats.

Two other endogenous inhibitors of arterial calcification, matrix gla protein and osteopontin, also appear to act through direct inhibition of hydroxyapatite formation but probably do not play a primary pathogenic role in the vascular calcification of CKD, inasmuch as both are upregulated in vessels from uremic rats. Matrix gla protein requires vitamin K–dependent γ-carboxylation. Deficiency—either genetic or related to warfarin use—leads to vascular calcification in animals and humans. Osteopontin is, molecule for molecule, the most potent known inhibitor of hydroxyapatite formation, but deficiency does not lead to vascular calcification unless coupled with deficiency of another inhibitor. These proteins have limited therapeutic potential because matrix gla protein is extremely insoluble, and osteopontin has other inflammatory actions. However, vitamin K could be of benefit because patients with advanced renal failure may have vitamin K deficiency. Magnesium also inhibits hydroxyapatite formation and accounts for most of the inhibitory activity in plasma, but its therapeutic potential has not been explored.

Thiosulfate is another compound that can inhibit vascular calcification in vivo and in vitro and is often used to treat calciphylaxis. Although it is present endogenously, the levels are far below those required to inhibit calcification. It is widely assumed that thiosulfate acts by chelating calcium, but recent data indicate that its interaction with calcium ions is extremely weak and that there is no effect on hydroxyapatite formation or dissolution. Thus, its mechanism of action remains to be determined.

It is clear that the arterial wall has a propensity to calcify, even in the absence of altered mineral metabolism, and that endogenous inhibitors, particularly pyrophosphate, are required to prevent this. Thus, arterial calcification must be seen as a failure of these endogenous mechanisms. Although these inhibitors can be the basis for future preventive and therapeutic strategies, their unwanted effects on skeletal mineralization must also be considered.

W. Charles O'Neill, MD, is affiliated with the renal division at the Emory University School of Medicine. He is an inventor of a patent owned by Emory University related to compounds discussed in this article.

Practice Pointers

In this month's issue, ASN Kidney News editorial board member Edgar Lerma interviewed John Asplin, MD, FASN, medical director of Litholink Corporation in Chicago.

Updates on Kidney Stones

John Asplin

Please discuss the epidemiology of kidney stones in today's world. Have there been any new changes or trends? How about renal transplant recipients?

The most recent studies highlight how common kidney stones are in industrialized countries. It has been estimated that 12 percent of men and 7 percent of women in the United States will develop urolithiasis during their lifetime. There are racial differences in prevalence; kidney stones are twice as common in Caucasians as in African Americans. Prevalence rates are increasing in the United States, and this finding is replicated in other industrialized countries. Nephrolithiasis is more common in men, although the rates seem to be increasing in women so that the prevalence in women is starting to approach equality.

Kidney stones are uncommon in renal transplant recipients, occurring in fewer than 1 percent of recipients. A major issue concerning stones in transplantation is whether to allow living donors to qualify if they have had kidney stones. There is not a clear consensus on this issue. Many centers will allow stone formers to donate if the stone condition has been mild and the nondonated kidney does not contain stones. Some centers perform ureteroscopy after the donor kidney has been removed to ensure that the recipient receives a stone-free kidney. Obviously, there is considerable concern about stone passage in both the donor and the recipient because obstruction of a unilateral kidney is an emergency.

Please discuss some of the newer medications that have been linked to stone formation.

Topiramate and zonisamide are used to control seizures and as prophylaxis for migraine headaches. Both of these drugs inhibit carbonic anhydrase, leading to renal tubular acidosis. Urine chemistry determination reveals a high urine pH and low urine citrate, putting the patients at risk for calcium phosphate stone formation. Serum bicarbonate may be low or normal. If possible, patients who form stones while using these drugs should be given alternative treatments. If the drugs must be continued, then most experts treat with potassium citrate, although that approach has not been well studied.

Do you know of any specific diet fads linked to stone formation? How about bariatric surgery?

Of particular concern are very-high-protein diets, such as the Atkins diet. The high protein intake can lower urine pH and urine citrate as well as increase urine calcium excretion. Given that dietary protein is usually accompanied by purine, uric acid excretion will increase as well. This constellation will put the patient at increased risk for both uric acid and calcium oxalate stones.

As for bariatric surgery, we are seeing increasing rates of nephrolithiasis among patients who have had malabsorptive bariatric surgery such as Roux-en-Y gastric bypass or biliopancreatic diversion. Hyperoxaluria from excess intestinal absorption seems to be the main risk factor; in some cases it is so severe that oxalate nephropathy and loss of kidney function occur. Hyperoxaluria often does not manifest itself until 6–12 months after surgery, when the patient's food intake has increased. Purely restrictive procedures such as gastric banding do not appear to increase the risk of stone formation.

What is the stone clinic effect? Is it reality or myth?

The stone clinic effect refers to the reduction in stone formation that occurs when the rate of stone formation before a patient seeks treatment is compared with the rate of stone formation after the patient is seen in clinic, even if no significant therapeutic intervention was done. Whether this is due to dietary advice, improved compliance by the time a patient reaches a specialty clinic, or regression to the mean is not clear. It is a real phenomenon, given that reduced stone formation rates can be seen in the placebo arm of most randomized prospective studies of nephrolithiasis. Clinicians should be wary of studies that show a reduction in stone formation rate before and after an intervention because the cause may be merely the stone clinic effect. Proof of therapeutic efficacy requires an appropriate control group.

Do all patients with renal colic require referral to a urologist? What is stone expulsion therapy?

Not all patients need a urology referral for renal colic because the majority will pass the stone spontaneously. The size of the stone as shown by x-ray will identify patients who are likely to need urologic intervention. Stones less than 5 mm pass 80–90 percent of the time; those greater than 6 mm pass only 25 percent of the time. The indications for emergent stone removal include fever, intractable pain, persistent nausea and vomiting, and obstruction of a unilateral kidney.

Medical expulsive therapy refers to the use of medications that increase the rate of spontaneous stone passage. Calcium channel blockers and α-1 blockers (such as tamsulosin) have been reported to improve stone passage rates. Both drugs are well tolerated, although there seems to be more risk of hypotension with the calcium channel blockers. Randomized controlled trials are currently under way to define the utility of these drugs.

What are the various imaging modalities recommended for diagnosing kidney stones? Is there still a role for a flat plate radiograph of the abdomen?

Computed tomography (CT) is the preferred method for evaluating suspected nephrolithiasis. CT scans do not require intravenous or oral contrast medium, can be performed rapidly, reliably detect stones too small to be seen with other techniques, and may detect other diseases that cause flank or abdominal pain if the patient does not have stones. There are concerns that repeated CT scans may lead to excess radiation exposure. In many patients with calcium stones, x-ray of the kidney, ureters, and bladder will be sufficient to monitor the stone burden, reducing radiation exposure and cost. Ultrasound is not as sensitive as CT, but the lack of radiation makes it the preferred technique in pregnant women and young children. Uric acid stones, which are radiolucent on x-ray, can be visualized with either CT or ultrasound.

With the recent advances in urology (e.g., robotic surgery), is open surgery a thing of the past?

Urologists have three approaches for removing kidney stones. Extracorporeal shock wave lithotripsy can be used for stones in the renal pelvis or the ureter. The advantages are that it is a noninvasive outpatient procedure and requires minimal anesthesia. For properly chosen patients, the success rates are quite high. This treatment is not the preferred approach in patients with multiple stones, very large stones, stones in the lower pole of the kidney, or stones composed of cystine or brushite (calcium phosphate monohydrate).

Ureteroscopy is often the preferred approach for stones in the ureter. Stones may be removed by using a basket or a laser lithotripter. Now that ureteroscopes have become thinner and more flexible, stones in the renal pelvis can also be treated by ureteroscopy.

In percutaneous nephrolithotomy, a small incision is made in the flank, and a nephroscope is inserted in the renal pelvis. The stones can be destroyed with either an ultrasonic lithotripter or a laser. Large fragments can be removed via the nephroscope. This treatment is the preferred approach for large stones in the lower pole of the kidney, multiple stones, staghorn stones, or stones composed of brushite or cystine.

Please discuss the correct approach to first-time stone formers and recurrent stone formers. Is a 24-hour urine collection always necessary as part of the evaluation?

For adults presenting with their first kidney stone, usually an abbreviated evaluation focused on identifying more serious forms of nephrolithiasis is appropriate. Such an evaluation should include a routine chemistry panel, including determination of serum creatinine to assess kidney function, serum calcium to rule out hypercalcemic disorders, and serum bicarbonate and potassium to check for renal tubular aci-

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dosis. Urinalysis or urine culture should be obtained to ensure that there is no infection. Crystals may also be identified on urinalysis, but only the hexagonal plates of cystine or the coffin lids of struvite have diagnostic significance, inasmuch as calcium and uric acid crystals may be found in people without kidney stones.

If a stone has been collected it should undergo crystallographic analysis. If a kidney stone is not available for analysis, a cystinuria screening test should be performed. Finally, a radiologic evaluation is needed to ensure that the patient is truly a single stone former. Although a patient may have only a single symptomatic episode, a patient who is found to have multiple stones at initial presentation should be treated as a recurrent stone former. All children should have 24-hour urine chemistry determination at the time of initial presentation because the prevalence of genetic stone disease such as cystinuria and primary hyperoxaluria is greater in children than in adults. Patients presenting with their first stone should be told that there is a 50 percent chance of having at least one stone event in the next 8 years. They should also be advised to increase their fluid intake and to follow a low-salt diet.

Patients with recurrent kidney stones will need 24-hour urine chemistry determination to identify the metabolic abnormalities that will guide dietary and pharmacologic treatment. Urine chemistries vary considerably from day to day, so I recommend that at least two 24-hour urine collections be performed at the initial evaluation. Optimally, one collection will be on a day when the patient is at work and the other on a day the patient is at home. At minimum, a 24-hour urine study should include determinations of volume, calcium, oxalate, citrate, uric acid, creatinine, and pH. Additional tests such as those for sodium, urea nitrogen, potassium, phosphorus, sulfate, and ammonium provide great insight into the patient's diet and acid–base physiology. Supersaturation calculations are available from many laboratories and are a useful tool to monitor therapeutic efficacy.

Please discuss the association between metabolic syndrome and stone formation.

Metabolic syndrome has been associated with increased risk of uric acid nephrolithiasis. Patients with metabolic syndrome have a low urine pH resulting from inadequate ammonium excretion, obligating them to excrete a larger fraction of their daily acid load as titratable acid. Insulin is a regulator of proximal tubule ammonium production, and insulin resistance—a common component of the metabolic syndrome—appears to be the cause of reduced ammonium excretion. Reversing metabolic syndrome through weight loss should improve ammonium excretion and increase urine pH, but this approach has not been formally tested. Uric acid stones in these patients can be treated with alkali to raise urine pH, just as in all uric acid stone formers.

Certainly, there are specific prophylactic measures that one can take to avoid forming various types of stones. Please discuss.

Treatment can be tailored to the metabolic abnormality causing nephrolithiasis. Patients with idiopathic hypercalciuria can be treated with low-sodium low-protein diets and/or thiazide diuretics. Hyperoxaluria is most commonly treated with diet oxalate restriction and a normal calcium diet, which provides sufficient calcium to bind oxalate in the gut and reduce absorption. Hypocitraturia is treated with alkali supplements, most commonly potassium citrate. Hyperuricosuria is treated with a low-purine diet and/or allopurinol. Inasmuch as most uric acid stones are caused by excessively acidic urine, these patients are treated with alkali. Allopurinol is used in uric acid stone formers if they also have gout or if they have severe hyperuricosuria.

Are there any practice pointers you would like to leave for our readers?

A critical issue in treating patients is to improve urine flow rates. I do not instruct patients to drink a particular amount of fluid but rather give them a goal to consistently excrete 2.5 L urine per day. Patients' fluid needs vary with their rates of perspiration and loss of fluid via the gastrointestinal tract, so the same fluid prescription cannot be used for all patients. Patients will need to determine the correct amount of fluid intake for themselves, and they can do so by increasing fluid intake and then measuring 24-hour urine flow at home by using an empty milk jug as a guide.

Protease inhibitors have been shown to crystallize in the urinary tract and lead to stone formation. Indinavir has been the drug most frequently reported with this complication, but other protease inhibitors have been linked to stones as well. The risk of stone formation is increased by the low fluid urine flow rates that may be found in HIV-infected patients, caused by persistent fevers and/or diarrhea. Many patients do not need to have the drug discontinued but do need to improve fluid intake so that urine volume consistently stays around 2 L per day.

Some adults will need a full evaluation at the time of first stone presentation on the basis of employment requirements such as those used with airline pilots.

In this month's issue, ASN Kidney News editorial board member Edgar Lerma interviewed Kevin J. Martin, MB, FACP, professor of internal medicine and director, division of nephrology, Saint Louis University in St. Louis, MO.

CKD-MBD Trends

Kevin J. Martin

Please define chronic kidney disease—mineral bone disorder (CKD-MBD). Is this interchangeable with renal osteodystrophy?

The term "CKD-MBD" was introduced to acknowledge the spectrum of abnormalities in bone and mineral metabolism that occur with CKD. Although traditionally the focus has been on bone, hence the term "renal osteodystrophy," this term is really meant to indicate the alteration in bone morphology in patients with CKD. It is now realized that the manifestations of disturbed bone and mineral metabolism are more widespread. Thus, CKD-MBD is characterized by

- a systemic disorder of mineral and bone metabolism caused by CKD and manifested by either one or a combination of abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism.
- abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- vascular or other soft tissue calcification.

Please discuss the intricacies of various PTH measurement assays.

The assay of PTH and blood has evolved over the years in such a manner that two-site immunometric assays are in widespread use. Although it was initially thought that such assays would measure intact PTH, it is now well recognized that most, if not all, of these assays will also detect a family of N-terminally truncated PTH peptides that circulate and accumulate in the blood of patients with advanced kidney disease.

The various PTH assays in use have varying sensitivities to detect these fragments, and this leads to widespread variation in results between the various commercial assays in use today. This is compounded by the fact that there is no universally accepted PTH preparation as an assay standard. It is therefore necessary to know the details of the particular assay in use, so that one may put the results obtained into proper perspective. Thus, some assays recognize N-terminally truncated PTH fragments to a great extent and yield high values, whereas others minimize the interaction with these peptides and result in lower values. Appropriate "target values" for PTH will thus vary widely depending on the assay used.

This problem is exemplified by the PTH recommendations laid out by the Kidney Disease: Improving Global Outcomes (KDIGO), which state that a reasonable target range for intact PTH in the setting of ESRD would range from two to nine times the upper limit of normal. This recommendation is somewhat problematic because of the accumulation of these fragments in patients with advanced kidney disease out of proportion to that seen in patients with normal renal function; therefore, the use of multiples of the upper limit of normal is likely not appropriate. The best advice at present is to be familiar with the particular assay in use and with knowledge of its performance to construct a reasonable range for targeting the control of hyperparathyroidism.

What is your take on the administration of vitamin D supplements (e.g., cholecalciferol) to CKD patients?

It is well recognized that there is a progressive decline in the levels of 1,25-dihydroxyvitamin D throughout the course of CKD. Many mechanisms are involved in this process, including phosphate retention, increases in FGF-23 levels, decreases in renal mass, suppression of 1-hydroxylase by uremic toxins, and, importantly, decreases in 25-hydroxyvitamin D, which are quite common in patients with CKD, particularly in those with proteinuria. Thus, levels of 25-hydroxyvitamin D below the lower limits of normal, estimated to be 30 ng/mL, are common in patients with CKD.

The practice guidelines of KDOQI recommend trying to supplement nutritional forms of vitamin D to correct the low levels of 25-hydroxyvitamin D, and they include recommendations for the therapeutic use of ergocalciferol. However, these recommendations perform poorly in clinical practice: correction of low levels of 25-hydroxyvitamin D to above 30 ng/mL is achieved in only approximately 50 percent of patients. More recent studies indicate that the use of cholecalciferol might be more effective because this results in a longer half-life for 25-hydroxyvitamin D in plasma. The implications of correcting the low levels of 25-hydroxyvitamin D to normal are not yet fully clear, although it appears that this will allow for a decreased need for active vitamin D sterols, and there may be other benefits as well. Although there are not yet any definitive studies, ergocalciferol and cholecalciferol are widely used in clinical practice, and further studies of the optimal regimen to achieve vitamin D repletion are required.

In your practice, do you use the recommended target PTH levels? Please discuss target PTH levels for stage V CKD in relation to the KDOQI and KDIGO recommendations.

The KDOQI practice guidelines recommended a desirable PTH range of 150–300 pg/mL, based on evidence from bone biopsy studies that demonstrated that this range was associated with a relatively normal bone turnover. However, there was wide variation in the data on which it was based, and the particular PTH assay that was used for these studies is no longer available. The later recommendations from KDIGO have broadened this range as a multiple of the upper limits of normal, that is, two to nine times the upper limits of normal as a reasonable target range. As discussed above, this is complicated by the accumulation of various PTH peptides that may cross-react in various PTH assays. These recommendations reflect the frustration with, and variability in, PTH assays such that this broad range has recently come to be associated with considerable uncertainty with regard to treatment targets.

A large body of epidemiologic evidence, however, both in the United States and more recently from South America and Europe, looking at overall mortality of the patients, shows that the lowest mortality appears to be associated with PTH ranges more in keeping with the original KDOQI recommendations. It is reasonable to consider these outcome-related ranges as targets rather than to focus on one parameter of bone turnover, for which it is now recognized that PTH is a relatively poor marker. Accordingly, in our current practice, using the intact PTH assay that is widely used among large dialysis providers, we believe that a reasonable range is 150–300 pg/mL. It should be emphasized that these ranges should be considered "soft," and may be extended, particularly on the higher side, without obvious detriment to clinical care.

The PTH assay results should be considered in conjunction with other parameters of bone and mineral metabolism, such as calcium and phosphate and alkaline phosphatase measurements, and with existing comorbidities. These considerations may move the desired range up or down according to the clinical circumstances.

When is a bone biopsy required in these patients?

Bone biopsy is not widely used in clinical practice because it is an invasive technique and requires specialized laboratory facilities for analysis. It is generally recommended that one might consider biopsies when the biochemical markers are indeterminate. Thus, a patient who describes bone pain, and whose PTH is within the target range, but in whom alkaline phosphatase is elevated, may well have hyperparathyroidism, and a bone biopsy would be helpful in guiding treatment. It was formally recommended that a bone biopsy is required in patients who are scheduled to undergo parathyroidectomy, but in the absence of aluminum-based phosphate binders, and if serum aluminum is low, this is probably not necessary.

What is calciphylaxis? What are the available treatment options for these patients? Is there a role for parathyroidectomy?

Calciphylaxis is a syndrome of vascular calcification, small vessel thrombosis, and tissue necrosis that is seen almost exclusively in patients with advanced kidney disease. The cause of calciphylaxis is not precisely known, although several risk factors are known to be associated with it. Because of the poor prognosis associated with calciphylaxis, many treatment options are initiated, often in combination. Thus, the treatment options may include aggressive phosphate control by the use of non–calcium-containing phosphate binders, more frequent or longer dialysis, and consideration of parathyroidectomy, if the calciphylaxis is associated with moderate to severe hyperparathyroidism. Cinacalcet, a calcimimetic, may be considered as an alternative to parathyroidectomy. In recent years, it has been noted that much of the calciphylaxis that occurs is proximal in the thighs or abdomen and is often not associated with severe hyperparathyroidism.

Anticoagulation with warfarin should be discontinued, and active vitamin D sterols should also be withdrawn. Hyperbaric oxygen may be helpful in achieving wound healing. More recently, the use of sodium thiosulfate has been advocated and appears to be efficacious, at least in some instances. Given that many thera-

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pies are often initiated together, it is often difficult to decide if there is more benefit associated with one form of treatment or another.

With regard to CKD-MBD, what is your treatment approach to patients with stage III–IV CKD and stage V CKD?

Inasmuch as abnormalities in bone and mineral metabolism begin early in the course of CKD, it is desirable to initiate treatment as early in the course of kidney disease as possible. Current practice recommendations are to screen for abnormalities in bone and mineral metabolism by the early measurement of intact PTH and, if PTH is elevated, to consider initiating treatment.

The initial step in treatment would be to measure the levels of 25-hydroxyvitamin D and, if they are low, to try to bring them into the normal range. If this is not sufficient to control the hyperparathyroidism, beginning an active form of vitamin D, such as calcitriol, paricalcitol, or doxercalciferol, should be considered. Although studies in experimental animals have shown the efficacy of phosphate restriction even in the early stages of CKD, one could consider efforts to decrease dietary phosphate intake or consider the use of phosphate binders, although these are not yet approved for use in early CKD.

As kidney disease advances, the need for active forms of vitamin D becomes more common, and phosphate binders are indicated when hyperphosphatemia occurs. In stage V CKD, or in patients receiving dialysis, the initial approach is to control phosphate first, then to correct hypocalcemia, to use active vitamin D sterols, and if this is insufficient to control PTH to target values, then to consider the addition of a calcimimetic agent. In terms of the types of phosphate binders used, one has to be cognizant of the existence of vasculature calcification and the risk of its progression and to consider limiting the ingestion of calcium-containing phosphate binders. Although this approach is somewhat controversial at present, it appears to be a prudent one, especially in the presence of existing vascular calcification.

When do you usually start calcimimetic therapy?

In patients receiving dialysis, it is our practice to try to control hyperparathyroidism with phosphate control and active vitamin D sterols. As you know, there is a broad spectrum of patients, some who are hypocalcemic and some of whom have serum calcium values at the upper limits of normal. The former are easily treated with active vitamin D sterols, whereas in the latter, the use of active vitamin D sterols may be limited by a tendency to hypercalcemia. If hyperparathyroidism cannot be controlled to target values, then the addition of a calcimimetic agent is indicated. It is our practice to use this in addition to the other measures.

What changes can be expected with CKD-MBD after successful kidney transplantation?

In general, the abnormalities associated with CKD-MBD begin to improve after successful kidney transplantation. The abnormalities may be influenced by concomitant therapy and, indeed, by a previous history of CKD, such that many patients come to transplantation with adynamic bone disease, which may be the result of the time spent receiving hemodialysis, or indeed with complicating factors, such as prior steroid therapy or postmenopausal osteoporosis. Further steroid therapy after transplantation is associated with bone loss, and it should be assessed in terms of fracture risk and treatment undertaken if necessary. The extent of the improvement in CKD-MBD after transplantation will, of course, vary according to the level of kidney function achieved.

What are the treatment options for osteoporosis with CKD? Please discuss bisphosphonates, PTH, and denosumab.

Osteoporosis and other causes of low bone density often occur in patients with CKD throughout the entire spectrum of patients seen. Many of the agents used for the treatment of osteoporosis, such as bisphosphonates, are problematic, mainly because of a scarcity of studies, the long half-life of bisphosphonates in bone, and the possible presence of adynamic bone disease. In general, a precise diagnosis should be made before therapy is initiated. In recent years, other options for the treatment of osteoporosis have included intermittent injections of PTH, and there are a few data to support this approach in patients with CKD. The most recent therapy with denosumab has not been studied in detail in osteoporosis associated with CKD, but it may be a reasonable option, at least in some patients.

What criteria do you use to recommend patients for parathyroidectomy?

Parathyroidectomy should be considered for patients who have severe hyperparathyroidism that cannot be controlled by medical means. The failure to control hyperparathyroidism may be from inability to control serum phosphorus or persistent hypercalcemia, which limits the use of active vitamin D sterols, and patient adherence may limit the use of calcimimetic agents. Then, parathyroidectomy should be considered.

Do you have any practice pointers for our readers?

The most important practice pointer at present is to consider the treatment of abnormalities in bone and mineral metabolism early in the course of CKD and to begin measures in an attempt to limit the severity of the problem. In patients with advanced CKD, consideration of associated comorbidities may be useful in deciding on a particular approach or combination of approaches to treatment.

New Agents Hold Promise in Diabetes Treatment

Sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors and bile acid sequestrants hold promise for the treatment of type 2 diabetes. Both were among the agents highlighted in the symposium, "Novel Therapies for Type 2 Diabetes -- Today and Tomorrow," at the American Diabetes annual meeting in San Diego

SGLT-2 inhibitors, eight of which are in clinical trials, are the first class of drugs to target renal glucose reabsorption for treating diabetes, said Ernest M. Wright, PhD, DSc, of UCLA. By increasing the urinary excretion of glucose, SGLT2 inhibition reduces blood glucose levels.

"Reabsorption of glucose in the kidney is not essential for life," as illustrated by the benign nature of familial renal glycosuria, Wright siad. However, this novel class of therapies may have a downside. "So far, there are no remarkable adverse effects, but since SGL2 expression occurs throughout the body, we need to be curious about off target sites," he said.

Among the SGLT2 compounds in development for blood glucose control are dapagliflozin.

Researchers presented results of a 104-week phase 3 study of dapagliflozin. Sustained reductions in blood glucose levels as well as body weight characterized study patients taking dapagliflozin added to metformin. In contrast, patients taking glipizide added to metformin gained weight Change from baseline in HbA1c in patients receiving glipizide plus metformin was 0.02 percent , compared to -0.48 percent for those treated with dapagliflozin (dap) 2.5 mg plus metformin (met); -0.58 percent for patients on dap 5 mg plus met; and -0.78 percent for those on dapa10 mg plus met. However, genital infections or urinary tract infections were more common in patients taking dap added to met.

David J. Mangelsdorf, PhD, of University of Texas Southwestern Medical Center at Dallas spoke about bile acid sequestrants (BASs) during the symposium on novel therapies.

The potential of bile acid sequestrants to improve blood glucose levels is not news. The agent's impact on glucose as well as cholesterol homeostasis was noted almost two decades ago. "We now know that this is a general feature of bile acid sequestrants," said David J. Mangelsdorf, PhD, of University of Texas Southwestern Medical Center at Dallas.

The introduction of HMG-CoA reductase inhibitors, or statins, has reduced the clinical use of BASs in tackling hyperlipidemia. However, these agents may play a role n type 2 diabetes therapy.

BASs absorb bile acids (BAs) in the intestine and inhibit enterohepatic circulation of BAs by preventing their reabsorption, resulting in increased excretion of BAs in the stool. In order to produce more BAs to compensate for the stool loss, the liver converts cholesterol into BAs, thereby lowering blood levels of cholesterol. BASs promote glucose homeostasis by suppressing glycogenolysis through the glucagon-like peptide 1 (GLP-1), a potent anti-hyperglycemic hormone that induces glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. When plasma glucose concentration is in the normal fasting range, GLP-1 no longer stimulates insulin, and hypoglycemia does not occur.

Thus far, colesevelam hydrochloride is the only BAS with FDA approval for both glycemic and lipid management. Colesevelam's use is limited by its ability to increase triglyceride levels in patients with type 2 diabetes.

The symposium also included presentations on peroxisome proliferator-activated receptor (PPAR) agonists. Several PPAR-γ agonists are already approved for the treatment of type 2 diabetes: thiazolidinediones and the insulin-sensitizing drugs rosiglitazone and pioglitazone.

The scientific—and pharmaceutical—community's interest in PPARs as drug targets is based on their effects on insulin sensitivity, atherosclerosis, and inflammation, said Jorge Plutzky, MD, of Harvard Medical School. Studies have shown that activating PPAR-γ may help prevent diabetic nephropathy by blocking the effects of glucose and renin-angiotensin-aldosterone system (RAAS) in triggering podocyte apoptosis.

Researchers' interest in the PPARS, however, is accompanied by substantial caution owing to the side-effects associated with the agents. They include bone fractures, fluid retention, weight gain as well as bladder cancer and cardiovascular risk.

"We face the issue of separating PPARs as a target from the issues seen with various PPAR-targeting drugs, but biologic studies continue to underscore the importance of the target itself," said Plutzky.

Charles F. Burant, MD, PhD, of the University of Michigan Medical concluded the symposium by highlighting fatty acid elongases, 1-beta HSD1 inhibitors, and G-protein-coupled receptors.

While there are numerous targets for diabetes drug development, "there is no perfect drug," he said. "There is no perfect target. Expecting that there is one is unreasonable."

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Journal View

Is Cranberry Useful in Preventing Recurrent Urinary Tract Infections?

Cranberry capsules aren't as effective as trimethoprim-sulfamethoxazole (TMP-SMX) in preventing recurrent urinary tract infections (UTIs), but TMP-SMX is associated with high rates of emerging antibiotic resistance, concludes a trial published in the *Archives of Internal Medicine*.

The randomized trial included 221 premenopausal women with a history of recurrent UTIs: at least three symptomatic infections in the previous year. In double-blind, double-dummy fashion, patients were assigned to receive prophylactic TMP-SMX 480 mg once daily, or cranberry capsules 500 mg twice daily. Over 1 year of treatment, the rates and numbers of symptomatic UTIs were compared between groups. The development of antibiotic resistance in native *Escherichia coli* was monitored as well.

During the study year, patients taking cranberry capsules had about twice as many infections as those taking antibiotics: 4.0 versus 1.8. At least one infection occurred in 78.2 percent versus 71.1 percent of patients; the median time to initial recurrence was 4 versus 8 months, respectively.

However, prophylactic TMP-SMX was associated with high rates of antibiotic resistance. Fecal *E. coli* isolates resistant to TMP-SMX were found at 1 month in 86.3 percent of the antibiotic group versus 23.7 percent of the cranberry group. Patients taking antibiotics also had higher rates of asymptomatic bacteriuria *E. coli* isolates as well as increased rates of trimethoprim, amoxicillin, and ciprofloxacin resistance. The differences in antibiotic resistance resolved 3 months after discontinuation of TMP-SMX.

Prophylactic antibiotics are widely used for prevention of recurrent UTIs. However, problems with antibiotic resistance have led to renewed interest in the potential for cranberry to reduce recurrent UTI risk.

The new trial found a lower rate of recurrent UTIs with prophylactic TMP-SMX than with cranberry capsules. However, this benefit of TMP-SMX was accompanied by high rates of antibiotic resistance. A formal cost-utility analysis of these two alternatives is planned [Beerepoot MAJ, et al. Cranberries vs. antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. *Arch Intern Med* 2011; 171:1270–1278].

Desensitization Shows Survival Benefit in Kidney Transplant Candidates

For HLA-sensitized patients awaiting a kidney transplant, desensitization therapy followed by HLA-incompatible kidney transplantation leads to better survival than continued waiting for a compatible organ, reports a study published in the *New England Journal of Medicine*.

The study included a "treatment group" of 211 HLA-sensitized patients who received an HLA-incompatible living donor kidney after undergoing desensitization treatment with plasmapheresis and low-dose intravenous immune globulin from 1998 through 2009. They were carefully matched to patients who continued to receive dialysis or who underwent dialysis or HLA-compatible kidney transplantation.

The Kaplan-Meier estimated survival for patients undergoing desensitization therapy was 90.6 percent at 1 year, 85.7 percent at 3 years, and 80.6 percent at both 5 and 8 years. This was significantly higher than for the "dialysis-only" control individuals, for whom survival was 91.1 percent at 1 year, 67.2 percent at 3 years, 51.5 percent at 5 years, and 30.5 percent at 8 years. It was also superior to the "dialysis-or-transplantation" group: 93.1, 77.0, 65.6, and 49.1 percent, respectively. Desensitization was linked to better survival at all levels of donor-specific anti-HLA antibody.

For HLA-sensitized patients, depletion of donor-specific antibodies may allow timely living donor kidney transplantation as an alternative to remaining on the waiting list. The new study suggests that desensitization therapy provides a significant survival advantage compared with continued dialysis or later HLA-compatible kidney transplantation. "By 8 years, this survival advantage more than doubled," the researchers write [Montgomery RA, et al. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med* 2011; 365:318–326].

As Diabetes Increases, So Does Diabetic Kidney Disease

Over the past two decades, the rates of diabetic kidney disease (DKD) in the United States have increased in proportion to the rising prevalence of diabetes, reports a study published in the *Journal of the American Medical Association*.

The researchers analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) 1988 to 1994, NHANES 1999–2004, and NHANES 2005–2008. On the basis of hemoglobin A1c level and use of glucose-lowering drugs, diabetes was present in 8.2 percent of individuals in NHANES III, 11.1 percent in NHANES 1999–2004, and 13.4 percent in NHANES 2005–2008.

On the basis of a urine albumin-to-creatinine ratio of 30 mg/g or higher and/or a GFR of less than 60 mL/min per 1.73 m^2, the prevalence of DKD was 2.2 percent in 1988–1994, 2.8 percent in 1999–2004, and 3.3 percent in 2005–2008. This trend reflected the rising prevalence of diabetes; among individuals with diabetes, the proportion with DKD was unchanged.

The use of glucose-lowering drugs by diabetic individuals increased from 56.2 percent in NHANES III to 74.2 percent in NHANES 2005–2008. The use of renin-angiotensin-aldosterone system inhibitors increased from 11.2 percent to 40.6 percent.

The percentage of diabetic individuals with impaired GFR increased significantly, from 14.9 percent to 17.7 percent. The albuminuria rate decreased nonsignificantly, from 27.3 percent to 23.7 percent.

These cross-sectional NHANES data show an increase in DKD in proportion to the rising prevalence of diabetes in the United States. Among people with diabetes, the prevalence of DKD has remained about the same, despite increased use of diabetes therapies. The researchers write, "[A]dditional interventions are needed to prevent the development of diabetes and to target GFR loss once diabetes is diagnosed." [de Boer IH, et al. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011; 305:2532–2539].

Ambulatory BP Data Predict Renal and Cardiovascular Risks in Chronic Kidney Disease

In patients with chronic kidney disease (CKD) not yet receiving dialysis, ambulatory BP monitoring improves the ability to predict renal and cardiovascular events, according to a study published in the *Archives of Internal Medicine*.

The Italian multicenter cohort study included 436 patients with stage 2–5 CKD who were not receiving dialysis. At baseline, the GFR was 42.9 mL/min per 1.73 m^2; diabetes was present in 36.5 percent of patients and cardiovascular disease in 30.5 percent. Office and ambulatory BP data were compared for their ability to predict time to renal death (ESRD or death) and time to fatal and nonfatal cardiovascular events. The median follow-up time was 4.2 years.

The mean office BP was 146/82 mm Hg. During ambulatory monitoring, the daytime BP was 131/75 mmHg and the nighttime BP 122/66 mmHg. At follow-up, 155 patients had reached the renal endpoint, and 103 had reached the cardiovascular endpoint.

Patients with daytime systolic BP greater than 126 to 135 mmHg had a higher rate of cardiovascular events: adjusted hazard ratios (HR) of 2.23 at a level of 136–146 mmHg and 3.07 at higher than 146 mmHg. The same groups were at increased risk of renal death: HR 1.72 and 1.85, respectively.

Patients with nighttime systolic BP greater than 106–114 mmHg were at increased risk of the cardiovascular endpoint: HR 2.52 at 125–137 mmHg and 4.00 at greater than 137 mmHg. They were also at

increased risk of renal death: HR 1.87 and 2.54, respectively. The rates of both outcomes were higher in patients who were "nondippers" and "reverse dippers" receiving ambulatory BP monitoring. Office BP measurements did not predict either outcome.

Ambulatory BP monitoring provides additional prognostic value in patients with essential hypertension. The new study suggests that ambulatory BP measurement—especially nighttime BP data—allows more accurate assessment of adverse renal and cardiovascular outcomes in patients with CKD who are not receiving dialysis. By contrast, office BP measurements provide little or no useful information about these risks [Minutolo R, et al. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011; 171;1090–1098].

Tacrolimus Linked to Allergies after Kidney Transplantation

The use of tacrolimus for immunosuppression after kidney transplantation may be associated with an increased risk of allergies, suggests a study published in *Clinical and Experimental Allergy*.

The researchers compared rates of allergic sensitization and allergic disease in two groups of kidney transplant recipients: 100 patients who received tacrolimus-based immunosuppression and 100 who received cyclosporin-based immunosuppression. Allergic symptoms were assessed by questionnaire. Sensitization was assessed by skin prick tests and measurement of specific IgE against common food and airborne allergens (such as pollens, dust mite, and pet dander).

Evidence of allergic sensitization was found in 34 percent of patients receiving tacrolimus versus 20 percent receiving cyclosporin. In both groups, sensitization was mainly against inhaled allergens. Clinically significant allergy symptoms were present in 15 percent of the tacrolimus group versus 8 percent of the cyclosporin group; this difference was not significant. On multivariate analysis, tacrolimus treatment was the only factor significantly associated with increased sensitization risk.

Type 1 allergic reactions are common after organ transplantation, even though patients are receiving T cell–targeted immunosuppressive drugs. As in a previous study, the authors found higher rates of sensitization, and possibly clinical allergy, in patients receiving the calcineurin inhibitor tacrolimus versus cyclosporin.

Tacrolimus may have a differential effect on T-helper 2–mediated immune responses. The authors discuss the implications for patient management, including the need for accurate recognition and prompt treatment of allergic reactions after transplantation [Gruber S, et al. Allergic sensitization in kidney-transplanted patients prevails under tacrolimus treatment. *Clin Exp Allergy* 2011; 41:1125–1132].

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