Diabetes and sleep problems often go hand in hand. It has been known for some time that diabetes-associated factors such as neuropathy and nighttime hypoglycemia can contribute to sleep problems in patients. Research is now providing growing evidence that insufficient sleep can also contribute to diabetes risk. The most recent studies reveal some of the potential mechanisms behind this link.

“Sleep can affect diabetes, and diabetes can affect sleep,” said Elizabeth Bashoff, MD, of the Joslin Diabetes Center in Boston. “For everyone, but especially for patients with chronic conditions such as diabetes, it’s important to take care of your health overall to improve sleep, and to take steps to get a good night’s sleep to restore the body.”

How diabetes affects sleep
Fluctuations in blood glucose can be particularly disruptive to sleep for many individuals with diabetes. “It’s not uncommon for people to experience hypoglycemia in the middle of the night, which can cause headaches, sweating, and nightmares," Bashoff said. “Blood glucose that is too high can also be a problem because it may cause people to wake up repeatedly to use the bathroom.”

Sleep apnea is also a major cause of sleep problems, and it is more common in individuals with diabetes than in the general population. Sleep apnea is linked to obesity, and weight loss is by far the most effective treatment for individuals with sleep apnea who have high BMIs.

Leg pain due to neuropathy can also keep diabetics up at night. Controlling blood sugar levels can help. Also, there are many medications to treat the condition, some of which also have a beneficial sedative effect at bedtime.

How sleep affects diabetes
While diabetes and its associated conditions can cause sleep problems, sleep disturbance can also worsen diabetes.

Elevated phosphate levels in the blood—even when levels are in the high normal range—carry increased heart-related risks, but taking a phosphate binder did not improve cardiovascular measures in patients with mild kidney disease in a recent study published in the Journal of the American Society of Nephrology. “It would appear that for now it would be better to lower the amount of phosphate in the diet rather than rely on pharmacological interventions,” said senior author Charles Ferro, MBChB, MD, of the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, in England.

Because adherence to the study medication was low, though, additional studies are warranted to test the true potential of phosphate binders for protecting the heart health of patients with mild kidney disease. Chronic kidney disease (CKD) is the most common condition associated with deranged phosphate homeostasis. Ferro and his colleague Colin Chue, MBChB, led a research team that conducted a double-blind, randomized, placebo-controlled trial of 120 patients with stage 3 CKD to test the effects of the phosphate binder sevelamer carbonate, which is approved only for patients with kidney failure. Sevelamer carbonate holds promise for improving cardiovascular health because high blood levels of phosphate promote calcification and stiffening of blood vessels and can cause structural changes in the heart, such as increased wall thickness.
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Sleep and Diabetes
Continued from page 1

Benefits
Cardiovascular
Sleep and
function between the groups. How-
binders with every meal, we would be
chronic kidney disease to take phosphate

carotid–femoral pulse wave velocity.

diastolic function with cardiovascular mag-
sessed left ventricular mass and systolic and
additional 36 weeks. The investigators as-
er carbonate, 109 patients were randomly
during which all patients received sevela-
significantly smaller amounts of phos-
rately, the group taking sevelamer excreted

Since then, studies have generated additional evidence that disrupted sleep affects insulin resistance, and that indi-
viduals with diabetes who keep regular sleep schedules seem to maintain better blood sugar control, perhaps in part due to

...to circadian rhythms connected to glu-
cose metabolism. Also, research suggests
that people who get less sleep tend to be
heavier than those who sleep well, which
puts them at increased risk for developing
type 2 diabetes.

“Research is starting to tease out the mecha-
nisms by which sleep affects diabe-
tes risk,” said study co-investigator
Ciaran McMullan, MD, a nephrolo-
ist at Brigham and Women’s Hospital
in Boston. “Hopefully this study will
prompt future research to examine what
influences a person’s melatonin secretion
and what is melatonin’s role in altering a
person’s glucose metabolism and risk of
diabetes.”

Cardiovascular Benefits
Continued from page 1

After a 4-week open label run-in period,
during which all patients received sevela-
em carbonate, 109 patients were randomly
assigned to sevelamer or placebo for an
additional 56 weeks. The investigators as-
...a detrimental association has been established
between nocturnal melatonin secretion
and type 2 diabetes risk,” said first au-
thor Ciaran McMullan, MD, a nephrolo-
ist at Brigham and Women’s Hospital
in Boston. “Hopefully this study will
prompt future research to examine what
influences a person’s melatonin secretion
and what is melatonin’s role in altering a
person’s glucose metabolism and risk of
diabetes.”

New evidence presented at SLEEP
2012, the 26th annual meeting of the
Associated Professional Sleep Societies,
links sleep apnea with carbohydrate crav-
ings. Researchers screened 55 individuals
(more than half of whom had diabetes)
for sleep apnea and carbohydrate crav-
ings. They found that among the diabetic
patients, the prevalence of sleep apnea was
82 percent, and they had almost twice the
risk of carbohydrate craving than nondia-
betics. In addition, patients with sleep
apnea were almost twice as likely to have
high carbohydrate craving than were pa-
ients without sleep apnea.

“Previous studies have shown that
sleep deprivation may lead to changes
in hormones that regulate appetite and
hunger. These hormonal changes can lead
to significant craving for high-calorie car-
bohydrates,” said study co-investigator
Mahmood Siddique, DO, of the depart-
ment of medicine at the Robert Wood
Johnson Medical School in New Brun-
swick, NJ. “This study supports previous
findings by validating this in a commu-
nity sample of diabetics.”

Getting a good night’s sleep
While some aspects of sleep may be out
of one’s control, experts agree that certain
measures can help improve sleep for most
people, leading to considerably better
health.

“Maintaining a regular schedule, get-
ing exercise, avoiding alcohol at night—
and for people with diabetes, testing
blood sugar at bedtime—can lead to a
better night’s sleep,” said Bashoff. “I of-
ten see patients who are so busy that they
don’t think of these simple steps.”

Individuals who sleep poorly are sus-
cceptible to depression and other mood
disorders, changes in eating, decreases
in physical activity—and as indicated by the
latest evidence, perhaps an in-
creased risk of developing diabetes.

He added that while the drug in the
doses used in this trial was not effective in
reducing an already normal level of phos-
phorus concentration, perhaps the partici-
pants increased their dietary phosphorus
intake, which would prevent an overall de-
cline in serum phosphorus.

Until more information is available
about the potential heart-related benefits
of phosphate binders for individuals with
mild CKD, these patients should focus
on dietary changes to reduce their phos-
phate levels. Foods with large amounts of
added phosphate are processed meat, ham,
sausages, canned fish, baked goods, cola
drinks, and other soft drinks.

“Fast food and ready-to-eat processed
food are the main contributors to today’s
rising dietary consumption of phosphorus,”
Ferro noted. He suggested that a com-
prehensive public education effort that
explains the harmful effects of high phos-
phate intake and provides clear labeling of
the phosphate content of food could help
limit the damage done by this cardiovascu-
lar risk factor.
Fewer Patients Now Required for Groups to Apply for ESRD Seamless Care Organizations

By Rachel Shaffer

CMS recently relaxed its requirement that ESRD programs applying to form ESRD Seamless Care Organizations (ESCOs) must have at least 500 matched beneficiaries. Applicants must now have 350 matched beneficiaries, and the deadline to submit a formal application has been pushed back to July 1, 2015.

The change came after requests for greater flexibility on the threshold from many in the kidney care community—including ASN. CMS stated that the reduction was in response to stakeholder feedback and suggestions from organizations interested in new models of ESRD care.

The lower threshold is welcome news,” said Doug Johnson, MD, vice chair of the board at Dialysis Clinic, Inc. “It will permit more providers to participate, leading to greater innovation and ultimately better care for patients with kidney disease.

CMS had originally emphasized in written communications and in conference calls with the kidney community that the 500-patient threshold was selected to ensure a statistically accurate shared savings calculation, and therefore could not be reduced.

However, some potential applicants noted that it would not be possible to achieve that minimum in a given “market”—which CMS defined as limited to just two Medicare Core-Based Statistical Areas—especialy given that patients who had already been matched to a Medicare ACO or another Medicare program involving shared savings would be excluded from attribution to an ESCO.

“ASN applauds CMS and the Innovation Center for making this important change,” said ASN Public Policy Board chair Thomas H. Hostetter, MD. “The society will continue to work with other kidney community stakeholders to encourage the agency to consider what we believe are further modifications that would strengthen the program’s ability to deliver innovative, higher-quality care, support further research, and allow more nephrologists and providers to participate in the ESCO program.

For instance, ASN believes it is important for CMS to describe a plan to develop dialysis-specific quality metrics in a transparent manner that allows for community input, as well as to prospectively describe the criteria it will use to determine whether an ESCO is a success or a failure.”

Also welcoming the news were stakeholders who are not eligible to apply as participants, but who are invested in the success of the program given its potential to improve care for patients on dialysis.

“The American Nephrology Nurses Association (ANNA) was delighted that CMS reconsidered the minimum number of ESRD participants in an ESRD Seamless Care Organization (ESCO) to allow smaller providers to participate in these innovative programs,” said ANNA immediate past president Glenda Payne.

Correction

The May Kidney News article on the Congressional Kidney Caucus Reception failed to note that the American Nephrology Nurses Association was a cosponsor of the March 20 event. ASN is proud to partner with ANNA to advance the care of patients with kidney disease and regrets the oversight.
Tubulointerstitial Nephropathies in Patients with HIV

Tubulointerstitial nephropathies are found in more than one-fourth of kidney biopsy specimens obtained from HIV-infected patients, reports a study in the Clinical Journal of the American Society of Nephrology.

The retrospective study included 59 consecutive renal biopsy specimens showing predominantly tubular lesions, interstitial lesions, or both in patients with HIV infection. The patients were referred to the nephrology department of a French hospital between 1995 and 2011; the analysis excluded patients with HIV-associated nephropathy and vascular diseases. Patterns of tubulointerstitial nephropathies in HIV-infected patients were analyzed, along with their therapeutic implications.

The cases of tubulointerstitial nephropathy represented 26.6 percent of 222 native renal biopsies performed in HIV-infected patients. Approximately equal numbers of tubulopathy cases and interstitial nephritis cases were included.

At referral, about three-fourths of patients had acute kidney injury, and close to 60 percent had high-grade proteinuria. A little more than half had drug-related nephrotoxicity. Other identified causes included infections, dysimmune disorders, and malignancies. Acute and chronic tubulointerstitial nephropathies of unknown origin accounted for 10 percent of cases each.

Toxic effects of antiretroviral drugs accounted for three-fourths of tubulopathies. Tenofovir toxicity was involved in more than half of these cases, causing proximal tubular dysfunction in nearly 90 percent of cases. Other manifestations included overt Fancconi’s syndrome and nephrogenic diabetes insipidus. The causes and pathologic findings were more variable in cases of interstitial nephritis.

With advances in HIV treatment and improved patient outcomes, patterns of HIV-related renal complications have changed. This study finds a high rate of tubulointerstitial nephropathies among HIV-infected patients referred for nephrology evaluation. Drug toxicity is the most common diagnosis, but other causes are possible. The findings highlight the need for monitoring of renal function in patients with HIV infection and the importance of renal biopsy for accurate diagnosis [Zaidan M, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinicopathologic study. Clin J Am Soc Nephrol 2013, in press].

Evidence Supports Health Benefits of Lower Sodium and Higher Potassium

Two updated meta-analyses show cardiovascular and other health benefits of decreased sodium and increased potassium intake, reports the British Medical Journal.

The researchers performed systematic reviews to identify randomized trials and cohort studies of lower sodium intake and higher potassium intake. In adults, lower sodium intake was associated with decreased systolic and diastolic blood pressure. Reducing sodium intake to less than 2 g/d was associated with a decrease of 3.47/1.81 mm Hg in blood pressure, with no evidence of adverse effects on blood lipid or catecholamine levels or kidney function.

The data were insufficient to show reduced mortality or cardiovascular morbidity associated with lower so-
Soliris® is the first and only approved therapy for atypical Hemolytic Uremic Syndrome (aHUS)

**Study 1**—In patients with progressing TMA

- Soliris treatment resulted in sustained improvement in renal function
- 80% (4/5) of patients eliminated dialysis

**Study 2**—In patients with long duration of disease

- Patients eliminated PE/PI and did not require new dialysis
- Soliris maintained renal function in patients with significant renal damage

**Important Safety Information**

**Contraindications**
Soliris is contraindicated in:
- Patients with unresolved serious Neisseria meningitidis infection
- Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

Please see brief summary of full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection on following pages.
Younger Age at Weight Gain Increases Later CKD Risk

People who are overweight by their mid-30s are more than twice as likely to experience chronic kidney disease (CKD) by their mid-60s, reports a study in the Journal of the American Society of Nephrology.

The study included data on 5,562 singleton children born during a single week in March 1946, drawn from a national health survey in the United Kingdom. A sample of 1,794 participants with complete data was expanded to 4,584 by multiple imputation analysis. Body mass index at age 20 to 26 (self-reported) and in subsequent decades of life (measured) was analyzed for association with CKD at age 60 to 64. The presence of CKD was based on estimated GFR (eGFR) of less than 60 mL/min/1.73 m², urine albumin-to-creatinine ratio of 3.5 mg/mmol or greater, or both.

With adjustment for social class in childhood and adulthood, being overweight at younger ages was associated with a higher risk of CKD at age 60 to 64. Cohort members who were overweight at age 26 or 36 had a twofold increase in risk of CKD before age 65, compared with those who never became overweight or who became overweight in their 60s.

The association between overweight in young adulthood and later CKD was only partly explained by adjustment for diabetes and hypertension. An increased wait-to-

Soliris® is the first and only approved therapy for atypical Hemolytic Uremic Syndrome (aHUS)1

- Soliris inhibited uncontrolled complement activation in all patients2,4
- Soliris inhibited complement-mediated TMA during the study period2
- Efficacy of Soliris is consistent across a broad range of patients, regardless of identified mutation, age, or duration of aHUS2
- Ongoing Soliris treatment is recommended to maintain inhibition of complement-mediated TMA, the cause of symptoms and clinical manifestations of aHUS2,4

Important Safety Information

Contraindications
Soliris is contraindicated in:
- Patients with unresolved serious Neisseria meningitidis infection
- Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

Warnings and Precautions

Serious Meningococcal Infections
The use of Soliris increases a patient’s susceptibility to serious meningococcal infections (sepsisemia and/or meningitis). Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Administer a polyvalent meningococcal vaccine according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations.

Other infections
Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Children treated with Soliris may be at increased risk of developing serious infections due to Streptococcus pneumoniae and Haemophilus influenzae type b (Hib). Administer vaccinations for the prevention of Streptococcus pneumoniae and Hib infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection.

Monitoring after Soliris Discontinuation

Treatment Discontinuation for aHUS

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical studies, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients.

Laboratory Monitoring
Multifocal sex of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

Infusion Reactions
As with all protein products, administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

Thrombosis Prevention and Management
The effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. Therefore, treatment with Soliris should not alter anticoagulant management.

Adverse Reactions
The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

References:

Please see brief summary of full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection on following pages.

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hip ratio at age 43 or 53 was also a risk factor for CKD at age 60 to 64. The association was similar across different definitions of CKD.

The study is one of the first to assess the relationship between body weight at different ages and the risk of CKD later in life. On the basis of their data, the researchers estimate that in the United States, more than 36 percent of cases of CKD in the elderly may be preventable with improved diet and physical activity if weight gain were prevented or delayed [Silverwood RJ, et al. Association between younger age when first overweight and increased risk for CKD. J Am Soc Nephrol 2013; 24:815–821].

For patients with an episode of acute kidney injury, early nephrology follow-up for 90 days after discharge free of dialysis, with follow-up information through 2 years after discharge. Of these, 1583 patients received early follow-up with a nephrologist and could be matched to a patient without nephrologist. The risk of all-cause mortality was compared on propensity score adjustment.

All-cause mortality was 8.4 per 100 patient-years for patients with early nephrologist follow-up versus 10.6 per 100 patient-years for those without nephrologist follow-up: hazard ratio 0.76. Within 2 years, 15.5 and 18.9 percent of patients had died, respectively. In subgroup analyses, the survival benefit was significant for men, patients younger than 65 years, those with a history of diabetes, and those with no previous nephrology consultation.

Even if kidney function recovers, patients with AKI remain at increased risk of death. Care after discharge may affect the prognosis; yet, only 8 percent of patients see a nephrologist within 1 year.

The new study suggests improved survival with early nephrologist follow-up of hospitalized patients who survive an episode of AKI. The authors call for further studies to clarify optimal care for AKI survivors, including the role of nephrology care [Harald Z, et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury. Kidney Int 2013; 83:901–908].

Nephrologist Care Improves Outcomes After AKI

For patients with multiple risk factors undergoing noncardiac, nonvascular surgery, peripartum β-blockers reduce mortality and cardiac morbidity, according to a study in the Journal of the American Medical Association. The protective effect is larger for patients with more risk factors, the authors found.

Using Veterans Health Administration (VA) databases, the researchers identified 37,805 propensity score-matched pairs of patients undergoing noncardiac surgery who did and did not receive peripartum β-blockade, defined as an active outpatient prescription or receipt of a β-blocker on the day of or the day after surgery. The 30-day mortality and cardiac morbidity were significantly lower for patients who received β-blockers (3.6% vs. 5.9%) [Silverwood RJ, et al. Peripartum β-blockade reduces mortality and morbidity after noncardiac surgery. JAMA Cardiol 2019; 4:684–692].
Perioperative β-Blockade

Continued from page 9

Perioperative β-blockade increased from 25.5 percent for patients with no revised cardiac risk index factors to 71.3 percent for those with four or more risk factors. The overall 30-day mortality was 1.1 percent, and cardiac morbidity was 0.9 percent.

On propensity-matched analysis, perioperative β-blockers were associated with lower mortality among higher-risk patients. The relative risk (RR) was 0.63 for patients with two revised cardiac risk index factors, with a number needed to treat (NNT) of 105. For patients with the risk factors, the RR was 0.54 and the NNT 41; for those with four or more risk factors, RR was 0.40 and the NNT 18.

Perioperative β-blockade reduced mortality risk only for patients undergoing nonvascular surgery. The nonvascular surgery group also had a significant reduction in cardiac morbidity; RR 0.67, NNT 339.


Nasal MRSA Carriage Predicts Worse Outcomes in Hemodialysis Patients

Even without clinical signs of infection, hemodialysis patients who are methicillin-resistant Staphylococcus aureus (MRSA) carriers are at increased risk of death, reports a study in BMC Nephrology.

The prospective cohort study included 289 hemodialysis outpatients at an urban dialysis unit. All underwent nasal swabs for MRSA culture at admission to the unit, after transfer from another unit, or on readmission after a hospital stay. Patients found to be nasal MRSA carriers were kept in a separate ward and treated with nasal mucirocin; appropriate treatments for extranasal (throat and skin) MRSA colonization were used as well. Clinical characteristics and outcomes were compared for MRSA carriers versus noncarriers.

Nasal MRSA carriage was identified in 11.7 percent of patients. About one-third of nasal MRSA carriers also had extranasal colonization. Patients with a history of cancer and those with increased comorbidity were more likely to be nasal MRSA carriers. Traditional MRSA risk factors were not significant, nor were markers of inflammation or malnutrition.

During follow-up, death occurred in 55.9 percent of patients whose test results for MRSA were positive versus 37.4 percent of MRSA-negative patients. The mortality difference was significant on Kaplan-Meier analysis. Mucirocin treatment eradicated nasal MRSA colonization in 75.7 percent of patients. For patients in whom eradication therapy was unsuccessful, all-cause mortality exceeded 85 percent.

Nasal MRSA carriage is a known risk factor for bacteremia and death in various patient groups. There is ongoing controversy regarding its clinical impact on patients receiving long-term hemodialysis.

About one of eight hemodialysis patients may be nasal MRSA carriers, the new study suggests. These patients are at increased risk of death during follow-up, especially if mucirocin is not effective in eradicating MRSA. The authors call for further study of nasal MRSA colonization as an independent outcome predictor in hemodialysis patients [Schmid H, et al. Persistent nasal methicillin-resistant staphylococcus aureus carriage in hemodialysis outpatients: a predictor of worse outcome. BMC Nephrol 2013; 14:93].

Simultaneous Pancreas-Kidney Transplantation May Reverse Microvascular Damage in Patients with Type 1 Diabetes

In patients with type 1 diabetes and diabetic nephropathy (DN), microvascular structural abnormalities are reversed within 1 year after simultaneous pancreas-kidney transplantation (SPK), reports a study in the American Journal of Transplantation.

The investigators used sidestream dark field (SDF) imaging—an emerging technology for noninvasive visualization of the microcirculation—to study the microvascular morphology of the oral mucosa. Imaging studies were performed in various groups, including 26 patients with DN, 38 patients undergoing SPK, 15 patients with type 1 diabetes, 15 DN patients undergoing kidney transplantation, and 20 healthy control individuals.

The study also included longitudinal SDF imaging in 21 patients with DN undergoing SPK. The microvascular findings were correlated with markers of endothelial dysfunction, including angiopoietin-1 and angiopoietin-2 (Ang-1 and Ang-2) and soluble thrombomodulin.

The SDF imaging studies showed increased capillary tortuosity in the DN patients and in the type 1 diabetes group: 1.83 and 1.55, respectively. This value was significantly reduced in patients undergoing SPK, 1.31, compared with no change after kidney transplantation, 1.64. Levels of soluble thrombomodulin and the Ang-2/Ang-1 ratio also normalized after SPK, compared with no change after kidney transplantation. The reversal of capillary tortuosity and decreased markers of endothelial dysfunction were observed within 12 months after SPK.

Simultaneous pancreas-kidney transplantation is an advanced treatment alternative for patients with type 1 diabetes and DN or other forms of microvascular disease. This study, using SDF imaging, suggests that reversal of systemic microvascular abnormalities occurs within 1 year after SPK in patients with DN. No such effect is noted in patients undergoing kidney transplantation only [Khairem M, et al. Microwascular damage in type 1 diabetic patients is reversed in the first year after simultaneous pancreas-kidney transplantation. Am J Transplant 2013; 13:1272–1281].

MMF for Lupus Nephritis Patients with Poor Kidney Function

For lupus nephritis patients with a very low eGFR, mycophenolate mofetil (MMF) may lead to faster recovery of kidney function compared with cyclophosphamide, reports a study in the American Journal of Kidney Diseases.

The study was a post hoc analysis of data from patients enrolled in the Aspreva Lupus Management Study, a large randomized trial of MMF versus cyclophosphamide for lupus nephritis. Of 370 patients enrolled, 32 had severely decreased kidney function: eGFR less than 30 mL/min/1.73 m². Of those, 20 received MMF, target dosage 3 g/d; and 12 received cyclophosphamide, given in monthly intravenous pulses of 0.5 to 1.0 g/ m². Response was defined as decreased proteinuria and stabilization or improvement in serum creatinine levels.

Over 24 weeks, the response rate was similar between groups: 20.0 percent with MMF and 16.7 percent with cyclophosphamide. However, MMF was associated with more rapid improvement in kidney function, with a between-group difference of 1.51 mL/min/1.73 m² per week. Serious adverse events occurred in 45.6 percent of patients with MMF versus 63.6 percent with cyclophosphamide.

Randomized trials suggest that oral MMF is an effective alternative to intravenous cyclophosphamide for the treatment of lupus nephritis. It has been unclear whether MMF is adequate therapy for patients with very low kidney function.

The new analysis finds similar response rates—but faster improvement in renal function—with MMF for lupus nephritis patients with low eGFR, compared with cyclophosphamide. The authors hope that their hypothesis-generating study will lead to further studies of the efficacy and safety of MMF for this group of patients [Walsh M, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis with poor kidney function: a subgroup analysis of the Aspreva Lupus Management Study. Am J Kidney Dis 2013; 61:710–715].
digoxin: Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information] concurrent therapy with a UGT inducer and require additional glycemic control when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) [see Warnings and Precautions].

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, when the postprandial plasma glucose concentration fell to less than 40 mg/dL. Biochemical hypoglycemia was documented [any glucose value below or equal to 70 mg/dL]. Severe hypoglycemia was defined as a symptomatic event consistent with at least one of the following: confused, disoriented, tremulous, sweating, pallor, or generalized weakness. It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 14 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilations) during gestation and lactation. Since human milk maturates occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother [see Warnings and Precautions].

Pregnancy: Use and effectiveness of INVOKANA in pediatric patients under 18 years of age has not been established.

Geriatric Use: Two thousand thirty-four (2,304) patients 65 years and older, and 395 patients 75 years and older were exposed to INVOKANA in one clinical trials of INVOKANA [see Clinical Studies (14.3) in full Prescribing Information]. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dizziness) compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older [see Dosage and Administration (2.3) in full Prescribing Information]. Adverse Reactions] (see Dosage and Administration (2.3) in full Prescribing Information). The efficacy and safety of INVOKANA have not been established in patients under severe renal impairment (eGFR less than or equal to 30 mL/min/1.73 m 2) and during the first 2 years of life. In trials of patients with prior history. Provide them with information on the signs and symptoms of balanitis and penile mycotic infections in males (e.g., balanitis or balanoposthitis): Inform male patients that yeast infections and balanitis are common in uncircumcised males. Ask male patients about treatment and reread it each time the prescription is renewed.

Drug Interactions: UGT CYP enzymes: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hyponatremia: Inform patients that symptomatic hyponatremia may occur with INVOKANA and advise them to contact their health care provider if they experience symptoms such as fatigue [see Warnings and Precautions]. Inform patients that dehydration may increase the risk for hyponatremia, and to have adequate fluid intake.

Genital Mycotic Infections in Males (e.g., balanitis or balanoposthitis): Instruct male patients that yeast infections and balanitis are common in uncircumcised males. Ask male patients about treatment and to reread it each time the prescription is renewed.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if symptoms occur.

Active ingredient made in Belgium

**Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypoglycemia</td>
<td>104 (26.4%)</td>
</tr>
<tr>
<td>Moderate Hypoglycemia</td>
<td>34 (8.4%)</td>
</tr>
<tr>
<td>Mild Hypoglycemia</td>
<td>165 (40.7%)</td>
</tr>
</tbody>
</table>

Part of the clinical study was a 26-week randomized, double-blind, placebo-controlled study comparing INVOKANA (canagliflozin) to placebo, metformin, pioglitazone, and glimepiride.

<table>
<thead>
<tr>
<th>Group</th>
<th>HbA1c Change</th>
<th>Placebo</th>
<th>Metformin + Pioglitazone</th>
<th>InvoKana 300 mg + Pioglitazone</th>
<th>InvoKana 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.9%</td>
<td>-0.8%</td>
<td>-0.8%</td>
<td>-0.9%</td>
<td>-0.7%</td>
</tr>
<tr>
<td>Overall (N=183)</td>
<td>7.8%</td>
<td>6.9%</td>
<td>6.9%</td>
<td>6.9%</td>
<td>7.0%</td>
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<tr>
<td>Overall (N=195)</td>
<td>7.8%</td>
<td>6.9%</td>
<td>6.8%</td>
<td>6.9%</td>
<td>7.1%</td>
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<tr>
<td>Overall (N=485)</td>
<td>7.5%</td>
<td>6.5%</td>
<td>6.5%</td>
<td>6.7%</td>
<td>6.7%</td>
</tr>
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</table>

**Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine**

**HYPOGLYCEMIA**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypoglycemia</td>
<td>13 (3.4%)</td>
</tr>
<tr>
<td>Moderate Hypoglycemia</td>
<td>15 (4.0%)</td>
</tr>
<tr>
<td>Mild Hypoglycemia</td>
<td>154 (40.7%)</td>
</tr>
</tbody>
</table>

**Teratogenic Effects: Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal tubular and tubular dilations were observed in the rat offspring exposed to INVOKANA during gestation and lactation.

**Carcinogenesis: An increased incidence of urinary bladder tumors was observed in male rats**

**Hypoglycemia: Hypoglycemia was documented [any glucose value below or equal to 70 mg/dL]. Severe hypoglycemia was defined as a symptomatic event consistent with at least one of the following: confused, disoriented, tremulous, sweating, pallor, or generalized weakness.**

**Drug Interactions: UGT CYP enzymes: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.**

**Hyponatremia: Inform patients that symptomatic hyponatremia may occur with INVOKANA and advise them to contact their health care provider if they experience symptoms such as fatigue [see Warnings and Precautions].**

**Urinary Tract Infections: Inform patients of the potential for urinary tract infections.**

**Active ingredient made in Belgium**

**Teratogenic Effects: Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal tubular and tubular dilations were observed in the rat offspring exposed to INVOKANA during gestation and lactation.
I am privileged to serve as the new Editor-in-Chief of the *Journal of the American Society of Nephrology* (JASN), and I am delighted to introduce our new team. Thanks to the leadership of Dr. Eric Neilson and his team, and prior leadership, JASN holds a premier position among kidney journals, dedicating itself to both the scientific and clinical communities by publishing the very best work in relevant fields. JASN will maintain this important commitment and publish cutting-edge scientific studies and the best in translational studies, epidemiology, clinical trials and research, renal therapies, and renal transplantation. In addition, JASN will be a vibrant voice for issues that are of broad and timely interest to the nephrology community in these challenging times.

To fulfill this mission, a roster of distinguished individuals with expertise encompassing these areas has been assembled, with Dr. Anupam Agarwal serving as Deputy Editor (University of Alabama at Birmingham; AKI, molecular biology, mutant mouse models). Associate editors are listed in Table 1.

JASN is most fortunate to have as its Managing Editor, Ms. Bonnie O’Brien, who has served this role with every distinction from the very first issue of the journal, which was published in July 1990.

Special appreciation and thanks go to Dr. Eric Neilson and Dr. Gary Curhan, Editor-in-Chief of CJASN, for quite helpful discussions, particularly during this transition period, and to Ms. Adrienne Lea, ASN Director of Communications, and Dr. Sharon Moe, President-Elect, ASN, and former Chair of the ASN Communications Committee, for their continued support and input.

The mission of the ASN is to “lead the fight against kidney disease.” JASN actively participates in this mission by publishing new, important, and influential literature pertaining to the science and practice of nephrology, and by engaging the nephrology community in dialog. The new team at JASN is honored to serve this journal and this community, and warmly welcomes feedback so that this remarkable journal can best serve our discipline, our community, and, ultimately, the welfare of patients with kidney disease.

Karl A. Nath, MBChB, is affiliated with the Division of Nephrology & Hypertension, Department of Medicine, and Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN

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**Table 1. JASN’s Associate Editors and their specialties**

- Phyllis August, MD, MPH, Weill Cornell Medical Center hypertension, pregnancy-related kidney disease, epidemiology
- Alfred Cheung, MD, University of Utah end-stage kidney disease, vascular access, CKD, clinical trials
- David Ellison, MD, Oregon Health and Science University renal physiology, tubular disease, molecular pathogenesis of hypertension, edema
- Robert Gaston, MD, University of Alabama, Birmingham transplantation
- Fernando Fervenza, MD, PhD, Mayo Clinic, Rochester human glomerulonephritis and other parenchymal diseases
- Agnes Fogo, MD, Vanderbilt University renal pathology, mechanisms of renal injury
- Ariel Gomez, MD, University of Virginia renal development, renin-angiotensin system, renal autacoids, pediatrics
- Matthew Griffin, MBChB, National University of Ireland, Galway immunology, transplant biology, AKI, regenerative medicine
- Peter Harris, PhD, Mayo Clinic, Rochester molecular genetics of kidney disease
- Keith Norris, MD, Charles R. Drew University of Medicine and Science CKD, renal epidemiology and outcomes, hypertension, health care disparities
- David Salant, MD, Boston University glomerular biology and pathology, glomerulonephritis
- Amy Williams, MD, Mayo Clinic, Rochester dialysis, CKD, public policy, career development, and professionalism

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The full list of abstract categories and their descriptions are available at www.asn-online.org/KidneyWeek

Please note that ALL abstract authors (including co-authors) must have current disclosures on file with ASN at time of submission.
Centers for Disease Control Debuts CKD Surveillance System

Chronic kidney disease (CKD) is a growing public health problem affecting 10–15 percent of the general U.S. population. Yet until recently, the United States lacked a comprehensive surveillance system to document the burden of CKD and its risk factors over time. To address this need, the Centers for Disease Control and Prevention (CDC), as a major part of its CKD Initiative, commissioned two research teams led by Neil Powe, MD, at the University of California, San Francisco, and Rajiv Saran, MD, of the University of Michigan to develop and implement a national CKD Surveillance System. The surveillance system was successfully launched in the fall of 2012 and is currently available on the CDC’s website at www.cdc.gov/ckd/surveillance.

The surveillance system tracks “the progress of our efforts to prevent, detect, and manage CKD,” the CDC writes on the website. It also “provides the means for evaluating, monitoring, and implementing quality improvement efforts by both federal and nonfederal agencies.” Highlights of the surveillance system include a national CKD fact sheet and a specific section to evaluate progress toward achieving Healthy People 2020 objectives for CKD.

Data is arranged within categories, so that specific indicators, such as “percentage of patients seeing a nephrologist by stage,” are nested within broader topics, such as “processes and quality of care in CKD.” There are currently nine broad topics: incidence, prevalence, awareness, burden of risk factors, health consequences, processes and quality of care, health care system capacity, CKD in children and adolescents, and CKD in the solid organ transplant population. Each broad topic contains multiple indicators. Tables and figures are downloadable.

“What’s novel about this surveillance system is that it brings CKD data from disparate data sources together into one location,” Powe said. “Integration of multiple data sources is one of the main goals of this project, enabling us to help provide a complete picture of national trends in CKD.”

The current surveillance system contains data from many resources, including measures derived from the National Health and Nutrition Examination Surveys (NHANES), the Veterans Affairs Healthcare System (National VA), the United States Renal Data System (USRDS), the National Kidney Disease Education Program (NKDEP), the College of American Pathologists (CAP), and the American Medical Association (AMA), to name a few. Data sources are rigorously evaluated for characteristics that would make them useful to include in a surveillance system, including representativeness and stability over time.

“Key goals of this surveillance system are to monitor trends, promote CKD prevention and stimulate improvement of CKD care,” Powe said. “We’re hoping to disseminate the data as widely as possible so that it may be used to its fullest public health potential.”

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Detective Nephron, world-renowned for expertise in analytical 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 consultant.

Ms. Curious Tubule enters the room along with L.O. Henle to present a case.

Nephron My apprentice, what do you have for me? And we have our medical student back. Good!

Henle and Tubule look at each other.

Henle I have a patient with a potassium level of 1.8 mmol/L.

Nephron (chuckling) Hmm. That is really low. Can the patient walk?

Tubule (confidently) No, that is why this 43-year-old woman is here with profound lower extremity weakness leading to being bedridden for the past 2 days.

Nephron That's always the problem. Figuring out the cause is more important. I am assuming the medical team has started replacing her potassium. What do you think is causing all this?

Henle Broadly speaking, hypokalemia can result from potassium losses or translocation.

Nephron Good place to start.

Tubule (curiously) Can you elaborate on translocation?

Nephron Good! And?

Henle Well, translocation refers to shifting of potassium into cells. This can result from two major mechanisms. The first is from increased work of Na-K ATPase, which can be noticed in patients with hyperinsulinemia. This is also the reason why patients in refeeding syndrome can become hypokalemic. An increase in β-2 adrenergic activity also increases the activity of this pump, leading to hypokalemia. The second mechanism is stimulation of the cellular H+ and K+ exchange that can be sometimes seen in alkalemia leading to potassium being pumped into the cells and hypokalemia. Also, sometimes in leukocytosis (e.g., in acute myeloid leukemia), there may be uptake of potassium by the leukocytes, leading to pseudohypokalemia.

Tubule Also, I have heard that increased blood cell production, as seen in treatments with folate and vitamin B12 for anemia and GM-CSF for neutropenia, can result in hypokalemia.

Henle I doubt this patient has any of them, because the leukocyte count, hemoglobin, and platelets are completely normal. She has been eating a regular diet, has normal blood glucose levels, and has not recently been using β-2 adrenergic agents. She really didn't have many symptoms except for this weakness and perhaps some dry eyes and mouth for the past 3 months.

Nephron Good thought process. Since you’ve started, let us now complete the other side of the equation.

Tubule (confidently) In terms of renal losses, that’s a long list.

Nephron Her 24-hour urine potassium must be more than 20 mmol.

Tubule Of course you can guess the number correctly. Actually, it was 41 mmol in 24 hours. Also, her urine pH is 6.5, and her random urine electrolytes are Na, 34 mmol/L; K, 21 mmol/L; and Cl, 35 mmol/L. Therefore, her urine anion gap is +20.

Henle Wait a second! Clearly, we know there are urinary losses here, and there is a positive anion gap, which suggests possibly a renal tubular acidosis (RTA), given that she had normal renal function. But there are other mechanisms we need to consider. Nephron: Please enlighten us, my friend.

Nephron Please enlighten us, my friend.

Henle I look at renal causes in physiology-based mechanisms. Increased distal sodium delivery as a cause of the K+ losses is one category (diuretics, vomiting, Bartter and Gitelman syndromes), but in those cases mostly there is some degree of alkalosis, which this patient lacks. I doubt this is Liddle syndrome, with increased epithelial sodium channel activity.

Tubule Do you want to know the magnesium level?

Nephron Of course I do. That is another mechanism via decreased renal outer medullary potassium inward rectification.

Tubule And the magnesium was 1.02 mmol/L (2.5 mg/dL).

Nephron Is hypertension present?

Tubule No, which rules out increased mineralocorticoid activity increase (again mostly with some metabolic alkalosis).
Aggressive potassium repletion was initiated with combined oral potassium tablets and intravenous fluids. By day 2 of hospitalization, the patient reported marked improvement in overall strength, and her potassium had risen to 3.5 mmol/L. She was discharged on hospital day 6, receiving potassium replacement with potassium citrate.
Medgenics’ Biopump Shows Good Early Results

Medgenics has announced early data from its phase II clinical trial with the EPODURE biopump device. This trial used the company’s proprietary biopump to deliver the drug erythropoietin, or EPO, to anemic patients with chronic kidney disease who had not yet begun dialysis.

The company, based in Karmiel, Israel, has produced biopump applications for treating several chronic diseases, including hepatitis C, and is in the early stages of developing a biopump application that would treat hemophilia. The biopump allows patients to produce, in their bodies on a long-term basis, their own natural human protein therapy. Cells are taken from patients, treated, placed in the biopump, and then the sterilized pump is implanted.

The recent trial results showed that the EPODURE pump produced an environment that let hemoglobin remain in a desired range for 2 to 4 months without any additional injections. The company noted that the treatment never went past the typical normal range for hemoglobin.

The company plans a larger phase II trial for later this year, according to the firm’s website.

“We believe that EPODURE could improve the safety and efficacy of anemia treatments while enhancing patient quality of life by providing a more reliable treatment that reduces or eliminates the need for frequent EPO or ESA injections,” said Medgenics chief executive Andrew Pearlman. He added that the system “could provide clear cost benefits to payers.”

In recent years EPO drugs have been in the news for several reasons, including investigations into dialysis provider DaVita for overuse of the drug Epogen (made by Amgen), and double billing the government for drug that is left in vials and reused, according to a July 2012 Denver Post story. DaVita agreed to pay $55 million to settle over allegations of drug overuse; the company denied any wrongdoing.

Amgen also has settled suits, entering a guilty plea at the U.S. District Court in Brooklyn for misbranding its anemia drug, Aranesp, which meant that the company was accused of selling it for uses not approved by the FDA.

NxStage Gets FDA Clearance for New High-Flow Capabilities

On April 30, the U.S. Food and Drug Administration (FDA) granted NxStage Medical clearance for its new high-flow capabilities with the NxStage System One, a portable hemodialysis system cleared for home use. With this clearance, NxStage Medical, based in Lawrence, Mass., expects to begin offering its System One with new higher flow capabilities in the United States later in 2013.

The higher flow capabilities will allow practitioners to adjust the duration and frequency of patient prescriptions for dialysis at home.

“This latest regulatory milestone reflects strong and systematic execution against our product pipeline,” said Jeffrey Burbank, chief executive officer at NxStage Medical, Inc. “NxStage therapy may be prescribed less frequently, for example, three times per week or every other day, at treatment times consistent with those that patients and physicians experience in-center (in dialysis centers) today.”

NxStage’s high flow capabilities also received CE mark approval (CE marking is the manufacturer’s declaration that a product meets the requirements of the applicable European Union rules for marketing a product freely in those areas).

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Join us in the beautiful Pacific Northwest! Our physicians enjoy competitive salaries in addition to an extensive benefit package which includes medical, dental, disability and life insurance; generous retirement plans; vacation, sabbatical and educational leave; and professional liability coverage. Physicians are also eligible for Senior Physician and Shareholder standing after approximately three years with the group (must be Board Certified by that time).

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