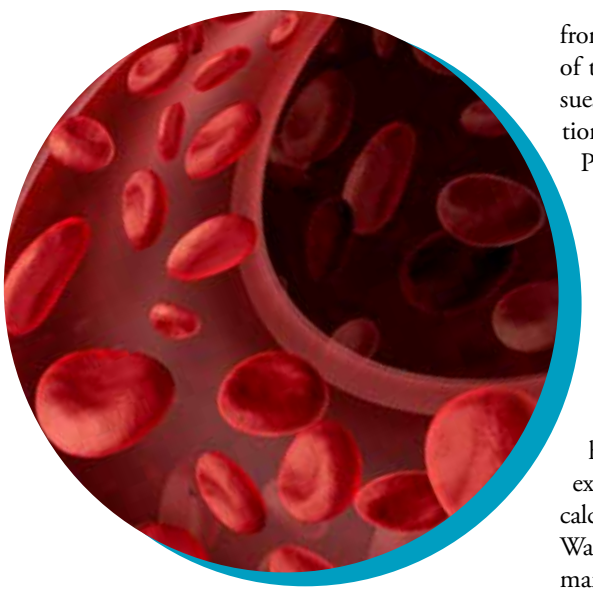
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# KidneyNews

February 2015 | Vol. 7, Number 2

## Small Changes in Blood Acidity May Affect CKD Patients' Health



Very small changes in pH levels in the blood may affect renal calcium reabsorption and parathyroid hormone (PTH) secretion, new research suggests. The findings, which are published in the *Journal of the American Society of Nephrology*, could have important implications for the health of patients with chronic kidney disease (CKD).

"In CKD, calcium and phosphate lost from the bone can end up in the walls of the blood vessels and in other soft tissues, causing potentially serious complications," said senior author Donald Ward, PhD, of the University of Manchester, in the UK. "The key protein that controls our blood calcium levels is the calcium-sensing receptor, and what we have found is that the mild acidity, or acidosis, that is often seen in CKD is sufficient to impair this protein from working properly."

In their efforts to uncover the health effects that patients with CKD experience due to the excess release of calcium and phosphate from the bones, Ward and his team found that in both human embryonic kidney cells and bovine parathyroid cells, slightly decreasing the extracellular pH from 7.4 to 7.2 rapidly inhibited intracellular calcium mobilization through the calcium-sensing receptor, whereas raising extracellular pH to 7.6 increased responsiveness to extracellular calcium. "It was known before that large changes in acidity—larger than would normally be seen in human blood—could affect calcium-sensing receptor activity," Ward said. However, what we have found here is that even relatively mild increases in blood acidity, similar to those commonly seen in CKD, could also inhibit the receptor in cell experiments in our laboratory."

Also, pH elevation suppressed PTH secretion from human parathyroid cells, while acidosis increased PTH secretion. The findings suggest that acid-base disturbances may affect the control of parathyroid function and calcium metabolism. While other pH-sensitive membrane proteins may also be involved, the extracellular pH changes had no effect in cells lacking the calcium-sensing receptor, or incubated in low extracellular concentrations of calcium.

Because metabolic acidosis and secondary hyperparathyroidism are both common consequences of CKD, the study's results point to a mechanistic link between the two. Also, the observation that raising extracellular pH promotes calcium-sensing receptor–mediated suppression of PTH secretion points to a new therapeutic strategy for treating secondary hyperparathyroidism in CKD.

"Past studies showed that extracellular pH is capable of affecting calcium-sensing

*Continued on page 6*

## *CKD Prevalence Stable, but Higher in Older Adults, Report Says*

The US prevalence of end stage renal disease (ESRD) continues to increase, but the rate of new cases may be leveling off. Meanwhile, mortality among patients on dialysis or with a kidney transplant continues to decline. Those are among the key findings of the recently released 2014 US Renal Data System Annual Data Report.

The report also finds that the prevalence of chronic kidney disease (CKD) has remained relatively stable, but continues to increase in the Medicare population. The 2014 report on the "state of kidney disease" in the United States was released by the US Renal Data System (USRDS) Coordinating Center, based at the University of Michigan in partnership with Arbor Research Collaborative for Health. Rajiv Saran, MD, is director of the USRDS Coordinating Center and associate director of the University of Michigan's Epidemiology and Cost Center.

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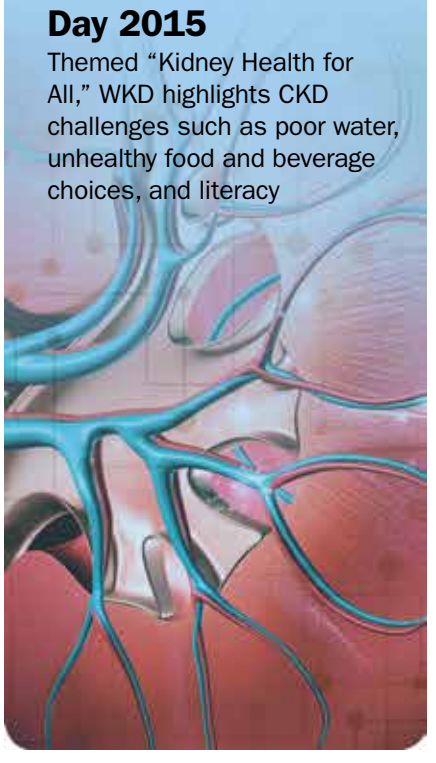
## Inside





# CKD Prevalence Stable

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### CKD remains stable, but higher in older adults

The USRDS is a national data system that collects, analyzes, and distributes information on kidney disease trends. Based on data from the National Health and Nutrition Examination Survey (NHANES), the report suggests an overall CKD prevalence of 13.6 percent.

Saran noted that while CKD prevalence was "certainly stable" during the periods 1999–2004 and 2007–2012, it was about 30 percent higher than in the 1988–1994 NHANES cohort.

"It's 13.6%, which is a pretty high prevalence," he said in an interview. "Let's say conservatively even if it's 12% . . . that is still higher than the prevalence of diabetes in the general population. That fact is not well-recognized."

Medicare data suggest an ongoing increase in CKD among Americans aged 65 years or older. In 2012, the most recent year for which data were available, the prevalence of recognized CKD in the Medicare population was 10.4 percent.

That is consistent with recent evidence suggesting that age may be the single strongest risk factor for CKD. "When we look at the risk factors for CKD, we look at diabetes, we look at hypertension, we look at BMI/obesity, the one thing that sticks out and has the highest odds ratio in terms of the strength of that relationship is age," Saran said. The growing body of evidence on CKD and age has "practical implications for screening, prevention, risk stratification, and treatment," according to the USRDS report. "Another point I'd like to make is, the prevalence of urine testing leaves a lot to be desired," Saran added. "Even in the Medicare data, only about 40 percent of diabetics are receiving the urine test. So it tells you that there's still lots of room for improvement, even among those that have clear-cut, known risk factors."

Although care patterns are difficult to assess, data suggest that while 91 percent of Medicare patients with CKD see a primary care physician and 62 percent see a cardiologist within a year of diagnosis, only 31 percent see a nephrologist. For patients with stage 3 to 5 CKD, the rate of nephrologist care increases to 55 percent.

All-cause mortality continues to decline among Medicare patients with CKD. But these patients remain at much higher risk of death than those without CKD, a risk that is "multiplied" for CKD patients with cardiovascular disease or diabetes. Cardiovascular morbidity remains very high among Medicare patients with CKD—about 70 percent, compared to 35 percent in patients without CKD.

The report also highlights the ongoing, age-related increase in hospitalizations for acute kidney injury (AKI)—a diagnosis associated with declines in both renal and functional status. Less than 20 percent of patients see a nephrologist within one year of AKI hospitalization, even though more than 90 percent undergo follow-up serum creatinine testing.

### Continued declines in ESRD incidence

For the third consecutive year, new cases of ESRD declined, with 114,813 new cases in 2012. In that year, the adjusted incidence rate was 353 per million per year—the lowest since 1997.

The population prevalence of ESRD continued to increase, although there were encouraging signs that the rate of growth may be slowing. "[T]he percentage increase in 2011 and 2012 was the lowest recorded over the last three decades," according to the USRDS report. At the end of 2012, there were a total of 636,905 dialysis and transplant patients receiving treatment for ESRD.

Analysis of Healthy People 2020 goals showed that about one-third of patients see a nephrologist at least one year before the start of renal replacement therapy. Nearly all mortality targets have been met, including promising trends in overall and cardiovascular mortality among dialysis and transplant patients.

Clinical indicators of hemodialysis care are also improving—nearly 80 percent of patients now have an ateriovenous fistula or graft during the first year. Mean hemoglobin levels have declined, reflecting changes in erythropoietin use. Although mortality rates continue to decline, they are up to eight times higher than for matched Medicare patients without ESRD.

Transplantation rates have decreased, while the percentage of dialysis patients wait-listed continues to increase. In 2012, nearly 29,000 patients were added to transplant waiting lists. For those who do receive a transplant, one-year survival rates are excellent: 96 percent for deceased donor transplant recipients, and 99 percent

for living donor transplant recipients.

The incidence of pediatric ESRD remained stable, with 1161 cases in 2012. At the end of that year, nearly three-fourths of children with ESRD had a functioning kidney transplant.

### Can nephrologists help keep the trends going?

The slow but steady decline in ESRD is encouraging news, Saran said. "But the question is what's causing [it] and can we accelerate that?" Noting that more in-depth studies are planned, he speculatesd on some possible reasons.

*Increased recognition of CKD*. "Certainly by claims, we notice that there is greater recognition of CKD in the health systems, by providers," Saran said. He said near-universal eGFR reporting has been an important contributor to the increased recognition of CKD. "There's better care of CKD, and there's better detection and care of upstream CKD risk factors such as diabetes and hypertension," Saran said. "So there may be a slower progression of CKD overall. Over time, perhaps, CKD in general is progressing slower, so people are not reaching ESRD as quickly as they used to in different settings."

*Changes in risk factors*. Saran also noted improvement in risk factor profiles nationwide, including stabilization of obesity rates and reduction in cardiovascular mortality.

*Starting dialysis later*. "In recent years there has been some evidence that earlier start to dialysis is not that advantageous, as some physicians had long believed," said Saran. So it could be that nephrologists may be starting dialysis "a little bit later." If so, "that could somewhat artificially lower the incidence of ESRD."

What can nephrologists do to keep that trend going? "Raising awareness, raising the ante for upstream CKD, earlier stages of CKD, and improving the recognition, awareness, management, continuing to harp on the importance of recognizing CKD earlier and earlier . . . . should be the mantra to be followed communitywide," Saran said. "The other thing is lifestyle factors. I'm going really upstream now. As a community, nephrologists have to be more and more in favor of practicing lifestyle medicine. They need to be part of that. They can't take care of all the CKD that there is, so I think they have to advise, guide, and work with their primary and other colleagues.



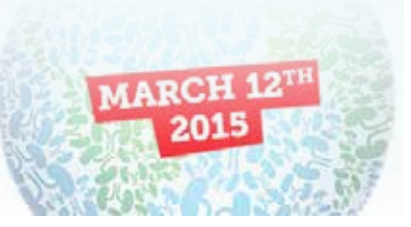
## Kidney Health for All

World Kidney Day kicks off on Thursday, March 12, with the theme "Kidney Health for All." This year's theme, on the 10th anniversary of WKD, recognizes that not everyone is equal with regard to risk for kidney disease and access to treatment.

African American, American Indian, Hispanic, Asian and Aboriginal populations are known to suffer from higher rates of diabetes and high blood pressure, which are both leading causes for CKD.

CKD is often difficult to prevent and treat in these populations owing to poor water hygiene, lack of hydration, unhealthy food and beverages, literacy levels, and lack of adequate health insurance. WKD highlights the importance of water to kidney health with the campaign, "Drink a Glass of Water and Give One Too." Just drink a glass of water, take a picture, and share: Today I celebrate #worldkidneyday. I drink and give a #glassofwater because #Isupport wkd.

**For more information, visit www.worldkidneyday.org**



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# Blood Acidity

*Continued from page 1*

receptor function. What distinguishes this paper from previous work is that not only does it demonstrate an effect of extracellular pH on calcium-sensing receptor signaling and PTH release, but it demonstrates that in human parathyroid tissue, changes in extracellular pH within the physiologic range are capable of causing measurable changes in PTH secretion," said R. Tyler Miller, MD, who was not involved in the study and is the vice chair of medicine at UT Southwestern Medical Center and chief of medicine at the Dallas VA Medical Center. "The paper also demonstrates that the effect of pH is on the receptor, not the cells or other components of the experimental system."

The calcium-sensing receptor is expressed in a variety of tissues and organs including the kidney, brain, intestine, bone, and skin where extracellular pH could also affect its function.

Miller noted that other work indicates that alterations in human pH that occur with kidney disease, high altitude, and possibly with diets of varying composition can alter metabolism, muscle mass, and bone structure, but the mechanisms for these effects are unclear. Also, the physiologic effects of PTH are complicated and involve not just the level of PTH, but also the frequency of its release. "A long-term effect of pH on parathyroid function via PTH release is a reasonable possibility for some of the physiologic consequences of altered extracellular pH," Miller said. "Precisely how PTH secretion is affected by extracellular pH will be interesting and valuable to learn as well as determining how pH and PTH secretion relate to long-term nutrition, body composition, and bone biology."

Ward stressed that additional studies are needed before any clinical applications might be realized. "Firstly, we would need to confirm that this effect is true not only in human cells in the laboratory, but also in live patients. However, if confirmed, then this might reveal a novel mechanism by which acidosis and bone mineral changes might be related in CKD patients," he said.

Article: "Pathophysiologic Changes in Extracellular pH Modulate Parathyroid Calcium-Sensing Receptor Activity and Secretion via a Histidine-Independent Mechanism" http://jasn.asnjournals.org/content/early/2015/01/01/ASN.2014070653.long

# Journal View

## Patiromer Reduces Potassium in CKD Patients Taking RAAS Inhibitors

The new oral potassium binder patiromer effectively lowers serum potassium levels in patients with chronic kidney disease (CKD) who are being treated with renin-angiotensin-aldosterone system (RAAS) inhibitors, reports a trial in the *New England Journal of Medicine*.

The multicenter study included 243 patients with stage 3 or 4 CKD who were taking RAAS inhibitors and had a serum potassium level of 5.1 to less than 6.5 mmol/L. All received 4 weeks of treatment with patiromer. The starting dose was 4.2 or 8.4 g twice daily. Patients whose potassium level decreased to the target range (3.8 to less than 5.1 mmol/L) were eligible for an 8-week randomized withdrawal phase, with one group continuing to receive patiromer and the other switching to placebo. Changes in potassium level were compared between groups.

The mean reduction in serum potassium during the initial treatment phase was 1.01 mmol/L, and 76 percent of patients reached the target range by 4 weeks. Among 107 patients enrolled in the withdrawal phase, potassium levels increased by 0.72 mmol/L within 4 weeks for those switching to placebo, compared with no change for those continuing to receive patiromer. The rates of recurrent hyperkalemia (potassium level 5.5 mmol/L or higher) were 60

*Continued on page 8*

# Journal View

## Patriromer

*Continued from page 1*

percent versus 15 percent, respectively. During the initial treatment phase, mild to moderate constipation occurred in 11 percent of patients and hypokalemia in 3 percent.

Patiromer—a nonabsorbed polymer that binds potassium in exchange for calcium—was developed to meet the need for effective outpatient treatments for hyperkalemia. This two-phase trial supports its effectiveness in reducing potassium levels and the rate of recurrent hyperkalemia in CKD patients taking RAAS inhibitors. Hypokalemia appears to be an infrequent and reversible event in patients taking patiromer [Weir MR, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* doi: 10.1056/NEJMoa1410853].



## Longer Steroid Courses Don't Affect Recurrence Rate in Nephrotic Syndrome

For children with steroid-sensitive nephrotic syndrome, extending initial steroid therapy from 3 to 6 months does not affect the subsequent relapse rate, reports a trial in *Kidney International*.

The randomized trial included 219 children with a first episode of steroid-sensitive nephrotic syndrome, enrolled at five academic hospitals in India. After 3 months of standard therapy with prednisolone, 181 children were assigned to receive 3 additional maonths of prednisone or 3 months of placebo therapy. The effects of extended steroid therapy on the risk of future relapse were assessed.

The cumulative initial prednisolone dosage was about 3500 mg/m$^2$ in the 6-month group versus 2800 mg/m$^2$ in the 3-month group. On intention-to-treat analysis, the numbers of steroid-sensitive relapses during the year after randomization were 1.26 and 1.54, respectively. The difference was not significant after adjustment for sex, age, and time to initial remission. The rates of sustained remission, frequent relapses, and adverse steroid effects were similar as well.

For children with idiopathic nephrotic syndrome, multiple relapses are associated with a risk of serious complications and medication-related adverse events. Some reports have suggested that a prolonged course of initial prednisolone therapy can reduce the relapse rate, although these studies have had important limitations.

The new trial finds no reduction in relapse rate for children with steroid-sensitive nephrotic syndrome assigned to 3 months versus 6 months of initial prednisolone therapy. Although extended treatment can postpone the occurrence of initial relapse, the 1-year relapse rates are similar between groups. A Japanese trial comparing 2 months versus 6 months of prednisolone, published in the same issue (*Kidney Int* 2015; 87:225–232), reaches a similar conclusion [Sinha A, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int* 2015; 87:217–224].

## Surgical Robots Linked to Increased Rates of Partial Nephrectomy

Hospitals acquiring surgical robots are more likely to perform guideline-recommended partial nephrectomy in patients with renal cancer, reports a study in *Medical Care*.

The researchers used payer data from seven states to identify nearly 21,600 nephrectomies performed in 2001, 2005, and 2008. Hospital-level rates of partial nephrectomy were analyzed in relation to the hospitals' acquisition of a surgical robotic system. The association was adjusted for nephrectomy volume, year of surgery, and other hospital factors.

Hospitals performed more partial nephrectomies after acquiring surgical robots. For hospitals acquiring robots between 2001 and 2004, the proportion of

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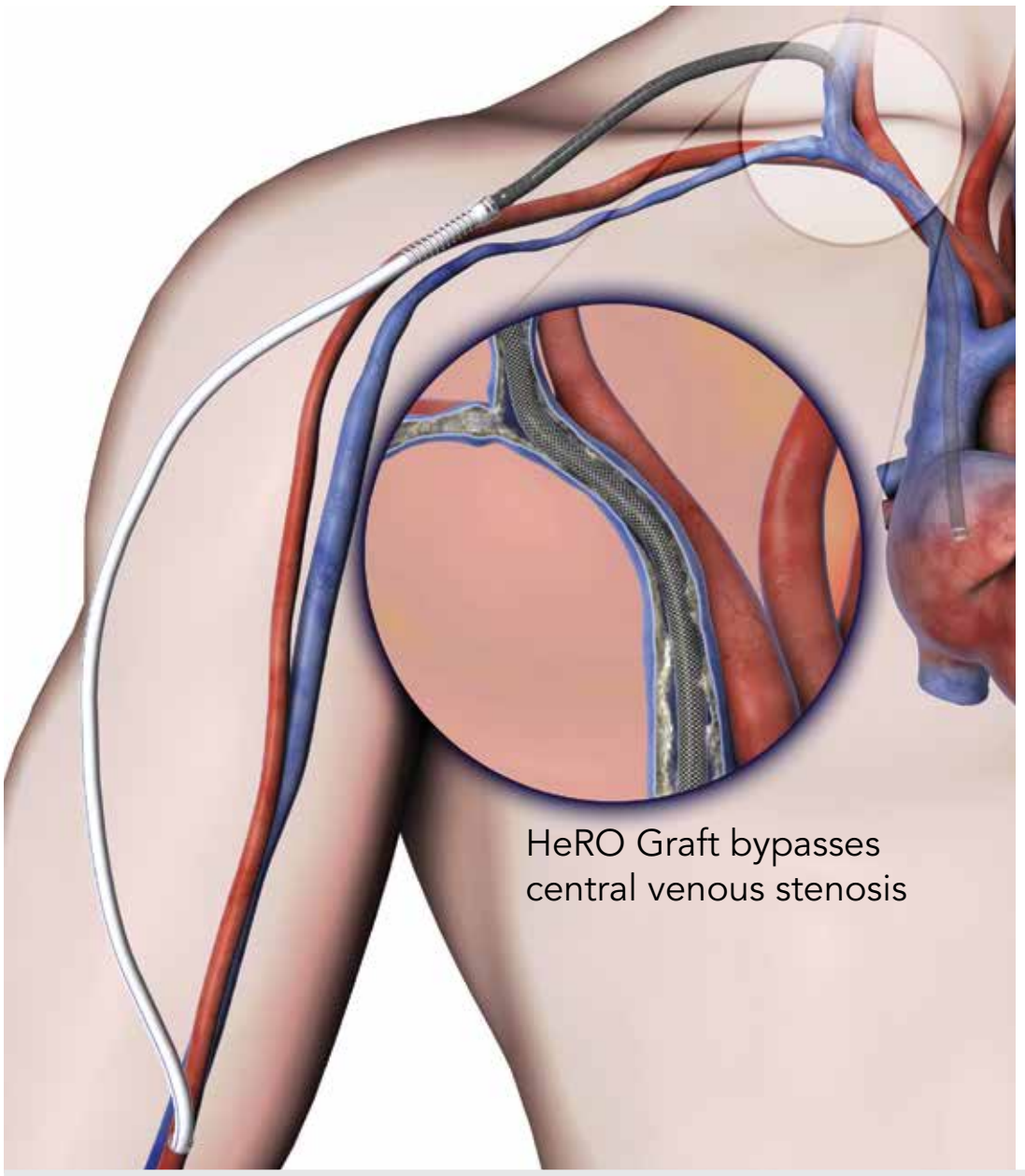

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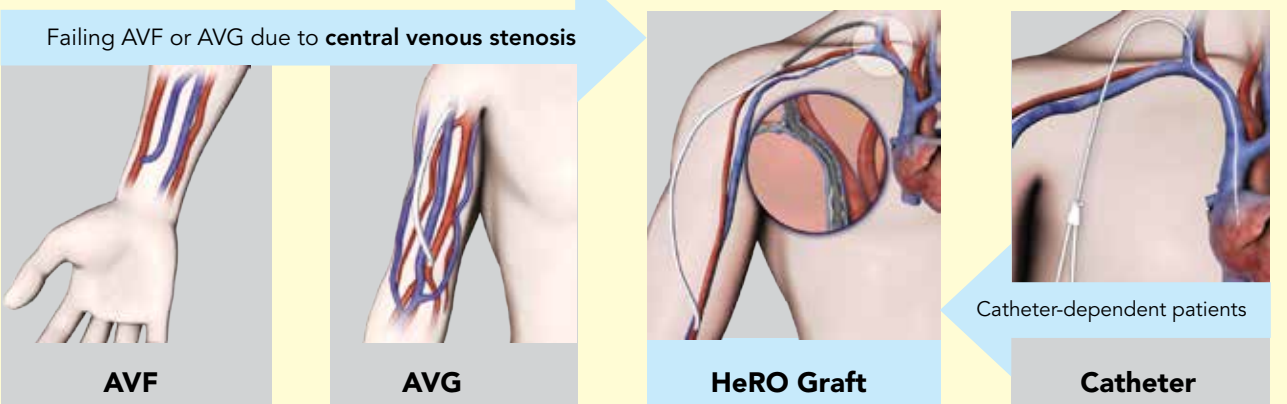


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1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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# Journal View

## Surgical Robots

*Continued from page 8*

partial nephrectomies increased by about 30 percent in 2005 and 35 percent in 2008. A smaller increase of 15.5 percent was noted for hospitals acquiring a surgical robot between 2005 and 2008.

Hospitals with a higher nephrectomy volume and those in urban locations had higher rates of partial nephrectomy. At hospitals that had not acquired a robotic system by 2008, partial nephrectomy was performed in just 20 percent of cases.

Nephron-sparing surgery is a guideline-supported but underused alternative to radical nephrectomy for patients with renal cancer. The new analysis suggests that surgical robots—a costly and controversial use of technology—facilitate the performance of partial nephrectomy in this group of patients.

"This is one of the few studies to suggest robot acquisition is associated with improvement in quality of patient care," the researchers write. They discuss the implications for adoption of new technologies, noting that the "earliest adopters" of surgical robots had the greatest increases in partial nephrectomy [Sivarajan G, et al. The effect of the diffusion of the surgical robot on the hospital-level utilization of partial nephrectomy. *Med Care* 2015; 53:71–78].

## Is Metformin Safe for Patients with Kidney Disease?

Available data support the "cautious expansion" of metformin use for patients with type 2 diabetes and mild to moderate chronic kidney disease (CKD), according to a systematic review in the *Journal of the American Medical Association*.

A literature search identified 65 publications providing data on the risk of lactic acidosis in metformin-treated patients with impaired renal function. Since its approval in 1994, metformin has been contraindicated for use in patients with "renal disease or renal dysfunction."

However, the evidence suggested that drug levels generally remained in the therapeutic range for metformin-treated patients with mild to moderate CKD (estimated GFR 30 to 60 mL/min/1.73 $m^2$). Despite renal clearance of metformin, the rates of lactic acidosis were low and in the range of the background rate among all patients with diabetes: about three to ten cases per 100,000 person-years.

There were no randomized trials evaluating the safety of metformin in patients with impaired kidney function. Some reports suggested that the guidelines regarding metformin use in kidney disease are "commonly disregarded," with no increase in adverse events. Observational studies suggested beneficial effects on macrovascular outcomes, even in patients with contraindications to metformin use.

On the basis of these data, the authors suggest a change in prescribing guidelines to permit metformin use in patients with mild to moderate CKD. They emphasize that any such strategy would require appropriate dosage reductions and careful monitoring of kidney function [Inzucchi SE, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; 312: 2668–2675].

# Industry Spotlight

## NephroCheck Test Gauges Risk for AKI

The NephroCheck test system is now being marketed by Ortho Clinical Diagnostics to help identify risk of acute kidney injury (AKI). The urine test is designed to detect both insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases, factors associated with AKI.

The test provides a score within 20 minutes that shows a patient's risk for the development of AKI, Ortho noted in an announcement. Patients with a positive NephroCheck risk (greater than the defined cutoff point of 0.3) have a one-in-four to a one-in-three chance of developing moderate or severe AKI within 12 hours of assessment, Ortho reported.

The U.S. Food and Drug Administration (FDA) approved the test, manufactured by Astute Medical, in September 2014.

The test has shown that it gives a positive result in about half of patients who do not have AKI, according to Medscape. Two studies compared NephroCheck results with the diagnoses in more than 500 critically ill patients at 23 hospitals; the test accurately detected 92 percent of AKI patients in one study and 76 percent in the other.

The test system may be used along with clinical evaluation in intensive care unit patients who currently have or have had within the preceding 24 hours an acute cardiovascular event, respiratory compromise, or both. The test should be used as an aid in the risk assessment for moderate or severe AKI within 12 hours of patient assessment in patients over age 21.

For more information about the product, visit www.astutemedical.com.

## New Combo Drug for Hypertension

For the first time, the U.S. Food and Drug Administration (FDA) has approved a fixed-dose antihypertensive pill combining angiotensin-converting enzyme inhibitor and beta blocker compounds. The drug, brand name Prestalia (Symplmed, Cincinnati, Ohio), contains perindopril arginine, an angiotensin-converting enzyme inhibitor, and amlodipine, a dihydropyridine calcium channel blocker.

Symplmed says Prestalia is intended for patients who fail to lower blood pressure with a single drug. Thus the drug may be used as a first-line therapy in patients likely to need multiple drugs to achieve blood pressure goals.

The FDA approved the drug based on phase III data from the 837-patient PATH trial (Perindopril Amlodipine for the Treatment of Hypertension trial), which demonstrated that the fixed-dose combination in one pill was more effective than either compound taken alone for reducing sitting diastolic and sitting systolic blood pressure after six weeks of treatment.

Both drugs alone can cause hypotension, and perindopril can cause swelling of the head and neck. Warnings include not giving diabetic patients aliskiren (a renin inhibitor for primary hypertension) along with ACE inhibitors, including Prestalia, as well as discontinuing Prestalia immediately when a patient learns she is pregnant.

The company has several other combination drugs for hypertension in the pipeline, all containing perindopril perindopril plus atorvastatin, perindopril plus indapamide, and perindopril plus amlodipine (the two drugs in Prestalia) plus indapamide. Its first product, perindopril erbumine (Aceon), is an antihypertensive drug that can be taken alone or in combination with other classes of hypertension-reducing drugs. Aceon is used to treat patients with high blood pressure and to reduce the risk of heart attack.

# Report Details Nephrology Fellow Demographics, Job Market Concerns

By Kurtis Pivert

ASN's latest nephrology workforce report provides a detailed portrait of future nephrologists and their perceptions of, and experiences in, the current job market. *Findings from the 2014 Survey of Nephrology Fellows* is the second in a series of workforce studies authored by George Washington University (GWU) investigators. The analysis of the 2014 ASN Nephrology Fellow Survey provides clues about demand for the specialty and a baseline for future research.

The report confirms recent trends in nephrology training. International medical graduates (IMGs) comprised the majority of respondents (64 percent), reflecting the continued decline in the number of US medical graduates (USMGs) choosing the specialty. Despite an increase in women entering nephrology, most of the 1st and 2nd year fellows who answered the survey were men (61 percent). Fellows' racial and ethnic composition remains unrepresentative of the communities they will serve—only 9 percent of fellow respondents were African American and 8 percent Hispanic.

Distributed to ASN fellow members in June 2014, the survey is an important component of ASN's ongoing collaboration with GWU to study all aspects of the specialty. Workforce research is one of ASN's many initiatives to increase interest in nephrology careers. Although this initial survey elicited a low response rate (35.8 percent), the participants' demographic characteristics were similar to those of all nephrology fellows, according to information from the Accreditation Council for Graduate Medical Education database.

"This kind of survey can provide a good picture of the future supply," said lead author Edward Salsberg, MPA. "The experience of new entrants into the job market can also provide a valuable snapshot of the regional and national demand."

Job search experiences and market perceptions differed between IMGs and USMGs. IMGs were more likely to practice in a Health Professional Shortage Area and to report difficulties in finding a satisfactory position. USMGs were more likely to note a lack of jobs in desired locations and to perceive more job opportunities nationally than locally.

A substantial proportion of nephrology fellows looking for employment reported changing their plans because of limited practice opportunities (43 percent). Although nephrology fellows' perceptions of local job opportunities (within 50 miles of their training site) were disappointing (71 percent said there were no, very few, or few nephrology practice opportunities), a vast majority indicated they would still recommend the specialty to medical students and residents (72 percent).

The report's release extended a continuing dialogue among the kidney community that started with the disappointing nephrology Match for academic year 2015–2016, which has expanded to social media. An ongoing discussion of the report, the Match, and nephrology careers on Twitter—at the #NephWorkforce hashtag—has explored many themes. These include the hurdles IMGs encounter in locating employment and research funding, student debt, and the importance of mentorship. ASN encourages all stakeholders to join this discussion using the #NephWorkforce hashtag.

Salsberg, together with Principal Investigator Leah Masselink, PhD, will focus future reports on the effects of changes in care delivery on the specialty, as well as geographic distribution of practicing nephrologists and training programs.

As of press time, ASN announced the Nephrology Match Task Force will be chaired by ASN President-Elect Raymond C. Harris, MD, FASN. Composed of Nephrology Training Program Directors, Division Chiefs, and ASN Councilors, the task force will address issues surrounding the Match, including an assessment of its future viability and identifying ways to ensure its integrity.

The nephrology fellow survey report is available at http://www.asn-online.org/education/training/workforce/.

# ABIM Announces Changes to MOC Program

Responding to concerns raised by ASN, the American College of Physicians, and other medical specialty societies, the American Board of Internal Medicine (ABIM) on February 3, 2015, announced it is suspending the Practice Assessment, Patient Voice, and Patient Safety requirements of its Maintenance of Certification (MOC) program for at least 2 years in order to engage the medical community's input regarding its MOC program.

Starting a year ago, ABIM changed its once-every-10-years MOC program to a more continuous one. The change generated substantial criticism among internists and medical specialties.

"Some believe ABIM has turned a deaf ear to practicing physicians and has not adequately developed a relevant, meaningful program for them as they strive to keep up to date in their fields," ABIM President and CEO Richard Baron, MD, MACP, said in a statement. "ABIM clearly got it wrong. We launched programs that weren't ready and we didn't deliver an MOC program that physicians found meaningful. We want to change that."

ABIM plans to institute the following changes:

- Within the next 6 months, ABIM will change the language used to publicly report a diplomate's MOC status on its website from "meeting MOC requirements" to "participating in MOC."
- ABIM is updating the Internal Medicine MOC exam. The update will focus on making the exam more reflective of what physicians in practice are doing, with any changes to be incorporated beginning fall 2015. More subspecialty MOC exams will follow.
- MOC enrollment fees will remain at or below the 2014 levels through at least 2017.
- By the end of 2015, ABIM will assure new and more flexible ways for internists to demonstrate self-assessment of medical knowledge by recognizing most forms of continuing medical education approved by the Accreditation Council for Continuing Medical Education.
- Effective immediately, ABIM is suspending the Practice Assessment, Patient Voice, and Patient Safety requirements for at least 2 years. This means that no internist will have his or her certification status changed for not having completed activities in these areas for at least the next 2 years. Diplomates who are currently not certified but who have satisfied all requirements for MOC except for the Practice Assessment requirement will be issued a new certificate this year.

The organization plans to work with medical societies and directly with diplomates to seek input regarding the MOC program through meetings, webinars, forums, online communications channels, and surveys. For more information, please see the ABIM MOC FAQ page.

# Detective Nephron

## Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

***Mr. Mac Uladensa, a visiting medical student, enters the room along with L.O. Henle to present a case.***

**Nephron** *(with surprise)*: My apprentice, what do you have for me? And who do we have here?

***Henle and Mac look at each other.***

**Henle** This is Mac, a visiting medical student, here to learn about nephrology.

**Nephron** *(with a smile)*: Glad to have you on board. Nephrology is a fun field of medicine and probably the most enigmatic. There is a lot of physiology, pharmacology, and pathology to learn in nephrology. The kidney is a smart organ!

**Mac** Glad to be on board. I just played NephMadness online and learned a lot of fun facts about nephrology.

**Henle** We have a case of a bicarbonate level of 60 MEq/L.

**Nephron** The patient is likely vomiting. What do you want me to do?

**Mac** The arterial blood gas determination shows a pH of 7.60 and $pCO_2$ of 66 mm Hg. Serum chloride is 68 mEq/L.

**Henle** So the patient has a metabolic alkalosis with good compensation.

**Nephron** I am still confused. Why are you presenting this to me? This sounds like a case of vomiting with some degree of volume depletion leading to metabolic alkalosis.

**Mac** Why is the urinary sodium not lower than 10 MEq/L? It is 45 MEq/L.

**Nephron** *(happy)*: Ah! There is an interesting and commonly asked question, but poorly understood. Let's start from the basics. What happens during vomiting?

**Mac** Vomiting removes gastric fluid from the stomach, although the parietal cells in the stomach still continue to produce hydrogen ions and release bicarbonate into the blood. Because this bicarbonate is not neutralized, this generates metabolic alkalosis.

**Nephron** What happens in the kidney?

**Mac** There is increased filtration of this bicarbonate, and it meets the proximal tubule. Given that there is no need to reabsorb this bicarbonate, it will just get excreted.

**Henle** But doesn't it need a cation to get excreted with?

**Mac** *(with a smile)*: Likely sodium….hence making urinary sodium high in the state of vomiting.

**Nephron** Good work, my friends. Normally, in the absence of volume depletion, metabolic alkalosis is corrected by the excretion of excess bicarbonate in the urine. To maintain electroneutrality, sodium gets excreted in the urine. But what do you think happens when there is volume depletion?

**Mac** Hmmm, does volume trump everything?

**Nephron** What is this patient's urinary pH? It has to be alkalemic.

**Henle** Suggesting loss of bicarbonate and hence urine sodium being high.

**Nephron** *(with a wink)*: Now let's assume this patient's systolic blood pressure drops because of excessive vomiting. What happens then?

**Henle** A tug of war between metabolic alkalosis and volume. There might be times when sodium will be taken back to maintain blood pressure but can fluctuate. Volume will win most of the time. So, if volume rules, the reabsorption of sodium with bicarbonate continues and maintains the metabolic alkalosis.

**Nephron** Bingo! Not only have you explained that volume trumps everything, but also you have mentioned one of the key components that maintains metabolic alkalosis, which is hypovolemia. So vomiting in this case is generating and maintaining metabolic alkalosis.

**Henle** Let's get back to our patient. So does urinary chloride help us in this situation?

**Nephron** The spot urine chloride is always appropriately low: below 20 MEq/L in metabolic alkalosis because of vomiting, and that can help in the diagnosis. The spot urine sodium might be low if the patient is in a volume-depleted state, or it can fluctuate as you mentioned, based on who is winning: volume or alkalemia. But the urine chloride will be low.

Let me ask you, then: what else will maintain this metabolic alkalosis besides the hypovolemia?

**Mac** *(confidently)*: Well, low volume will maintain it by stimulating aldosterone, and excess mineralocorticoid activity would then be the second way to maintain it. Aldosterone will enhance the activity of the $H^+$-ATPase pumps in the intercalated cells and lead to reabsorption of bicarbonate. Aldosterone also increases sodium absorption in the principal cells, leaving the lumen negatively charged, promoting hydrogen ion secretion leading to bicarbonate generation.

**Nephron** Good points. Anything else that maintains this?

**Henle** *(jumping in)*: Chloride depletion itself in this vomiting state will lead to maintaining the alkalosis. In type A intercalated cells, there is a $Cl/HCO_3^-$ exchanger in the basolateral membrane. If there is less chloride in the lumen, there is loss of chloride and hydrogen secretion, leading to bicarbonate reabsorption. In addition, in the

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# Detective Nephron

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type B intercalated cells, the Cl/$HC0_3$– exchanger is in the luminal side, leading bicarbonate to be retained and not secreted because chloride in the tubular flow is low.

**Nephron** Sounds as if you know most of this very well. Good work, Henle. This is an important concept to understand.

**Mac** *(interrupting)*: I think the last factor would be hypokalemia. This is partly due to aldosterone again. The distal nephron hydrogen secretion is stimulated by the low potassium state, leading to increased bicarbonate generation.

**Nephron** Also, $NH4^+$ is made from glutamine in the proximal tubule. The latter is unregulated in hypokalemia. $NH4^+$ is excreted in the lumen (trapped). Therefore, HCO3– is reabsorbed. This is an additional mechanism.

**Henle** Now, back to our patient. As we know, this patient has active metabolic alkalosis. But the team is puzzled about the cause of this?

**Nephron** *(with a bored face)*: Why are they so puzzled?

**Mac** *(scared)*: Did we mention to you that the patient has ESRD and is receiving hemodialysis?

**Nephron** *(with a surprised look)*: Ahhh! So now you tell me, after that long discussion regarding urinary losses and urinary bicarbonate generation and so forth, that there is not much urine!

**Mac** Affirmative.

**Nephron** Well, that whole discussion is off the table, then, because this patient makes no urine. Am I repeating myself?

**Mac** Affirmative.

**Nephron** Nothing gets a nephrologist more excited than seeing metabolic alkalosis in a dialysis patient, because it's not the usual situation.

**Henle** *(jumping in)*: In a dialysis patient, the increase in serum bicarbonate concentration can be caused only by metabolic alkalosis. Primary respiratory acidosis with compensatory metabolic alkalosis cannot be possible because there is no kidney function.

**Nephron** Good point—and in this case, it doesn't matter that the urine sodium was 45 mEq/L, because overall the patient doesn't make that much urine.

**Henle** Also, given that the patient has no kidney function, metabolic alkalosis can occur only if there was excess alkali intake or significant hydrogen ion loss.

**Mac** So in this case, we don't need to consider mineralocorticoid excess and or other urinary transport problems?

**Nephron** *(with a smirk)*: Affirmative.

**Mac** So this has to be a gastrointestinal loss? Should we image the abdomen?

**Nephron** I would. This could be as simple as a "bad" ulcer or a gastrointestinal outlet obstruction or increased gastrin production producing a tumor?

**Mac** When we lose hydrogen ion in emesis, how much bicarbonate gets generated?

**Nephron** One millimole of bicarbonate is generated in body fluids for each millimole of hydrogen ion lost in emesis—although this added alkali is buffered, but given that this patient has no kidney function, the increased bicarbonate is sustained.

***Henle and Mac exit to order the suggested tests.***

***A day later:***

**Henle** A computed tomographic scan revealed a gastric mass, and a biopsy was performed. Hemodialysis was initiated with the goal of helping decrease the alkalosis.

**Nephron** Isotonic fluids may restore the volume loss here, and it may dilute the body's alkali stores, but it will not correct alkalosis because no bicarbonate excretion is happening. Hence, hemodialysis with a reduced bicarbonate bath is a safe and effective treatment.

***Henle and Mac exit to order the suggested tests.***

***A day later:***

**Nephron** What do we have as the final diagnosis?

**Mac** A gastrinoma.

**Henle** The patient was also prescribed a proton pump inhibitor. His electrolytes normalized, and currently he is awaiting evaluation by the hematology and oncology services.

**Nephron** Mac and Henle, you have stumped me this time with an excellent case of alkalosis in a dialysis patient. Again, nephrologists can always be amazing detectives. With one electrolyte disorder in a patient with ESRD, you made a systemic diagnosis! The problem is not always in the kidney! Let's have some coffee to celebrate!

*Detective Nephron was developed by Kenar Jhaveri, MD, associate professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Rimda Wanchoo, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine, for her editorial assistance.*

# Classified Ads



## *High School Student Develops Noninvasive Screening Tool for Chronic Kidney Transplant Rejection*

Kidney transplantation has been the preferred treatment for people suffering from kidney failure since Dr. Joseph E. Murray completed the first successful kidney transplant in 1954. Although recent advances in transplant medicine have drastically lowered the risk of acute transplant rejection, these advances have failed to deliver an effective treatment for chronic allograft nephropathy (CAN), which remains the leading cause of organ loss following transplantation and limits the 10-year survival rate of a kidney transplant to 54%. If detected early, intervention can minimize CAN, but the current "gold standard" for diagnosis is tissue biopsy, which is heavily invasive and cannot detect the disease until after substantial kidney damage has already occurred.

For Demetri Maxim, a high school junior in Maine, the difficulties of kidney transplants and kidney disease are personal. In August 2004, Demetri's mother, Lefki, lost both her kidneys to polycystic kidney disease (PKD) and was forced to go on dialysis. Fortunately, she received a kidney transplant in October 2005, just 14 months later. Demetri also has PKD and may someday lose his kidney function as well.

Demetri's mother experienced four different rejection episodes in the first 18 months of her transplant. Each episode necessitated a painful biopsy that involved removing a small piece of the kidney to test for rejection, a process that further reduces the long-term success of the organ. Demetri knew there had to be another way to tell whether or not she was rejecting her kidney. So the summer before he started high school he set out to invent an alternative method of detecting CAN. Two years later, in March 2014, following countless hours of background research and lab work, Demetri's invention won grand prize at the Maine State High School Science Fair and qualified for the Intel International Science and Engineering Fair.

At Kidney Week 2014, Demetri presented a poster describing the simple, portable, patent-pending device that can be used to non-invasively monitor CAN in kidney transplant recipients. The device works by screening patient blood samples for the biomarker VEGF-C, which is upregulated during CAN. The device is 11 times faster and 16 times less expensive than the current gold standard for biomarker detection, ELISA. He hopes to publish his work.

Demetri currently works in Dr. Joseph Bonventre's Laboratory of Kidney Injury and Repair at the Brigham and Women's Hospital and Harvard Medical School on research to bioengineer an artificial kidney. He plans to continue this work and pursue pre-med studies to ultimately become a nephrologist and lead the fight against kidney disease in the next generation.

## Index to Advertisers

# Time out.

## Let’s take a moment to look at the current state of the lab industry.

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