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Standardized Care Practices and Risk of Catheter-Related Bloodstream Infections in Children

In the United States, children with kidney failure are most commonly treated initially with hemodialysis. In children undergoing hemodialysis, infections are a major cause of both morbidity and mortality. Rates of infection-related complications are particularly high among children who receive dialysis via a catheter. The risk of infection among children with catheter access is nearly five-fold that of children with arteriovenous (AV) fistulas or grafts.

Due to increased longevity and lower infection rates compared with catheters, AV accesses are the preferred access types. However, catheters remain the most commonly used form of hemodialysis access in children.

According to **Rebecca L. Ruebner, MD, MSCE,** and colleagues infection prevention rates should include measures to reduce catheter-associated bloodstream infections (CA-BSIs). The Children's Hospital Association's Standardizing Care to Improve Outcomes in Pediatric End-Stage Kidney Disease (SCOPE) Collaborative is a multicenter quality transformation initiative designed to utilize standardized care practices to minimize infection-related complications among children receiving maintenance dialysis.

Previous studies of SCOPE's hemodialysis project have focused on infection

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Neighborhood Disadvantage and Progression in Pediatric Chronic Kidney Disease

The risk for disease progression among children with chronic kidney disease (CKD) is high, a risk that is modified by specific demographic and socioeconomic factors. Evidence suggests that the racial, ethnic, and socioeconomic disparities in outcomes seen in adults with CKD extend to the pediatric CKD population. Black children with CKD are more likely to experience faster disease progression and earlier initiation of kidney replacement therapy (KRT). They are also more likely to initiate dialysis rather than undergo kidney transplantation.

In addition, White children with kidney failure are more likely to have undergone kidney transplantation within 2 years of initiation of dialysis (70% vs 44%, respectively). Children from households with lower income are more likely to develop

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Self-reported Race and GFR in Children and Young Adults

The best measure of kidney health is glomerular filtration rate (GFR). Recent reassessment of the use of race in estimated GFR (eGFR) in adults has raised questions regarding the role of race in equations used to calculate eGFR in children and young adults.

Pediatric eGFR equations from the Chronic Kidney Disease in Children (CKiD) cohort do not have a coefficient for Black race, including recent equations designed for patients under 25 years of age (U25 equations). There are few data available on the associations of self-reported race with measured GFR (mGFR) adjusting for serum creatinine or cystatin C in children and young adults with chronic kidney disease (CKD).

Data from the CKiD study offer an opportunity to examine the biomarkers in that patient population, using centrally measured GFR, serum creatinine, and serum cystatin-C to assess putative differences in the biomarkers across ages and levels of kidney function in the context of self- and parental-reported race. **Derek K. Ng, PhD,** and colleagues reported results of an observational cohort study examining the differences. The researchers also sought to evaluate the

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What's Up with Magnesium in Patients With CKD?

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Like many in practice, I have not paid much attention to the serum magnesium (Mg) in patients with chronic kidney disease (CKD)—usually not checking the Mg level unless the patient is hypokalemic on a diuretic or has underlying cardiac disease, or in an acute setting when there might be evidence of ventricular dysrhythmias. However, over the past few years, there has been a spate of articles on the association between serum magnesium, high or low, and adverse outcomes in patients with CKD. Should we be paying more attention to Mg?

Mg is a divalent ion that is mostly stored in bone or intracellularly (>99%). The serum Mg accounts for about 0.3% of total-body Mg. A normal Mg level is in the 1.3-2.0 mEq/L (1.6-2.4 mg/dl) range. Excretion of Mg occurs mostly via the gastrointestinal tract (70%). Of the 30% of Mg that is excreted by the kidneys, 30% is reabsorbed by the proximal tubule and the remainder is handled more distally: 70% reabsorbed in the thick ascending limb, and 10%-15% handled via a Mg channel, the melastatin-related transient receptor potential cation channel 6 (TRPM6) in the distal convoluted tubule.[1]

A typical diet contains approximately 360 mg magnesium, and three-quarters is excreted in the feces. Normal kidneys excrete about 100 mg magnesium per day. A low Mg is relatively common in CKD patients—a prevalence rate of about 15% even in CKD stages G4 and G5,[1,2] especially among proteinuric patients,[2] or if they are being treated with high doses of diuretics or with a proton pump inhibitor (PPI). In ESRD patients, a modestly elevated Mg level may be seen but its significance has been unclear and may depend on dialysis clearance.[3]

The evidence of an association between Mg and cardiovascular outcomes in CKD patients is quite tenuous. In the best study so far, an observational analysis of the CRIC dataset,[4] Negrea and colleagues suggest a U-shaped association between Mg <1.9 mg/dL and Mg >2.1 mg/dL and cardiovascular outcomes. However, the association was observed only in crude models and became statistically nonsignificant in models adjusted for demographic, laboratory, and clinical factors. Hardly very convincing. In an accompanying editorial,[5] Kula and Bansal agree. Both Negrea et al and Kula et al acknowledge the many limitations of the study using the CRIC dataset, including the limitations of having only one Mg measurement, the limitation of serum Mg in estimating total-body Mg stores, and the almost universal criticism of any observational study, namely residual confounding.

Hypomagnesemia has also been studied as a risk factor for renal progression. Sakaguchi has suggested hypomagnesemia to be a predictor of progression to ESRD in diabetic nephropathy.[7] In one study, a retrospective analysis, hypomagnesemia increased the risk of phosphate-induced renal injury.[8] The possibility that hypomagnesemia enhances (and Mg administration might prevent) calcium-phosphate crystal formation within the proximal tubular lumen has been invoked. The hypothesis being that CaxPhos crystals cause damage to the tubular epithelium and thus induce interstitial fibrosis.[9] Still, my review of the studies published so far indicates a connection between Mg and renal fibrosis that is unproven.

Mg in preventing vascular calcification has also been suggested in the literature.[2] While the inhibition of calcium phosphate crystal formation by Mg, both in vitro and in animal models, has been reported,[2] reducing cardiovascular complications or reducing mortality by treating CKD patients with Mg has not been convincingly demonstrated.[2]

Treatment with a thiazide diuretic has been associated with hypomagnesemia. In a small double-blind randomized trial, Odvina et al[10] reported higher rates of hypomagnesemia in thiazide-treated patients that could be prevented by K-Mg-citrate treatment. The diuretic-induced magnesium deficiency influences potassium metabolism. Magnesium is a necessary activator of Na-K-ATPase, which supplies the Na-K pump with energy.[11] Lack of magnesium will therefore impair the pumping of sodium out of the cell and of potassium into the cell.

So, my take on the relationship between Mg and clinical outcomes is that the jury is still out. Should we check serum Mg in CKD patients? Checking Mg could be worthwhile, especially in hypokalemic patients with CKD who are receiving aggressive diuretic therapy with either thiazide or loop diuretics. This is because correcting hypomagnesemia might allow for the successful treatment of hypokalemia. Monitoring the Mg level and correcting as necessary would also be reasonable in CKD patients with ischemic heart disease, especially where there is a concern about arrhythmias. But I do not think we are at a stage where we should be monitoring Mg in all our CKD patients on a regular basis. ■

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Neighborhood Disadvantage and CKD

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kidney failure and less likely to be waitlisted for transplant following dialysis initiation.

The Chronic Kidney Disease in Children (CKiD) study is an ongoing multicenter, prospective cohort study examining pediatric CKD. The study collects individual and neighborhood-level socioeconomic data from participants, including Census block group data. **Sara A. Boynton, MPH,** and colleagues utilized data from the CKiD study to examine the relationship between neighborhood poverty and deprivation, CKD comorbidities, and disease progression in children with CKD. Results were reported in the *American Journal of Kidney Diseases* [2022;80(2):207-241].

The outcomes of interest were binary outcomes of short stature, obesity, hypertension, and health care utilization for cross-sectional analysis; a CKD progression end point (defined as incident KRT or 50% loss in estimated glomerular filtration rate [eGFR]), and mode of first KRT for time-to-event analysis. Logistic regression was used to estimate odds ratios with data on health characteristics at the time of the first Census data collection. A Cox proportional hazard model was used to analyze the risk for CKD progression. Multivariable models were adjusted for race, ethnicity, sex, and family income.

The cohort included 578 individuals who completed at least one study visit. Median age was 11.9 years, 60% were male, 26% were Black, and 17% were Hispanic. Approximately 45% of participants reported annual household income of less than $36,000. The majority (92.3%) had lived within the same ZIP code for more than 1 year. Only 2% were uninsured, and 47% had pubic insurance.

Thirteen percent of the cohort had short stature, 18.4% had obesity, and 47.2% had hypertension. In the year prior to the study visit, 28% had been hospitalized and 42% had at least one visit to the emergency department (ED). Median eGFR was 51 mL/min/1.73 m^2, corresponding to stage 3 CKD. Thirty-two percent of participants included in the analysis progressed to KRT during the follow-up period. The initial mode of KRT was preemptive kidney transplant in 37% of that subgroup.

Neighborhood characteristics of participants' Census blocks included median household income that was similar to the national median income ($42,148) in 2000. Neighborhood residents were majority non-Black, non-Hispanic.

In analyses of the association between individual and neighborhood characteristics, median neighborhood income was significantly higher for participants whose family income was more than $36,000, and significantly higher for non-Black and non-Hispanic participants. The Area Deprivation Index (ADI) is a composite measure to 17 Census markers that encompass neighborhood poverty, education, employment, and housing. ADI was significantly higher for lower income participants and for Black participants; there was no statistically significant difference between Hispanic and non-Hispanic participants.

The median percentage of neighborhood population that was Black was significantly higher for Black participants than non-Black participants. Likewise, the median percentage of Hispanic neighborhood population that was Hispanic was significantly higher for Hispanic participants than for non-Hispanic participants. Those results suggest that the participants lived in neighborhoods that were relatively homogeneous in terms of race, ethnicity, and socioeconomic status.

Analyses of the association between neighborhood economic factors and participant clinical characteristics revealed that participants in the lowest income neighborhoods were more likely to have short stature than those in the higher neighborhood income quartiles (odds ratio [OR], 1.77; 95% CI, 1.06-2.96), and more likely to have been hospitalized and to have had a visit to the ED in the past year. For participants residing in the lowest income quartile neighborhoods, preemptive kidney transplant was significantly less likely (OR, 0.47; 95% CI, 0.24-0.96).

Following adjustment for individual family income, sex, race, and ethnicity, only the association between lowest neighborhood income and hospitalizations and ED visits remained significant (OR, 1.71; 95% CI, 1.08-2.71 and OR, 1.56; 95% CI, 1.02-2.40, respectively). There was no significant association between high ADI and any health characteristics in the multivariable model.

Results of univariate analysis suggested that participants residing in the lowest neighborhood median income quartile had a nearly 40% greater hazard of reaching the outcome of CKD progression compared with those in the higher quartiles. Following adjustment for participant race, ethnicity, sex, and family income, the association was no longer significant. There was no significant association between ADI and the hazard of the CKD progression outcome in either the univariate or adjusted analyses.

Limitations to the study cited by the authors included limited generalizability, and the lack of data on the clinical indications for urgent health visits or hospitalizations as well as on other neighborhood-level factors such as the presence of food banks or social workers that influence health outcomes. The study data was taken from a single, early study time point, resulting in an inability to determine how changes in neighborhood-level factors were associated with outcomes over time.

In summary, the researchers said, "Neighborhood-level socioeconomic status was associated with poorer health characteristics and CKD progression in univariable analysis. However, the relationships were attenuated after accounting for participant factors including race. A persistent association of neighborhood poverty with hospitalizations and ED suggests an independent effect of socioeconomic status on health care utilization, the causes for which deserve additional study." ■

TAKEAWAY POINTS

- Researchers conducted an observational cohort study designed to assess the relationship between neighborhood poverty and deprivation and comorbidities and disease progression in children with chronic kidney disease.
- There were significant associations between the risks for short stature, hospitalization, and emergency department visits and lower neighborhood income.
- In unadjusted analyses, the likelihood of undergoing a preemptive transplant was decreased with lower neighborhood income, an association that did not persist after adjustment for patient characterisitcs.

Self-reported Race and GFR in Children

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performance of U25 equations in a large cohort of children and young adults with CKD. Results of the study were reported in the *American Journal of Kidney Diseases* [2022;80()2):174-185].

The study cohort included 190 Black and 675 non-Black participants in the CKiD study, representing 473 and 1897 annual person-visits, respectively. The study exposure was self- or parental-reported race (Black, non-Black). Analyses were adjusted for serum creatinine, cystatin-C, body size, and socioeconomic status. The outcome of interest was mGFR based on iohexol clearance.

Linear regression models were fit with mGFR as the dependent variable and serum creatinine as an independent variable, with additional independent variables for Black race and body size metrics. Each body size variable was included separately (none, sex, age as a continuous variable, height, body surface area, and estimated lean body mass [eLBM] without and with ancestry).

Both groups (Black and non-Black) were similar in age distribution (median age, 9 years) and in proportions of male participants (66.2% among Black person-visits and 61.3% among non-Black person-visits). Of the participants who self-reported Black race, 22.6% self-reported mixed race. Of the non-Black participants, 85.0% self-reported White race, and 5.6% reported non-Black mixed race.

Black participants were more likely to report household income less than $36,000 (65.5% vs 33.3%) and a maternal education level of less than college (77.0% vs 64.6%). Body size and Tanner stage were similar; however, the average eLBM was greater among Black participants. The two groups were similar in median serum creatinine (1.2 mg/dL), but serum cystatin-C was lower in Black versus non-Black participants (1.51 vs 1.73 mg/dL, respectively). Median mGFR was higher in Black participants than in non-Black participants (52.9 vs 46.2 mL/min1.73 m^2).

In analyses of the association of self-reported race, mGFR, and serum creatinine, in unadjusted models without age stratification, mGFR was 12.8% (95% CI, 7.8%-18.1%) higher in Black participants. When models were fit by age groups older than 6 years, the difference ranged from +10% to +13.4%; the differences were significant for all older-than-6 age groups. In children younger than 6 years, the difference was similar but did not reach statistical significance (+7.4%; 95% CI, –1.0% to +16.5%); there was no statistical difference across age groups (*P*=.7).

In models assessing the relationship between serum cystatin-C and mGFR, there were minimal differences observed between Black and non-Black person-visits. Among participants younger than 6 years of age, Black person-visits had systematically (slightly) lower mGFR values, adjusting for serum cystatin C; the differences diminished in older age groups.

In regression models that included serum cystatin C, across all age groups in the unadjusted model, Black race was associated with lower mGFR (percent difference, –3.5% [95% CI, –5.7% to –1.4%]). There was no interaction across ages, but differences were attenuated as age increased: for ages 6 to 12, 12 to 18, and >18 years, the differences were –5.0% (95% CI, –8.3% to –1.5%), –2.5% (95% CI, –5.6% to +0.6%), and –0.9% (95% CI, –6.4% to +5.0%), respectively.

> In analyses of the association of self-reported race, mGFR, and serum creatinine, in unadjusted models without age stratification, mGFR was 12.8% (95% CI, 7.8%-18.1%) higher in Black participants.

When other markers of body size and indicators of socioeconomic status were used as variables, the relationships remained essentially the same. Among participants under 6 years of age, self-reported Black race was consistently associated with mGFR (range, –7.5% to –9.3%). For those older than 18 years of age, nonsignificant differences ranged from –0.3% to –3.3%. There were similar associations across ages in multivariable models, but there were no interactions by age group.

There were some limitations to the study findings cited by the authors, including the lack of directly measured muscle mass, the possibility that the participant- or parent-reported question on race may have been interpreted differently by respondents, adjusting for only two socioeconomic variables (household income and maternal education), the small number of children under 6 years of age, and the lack of data on dietary patterns.

In conclusion, the researchers said, "Differences in the creatinine-mGFR relationship by self-reported race were observed in children and young adults with CKD and were consistent with findings in adults. Smaller and opposite differences were observed for the cystatin C-mGFR relationship, especially in the younger age group. We recommend inclusion of children for future investigations of biomarkers to estimate GFR. Importantly, for GFR estimation among those under 25 years of age, the average of the new U25 creatinine and cystatin C equations without race coefficients yields unbiased estimated of mGFR." ■

TAKEAWAY POINTS

- Researchers conducted a observational cohort study to examine relationships of self-reported race with measured glomerular filtration rate (mGFR) adjusting for serum creatinine or cystatin C in children and young adults with chronic kidney disease (CKD).
- Following adjustment for serum creatinine, there was an association between self-reported Black race and slightly higher GFR in children more than 6 years of age and in young adults; following adjustment for cystatin C, there was a smaller and opposite difference.
- The average of creatinine- and cystatin C-based equations designed for populations under the age of 25 was unbiased by self-reported race groups.

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Standardized Care Practices

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rates at a collaborative-wide level. The current prospective cohort study, led by Dr. Reubner, was designed to describe the epidemiology of and identify patient-level factors for infections associated with hemodialysis in children. The researchers also sought to examine the association between change in dialysis center-level compliance with SCOPE hemodialysis care practices over time and the risk of CA-BSI. Results were reported in the *American Journal of Kidney Diseases* [2022;80(2):186-195].

The study cohort included children who were enrolled in the SCOPE project between June 2013 and July 2019. Data on patient characteristics and center-level compliance with hemodialysis catheter care practices across the study period were collected. The centers were characterized as consistent, dynamic (improved compliance over the study period), or inconsistent performers based on frequency of compliance audit submission and changes in compliance with hemodialysis care practices over time. The outcome of interest was CA-BSI incidence.

The SCOPE hemodialysis catheter care bundles address five categories of catheter care: (1) catheter dressing/site assessment; (2) catheter connection; (3) catheter disconnection; (4) cap care; and (5) catheter dressing change/exit site care. At each participating center, compliance with hemodialysis care bundles was assessed through direct observation of patient care on a randomly selected group of patients. Monitoring was conducted by study team members and submitted via a care observation form.

The study cohort included 1277 children from 35 pediatric dialysis centers. Of the 1277 participants, 79.7% (n=1018) had a catheter and 20.3% (n=259) had an AV access. In comparisons of demographic characteristics of children with catheter access with children with AV access, older age and a history of kidney transplant were associated with increased likelihood of AV access versus catheter use (P<.001 for both).

During the study period, there were 277 positive blood cultures reported. Of those, 67% (n=185) were adjudicated as an access-related BSI and 33% (n=92) were attributed to a source that was not related to dialysis access. There were 171 CA-BSIs among 123 catheters and 14 AV access-associated BSIs among 13 AV accesses (11 in fistulas and three in grafts). The overall rates of infection were 0.95 per 100 patient-months for CA-BSIs and 0.27 per 100 patient-months for BSI associated with AV access.

Results of a generalized linear mixed model of individual patient-level risk factors for CA-BSI demonstrated that mupirocin use at the catheter exit site was associated with an increased rate of CA-BSI (rate ratio [RR], 4.45; 95% CI, 1.60-12.35 vs chlorhexidine-impregnated dressing; P=.004). There was a nominal association between the use of no antibiotic ointment at the exit site and an increased rate of CA-BSI (RR, 1.79; 95% CI, 1.01-3.18 vs chlorhexidine-impregnated dressing), but the difference was of borderline statistical significance (P=.05). There were no significant associations between rates of CA-BSI and age, underlying cause of kidney failure, history of kidney transplant, or type of dressing used.

The secondary analysis included 33 centers and 983 children with catheters. Of the 33 centers, six were classified as consistent performers, 11 as dynamic performers, and 16 as inconsistent performers. Of the 16 inconsistent performers, eight centers did not submit the required number of audits and eight submitted the audits but did not achieve the target improvement in compliance. The centers designated as consistent performers tended to have longer participation in SCOPE and contributed significantly more catheter-months to the analysis. There were no significant differences in patient characteristics or in the proportion of patients with multiple infections across compliance groups.

Overall median compliance with hemodialysis catheter care practices was 87.5%. Centers classified as dynamic performers demonstrated a significant decrease in CA-BSI rates over time (from 2.71 to 0.71 per 100 person-months; RR, 0.98; 95% CI, 0.97-0.99; P<.001). There was no change in CA-BSI rate over time among consistent (RR, 1.00; 95% CI, 0.98-1.01; P=.5) or inconsistent centers (RR, 1.00; 95% CI, 0.98-1.02; P=.9).

The researchers cited some limitations to the study findings, including the inability to draw conclusions regarding the influence on risk of infection of individual patient-level adherence to SCOPE hemodialysis care practices, the inability to assess risk factors associated with AV access due to the small number of infections, and missing data on treatment for CA-BSIs (including whether the catheter was removed) resulting in the inability to comment on the association between catheter removal and risk of infections.

In summary, the authors said, "Dialysis-associated BSIs are an important complication among children with kidney failure and are associated with significant morbidity. Consistent improvement in compliance with standardized hemodialysis care practices can lead to a reduction in the risk of dialysis-associated infections among children with kidney failure." ■

TAKEAWAY POINTS

- Researchers reported results of a prospective cohort study describing patient-level risk factors for catheter-associated bloodstream infections (CA-BSIs) in children on hemodialysis; the study also examined the association between center-level compliance with standardized care practices and the risk of CA-BSI.
- Among the participants with a catheter for dialysis access, the use of mupirocin at the catheter exit site was associated with an increased rate of CA-BSIs.
- Among the 33 centers included in a secondary analysis, overall mean compliance with hemodialysis catheter care practice was 87.5%.

Disrupting Kidney Disease Care… For the Better

Monogram Health CMO sees many opportunities to improve care for people living with chronic kidney and end-stage renal disease

Shaminder Gupta, MD

Recent data show an estimated 37 million Americans, (one in seven adults, or up to 15% of the US adult population) are affected by chronic kidney disease (CKD).[1] Another one in three adults are at risk for developing CKD, which can be driven by comorbid conditions such as hypertension and diabetes. This heavy public health burden is also expensive. The costs of caring for individuals with kidney disease represent around 20% ($114 billion) of traditional Medicare expenditures, and these costs continue to rise.[2]

Unfortunately, the downstream effects of kidney disease and renal failure are poor health outcomes and decreased quality of life, which are often compounded by barriers to accessing essential care, as well as a "volume-first" health care system that remains deeply entrenched.

Prior to joining as the medical director (and later CMO) of Monogram Health, I was a practicing nephrologist in the charity hospital system in Louisiana, caring for patients with CKD and end-stage renal disease (ESRD). I saw firsthand the impact prevalent and poorly managed kidney disease can have on individuals, families, communities, and the broader health care system. It was during these years that I developed a passion for population-based health. So, it was serendipitous that while serving as president of the National Kidney Foundation I met Monogram Health CEO Mike Uchrin and discovered we shared a common desire to do more for high-risk kidney patients—in their own homes.

Monogram now operates in more than 30 states, deploying an innovative care model that is improving the lives and health of this patient population.

DISRUPTING DIALYSIS

When you think about common treatments for CKD and ESRD, dialysis comes to mind. Dialysis care is usually delivered in an emergency department, an acute-care setting, or a dialysis center. This means much of a patient's care is transferred from their home to an off-site location they'll need to visit several times a week, or until they receive a transplant. In-center dialysis is the most cost-, resource-, and time-intensive intervention in the nephrologist's arsenal. We are upending that model to bring care back into the home.

Monogram seeks to fill a systemic gap and transform the way patients with kidney disease are treated to help slow progression of the disease and ensure increased access to evidence-based renal care for more individuals as early as possible. We believe in-center dialysis should not be a first-line therapy but a last resort. We focus exclusively on managing CKD and ESRD in the home, transforming care so a kidney disease diagnosis is no longer synonymous with dialysis and patients can enjoy better outcomes and better quality of life.

In fact, one of the unique aspects of Monogram's model is that we are not in the dialysis business. We care about the *appropriateness* of dialysis and do not derive any income from it when dialysis is the right option for our patients. This allows us to stay focused on the evidence-based pathways that are most appropriate for each individual.

NEW PRACTICE MODEL

Another unique attribute of Monogram's approach is our non-reliance on clinical contractors for care delivery. All our clinicians are full-time employees of Monogram. We employ a clinical practice of nephrologists as well as cardiologists, geriatricians, endocrinologists, internal medicine specialists, nurse practitioners, registered nurses, social workers, and pharmacists. They are empowered to drive patient care—diagnosing and treating kidney disease right in the patient's home and, when necessary, guiding care teams in the field through all types of evidence-based complex case management and disease management care pathways.

In addition to home doctor visits, our teams deliver a suite of tech-enabled clinical services, including in-home care management, medication therapy management, family counseling, advance care plans, nutrition management, referral management, remote monitoring/biometrics, telehealth, concurrent hospitalization review, and post-discharge follow-up. Our artificial intelligence (AI) platform and industry-leading medical economics analytics identify individuals with kidney disease earlier, as well as those at high risk for progression, and identifies gaps in evidence-based medical care and medication therapies. These insights enable Monogram to deliver care to delay the progression of CKD, avoid hospital admissions and readmissions, and avoid dialysis crashes while increasing patients' access to evidence-based care pathways.

Perhaps a patient isn't thriving and could benefit from in-home dialysis. Maybe they're stuck in a transplant log jam and need to lose weight. Busy nephrologists and specialists may not have time to manage these things, but Monogram can step in, assess, and assist to ensure the patient succeeds.

GUIDED BY EXPERTISE

This spring we launched a distinctive and independent Clinical Advisory Board consisting of 25 of the nation's leading clinician executives covering a variety of areas of expertise, including nephrology, emergency medicine, geriatrics, health plans, academic medical centers, device manufacturers, and research ecosystems. Our Board of Directors includes industry-leading talent and thought leaders, and is led by former Senate Majority Leader Bill Frist, MD, a former heart and lung transplant surgeon, and cofounder of the company.

With the support of the Clinical Advisory Board, we ensure our work is grounded in evidence-based care guidelines, which drive quality outcomes and reduce costs. Our model disrupts where health care dollars go and improves affordability across the health care continuum.

BRINGING IT HOME

Bottom line: we are transforming the way kidney disease care is delivered. It's long overdue, and we've created a model that works.

When we can create alignment for all stakeholders involved in the patient's care and rely on the clinical evidence to determine the most appropriate care, the result is a win for the patient, the nephrologist, and ultimately, the entire health care system. ■

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Dr. Gupta is the chief medical officer of Monogram Health, and is a practicing internist and nephrologist in the greater New Orleans area. His practice focuses on the long-term management of chronic kidney disease and end-stage renal disease. He has a special interest in population health and has served as the state lead for hypertension and chronic kidney disease in Louisiana.

Conference Coverage

Fort Worth, Texas | May 22-25, 2022

ANNA 2022 NATIONAL SYMPOSIUM

The American Nephrology Nurses Association (ANNA) celebrated more than 50 years of education, advocacy, networking, and science for nephrology nurses at its 2022 National Symposium. ANNA's membership includes more than 8500 members, representing health care professionals working in areas that include conservative management, hemodialysis, peritoneal dialysis, continuous renal replacement therapy, transplantation, industry, and government and regulatory agencies.

The symposium provided an opportunity to learn, collaborate, and network with fellow nephrology professionals from across the country and around the world. Expert speakers and colleague nurses presented innovations and knowledge in all areas of quality patient care in the nephrology setting. This is part 2 of our coverage of selected posters and presentations.

Managing Hyperphosphatemia in Patients on Dialysis

Patients with chronic kidney disease on dialysis commonly develop hyperphosphatemia, a condition associated with poor outcomes. **Emily Belcher, BS,** and colleagues conducted a survey designed to aid understanding of current approaches to the management of hyperphosphatemia in patients on dialysis to identify needs for continuing education across the patient care team.

Results were reported in a presentation at the ANNA 2022 National Symposium. The presentation was titled *Current Practice and Educational Needs of Clinicians Who Manage Hyperphosphatemia in Patients With Chronic Kidney Disease (CKD)*.

The survey included two case scenarios to assess approaches to the management of hyperphosphatemia. Survey responses were collected in January 2021 from US nephrologists (n=125), nephrology nurses (n=52), and dietitians (n=50).

Most of the respondents (72%) recommended restriction of dietary phosphate and use of phosphate binders as initial treatment for hyperphosphatemia. Only 19% recommended phosphate restriction alone and only 5% recommended pharmacotherapy alone. Nephrologists and nurses recommended a maximum average daily dietary phosphate intake of 960 mg; dietitians recommended 1040 mg. The respondents were moderately likely to recommend dialysis adjustments for patents with refractory hyperphosphatemia; nurses were more likely to do so than dietitians and nephrologists.

When asked about preference for phosphate binders, 55% of nephrologists, 37% of nurses, and 32% of dietitians preferred sevelamer; the rest were divided between calcium-based and iron-based phosphate binders. Barriers to use of phosphate binders cited by the respondents included side effects, tablet burden, and affordability.

Most to the respondents reported they would select a therapy with a new mechanism of action (MOA) as initial or combination therapy for patients with hyperphosphatemia. Familiarity with the MOAs of new and emerging therapies among the respondents was low to moderate.

In summary, the authors said, "Health care providers perceive significant barriers to optimally managing hyperphosphatemia in patients on dialysis. There is no consensus for phosphate binder preferences, and most health care providers perceive a need for therapies with new MOAs. All health care providers may benefit from continuing education focused on optimal hyperphosphatemia management, approaches to dietary restriction and phosphate binders, and emerging therapies."

Source: Belcher E, Cerenzia W, Stacy S, Rosenbaum DP, Spiegel DM. Current practice and educational needs of clinicians who manage hyperphosphatemia in patients with chronic kidney disease (CKD). Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

Screening for Latent TB in Patients on Hemodialysis

As the global burden of chronic kidney disease (CKD) increases in the coming decades, patients with CKD will be at risk of developing tuberculosis disease (TB). Worldwide, 1.5 million people died of TB in 2020, and TB is the second most common infectious killer after COVID-19.

At the ANNA 2022 National Symposium, **Carmen J. Sierra, DNP, RN, CCTN,** a PhD nursing student at the University of Miami School of Nursing and Allied Health Studies, Coral Gables, Florida, offered a review of the risk of latent tuberculosis infection (LTBI) among patients on dialysis in a presentation titled *Dialysis: A Key population for LTBI Screening and Treatment*.

Individuals with compromised immune systems, including patients with CKD requiring dialysis, who have the subclinical condition LTBI have six to 25 times the risk of TB reactivation. Unlike TB disease or active TB, LTBI is not contagious and is asymptomatic.

Results of some studies suggest a prevalence of LTBI of 6.4% to 40% in dialysis patients. In that patient population, TB is mainly extrapulmonary, difficult to diagnose in a timely manner, and is associated with high morbidity and mortality. In countries where TB is endemic, the risk of exposure to TB is high, and in California, Texas, Florida, and New York, TB is more prevalent than in the remainder of the United States. In addition, most reported cases of TB in the United States are among foreign-born individuals.

Between 2000 and 2020, an estimated 66 million lives were saved due to screening and treatment for TB. As part of a strategy to eliminate TB in the United States, LTBI screening that focuses on identifying at-risk patients is recommended for treatment planning and intervention.

Screening and prioritizing patient care planning to prevent TB disease and contamination of others relies heavily on nursing staff. Nurses are able to develop individual knowledge base practice to align with protocols for coordination and integration of care in a multi-disciplinary setting for patients receiving dialysis who are at risk for TB.

"Within their scope of practice, nurses can focus on each patient to improve patient outcomes by implementing culturally sensitive, effective patient-centered interventions in [dialysis] populations," the author said.

Source: Sierra CJ. Dialysis: a key population for LTBI screening and treatment. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

Health Care Disparities Among BIPoC Communities

Chronic kidney disease (CKD) is a continuing significant health problem. Among the Black, indigenous, and people of color (BIPoC) population, patients experience health disparities in access, burden, and care, leading to adverse health outcomes. Rates of diabetes and hypertension, the two leading causes of end-stage renal disease (ESRD), are high among BIPoC; CKD and ESRD are among the most notable examples of disparities in health care.

At the ANNA 2022 National Symposium, **Jami S. Brown, DHEd, MSN, RN, CNN,** University of Tennessee Health Science Center, Memphis, provided an overview of known causes of disparities in health care among the BIPoC population, in a presentation titled *Health Disparities: Preventing Chronic Kidney Disease and Its Progression Among BIPoC Communities.*

Disparities are associated with social determinants of health (SDOH), including access to health care, quality of health care, neighborhood and environment, economic stability, social and community context, and education access and quality. Lack of access to care, food, safe drinking water, as well as community safety concerns, and poor education and employment opportunities are all related to poor health outcomes.

Results of various studies have demonstrated that individuals with an increased number of negative SDOH are at higher risk for progression to ESRD, and face inadequate dialysis treatment, reduced access to kidney transplantation, and poorer health outcomes. Alleviation of health inequities among BIPoC calls for implementation of strategies designed to reduce and eliminate health care disparities.

"Nephrology nurses must increase their awareness and education of health disparities to address the many challenges of kidney disease to achieve health equity," the author said. "Understanding the basics of SDOH, reducing health disparities, advancing health equities, and improving health outcomes can help to prevent CKD and its progression among BIPoC communities."

Source: Brown JS. Health disparities: preventing chronic kidney disease and its progression among BIPoC communities. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

Results of Initiatives to Reduce CAUTIs

The fourth most common type of hospital acquired infection is catheter-associated urinary tract infection (CAUTI), the cause of 93,000 urinary tract infections in the acute hospital care setting (CDC, 2011). CAUTI is one of the most common and expensive health care-associated infections reported by the National Health Safety Network.

At the ANNA 2022 National Symposium, **Rebecca McKee-Waddle, MSN, FNP-BC,** and **Angela Raney, MSN, APRN,** Emory University Hospital Midtown, Atlanta, Georgia, reviewed an initiative designed to avoid CAUTIs in a presentation titled *Reducing Hospital's Indwelling Urinary Catheter Utilization, "1 CAUTI-ous Step" at a Time*

Prior to implementation of the initiative, the role of the bedside nurse was limited to general communication with the provider. CAUTI-specific nurse champion responsibilities were not identified or empowered, and there was little interaction between nurses and the role of infection prevention and no coordinated process to review CAUTIs.

Several initiatives were implemented to reduce CAUTIs, and the rate of indwelling urinary catheter (IUC) utilization, including the Nurse-Driven Urinary Catheter Removal protocol, development of the CAUTI nurse champion role, bi-weekly CAUTI leadership rounds, and formal interdisciplinary CAUTI apparent cause analysis review with staff and leadership.

Unit leadership, (including CAUTI champion), medical staff, and executive team members were involved in the formal review process and strategic education initiatives. All efforts were data-based and utilized clinical informatics reports to track improvements and identify areas of opportunities.

In 2091, the rolling 3-month standardized infection ratio (SIR) was >1 and not consistent throughout the year. In 2020, during the pandemic, there was an increase in the overall SIR during peak months of COVID-19. Despite an increase in the overall SIR, the center maintained a rolling 3-month SIR of <1. The number of CAUTIs were reduced by 20% in women and 8% in men.

"The process barriers identified by nursing CAUTI champions allowed the CAUTI team to identify defects and areas of opportunities that contributed to the decrease in the number of IUCs, and the number of CAUTIs identified. This journey led to a more multidisciplinary approach to reducing CAUTIs and greater engagement/collaboration between the nurse at the bedside with infection prevention, physicians, and executive leadership," the authors said.

Source: McKee-Waddle R, Raney A. Reducing a hospital's indwelling urinary catheter utilization, "1 CAUTI-ous step" at a time. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

The CCP was created to serve undocumented Kansas residents with ESRD with no access to dialysis care. Patients accepted into the CCP receive dialysis two or three times per week at an inpatient dialysis department...The CCP was implemented in 2019 and currently supports 30 patients.

Providing Care for Undocumented Patients With ESRD

The Compassionate Care Program (CCP) was developed by the University of Kansas Health System to address the dialysis needs of undocumented patients with end-stage renal disease (ESRD). The overall goal of the program is to improve access to care as well as quality of life for patients in that population, while decreasing morbidity and mortality.

Kim Arthur, MSN, APRN, ACNS-BC, CMSRN, and **Melinda Loy, MSN, RN, CCRN-CMC,** University of Kansas Health System, Kansas City, Kansas, provided an overview of the CCP and its impact during a presentation at the ANNA 2022 National Symposium. The presentation was titled *Dialysis and the Undocumented: Overcoming Barriers to Care.*

An estimated 8500 undocumented immigrants in the United States have kidney failure. Due to their undocumented status, those patients are ineligible for government supported medical benefits, including outpatient dialysis sessions three times per week. Patients in this population commonly utilize emergency department (ED) services to address their care needs, including emergency dialysis.

The CCP was created to serve undocumented Kansas residents with ESRD with no access to dialysis care. Patients accepted into the CCP receive dialysis two to three times per week at an inpatient dialysis department. Patients in the ED are assessed using a protocol developed to identify patients in need of dialysis treatment. Following dialysis treatment, patients are transferred back to the ED for medical clearance and determination of next steps. Medically stable patients are transferred to an outpatient facility, with specific days and times to receive dialysis funded by the CCP.

The CCP was implemented in 2019 and currently supports 30 patients. Of those, 21 patients receive care in an outpatient dialysis facility. Visits to the ED among CCP patients have been reduced by 94%, hospital admissions have been reduced by 52%, and other outpatient services have been reduced by 71%. In 2 years, the organization has seen an overall cost reduction of 47%. Related positive outcomes of the CCP include 57% of patients report being currently employed, 76% have primary care services, 19% had obtained health insurance, and of those insured, two are on the kidney transplant waiting list.

In summary, the authors said, "The CCP addresses core health care inadequacies for undocumented patients with ESRD. This program supports an improved quality of life for patients while decreasing emergency services utilization and risk of caregiver distress."

Source: Arthur K, Loy M. Dialysis and the undocumented: overturning barriers to care. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

Conference Coverage

Boston, Massachusetts | June 4-8, 2022

AMERICAN TRANSPLANT CONGRESS

The American Transplant Congress is the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation. The Congress provides a forum for the exchange of new scientific and clinical information related to solid organ and tissue transplantation. Presentations and posters provide information on advances in research and care to transplant physicians, scientists, nurses, organ procurement professionals, pharmacists, and other transplant professionals.

The 2022 American Transplant Congress was held June 4–8 in Boston, providing a showcase for the latest research and advances made by the transplant community in the past year. This is part 2 of our coverage of selected posters and presentations.

Early Outcomes in Four-Drug Immunosuppressive Regimen

There are associations between belatacept-based immunosuppression regimens in kidney transplant recipients and improved kidney function, better metabolic profile, less de novo donor-specific antibody (DSA) formation, and improved preformed DSA at the expense of a higher risk of acute rejection. The risk of rejection seems to be reduced with the transient addition of tacrolimus to de novo belatacept, mycophenolate, and steroids regimens, with no apparent increased risk of BK virus or cytomegalovirus (CMV) viremia.

S. Mouawad and colleagues in Virginia conducted a single-center, retrospective study to examine the safety and early outcomes (6-month follow-up) in adult kidney, pancreas, and kidney-pancreas transplant recipients who underwent conversion from standard immunosuppression to a four-drug regimen of belatacept, steroids, mycophenolate or azathioprine, and calcineurin inhibitors. Results were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Early Experience With 4-Drug Maintenance Immunosuppression in Kidney and Pancreas Transplant Recipients*.

The analysis included 18 transplant recipients (16 kidney, 1 pancreas, and 1 kidney-pancreas). Mean age was 42 years, 27.8% were female, 44.4% were Black, and 22.2% were CMV-high risk. Most donors (88.9%) were deceased, with a mean Kidney Donor Profile Index of 38. All patients were induced with anti-thymocyte globulin.

The most common indication for the four-drug regimen was tacrolimus intolerance (4.44%). The median time from transplant to initiation of the four-drug regimen was 201 days. Mean estimated glomerular filtration rate was 46.2 mL/min/1.73 m^2 prior to initiation of the four-drug regimen and 55.4 mL/min/1.73 m^2 6 months following initiation of the regimen.

At 1 month following initiation, tacrolimus level was 6.5 ng/dL; at 6 months, it was 4.2 ng/dL. There were no acute rejections and all allografts were functioning at 6 months. The incidence of CMV viremia and BK viremia were both 11%. There were no reported cases of post-transplant lymphoproliferative disorder or Epstein-Barr virus.

In conclusion, the researchers said, "Our study illustrates the early 6-month outcomes and safety of a belatacept based four-drug maintenance immunosuppressive regimen. There was evidence of eGFR improvement at 6 months and limited incidence of viral infections. Longer follow-up and prospective randomized trials are needed to confirm these results."

Source: Mouawad S, Shoemaker C, Geyston J, Nishio Lucar A. Early experience with 4-drug maintenance immunosuppression in kidney and pancreas transplant recipients. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1707), Boston, Massachusetts, June 7, 2022.

COVID-19 Knowledge and Practices Among Transplant Recipients

L. Wang and colleagues at Methodist Dallas Medical Center, Dallas, Texas, conducted a study designed to assess the knowledge, attitude, and practices (KAP) of patients who underwent kidney and/or liver solid organ transplants during the COVID-19 pandemic.

Results of the single-center cross-sectional study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Knowledge, Attitude, and Practices Regarding COVID-19 Among Solid Organ Transplant Patients at a Transplant Center in the United States: A Cross-Sectional Study*.

The study cohort included patients who underwent a liver and/or kidney transplantation at the Methodist Dallas Medical Center between June 1, 2020, and June 30, 2021. The researchers designed a 26-question KAP questionnaire regarding COVID-19. The questionnaire was sent to 1053 solid organ transplant recipients. A score of 70% or higher was considered sufficient for each corresponding category. Chi-square test or Fisher's exact test were used to determine statistical significance among parameters.

Of the 1053 patients who received the survey, 22.6 % (n=238) responded to the questionnaire. Of the respondents, 42% were female, 7.1% were <40 years of age, 39.1% were 41 to 60 years of age, and 53.8% were >61 years of age.

Those who scored sufficiently in knowledge were more likely to score higher in the practices portion of the survey (odds ratio [OR], 4.25; 95% CI, 1.59-11.38; $P<.01$). Participants more than 61 years of age were less likely to score higher than those between 41 and 60 years of age (OR, 0.46; 95% CI, 0.23-0.93; $P=.0314$).

Patients who underwent combined liver and kidney transplant were more likely to score higher than patients who underwent liver only transplants (OR, 4.84; 95% CI, 1.01-23.24; $P<.05$). Patients on triple immunosuppression were more likely to adhere to sufficient COVID-19 practices than those who were not on triple immunosuppression (OR, 4.07; 95% CI, 1.99-8.33; $P<.001$).

In conclusion, the authors said, "In this study we observed correlations between practice scores and knowledge, age, type of solid organ transplant, and use of triple immunosuppression. This information will better help medical workers, public health officials, and health education programs target areas of improvement to improve overall safety of this vulnerable population against COVID-19."

Source: Wang L, Oduor H, Abualfoul M, Acharya P, Pagadala M. Knowledge, attitude, and practices regarding COVID-19 among solid organ transplant patients at a transplant center in the United States: a cross-sectional study. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1209), Boston, Massachusetts, June 5, 2022.

Predialysis Wait Time and Survival Benefit of DDKT

Candidates for deceased donor kidney transplant not yet on dialysis are allowed by the US Kidney Allocation System (KAS) to accrue waiting time points by listing at a transplant center with a low estimated glomerular filtration rate. According to **W. F. Parker** and colleagues at the University of Chicago, Chicago and Hinsdale, Illinois, the policy has led to racial and socioeconomic disparities in pre-emptive transplantation, adding to the existing inequity in access. Pre-emptive deceased donor kidney transplantation is associated with higher graft survival; there are few data available on the association between dialysis time and the survival benefit of deceased donor kidney transplant.

The researchers developed a novel mixed-effects model to estimate the survival benefit of deceased donor kidney transplantation. The model was described in a presentation at the 2022 American Transplant Congress. The presentation was titled *The Association of Pre-Transplant Dialysis Time and the Survival Benefit of Deceased Donor Kidney Transplantation*.

The model was based on data from all adult deceased donor kidney transplant candidates listed from 2005 to 2010. The single joint model of the pre- and post-transplantation periods improved on existing literature by accounting for center-level effects, time-dependent covariates, non-proportional hazards, and interactions between candidate and donor variables. The researchers estimated the 5-year survival benefit of deceased donor kidney transplantation for pre-emptive transplants and for each additional year of dialysis, adjusted for transplant center effect. Ischemic time, donor Kidney Donor Profile Index (KDPI), recipient age, and history of previous transplant or dialysis.

The study cohort included 132,909 transplant candidates; mean age at listing was 52 years and 60% were male. Of those, 48.6% (n=64,589) received a transplant by the end of follow-up on March 1, 2021. There was an association between deceased donor kidney transplant and an improvement in estimated 5-year survival from 50.8% to 82.4%, a 31.6% absolute benefit.

With each additional year of waiting on dialysis for patients with and without diabetes, the survival benefit of transplantation increased. For median age recipient (55 years) without diabetes, a pre-emptive transplant with a KDPI 43% kidney improved survival from 73% to 93%, an absolute 5-year survival benefit of 19%. For a similar recipient with 5 years of waiting on dialysis, survival improved from 31% to 78% with a deceased donor kidney transplant with a 43% KDPI kidney, an absolute 5-year survival benefit of 47%.

In conclusion, the authors said, "Candidates on dialysis have a higher risk of death without transplantation, leading to a greater survival benefit from deceased donor kidney transplant than candidates transplanted pre-emptively. By assigning waiting time points to patients not yet on dialysis, KAS ignores the Final Rule requirements to rank-order candidates by medical urgency and exacerbates disparities in kidney transplantation. To improve efficiency and equity, KAS should be revised to eliminate pre-dialysis waiting time points."

Source: Parker WF, Becker Y, Gibbons R. The association of pre-transplant dialysis time and the survival benefit of deceased donor kidney transplantation. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 310), Boston, Massachusetts, June 6, 2022.

Gender Disparities in Early Transplant Access Steps

Men are more likely than women to receive a kidney transplant or to be added to the transplant waitlist. It is unclear whether there are similar gender disparities in earlier transplant steps, such as referral for transplant. **L. Smothers** and colleagues conducted a study designed to (1) quantify gender disparities in transplant referral and (2) examine whether gender disparities in transplant referral are modified by age, race, or obesity in a Southeastern US population.

Results of the study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Gender Disparities in Kidney Transplantation Referral Vary by Age and Race in the Southeast US*.

The study cohort included 39,923 adults 18 to 80 years of age who initiated dialysis in Georgia, North Carolina, or South Carolina from 2012 to 2106. Data for the US Renal Data System were linked to the Early Transplant Access Registry, with follow-up through December 2017. The researchers assessed the association between gender and referral within 12 months, including interaction terms for age, race/ethnicity, and obesity, using a mixed-effects Cox proportional hazards model adjusted for several patient characteristics.

In the total cohort, 29.1% of women and 33.8% of men were referred with 12 months of dialysis initiation. In fully adjusted models, women (vs men) were 12% less likely to be referred (hazard ratio [HR], 0.88; 95% CI, 0.84-0.91). HRs for women (vs men) 45 to 64 years of age and 65 to 80 years of age were 0.90 (95% CI, 0.85-0.95) and 0.76 (95% CI, 0.70-0.83), respectively.

HRs for women (vs men) of non-Hispanic White and non-Hispanic Black race were 0.79 (95% CI, 0.73-0.84) and 0.93 (95% CI, 0.86-0.98), respectively. For other race (Hispanic, other) and age (18-44) subgroups, and all obesity subgroups, there were no gender differences in referral rates observed.

In summary, the authors said, "In the Southeast, women are less likely to be referred for a transplant and this disparity is specific to older and non-Hispanic Black and White women. These findings have important implications for known gender disparities in upstream (i.e., waitlisting) transplant steps and in the design of interventions to reduce gender disparities in transplant."

Source: Smothers L, Patzer, Pastan S, DuBay D, Harding J. Gender disparities in kidney transplantation referral vary by age and race in the Southeast US. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1729), Boston, Massachusetts, June 7, 2022.

HLA-DQ Mismatches Produce Higher Rates of UA Racial/Ethnic Minorities

Recent data suggest that donor-recipient mismatches at the human leukocyte antigen (HLA)-DQ locus are the most immunogenic and pathogenic, as evidenced by generation of DQ donor-specific antibodies (DSA). Access to HLA-matched kidneys is limited among racial/ethnic minorities in the United States, and patients in that population experience greater sensitization following graft loss.

According to **D. Isaacson** and colleagues, the contribution of DQ DSA in racial/ethnic minority patients is not well characterized. DSA is not included in data in the Scientific Registry of Transplant Recipients (SRTR), hindering direct study of DQ DSA and transplant outcomes. To compensate for this limitation, the researchers applied a novel approach that focused on patients in the SRTR who lost their initial graft and were relisted with new unacceptable antigens (UA) corresponding to donor HLA type.

The appearance of UAS following graft loss suggests that the mismatches contributed to the graft failure. Application of the metric was used to assess the effect of HLA-DQ on graft failure in racial/ethnic groups. Results of the assessment were reported during a presentation at the 2022 American Transplant Congress in a presentation titled *HLA-DQ Mismatches Are More Likely To Be Listed as Unacceptable Antigens After Renal Graft Failure in African American Recipients as Compared to Other Racial/Ethnic Groups*.

The study cohort included adult patients in the SRTR who received a primary kidney transplant from January 1, 2010, to March 1, 2020, and were relisted following graft failure and who had donor-recipient typing and UA data available at the HLA-A, B, C, DR, and DQ loci. Multiple linear regression was applied to evaluate (1) the probability of donor HLA mismatches being recorded as new UA after relisting; (2) the likelihood that HLA-DQ was designated as an UA as compared with other HAL loci; and (3) the comparative probabilities of developing a donor-specific DQ UA in African American, White, and Hispanic recipients.

There were 3189 deceased donor and 1356 living donor recipients included in the study cohort. Overall, DQ mismatches resulted in a higher probability of donor-specific UA as compared with all other HLA loci ($P<.05$). Following graft failure in deceased donor recipients, African American recipients were more likely to be relisted with new DQ UA compared with White and Hispanic recipients ($P<.05$). Compared with White recipients, African American and Hispanic recipients were more likely to be relisted with a new DQ UA.

In conclusion, the researchers said, "HLA-DQ mismatches produce proportionally higher rates of UA after graft failure compared to other HAL loci. This effect is most pronounced in African American recipients. Future changes to kidney allocation priority should consider the effects of HLA-DQ matching on equity."

Source: Isaacson D, Gmeiner MW, Kosmoliaptsis V, Schold JD, Tambur AR. HLA-DQ mismatches are more likely to be listed as unacceptable antigens after renal graft failure in African American recipients as compared to other racial/ethnic groups. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 511), Boston, Massachusetts, June 7, 2022.

Gender Disparities in Access to and Outcomes After SLKT

Since the implementation of the Model for End-Stage Liver Disease (MELD)-liver allocation in 2002, the frequency of simultaneous liver-kidney transplantation (SLKT) has been increasing. There are few data available on gender disparities in access to SLK transplant and post-transplantation outcomes.

G. Peschard and colleagues conducted a study to determine whether gender disparities existed in access to SLK transplant and post-SLK transplant survival in the MELD era. Results were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Simultaneous Liver and Kidney Transplantation and Gender Disparities in Transplant Access and Outcomes*.

The retrospective study cohort included patients with renal dysfunction who were wait-listed for liver transplant between 2002 and 2017. The likelihood of receiving SLKT was assessed using multilevel time-to-competing events regression, adjusting for center effect. Post-transplant mortality outcomes were analyzed using inverse probability of treatment weighted survival analyses. Sensitivity analysis was performed using two alternative definitions of renal dysfunction for liver transplant candidates: (1) received dialysis or creatinine ≥2.0 mg/dL at listing for liver transplant and (2) received dialysis or estimated glomerular filtration rate <35 mL/min/1.73 m^2 at listing for liver transplant.

Among candidates not listed for SLKT at the time of listing, women had a ≥50% lower likelihood of receiving SLKT compared with men. Women continued to have reduced access despite being listed for SLKT. There was no statistically significant difference in post-transplant survival by sex for SLKT or liver transplant alone.

In summary, the authors said, "Prior to the implementation of the SLKT allocation policy, gender disparities were found in access to SLKT but not in post-transplant survival. A tighter gender difference in access to SLKT was found amongst patients listed for SLKT compared to those not listed simultaneously."

Source: Peschard G, Wang M, Al-Hosni Y, Lentine K, Chang S, Alhamad T. Simultaneous liver and kidney transplantation and gender disparities in transplant access and outcomes. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1199), Boston, Massachusetts, June 5, 2022.

Decline in US Kidney Transplants Over the COVID-19 Pandemic

Since the onset of the COVID-19 pandemic, the number of kidney transplants has decreased. However, according to **E. Tantisattamo** and colleagues, the magnitude of the effect of the COVID-19 pandemic over the past 2 years on the number of kidney transplants in the United States is unclear.

The researchers conducted an interrupted time series analysis to test the magnitude of the decline in kidney transplants since the pandemic's onset. Results were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Impact of the Second Year COVID-19 Pandemic on the US Kidney Transplantation: Interrupted Time Series Analysis.*

Linear regression was used to examine the association of COVID-19 cases and deaths in 2020 and 2021 with the change in the number of kidney transplantations. The magnitude of the decline in kidney transplantation since the beginning of the pandemic was assessed using Poisson regression and interrupted time s eries defining the beginning of the pandemic in late 2019 as the time reflecting event change.

From 1988 until 2019, the number of kidney transplants had generally trended up. The number trended down beginning in 2019 (23,401; 22,817; and 20,736 in 2019, 2020, and 2021, respectively). The number of COVID-19 cases increased from 2019 to 2020 (19,759,635 and 27,284,847, respectively), and the mean COVID-19 death rate increased from 227 deaths per 10,000 cases to 340 deaths per 10,000 cases.

Compared with 2020, there was a significant association between every 10,000 increase in COVID-19 cases and a decrease of 18 kidney transplants (β_{cases}, 0.00018, 95% CI, 0.00006 to 0.00030; $P<.005$). There was no significant association between changes in COVID-19 deaths and kidney transplants between 2020 and 2021. The number of kidney transplants after the pandemic is 1.43 % lower than before the pandemic.

In conclusion, the authors said, "Although [the] ongoing COVID-19 pandemic over the past 2 years led to increasing number of COVID-19 cases and deaths, only the number of COVID-19 cases, but not deaths, has significantly affected the number of kidney transplants in the United States."

Source: Tantisattamo E, Polpichai N, Mutirangura P, Tanariyakul M. Impact of the second year COVID-19 pandemic on the US kidney transplantation: interrupted time series analysis. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1752), Boston, Massachusetts, June 7, 2022.

SGLT-2i Therapy in Kidney Transplant Recipients With Diabetes

In non-transplant patients with chronic kidney disease (CKD) and diabetes, the use of sodium glucose linked transporter inhibitors (SGLT-2i) has been shown to reduce cardiovascular mortality, delay CKD progression, and decrease proteinuria. The early safety outcomes of SGLT-2i has been validated in published data. However, there are few data available on the long-term benefits among kidney transplant recipients.

In an oral presentation at the 2022 American Transplant Congress, **C. Song** and colleagues reported on outcomes of a 12-month experience with SGLT-2i at a center in Virginia. The presentation was titled *Intermediate Term Outcomes of SGLT2 Inhibitors Amongst Diabetic Kidney Transplant Recipients*.

The single-center, retrospective study included adult kidney transplant recipients at the center who met SGLT-2i initiation criteria. Eligible patients had type 2 diabetes, no acute kidney injury ≤30 days before initiation of SGLT-2i therapy, and estimated glomerular filtration rate (eGFR) >25 mL/min/1.73 m^2.

The primary outcomes of interest were changes in urine protein creatinine ratio (UPCR), weight, hemoglobin A1c (HbA1c), and eGFR. Secondary outcomes were rates of treated urinary tract infections (UTI), diabetic ketoacidosis, amputations, and episodes of dehydration. Insurance preference decided the choice of the specific SGLT-2i agent.

A total of 123 patients met enrollment criteria. Of those, 91% (n=112) received empagliflozin, 2% (n=2) received canagliflozin, and 7% (n=9) received dapagliflozin. Median time from transplant to initiation of SGLT-2i therapy was 250 days. Mean increase in eGFR from initiation of SGLT-2i therapy to 6 months was 2.95 mL/min/1.73 m^2 (95% CI, 0.19-5.72; $P=.04$); at 12 months, the mean increase was 4.09 mL/min/1.73 m^2 (95% CI, 0.60-7.57; $P=.02$).

There were significant improvements in UPCR (mean decrease of -0.53 mg/mg (95% CI, -0.02 to -1.04; $P=.021$) and in weight (mean decrease of -1.35 kg (95% CI, -0.75 to -1.96; $P=.001$) over 12 months. The mean change in HbA1c was 0.05, which did not reach statistical significance.

One patient had euglycemic DKA, 15% (n=18) experienced UTIs, 6% (n=7) had mild episodes of dehydration, and no patient required amputation.

In conclusion, the authors said, "In this follow-up report, we found that patients treated with SGLT-2i had statistically significant improvement in eGFR at 6 and 12 months, along with reductions in UPCR. These 12-month trends point towards both improvements in renal function and metabolic profiles. The risk of adverse events with SGLT2 inhibitor initiation post-kidney transplant was comparable with previously published data."

Source: Song C, Brown A, Winstead R, et al. Intermediate term outcomes of SGLT2 inhibitors amongst diabetic kidney transplant recipients. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 30), Boston, Massachusetts, June 5, 2022.

Patient-Level Factors and Transplant Evaluation Process

Depending on several factors, including patient health status and level of engagement, the duration of the kidney transplant evaluation process can range from several months to years. **T. Menser** and colleagues at Houston Methodist, Houston, Texas, conducted a study to assess the ways patient success in completing the pre-transplant workup process can be influenced by demographic factors and socioeconomic status (SES). Patient success was measured as total time from initiation of the evaluation to presentation to the candidate selection committee (CSC).

Results of the study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *A More Equitable Transplant Evaluation: What Patient-Level Factors Impact Time to Kidney Transplant Evaluation Completion?*

The study included data for all kidney evaluation patients referred to the transplant center from June 1, 2016, to August 31, 2021. Referrals after May 2021 were excluded to allow for a minimum of 3-month post-referral follow-up.

The depended variable in the analysis was patient completion of the pre-transplant evaluation, which was calculated based on days between the evaluation and CSC data. Following adjustment for demographic, SES, and clinical factors, the number of days from pre-transplant evaluation to medical review board review were identified with regression analysis. The Area Deprivation Index (ADI), a proxy measure based on census cell block, was used to measure SES by quartile. Scores are between 1 and 100; a score of one equates to the lowest level of disadvantage and high SES.

During the study period, 60% (n=2267/3757) of patients who initiated pre-transplant evaluation process completed the workup process and were presented to the CSC. Mean time to CSC was 200 days (95% CI, 194-207). After controlling for all other covariates, there was an association between pre-emptive status and the largest decrease of wait time (72 days; $P<.001$).

There was also an association between Black race and the largest increase of wait time (44 days; $P<.001$). In addition, compared with White candidates, all non-White races/ethnicities were significantly associated with increased time to CSC evaluation.

There was no clear association between ADI quartile and evaluation time, although the need for more time was observed in patients in the third quartile of the ADI. The difference did not reach statistical significance.

In conclusion, the authors said, "The total time from initiation of pre-transplant evaluation to its completion and subsequent review by the candidate selection committee presentation ranged widely. Pre-emptive candidates experienced the shortest time to CSC. All non-White candidates (eg, Black, Hispanic, and Asian) demonstrated longer total workup times. Further study to means to stratify patients based on SES is timely in order to target social determinants of health and as a means to increase equity in evaluation and waitlisting times."

Source: Menser T, Hobeika MJ, Hsu E, et al. A more equitable transplant evaluation: what patient-level factors impact time to kidney transplant evaluation completion? Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1732), Boston, Massachusetts, June 7. 2022.

Short-term Outcomes Before and After SLK Allocation Change

On August 10, 2017, the United Network for Organ Sharing and the Organ Procurement and Transplantation Network implemented new allocation criteria for simultaneous liver-kidney (SLK) transplants. **A. P. Bregman** and colleagues recently conducted a study to assess the association between the new allocation criteria and short-term kidney graft outcomes.

Results were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Kidney Allograft Loss After Simultaneous Liver Kidney (SLK) Transplant Before and After the New SLK Allocation Criteria Implementation.*

The researchers utilized the Scientific Registry of Transplant Recipients standard analysis to identify all adult primary SLK recipients who received a SLK transplant between January 1, 2014, and August 9, 2017, (pre SLK allocation change) and those both listed and transplanted between August 10, 2017, and September 1, 2020, (post SLK allocation change). The study compared baseline characteristics of SLK recipients pre (n=2252) and post (n=1754) the allocation change; short-term outcomes were also compared.

Rates of kidney allograft failure or death within 90 days of transplant were compared using a generated Kaplan-Meier curve. The association between the new allocation criteria and all-cause loss of kidney graft within 90 days was examined using Cox proportional hazard models, adjusted for recipient age, sex, body mass index, diabetes status, ethnicity, dialysis status, admission to the intensive care unit (ICU) at the time of transplant, Model for End-Stage Liver Disease (MELD), portal vein thrombosis, indication for liver transplant, hepatitis C virus infection, donor age, donor sex, kidney cold ischemia time (CIT), donation after cardiac death, donor height, and organ importation status.

After the allocation change, nonalcoholic steatohepatitis as an indication for transplantation increased from 22.4% to 31.2% and viral hepatitis decreased from 27.2% to 14.3%. Use of imported organs increased from 34.1% to 43.4%. There were no differences between the pre and post allocation eras in short-term outcomes.

In the Kaplan-Meier analysis, there was no difference in kidney allograft survival or death within 90 days of transplant following the allocation change. There was no association between the change in allocation and kidney graft loss or death within 90 days in the multivariable Cox proportional hazard analysis. Deleterious predictors of kidney graft loss or death within 90 days of transplant were being in the ICU at time of transplant, older donor age, and longer kidney CIT. Increased donor height was a favorable predictor of kidney graft loss or death by 90 days.

In conclusion, the researchers said, "The new SLK allocation scheme did not seem to influence kidney allograft loss or death by 90 days. Identifying deleterious predictors of kidney graft loss or death by 90 days post ALK may improve the appropriateness of kidney utilization in SLK."

Source: Bregman AP, Jackson S, Lim N, Lake J, Riad S. Kidney allograft loss after simultaneous liver kidney (SLK) transplant before and after the new SLK allocation criteria implementation. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1083), Boston, Massachusetts, June 5. 2022.

Survival With SPK Transplant Versus PALK Transplant

There are conflicting data on the survival benefit of simultaneous pancreas-kidney (SPK) transplant compared with pancreas following living-donor kidney (PALK) transplant. There are wide variations by center in wait times for SPK and in donor risk indices.

Since the introduction of the 2014 pancreas allocation system (PAS), wait times have decreased. **G. R. Lyden** and colleagues conducted an analysis to describe how differences in wait time and organ quality affect survival for patients waiting for SPK compared with patients who opt for PALK. Results were reported during a poster session at the 2022 American Transplant Congress in a poster title *Survival Comparison of Simultaneous Pancreas-Kidney Transplant With Pancreas After Living-Donor Kidney Transplant by Wait time and Organ Quality.*

The researchers utilized kidney-pancreas listing data from the Scientific Registry of Transplant Recipients 2001-2019 (n=10,335; 18 to 60 years of age). Post-listing patient survival was estimated using inverse probability weighted Kaplan-Meier models for two strategies: (1) wait for SPK and (2) get living-donor kidney transplant within 6 or 12 months, then list for pancreas alone (PALK-6; PALK-12, respectively). Survival was estimated for varying rates of transplant and organ quality distributions in different centers and eras (2010/pre-PAS vs 2017/post-PAS).

The end point of interest was death or removal from the wait list due to deteriorated conditions. Inverse probability weights were adjusted for standard confounders.

Averaged across centers, the 5-year survival rate for pre-PAS SPK was 80% (95% CI, 79% to 81%), which was significantly lower than 5-year survival for PALK-6 (91%; 95% CI, 88% to 94%) or PALK-12 (88%; 95% CI, 95% to 92%) ($P<.001$). In the post-PAS era, when median wait time decreased from 13 months to 7 months, the 5-year survival for SPK was 86% (95% CI, 85% to 87%), which was lower than for PALK-6 (91%; 95% CI, 88% to 95%; $P=.01$), but comparable to PALK-12 (89%; 95% CI, 86% to 92%; $P=.16$).

In the post-PAS era, there was variation in survival by center, including several centers where waiting for SPK was estimated to outperform PALK, due primarily to shorter-than-average SPK wait times at those centers.

In summary, the authors said, "Survival differences between SPK and PALK strategies depend on the rate of SPK transplant. Under the new PAS, survival may be comparable for some patients whether they wait for SLK or pursue a living-donor transplant within the year, indicating some potential living donors could be spared the risk of donation."

Source: Lyden GR, Helgeson ES, Finger EB, Matas AJ, Snyder JJ, Vock DM. Survival comparison of simultaneous pancreas-kidney transplant with pancreas after living-donor kidney transplant by wait time and organ quality. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1147), Boston, Massachusetts, June 5, 2022.

Variations in Center-Level Acceptance of Suboptimal Kidneys

According to T. P. Chiang and colleagues, understanding center-level differences in the use of marginal deceased-donor kidney (suboptimal kidneys, SOK) could help centers increase their deceased-donor transplant rate and direct SOK offers to centers willing to utilize them.

The researchers conducted a study to examine differences in the use of SOK using data from the Scientific Registry of Transplant Recipients. Results of the study were reported during an oral presentation at the 2022 American Transplant Congress. The presentation was titled *Quantification of Center Aggressiveness in Accepting Suboptimal Kidney Donations From Deceased Donors in the US.*

The study included 5 646 748 offers of 8539 SOK donors from January 1, 2018, to December 31, 2019. Pediatric centers, centers with annual volume <1, or multiple match-runs were excluded.

SOK were defined as age >60 years, cold ischemia time (CIT) >24 hours, hepatitis C, serum creatinine >2.0 mg/dL, donated following cardiac death, Kidney Donor Profile Index >84, or infectious risk donors. The median odds ratio for each center, a measure of center-level variation, was calculated using multilevel logistic regression.

Among 28 676 deceased-donor kidney transplants, there were 18 471 SOK (64%). Among 197 centers, acceptance of SOK ranged from 0% to 44.7%; median was 10.6%. The SOK subtypes with the least center-level variance were those donated following cardiac death (acceptance range, 0-95%; median 10.2%) and infectious risk donors (acceptance range, 0-63.6%; median 16.0%). The SOK with the most center-level variance was CIT >24 hours (acceptance range, 0-55.1%; median 2.7%).

In summary, the authors said, "There was substantial center-level variation in acceptances of SOK offers for each of the SOK subtype categories. Informing centers of donor phenotypes for which that center's acceptance rate is lower than the national average may motivate centers to accept more marginal kidneys, improving access to deceased-donor kidney transplant for patients at those centers."

Source: Chiang TP, Eagleson M, Massie A, Krach M, Segev D, Garonzik Wang J. Quantification of center aggressiveness in accepting suboptimal kidney donations from deceased donors in the US. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 313), Boston, Massachusetts, June 6, 2022.

Print-only Content

Biomarkers After AKI as Predictors of Long-term Renal Outcomes

The risks of a number of adverse long-term health outcomes are often increased with the presence of acute kidney injury (AKI). Development or progression of chronic kidney disease (CKD) commonly occurs after AKI and is associated with an increased risk of cardiovascular events, kidney failure, and mortality. Previous studies have identified the lack of timely recognition and management of AKI as an important gap in care.

The AKI guidelines from the KDIGO (Kidney Disease: Improving Global Outcomes) recommend measurements of estimated glomerular filtration rate (eGFR) and albuminuria 3 months following an episode of AKI, along with subsequent annual follow-up assessments for all patients considered at risk for CKD. Guidelines from the National Institute for Health and Care Excellence in the UK call for all patients who have had AKI to be followed up for 2 to 3 years.

Due to the high incidence of AKI, long-term follow-up of all patients with AKI would create a substantial burden on health care systems and resources. Identification of biomarkers measured in the recovery period of AKI with the aim of assessing the risk of long-term kidney damage would potentially allow stratification of follow-up.

Michelle Wilson, MSc, and colleagues conducted a prospective cohort study to identify biomarkers at 3 months after an episode of AKI to determine whether those biomarkers could discriminate between those with and without subsequent progression of kidney disease after 3 years. Results were reported in the *American Journal of Kidney Diseases* [2022;79(5):646-656].

The study included adults from a single clinical center who experienced AKI between May 2013 and May 2016 and who survived until 3 years following the hospitalization when AKI occurred. The cohort included patients with and without preexisting CKD. The primary outcome of interest was progression of kidney disease, defined as a ≥25% decrease in eGFR combined with worsening CKD stage, assessed 3 years after the AKI episode.

The predictor of interest was a panel of 11 plasma biomarkers measured at 3 months after hospitalization. The biomarkers included 10 renal-associated biomarkers, measured using multiplexed Biochip arrays with an Evidence Investigator analyzer according to the manufacturer's instructions (Randox Laboratories). CKD Biochip array I comprised five biomarkers (fatty acid-binding protein 1 [FABP1], soluble tumor necrosis factor receptor (sTNFR] 1, sTNFR2, macrophage inflammatory protein 1α [MIP-1α], and D-diner). CKD Biochip array II comprised four biomarkers (C3a desArg, cystatin C, neutrophil gelatinase-associated lipocalin [NGAL], and C-reactive protein [CRP]). A third Biochip comprised an individual assay for kidney injury molecule 1 (KIM-1). A commercially available enzyme-linked immunosorbent assay (R&D Systems) was used to measure an additional biomarker, galectin 3.

Of the 500 patients with samples collected for biomarker measurement, following exclusion of patients without outcome data (n=12) or who died without progression to kidney disease (n=47), the analysis cohort included 441 patients. Of those, 266 did not have progression of kidney disease within 3 years and 175 had disease progression within 3 years. The cohort was typical of a general hospitalized AKI population; 58.4% had AKI stage 1 with the remaining 41.6% having AKI stage 2 or 3.

The most common causes of AKI in the overall cohort were volume depletion (21%), mixed etiology (18.2%), postoperative status (16%), and sepsis (15%). Only 3.4% of participants had intrinsic glomerular/tubulointerstitial kidney disease. One point eight percent of participants received kidney replacement therapy for AKI, and 5.8% were admitted to the intensive care unit. Thirty percent of participants had diabetes, and 28.8% had preexisting CKD.

There was a near-complete set of measurements for all 11 biomarkers; 0% to 3% had missing values. Median time between sample collection and processing was 50 minutes, with 96.5% of samples processed within 6 hours. The highest pairwise correlation was observed between sTNFR1 and sTNFR2 (r=0.74), and sTNFR1 and sTNFR2 both correlated with cystatin C (r=0.62). sTNFR1 correlated with NGAL (r=0.64), sTNFR2 correlated with MIP-1a (r=0.63), and NGAL correlated with cystatin C (r=0.62). All other correlation coefficients were <0.60.

There were associations between several biomarkers and age and sex, and all were associated with comorbidity and baseline CKD stage; biomarker levels were generally higher in patients with comorbidity score >2 and in patients with lower baseline eGFR. There were independent associations between progression of kidney disease and sTNFR1, sTNFR2, cystatin C, NGAL, 3-month eGFR, and urinary albumin-creatinine ratio; the biomarkers were more important than severity or duration of AKI.

Higher biomarker concentrations were associated with greater odds of disease progression, most notably sTNFR1 (odds ratio [OR], 2.53; 95% CI, 1.89-3.47; P<.001); sTNFR2 (OR, 2.65; 95% CI, 1.98-3.64; P<.001), NGAL (OR, 2.06; 95% CI, 1.54-2.83; P<.001); and cystatin C (OR, 2.29; 95% CI, 1.82-2.92; P<.001). When biomarkers were sequentially included as predictor variables in multivariable models with progression of kidney disease as the outcome and other clinical and demographic variables as additional predictor variables, the only independent associations with kidney disease progression were sTNFR1 and sTNFR2.

A multivariable model containing sTNFR1, sTNFR2, cystatin C, and eGFR discriminated between those with and without progression of kidney disease (area under the curve, 0.79; 95% CI, 0.70-0.83).

Limitations to the study cited by the authors included using only an internal validation rather than an external validation cohort, the possibility that the single-center design limited the generalizability of the findings, the mixed population of patients with and without CKD, and using a surrogate outcome measure as the primary study outcome measure.

In conclusion, the researchers said, "We have shown how a combined plasma biomarker approach incorporating sTNFR1, sTNFR2, cystatin C, and eGFR demonstrated utility on assessing the long-term risk of kidney disease at 3 months after discharge from a hospitalization complicated by AKI. The high negative predictive value suggests potential clinical utility to identify patients with AKI who are at very low risk of incident or worsening CKD. Further study is required to determine the clinical utility of our approach through independent prospective validation." ■

TAKEAWAY POINTS

- Results of a prospective cohort study designed to identify biomarkers for the estimation of the risk of new or worsening chronic kidney disease following discharge from hospitalization complicated by acute kidney injury (AKI).
- The study included a panel of 11 biomarkers. Of the 11, the most promising predictor was a combination of soluble tumor necrosis factor receptors 1 and 2, cystatin C, and estimated glomerular filtration rate.
- The combination discriminated between patients with and without worsening CKD 3 years after hospital discharge.

Clinically Recommended Difelikefalin Dose for Uremic Pruritus

Patients with end-stage kidney disease undergoing dialysis frequently develop uremic pruritus. There are direct associations between pruritus and reduced quality of life (QoL), depression, poor sleep quality, and increased mortality. The most common treatments for pruritus are antihistamines, antiallergic agents, topical moisturizers, and corticosteroids. However, despite the use of these medications, moderate to severe pruritus persists in 40% of patients undergoing hemodialysis.

In Japan, nalfurafine, an oral k-opioid receptor (KOR), is approved for the treatment of moderate to severe pruritus. However, the oral formulation is problematic for many patients undergoing dialysis.

Difelikefalin is a selective KOR agonist with low membrane permeability and limited transfer to the central nervous system. It is expected to have a more favorable safety profile and improved tolerability compared with other KOR agonists. The intravenous formulation of difelikefalin allows direct administration at the end of the dialysis session.

Ichiei Narita, MD, PhD, and colleagues in Japan conducted a randomized, double-blind, placebo-controlled, four-arm phase 2 trial to identify the clinically recommended dose of difelikefalin based on efficiency, dose response, safety, and pharmacokinetics. Results were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2022.10339].

The trial was conducted from February 1, 2019, to October 22, 2019, at 94 sites in Japan. The study population included patients with moderate to severe pruritus receiving hemodialysis. The study intervention was difelikefalin (0.25, 0.5, and 1.0 µg/kg) or placebo administered intravenously three times a week at the end of each hemodialysis session for 8 weeks.

The primary end point was the change from baseline in the weekly mean Worst Itching Intensity Numerical Rating Scale (NRS) score at week 8. Secondary outcomes included measured changes in itch-related QoL score using the Skindex-16 and 5-D itch scale. Safety outcomes were assessed using adverse events, laboratory test results, vital signs, body weight, and 12-lead electrocardiogram.

A total of 311 Japanese patients provided informed consent. Of those, 247 (75% [n=186] male; mean age 64.5 years) were randomized and received at least one dose of the study drug: placebo (n=63), 0.25 µg/kg of difelikefalin (n=61), 0.5 µg/kg of difelikefalin (n=61), and 1.0 µg/kg of difelikefalin (n=62). Of those patients, 225 completed the study treatment: 59 in the placebo group; 59 in the 0.25 µg/kg of difelikefalin group; 53 in the 0.5 µg/kg of difelikefalin group; and 54 in the 1.0 µg/kg of difelikefalin group. In the full analysis set, baseline characteristics were similar across treatment groups. Treatment adherence in all groups was more than 98%.

The change from baseline in the weekly mean NRS score at week 8 was –2.86 in the placebo group, –2.97 in the 0.25 µg/kg of difelikefalin group; –3.65 in the 0.5 µg/kg of difelikefalin group; and –3.64 in the 1.0 µg/kg of difelikefalin group. Compared with the placebo group, there were significant differences for 0.5 µg/kg of difelikefalin (adjusted mean difference, –0.80; 95% CI, –1.55 to –0.04; P=.04) and for 1.0 µg/kg of difelikefalin (adjusted mean difference, –0.78; 95% CI, –1.54 to –0.03; P=.04). Sensitivity analyses revealed similar results.

Throughout the study, compared with placebo, there were significant reductions in weekly mean NRS score in the 0.5- and 1.0-µg/kg difelikefalin groups. At week 2, the difference in change from baseline in the weekly mean NRS score was –0.06 for the 0.25 µg/kg of difelikefalin group, –0.69 for the 0.5 µg/kg of difelikefalin group, and –0.95 for the 1.0 µg/kg of difelikefalin group. At week 8, the differences were –0.11 in the 0.25 µg/kg of difelikefalin group. –0.80 in the 0.5 µg/kg of difelikefalin group, and –0.78 in the 1.0 µg/kg of difelikefalin group and –0.78.

For the secondary end points, the Skindex-16 overall score and the 5-D itch scale total score indicated improvement with treatment with 0.5 and 1.0 µg/kg of difelikefalin (adjusted weekly mean Skindex-16 overall score at week 8, –27.79 (95% CI, –31.83 to –23.74) for 0.5 µg/kg of difelikefalin and –22.69 (95% CI, –26.71 to –18.68) for 1.0 µg/kg of difelikefalin. The adjusted weekly mean 5-D itch scale total score at week 8 was –6.5 (95% CI, –7.2 to –5.8) for 0.5 0.25 µg/kg of difelikefalin and –6.8 (95% CI, –7.5 to –6.2) for 1.0 µg/kg of difelikefalin.

Analysis of safety outcomes identified adverse events in 42 of 63 patients in the placebo group (67%), in 44 of 61 patients in the 0.25 µg/kg of difelikefalin group (72%), in 47 of 61 patients in the 0.5 µg/kg of difelikefalin group (77%), and in 53 of 62 patients in the 1.0 µg/kg of difelikefalin group (85%). The incidence of adverse events increased in a dose-dependent manner, and the incidence was significantly higher in the 1.0 µg/kg of difelikefalin group compared with the placebo group (85% vs 67%, respectively; *P*=.02).

Adverse events related to the central nervous system (CNS), including somnolence and dizziness, were more frequent in the 1.0 µg/kg of difelikefalin group; the incidence of CNS adverse events in the 0.5 µg/kg of difelikefalin group and in the 0.25 µg/kg of difelikefalin group was similar to that in the placebo group. Most adverse events were mild and occurred relatively early in treatment, and patients improved or received without discontinued or suspended use of the study drug.

There were no deaths reported in any group. Serious adverse events occurred in three patients in the 0.25 µg/kg of difelikefalin group (5%), in eight patients in the 0.5 µg/kg of difelikefalin group (13%), and in five patients in the 1.0 µg/kg of difelikefalin group (8%).

The authors cited some limitations to the study findings, including the relatively large placebo effect due to the subjective symptoms of itching being evaluated based solely on patient-reported outcomes, not including depression and anxiety in the analyses, not evaluating objective end points such as skin findings, and the small sample size.

In conclusion, the researchers said, "This phase 2 trial in Japanese patients with pruritus receiving hemodialysis demonstrated that, compared with placebo, 0.5 µg/kg of difelikefalin significantly improved moderate to severe pruritus and this dose can be considered to be the clinically recommended dose. Difelikefalin at a dose of 0.5 µg/kg is expected to be a new option for the treatment of moderate to severe pruritus in patients receiving hemodialysis." ■

Throughout the study, compared with placebo, there were significant reductions in weekly mean NRS score in the 0.5- and 1.0-µg/kg difelikefalin groups.

TAKEAWAY POINTS

- Researchers in Japan conducted a phase 2 trial in patients on hemodialysis with pruritus to determine the clinically recommended dose of difelikefalin based on efficacy, dose response, safety, and pharmacokinetics.
- At 8 weeks of treatment with difelikefalin (0.5 to 1.0 µg/kg), there was significant reduction in weekly mean Worst Itching Intensity Numerical Rating Scale from baseline.
- Difelikefalin at 0.5 µg/kg is expected to be a new option for the treatment of pruritus in patients receiving hemodialysis, with high adherence, safety, and tolerability.

Plasma KIM-1 Levels and Risk of CKD Progression

Kidney injury molecule 1 (KIM-1) is virtually undetectable in healthy kidneys. KIM-1, also known as hepatitis A virus receptor (HANCR-1; also known as TIM-1) is a type 1 transmembrane glycoprotein that is strongly upregulated by ischemic and toxic kidney injuries. In acute kidney injury (AKI) and chronic kidney disease (CKD), KIM-1 expression is upregulated in proximal tubules. There are few data available on the association between KIM-1 and risks of adverse clinical outcomes across a variety of kidney diseases.

Insa M. Schmidt, MD, MPH, and colleagues conducted a prospective, observational cohort study to test the hypothesis that there is an association between higher levels of plasma KIM-1 and underlying histopathologic lesions, clinicopathologic diagnoses, and increased risks of subsequent progression to kidney failure and death in patients with CKD. Results were reported in the *American Journal of Kidney Diseases* [2022; 79(2):231-243].

The study cohort included 524 patients enrolled in the Boston Kidney Biopsy Cohort (BKBC) Study undergoing clinically indicated native kidney biopsy with biopsy specimens adjudicated for semiquantitative scores of histology by two kidney pathologists and 3800 individuals with common forms of CKD who were enrolled in the CRIC (Chronic Renal Insufficiency Cohort (CRIC) study.

The study exposure was histopathologic lesions and clinicopathologic diagnosis in cross-sectional analyses, and baseline plasma KIM-1 levels in prospective analyses. Outcomes of interest were baseline plasma KIM-1 levels in cross-sectional analyses, kidney failure (initiation of kidney replacement therapy [dialysis or kidney transplantation]), and death in prospective analyses.

Associations of plasma KIM-1 levels with future kidney failure

were assessed using Cox proportional hazards models. Associations of plasma KIM-1 levels with histopathologic lesions and clinicopathologic diagnoses were tested using multivariable-adjusted linear regression models.

BKBC STUDY

At baseline, the median plasma KIM-1 concentration using the monoclonal detection antibody from Enzo Life Sciences was 210.2 pg/mL. Mean age was 53 years and mean estimated glomerular filtration rate (eGFR) was 56 mL/min/1.73 m^2. The most common primary clinicopathologic diagnoses were proliferative glomerulonephritis (29.1%), nonproliferative glomerulopathy (18.3%), advanced glomerulosclerosis (11.3%), and diabetic nephropathy (11.1%). There was a negative correlation of plasma KIM-1 and eGFR and a positive correlation of plasma KIM-1 and proteinuria.

Plasma KIM-1 levels were significantly higher in participants with more severe interstitial fibrosis/tubular atrophy, acute tubular injury, inflammation in the nonfibrosed and fibrosed interstitium, global glomerulosclerosis, mesangial expansion, and arterial and arteriolar sclerosis compared with those with less severe lesions. Following adjustment for age, sex, race, and eGFR, plasma KIM-1 levels were significantly higher in participants with more severe acute tubular injury, more severe mesangial expansion, and the presence of inflammation in the

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nonfibrosed interstitium than those with less severe lesions. Following adjustment for proteinuria, plasma KIM-1 levels remained significantly higher in those with more severe acute tubular injury and the presence of inflammation in the nonfibrosed interstitium.

During a median follow-up time of 5 years, CKD progressed in 124 participants and 85 participants died. In the fully adjusted model, there was an association between each doubling of plasma KIM-1 level and a 1.19-fold increased risk of progression to kidney failure (hazard ratio [HR], 1.19; 95% CI, 1.03-1.38). Participants in the highest tertile of plasma KIM-1 had a higher risk of kidney failure; however, the confidence interval crossed 1.0 in the fully adjusted model. There was no evidence of statistical interaction between plasma KIM-1 level and primary clinicopathologic diagnosis for progression to kidney failure (P=3 for interaction) or death (P=7 for interaction). There were associations between higher levels of plasma KIM-1 and higher risk of death; however, the associations were not statistically significant following multivariable adjustment, including eGFR.

CRIC STUDY

Median plasma of the 3800 CRIC Study participants using the polyclonal detection antibody from R&D Systems was 1073.0 pg/mL. Mean age was 58 years and mean eGFR was 45 mL/min/1.73 m^2. Participants with higher levels of plasma KIM-1 were more

In a fully adjusted model, each doubling of plasma KIM-1 level was associated with a 1.10-fold increased risk for progression to kidney failure (HR, 1.10; 95% CI, 1.06-1.15).

likely to be non-White, had greater prevalence of diabetes mellitus and cardiovascular disease, had higher systolic blood pressure, and had lower hemoglobin levels. There was a negative correlation between plasma KIM-1 and eGFR and a positive correlation between plasma KIM-1 and urine albumin-creatinine ratio.

A total of 1153 participants with CKD progressed to kidney failure during a median follow-time of 11.5 years; 1356 participants died during the follow-up period. In a fully adjusted model, each doubling of plasma KIM-1 level was associated with a 1.10-fold increased risk for progression to kidney failure (HR, 1.10; 95% CI, 1.06-1.15). Among participants in the highest quintile of plasma KIM-1 level, there was a 1.58-fold increased risk of progression to kidney failure compared with those in the lowest quintile.

There was an association between higher levels of plasma KIM-1 and higher risk of death. However, following adjustment for eGFR, the association was attenuated and no longer statistically significant.

Strengths of the study noted by the authors included the inclusion of two large cohorts of individuals with established kidney disease; both studies have long follow-up duration and low rates of missing data on outcomes. The researchers also cited limitations to the findings, including differences between the two studies in the ascertainment of variables, and the possibility of residual confounding from unmeasured confounders.

In conclusion, the researchers said, "We found that higher levels of plasma KIM-1 are associated with more severe tubulointerstitial and mesangial lesions and progression to kidney failure in two cohort studies of individuals with kidney diseases. The strong associations with histopathologic lesions and progression to kidney failure suggest that plasma KIM-1 may potentially serve as a kidney-specific marker to enhance estimation of the risk of progression to kidney failure across a broad spectrum of kidney diseases." ■

TAKEAWAY POINTS

- Researchers analyzed data from the Boston Kidney Biopsy Cohort (BKBC) and the Chronic Renal Insufficiency Cohort (CRIC) studies to examine the association between level of plasma kidney injury molecule (KIM-1) and risks of adverse clinical outcomes across various kidney diseases.
- In BKBC, there were associations between higher plasma KIM-1 levels and more severe acute tubular injury, tubulointerstitial inflammation, and more severe mesangial expansion.
- In both cohorts, each doubling of plasma KIM-1 level was associated with an increased risk of kidney failure. There was no statistically significant association between plasma KIM-1 level and death in either cohort.

Outcomes in Kidney Transplant Recipients With COVID-19

Worldwide, elderly people and individuals with underlying chronic conditions such as diabetes and heart, lung, and kidney disease face increased risk of serious and life-threatening complications from COVID-19. For survivors of COVID-19, there is also risk for long-term consequences, including prolonged fatigue, muscle weakness, dyspnea, sleeping problems, and anxiety and depression.

According to **Raphael Duivenvoorden, MD, PhD,** and colleagues, there are few data available on the clinical, functional, and mental health outcomes among kidney transplant recipients who survive COVID-19. The researchers conducted an analysis of data from adult kidney transplant recipients in the European Renal Association COVID-19 Database who presented with COVID-19 between February 1, 2020, and January 31, 2021. Results of the analysis were reported in *Transplantation* [2022;106(5):1012-1023].

Detailed data were collected on patient and COVID-19-related characteristics. The Clinical Frailty Score developed by Rockwood et al was used to assess frailty; low scores (1-3) indicate that patients are fit and managing well, middle scores (4-6) indicate that patients are vulnerable to moderately frail, and higher scores (7-8) indicate patients are severely to very severely frail or terminally ill (9). Patient charts were used to identify comorbidities. Graft function outcomes and functional and mental health outcomes were collected at 3 months following initial presentation with COVID-19.

Analysis of variance for continuous variables was used to compare characteristics among groups. A Kaplan-Meier plot was created to show cumulative survival probability by hospitalization and intensive care unit (ICU) admission status. Cox proportional-hazards models were used to examine predictors of 3-month vital status (being dead or alive). In addition, the use of immunosuppressive drugs was assessed as a risk factor for 3-month vital status in a multivariable Cox proportional-hazards model adjusted for age, sex, frailty, obesity, hypertension, diabetes, heart failure, chronic lung disease, estimated glomerular filtration rate (eGFR), and time after transplantation in a stepwise manner.

Following application of exclusion criteria, the analysis cohort included 912 patients. Mean age was 56.7 years, 61.5% were male, and 85.3% were White.

Patients who were hospitalized more often presented with shortness of breath, fever, nausea, and vomiting. Their respiration rate was higher and oxygen saturation lower at presentation. Those who required hospital admission also had lower eGFR at presentation and had a 25% increase in creatinine compared with the pre-COVID-19 baseline value. Of the 147 patients admitted to the ICU, 72.5% (n=107) were intubated.

Three-month survival was 98.8% for patients who were not hospitalized and 84.2% for those who were hospitalized but not admitted to the ICU. In those two groups, death occurred primarily within the first 14 days after presentation. Among patients who were admitted to the ICU, 3-month survival was 49.0%, and the mortality plateaued later at around 50 days following presentation.

Overall, patients who survived were younger, had a lower Clinical Frailty Score, and fewer comorbidities. Symptoms and signs of disease at presentation were less severe, particularly respiratory symptoms and markers of inflammation. In multivariate analysis, the most important predictors for survival at 3 months were age, frailty, heart failure, respiratory rate, and lymphocyte count. There was a hazard ratio pointing toward better survival for patients on dual therapy versus triple-drug immunosuppression therapy; however, the difference did not reach statistical significance. There was no association between type of immunosuppressive drug and survival.

Of the 751 patients alive at 3 months, 487 had available data for analysis of outcomes related to graft function and 450 had data available for analysis of physician-reported functional and mental health outcomes. Baseline characteristics were similar for those with complete data and those with missing data.

Of the 487 patients with data on graft function, median eGFR at presentation was 40 mL/min/1.73 m^2. At presentation, 21.8% had an increase in creatinine of >25% compared with their pre-COVID-19 baseline creatinine level. Biopsy-proven acute rejection occurred in only four (0.8%) patients who survived COVID-19. Two of the four patients who experienced acute rejection developed temporary graft failure, but at 3 months all four had a functioning graft.

The need for renal replacement therapy occurred in 2.6% of all surviving patients. In the subset of surviving patients who had been admitted to the ICU, the need for renal replacement therapy was 10.6%.

Graft survival was good in patients who survived COVID-19; 97.3% had a functioning graft 3 months after presentation, with a median eGFR of 49 mL/min/1.73 m^2. Graft failure within 3 months of presentation occurred at similar rates in patients who were not hospitalized (0.7%) and those who were hospitalized but not admitted to the ICU (1.0%). In patients who were admitted to the ICU, five of 47 (10.7%) experienced irreversible loss of graft function within 3 months after presentation; 89.4% had a functioning graft at the 3-month follow-up.

Of the 450 patients with complete data on functional and mental health status, 83.3% reached their pre-COVID-19 functional status. The percentage of patients who reached pre-COVID-19 functional status was similar in non-hospitalized patients and hospitalized patients not admitted to the ICU (87.9% and 87.0%, respectively). Only 42.5% of patients admitted to the ICU reached their pre-COVID-19 functional status within 3 months after presentation. Pre-COVID-19 physician- reported mental health status was reached within 3 months by 94.4% of the 450 patients with available data.

Of the patients who had not yet reached their prior functional and mental health status, their treating physicians expected that 79.6% and 80.0%, respectively, would do so within the coming year.

Limitations to the study findings cited by the authors included the possibility that the database did not include all kidney transplant recipients with COVID-19 in the participating centers, and lack of detailed data on in-hospital management of patients.

In summary, the authors said, "Our study shows that >80% of kidney transplant recipients are alive at 3 months after presentation with COVID-19. In these survivors, acute rejection and graft failure within 3-month follow-up were rare, and most patients reached their pre-COVID-19 physician-reported functional and mental health status. ICU admission was associated with poor recovery from COVID-19." ■

TAKEAWAY POINTS

- Results of an analysis of clinical, functional, and mental health outcomes in kidney transplant recipients 3 months after presenting with COVID-19.
- For patients not hospitalized and for those hospitalized who survived to 3 months after presentation, clinical, functional, and mental health status was good.
- For hospitalized patients admitted to the intensive care unit, recovery was less favorable.

Post-Transplant Pregnancy and eGFR Slope

Pregnancy following kidney transplantation has become more common in recent years. The voluntary Transplant Pregnancy Registry International (Philadelphia, Pennsylvania) has registered more than 1100 pregnancies after kidney transplantation. Previous data have suggested that pregnancy may lead to increased risk of death-censored graft loss (DCGL) if there are risk factors such as creatinine >1/5 mg/dL.

In multiple previous studies, there was no difference in the incidence of DCGL for kidney transplant recipients with a history of pregnancy than for nulliparous kidney transplant recipients. Those studies did not account for the possibility that nulliparous kidney transplant recipients might have other underlying conditions that could influence the choice of not conceiving or could affect the incidence of DCGL.

There are few data available on the effect of pregnancy on the course of estimated glomerular filtration rate (eGFR) in kidney transplant recipients. **Marleen C. van Buren, MSc,** and colleagues conducted a nationwide multicenter cohort study in kidney transplant recipients with pregnancy (>20 weeks) following kidney transplantation. Results were reported in *Transplantation* [2022;106(6):1261-1270].

The study utilized data from the Dutch PARTOUT (Pregnancy after Renal Transplantation Outcomes) network. All women who underwent kidney transplantation in the Netherlands since 1971 and became pregnant afterward were included in the data set. Data were collected until December 31, 2017.

Baseline kidney transplant data included specifications of the cause of end-stage renal disease, type of kidney transplant, immunosuppressive and antihypertensive drug use, and medical history. Rejection was defined as biopsy-proven rejection or treatment for rejection by clinician diagnosis.

Obstetric outcomes data were also collected. Preexisting hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure 90 mm Hg, or antihypertensive drug use prior to pregnancy. The same definition was used for pregnancy-induced hypertension in kidney transplant recipients who developed hypertension during pregnancy without preexisting hypertension.

Outpatient clinic serum creatinine levels were collected after 1 year following kidney transplantation for the longitudinal analysis of kidney function and for every year thereafter until graft loss or death or until the end of Follow-up (December 31, 2017).

Data were analyzed using SPSS, version 2.5 (SPSS) and Graph Pad Prism version 8.4 (Graft Pad Software). Generalized estimating equation analysis was used to examine the effect of pregnancy on eGFR. Kaplan- Meier and Cox proportional hazards regression analyses were performed to calculate hazard ratio (HR) and 95% CI in assessment of the association between possible predictors and DCGL after pregnancy.

The analysis cohort included 197 women who had 295 pregnancies during follow-up. Pregnancy outcomes were complicated by preterm birth (<37 weeks) in >50% of the pregnancies; mean birthweight was 2281 grams. Ninety-nine women had hypertension prior to their first pregnancy. Of those, there were data on the hypertensive agents of 87 kidney transplant recipients during the first trimester of their first pregnancy after transplantation. Seventy percent had one antihypertensive agent, 29% had two antihypertensive agents, and one women had three antihypertensive agents. Gestational hypertension occurred in nearly 46% of the analysis cohort and 31% experienced preeclampsia. Nearly half had midterm hyperfiltration (increase in serum creatinine >15%).

Nine of the 197 women did not have available data on eGFR prior to pregnancy, primarily due to the fact that the pregnancy occurred within 6 months after kidney transplant. In 17 women, there were data on eGFR for pregnancy interval 1, because a second pregnancy followed soon after the first.

In the total study population (n=197), the overall effect of transplant vintage on eGFR slope was –0.58 mL/min/1.73 m^2 per year (standard error of the mean [SEM], 0.13; 95% CI, –0.84 to –0.31); *P*<.001). The overall mean eGFR following the first, second, and third pregnancies was not significantly worse than prepregnancy eGFR.

In pregnancy interval 1, adjusted mean decline in eGFR was –2.80 mL/min/1.73 m^2 (SEM 1.59; 95% CI, –5.92 to 0.33; *P*=.08) over a median of 2.57 years. During pregnancy interval 2, mean decline in eGFR was –3.45 mL/min1.73 m^2 (SEM 2.24; 95% CI, –7.84 to 0.94; *P*=.12) over a median of 5.02 years. During pregnancy interval 3, mean eGFR decline was –4.31 mL/min/1.73 m^2 (SEM 8.89; 95% CI, –27.73 to 13.11; *P*=.63) over a median of 6.52 years.

In GEE analysis to determine which other predictors might have an effect on eGFR after kidney transplant, the researchers tested time-related variables. Women who received a kidney transplant and were pregnant prior to 1990 had significantly better post-transplant eGFR compared with women who were transplanted and pregnant more recently (*P*<.001). Further, kidney transplant at a younger age was related to better eGFR after transplant. Following exclusion of women who received a transplant prior to 18 years of age, the effect was no longer significant.

In univariate analysis of the effect of pregnancy outcomes on eGFR after pregnancy (excluding eGFR measurements after second and third pregnancies), midterm hyperfiltration was related to better eGFR after pregnancy (*P*=.04). Low birthweight tended to be related to worse eGFR after the first pregnancy (*P*=.06). When added to a multivariate model, none of those outcomes were identified as independent predictors for worse eGFR after pregnancy.

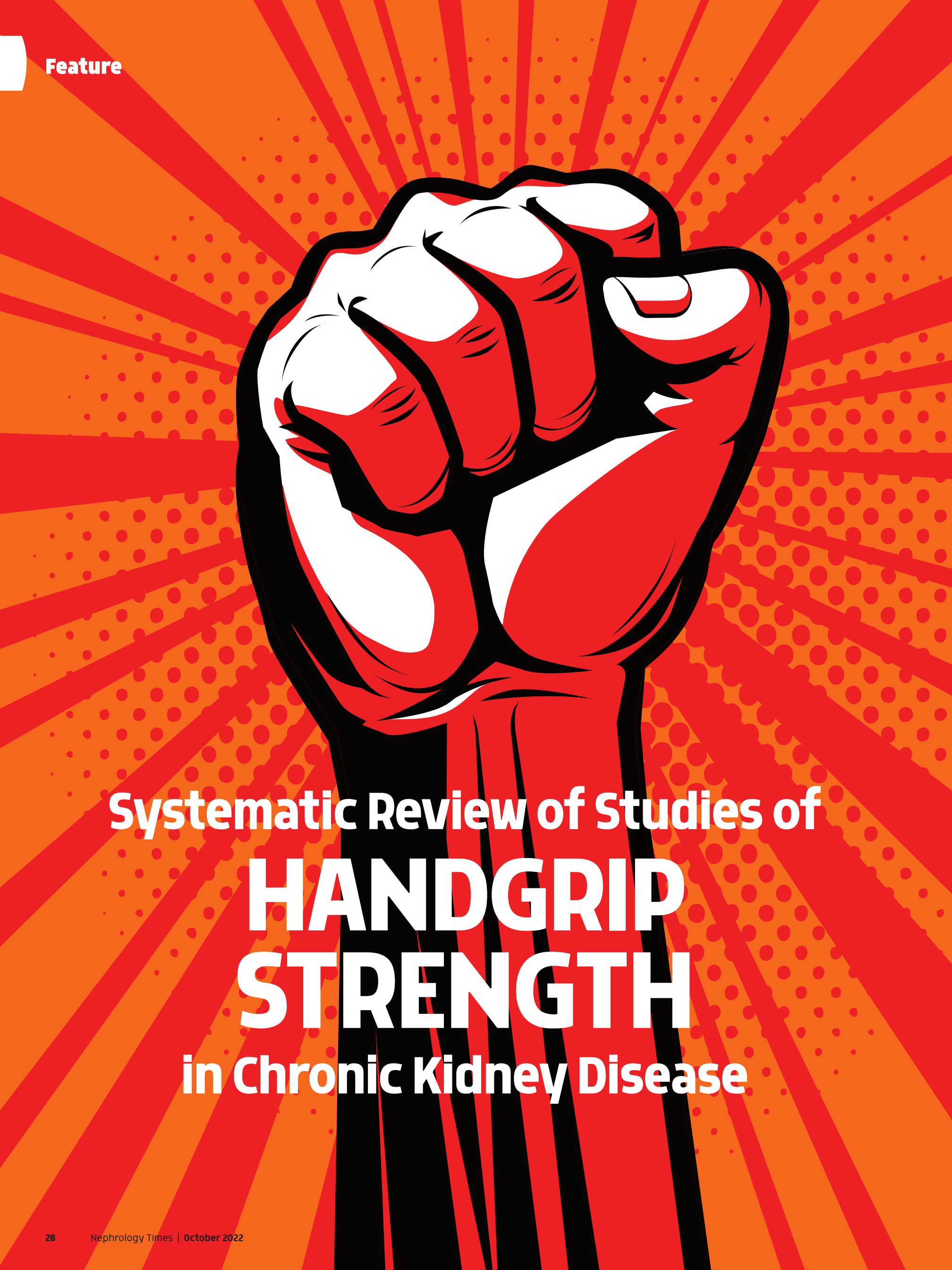
In Kaplan-Meier and Cox regression analyses, approximately 10% of the women lost their graft within 5 years of delivery and 20% within 10 years after first delivery. Women with a prepregnancy eGFR <45 mL/min/1.73 m^2 had shorter graft survival (HR, 0.48; 95% CI, 0.24-0.94; *P*=.03). There was no observed difference in DCGL between women with eGFR values between 45 and 60 mL/min/1.73 m^2 and eGFR values >60 mL/min/1.73 m^2. There was no effect of the transplant-to-conception interval on DCGL.

The researchers cited some limitations to the study, including the retrospective study design and the lack of measurement of 24-hour urine creatinine clearance.

In conclusion, the authors said, "To the best of our knowledge, this is the largest study analyzing the effect of pregnancy in kidney transplant recipients on eGFR slope to date. The outcomes of our study demonstrate that pregnancy causes a small and nonsignificant decline in adjusted mean eGFR after the first pregnancy but does not accelerate eGFR slope after the first or subsequent pregnancies. Furthermore, pregnancy does not amplify the negative effect of known risk factors on eGFR after kidney transplant. Midterm hyperfiltration might be a marker for favorable graft outcomes after pregnancy. The absence of midterm hyperfiltration as a marker of renal reserve might be considered as a risk factor for long-term graft loss in addition to traditional risk factors." ■

TAKEAWAY POINTS

- Results of a retrospective cohort study to examine the effect of pregnancy on the course of estimated glomerular filtration rate (eGFR) in kidney transplant recipients.
- Overall eGFR slope after the first, second, and third pregnancies after kidney transplant was not significantly worse than prepregnancy.
- There was an association with midterm hyperfiltration and better eGFR and death-censored graft survival.



Systematic Review of Studies of HANDGRIP STRENGTH in Chronic Kidney Disease

There are associations between chronic kidney disease (CKD) and reductions in physical function and strength, with resulting decreases in quality of life and increases in the risk of morbidity and mortality. A simple and reliable measure of muscle strength is handgrip strength. In studies of the general population, older adults, and clinical conditions, low handgrip strength has been shown to be an independent predictor of poor cognition, mobility, and mortality.

Due to its low cost and ease of assessment, handgrip strength is commonly used in clinical and epidemiological studies of nutritional and functional assessment among patients with CKD. In patients with non-dialysis-dependent CKD, handgrip strength is an independent predictor of mortality and dialysis initiation; in patients undergoing hemodialysis, there is an association between handgrip strength and nutritional status.

Recommendations in the 2020 Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in CKD call for the use of handgrip strength as a surrogate measure of protein-energy status and functional status in adults with CKD stages 1-5D. The recommendation is based on the relationship of handgrip strength with nutritional status and markers of inflammation.

However, according to **Thomas J. Wilkinson, PhD,** and colleagues, while handgrip strength is widely used in clinical studies, it is not routinely used in practice. The lack of application may be due, in part, to inconsistencies in guidance regarding the optimal timing of the measurement (before or after hemodialysis session, nondialysis day), and specific information on technique.

Dr. Wilkinson et al conducted a systematic review to examine the current literature on handgrip strength methodology, and to define the degree of protocol variation in handgrip strength assessment. The researchers also sought to propose a standardized method for measurement of handgrip strength in patients with CKD. Results were reported in the *Journal of Renal Nutrition* [2022;32(4):371-381].

The review included searches of National Center for Biotechnology Information PubMed (includes the Medical Literature Analysis and Retrieval System Online [MEDLINE]), Excerpta Medica data base (EMBASE), and the Cochrane Central Register of Controlled Trials. The outcome of interest was handgrip grip strength and its use in any form, with particular emphasis on the variation in handgrip strength protocol and methodology. Search terms included kidney, kidney diseases, kidney transplantation, dialysis, peritoneal dialysis, renal dialysis, handgrip, handgrip strength, pinch strength, and muscle strength dynamometer.

A total of 129 studies with a total population of 35 192 participants met eligibility criteria for inclusion in the review. The study samples ranged from 14 to 18 765 participants; the median study sample size was 90. Thirty of the studies (23%) included only patients with non-dialysis-dependent CKD stage 1-5; 80 of the studies (62%) included only patients on dialysis (41% [n=52) on hemodialysis); and 11 of the studies (9%) included kidney transplant recipients only. The studies were conducted in 28 countries; most were conducted in Brazil (n=20), and the United Kingdom (n=10). Ninety-three of the studies (73%) were observational and 24 (19%) were experimental.

Mean age of the study participants was 59.5 years. A total of 105 of the studies did not report data on participant race/ethnicity; of the studies that did report race/ethnicity, 54% of participants were White. On average, 62% of the study cohorts were male. In the studies that reported estimated glomerular filtration rate (eGFR), the average eGFR was 38.5 mL/min/1.72 m^2. Mean body mass index was 25.7 kg/m^2, mean albumin was 30.9 mg/g, and mean hemoglobin was 112.1 g/L. Reported prevalence of hypertension was 65.3%, 35.4% of participants had diabetes, and 27.8% had cardiovascular disease.

A total of 75 studies (59%) did not report hand grip strength. Of those that did, mean hand grip strength was 26.4 kg. Hand grip strength was measured in kilograms in most of the studies (n=88; 69%); 10 studies used kilogram-force (KGF) and one study used kg/m^2. Two studies reported hand grip strength in pounds and one in Newtons. A total of 25 studies did not report units of hand grip strength.

Of the studies that used hand grip strength as a measure of sarcopenia or as a definition of low strength, six used the Asian Working Group for Sarcopenia cutoffs and 20 used variations of the European Working Group on Sarcopenia in Older People (EWGSOP) cutoff (15 used the older EWGSOP cutoff and five used the revised EWGSPO cutoff).

There were wide variations in all aspects of the methodology used in the studies, including body and arm position, repetitions, rest time, familiarization, and how scores were calculated. Thirty studies required that measurement of hand grip strength be conducted while sitting, while 14 were conducted standing. Two were conducted while supine and one indicated patients could be either seated or standing.

Of the studies that reported which hand was tested, 41 tested both hands and 59 tested hand grip strength in one hand only. In 27% of the studies that reported which hand was tested, the test was conducted on the dominant hand. Among participants with a fistula, 36 studies reported assessing hand grip strength in the nonfistula arm. One study tested hand grip strength on both hands of patients undergoing hemodialysis.

Most of the studies (n=86; 67%) reported three assessments in each hand. Only one study reported that hands were tested alternatively. Forty of the studies that included participants undergoing dialysis reported data on the time-of-day that the assessments occurred, relative to the dialysis schedule. Hand grip strength was tested following dialysis in 6 studies (5%). Some studies stipulated that assessment should occur at least 18 to 24 hours after the last dialysis session. One study noted that to avoid alteration in hydration status, the assessment should occur after the middle dialysis session of the week.

The inability to evaluate the quality of the studies included in the systematic review was cited by the authors as a limitation to the findings.

In conclusion, the researchers said, "The diverse methodologies used in CKD research reinforce the need to standardize hand grip strength measurement. After reviewing previously used methodologies in the literature, we have proposed a comprehensive hand grip strength assessment protocol for use in CKD. Researchers should always include a detailed description of the methodology used...Any differences in protocols can influence hand grip strength results and, consequently, affect the comparability between the studies. A collective approach is not only important for research purposes but also for clinical practice." ■

TAKEAWAY POINTS

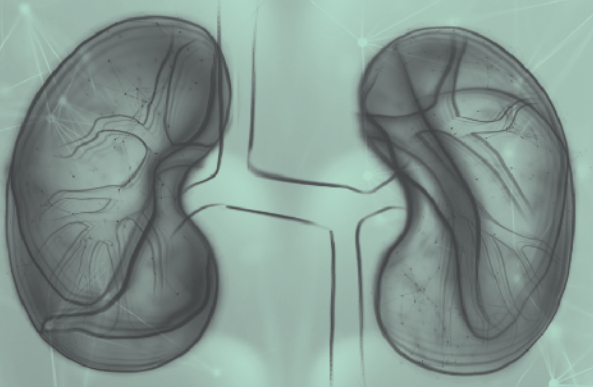
- Handgrip strength can be used as a surrogate measure of protein-energy status and functional status in patients with chronic kidney disease (CKD).
- Researchers reported results of a systematic review of studies of handgrip strength measurement in clinical and epidemiological studies of patients with kidney disease.
- The review revealed wide variations in all aspects of the methodology of measurement of hand grip strength, including body and arm position, rest time, timing, and methods of calculating scores.

Conference Coverage

Copenhagen, Denmark | June 1-4, 2022

EULAR 2022: EUROPEAN CONGRESS OF RHEUMATOLOGY

The European Alliance of Associations for Rheumatology hosts the European Congress of Rheumatology to provide a forum for basic and clinical science as well as social exchange between professionals engaged in the clinical care of people with rheumatic diseases.



Results From AURORA 2 Continuation Study Reported

In January 2021, the US FDA approved the use of voclosporin for the treatment of adult patients with active lupus nephritis (LN) in combination with background immunosuppressive therapy. Voclosporin is a novel calcineurin inhibitor. Results of the phase 3 AURORA 1 study demonstrated that the 52-week rates of complete renal response in patients with LN were significantly increased with the addition of voclosporin to mycophenolate mofetil (MMF) and low-dose steroids.

In a poster session during the EULAR 2022 European Congress of Rheumatology, **Amit Saxena, MD,** and colleagues presented results of AURORA 2, a 2-year continuation study that assessed the long-term safety and tolerability of voclosporin compared with placebo in patients with LN who received treatment for an additional 24 months following completion of the AURORA 1 study. The poster was titled *Voclosporin for Lupus Nephritis: Results of the Two-Year AURORA 2 Continuation Study*.

Inclusion criteria for AURORA 1 were a diagnosis of biopsy-proven active LN (Class III, IV, or V ± II/IV), proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V), and estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2. Patients who completed AURORA 1 and who elected and were eligible to enter AURORA 2 continued in the same blinded therapy as at the end of AURORA 1 (either voclosporin or placebo twice daily in combination with MMF and low-dose steroids). Safety and tolerability were monitored, and eGFR, serum creatinine (SCr), and urine protein creatinine ratio (UPCR) were assessed.

A total of 116 patients in the voclosporin arm and 100 patients in the control arm enrolled in AURORA 2; of those, 92 (79.3%) and 73 (73.0%) patients in each respective arm received treatment to the end of AURORA 2. There were no unexpected safety signals in the voclosporin arm compared with the control arm. Rates of serious adverse events were similar in the two arms (voclosporin [18.1%] vs control [23.0%]).

In each arm, eight patients experienced serious adverse events of infection; serious coronavirus infections were observed in two patients in the voclosporin arm and five patients in the control arm. There were four adverse events by preferred term of renal impairment reported in the voclosporin arm and two in the control arm; none of the six events were considered serious. There were no reports of acute kidney injury by preferred term in either arm. There were no deaths reported in the voclosporin arm; there were four deaths in the control arm (pulmonary embolism, n=1; coronavirus infection, n=3).

Mean eGFR and Scr remained stable through the end of the study period. At 4 weeks following discontinuation of the study drug, the difference between the voclosporin arm and the control arm in least squares mean change from baseline in eGFR was 2.7 mL/min/1.73 m^2. The mean reductions in UPCR seen in patients treated with voclosporin in AURORA 1 were maintained in AURORA 2, with no increase in UPCR noted at the follow-up visit 4 weeks after discontinuation of the study drug.

In summary, the authors said, "Voclosporin was well tolerated over 3 years of treatment with no unexpected safety signals detected. Further, eGFR remained stable throughout the study period, and the significant and meaningful reductions in proteinuria achieved in AURORA 1 were maintained. These data provide evidence of a long-term treatment benefit of voclosporin in patients with LN."

Source: Saxena A, Teng YKO, Collins C, England N, Leher H. Voclosporin for lupus nephritis: results of the two-year AURORA 2 continuation study. Abstract of a poster presented at the EULAR 2022 European Congress of Rheumatology, Copenhagen, Denmark, June 1-4, 2022.

Within the first 3 months of treatment, 78.4% of patients in the voclosporin group and 62.4% of patients in the control group achieved ≥25% reduction in urine protein creatinine ratio (odds ratio [OR], 2.25; 95% CI, 1.52-3.33; *P*<.001). At 6 months, the percentage of patients achieving a reduction of ≥50% was greater in the voclosporin group than in the control group (66.0% vs 47.0%, respectively; OR, 2.24; 95% CI, 1.57-3.21; *P*<.001).

Voclosporin Meets Proteinuria Treatment Targets in Lupus Nephritis

The novel calcineurin inhibitor voclosporin is approved in Europe and the United States in combination with background immunotherapy for the treatment of adult patients with active lupus nephritis (LN). Voclosporin has a favorable metabolic profile and a consistent dose-concentration relationship that eliminates the need for therapeutic drug monitoring.

Results of the phase 2 AURA-LV (Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin) trial and the phase 3 AURORA 1 trial showed that the addition of voclosporin to mycophenolate mofetil (MMF) and low-dose steroids was associated with significantly higher rates of complete renal response compared with placebo in AURA-LV at 24 weeks (32.6% vs 19.3, respectively; odds ratio [OR], 2.03; *P*=.046) and in AURORA 1 at 52 weeks (40.8% vs 22.5% placebo; OR, 2.65; *P*<.001) of treatment in patients with LN.

The European League Against Rheumatism and the European Renal Association (EULAR/ERA) issued updated treatment recommendations for LN, with targeted reduction in proteinuria over the course of the first year of therapeutic intervention. At the EULAR 2022 European Congress of Rheumatology, **Hans-Joachim Sanders, MD,** and colleagues presented results of a post hoc analysis of pooled data from the 48-week AURA-LV and the 52-week AURORA 1 studies based on the new recommendations. The presentation was titled *Voclosporin Is Effective in Achieving Proteinuria Treatment Targets in Lupus Nephritis Defined by EUALR/ERA Recommendations*.

Within the first 3 months of treatment, 78.4% of patients in the voclosporin group and 62.4% of patients in the control group achieved ≥25% reduction in urine protein creatinine ratio (UPCR) (OR, 2.25; 95% CI, 1.52-3.33; *P*<.001). At 6 months, the percentage of patients achieving a reduction of ≥50% was greater in the voclosporin group than in the control group (66.0% vs 47.0%, respectively; OR, 2.24; 95% CI, 1.57-3.21; *P*<.001).

The percentages of patients who had achieved a UPCR ≤0.7 mg/mg after 12 months of treatment in the voclosporin and control group were 52.6% and 33.1%, respectively (OR, 2.52; 95% CI, 1.75-3.63; *P*<.001). Given the protocol-defined steroid taper, at both 3 and 6 months, the proportions of patients in both groups who had achieved the recommended steroid dose were similar (>90%).

The proportion of patients who met all three UPCR targets during the 1-year study period and having a steroid dose ≤7.5 mg/day at 12 months was 37.3% in the voclosporin group and 23.3% in the control group (OR, 2.11; 95% CI, 1.43-3.10; *P*=.001).

In summary, the researchers said, "The addition of voclosporin to a background regimen of MMF and low-dose steroids in patients with LN significantly increased the likelihood of achieving the 3-, 6-, and 12-month UPCR targets of therapy recommended by EULAR/ERA."

Source: Anders HJ, Federico R, Randhawa S, Leher H. Voclosporin is effective in achieving proteinuria treatment targets in lupus nephritis defined by EULAR/ERA recommendations. Abstract of an oral presentation at the EULAR 2022 European Congress of Rheumatology, Copenhagen, Denmark, June 1-4, 2022.

Conference Coverage

Paris, France | May 19-22, 2022

ERA CONGRESS

The European Renal Association Congress is the largest annual nephrology congress in Europe, welcoming thousands of attendees from all over the world. The program focused on key learning features in the clinical field as well as the scientific and latest innovations.

Kidney Impairment in Patients With SARS-CoV-2 Infection

At the 59th ERA Congress, Maria-Daniela Tanasescu and colleagues presented results of a study designed to compared renal impairment between patients with SARS-CoV-2 infection in two different time periods with dominant beta and delta SARS-CoV-2 variants, with or without prior chronic kidney disease (CKD). The results were reported in a presentation titled *SARS-CoV-2 Infection and Kidney Impairment*.

The study cohort included 80 patients from the Bucharest Emergency University Hospital nephrology ward. Of the 80 patients, 40 were diagnosed with SARS-CoV-2 beta variant dominant and 40 were diagnosed with SARS-CoV-2 delta variant dominant. Positive PCR tests confirmed SARS-CoV-2 infections in all of the 80 patients. The values of urea, creatinine, sodium, potassium, calcium, phosphorous, and hemoglobin were observed for all patients during hospitalization.

In the group with the beta variant, only four of the 40 patients had documented preexisting CKD. The average length-of-stay was 14 days; advancement of acute respiratory failure in three patients required transfer to the intensive care unit (ICU). In the delta variant group, three of the 40 patients were diagnosed with acute kidney injury (AKI). Average length-of-stay was 14 days; advancement of acute respiratory failure in three patients required transfer to the ICU.

In the beta variant dominant group, 90% of patients (36/40), analysis of biologic parameters showed minimal change in values during hospitalization with normal maintenance of renal function. In two patients diagnosed with CKD, renal function improved with an average of three to four hemodialysis sessions, while maintaining a minimum nitrogen level. Two patients with CKD experienced a decline in renal function, leading to initiation of hemodialysis.

In the delta variant dominant group, 82.5% of patients (33/40) showed minimal change in the examined parameters during hospitalization with normal maintenance of renal function. In 10% of the cohort (4/40), renal function declined in the context of multiple system organ failure, followed by death. Three patients who were admitted with AKI had renal dysfunction resolved by the time of hospital discharge.

There were no statistically significant differences in measured parameters between the two time periods with the different SARS-CoV-2 strings.

In summary, the authors said, "According to this statistical analysis, the delta variant does not cause more kidney damage than the beta variant of SARS-CoV-2. For the six patients (7.5%) with renal impairment, two from the beta batch (2.5%) and four from the delta batch (5%), the suspicion of renal damage in SARS-CoV-2 infection may be raised, but excluding other causes of renal damage is necessary. For the three patients (7.5%) with AKI from the delta batch, the suspicion of renal damage caused by COVID-19 may be raised because there were no other causes for renal impairment."

Source: Tanasescu M-D, Botocan A, Tanase EGB, et al. SARS-CoV-2 infection and Kidney Impairment. Abstract of a presentation at the 59th European Renal Association Congress, Paris, France, May 19-22, 2022.

Voclosporin for Lupus Nephritis: AURORA 2 Continuation Study Results

In January 2021, the US FDA approved voclosporin for the treatment of adult patients with active lupus nephritis in combination with background immunosuppressive therapy. Voclosporin, a novel calcineurin inhibitor, has a favorable metabolic profile and a consistent dose-concentration relationship, eliminating the need for therapeutic drug monitoring

Results from the phase 2 AURA-LV and phase 3 AURORA 1 studies demonstrated that the addition of voclosporin to mycophenolate mofetil (MMF) and low-dose steroids in patients with lupus nephritis significantly increased rates of complete renal responses at 48 weeks (AURA-LV) and 52 weeks (AURORA-1).

During a presentation at the 59th ERA Congress, **Y. K. O. Teng** and colleagues reported results of the completed continuation study, AURORA 2. The continuation study examined the long-term safety and tolerability of voclosporin versus placebo in patients with lupus nephritis receiving treatment for an additional 24 months after completion of AURORA 1. The presentation was titled *Voclosporin for Lupus Nephritis: Results of the Two-Year AURORA 2 Continuation Study.*

Inclusion criteria for the AURORA 1 study were a diagnosis of biopsy proven active lupus nephritis (Class III, IV, or V), proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V), and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2. Patients enrolled in AURORA 1 were eligible to enroll in AURORA 2 and continued with the same blinded treatment of voclosporin (23.7 mg BID) or placebo in combination with MMF (target dose 2 g/day) and low-dose oral steroids. Adverse events and laboratory assessments including eGFR were used to monitor safety and tolerability; changes in urine protein creatinine ratio (UPCR) were also examined.

A total of 116 patients in the voclosporin arm and 100 patients in the control arm were enrolled in AURORA 2. Ninety-two patients in the voclosporin arm (79.3%) and 73 patients in the control arm (73.0%) completed treatment to the end of AURORA 2. Compared with patients in the control arm, there were no new or unexpected safety signals detected in patients in the voclosporin. The rates of serious adverse events were 19.0% in the voclosporin arm and 24.0% in the control arm; in both arms there were eight serious events of infection.

Through the end of the study period, eGFR remained stable. The slopes of least-squares (LS) mean change in corrected eGFR from AURORA 2 baseline to the end of the study were -0.2 in the voclosporin arm and -5.4 in the control arm. There were no deaths in the voclosporin arm and four deaths in the control arm (one due to pulmonary embolism and three due to coronavirus infection). The LS mean reduction in UPCR seen in AURORA 1 were maintained in AURORA 2 with no increase in UPCR at the follow-up visit 4 weeks following discontinuation of the study drug.

In conclusion, the researchers said, "Voclosporin was well tolerated over three years of treatment with a similar safety profile to control and no unexpected safety signals detected. Further, the significant and meaningful reductions in proteinuria initially achieved in AURORA 1 were maintained throughout AURORA 2. These data provide evidence of a long-term treatment benefit of voclosporin in patients with lupus nephritis."

Source: Teng YKO, Saxena A, Palmen M, Birardi V, Lisk L. Voclosporin for lupus nephritis: results of the two-year AURORA 2 continuation study. Abstract of a presentation at the 59th European Renal Association Congress, Paris, France, May 19-22, 2022.

Progression and Prognosis in Patients With ADPKD Without Family History

Among patients with autosomal dominant polycystic kidney disease (ADPKD), a small percentage have no clear family history. This subgroup of patients may face a different clinical course and disease prognosis than those with family history of ADPKD.

Vasiliki Gkika and colleagues conducted a study to examine the progression and prognostication of end-stage renal disease (ESRD) in a large cohort of patients with and without a family history of ADPKD. Results were reported at the ERA 59th Congress in a presentation titled *Patients With Autosomal Dominant Polycystic Kidney Disease (ADPKD) Without a Clear Family History Have Rapid Progression and Poor Prognosis*.

The study included 291 patients who were being followed in a specialized ADPKD outpatient clinic. Patients with and without a clear family history or confirmatory genetic test for ADPKD who had more than ten kidney cysts in a recent magnetic resonance imaging (MRI) scan were included in the study.

Total kidney volume was calculated by MRI at study enrollment, and the Mayo Clinic Imagining Category was determined (MCIC). ESRD was defined as future estimated glomerular filtration rate <10 mL/min/1.73 m^2 based on the Mayo Clinic Formula that takes into consideration age, total kidney volume, eGFR, sex, race, and MCIC.

Of the 291 patients in the overall study cohort, 11.68% (n=34) had no clear family history of ADPKD, and 88.32% (n=257) had a clear family history. The two groups were similar in age, sex, the presence (or not) and age at diagnosis of hypertension, and body mass index. The groups were also similar in age at diagnosis of ADPKD, eGFR, chronic kidney disease stage, and albuminuria.

Total kidney volume tended to be higher in the group of patients without a clear family history compared with those with a family history of ADPKD (median, 2210.3 mL vs 1649.9 mL, respectively; P=.09). Height-adjusted total kidney volume was also higher in the group without family history (P=.08).

In MCIC classification, more patients in the non-family history group were classified 1C, 1D, and 1E than those in the group with family history of ADPKD (88.89% vs 70.14%, respectively); the opposite was true for MCIC 1A and 1B (11.11% vs 29.86%, respectively; P=.04). For patients without a clear family history of ADPKD, the ESRD prediction was 15.66 years versus 34.1 years for those with a clear family history of ADPKD (P=.025).

In summary, the authors said, "Patients with ADPKD without a clear family history tend to have more rapid progression and a worse renal prognosis than those with a clear family history of the same disease."

Source: Gkika V, Louka M, Fokas S, et al. Patients with autosomal dominant polycystic kidney disease (ADPKD) without a clear family history have rapid progression and poor prognosis. Abstract of a presentation at the European Renal Association 59th Congress (M0008), Paris, France, May 19-22, 2022.

Prevalence of Pruritus in Patients With Advanced CKD

Results of studies of chronic kidney disease-associated pruritus (CKD-aP) have reported a range of prevalence from 40% to 90% among patients undergoing hemodialysis and from 19% to 29% in non-dialysis patients. Pruritis negatively affects patient quality of life (QoL) and clinical outcomes and is associated with an increased risk of mortality.

However, according to **Nuria Areste-Fosalba** and colleagues, clinicians may underestimate the number of patients with CKD-aP. The researchers conducted a study to determine the prevalence of pruritus and its impact in various dimensions of QoL in patients in Spain with CKD. Results were reported at the European Renal Association 59th Congress in a presentation titled *Prevalence of Pruritus in Spanish Patients With Chronic Kidney Disease and Affectation of Quality of Life*.

The researchers designed a survey that used seven questions included in several validated tools for assessment of pruritus. The Spanish Society of Nephrology distributed the questionnaire to all their members in the framework of Pruritus Week. Patients with advanced CKD were asked to respond to the questionnaire voluntarily.

A total of 1605 patients answered the questionnaire; 92% were receiving hemodialysis, 5% were receiving peritoneal dialysis, and 3% were not on dialysis. The prevalence of CKD-aP was 50.5%, 26.7% of which was reported as moderate to severe. The prevalence was higher in the non-dialysis patients with advanced CKD, suggesting a benefit of dialysis in reducing itch.

Patients who reported having CKD-aP described itching throughout their body and at any part of the day, but more at night. As the severity of itch increased, the percentage of patients with changes in mood increased; the parameters most affected were anguish and lack of rest. As itch severity increased, impairment in sexual function and desire increased.

All patients with CKD-aP reported more sleeping disturbances that those without CKD-aP. Sleep impairment included difficulty to sleep, restless sleep, and intake of sleep medication. Sleeping disturbances increased with increase of pruritus severity.

In conclusion, the researchers said, "CKD-aP is highly prevalent in patients with advanced CKD (non-dialysis and dialysis), which affects patients' quality of life by inducing mood changes, including depression, impairing sexuality, and affecting sleep."

Source: Areste-Fosalba N, Emilio SAJ, Henriquez F, Lloret M, Ulloa C. Prevalence of pruritus in Spanish patients with chronic kidney disease and affectation of quality of life. Abstract of a presentation at the European Renal Association 59th Congress (Abstract M0131), Paris, France, May 19-22, 2022.

Kidney Biopsy for Fabry Disease Treatment Indication

Patients with Fabry disease face progressive decline in kidney function, as well as disorders of the nervous system and the heart. Disease progression may be stopped or mitigated with specific therapy, but results depend significantly on early initiation of treatment.

Kidney biopsy in patients with Fabry disease carries crucial diagnostic, prognostic, and therapeutic implications. In some countries, renal biopsy evidence related to Fabry disease is a criterion for reimbursement for Fabry disease-specific therapy. Criteria for initiating Fabry disease specific therapy related to renal involvement include estimated glomerular filtration rate (eGFR) <80 mL/min/1.73 m2 and/or proteinuria >300 mg per day.

Elena Emanuela Rusu and colleagues in Romania conducted a retrospective study to examine clinical and histologic aspects of renal involvement in untreated female patients diagnosed with Fabry disease by genetic test between 2015 and 2021 in a single center. Results of the study were reported at the European Renal Association 59th Congress in a presentation titled *Kidney Biopsy in Females With Fabry Disease Is an Important Tool to Establish the Indication for Fabry-Specific Therapy*.

Serum creatinine, albumin creatinine ratio, and proteinuria were measured to assess biologic renal manifestations. The presence of neurological involvement was determined by clinical exam, electroneurographic examination, and brain magnetic resonance; heart manifestations were assessed by echocardiography., electrocardiogram (ECG), ECG Holter, and cardiac magnetic resonance

Light and electron microscopy were utilized to analyze kidney biopsy specimens. The International Study Group of Fabry Nephropathy Score Sheet was used to evaluate specific renal Fabry disease lesions, as well as general lesions of progression.

From a total of 25 female patients, the study included 11 patients who had a kidney biopsy performed. Mean age at time of diagnosis was 47.7 years; mean age at symptom onset was 36.1 years. Mean eGFR was 72.7 mL/min/1.73 m^2 and mean proteinuria was 0.72 mg/day. The average Mainz score was 16.6. Five patients had heart involvement and five had neurological manifestations. Comorbidities included arterial hypertension (6 patients), diabetes mellitus (1 patient), and obesity (2 patients).

All kidney biopsies showed lysosomal accumulation in the podocytes, in the parietal cells of the Bowman capsule, and in the tubules. In nine cases, vascular inclusions were found. There was segmental glomerular sclerosis in four cases, global glomerular sclerosis in three cases, interstitial fibrosis in six cases, tubular atrophy in five cases, arteriosclerosis in four cases, and arteriolar hyalinosis in five cases.

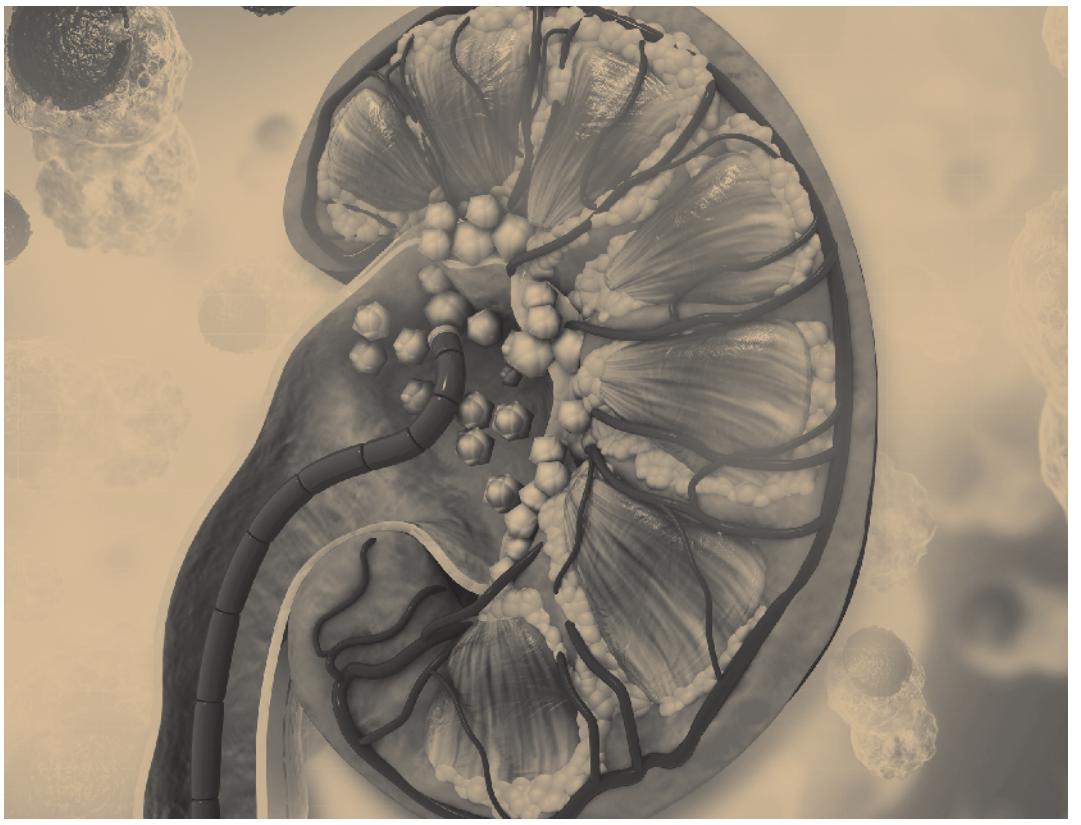
Regarding national criteria for initiation of Fabry disease therapy, five patients fulfilled the renal criteria, three presented criteria for other organ involvement, and three (mean age 37.7 years) did not fulfill any criteria.

The researchers noted that even in the six patients without renal criteria for Fabry disease therapy, the kidney biopsy showed Fabry disease-specific lesions (lysosomal accumulation) in all cases.

In conclusion, the researchers said, "The data from our small cohort of females with Fabry disease underline the importance of kidney biopsy for detection of early kidney involvement and provide additional support to the consideration of early initiation of Fabry disease-specific therapy, potentially improving long-term outcomes. Thus, proof of specific Fabry disease lesions as revealed by kidney biopsy could become a distinct criterion for initiation of Fabry disease therapy, in the absence of other criteria according to current guidelines. Future studies are necessary in order to specify the role of renal histology in the establishment of the proper timing to start the Fabry disease treatment, especially in young patients."

Source: Rusu EE, Zilisteanu D, Ciobotaru LM, et al. Kidney biopsy in females with Fabry disease is an important tool to establish the indication for Fabry-specific therapy. Abstract of a presentation at the European Renal Congress 59th Congress (Abstract M0028), Paris, France, May 19-22, 2022.

Green Tea in Combination With ERT in Patients With Fabry Disease



Fabry disease, an X-linked rare disease, is characterized by deficient expression and activity of alpha-galactosidase A and consequent lysosomal accumulation of Gb3 and derivatives in various organs. First-line treatment includes enzyme replacement therapy (ERT). However, Fabry disease is progressive and is associated with serious cardiovascular, renal, and cerebral complications, particularly in patients with late diagnosis, suggesting the involvement of secondary parallel mechanisms to Gb3 accumulation.

Previous studies have shown that patients with Fabry disease have increased and active oxidative stress that plays a primary role in the induction of cardiovascular-renal remodeling and related to left ventricular hypertrophy (LVH) seen in patients with Fabry disease. Other studies have demonstrated significant reductions in oxidative stress-related cell signaling mechanisms with antioxidant treatment with green tea in patients with chronic kidney disease stage 3-4 and those on dialysis, thus improving LVH.

Giovanni Bertoldi and colleagues conducted a study to test the hypothesis that treating patients with Fabry disease with green tea in combination with ERT would have additive positive effects toward oxidative stress and oxidative stress-induced cardiovascular and renal remodeling using a molecular biologic approach. Results were reported at the ERA 59th Congress in a presentation titled *Effect of Green Tea on Top of Enzyme Replacement Therapy in Patients With Fabry Disease: A Molecular Biology Approach.*

The study enrolled ten patients with Fabry disease. The status of oxidative stress was evaluated ex vivo in mononuclear cells prior to ERT, after 12 months of ERT, and after 6 months of additional treatment with two capsules of green tea (600 mg Camellia Sinensis leaves dry extract, 40% Epigallocathechinegallate, Frama S. r. l., Noventa Padovana, Italy) per day taken in the morning at fast in combination with ERT.

Oxidative stress was evaluated and compared in the three time periods in terms of protein expression of p22phox (subunit of NADH/NADPH oxidase essential for the production of superoxide), phosphorylation state of MYPT-1 (regulatory subunit of the myosin light chain phosphatase), ERK 1/2 (effectors at nuclear level of cardiovascular modality), and plasma levels of MDA (marker of lipid peroxidation). HO-1 levels (antioxidant and protective from oxidative stress) were also evaluated.

After 12 months of ERT, there was significant decrease in p22phox; after 6 months of add-on green tea treatment, there was further decrease. There were also significant decreases in MYPT-1 phosphorylation. After 12 months of ERT, the phosphorylation of ERK 1/2 remained unchanged; after 6 months of supplementation with green tea, there was significant decrease in phosphorylation of ERK 1/2 as well as in MDA levels. There was significant increase in HO-1 with both ERT and green tea supplementation.

In summary, the authors said, "This study provides data pointing toward an antioxidant effect exerted by ERT itself, which is further amplified by the treatment with green tea on top of ERT. These data while on one hand highlight the fundamental importance of an early diagnosis and treatment of Fabry disease, on the other hand suggest the need of adjuvant antioxidant treatments to prevent or improve specific disease manifestations."

Source: Bertoldi G, Carrano G, Ravarotto V, et al. Effect of green tea on top of enzyme replacement therapy in patients with Fabry disease: a molecular biology approach. Abstract of a presentation at the 59th European Renal Association Congress (M0024), Paris, France, May 19-22, 2022.

Pre-Eclampsia and Chronic Kidney Disease

Pregnant women with chronic kidney disease (CKD) are at increased risk for pre-eclampsia, yet there are few data available on the features of pre-eclampsia in that patient population. **Natalia Kozlovskaya** and colleagues conducted a study to examine the incidence and characteristics of pre-eclampsia in patients with CKD.

Results of the study were reported during a presentation at the European Renal Association 59th Congress. The presentation was titled *Pre-Eclampsia in Patients With Chronic Kidney Disease (CKD).*

The retrospective analysis included 60 case histories of pregnant women with CKD stages 1-4 (27 of those had CKD stage 3a-4), who were followed in a dedicated center from 2018 to 2021. Ten of the women with CKD stage 3a-4 developed pre-eclampsia; the researchers examined the course of the pregnancies of those 10 women.

At the first visit to the center, indicators of creatinine, proteinuria, and blood pressure were measured; the markers were measured again at the time of pre-eclampsia. In six women with a known creatinine value prior to pregnancy and who had a 10% decrease in creatinine concentration from the pre-pregnancy value, the physiological response of the kidneys to pregnancy was assessed.

Among the patients with pre-eclampsia and advanced CKD, mean age was 32 years. The most common cause of CKD was glomerulonephritis (6 patients); other causes were tubulointerstitial nephritis (1 patient), diabetic nephropathy (1 patient), atypical hemolytic uremic syndrome (1 patient), and antiphospholipid-associated nephropathy (1 patient). Three of the 10 patients had complicated obstetric history. Mean term of gestation at the time of the first visit to a nephrologist was 15.6 weeks.

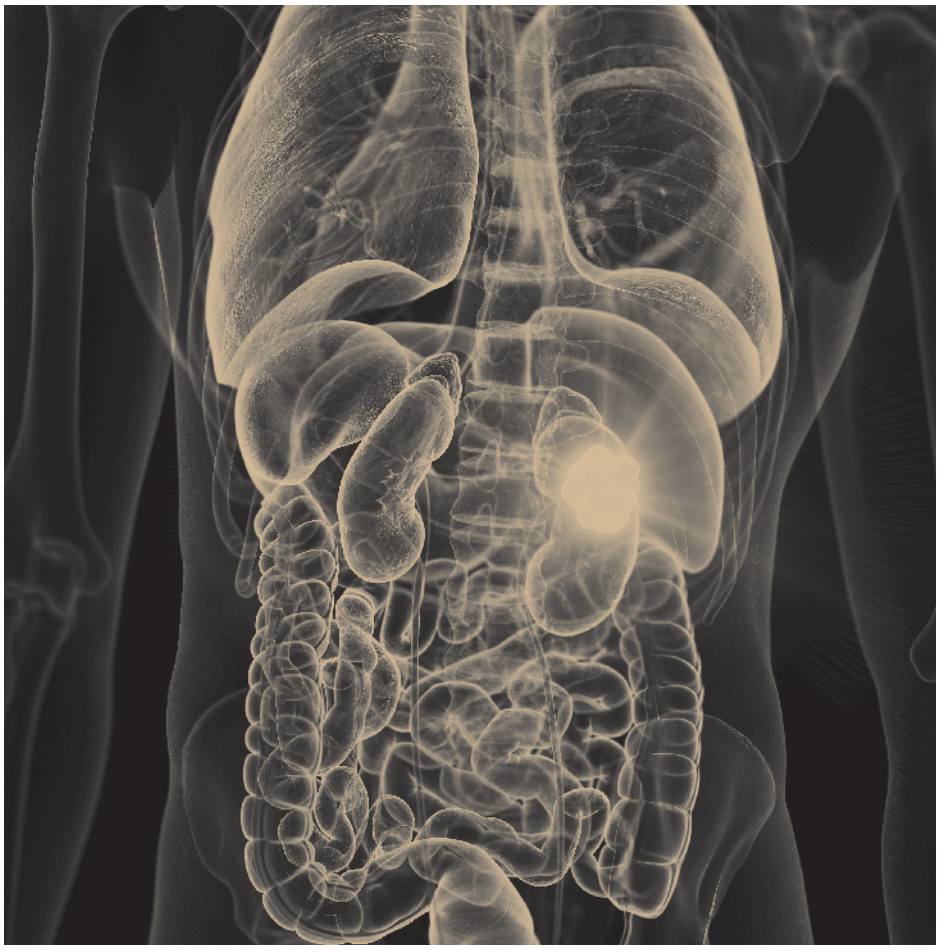
Mean serum creatinine at the first measurement during pregnancy was 157 mmol/L. Physiological response of the kidneys to pregnancy was noted in only one of the six women with pre-pregnancy data; mean proteinuria was 1.2 g/L.

Three patients had arterial hypertension; only one women received antihypertensive therapy prior to pregnancy. Mean blood pressure at the first visit was 131/84 mm Hg. In six women, aspirin for the prevention of pre-eclampsia was prescribed; in the other four patients, aspirin was either not prescribed or added to therapy after 12 weeks of pregnancy.

Early pre-eclampsia (prior to 34 weeks of gestation) developed in seven patients; mean term for the development of pre-eclampsia was 31.3 weeks. Mean blood pressure at the time of pre-eclampsia was 142/90 mm Hg. Six women developed acute kidney injury. Mean delivery term was 32.4 weeks of gestation; all infants were alive and viable with a mean weight of 1514 g.

In summary, the researchers said, "According to our data, the main features of pre-eclampsia in patients with advanced CKD are its early onset (up to 34 weeks), severe course with AKI in 60% of cases, with relatively low blood pressure values."

Source: Kozlovskaya N, Alekseeva M, Demyanova K, Korotchaeva Y, Chegodaeva A, Apresyan S. Pre-eclampsia in patients with chronic kidney disease (CKD). Abstract of a presentation at the European Renal Association 59th Congress (M0080), Paris, France, May 19-22, 2022.



Blood Pressure in Kidney Transplant Recipients Versus CKD Patients

In patients with chronic kidney disease (CKD) and in kidney transplant recipients, hypertension is a major cardiovascular risk factor. In both of those patient populations, ambulatory blood pressure monitoring (ABPM) is considered the gold standard for managing hypertension.

Maria Korogiannou and colleagues conducted a study designed to compare the full ambulatory blood pressure profile and short-term blood pressure variability in kidney transplant recipients versus patients with CKD without kidney replacement therapy. Results of the study were reported during an oral session at the 59th ERA Congress in a presentation titled *Ambulatory Blood Pressure Trajectories and Blood Pressure Variability in Kidney Transplant Recipients: A Comparative Study Against Chronic Kidney Disease Patients.*

The study cohort included 93 kidney transplant recipients who were matched with 93 CKD patients for age, sex, and estimated glomerular filtration rate. All participants underwent 24 hour ABPM. Mean ambulatory blood pressure levels, blood pressure trajectories, and blood pressure variability indices in the two groups were compared.

There were no significant differences between kidney transplant recipients and CKD patients in 24-hour systolic blood pressure/diastolic blood pressure (126.9 vs 128.1 mm Hg, respectively), daytime systolic blood pressure/diastolic blood pressure and nighttime systolic blood pressure. Nighttime diastolic blood pressure was slightly higher in kidney transplant recipients compared with CKD patients (76.5 vs 73.8 mm Hg; P=.04).

For both ambulatory systolic blood pressure/diastolic blood pressure, repeated measurement-ANOVA (analysis of variance) showed a significant effect of time but not of kidney transplant recipient or CKD patient status. There were no differences in ambulatory systolic/diastolic blood pressure variability indices between the two groups, with the exception of 24-hour diastolic blood pressure standard deviation that was slightly higher in CKD patients (10.2 mm Hg in kidney transplant recipients vs 10.9 mm Hg in CKD patients; P=.041). There were no differences observed between the two groups in dipping pattern.

In conclusion, the authors said, "Mean ambulatory blood pressure levels, blood pressure trajectories, and short-term blood pressure variability indices are not significantly different between kidney transplant recipients and CKD patients, suggesting that kidney transplant recipients have a similar ambulatory blood pressure profile compared with CKD patients without kidney replacement therapy."

Source: Korogiannou M, Therdorakopoulou M, Sarafidis P, et al. Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against chronic kidney disease patients. Abstract of a presentation at the 59th European Renal Association Congress, Paris, France, May 19-22, 2022.

Third COVID-19 Vaccine Dose in Kidney Transplant Recipients

Solid organ transplant recipients with COVID-19 are at increased risk of morbidity and mortality due to comorbidities and immunosuppression status. Vaccines represent the best tool to control the COVID-19 pandemic. However, results of studies in solid organ transplant recipients have demonstrated low immunogenicity of a two-dose mRNA COVID-19 vaccine regimen compared with the general population. Based on those results, in September 2019, the Italian Medicine Agency authorized administration of a third vaccine as additional primary dose to immunocompromised patients.

At the 59th ERA Congress, **Giulia Fonto** and colleagues reported results of a study designed to evaluate the seroconversion rate after the third dose of BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 mRNA vaccine in kidney transplant recipients in a presentation titled *Third COVID-19 Vaccine Dose Maximizes Antibody Titer in Kidney Transplant Recipients.* The researchers also sought to determine the baseline factors associated with the absence of the antibody response.

The prospective observational study included a monocentric cohort of 329 consecutive White kidney transplant recipients given three doses of the BNT162b2 COVID-19 vaccine. Exclusion criteria were history of COVID-19 infection, and transplantation or undergoing chemotherapy within the last year.

Antibody response against the spike protein was tested on blood sample collected before the administration of vaccine (T_0), at 15 and 90 days after the second dose (T_2 and T_3, respectively) and 1 month after the third dose (T_5). The Roche Elecsys anti-SARS-CoV-2 enzyme immunoassay (positive cut-off >0.8 U/mL) was used to assess the antibody level.

The study cohort included 307 kidney transplant recipients. Mean age was 57.10 years and 64.1% were male. Median time from transplantation to vaccine was 1-0 years. At baseline, mean estimated glomerular filtration rate (eGFR) as assessed by the Chronic Kidney Disease Epidemiology Collaboration equation was 56.95 mL/min/1.73 m^2.

Standard immunosuppressive regimen consisted of glucocorticoids in all patients, calcineurin inhibitors (88.6% of patients), antimetabolites (73.3%), and mTOR inhibitors (15.6%). The first two vaccine doses were administered 21 days apart, and the third dose was administered 172 days after the second dose.

Of the 307 patients, 43.3% (n=133) responded to the vaccine at T_2. At T_3, the proportion of responders increased to 68.4% (n=186/272) (median antibody level: 5.2). One month after the third dose, a positive antibody titer was detected in 81.8% of patients (n=251/307). Median antibody titer was 1137.50.

Multivariate analysis demonstrated an association between the negative response to the third primary dose and antimetabolite immunosuppressants (P=.001), lower eGFR (P<.001), and female sex (P=.04). There were no serious adverse events reported. Neither de novo donor-specific antibodies or change in proteinuria were reported after vaccination.

In conclusion, the researchers said, "Although the exact threshold of antibody titer for protection against SARS-CoV-2 infection remains unclear, the ability of the additional mRNA COVID-19 vaccine dose to increase both immune response and the prevalence of seroconversion rate associated with the acceptable safety profile supports its use after an initial two-dose mRNA COVID-19 primary vaccine series in immunocompromised patients."

Source: Fonto G, Simone S, Pesce F, et al. Third COVID-19 vaccine dose maximizes antibody titer in kidney transplant recipients. Abstract of a presentation at the 59th European Renal Association Congress, May 19-22, Paris, France.

AOPO Initiative Increases Diversity in the OPO Community

In a recent press release, the Association of Organ Procurement Organizations (AOPO) announced several initiations designed to increase diversity, equity, and inclusion (DEI) in the organ procurement organization (OPO) community. The efforts are part of AOPO's 50K organ transplants in 2026 campaign that aims to reduce health inequities present in the process of organ donation and transplantation.

AOPO has launched a survey to assess DEI within its membership, with an eye toward helping OPOs raise awareness and foster DEI within the individual organizations. The survey focuses on organizational improvements and individual staff engagement with DEI at various leadership levels. Topics will include type of training, educational needs, as well as other target areas. The assessment will aid the AOPO DEI Committee in determining next steps to provide OPOs with resources to improve DEI.

Joe Ferreira, chair of the AOPO DEI Committee, said, "Through the assessment, we can identify disparities between OPO staff and leadership and the communities they serve. This information will help create an inclusive and equitable culture throughout the OPO community, promoting more fairness within the diverse communities we serve and resulting in more lives saved."

FDA Approves KERENDIA® Label Update

The US FDA has granted approval for an update to the label for KERENDIA® (finerenone), a first-in-class nonsteroidal mineralocorticoid receptor antagonist (MRA) for the treatment of patients with chronic kidney disease (CKD) associated with type 2 diabetes. The updated label will include findings on cardiovascular outcomes from the FIGARO-DKD study. FIGARO-DKD is the first phase 3 cardiovascular outcomes trial to include a majority of patients with earlier stage CKD (stage 1-2) with albuminuria to show cardiovascular benefit in patients with CKD associated with type 2 diabetes.

In a press release from Bayer, **George Bakris, MD,** professor at the University of Chicago Medicine and principal investigator of FIDELIO-DKD, said, "The FIDELIO-DKD and FIGARO-DKD studies demonstrated KERENDIA's dual risk reduction in patients with chronic kidney disease associated with type 2 diabetes. This label update reaffirms KERENDIA as a fundamental pillar in the treatment algorithm to improve cardiovascular and renal outcomes in patients with chronic kidney disease associated with type 2 diabetes."

Sameer Bansilal, MD, MS, FACC, vice president, cardiovascular US medical affairs at Bayer, said, "Our large body of clinical data demonstrates that KERENDIA preserves kidney function and provides

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dual cardiovascular risk reduction in type 2 diabetes patients with a broad range of chronic kidney disease severity. We are committed to equipping clinicians with treatment options, such as KERENDIA, that offer benefits to patients with chronic kidney disease associated with type 2 diabetes as patients work with their treatment teams to manage their disease and slow their chronic kidney disease progression."

VA Awards 5-Year Contract to FMCNA

The US Department of Veterans Affairs (VA) has awarded a 5-year contract to Fresenius Medical North America's (FMCNA) Renal Therapies Group. According to a recent press release, the VA awarded the contract to FMCNA in five different categories, the most of any medical device company, including home dialysis machines, critical care equipment, water purification systems, and in-center hemodialysis.

Joe Turk, president of the Renal Therapies Group at FMCNA, said, "We are extremely proud to continue our decades-long relationship with Veterans Affairs and serving the men and women who have given so much for their country. This contract is a testament to our innovation, industry-leading technology, and our ability to meet the needs of our veterans, whether they require dialysis in the hospital, in an outpatient setting, and more increasingly at home."

The 5-year national contract allows VA's 106 hospitals and clinics to purchase Fresenius Medical Care's complete in-center, acute, and home dialysis offerings. The VA endorsement includes the 2008T BlueStar hemodialysis machine that provides life-sustaining dialysis care with the addition of the industry's only integrated fluid management technology. The contract also includes the NxStage® System One S™ with NxView for hospital systems to provide continuous renal replacement therapy to patients with acute kidney injury, as well as the AquaC UNO H, a portable water treatment system featuring a compact footprint.

Two home dialysis systems are also included in the contract: NxStage Versi™–HD and Liberty® Select Cycler. Fresenius is committed to empowering more patients to choose home dialysis and this contract will provide veterans greater lifestyle flexibility and independence.

"Fresenius Medical Care has been a leader in dialysis services for many decades," said **Mink Chawla, MD,** the former chief of critical care at the Washington, DC, VA Medical Center. "Our veterans deserve the best care, and I am delighted they will have access to Fresenius Medical Care's state-of-the-art devices and services."

The VA contract is effective from August 1, 2022, through July 31, 2027. ■

Print-only Content

Sarah Tolson

Telehealth and the End of the Public Health Emergency

During the early months of the COVID-19 pandemic, the US government declared a public health emergency (PHE) that allowed some flexibility in the services CMS was able to provide coverage for. At the time, swift change was needed in the way providers were able to deliver care to patients and receive reimbursement to keep their practices operating. While there were many changes to how and where providers were practicing medicine due to the pandemic, the changes made to telehealth coverage felt as though they were bringing coverage standards into alignment with available technology and the needs of many patients.

Prior to the PHE, CMS had quite a few conditions for coverage of telehealth that were rather restrictive. The technology approved for use for telehealth communications was prohibitively expensive for some providers whose patients would greatly benefit from telehealth visits. In addition to technological restrictions, telehealth was only covered if the originating site and distant site met specific criteria, and not all Medicare provider types were able to furnish services via telehealth. During the PHE, telehealth went from being an option for a small percentage of patients to a common way for providers to deliver care to their patients.

It goes without saying that not all patient-provider encounters can or should take place via telehealth, but the PHE has allowed us to see some of the practical benefits of using telehealth. In the nephrology practices my company works with, one of the biggest benefits of the telehealth flexibilities during the PHE was the ability to have a visit with a patient over a telephone call. A sizable percentage of elderly patients with kidney issues encountered barriers using technology that allowed for the visual portion of the telehealth encounter, but they were able to review lab results and medications as well as discuss other pertinent information regarding their health with their nephrologist during a telephone call. This was incredibly beneficial for this already medically fragile patient population to have the option to avoid crowds at their physician office and still receive the care they needed.

Unfortunately, CMS doesn't have the sole authority to keep telehealth coverage the way it is after the PHE ends; for that, they will need congressional action. CMS appears to be gearing up for an end to the PHE, publishing a roadmap for the end of the PHE. To help provider offices prepare for the end of the PHE and the changes that will occur, the Secretary of Health and Human Services (HHS) has agreed to provide a 60-day notice before ending the PHE. At the time of this writing, the PHE is set to last through mid-October. However, as HHS has not given a 60-day notice, it is likely the PHE will last through at least mid-January and possibly mid-April 2023.

CMS is encouraging providers to prepare for the end of these flexibilities and begin to move forward reestablishing previous health and safety standards and billing practices.

CMS is encouraging providers to prepare for the end of these flexibilities and begin to move forward reestablishing previous health and safety standards and billing practices. These documents outline the changes specific to these provider types that can be expected at the end of the PHE.

Several key telehealth flexibilities have been proactively extended for 151 days after the end of the PHE. The flexibilities include no rural limitation, originating and distant sites allowing services to occur from the patient's (and provider's) home, and coverage for audio-only encounters. As the PHE has existed for more than 2.5 years, it is possible that some of the staff in provider offices are not familiar with many of the rules, regulations, and administrative requirements that will be coming back with the end of the PHE. Now may be a good time for providers, practice managers, and facility administrators to get together and review the CMS roadmap and plan for any needed training or policy changes. ■

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