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Treating Osteoporosis in Older Female Dialysis-Dependent Patients

Postmenopausal women commonly develop osteoporosis, which is associated with a loss of bone density, weak and brittle bones, and increased risk of fracture. Compared with the general population, patients with chronic kidney disease (CKD) have a greater risk of fracture. Among patients undergoing long-term dialysis, the prevalence of CKD-mineral and bone disorder (CKD-MBD) is high.

CKD-MBD is characterized by abnormalities of serum phosphorus, calcium, parathyroid hormone, and vitamin D; abnormalities in bone turnover, mineralization, volume, and strength; and vascular calcification. Older dialysis-dependent patients are at high risk of low bone mass associated with primary osteoporosis, CKD-MBD, or both.

The Kidney Disease: Improving Global Outcomes guidelines do not endorse a specific treatment strategy for bone disease in patients dependent on dialysis but recommend that the risks of treatment be weighed against the underlying bone phenotype. **Steven T. Bird, PhD, PharmD,** and colleagues sought to examine the incidence and differential risk of severe hypocalcemia in female patients receiving long-term dialysis treated for osteoporosis with denosumab or oral bisphosphonates. Results were reported in *JAMA* [2024:331(6):491-499].

The retrospective, cohort study included women who were Medicare beneficiaries, dependent on dialysis, and ≥65 years of age. Eligible patients

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A Look at Pregnancy-Related End-Stage Kidney Disease Outcomes

US rates of maternal severe morbidity and mortality are much higher than elsewhere in the world. Contributing significantly to maternal morbidity is acute kidney injury (AKI) during pregnancy. AKI during pregnancy is associated with 13 times greater odds of maternal mortality and a 30% to 60% greater risk of fetal mortality and morbidity. Pregnancy-related AKI is increasing and likely to continue trending upward. Incidence more than doubled, from 2.4 to 6.3 cases per 10,000, between 1999 and 2011. Meanwhile, Black patients are three times more likely than White patients to experience death from a pregnancy-related cause, which is likely an effect of structural racism.

A 2017 systematic review and meta-analysis of 845 pregnancies affected by AKI found that in about 2.4% of cases, pregnancy-related AKI resulted in end-stage kidney disease (ESKD). However, that number is likely too low, because it may not

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Assessing the Risk of Recurrent Gout Using Serum Urate Level

More than 12 million adults in the United States are affected by gout. There are associations between episodes of acute gout and severe pain, and reductions in quality of life, as well as a transient increase in major cardiovascular and venous thrombotic events. Accumulation of monosodium urate crystallization in the joints, often due to chronic hyperuricemia, is the primary cause of acute gout.

According to **Natalie McCormick, PhD,** and colleagues, there are few data available on the associations between serum urate levels and the risk of recurrent gout among patients with a history of gout. The researchers conducted a retrospective study of patients with a history of gout treated in the primary care setting to identify the associations between baseline serum urate levels and subsequent episodes of acute gout, including acute gout requiring hospitalization. Results were reported in *JAMA* [2024;331(5):417-424].

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IgA Nephropathy: On the Cusp of a Definitive Treatment?

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IgA nephropathy (IgAN) is the commonest primary glomerular disease globally.[1] It can present quite benignly as microscopic hematuria with scattered mesangial deposits of IgA, as nephrotic syndrome, or in a more fulminant form as rapidly progressive glomerulonephritis with crescents on kidney biopsy. It affects children and adults, young and old. Some studies suggest that IgAN might be more common among Asian populations, but ascertainment bias for this observation has been suggested. Hitherto, the main approaches to therapy have centered around supportive measures such as renin angiotensin system (RAS) blockade and, more recently, sodium-glucose cotransporter-2 inhibitor therapy, both of which aim to slow kidney progression. In patients at high risk, including those with heavy proteinuria (>1 g/24 hours) or whose renal biopsy findings suggest a more aggressive course, therapy with corticosteroids and endothelin blockade (eg, sparsentan) has been recommended. Specific therapy targeted at the underlying etiology has proved elusive, at least so far.

In 1993, Mestecky proposed that defective galactosylation and clearance of IgA1 molecules could be of etiopathogenic significance in IgAN.[2] Subsequently, in 1999, Tomana, from Mestecky's group, demonstrated that the circulating immune complexes in IgAN consist of IgA1 with galactose-deficient hinge region and published the results in the *Journal of Clinical Investigation*.[3] That the central defect in IgAN is the production of IgA1 deficient in galactose residues in its hinge region was a pivotal discovery. It quickly became evident that galactose-deficient IgA1 (Gd-IgA1) stimulates the production of pathogenic or nephritogenic autoantibodies, which in turn lead to the production of circulating Gd-IgA1 immune complexes that deposit in the mesangium. However, because mesangial IgA deposition in and of itself does not cause disease, a multihit process has been proposed. Other hits are also thought to be very important: abnormal signaling in IgA1-producing cells; cytokines such as the TNF superfamily molecule, "a proliferation-inducing ligand," or APRIL; activation of complement; and genetic factors, because increased levels of Gd-IgA1 is a hereditable trait.

The immunopathologic mechanisms underlying IgAN had been poorly understood, resulting in a lack of a specific therapy. The unraveling of the immunopathogenesis of IgA1 has resulted in many lines of investigation and drug development.[4] Now, we are on the verge of having definitive targeted therapy available for IgAN.

APRIL has emerged as a critical factor in the pathogenesis of IgAN and is the focus of several clinical development programs. It has been implicated in two processes in IgAN (see **Figure**): mediating the Ig isotype switch during B-cell development that leads to production of IgA and galactose-deficient IgA1 and prolonging plasma cell survival.

Serum APRIL levels are elevated in patients with IgAN, and higher APRIL levels are associated with more rapidly progressive kidney disease. Visterra, which is now part of Otsuka, was the first major company to develop and publish its work on APRIL. Other companies are not far behind.

The Visterra molecule is sibeprenlimab, a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL. In first-to-human studies, sibeprenlimab demonstrated remarkable efficacy in reversibly reducing serum IgA and Gd-IgA1 in human volunteers.[5] In a mouse model of IgAN (ddY mice), anti-APRIL antibodies reduced both IgA and Gd-IgA1 levels, reduced kidney-localized complement C3, and substantially reduced immune deposits in the kidney.[6] In January 2024, the phase 2 ENVISION study of sibeprenlimab was published in the *New England Journal of Medicine*.[7] In that study, Mathur and colleagues provided the first clinical glimpse of a therapy that specifically interfered with the immunopathogenesis of IgAN. Briefly, ENVISION was a double-blind, randomized, placebo-controlled, parallel group trial. Patients with IgAN at high risk of progression despite standard care for IgAN and maximized RAS blockade received 2, 4, or 8 mg/kg body weight or placebo monthly over 12 months. The primary end point was a surrogate outcome: change from baseline in the log-transformed 24-hour urinary protein to creatinine ratio (UPCR) at 12 months. Secondary end points included a change in estimated glomerular filtration rate (eGFR) at 12 months compared with baseline, changes in UPCR at 9 and 16 months compared with baseline, and changes in immunoglobulin levels of IgA, IgM, and IgG at various points.

ENVISION enrolled 155 patients. A total of 117 were randomized to one of three different monthly doses of sibeprenlimab, and 38 received placebo. At 12 months there

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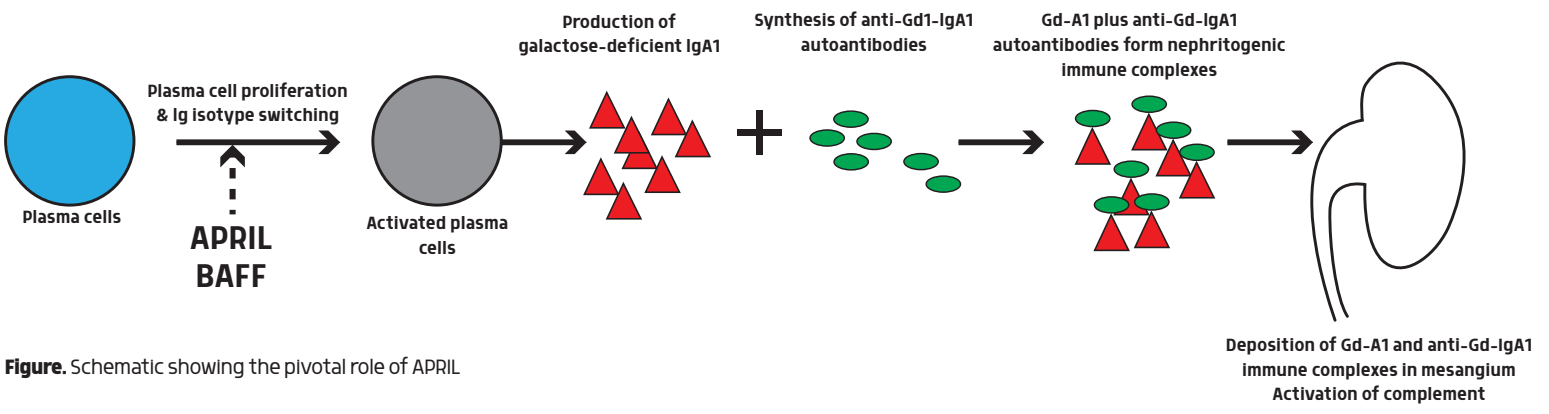

Figure. Schematic showing the pivotal role of APRIL

From the Chair

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was a dose-dependent 47% to 62% reduction in UPCR in patients who received sibeprenlimab (2-mg dosing was associated with a 47% reduction, 4 mg with 59%, and 8 mg with 62%, respectively, in UPCR). There also appeared to be a less steep decline in eGFR over 12 months in patients treated with sibeprenlimab as compared with placebo. Patients treated with higher doses of sibeprenlimab (4 mg and 8 mg) had an approximate 65% reduction in Gd-IgA1 and IgA, which then recovered to their baseline levels after discontinuation of sibeprenlimab. Treatment with the higher doses of sibeprenlimab led to a persistent reduction in proteinuria (even at 16 months, ie, several months after discontinuation of sibeprenlimab therapy). However, higher levels of sibeprenlimab (4 mg and 8 mg) were needed to persistently suppress APRIL and Gd-Ig-A1 antibody levels beyond 12 months.

Sibeprenlimab was well-tolerated, at least over the duration of the study. Adverse events in patients treated with sibeprenlimab were similar to those in the placebo group. There was no heightened risk of infection among sibeprenlimab patients compared with placebo.

What does this all mean? First, blocking APRIL with sibeprenlimab effectively inhibits the causal pathway to IgAN with no obvious adverse consequences. Second, and more broadly, designer-made antibodies like sibeprenlimab can target important mediators and could be applied to many other diseases—an obvious example being lupus nephritis. Third, targeting APRIL, which works by depleting B-cell activity but does so specifically, may allow future therapies to become more focused and therefore better tolerated.

The ENVISION study was only a phase 2 trial, and so additional work (eg, a phase 3 study) on a larger number of patients with longer follow-up and more hard end points is needed, although an interim approval based on the phase 2 data is possible.

Questions remain. It is unclear how long patients should be exposed to the therapy and what the longer-term side effects might be, but much progress has been made. We are now at the threshold of a new era.

Disclosure: Dr. Singh is chair of the Data Monitoring Committee for the BEYOND clinical trial (BION-1301) sponsored by Chinook. ■

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Pregnancy-Related ESKD Outcomes

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include instances of ESKD that occurred in the months to years following a pregnancy rather than developing immediately. Research is lacking on the longer-term outcomes of patients who develop pregnancy-related ESKD. A group of researchers led by **Lauren M. Kucirka, MD, PhD,** sought to fill this gap with a study published in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.46314].

The researchers pursued a threefold objective: to describe the demographic and clinical characteristics of patients who developed pregnancy-related ESKD in a national cohort; to look at ESKD outcomes, including survival and access to kidney transplantation, for patients with pregnancy-related ESKD compared with reproductive-aged women with other causes of ESKD; and to examine differences in predialysis care for patients with pregnancy-related ESKD.

The study examined a cohort of 183,640 birthing-aged women (ages 14-50 years) with incident ESKD between January 2000 and November 2020 from the US Renal Data System, a national registry of all patients with ESKD in the United States, and publicly available birth certificate data from the Centers for Disease Control and Prevention National Center for Health Statistics. Multivariable Cox proportional hazards and competing risk models were created to examine time to mortality, access to kidney transplant (joining the waiting list or receiving a live donor transplant), and the receipt of a transplant after joining the waiting list.

Researchers identified 341 patients with a pregnancy-related primary cause of ESKD (mean [SD] age, 30.2 [7.3] years). Black patients were overrepresented among those with pregnancy-related ESKD compared with the general US birthing population (31.9% vs 16.2%). The primary cause of kidney failure was determined via Centers for Medicare & Medicaid Services form 2728. A pregnancy-related primary cause of ESKD was identified if any of the following *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis codes were reported per form 2728: 64620, 64620A, 64620a, 64620Z, 64620z, 6462Z, 6462z, or O904. Although pregnancy may have been a contributing cause in some cases, this study captures only patients for whom pregnancy was considered the primary cause of ESKD.

In adjusted analyses, patients with pregnancy-related ESKD had similar or lower hazards of mortality compared with those with glomerulonephritis or cystic kidney disease (adjusted hazard ratio [aHR], 0.96; 95% CI, 0.76-1.19), diabetes or hypertension (aHR, 0.49; 95% CI, 0.39-0.61), or other or unknown primary causes of ESKD (aHR, 0.60; 95% CI, 0.48-0.75). However, patients with pregnancy-related ESKD had significantly lower access to kidney transplant compared with those with other causes of ESKD, such as glomerulonephritis or cystic kidney disease (adjusted subhazard ratio [aSHR], 0.51; 95% CI, 0.43-0.66), diabetes or hypertension (aSHR, 0.81; 95% CI, 0.67-0.98), or other or unknown causes (aSHR, 0.82; 95% CI, 0.67-0.99). Those with pregnancy-related ESKD also were less likely to have nephrology care or have a graft or arteriovenous fistula placed before onset of ESKD (nephrology care: adjusted relative risk [aRR], 0.47; 95% CI, 0.40-0.56; graft or arteriovenous fistula placed: aRR, 0.31; 95% CI, 0.17-0.57).

The findings underline a significant lack of kidney transplant and predialysis access for those with pregnancy-related ESKD. Patients with pregnancy-related ESKD were significantly less likely to have nephrology care or be informed about kidney transplant before ESKD onset, and only 4% had a graft or fistula placed. Early access to nephrology care has been repeatedly shown to improve dialysis outcomes and likelihood of receiving a kidney transplant, so early referral to nephrology care and long-term follow-up is critical.

The study likely underestimated the burden of pregnancy-related ESKD because it only captured extreme cases in which the nephrologist felt that pregnancy was a primary contributing cause. Furthermore, the use of form 2728 for collecting data has limitations. Relying on form 2728 could lead to misclassification of the primary cause of ESKD. Previous research indicates that Black patients with ESKD may be more likely to be incorrectly categorized as having hypertension as the primary cause. Thus, results may underestimate the real racial disparity in pregnancy-related ESKD. Also, details about specific clinical events that led to a diagnosis of pregnancy-related ESKD are lacking. Processes for verifying the accuracy of details on form 2728 vary by center and clinician. In addition, comorbidities are reported on the medical evidence form at the time of ESKD onset, so researchers were unable to account for changes in comorbidity status or severity over time, which could have negatively impacted access to transplant.

In conclusion, the study's findings draw attention to racial disparities in pregnancy-related AKI incidence, which increases Black patients' odds for significant maternal morbidity, including progression to ESKD. The authors remarked, "In this study, those with pregnancy-related ESKD had reduced access to transplant and nephrology care, which could exacerbate existing disparities in a disproportionately Black population. Increased access to care could improve quality of life and health outcomes among these young adults with high potential for long-term survival." They also noted that, although this study focused on patients with a pregnancy-related primary cause of ESKD, the results should inspire improvements in clinical care and future research for the larger population of patients with pregnancy-related AKI who are at significant risk for severe morbidity and mortality. ■

Assessing the Risk of Recurrent Gout

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The study cohort included patients in the United Kingdom with a history of gout between 2006 and 2010 who were followed up through Primary Care Linked Data medical record linkage through 2017 and through the Hospital Episode Statistics database until 2020. The study exposure was serum urate level at baseline. The primary outcome of interest was the rate of recurrent acute gout, assessed by hospitalization, outpatient, and prescription records, and adjusted rate ratios using negative binomial regressions.

Based on population studies for incident gout risk among individuals without gout at baseline, serum urate levels were categorized as: (1) <6.0 mg/dL; (2) 6.0 to 6.9 mg/dL; (3) 7.0 to 7.9 mg/dL; (4) 8.0 to 8.9 mg/dL; (5) 9.0 to 9.0 mg/dL; and (6) ≥10.0 mg/dL. A serum urate level <6.0 mg/dL served as the reference group.

Following exclusion of patients with missing covariate values for body mass index (BMI) and estimated glomerular filtration rate (n=21), the final study cohort included 3613 individuals from the UK database who had a history of gout and underwent measurement of serum urate between April 28, 2007, and September 29, 2019. Of the 3613 study participants, 86% (n=3104) were men and the mean age was 60 years. At baseline, the mean serum urate level was 6.87 mg/dL.

There were associations between higher serum urate categories and male sex, higher BMI, greater alcohol consumption, smoking, greater intake of red meat, and the presence of chronic kidney disease (CKD). There were also associations between lower serum urate categories and older age and use of urate-lowering therapy.

Follow-up continued for a mean of 8.3 years. During follow-up, there were 1773 new episodes of gout treated in the primary care setting or requiring hospitalization. Of the 3613 study participants, 72% had zero acute gout episodes, 16% had one acute gout episode, 6% had two acute gout episodes, and 5% had at least three acute gout episodes. Overall, 95% (n=1679/1773) of acute gout episodes occurred in patients with baseline serum urate ≥6 mg/dL and 98% (n=1731/1773) in those with baseline serum urate ≥5 mg/dL.

There were associations between serum urate levels and recurrent gout in a graded manner. Following adjustment of rate ratios (RRs) for age, sex, and race, the rates of acute gout flares per 1000 person-years were 10.6 for those with baseline urate levels <6 mg/dL (adjusted RR, 1.0), 40.1 for levels of 6.0 to 6.9 mg/dL (adjusted RR, 3.37; 95% CI, 2.60-4.39), 82.0 for levels of 7.0 to 7.9 mg/dL (adjusted RR, 6.93; 95% CI, 5.43-8.84), 101.3 for levels of 8.0 to 8.9 mg/dL (adjusted RR, 8.67; 95% CI, 6.74-11.14), 125.3 for levels of 9.0 to 9.9 mg/dL (adjusted RR, 10.81; 95% CI, 8.02-14.56), and 132.8 for levels ≥10 mg/dL (adjusted RR, 11.42; 95% CI, 7.72-16.90); *P* for trend <.001.

Following further adjustment for BMI; smoking status; consumption of alcohol, coffee, red meat, fish, and poultry; use of diuretic and urate-lowering therapy; and diabetes, cardiovascular disease, hypertension, and CKD, the corresponding RRs were 1.00, 3.16, 6.20, 7.77, 9.80, and 11.26 (95% CI, 7.47-16.97), respectively; *P* for trend <.001. There was an association between each increase in serum urate of 1 mg/dL and a 61% increase in recurrent flare rate (RR, 1.61; 95% CI, 1.54-1.68). In the fully adjusted model, the corresponding RR was 1.58 (95% CI, 1.50-1.66) per mg/dL.

The RRs of flares were 1.00, 3.37, 6.93, 8.67, 10.81, and 11.42, respectively, over 10 years. Associations between baseline serum urate level and flare rate were similar among subsets defined by sex, race, presence of CKD, diuretic use, and urate-lowering therapy.

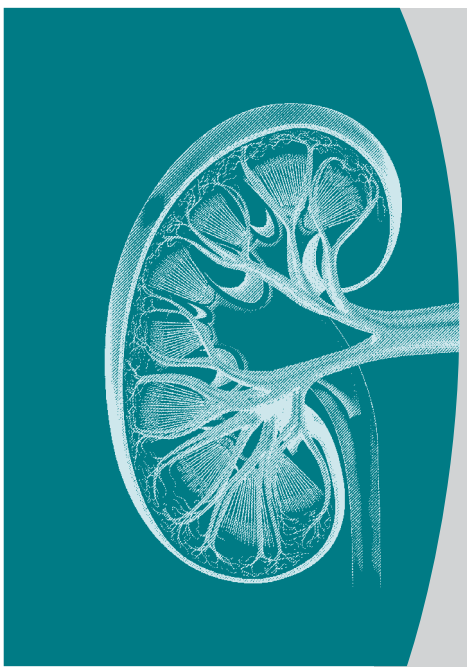
There were 64 documented hospitalizations with gout as the primary discharge diagnosis. Of those, 62 (97%; 95% CI, 93%-100%) occurred in individuals with baseline serum urate ≥6 mg/dL and all 64 (100%; 95% CI, 94%-100%) occurred in those with baseline serum urate ≥5 mg/dL. The rates of hospitalization for gout (and RRs adjusted for age, sex, and race) per 1000 person-years were 0.18 for serum urate ≤6.0 mg/dL (adjusted RR, 1.0), 0.97 for serum urate 6.0 to 6.9 mg/dL (adjusted RR, 4.70; 95% CI, 0.98-22.53), 1.8 for serum urate 7.0 to 7.9 (adjusted RR, 8.94; 95% CI, 2.03-39.39), 2.2 for serum urate 8.0 to 8.9 mg/dL (adjusted RR, 10.37; 95% CI, 2.31-46.62), 6.7 for serum urate 9.0 to 9.9 (adjusted RR, 33.92; 95% CI, 7.50-153.36), and 9.7 for serum urate ≥10 mg/dL (adjusted RR, 45.29; 95% CI, 9.01-227.70).

The researchers cited some limitations to the study findings, including the inability to measure acute gout flares that were not treated by medical personnel, the relatively small size of some of the subgroups, and the study design that may have led to confounding.

In conclusion, the researchers said, "In this retrospective study of patients with history of gout, serum urate levels at baseline were associated with the risk of subsequent gout flares and with rates of hospitalization for recurrent gout. These findings support using a baseline serum urate [value] to assess risk of recurrent gout over nearly 10 years of follow-up." ■

TAKEAWAY POINTS

- Researchers in the United Kingdom conducted a retrospective study to determine whether serum urate levels can predict recurrence of gout flares.
- In a cohort of patients with a history of gout, there was an association between higher serum urate levels at baseline and higher rates of recurrent gout and hospitalization for gout.
- The findings support using a baseline serum urate value to assess the risk of gout flares over nearly 10 years of follow-up.



Treating Osteoporosis

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initiated treatment for osteoporosis with denosumab or oral bisphosphonates from 2013 to 2020. Linkage to the Consolidated Renal Operations in a Web-Enabled Network database was used to obtain clinical measures. The study exposures were denosumab 60 mg or oral bisphosphonates.

The primary outcomes of interest were severe hypocalcemia, defined as total albumin-corrected serum calcium below 7.5 mg/dL, or a primary hospital or emergency department hypocalcemia diagnosis (emergent care). The study also assessed the incidence of very severe hypocalcemia, defined as serum calcium below 6.5 mg/dL, or emergent care. During the first 12 weeks of treatment, inverse probability of treatment-weighted cumulative incidence, weighted risk differences, and weighted risk ratios were calculated.

The study included 1523 women who were treated with denosumab and 1281 who were treated with oral bisphosphonates, weighted to 1501 oral bisphosphonate users in the balanced cohort. More than 90% of those in the oral bisphosphonate users group received alendronate (91.8%); 75.7% of those received 70 mg weekly. In both groups, nearly all participants had no antiresorptive treatment in the prior 15 months (95.8% in the denosumab group and 99.1% in the oral bisphosphonate group).

Because the participants in the denosumab group received an injection every 6 months, they were considered exposed for the entire study time. In the oral bisphosphonate group, 322 (21.5%) women discontinued treatment in month 2 and 90 (6.09%) discontinued treatment in month 3. Following weighting, the two groups were well balanced for all covariates. The mean age in the denosumab group was 74.5 years versus 73.8 years in the oral bisphosphonate group.

In both groups, nearly all participants had a diagnosis of osteoporosis (98.4% in the denosumab group and 97.8% in the oral bisphosphonate group), as well as markers for CKD-MBD, including hyperparathyroidism (97.0% vs 97.3%), use of a vitamin D analogue (62.1% vs 66.4%), and use of a phosphate binder (non-calcium based, 54.7% vs 55.5%; calcium based, 31.0% vs 33.3%).

Most denosumab (55.7%) and oral bisphosphonate (90.7%) prescriptions were from primary care physicians. Endocrinologists and rheumatologists prescribed a larger share of denosumab (29.2%) than of oral bisphosphonates (2.3%). Nephrologists infrequently prescribed either denosumab (2.3%) or oral bisphosphonates (2.6%).

Prior to initiation of therapy, median total albumin-corrected serum calcium levels were similar between the two groups (9.3 mg/dL for the denosumab group and 9.2 mg/dL for the oral bisphosphonate group). Following initiation of denosumab, median levels of serum calcium dropped sharply within the first month and remained below baseline for 4 months. In the oral bisphosphonate group, median serum calcium levels remained unchanged. Most cases of severe hypocalcemia with denosumab occurred during weeks 2 through 5; an increased probability of severe hypocalcemia remained through approximately post-treatment week 10.

In unweighted cohorts, 39.9% (n=607) of the 1523 patients treated with denosumab and 1.8% (n=23) of the 1281 patients treated with oral bisphosphonates developed severe hypocalcemia. There was a sharp rise in the weighted cumulative incidence of severe hypocalcemia within 1 week of initiation of denosumab, and by 12 weeks reached 41.1% (95% CI, 38.5%-43.6%), compared with 2.0% (95% CI, 1.0%-3.0%) among oral bisphosphonate users (weighted risk difference, 39.1% [95% CI, 36.3%-41.9%]; weighted risk ratio, 20.7 [95% CI, 13.2-41.2]; and weighted hazard ratio [HR], 26.6 [95% CI, 15.8-44.9]).

By 12 weeks, the weighted cumulative incidence of very severe hypocalcemia was 10.9% in the denosumab group, compared with 0.4% in the oral bisphosphonate group (weighted risk difference, 10.5% [95% CI, 8.8%-12.0%]; weighted risk ratio, 26.4 [95% CI, 9.7-449.5]; and weighted HR, 28.0 [95% CI, 8.4-93.6]).

In the denosumab group, the incidence of severe hypocalcemia was substantially higher among those with mild to moderate hypocalcemia (7.5 mg/dL to <8.5 mg/dL) at treatment initiation compared with those with normal baseline serum calcium (>8.5 mg/dL; incidence, 62.9% vs 30.0%, respectively).

Among patients with severe hypocalcemia, 10.7% (n=65/607) treated with denosumab and none treated with oral bisphosphonates required hospitalization following diagnosis. Among 549 patients in the denosumab group who had 90 days or more of subsequent Medicare enrollment, serum calcium returned to normal by day 90 in 65.8% (n=361).

Limitations to the study findings cited by the authors included not using a randomized trial design, lack of data on the decision to prescribe denosumab versus oral bisphosphonates, as well as lack of laboratory data for levels of vitamin D, alkaline phosphatase, or parathyroid hormone. They also noted an inability to measure over-the-counter supplementation with calcium and vitamin D and adherence to supplementation recommendations.

In conclusion, the researchers said, "This study identified a higher incidence of severe and very severe hypocalcemia after denosumab initiation compared with oral bisphosphonates in dialysis-dependent patients with mild to moderate hypocalcemia at baseline. Given the complexity of diagnosing the underlying bone pathophysiology in dialysis-dependent patients, the high risk posed by denosumab in this population and the complex strategies required to monitor and treat severe hypocalcemia, denosumab should be administered after careful patient selection and with plans for frequent monitoring." ■

TAKEAWAY POINTS

- Researchers reported results of a study evaluating the incidence and differential risk of severe hypocalcemia in female dialysis-dependent patients treated for osteoporosis with denosumab or oral bisphosphonates.
- At 12 weeks of treatment, the weighted cumulative incidence of severe hypocalcemia was 41.1% in the denosumab group versus 2.0% in the oral bisphosphonate group.
- The results suggested that denosumab should be administered in this patient population only after careful patient selection and with frequent monitoring.

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Diet and Nutrition in Diabetic, Nondiabetic Patients With CKD

Diet and nutrition are vital to nephroprotection in patients with chronic kidney disease (CKD); hence, it is standard practice to advise decreased protein intake in CKD to slow the decline of renal function. In adults with stage 3-5 CKD, current Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines suggest reducing dietary protein intake (DPI) to 0.55-0.60 g/kg/day or to 0.28-0.43 g/kg/day with keto acid supplementation. Achieving a sufficient dietary energy intake (DEI) can improve low-protein diet safety and adherence. In the late stages of CKD, the current recommendation is to maintain a DEI around 25-35 kcal/kg/day.

Nutritional status did not differ significantly between diabetic and nondiabetic patients; however, patients with stage 4-5 CKD with diabetes consumed less calcium and had lower lean body mass and higher BMI compared with subjects without diabetes.

TAKEAWAY POINTS

- Researchers assessed the dietary intake and nutritional status of patients with stage 4-5 CKD according to the presence of diabetes.
- Both diabetic and nondiabetic patients had lower than recommended dietary energy intake (DEI) and fiber and calcium intakes.
- DEI and dietary protein intake did not differ significantly between diabetic and nondiabetic CKD patients. Diabetes was not associated with dietary intake in the present cohort.

Studies have demonstrated that high protein intake increases intraglomerular pressure and glomerular hyperfiltration, leading to kidney injury and decreased kidney function. Conversely, experimental models and studies in humans have shown improved kidney function when protein was restricted in CKD patients without diabetes. Therefore, protein restriction is thought to help reduce progression toward end-stage kidney disease (ESKD).

Diabetic kidney disease (DKD) is distinguished by albuminuria and reduced estimated glomerular filtration rate (eGFR). These are independent risk factors for ESKD, cardiovascular events, and death. Although DKD is the most common cause of CKD worldwide, current practice guidelines do not address dietary management specific to DKD, due in part to a lack of knowledge regarding specific interventions for DKD; most nutrition studies in DKD have been observational and often retrospective. KDIGO guidelines for diabetes management in CKD recommend maintaining a DPI of 0.8 g protein/kg/day for patients with concurrent diabetes and CKD. The guidelines further specify that patients with DKD should consume a high volume of fruits and vegetables and plant-based proteins and limit consumption of processed meats.

An observational, cross-sectional study led by **Mariana Cassani Oliveira, PhD,** and published in the *Journal of Renal Nutrition* [2024;34(1):19-25] sought to assess the dietary intake and nutritional status of patients with stage 4-5 CKD according to the presence of diabetes. The study included 75 subjects with CKD who were referred to a nephrology unit between October 2018 and March 2019. These subjects had a median age of 71 years, and 36 (48%) of them had diabetes in addition to CKD.

Patients aged older than 18 years, with eGFR ≥30 mL/min/1.73m^2 (stage 4-5 CKD) according to the CKD-Epidemiology Collaboration formula, and nondialyzed were included. The study excluded those not able to report a reliable nutritional intake diary or undergo clinical assessment. Age, sex, diabetes status, renal disease, and biochemical parameters were recorded for all patients. Diabetes was defined by an HbA1C >6.5%, fasting glycemia >7 mmol/L, and/or use of a hypoglycemia treatment or insulin, and/or diabetes diagnosis.

Researchers evaluated subjects' daily dietary intake by 24-hour dietary inquiry and urine excretion. They assessed nutritional status by measuring body composition using bioimpedance analysis and muscle function using handgrip strength. Undernutrition was considered using the protein energy wasting (PEW) score.

Patients were considered to have PEW if they presented at least three of the following criteria: body mass index (BMI) <23 kg/m^2, albumin <38 g/L, prealbumin <300 mg/L, and normalized protein catabolic rate <0.8 g/kg/24 hours according to Fouque et al. Handgrip strength measures were evaluated by the Takei Digital Handgrip Dynamometer.

The median weight-adjusted DEI was 22.6 (range, 19.1-28.2) kcal/kg/day, while the mean weight-adjusted DPI was 0.86 ± 0.19 g/kg/day. There was no significant difference in DEI and DPI between patients with and without diabetes, but weight-adjusted DPI was significantly lower in diabetic patients (P=.022). Diabetic and nondiabetic patients had similar characteristics in terms of renal function, serum albumin, and urinary parameters.

In univariate analysis, diabetes was associated with weight-adjusted DPI (95% CI, −0.237 [−0.446 to −0.004] kcal/kg/day; P=.040). However, this association did not remain significant in multivariate analysis. Nutritional status did not differ significantly between diabetic and nondiabetic patients; however, patients with stage 4-5 CKD with diabetes consumed less calcium and fiber (well below recommended levels) and had lower lean body mass (P=.046) and higher BMI compared with subjects without diabetes.

The ratio of patients with PEW was not significantly different between diabetic and nondiabetic patients (13.9% vs 10.2%, respectively). When adjusted for body weight, patients with diabetes had a DPI meeting current recommendations but nondiabetic patients had a higher than recommended DPI according to the most recent KDIGO clinical practice guidelines. Both diabetic and nondiabetic patients had DEI lower than the recommendations, which is important because low DEI is a risk factor for developing PEW. However, other than DEI below recommendations, no sign of undernutrition was found in the subjects. This finding suggests that the DEI of the present cohort was adequate for maintaining nutritional status.

Limitations of the study include the small number of subjects and potential recall bias because researchers relied mainly on dietary inquiries to assess dietary intakes. Larger multicenter studies are needed, using a longitudinal analysis, to determine whether a low-protein diet in CKD patients with diabetes would help stem CKD progression. Further, the researchers suggest that revisions to dietary advice should include increasing fiber and calcium intakes, which were well below recommended levels.

In summary, the authors stated, "In the present cohort, DPI and DEI were not significantly different between diabetic and nondiabetic CKD patients. Diabetes was not found to be associated with dietary intakes in CKD stage 4-5 patients." ■

Statin Initiation, Mortality in Older Individuals With Moderate CKD

The leading cause of death among older adults with chronic kidney disease (CKD) is atherosclerotic cardiovascular disease (ASCVD). There are few data available on the role of statins for the prevention of primary ASCVD in patients with moderate CKD (stages 3-4). Results of a meta-analysis of 8834 participants in primary prevention trials with CKD, primarily stage 3, demonstrated a 41% reduction in ASCVD events and a 34% reduction in total mortality. Conversely, there is evidence that there is no benefit to initiating statins in those receiving hemodialysis.

According to **Odeya Barayev, MD, MBA,** and colleagues, the trials supporting use of statins for primary prevention of ASCVD in patients with moderate CKD included only a few older adults. Using data from the Veterans Health Administration (VA), Dr. Barayev et al conducted a study to assess the association of statin initiation with mortality and major adverse cardiovascular events (MACE) among older adults following a diagnosis of moderate CKD (stages 3-4). Results of the study were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.46373].

Using nested trials with a propensity weighting approach, the cohort study employed a target trial emulation for statin initiation among veterans with moderate CKD. Linked data from the VA Healthcare System, Medicare, and Medicaid were used. The study population included US veterans newly diagnosed with moderate CKD between 2005 and 2015 in the VA, with follow-up through December 31, 2017. Eligible veterans were older than 65 years, within 5 years of CKD diagnosis, had no prior ASCVD or statin use, and had at least one clinical visit in the year prior to trial baseline

For each nested trial, researchers assessed eligibility criteria and ran Cox proportional hazards models with bootstrapping. Data analysis was conducted from July 2021 to October 2023. The primary outcome of interest was all-cause mortality. Time to first MACE (myocardial infarction, transient ischemic attack, stroke, revascularization, or mortality) was also assessed.

The study analysis included 14,828 individual veterans contributing to 154,167 nested person-trials. Mean age at the time of CKD diagnosis was 76.9 years, 99% (n=14,616) were men, 72% (n=10,539) were White, and 17% (n=2568) were Black.

After expanding to person-trials and assessing eligibility at baseline, the analyses included 151,243 person-trials (14,685 individuals) of nonstatin initiators and 2924 person-trials (2924 individuals) of statin initiators. Compared with the nonstatin initiators, the veterans in the statin initiator group were younger, had higher body mass index, and were more likely to have diagnostic codes for diabetes, hypertension, and hyperlipidemia. They were also more likely to have polypharmacy, take antihypertensives, be frail, and have CKD stage 4 (vs 3) at baseline.

In the statin initiator group, statin initiation, or trial baseline date, tended to occur closer to the date of the diagnosis of moderate CKD, approximately 17 months following diagnosis, compared with the mean of approximately 22 months after diagnosis among the noninitiator person-trials. Following propensity score overlap weighting, all baseline characteristics were balanced. The most common prescribed statin was simvastatin (46%; n=1357), followed by atorvastatin (33%; n=973), pravastatin (15%; n=434), and lovastatin (3%; n=80).

During a mean follow-up of 3.6 years, there were 744 deaths among the statin initiator person-trials and 47,743 deaths in the noninitiator person-trials. The estimated hazard ratio (HR) for all-cause mortality was 0.91 (95% CI, 0.85-0.97), indicating a 9% lower risk of death for those who initiated statins within the first 5 years after a diagnosis of moderate CKD.

In analyses of subgroups by sex, age, race, risk of ASCVD, frailty, diabetes, hyperlipidemia, and CKD stage, there was a similar protective pattern for statin therapy initiators compared with noninitiators (for example, age, 64-74 years: HR, 0.85; 95% CI, 0.76-0.96 and age, ≥75 years: HR, 0.89; 95% CI, 0.82-0.97).

For the secondary outcome of time to first MACE, there were a total of 57,772 MACE: 988 among statin initiator person-trials and 56,734 among nonstatin initiator person-trials. Following propensity score overlap weighting, there was a 4% lower risk of MACE with statin initiation (HR, 0.96; 95% CI, 0.91-1.02). However, the results did not reach statistical significance. Results were unchanged in analysis by subgroups (for example, age, 64-74 years: HR, 0.95; 95% CI, 0.86-1.06 and age, ≥75 years: HR, 0.93; 95% CI, 0.86-1.01).

The estimated hazard ratio for all-cause mortality was 0.91 (95% CI, 0.85-0.97), indicating a 9% lower risk of death for those who initiated statins within the first 5 years after a diagnosis of moderate CKD.

The researchers cited some limitations to the study, including the study population being predominantly male and White, potentially limiting the generalizability of the findings to other populations; the possibility of residual unmeasured confounding due to the nature of administrative data; not evaluating the per-protocol effect size for statin use after the initial prescription; and not evaluating the dose or duration of statin therapy during the follow-up period.

In conclusion, the authors said, "Among US veterans older than 65 years with CKD stages 3 to 4 and no prior ASCVD, statin initiation was associated with a lower risk of all-cause mortality compared with no statin initiation. Results should be confirmed in a randomized, clinical trial. However, until such trials are completed, these data argue against withholding or deprescribing statins for primary prevention in older patients with CKD stages 3 to 4." ■

TAKEAWAY POINTS

- Researchers conducted a study to examine the association of statin use with all-cause mortality and major adverse cardiovascular events (MACE) among US veterans older than 65 years of age with chronic kidney disease stages 3 to 4.
- There was a significant association between statin initiation and lower risk of all-cause mortality among US veterans older than 65 years of age.
- The association between initiation of statin use and MACE did not reach statistical significance.

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SARS-CoV-2 Vaccine Response During Maintenance Dialysis

Patients receiving maintenance hemodialysis face substantial risk of morbidity and mortality associated with COVID-19 infection. Early studies have shown that two doses of a SARS-CoV-2 messenger RNA vaccine elicit a seroresponse in more than 90% of patients on maintenance hemodialysis, but that response is lower compared with the general population.

In late June 2021 when the Delta variant became the dominant SARS-CoV-2 strain in the United States, the rate of breakthrough infection among those fully vaccinated was higher than expected. Among initial responders to the vaccine, more than half had waning immunity by 4 to 6 months. Waning immunity was particularly noted in those whose initial response was lesser.

There are few data on the impact of lesser initial vaccine response and subsequent waning antibody levels on clinical outcomes among patients on maintenance dialysis. **Harold J. Manley, PharmD,** and colleagues conducted a retrospective, observational study to describe the incidence of COVID-19 diagnoses and COVID-19-related hospitalization or death in unvaccinated, partially vaccinated, and fully vaccinated adults on dialysis during the pre-Delta and Delta-dominant periods. The researchers also sought to examine the association between antibody levels and clinical outcomes in those patient populations. Results were reported in the *American Journal of Kidney Diseases* [2023;81(4):406-415].

Eligible study participants were adults 18 years of age or older with no history of COVID-19 receiving hemodialysis through a national provider and treated between February 1 and December 18, 2021.

The outcomes of interest were all SARS-CoV-2 infections and a composite of hospitalization or death following COVID-19. COVID-19 case rates and vaccine effectiveness were determined using logistic regression analysis. All new COVID-19 diagnoses that occurred during the study period were assigned to the appropriate vaccination status at the time of diagnosis: unvaccinated, partially vaccinated, or fully vaccinated. COVID-19 cases, hospitalizations, and deaths were identified during the study period and further divided into pre-COVID-19 Delta variant (February 1 to June 25, 2021) and COVID-19 Delta variant-dominant (June 26 to December 18, 2021) periods. Those diagnosed with COVID-19 were followed for hospitalization or death through January 17, 2022.

Of the 18,028 maintenance dialysis patients at Dialysis Clinic Inc. facilities during the study period, 15,942 (88%) met inclusion criteria and were included in the analysis. Among the eligible patients, 78.0% (n=12,403) were fully vaccinated by December 18, 2021, 55% (n=6853) with mRNA-1287, 41.0% (n=5132) with BNT162b2, 3.0% (n=368) with Ad26.COV2.S, and 0.4% (n=50) with some combination of vaccines. An additional 3% (n=480) were partially vaccinated (276 with mRNA-1273 and 204 with BNT162b2), and 19% (n=3059) were unvaccinated.

In the overall cohort, mean age was 63 years and mean dialysis vintage was 43 months. Eighty-seven percent of the cohort were receiving in-center hemodialysis, 57% had diabetes, and 26% were considered immunocompromised per Centers for Disease Control and Prevention (CDC) criteria.

There were 1173 documented cases of COVID-19 during the study period. Of those, 70% (n=826) occurred during the Delta variant-dominant period. Overall, 46% of cases of COVID-19 (n=535) occurred among those in the fully vaccinated group. Most of those breakthrough cases (96%; n=511) occurred during the Delta-dominant period; 26% (n=137) of patients with breakthrough cases met CDC criteria for being immunocompromised. Median time to follow-up for all patients was 57 days, including time to infection or censoring point for non-event cases. Among those diagnosed with COVID-19, median time from being considered fully vaccinated was 153 days.

The COVID-19 case rate was significantly lower among fully vaccinated patients than among those who were unvaccinated: 2.21 versus 3.65 per 10,000 patient-days. Overall, vaccine effectiveness was 45%; mRNA-1273 had the highest vaccine effectiveness at 50%, followed by BNT162b2 at 37%.

Across all vaccination status groups, COVID-19 case rates increased during the Delta variant-dominant period. Case rates were lower among fully vaccinated patients (3.25 vs 6.49 per 10,000 patient-days) with 54% vaccine effectiveness compared with unvaccinated patients. The highest vaccine effectiveness was seen in patients vaccinated with mRNA-1273 (60%).

During the study period, there were 424 hospitalizations or deaths related to COVID-19, including 112 COVID-19-related deaths. Of the 112 deaths, 60 were among unvaccinated patients, five among partially vaccinated patients, and 47 among fully vaccinated patients. Thirty percent (n=33) of the COVID-19-related deaths occurred among immunocompromised patients.

The rates of COVID-19-related hospitalizations or deaths were 1.45 per 10,000 patient-days among unvaccinated patients and 0.78 per 10,000 patient-days among vaccinated patients. For patients who were fully vaccinated, the vaccine effectiveness against hospitalization or death was 53% overall (63% with nRNA-1273 and 39% with BNT162b2).

During the Delta variant-dominant period, COVID-19 case rates and vaccine effectiveness against COVID-19-related hospitalization or death worsened among all vaccination groups. In the model comparing patients by vaccination status, fully vaccinated patients had the lowest case rate per 10,000 patient-days in both the pre-Delta and Delta-dominant periods. In the model comparing vaccination status and vaccine types, patients fully vaccinated with mRNA-1273 had the lowest case rate per 10,000 patient-days and the highest vaccine effectiveness against COVID-19-related hospitalization or death in both the pre-Delta and the Delta-dominant periods.

In a subset of 3202 vaccinated patients with at least one antispike immunoglobulin G (IgG) assessment, there was an association between lower antispike IgG levels and higher case rates per 10,000 patient-days and higher adjusted hazard ratios for infection and COVID-19-related hospitalization or death.

Limitations to the study included the observational design, residual biases, and possible confounding.

"SARS-CoV-2 vaccines were effective in maintenance dialysis patients, reducing the risks of COVID-19 cases and COVID-19-related hospitalization or death during the pre-Delta and Delta variant-dominant periods," the researchers said. "Further research is needed to evaluate SARS-CoV-2 vaccine effectiveness and the utility of antibody titer monitoring to determine which patients are at the highest risk for COVID-19 and to guide the timing of additional vaccine administration." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective, observational study examining the incidence of COVID-19 diagnoses and COVID-19-related hospitalization or death among patients receiving maintenance dialysis.
- Study participants were stratified by vaccination status: fully vaccinated, partially vaccinated, or unvaccinated.
- SARS-CoV-2 vaccination was linked to a lower risk of COVID-19 diagnosis and associated hospitalization or death in patients on hemodialysis.

Dialysis Facility Density, Timing of Dialysis Initiation

Over the past decade, the prevalence of kidney failure has doubled in the United States, with substantial cost implications for the US health care system. In the absence of a formalized threshold of estimated glomerular filtration rate (eGFR) below which hemodialysis is recommended nationwide, there is wide variability in the timing of initiation of dialysis across the country.

Results of a previous study suggested that 11.4% of the variability attributed to physician decision-making in eGFR at dialysis initiation occurred across physicians, while 88.6% occurred within physicians. Most of the variability was explained by patient case mix. In another study of older veterans receiving care through Medicare versus the Veterans Health Administration (VA), with Medicare providing higher reimbursements to physicians for dialysis services than the VA, a higher proportion of patients who received predialysis kidney care via Medicare initiated dialysis compared with those who received predialysis care in the VA system.

Vagish Hemmige, MD, MS, and colleagues conducted a cross-sectional data analysis to examine whether there is an association between area dialysis facility density and early initiation of dialysis. Results were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.50009].

The analysis utilized data from the US Renal Data System from the calendar years 2011 through 2019. Those data were linked to the American Community Survey using residential zip codes, and then to health service area (HSA) primary care and hospitalization benchmarks using the Dartmouth Atlas crosswalk. Data analysis was conducted from November 1, 2021, to August 31, 2023.

The analysis exposure was density of dialysis facilities at the level of HSA (the number of dialysis facilities per 100,000 HSA residents) split into five categories. Category 1 had zero facilities, category 2 represented HSAs with more than zero and less than the 25th percentile of facility densities, category 3 represented the 25th and less than the 50th percentile of facility densities, category 4 represented the 50th and less than the 75th percentile of facility densities, and category 5 represented the highest facility densities, or the 75th or greater percentile. The main outcomes and measure were the odds of initiation of hemodialysis at an eGFR greater than 10 mL/min/1.73 m^2 versus less than or equal to 10 mL/min/1.73 m^2.

There were 3397 HSAs and 844,466 patients receiving incident hemodialysis between 2011 and 2019 who met the study inclusion criteria. Of those, 42.6% were women (n=360,120) and 57.4% were men (n=483,346). Mean age was 63.5 years, 28.1% were Black, and 15.1% were Hispanic. Thirty percent of the overall cohort had heart failure and 59.1% had diabetes; 24.1% had no nephrology care prior to developing kidney failure. Most (80.5%) initiated dialysis with a catheter.

The mean facility density was 4.1 centers per 100,000 population in the most dialysis-dense HSAs. Median HSA-level dialysis facility density nationwide was 1.95 centers per 100,000 population. Dialysis-dense HSAs, defined as those with the highest density of dialysis facilities and dialysis stations within facilities, were located primarily in areas of the Midwest and Southeast. The mean eGFR at which dialysis was initiated between 2011 and 2019 was 8.9 mL/min/1.73 m^2.

Those who initiated hemodialysis in the most dialysis-dense HSA category were younger (63.3 vs 65.2 years in categories 5 vs 1 of HSA-level dialysis facility density), more commonly women (44.4% vs 41.3%), more commonly Black (40.6% vs 11.3%), and had a higher proportion with diabetes (60.1% vs 58.5%), alcohol or drug use disorder (2.9% vs 2.5%), and cerebrovascular disease (9.8% vs 9.2%) than those in the least dialysis-dense HSAs.

In multivariable models with eGFR as a continuous variable, 10% of the total variability of mean eGFR at dialysis initiation was explained by the HSA-level characteristics. There was an association of odds increasing by progressively higher-density categories between HSA-level dialysis facility density and odds of early hemodialysis initiation (eGFR greater than 10 mL/min/1.73 m^2).

There was a 1.06-higher odds (95% CI, 1.02-1.11; *P*=.004) of initiating hemodialysis in the highest-density HSAs compared with HSAs with zero dialysis facilities and a 1.07-higher odds (95% CI, 1.06-1.07; *P*<.001) of initiating hemodialysis in the highest-density HSAs compared with category 2 of HSA-based dialysis facility density, where the mean density was 1.0 facilities per 100,00 residents.

In multivariable models with eGFR as a continuous variable, 10% of the total variability of mean eGFR at dialysis initiation was explained by the HSA-level characteristics.

Across all HSA types, Black patients initiated hemodialysis at a significantly lower eGFR than patients of other races. The researchers stratified by individual race, and, in subgroup analyses, there was a significant association between HSA-level dialysis facility density and odds of dialysis initiation at an eGFR greater than 10 mL/min/1.73 m^2 in White patients, with higher odds of initiating at an eGFR greater than 10 mL/min/1.73 m^2: 1.08 (95% CI, 1.04-1.12; *P*<.001) in unadjusted models and 1.05 (95% CI, 1.00-1.10; *P*=.03) in adjusted models in the highest-density HSAs compared with HSAs with zero dialysis facilities. In Black patients, there were also higher odds of dialysis initiation at an eGFR greater than 10 mL/min/1.73 m^2, but the finding was not statistically significant (odds ratio, 1.03; 95% CI, 0.94-1.13; *P*=.50).

There were some limitations to the findings cited by the authors, including the inability to account for patients who did not initiate hemodialysis when indicated and the inability to determine the degree to which distance from dialysis facilities was associated with eGFR at dialysis initiation.

In summary, the researchers said, "In this cross-sectional study, HSA-based higher density of dialysis facilities was associated with earlier dialysis initiation among an incident kidney failure population. This finding lends support to the notion that dialysis facility saturation of HSAs may represent practice patterns that affect timing of hemodialysis initiation." ■

TAKEAWAY POINTS

- There is wide variation in the timing of dialysis initiation among patients with incident kidney failure.
- Researchers conducted a study to examine whether there is an association between area dialysis facility density and earlier initiation of hemodialysis.
- Results of the cross-sectional study indicated that health service area dialysis density was associated with early hemodialysis initiation.

Transplant Outcomes, Kidney Disease Type, and Donor Relatedness

For patients with kidney failure, kidney transplantation remains the best treatment and is associated with positive survival and quality-of-life outcomes. The median waiting time for a deceased donor kidney transplant in 2019 in Australia was 2.1 years; more than 1000 patients were actively awaiting kidney transplantation. Live donor kidney transplants reduce the strain on waiting lists and are associated with shorter dialysis vintage and improved graft and recipient survival compared with deceased donor transplants.

Worldwide, the majority of living kidney donors are biologically related to their recipient, resulting in improved human leukocyte antigen matching but carrying an increased risk of recurrence of primary kidney disease.

According to **Dong Yu, MD,** and colleagues, there are few data available on the association between primary kidney disease and donor relatedness with kidney transplant outcomes. The researchers conducted a retrospective, observational study to examine clinical outcomes following kidney transplantation in a cohort of recipients of living donor kidneys as a function of primary kidney disease type and donor relatedness in Australia and New Zealand. Results were reported in the *American Journal of Kidney Diseases* [2023;82(5):569-580].

TAKEAWAY POINTS

- Researchers conducted a study to examine the association between primary kidney disease and donor relatedness with kidney transplant outcomes.
- The outcomes of interest were recurrence of primary kidney disease and graft failure in recipients of kidneys from donors with primary kidney disease categorized as majority monogenic, minority monogenic, or other primary kidney disease.
- Monogenic primary kidney disease was associated with lower rates of primary kidney disease recurrence and allograft failure.

The cohort included individuals who underwent kidney transplantation with allografts from living donors between January 1, 1998, and December 31, 2018, as listed in the Australian and New Zealand Dialysis and Transplant Registry. The study exposure was primary kidney disease type.

Type of kidney disease was categorized into majority monogenic, minority monogenic, and other primary kidney disease based on disease heritability as well as donor relatedness. The primary outcomes of interest were recurrence of primary kidney disease and graft failure. Hazard ratios (HRs) for the primary outcomes were generated using Kaplan-Meier analysis and Cox proportion hazards regression. Possible interactions between primary kidney disease type and donor relatedness for both outcomes were examined using a partial likelihood ratio test.

The study cohort included 5500 living donor kidney transplant recipients. Most of the primary kidney diseases (65.8%; n=3619) had no monogenic basis. Of the transplants, 3236 involved a living donor and 2264 involved a living nonrelated donor. More than half of the transplants occurred between immediate relatives (53.7%; n=2954), and 41.2% occurred between unrelated donors (n=2264).

Mean age of recipients was 42 years, 62.1% (n=3416) of the recipients were male, and 57.8% (n=2825) of the donors were female. Total follow-up time was 50,954.67 person-years. Median follow-up time was 8.928 years. Polycystic kidney disease contributed to 77.1% (n=794/1030) of majority monogenic primary kidney disease cases, and reflux nephropathy contributed to 63.5% (n=540/851) of minority monogenic primary kidney disease cases.

For people with majority monogenic primary kidney disease, living kidney transplant from relatives comprised a smaller proportion of the total transplants compared with those with minority monogenic kidney disease and other primary kidney disease (41.6% majority monogenic primary kidney disease vs 73.1% minority monogenic primary kidney disease and 60.5% other primary kidney disease).

Recurrence of primary kidney disease was seen in 407 cases (7.4%). The rate of primary kidney disease recurrence per 1000 person-years was 5.43 for majority monogenic primary kidney disease, 6.32 for minority monogenic primary kidney disease, and 10.07 for other primary kidney disease. The recurrence rate per 1000 person-years was 8.93 for immediate relatives (identical twin and first degree), 7.79 for distant relatives (second and third degree), and 8.07 for unrelated donors.

In univariate analysis, there were associations between reduced primary kidney disease recurrence and majority monogenic primary kidney disease (HR, 0.54; 95% CI, 0.40-0.74; $P<.001$) and minority monogenic primary kidney disease (HR, 0.67; 95% CI, 0.50-0.90; $P=.01$) compared with other primary kidney disease. Results remained significant in multivariable analyses (majority monogenic primary kidney disease, adjusted HR [aHR], 0.58; 95% CI, 0.42-0.79; $P<.001$; minority monogenic primary kidney disease, aHR, 0.64; 95% CI, 0.47-0.87; $P=.004$). There was also a dose-dependent effect present.

In univariable analyses, grafts from immediate relatives were associated with increased primary kidney disease recurrence (aHR, 1.25; 95% CI, 1.01-1.54; $P=.04$). However, this result was not statistically significant in multivariable analyses (aHR, 1.11; 95% CI, 0.84-1.47; $P=.5$).

In multivariable analysis, there was an association between increased recipient age and reduced primary kidney diseased recurrence; former smoking status was linked to increased primary kidney disease recurrence. Results of a partial likelihood ratio test did not show interaction effects between primary kidney disease type and donor relatedness on primary kidney disease recurrence.

There were 941 cases of graft failure (17.1%). For majority monogenic primary kidney disease, the graft failure rate per 1000 person-years was 15.1. The graft failure rates per 1000 person-years for minority monogenic primary kidney disease and other primary kidney diseases were 24.8 and 21.2, respectively. The graft failure rate per 1000 person-years was 22.3 for immediate relative donors, 27.6 for distant relative donors, and 17.1 for unrelated donors. Compared with other primary kidney disease, Kaplan-Meier curves showed improved graft survival for majority and minority monogenic primary diseases. Compared with distant relative and nonrelated donor transplants, Kaplan-Meier curves showed improved graft survival for immediate relative donor transplants.

The authors cited some limitations to the study findings, including potential misclassification of primary kidney disease type, incomplete ascertainment of primary kidney disease recurrence, and unmeasured confounding.

In conclusion, the researchers said, "Majority monogenic primary kidney disease was associated with reduced graft failure compared with other primary kidney disease. Donor relatedness was not associated with primary kidney disease recurrence nor with graft failure. There was no interaction between primary kidney disease type and donor relatedness in primary kidney disease recurrence or graft failure.

"Our findings inform the clinical care and prognostication of live donor kidney transplant recipients in terms of potential recipient and graft outcomes. This includes illuminating clinical scenarios for heightened focus on nonmonogenic primary kidney disease and managing underlying comorbidities. These findings are important for counseling with regard to outcomes after live donor kidney transplantation for potential recipients in the context of their individualized primary kidney disease and donor source." ■

25-Year Risk of Fracture Among Living Kidney Donors

Worldwide, the prevalence of living kidney donation is increasing; approximately 30,000 individuals become living donors each year. In the United States, of 459,849 transplants performed, 187,194 individuals have donated a kidney. In 2022, 29.2% of kidney transplants performed in the United States were from living donors.

According to **Hilal Maradit Kremers, MD,** and colleagues, there are health risks to the donor associated with living kidney donation. While the 15-year observed risk of end-stage kidney disease in kidney donors is low, it is reported to be 3.5 to 5.3 times higher than the projected risk in the absence of donation. Results of previous studies of markers of mineral and bone metabolism among kidney donors following kidney donation have suggested that bone quality may be impaired in kidney donors, due to reductions in kidney mass, lower concentrations of serum 1,25 dihydroxyvitamin D, and secondary increases in serum parathyroid hormone.

Dr. Kremers et al conducted a survey-based study designed to compare the overall and site-specific risk of fracture among living kidney donors. The survey included strictly matched controls from the general population who would have been eligible to donate a kidney but did not do so. Results of the study were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.53005].

The study exposure was living kidney donation. The primary outcome of interest was a comparison of the rates of overall and site-specific fractures between living kidney donors and controls. Standardized incidence ratios (SIRs) were used in the comparison.

The survey was conducted between December 1, 2021, and July 31, 2023. Living donors (n=5065) at three large transplant centers in Minnesota were invited to participate in a survey regarding their bone health and history of fractures. Using the Rochester Epidemiology Project database, the researchers invited a nondonor control population of 16,156 individuals with no history of comorbidities to complete the same survey.

Survey questions were derived from validated surveys used in the National Health and Nutrition Examination Survey, Framingham Study, Women's Health Initiative, Study of Osteoporotic Fractures, and the Nurses' Health Study. The survey included questions on bone health and fracture history, self-reported race and ethnicity, height, weight, smoking, alcohol use, menstrual status, self-reported osteoporosis diagnosis, and use of medications known to interfere with mineral metabolism.

A total of 2132 living kidney donors and 2014 nondonor controls responded to the survey. Of the 2132 donors who responded, mean age was 67.1 years and 58.4% (n=1245) were female. Of the 2014 controls, mean age was 68.6 years and 56.6% (n=1140) were female. There was substantial variation in participation rates between the two groups: 42.1% (2131/5065) of donors responded versus 12.5% (2014/16,156) of controls. There were also variations in participation rates by age (rates were similarly highest among individuals 67 to 72 years of age for both donors and controls). Participation rates were highest among White participants compared with those of a racial or ethnic minority group or unknown race. Rates varied across donation medical centers as well.

Forty-two donors and 137 controls were excluded from analyses due to incomplete survey data. All further analyses comparing the observed and expected number of fractures were limited to the 2090 donors and 1877 controls with complete information on fractures. Among the final analysis cohort, mean time between donation or index date and completion of the survey was 24.2 years for donors and 27.6 years for controls. Controls were 1.5 years older than the donors (68.6 years vs 67.1 years).

Among the 2090 donors, the rate of all types of fractures was significantly lower than among the 1877 controls: 443.0 observed versus 499.8 expected fractures (SIR, 0.89; 95% CI, 0.81-0.97; *P*=.009). However, there were significantly more vertebral fractures among donors than among controls: 51 observed versus 36 expected vertebral fractures (SIR, 1.42; 95% CI, 1.05-1.83; *P*=.02). Among men, there were 21.0 observed vertebral fractures versus 12.5 expected (SIR, 1.67; 95% CI, 1.04-2.47; *P*=.04).

Among the 2090 donors, the rate of all types of fractures was significantly lower than among the 1877 controls. However, there were significantly more vertebral fractures among donors than among controls.

Results of two separate validation studies among the controls demonstrated that controls who returned surveys were similar to controls who did not return surveys in terms of frequency and types of fractures. The fracture survey instrument was validated among a random sample of 332 controls who returned surveys (166 who reported any fracture and 166 who reported no fractures). Overall agreement of fractures reported on the survey versus fractures found by a nurse in the complete historical medical records was good (89.5% raw agreement). The agreement was better than would be expected by chance alone.

The researchers cited some limitations to the study findings, including the historical nature of the study that resulted in an inability to screen nondonor controls for factors such as laboratory test and imaging results that would have precluded kidney donation. Other limitations included the inability to conduct stratified analyses by race and ethnicity due to small numbers of those groups, and the possibility of inaccurate recall among participants of the exact timing of fractures.

In summary, the authors said, "In this survey-based study, we observed a reduction in overall fractures but an excess risk of vertebral fractures among living kidney donors compared with controls after a mean follow-up of 25 years. Treatment of excess vertebral fractures with dietary supplements such as vitamin D3 may reduce the numbers of vertebral fractures and patient morbidity." ■

TAKEAWAY POINTS

- Researchers reported results of a survey-based study of the overall and site-specific risk of fracture among living kidney donors 25 years after donation compared with controls.
- Donors had a reduced rate of overall fracture versus controls: standardized incidence ratio (SIR), 0.89; 95% CI, 0.81-0.97.
- The rate of vertebral fractures among living kidney donors was higher than among controls: SIR, 1.42; 95% CI, 1.05-1.83.

Whole Food, Plant-Based Diets for Patients With CKD

Many in the nephrology community, including the National Kidney Foundation, have promoted the benefits of plant-based diets for patients with chronic kidney disease (CKD). However, the current Kidney Disease Outcomes Quality Initiative guideline recommendations for patients with CKD do not outright suggest whole food, plant-based (WFPB) diets. Instead, they continue to recommend a diet that is low in protein (0.55-0.60 g/kg/day for nondiabetics and 0.60-0.80 g/kg/day for those with diabetes) and sodium (2.3 g/day) and high in fruits and vegetables (considering potassium and phosphorous content).

Natasha S. Freeman, MD, and **Jeffrey M. Turner, MD,** undertook a review of the literature with the goals of summarizing the risks and benefits of WFPB diets for CKD, offering advice on how to guide patients regarding healthy eating, and determining areas that need further investigation. Their review was published in the *Journal of Renal Nutrition* [2024;34(1):4-10].

The review focused on WFPB diets, including pescatarian, lacto-ovo-vegetarian, lacto-vegetarian, ovo-vegetarian, and vegan diets under the "plant-based" umbrella. By the authors' definition, WFPB diets limit animal products; focus on fresh, minimally processed, nutrient-dense plant foods; and exclude heavily processed, refined, and sugary foods.

A whole food, plant-based diet, which emphasizes fresh, minimally processed or refined plant-based foods and limits animal products, has shown benefits for patients with CKD.

Research has determined that there is an association between WFPB diets and improvements in mortality, cardiovascular health, and disease progression in patients with CKD. This is because WFPB diets:

Reduce dietary acid load. Fruits and vegetables can raise serum bicarbonate, which can help mitigate negative effects of metabolic acidosis that can lead to CKD progression, mineral bone disease, and sarcopenia. These foods produce alkali, and many contain citrate and malate, which metabolize to bicarbonate. Research in nondiabetic CKD patients found that supplementation of fruits and vegetables was as effective as oral bicarbonate tablets in raising serum bicarbonate in all stages of CKD for up to 5 years. Eating fruits and vegetables also resulted in reduced body weight, blood pressure, and net urinary acid excretion. Furthermore, plant-based proteins may have alkali-producing and anti-inflammatory attributes that protect kidney function.

Decrease bioavailability of dietary phosphorus. Patients with CKD generally need to limit phosphorus intake because hyperphosphatemia can cause hyperparathyroidism, mineral bone disease, vascular calcification, coronary events, CKD progression, and mortality in patients with CKD. Phosphorus is present in most foods, so limiting it can be challenging. However, phosphorus from plant-based foods tends to be less bioavailable than that from animal products. Phytates, a form of dietary phosphorus found in plants, cannot be processed by humans, resulting in an intestinal phosphorus absorption of less than 40%, compared with at least 40% to 60% absorption for phosphorus from animal products. A crossover study of nine patients with stage 3-4 CKD found a significant reduction in serum phosphorus and fibroblast growth factor 23 levels after consuming 7 days of a vegetarian diet, while a significant increase was seen after 7 days of a meat diet.

Increase fiber consumption. A diet rich in fruits, vegetables, and whole grains tends to be naturally high in fiber, which has many known health benefits. A high-fiber diet (median, 27 g/day) has been shown to reduce serum urea and creatinine in patients with CKD, yet restricting potassium and phosphorus, which is typically recommended for patients with CKD, can cause lower fiber intake. As of 2012, patients with CKD only consumed 15.4 g/day of fiber; the recommended intake is 25-35 g/day.

The review also found potential downsides associated with a WFPB diet for those with CKD. These include:

Risk of hyperkalemia. Hyperkalemia in patients with CKD carries a risk for mortality; thus, diets low in fruits and vegetables are typically recommended for these patients. However, there is a body of literature suggesting that such dietary restrictions may unintentionally limit intake of healthy foods, with a potential impact on overall health. One meta-analysis found that,

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in normokalemic patients with CKD, potassium restriction was associated with a 40% reduction in mortality, but their serum potassium levels only decreased by 0.22 mEq/L. In another study, random provision of fruits and vegetables did not increase incidence of hyperkalemia (baseline K, <4.6 mEq/L; mean estimated glomerular filtration rate, 33 mL/min/1.73 m^2); it also resulted in better blood pressure and body weight and increased urinary potassium excretion.

Insufficient nutrition. This is a leading risk factor for morbidity and mortality in those with CKD. Inadequate protein consumption is a key concern with plant-based diets, although diets tailored to patients with CKD tend to restrict protein. A 2021 cohort study of patients with stage 3-5 CKD found that a low-protein diet (<0.8 g/kg/day) was difficult to achieve (34% adherence) and associated with insufficient calorie intake (23 kcal/kg/day vs the recommended 30-35 kcal/kg/day). However, patients with and without CKD who eat mostly plant-based diets have been shown to consume 0.7-0.9 g/kg/day of protein and do not present any evidence of nutritional deficiency. Sufficient nutrition from WFPB diets depends on making healthy food choices; a registered dietitian could help steer patients toward healthier dietary decisions.

Difficulty of adopting a WFPB diet. When surveyed, most people demonstrated a low readiness to adopt a plant-based diet. Reasons for this include insufficient knowledge of the health benefits, ways to create appealing plant-based meals, and nonmeat sources of protein. Cultural and socioeconomic factors can also create barriers; some people find it difficult to give up cultural and familial traditions relating to food, and it can be more expensive to purchase fresh foods. The latter point is crucial when considering that an estimated 4.5% of adults with CKD experience food insecurity.

Current data are limited by a lack of standardization of dietary interventions across studies, reliance on observational data, small sample sizes, and modest effect size. It remains unclear whether the benefits of WFPB diets come from the avoidance of animal products versus choosing whole, fresh foods over processed ones. More research is needed to determine if the same effects might occur with less restrictive diets that do not eliminate animal products completely, instead focusing on fruits, vegetables, whole grains, nuts, and legumes, with lean meats, fish, and eggs in moderation. Large randomized, controlled trials of representative samples of the CKD population, involving practical diets such as the WFPB diet, Mediterranean diet, DASH diet, and standard CKD diet, could further elucidate this question.

In sum, the researchers said, "A whole food, plant-based diet, which emphasizes fresh, minimally processed or refined plant-based foods and limits animal products, has shown benefits for patients with CKD. These include reduced dietary acid load, lower bioavailability of potassium and phosphorus, increased dietary fiber intake, nutritional adequacy, and cardiovascular and mortality benefits. Potential drawbacks include the need for specific knowledge, skills, and cost involved in preparing varied, healthy, and appetizing plant-based

meals, leading to lower acceptability and accessibility to certain populations. Liberalization of the standard CKD diet to include healthy, minimally processed foods such as fruits, vegetables, nuts, legumes, and whole grains is likely beneficial, though more research is needed to determine whether a plant-based-only diet is the optimal way to achieve healthier eating in patients with CKD." ■

TAKEAWAY POINTS

- The authors conducted a literature review to summarize the risks and benefits of plant-based diets for CKD and determine areas for further investigation.
- A whole food, plant-based diet has benefits for patients with CKD, including reduced dietary acid load, lower bioavailability of potassium and phosphorus, increased fiber intake, nutritional adequacy, and cardiovascular and mortality benefits.
- Barriers to adopting a plant-based diet remain, and further research is needed to determine whether such diets are the best way to achieve healthier eating with CKD.

Print-only Content

NKF Innovation Fund Supports ImmunoFree

In a recent press release, the National Kidney Foundation (NKF) announced an investment through its NKF Innovation Fund to support ImmunoFree. ImmunoFree is a biomedical company focused on reshaping the landscape of organ transplantation by eliminating the need for immunosuppressive medications.

Since its founding in 2023, ImmunoFree has been developing stem cell transplant technology that will eliminate the need for immunosuppressive medications in recipients of solid organ transplants and usher in a new era of transplant medicine, according to the press release.

Garet Hil, co-founder and CEO of ImmunoFree, said, "More than 15 years ago, we embarked on a mission to solve the pervasive problem of incompatible living donors in order to facilitate more living donor kidney transplants. Through the formation and growth of the National Kidney Registry, we have solved this problem. With the launch of ImmunoFree, we intend to solve the problems related to chronic immunosuppression by eliminating the need for immunosuppressive medications for transplant recipients."

NKF's CEO, **Kevin Longino,** said, "In a post-COVID world, solving the issues raised by immunosuppressive medication for transplant patients has never been more critical. ImmunoFree's goals align perfectly with NKF's commitment to advancing kidney health and improving the lives of transplant recipients."

Print-only Content

AKF Releases 2024 American Kidney Fund Report Card

The American Kidney Fund (AKF) released its fourth annual State of the States: Living Donor Protection Report Card. The report ranks the performance of all 50 states and the District of Columbia on how well their laws encourage living organ donation and reduce barriers for donors.

The report assigns a grade A, B, C, D, or F for seven different categories of publicly reported laws in each state and the District of Columbia: antidiscrimination laws for life, disability, or long-term care insurance; job-protected leave from private employers; job-protected leave from public employers; tax credits for employers who provide paid leave; direct reimbursements, tax credits, or tax deductions for donor expenses; paid leave via state family and medical leave laws; and extended family and medical leave of more than 60 days.

Living kidney donation is the best option for someone needing a new kidney, yet six states—Alabama, Montana, New Hampshire, South Dakota, Tennessee, and Vermont—received an F for offering no protections for donors. Only three states—Arkansas, Connecticut, and Louisiana—earned an A. Especially troubling

FDA Veteran Dr. Stephen Grant Is New Saghmos Therapeutics CRO


Stephen Grant, MD

Stephen Grant, MD, has been named chief regulatory officer of Saghmos Therapeutics, Inc. Dr. Grant is the former deputy director of the Division of Cardiology and Nephrology at the Center for Drug Evaluation and Research of the US Food and Drug Administration (FDA).

Saghmos, a privately held biopharmaceutical company, is currently developing ST-62516 (trimetazidine) to reduce the risk of acute kidney injury and major adverse cardiac and kidney events after contrast procedures such as percutaneous coronary intervention (PCI).

"We are honored and privileged to work with Dr. Grant. His guidance and his wealth of regulatory experience in the cardio-renal area at the FDA will tremendously benefit our mission to bring ST-62516 to patients," said **Anna Kazanchyan, MD,** founder and CEO of Saghmos.

"Impaired kidney function is associated with a high risk of morbidity and mortality after [PCI]. Hence, providers must frequently make a difficult choice in this population between not performing PCI, even when indicated, or exposing patients to the risk of complications," Dr. Grant said. "In this context, a drug such as trimetazidine will be a useful addition to the treatment armamentarium to prevent complications after PCI. I am excited about working with Saghmos to bring this drug to patients."

is that the 15 states receiving D OR F grades are home to nearly one in four of the nation's rural population, which already faces challenges in accessing health care.

The results highlight the need for legislation focused on better support for living organ donors. "Where you live should not impact whether you are able to save a life through kidney donation, but our 2024 Report Card suggests that this may be the case," said **LaVarne A. Burton,** president and CEO of AKF. "As a nation, we must come together to prioritize solutions at the state level for living organ donors to ultimately help improve treatment of kidney disease for all."

To access the full report, visit kidneyfund.org/livingdonors.

AbbVie CEO to Step Down

Drugmaker AbbVie has announced that its CEO, **Richard A. Gonzalez,** will step down effective July 1. Gonzalez is the sole chief executive in the company's history and led AbbVie through its separation from Abbott Laboratories in 2013. He was a 30-year veteran of Abbott prior to AbbVie's founding.


Richard A. Gonzalez

Upon retirement, he will become AbbVie's executive chairman and will be succeeded as CEO by current chief operating officer **Robert Michael**. In a statement, Gonzalez said of Michael, "As a key member of the executive leadership team, he has had a tremendous impact on AbbVie. From establishing our financial planning organization, to the development of our diversified business strategy, to successfully navigating the end of exclusivity for Humira in the [United States], Rob has been integral to AbbVie's impact since inception."

The leadership change comes at a pivotal time for AbbVie, as its cornerstone autoimmune drug Humira faces new biosimilar competition. However, the company has been buoyed by the success of immunology drugs Rinvoq and Skyrizi.

Gonzalez said, "The board and I have been planning for a seamless CEO succession for some time. Now is the opportune time to hand the CEO role over to Rob. The business is performing very well and is in a strong position for the long term. Our pipeline contains multiple promising candidates to sustain our future strong growth."

FDA Grants Breakthrough Therapy Designation to Sibeprenlimab for IgAN

The FDA has granted Breakthrough Therapy designation for Otsuka Pharmaceuticals' sibeprenlimab for the treatment of immunoglobulin A nephropathy (IgAN). IgAN is the most common form of primary glomerulonephritis worldwide and the most common cause of kidney failure in young adults.

Breakthrough Therapy designation is granted for a drug intended to treat a serious condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on at least one clinically significant end point. Sibeprenlimab is a humanized monoclonal antibody that blocks the action of the B-cell growth factor APRIL (a proliferation-inducing ligand), which plays a key role in the development and progression of IgAN. The *New England Journal of Medicine* previously reported positive results from the phase 2 ENVISION trial (NCT04287985) for IgAN in November 2023 [2024;390:20-31].

"We are encouraged by the FDA's decision to grant Breakthrough Therapy status for the sibeprenlimab program," said **John Kraus, MD, PhD,** executive vice president and chief medical officer at Otsuka. "This is an important milestone that recognizes the potential value that this investigational candidate may have in the future for people living with one of the most common causes of kidney failure."

Boston Area Man Is First to Receive Genetically Modified Pig Kidney

Richard Slayman of Weymouth, Massachusetts, has become the first person in the world to have a genetically modified pig kidney transplanted into his body. The transplant took place at Massachusetts General Hospital in Boston on March 16.

The surgery took 4 hours, and 15 people were present in the operating room. **Tatsuo Kawai, MD, PhD,** the transplant surgeon, said the team believes the pig kidney will function for at least 2 years.

The pig kidney for Slayman's transplant was provided by eGenesis of Cambridge, Massachusetts. The US Food and Drug Administration gave special permission for the transplant under "compassionate use" rules.

Other xenotransplantation efforts through the years have failed because the human immune system quickly destroyed foreign animal tissue. More recent attempts, including Slayman's transplant, have involved genetically modifying pigs' genes to make their organs more compatible with humans. ■

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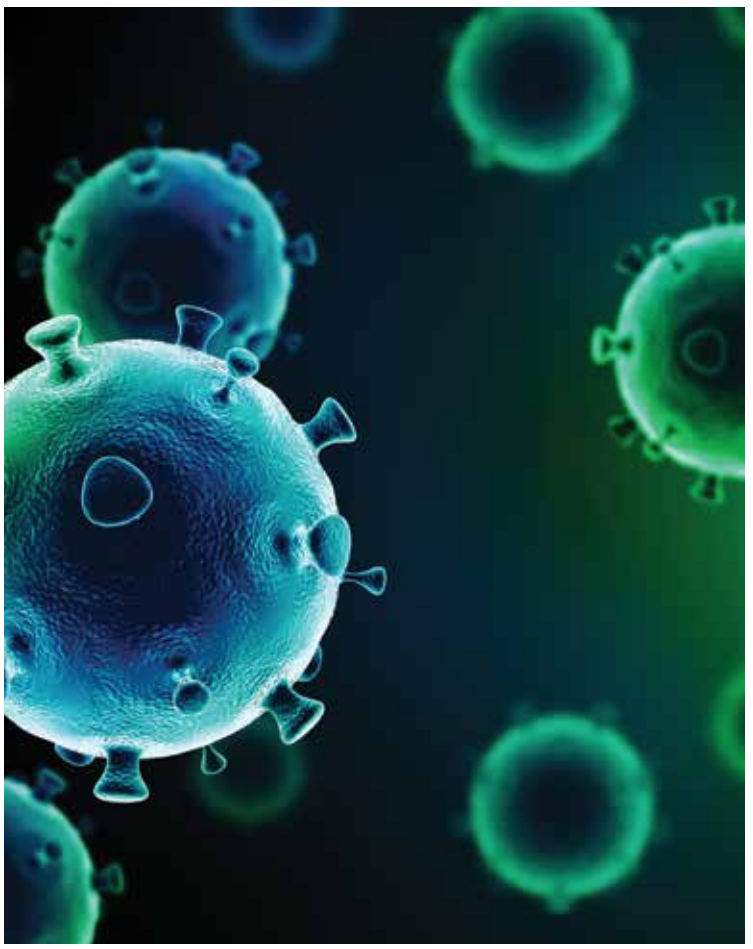

COVID-19

Dual-Drug Resistant Mutations in Kidney Transplant Recipients With COVID-19

Infection and Drug Resistance. 2024:17:531-541

Various therapeutic agents are available for the treatment of COVID-19. **Yoko Tanino** and colleagues reported results of an investigation of the emergence of dual-drug resistance in a kidney transplant recipient who received sotrovimab from day 0 and remdesivir (RDV) from days 8 to 17. The researchers sequenced the whole viral genomes from nasopharyngeal swabs taken on day 0 and at seven points following the start of treatment (days 12, 19, 23, 37, 43, 48, and 58).

The genomes were compared with those of a Wuhan strain and the day 0 wild-type strain to determine the genetic traits of the wild-type (day 0) and descendent (after day 12) viruses, respectively. Three viral isolates from samples collected on days 0, 23, and 37 were examined for their escape ability and growth kinetics in vitro.

Within 12 days (day 12) after treatment with sotrovimab, the sotrovimab-resistant mutation (S:E340K) emerged, and within 11 days (day 19) after treatment with RDV, the RDV-resistant mutation (RdRp:V7921 [nt: G15814A]) emerged. The day 23 isolate harboring S:E340K/RdRp:V792I was resistant to both sotrovimab and RDV, showing 364.00- and 2.73-fold higher resistance, respectively, compared with the wild-type virus. In addition, the day 37 isolate accumulated multiple additional mutations and had a higher level of resistance to both drugs compared with the day 23 isolate.

In conclusion, the researchers said, "Drug-resistant variants with double mutations (S:E340K/RdRp:V792I) became dominant within 23 days after starting treatment, suggesting that even [with] a combination therapy involving sotrovimab and RDV, dual-drug resistant viruses may emerge rapidly in immunocompromised patients. The dual-resistant variants had lower yields than those of the wild-type virus in vitro, suggesting that they paid a fitness cost."

ACUTE KIDNEY INJURY

CKRT in Patients With Acute Kidney Injury, Liver Failure

Clinical Journal of the American Society of Nephrology. 2024;19(2):151-160

There are conflicting opinions on the efficacy and safety of no anticoagulation versus regional citrate anticoagulation for treatment of acute kidney injury (AKI) with continuous renal replacement therapy (CKRT) in patients with severe liver failure at high risk for bleeding. **Ming Bai** and colleagues reported results of a randomized, controlled trial assessing both therapies for CKRT in that patient population.

The study cohort included patients who were randomized to receive regional citrate anticoagulation or no-anticoagulation CKRT. The primary end point of interest was filter failure.

Forty-two patients were randomized to the regional citrate anticoagulation CKRT group and 45 were randomized to the no-anticoagulation CKRT group. The filter failure rate in the no-anticoagulation group was significantly higher than in the regional citrate anticoagulation group (25 [56%] vs 12 [27%], respectively; *P*=.003).

The finding was confirmed by cumulative incidence function analysis and sensitivity analysis including only the first CKRT sessions. In the cumulative incidence function analysis, the cumulative filter failure rates at 24, 48, and 72 hours of the no-anticoagulation group were 31%, 58%, and 76%, respectively, compared with 11%, 23%, and 35% in the regional citrate anticoagulation group.

The incidences of $CA^{2+}_{tot}/Ca^{2+}_{ion}$ >2.5, hypocalcemia, and severe hypocalcemia were significantly higher in the regional citrate group than in the no-anticoagulation group (7% vs 57%; *P*<.001, 51% vs 82%; *P*=.002, and 13% vs 77%; *P*<.0010). Most (73%) of the increased $CA^{2+}_{tot}/Ca^{2+}_{ion}$ ratios were normalized following the upregulation of the calcium substitution rate. There was no significant additional increase in the systemic citrate concentration after 6 hours in the regional citrate anticoagulation group.

In conclusion, the researchers said, "For patients with liver failure with a higher bleeding risk who required CKRT, regional citrate anticoagulation resulted in significantly longer filter lifespan than no anticoagulation. However, regional citrate anticoagulation in patients with liver failure was associated with a significantly higher risk of hypocalcemia, severe hypocalcemia, and $CA^{2+}_{tot}/Ca^{2+}_{ion}$ >2.5."

ADPKD

Factors Associated With Intracranial Aneurysm in Patients With ADPKD

Journal of Nephrology. doi:10.1007/s40620-023-01866-8

Yusuke Ushio and colleagues reported results of a study comparing the factors associated with intracranial aneurysm in patients with autosomal dominant polycystic kidney disease (ADPKD) stratified by age: ≥50 years and <50 years.

The study included 519 patients with ADPKD. Median age was 44 years, median estimated glomerular filtration rate (eGFR) was 54.5 mL/min/1.73 m^2, and total follow-up duration was 3104 patient-years.

There were significant associations between the presence of intracranial aneurysm and age ≥50 years, female sex (*P*=.0027 for interaction), and hypertension (*P*=.0074 for interaction). The associations between female sex and hypertension were seen only in patients ≥50 years of age.

In patients <50 years of age, there were significant associations between intracranial aneurysm and stage 4-5 CKD (odds ratio [OR], 3.87; *P*=.0007) and family history of intracranial aneurysm or subarachnoid hemorrhage (OR, 2.30; *P*=.0217). For patients ≥50 years of age, there were associations between intracranial aneurysm and stage 4-5 CKD (OR, 2.38; *P*=.0355), family history of intracranial aneurysm or subarachnoid hemorrhage (OR, 3.49; *P*=.0094), female sex (OR, 4.51; *P*=.0005), and hypertension (OR, 5.89; *P*=.0012).

In conclusion, the authors said, "Kidney dysfunction and family history of intracranial aneurysm or subarachnoid hemorrhage are risk factors for early-onset intracranial aneurysm. Patients aged <50 years with a family history of intracranial aneurysm or subarachnoid hemorrhage or with CKD stages 4-5 may be at an increased risk of early-onset intracranial aneurysm."

CHRONIC KIDNEY DISEASE

Antidepressants in Patients With CKD and Depression

Clinical Journal of the American Society of Nephrology. 2024;19(2):178-188

Patients with CKD commonly experience depression, putting them at risk for a poor prognosis. The use of antidepressants in the population with CKD is widespread. However, according to **Nanbo Zhu** and colleagues, there are few data available on the safety of those agents in patients with CKD.

Dr. Zhu et al conducted an analysis that included data on adults with stage 3-5 CKD (eGFR <60 mL/min/1.73 m^2 not treated with dialysis) and a diagnosis of incident depression from 2007 to 2019. The data were included in the Stockholm Creatinine Measurements project. The researchers compared three treatment strategies using the target trial emulation framework: (1) initiating versus not initiating antidepressants; (2) initiating mirtazapine versus selective serotonin reuptake inhibitors (SSRIs); and (3) initiating SSRIs with a lower dose versus a standard dose.

The dataset included 7798 eligible individuals. Of those, 74% (n=5743) initiated treatment with an antidepressant. Compared with noninitiation, there was an association between initiation of antidepressants with higher hazards of short-term outcomes: hip fracture (hazard ratio [HR], 1.23; 95% CI, 0.88-1.74) and upper gastrointestinal bleeding (HR, 1.38; 95% CI, 0.82-2.31). The associations did not reach statistical significance. There was no association between initiation of antidepressants and the long-term outcomes of all-cause mortality, major adverse cardiovascular events, progression of CKD, and suicidal behavior.

Compared with SSRIs, there was an association between initiation of mirtazapine and lower hazard of upper gastrointestinal bleeding (HR, 0.52; 95% CI, 0.29-0.96). However, there was also an association between initiation of mirtazapine and a higher hazard of mortality (HR, 1.11; 95% CI, 1.00-1.22). Compared with the standard dose, there was a nonstatistically significant association between initiation of SSRIs at a lower dose and a lower hazard of upper gastrointestinal bleeding (HR, 0.68; 95% CI, 0.35-1.34) and progression of CKD (HR, 0.80; 95% CI, 0.63-1.02). There was also a nonstatistically significant association with a lower dose of SSRIs and a higher hazard of cardiac arrest (HR, 2.34; 95% CI, 1.02-5.40).

"Antidepressant treatment was associated with short-term adverse outcomes but not long-term outcomes in people with CKD and depression," the authors said.

DIALYSIS

Dialysate, Plasma Sodium, Mortality in Hemodialysis Patients

Journal of the American Society of Nephrology. 2024;35(2):167-176

Cardiovascular disease is a major contributor to mortality in patients receiving hemodialysis, due in part to abnormal fluid status and plasma sodium concentrations. Removal of fluid and sodium is facilitated with ultrafiltration, and diffusive exchange of sodium is pivotal in sodium removal and tonicity adjustment. Lower dialysate sodium may increase sodium removal at the expense of tonicity, reduced blood volume refilling, and intradialytic hypotension risk. Higher dialysate sodium preserves blood volume and hemodynamic stability but reduces sodium removal.

Julie Pinter and colleagues conducted a study involving a multinational cohort of 68,196 patients to determine whether a dialysate sodium of ≤138 mmol/L would have an effect on survival outcomes compared with dialysate sodium >138 mmol/L, after adjusting for plasma sodium concentration.

The cohort included incidence hemodialysis patients from 875 Fresenius Medical Care Nephrocare clinics in 25 countries between 2010 and 2019. The association between time-varying dialysate and plasma sodium exposure and all-cause mortality was modeled using a multivariable Cox regression model stratified by country and adjusted for demographic and treatment variables, including bioimpedance measures of fluid status.

On average, the 68,196 patients underwent three hemodialysis sessions per week. Dialysate sodium of 138 mmol/L was prescribed in 63.2%, 139 mmol/L in 15.8%, 140 mml/L in 20.7%, and other concentrations in 0.4% of the cohort. The majority (78.6%) of the centers used a standardized concentration.

Follow-up continued for a mean of 40 months. During that period, 21,644 patients (one-third) died. Following adjustment for plasma sodium concentrations and other confounding variables, there was an association between dialysate sodium ≤138 mmol/L and higher mortality (multivariate HR for the total population, 1.57; 95% CI, 1.25-1.98).

Results of subgroup analyses did not show evidence of effect modification by plasma sodium concentrations or other patient-specific variables.

"These observational findings stress the need for randomized evidence to reliably define optimal standard dialysate sodium prescribing practices," the authors said.

PRURITUS

Physician Awareness, Prevalence of Pruritus in Patients Receiving Hemodialysis

Nephrology Dialysis Transplantation. 2024;39(2):277-285

Pruritus associated with CKD (CKD-aP) may be under-recognized in patients with impaired kidney function. **Franziska Engler** and colleagues conducted a study to examine the prevalence, risk factors, and impacts on quality of life (QOL) of CKD-aP in a cohort of patients receiving hemodialysis in Austria. The researchers also sought to assess attending physicians' awareness of and approach to therapy for pruritus.

The study utilized responses on patient and physician questionnaires on pruritus severity and QOL linked with information from the Austrian Dialysis and Transplant Registry.

In the cohort of 962 patients, 34.4% reported mild pruritus, 11.4% reported moderate pruritus, and 4.3% reported severe pruritus. The physicians' estimated prevalences were 25.0%, 14.4%, and 6.3%, respectively. The estimated national prevalence estimate extrapolated from the study cohort was 45.0% for any stage, 13.9% for moderate, and 4.2% for severe CKD-aP. Severity was significantly associated with impaired QOL.

The risk factors for CKD-aP were identified as higher C-reactive protein (OR, 1.61; 95% CI, 1.07-2.43) and parathyroid hormone (PTH) values (OR, 1.50; 95% CI, 1.00-2.27). Therapy included changes in the dialysis regimen, topical treatment, antihistamines, gabapentin and pregabalin, and phototherapy.

In summary, the authors said, "While the prevalence of CKD-aP in our study was similar to that in previously published literature, the prevalence of moderate-to-severe pruritus is lower. CKD-aP was associated with reduced QOL and elevated markers of inflammation and PTH. The high awareness of CKD-aP in Austrian nephrologists may explain the lower prevalence of more severe pruritus." ■

Sarah Tolson

The Dialysis Dilemma: Navigating the Rough Waters of Medicare Advantage Plans

In the ever-evolving landscape of health care, dialysis programs face a formidable challenge that is quietly undermining the sustainability of their services. The crux of the issue lies with the burgeoning influence of Medicare Advantage (MA) plans, which, while offering an alternative to traditional Medicare, are posing significant operational and financial hurdles for dialysis programs. This column delves into the multifaceted challenges these plans present, shedding light on the precarious position in which many dialysis programs find themselves.

At the heart of the matter is the mechanism of Medicare bad debts and the Prospective Payment System (PPS), foundational elements in the funding of dialysis care. Traditional Medicare has created a reimbursement framework for dialysis programs that closely monitors the average cost of providing a dialysis treatment and allows for reimbursement that is intended to be close to the average cost. Medicare assigns 20% of the allowable reimbursement to the patient as a coinsurance. Over the years, dialysis facility social workers have become experts in helping patients obtain secondary insurance coverage that will cover the 20% of patient medical expenses not covered by Medicare. Whether due to a patient's inability to pay or due to the reimbursement policies of a patient's secondary insurance, there are instances where dialysis programs are unable to collect the coinsurance and deductible amounts assigned by Medicare. This leaves the facility in a position where it costs more to provide treatment than it can collect. Decades ago, the Centers for Medicare & Medicaid Services (CMS) created a pathway for dialysis programs to recoup a portion of these uncollectable Medicare-assigned coinsurances and deductibles.

However, the transition of patients to MA plans disrupts this process, as there is no pathway for reimbursement of those coinsurances and deductibles not covered by the MA plan. The result is essentially reducing the program's operational funds to 80% of their costs. This reduction is particularly crippling in the context of the PPS, which has not kept pace with the escalating costs of labor, supplies, and medications—a situation amplified by the pandemic. The growing penetration of MA plans not only exacerbates these financial deficits but also portends a grim future for many, especially small rural facilities that have historically survived on the thin margins of bad debt reimbursements.

The operational burden on facilities is further intensified by the MA plans' deviation from established CMS billing rules. In some markets, MA plans require authorizations for dialysis services, which is not necessarily problematic, but many MA plans require reauthorization every 90 days, and calling the utilization department and speaking with a representative is the only way to obtain the necessary authorization. Arbitrary rejections of claims, citing noncompliance with MA plans' unique billing standards, leave providers in a quagmire of lengthy appeals processes, delaying payments essential for the continuity of care. This systemic delay tactic strains the financial viability of providers and underscores the need for regulatory oversight to ensure that MA plans adhere to a standardized set of billing rules, particularly for services as critical as dialysis.

In the broader context of health equity, the situation is stark. The aggressive push by insurance companies to enroll patients with end-stage renal disease (ESRD) in MA plans has wrested control from providers. This shift not only jeopardizes the quality of care but also the very existence of dialysis programs, particularly those serving vulnerable populations in rural areas.

As we stand at this critical juncture, it is imperative for CMS to intervene and ensure that MA plans do not deviate from the core mission of providing comprehensive and accessible care to all patients, regardless of their insurance. The survival of dialysis programs—and by extension, the well-being of countless patients—hinges on the establishment of a more equitable, transparent, and sustainable framework that bridges the gap between the ideals of health care provision and the realities of insurance-driven market dynamics.

You can share your program's and your patients' experience with MA plans with CMS to inform coming changes to the MA landscape. CMS has released a request for information specific to the challenges surrounding MA plans. Share your story with CMS before the end of the comment period on May 29, 2024, here: www.federalregister.gov/documents/2024/01/30/2024-01832/medicare-program-request-for-information-on-medicare-advantage-data. ■

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