Nephrology Times

Practical News, Trends, and Analysis

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Perspectives of Black US Veterans With CKD on Racism in Health Care

In the United States, the burden of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) disproportionally falls on individuals of Black race. Black US veterans with CKD experience substantial adverse consequences; compared with White veterans, Black veterans with CKD are twice as likely to progress to ESKD and account for approximately 37% of all patients with ESKD in the US Department of Veterans Affairs (VA) health care system, while representing only 12% of the veteran population.

Several factors are associated with the racial disparities seen among Black individuals with CKD, including limited access to high-quality health care, lower socioeconomic status (SES), exposure to environmental toxins, and health beliefs and behaviors. Only part of the disparities in health is associated with nonbiological factors.

According to **Kevin A. Jenkins, PhD,** and colleagues, racism is likely one of the factors associated with the disparities in health conditions and health care. The researchers recently conducted a qualitative study to examine the consequences of racism and the resulting social structures that establish and perpetuate racial disparities. Results of the study were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2022.11900].

The study utilized semi-structured interview guides to examine the health care experiences of 36 Black

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Short-Term Outcomes of PCI in Dialysis Patients With STEMI

Patients receiving maintenance dialysis have a high prevalence of cardiovascular and noncardiovascular comorbidities are considered a high-risk group. Further, life expectancy in dialysis patients is considerably lower than their counterparts who are not receiving dialysis, despite improvements in dialysis access and care.

According to **Akram Kawsara, MD,** and colleagues, due to those risks and perceived futility of invasive interventions, dialysis patients may not receive standard-of-care life-saving therapies such as primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI). Previous studies of the use of pPCI in patients with dialysis have compared absolute mortality and adverse events in dialysis patients

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Using Race-Free Equations to Estimate GFR

To account for higher mean serum creatinine concentrations in Black versus non-Black individuals, previous studies have used a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with creatinine (alone or with cystatin C) and included a coefficient for race (Black vs non-Black). Results documented racial differences in the association of a low estimated glomerular filtration rate (eGFR) with the risk of kidney failure with replacement therapy (KFRT) and mortality. However, there have been challenges to the use of race in the estimation of GFR because race is a social and not a biologic construct and does not fully capture the diversity within versus between racial groups.

In 2021, a creatinine-based eGFR equation not incorporating race was developed by CKD-EPI. The equation was recommended by the National Kidney Foundation–American Society of Nephrology (NKF-ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease for use in clinical laboratories.

At a given eGFR, individuals who are Black have higher rates of mortality and KFRT compared with non-Black individuals. There are few data available on whether the equations without race preserve racial difference in the risk of mortality and KFRT at a given eGFR.

Orlando M. Gutiérrez, MD, MMSc, and colleagues conducted a retrospective individual-level data analysis to examine whether eGFR equations with and without race and cystatin C document racial differences in the risk of KFRT and mortality in populations including Black and non-Black participants. Results were reported online

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Are All HIF-PHIs Being Developed for CKD Anemia Safe?

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The discovery of the HIF pathway and the identification of key steps in the oxygen sensing apparatus has led to the development of agents that stimulate endogenous erythropoietin synthesis. In the United States there are three agents: roxadustat, vadadustat, and daprodustat that are in a race to become the first approved oral therapy for the treatment of chronic kidney disease (CKD) anemia. Of the three, only daprodustat is currently in active review by the US FDA. The other two, roxadustat and vadadustat, have both been declined approval by the FDA due to safety concerns that range from an excess of thromboembolic events in non-dialysis CKD patients treated with roxadustat to a major cardiovascular adverse event (MACE) signal with vadadustat in non-dialysis CKD patients. (Full disclosure: I am the principal investigator of the ASCEND [daprodustat] clinical trials program.)

The failure to receive approval for the roxadustat and vadadustat programs prompts the following question: will the FDA lump these concerns with roxadustat and vadadustat together with other agents coming to the FDA for review? Or will the FDA take a more "splitter" view and accept that differences in how the trials were conducted and/or accept that pharmacologic differences between the different PHI drugs merit a more individualized approach in the approval process? Charles Darwin is credited with the concept of lumping versus splitting,[1] but it is as relevant for the HIF-PHI approval process as it was for Darwin.

For sure, all the HIF-PHIs are potent prolyl hydroxylase domain (PHD) inhibitors that are orally bioavailable small-molecule compounds.[2,3] In general, many HIF-PHIs have a common moiety containing glycinamide with a carboxylic group at the terminal. They are all potent inhibitors of all three HIF prolyl hydroxylase isozymes, PHD1, PHD2, and PHD3. And they are all mostly metabolized by the liver. HIF-PHI phase 1 through phase 4 clinical trials have demonstrated that by stimulating endogenous erythropoietin they are all as good as conventional erythropoiesis stimulating agents (ESAs) at correcting hemoglobin.

Looking at differences in the trials and the structural aspects of the molecules requires some assumptions. For example, to explain a significantly higher risk of MACE in patients randomized to vadadustat as compared with darbepoetin as reported in the non-dialysis CKD trial PRO$_2$TECT study,[4] the observation that vadadustat increases the risk of MACE in non-US but not in US patients requires one to accept that patient factors might contribute to the differential higher MACE risk in vadadustat treated patients. Likewise, with respect to roxadustat, the higher rate of thrombovenous embolic events among patients randomized to roxadustat compared with placebo could be explained by a dosing protocol that used higher doses of roxadustat.[5] If this assumption is correct, the higher risk is explained by a protocol-driven higher rate of rise of hemoglobin in the roxadustat arm, causing the higher risk of thrombovenous embolism in this arm.

Suggesting that pharmacologic differences between HIF-PHIs might explain the disparate safety signals observed with HIF-PHIs may have some validity because these agents are *different*. HIF-PHIs differ in their half-life, metabolism, and excretion (TABLE 1). As well, the pattern of inhibition of the three PHD targets differ—roxadustat targets all three PHDs equally whereas vadadustat and daprodustat preferentially target PHD3.[6] The three HIF-PHI small molecule compounds also differ structurally (FIGURE 1) and in how they are metabolized. For example, daprodustat has sp3 rich cyclohexyl ring leading to the formation of several polyoxygenated metabolites mediated by CYP2C8 and secondarily by CYP3A4.[7] Vadadustat,

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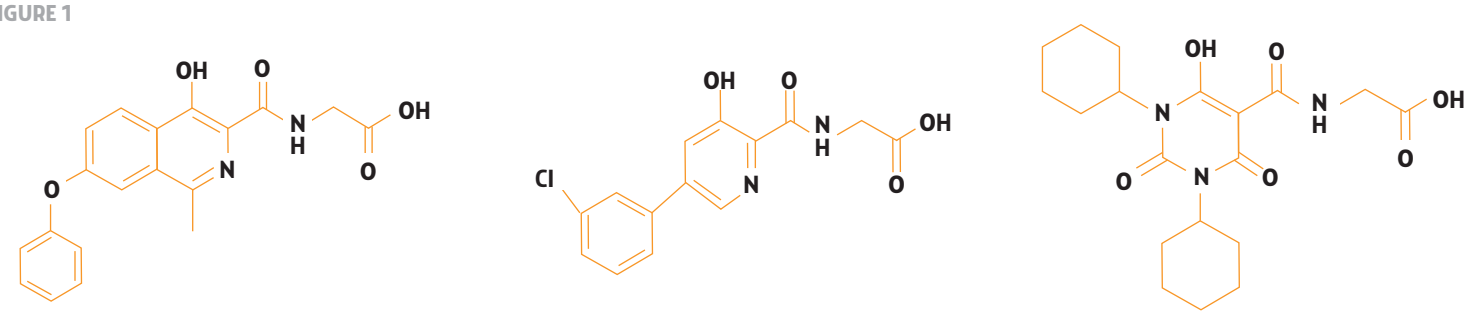
TABLE 1

Attributes	Daprodustat	Vadadustat	Roxadustat
Half-life	Short ($T_{1/2}$=1.5-4hr)	Short ($T_{1/2}$ ~5-7 hr)	Long ($T_{1/2}$ ~12-19 hr)
Metabolism	Hydroxylation, active metabolite	Glucuronidation, inactive metabolite	Unknown, presumed inactive metabolite
Excretion	Mostly liver metabolism	Liver metabolism + renal excretion	Primarily liver (?)
Tissue Distribution (rodent)	Broad distribution (liver, kidney, lung, BM)	Unknown	Unknown
Dosing	1 mg-12 mg (QD), 6 mg-48 mg TIW	150-400 mg (QD or TIW)	60-300 mg (QD or TIW)

FIGURE 1



on the other hand, forms GSH-adducts during metabolism. Studies have shown that GSH-adducts induce reactive metabolite formation that can be associated with drug-induced liver, skin, and hematopoietic toxicity of many drugs leading to clinical toxicities.[8] These differences in pharmacology do impact clinical use. For example, daprodustat has a drug-drug interaction with gemfibrazole.[9]

So, back to Charles Darwin and the concept of lumping versus splitting: my take on this is that while it may be convenient to lump all the individual HIF-PHIs together when thinking about approval, it may be too simplistic an approach. Rather, individual differences in study design or in pharmacologic aspects support a more individualized approach, ie, being a "splitter." ■

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versus nondialysis patients, rather than comparing the differential impact of pPCI in those populations (the treatment effect).

Dr. Kawsara et al conducted a retrospective cohort study to examine the relative benefit of pPCI (the pPCI treatment effect) in patients differing by dialysis status. The study utilized data from the National Inpatient Sample (2016-2018). Results were reported in the *American Journal of Kidney Diseases* [2022;79(6):832-840].

The primary study exposure was PCI. Confounders included dialysis status, demographics, insurance status, household income, comorbidities, and the elective nature of the admission. The primary outcome of interest was in-hospital mortality. Secondary outcomes included stroke, acute kidney injury (AKI), new requirement for dialysis, vascular complications, gastrointestinal bleeding, blood transfusion, mechanical ventilation, palliative care, home discharge, and transfer to a skilled nursing facility. The researchers also compared the length of stay and cost between dialysis and nondialysis patients with and without pPCI.

Propensity score matching was used to estimate the average treatment effect (ATE) of PCI in each group (dialysis or nondialysis). Separately within each group, a logistic regression model was used to predict the probability of receiving pPCI for each hospitalization, using several covariates (age, sex, race, insurance [Medicaid/Medicare], household income, hypertension, diabetes, heart failure, atrial fibrillation, peripheral vascular disease, prior stroke, prior sternotomy, conduction disorder, anemia, liver disease, obesity, malignancy, dementia, and elective admission status).

The study population included hospitalized adult (≥18 years of age) patients with a primary diagnosis of STEMI using *International Classification of Diseases, Tenth Clinical Modification* codes. Patients were excluded if they were coded to have STEMI as a secondary diagnosis. Patients transferred to another hospital were also excluded.

The final cohort included 413,500 weighted STEMI hospitalizations; of those, 1.07% (n=4220) involved patients receiving dialysis. In the nondialysis group, 326,735 PCI hospitalizations were matched to 325,955 non-PCI hospitalizations. In the dialysis group, 2420 PCI hospitalizations were matched to 2420 non-PCI hospitalization. Patients in the dialysis cohort were older (65.2 vs 63.4 years; *P*<.001), had a higher proportion of women (42.4% vs 30.6%; *P*<.001), had a lower proportion of White patients (41.1% vs 71.7%; *P*<.001), and had a higher prevalence of cardiac and noncardiac comorbidities.

Patients on dialysis were less likely to undergo standard-of-care procedures for STEMI, including coronary angiography (73.1% vs 85.4%; *P*<.001; adjusted odds ratio [OR], 0.63; 95% CI, 0.51-0.77; *P*<.001) and pPCI (57.5% vs 79.8%; *P*<.001; adjusted OR, 0.58; 95% CI, 0.50-0.68; *P*<.001). While infrequent, utilization of bare metal stent and bypass surgery was similar in both groups. Mechanical circulatory support use was higher in the dialysis group (12.8% vs 9.4%; *P*<.001).

In both the dialysis and nondialysis group, patients who underwent pPCI were younger and more likely to be treated at large or teaching hospitals. There was modest difference in most cardiovascular comorbidities between pPCI patients and non-pPCI patients; noncardiovascular comorbidities were more frequent among those who did not undergo pPCI.

In-hospital mortality was lower in patients who underwent pPCI compared with those who did not undergo pPCI. In the dialysis cohort, in-hospital mortality was 15.7% with pPCI versus 27.1% without pPCI (*P*<.001); in the cohort not receiving dialysis, in-hospital mortality was 5.0% with pPCI versus 17.4% without pPCI (*P*<.001). Major complications were more common in the non-pPCI patients only in the nondialysis group.

There were no statistically significant differences between pPCI and no pPCI regarding cardiogenic shock, stroke, vascular complications, gastrointestinal bleeding, blood transfusion, or mechanical ventilation in patients receiving dialysis. Those who underwent pPCI were more often discharged home than to a rehabilitation skilled nursing facility in both groups.

There were no significant differences in the ATE of pPCI on the primary end point of in-hospital mortality between the group not receiving dialysis (ATE, –8.2%; 95% CI, –8.8% to –7.5%; *P*<.001) and the group receiving dialysis (ATE, –8.6%; 95% CI, –15.6% to –1.6%; *P*=.02).

In the group not receiving dialysis, patients who had pPCI had shorter median hospital stays (2 vs 3 days; *P*<.001) but higher median costs ($21,125 vs $13,901; *P*<.001). After risk adjustment, the length of stay was not significantly different, but the costs remained higher with the pPCI group. In the group receiving dialysis, patients who had pPCI had longer median stays (4 vs 3 days; *P*<.001) and higher median costs ($28,410 vs $13,950; *P*<.001). Following risk adjustment, length of stay remained longer and costs remained higher in the pPCI group.

There were some limitations to the study findings cited by the authors, including the use of administrative data that may be subject to coding errors, the lack of pharmacotherapy data, the lack of information on laboratory data or long-term outcomes, the possibility of residual confounders, and the wide confidence intervals in the dialysis group.

In conclusion, the researchers said, "Patients receiving maintenance dialysis are less likely to receive pPCI for STEMI than patients not receiving dialysis, despite a comparable effect of pPCI on in-hospital morbidity and mortality in both groups. Further studies are needed to optimize STEMI care in the growing dialysis population." ■

TAKEAWAY POINTS

- Results of a study examining the relative benefit of primary percutaneous coronary intervention (pPCI) in patients on dialysis compared with nondialysis patients presenting with ST-elevation myocardial infarction (STEMI).
- In-hospital mortality was lower in dialysis and non-dialysis patients who underwent pPCI compared with those who did not undergo pPCI.
- The study findings suggested that pPCI was associated with comparable reductions in short-term mortality in patients regardless of dialysis status.

Using Race-Free Equations to Estimate GFR

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in *JAMA* [doi:10.1001/jama.2022.8801].

The analysis included data from five general population and three CKD US-based cohorts with serum creatinine, cystatin C, and follow-up for KFRT and mortality from 1988 to 2018. The exposures of interest were CKD-EPI equation with serum creatinine ($eGFR_{cr}$ with and without race) cystatin C ($eGFR_{cys}$ without race), or both markers ($eGFR_{cr\text{-}cys}$ without race).

The primary outcome of interest was the prevalence of decreased eGFR at baseline and hazard ratios (HR) of KFRT and mortality in Black versus non-Black participants. HRs were calculated with adjustment for age and sex. Demographic variables were age, sex, and/or race (ASR). Analyses were conducted within each cohort and with random-effect meta-analyses of the models.

The five population-based cohorts included 18,073 Black participants and 38,017 non-Black participants (2% Asian, 8% Hispanic, 89% non-Hispanic White, and 1% other race and ethnicity). The three CKD cohorts included 2700 Black participants and 321 non-Black participants (15% Hispanic, 78% non-Hispanic White, and 7% other race and ethnicity). The analyses included a total of 62,011 participants. Mean age was 63 years and 53% were women. There were no missing data for age, sex, or race.

The prevalence of eGFR <60 mL/min/1.73 m^2 (CKD stage G3+) in Black versus non-Black individuals was 11% versus 12% for eGFRcr(AS), 17% versus 18% for $eGFR_{cys}$(AS), and 13% versus 11% for $eGFR_{cr\text{-}cys}$(AS) compared with 15% versus 9% among Black versus non-Black individuals for $eGFR_{cr}$(AS). The Black relative to non-Black prevalence rates of eGFR <60 mL/min/1.73 m^2 were 0.98 (95% CI, 0.93-1.03) for $eGFR_{cr}$(ASR), 0.95 (95% CI, 0.91-0.98) for $eGFR_{cys}$(AS), 1.2 (95% CI, 1.2-1.3) for $eGFR_{cr\text{-}cys}$(AS), and 1.8 (95% CI, 1.7-1.8) for $eGFR_{cr}$(AS).

During mean follow-up of 13 years, 8% and 4% of Black and non-Black participants, respectively, experienced KFRT, and 34% and 39%, respectively, died. The 5-year estimated absolute risks of KFRT were 7.3% (95% CI, 6.9%-7.7%) in Black participants and 3.9% (95% CI, 3.7%-4.1%) in non-Black participants overall. For all equations, in both Black and non-Black populations, there was a significantly greater risk of KFRT at lower versus higher eGFR. After adjustment for age and sex, the risks of KFRT were significantly higher in Black participants compared with non-Black participants for $eGFR_{cr}$(ASR), $eGFR_{cys}$(AS), and $eGFR_{cr\text{-}cys}$(AS) across all eGFR levels.

The 5-year absolute risk differences for KRFT comparing Black with non-Black participants were 1.4% (95% CI, 0.2%-2.6%) for $eGFR_{cr}$ with race, 1.1% (95% CI, 0.2%-1.9%) for $eGFR_{cys}$, and 1.3% (95% CI, 0%-2.6%) for $eGFR_{cr\text{-}cys}$ versus 0.37% (95% CI, –0.32 to 1.05%) for $eGFR_{cr}$ without race. Patterns were similar for mortality.

The researchers cited some limitations to the study findings, including the lack of specific data on factors that may differ between racial groups (eg, measures of social determinants of health), the possibility of unmeasured heterogeneity in methods of measurements across cohorts, insufficient numbers of participants from racial and ethnic groups other than Black and White

> Compared with non-Black participants, Black participants had a significantly higher risk of mortality at an eGFR of 60 mL/min/1.73 m^2 for nearly all estimates for $eGFR_{cr}$(age, sex, race [ASR]), $eGFR_{cys}$(AS), and $eGFR_{cr\text{-}cys}$(AS).

For all equations, there were associations between decreased eGFR and significantly higher age- and sex-adjusted risk for all-cause and cardiovascular mortality. Compared with non-Black participants, Black participants had a significantly higher risk of mortality at an eGFR of 60 mL/min/1.73 m^2 for nearly all estimates for $eGFR_{cr}$(ASR), eGFRcys(AS), and $eGFR_{cr\text{-}cys}$(AS).

There were associations between decreased eGFR and significantly greater risk for both outcomes for all equations. At an eGFR of 60 mL/min/1.73 m^2, the HRs for KFRT comparing Black with non-Black participants were 2.8 (95% CI, 1.6-4.9) for $eGFR_{cr}$ with race, 3.0 (95% CI, 1.5-5.8) for $eGFR_{cys}$, and 2.8 (95% CI, 1.4-5.4) for $eGFR_{cr\text{-}cys}$ versus 1.3 (95% CI, 0.8-2.1) for $eGFR_{cr}$ without race.

precluding comparison of outcomes across other race and ethnic groups, lack of data on measured GFR in some of the cohorts, and the study design addressing discrimination but not calibration.

In conclusion, the researchers said, "In this retrospective analysis of eight US cohorts including Black and non-Black individuals, the eGFR equation without race that included creatinine and cystatin C, but not the eGFR equation without race that included creatinine without cystatin C, demonstrated racial differences in the risk of KFRT and mortality throughout the range of eGFR. The $eGFR_{cr\text{-}cys}$ equation may be preferable to the $eGFR_{cr}$ equation without race for assessing racial differences in the risk of KFRT and mortality associated with low eGFR." ■

TAKEAWAY POINTS

- Results of an analysis assessing whether estimated glomerular filtration rate (eGFR) equations with and without race and cystatin C altered risk estimates for kidney failure with replacement therapy (KFRT) and mortality for Black versus non-Black participants.
- There was a relationship between decreased eGFR and higher risk for all equations and within both racial groups.
- The eGFR equation including both creatinine and cystatin c, but not the equation including creatinine without cystatin C, yielded racial differences in the risks of KFRT and mortality.

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

Single Port Robotic Transplantation Versus Standard Open Transplantation

M. Eltmamy and colleagues at the Glickman Urological & Kidney Institute at the Cleveland Clinic, Cleveland, Ohio, conducted an analysis to compare outcomes of the initial series of patients who underwent single port (SP) robotic kidney transplantation with standard open kidney transplantation. Results were reported during a presentation at the 2022 American Transplant Congress in an presentation titled *Single Port Robotic Kidney Transplantation: Comparison of Outcomes with Standard Open Kidney Transplantation*.

The review utilized the clinic's institutional review board approved databases to compare a prospective cohort of 12 consecutive patients who underwent SP robotic kidney transplantation from October 2019 to October 2021 with a retrospective cohort of 12 matched patients who had open kidney transplantation. Patients were matched for donor type, Kidney Donor Profile Index in recipients of deceased-donor transplants, recipient age, and history of diabetes. The T-test was used for the comparison of normal data and the "N-1" Chi-squared test was used to compare percentages.

Age at transplantation was 55.04 years in the SP kidney transplant group and 55.50 in the open kidney transplant group, and body mass index was 29.95 kg/m^2 in the SP group and 30.38 kg/m^2 in the open group. Nine of the transplants in each group were living-donor transplants. No patient in the SD group had delayed graft function (DGF); one in the open group had DGF.

No patient in the SP arm was converted to open surgery. There were no intra- or postoperative complications ≥*Clavien* grade 2 in either group. The mean inpatient morphine milligram equivalents score was 44.91 in the SP group and 149.16 in the open group (P=.0091). In both arms, 12-month graft and patient survival was 100%. There were no significant differences between the two groups in mean creatinine level at 1, 6, and 12 months.

In conclusion, the authors said, "Single port robotic kidney transplantation is associated with similar safety and allograft function compared with open kidney transplantation with the added benefit of less postoperative narcotics requirement. Larger series are required in this setting."

Source: Eltmamy M, Kaviani A, Lin Y, et al. Single port robotic kidney transplantation: Comparison of outcomes with standard open kidney transplantation. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 288), Boston, Massachusetts, June 6, 2022.

Racism in Health Care

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veterans with CKD who received care at the Corporal Michael Crescenz VA Medical Center in Philadelphia, Pennsylvania. The interviews were conducted from October 2018 to September 2019. Applied thematic analysis was used to analyze the interview transcripts.

All participants had a diagnosis of CKD and were (1) not dependent on dialysis (stage 3 [moderate; glomerular filtration rate (GFR), 30-59 mL/min/1.73 m^2] or stage 4 [severe; GFR, 15-29 mL/min/1.73 m^2] kidney disease); (2) dependent on dialysis (stage 5, ESKD; GFR <15 mL/min/1.73 m^2 kidney disease); or (3) post-transplant (stage 5 kidney disease). The study interviews were conducted before or after appointments or during dialysis.

The study was framed by an a priori conceptual framework using *The House that Racism Built* by Williams et al that established three evidence-based pathways of racism directly associated with health and health care: cultural racism; institutional racism; and individual discrimination. According to the authors, individual discrimination can have "consequences for health through psychological, biological, and behavioral factors; health care use; and individual and collective factors."

Mean age of the 36 participants was 66.0 years and 97.2% (n=35) were male. Nineteen participants were married. Mean duration of military service was 8.0 years. Of the 36 participants, 41.7% (n=15) were not dependent on dialysis and 27.8% reported having a immediate family member (parent or sibling) with CKD. The most common comorbidity was hypertension (25.0% [n=9]).

The researchers identified four themes across all responses: (1) association of racism with emotional and physical stress; (2) distrust in the health care system and hypervigilance; (3) bottling up of feelings and maladaptive behavior; and (4) positive coping strategies.

The participants reported a sense of hopelessness related to psychological reactions to racism, as well as feelings of deep anger and resentment derived from a sense of hurt and betrayal. Most of the participants believed racism had an impact on their physical health, manifesting as headaches and high blood pressure.

Addressing distrust in the health care system, participants said they felt they always had to prove themselves to medical staff and clinicians. They described feeling dismissed in the dialysis clinic, creating a need to carefully navigate those settings and to act as their own advocate. In some cases, participants reported leaving the VA health care system or skipping appointments to avoid experiencing racism.

Participants said their immediate behavioral reactions to racism often began with ignoring the racist event. They said that downplaying the initial encounter with discrimination and the subsequent stress helped to numb their ability to internalize the experience. Another maladaptive behavior was the need to be hypervigilant to perceived social compliance, including the need to be perfect.

When asked about positive coping strategies, participants described a variety of strategies for managing the stress associated with racism. Positive coping strategies included community involvement, mentoring young adults, and wanting to influence and help the next generation. Another coping mechanism mentioned by the participants was faith, in the form of family prayer or church attendance. Family was also a fundamental source of support; spending time with grandchildren was described as a source of joy. Talking and sharing stressful events with family was also a major source of support.

The researchers cited some limitations to the study findings, including the high percentage of male participants, limiting the participants to individuals who use the VA for their health care, collecting data at a single center only, and the assumption in the questions that participants experienced racism and that racism is associated with health.

In conclusion, the authors said, "In this qualitative study, Black veterans with CKD described health care experiences that were retraumatizing and further worsened their psychological and physical responses to racism, potentially exacerbating CKD symptoms. Implementing care models that acknowledge racism as traumatic experience is one way the VA and other health care institutions can lead the nation in developing antiracist health care." ■

TAKEAWAY POINTS

- Researchers conducted a study to examine health care experiences of Black US veterans with chronic kidney disease (CKD) to identify and examine racial discrimination encountered by that patient population.
- In the single-center study, 36 Black veterans with CKD described feeling angry and resentful and dealing with stress as a result of encounters with racism; some said they did not trust the health care system.
- The findings provided an opportunity to train health care professionals to implement a trauma-informed approach to care to address stress and trauma based on racism.

Nephrology Referral Based on Kidney Failure Risk or Laboratory Values

There are national and international guidelines to identify patients who may benefit from referral to nephrology care to delay progression of chronic kidney disease (CKD), manage complications associated with CKD, and prepare for kidney failure. Timely referral to nephrology care depends on recognition of CKD, facilitated by automated reporting of estimated glomerular filtration rate (eGFR) by laboratories.

Guidelines from Kidney Disease Improving Global Outcomes and other organizations include level of eGFR as well as additional indications for referral that can be identified through laboratory testing (eg, albuminuria level and rapid disease progression). However, according to **Vishal Duggal, MD,** and colleagues, despite the availability of guidelines to facilitate recognition of CKD, there has been little progress in reducing the burden of CKD or improving preparation among patients who progress to kidney failure.

The researchers conducted a retrospective observational cohort study to examine whether patterns of nephrology referral reflect current clinical practice guidelines and to estimate the change in referral volume if referrals were based on the estimated risk of kidney failure. Results were reported in the *American Journal of Kidney Diseases* [2022;79(3):347-353].

The study cohort included 399,644 veterans being cared for in the US Veterans Health Administration of the Department of Veterans Affairs (VA) with CKD from October 1, 2015, through September 30, 2016. The study exposure was laboratory referral based on VA/Department of Defense guidelines, categories of predicted risk of kidney failure using the Kidney Failure Rusk Equation, and the combination of laboratory referral criteria and predicted risk. The primary outcome of interest was the number of patients identified for referral to nephrology care.

The researchers evaluated the number of patients who were referred to nephrology care and their predicted 2-year risk for kidney failure. For each exposure, they estimated the number of patients who would be identified for referral. Referral was defined as either the placement of a consultation order or a completed visit with a nephrologist between October 1, 2015, and September 30, 2016. Kidney failure was defined as the initiation of maintenance dialysis or receipt of kidney transplantation; data on kidney failure were obtained with a linkage to the US Renal Data System. Patients were followed for 2 years following the index date.

Among patients who met each referral indication, the number of patients who were referred, the predicted 2-year risk for kidney failure, and the frequency of progression to kidney failure over 2 years were evaluated. Among all patients with CKD who had not received nephrology care in the prior year, the study estimated the maximum referral volume that would be generated it VA providers referred all patients in each of three scenarios: (1) patients who met laboratory-based indications for nephrology referral; (2) patients who met a specified kidney failure risk threshold in addition to laboratory-based indications; and (3) patients who met a specified kidney failure risk threshold alone. Two-year kidney failure risk thresholds of 1%, 2%, 3%, 5%, and 10% were evaluated.

Of the 399,644 patients under VA primary care with CKD, 37,560 had visited a nephrologist in the previous year, and 362,084 had not. Of those who had not visited a nephrologist in the previous year, 18.3% (n=66,276) met an indication for referral, and 17.7% (n=11,752) of those were referred to nephrology care in the following year. A total of 295,808 patients did not meet a referral indication, and 10,015 (3.4%) were referred. The median 2-year predicted risk for kidney failure was 1.5%.

The majority of patients meeting an indication for referral did so based on the criterion of eGFR <30 mL/min/1.73 m^2. Patients who were referred were more likely to meet multiple potential indications for referral, particularly eGFR <30 mL/min/1.73 m^2 and heavy proteinuria. The highest predicted risk of kidney failure at 2 years was seen in patients who met the indication of heavy proteinuria with diabetes indication or the eGFR <30 mL/min/1.73 m^2 indication. The lowest predicted 2-year risk for kidney failure was associated with the rapid eGFR decline indication.

When using a more stringent definition for rapid decline in eGFR, 50,690 patients met an indication for referral, including 30.9% who met the rapid eGFR decline indication. The median predicted risk of kidney failure was 0.6% in those meeting an indication for referral using the stringent definition of rapid eGFR decline. The rapid eGFR decline indication had the lowest predicted risk of kidney failure, similar to the primary analysis.

Using both laboratory-based indication and the risk of kidney failure, among patients with computable kidney failure risk, approximately 57.7% had a value exceeding 1%. If referrals were restricted to patients with a predicted risk of ≥1% in addition to laboratory indications, the potential referral volume would be reduced from 66,276 to 38,229 patients.

Using the risk of kidney failure alone, we estimated that 72,948 patients would meet a 1% 2-year risk threshold, comparable to the number of patients meeting laboratory-based indications. Among all patients meeting the 1% 2-year risk threshold, the median 2-year predicted risk was 2.3%. If the threshold for referral were increase to 2%, an estimated 41,101 patients would be identified.

The researchers cited strengths and limitations to the study findings. Strengths included use of a national, integrated health care system that serves a large population of patients with CKD, and the use of a validated risk prediction tool. While the study did not account for all care outside of the VA, sensitivity analyses limited to patients eligible for Medicare suggested similar results. Limitations included the inability to determine the reasons for nephrology referral, or the extent to which increased referral volumes would affect wait times or clinical outcomes. Missing measurements of proteinuria were also cited as limitations. Finally, the analyses may not be generalizable to other health care systems.

In conclusion, the researchers said, "A significant proportion of patients identified by laboratory-based indications for nephrology referral have a predicted risk of kidney failure less than 1%. A referral system based on a 2-year kidney failure risk exceeding 1% would identify a similar number of patients while targeting those with higher risk for kidney failure. These findings may inform clinical decision support development to target nephrology referrals to patients most likely to benefit." ■

TAKEAWAY POINTS

- Results of a retrospective, observational cohort study to assess whether patterns of referral to nephrology care based on laboratory values reflect current clinical practice guidelines, and to estimate change in referral volume if referrals were based on the estimated risk of kidney failure.
- The study cohort included 399,644 veterans with chronic kidney disease treated in the Veterans Health Administration of the Department of Veterans Affairs between October 1, 2015, and September 30, 2016.
- Current laboratory-based guidelines for nephrology referral identify patients at low risk for progression of CKD; referral based on a 2-year kidney failure risk exceeding 1% would identify a similar number of patients but with a higher median risk of kidney failure.

Mortality Risk After an Episode of Acute Severe Hyperkalemia

Patients with comorbidities such as chronic kidney disease or congestive heart failure commonly experience hyperkalemia. Severe hyperkalemia is associated with increased risk of adverse clinical events including ventricular arrhythmias and sudden cardiac death. Previous studies have focused on the prognostic implications of chronic hyperkalemia. However, according to **José Luis Gorriz, MD,** and colleagues, there are few data available on the long-term clinical consequences following an episode of severe hyperkalemia.

The study was designed to examine the association between the trajectory of potassium measurements in patients with acute hyperkalemia and long-term all-cause mortality. Results were reported online in *Nephrology Dialysis Transplantation* [doi:10.1093/ndt/gfab003].

The retrospective observational study included patients with acute severe hyperkalemia, defined as potassium >6 mEq/L, without hemolysis. Eligible study patients presented to the emergency department (ED) of Doctor Peset University Hospital in Valencia, Spain, from January 2016 to March 2017. Comprehensive state-of-the-art regression models that can accommodate time-dependent exposure modeling were used to assess the multivariable-adjusted association of serum potassium with mortality.

During a median follow-up period of 17.3 months, there were 172 episodes of acute hyperkalemia in 160 patients in the ED. Mean age of the patients was 77 years, 47% were >80 years of age, 59% had non-dialysis CKD (estimated glomerular filtration rate, <60 mL/min/1.73 m^2), and 27.3% did not have renal dysfunction. Among the patients with CKD, the underlying cause of kidney disease was nephroangiosclerosis (28%), diabetic kidney disease (25%), interstitial disease (7%), glomerulonephritis (8%), polycystic kidney disease (3%), and other/unknown cause (29%).

Mean potassium level at presentation was 6.6 mEq/L; 76.7% of patients had potassium level between 6 and 7 mEq/L. Approximately one-quarter (23.3%) of the hyperkalemia episodes were life-threatening (potassium >7 mEq/L). Mean potassium level in the last measurement prior to the acute hyperkalemia episode was 4.8 mEq/L. Of the 160 patients, 72.7% (n=125) were hospitalized.

Most of the patients (84.3%) had one to four comorbidities, and 7.5% had more than four comorbidities. The most common comorbidities were CKD (71.2%), diabetes (56.9%), and hypertension (56.9%), followed by coronary heart disease (36.3%), congestive heart failure (35%), and cerebrovascular disease (12.5%).

In 107 episodes (67.7% of patients with electrocardiogram [ECG] reports in electronic health records), there were ECG alterations; of those, 44.9% presented at least one ECG alteration, primarily peaked T waves. Thirty-six percent of the patients were on chronic treatment with renin-angiotensin-aldosterone system inhibitors (RAASi), 28.5% were being treated with mineral receptor antagonists, and 53.4% received both treatments.

Only seven patients (4.1%) were receiving potassium-binding resins prior to the acute hyperkalemia episode; of those, three were receiving hemodialysis. Patients with better renal function were more likely to be treated with RAASi, loop-diuretics, and potassium-sparing diuretics.

Treatments for hyperkalemia received in the ED were dextrose fluid plus insulin (43%), intravenous (IV) loop diuretics (28.5%), inhaled salbutamol (26.7%), oral calcium polystyrene sulphonate (25%), IV sodium bicarbonate (25%), IV calcium gluconate (16.32%), hemodialysis (10.5%), and calcium polystyrene sulphonate enema (8.1%). Of the patients treated with hemodialysis, 61% had CKD stage 5 and were receiving dialysis prior to the acute hyperkalemia episode.

Potassium was measured at six time points: (1) prior to the severe hyperkalemia episode; (2) at the time of the episode; (3) at the time of discharge; (4) 30 days following discharge; (5) between 30 and 90 days following discharge; and (6) later than 90 days following discharge. The rates of hyperkalemia were higher in the ED and decreased throughout successive visits. Of the 786 potassium measurements at the different time points, 57.3% (n=451) were <5.5 mEq/L, 10.2% (n=80) were 5.5-6 mEq/L, 26.2% (n=206) were 6-7 mEq/L, and 6.4% (n=50) were >7 mEq/L.

Among the patients who were monitored during follow-up, 39.5% had recurrences of hyperkalemia (potassium >5.5mEq/L); 16% of those patients had one recurrence, 13.6% had two recurrences, and 9.9% had three recurrences. The recurrences occurred within the first month after discharge in 22.8%, between 30 and 60 days after discharge in 26.3%, and later than 90 days after discharge in 17.2% of patients with recurrences.

At the end of the median follow-up of 17.3 months, 42.5% (n=68) of the patients had died. Most of them died due to cardiovascular events (47.2%) or infection (23.5%). Other causes of death were liver-gastrointestinal (11.8%), malignancies (16.2%), and other (1.5%). Mean survival was 18 months; survival at 3, 6, 12, 18, and 24 months was 73%, 66%, 63%, 60%, and 55%, respectively.

Multivariate Cox proportional hazards models of death demonstrated that age, low serum sodium levels, absence of RAASi treatment before the episode of acute hyperkalemia, presence of ventricular tachycardia, and lack of routine laboratory follow-up after discharge were independent factors related to increased risk of mortality. For each year of age, the risk of mortality increased by 3%, RAASi treatment was associated with a 67% reduction in mortality risk, the presence of ventricular tachycardia was associated with a 12-fold increase in mortality risk, the performance of analytics at follow-up was associated with a 75% reduction in mortality risk, and each decrease of 1 mEq/L in serum sodium levels was related to an increase in the risk of death by 0.08%.

Previous potassium levels during an acute severe hyperkalemia episode were not predictors of mortality. Conversely, the post-discharge longitudinal trajectories of potassium were able to predict all-cause mortality (overall *P*=.0015). The effect of transitioning from hyperkalemia to normokalemia (potassium >5.5 mEq/L to potassium ≤5.5 mEq/L) following the acute episode was significant, and was inversely associated with the risk of mortality.

The researchers cited some limitations to the study findings, including the retrospective design that resulted in missing relevant clinical information, and the single-center design that possibly limits the generalizability of the findings to other centers.

In conclusion, the authors said, "Potassium levels prior to a severe hyperkalemia event do not predict mortality. Conversely, following an episode of acute severe hyperkalemia, serial kinetic of potassium trajectories predict the risk of death. Further evidence is needed to confirm these findings and clarify the optimal long-term management of these patients." ■

TAKEAWAY POINTS

- Results of a retrospective observational study to assess the long-term trajectory of potassium and the risk of mortality in patients with acute severe hyperkalemia (potassium >6 mEq/L).
- Following an episode of severe hyperkalemia, recurrent hyperkalemia was a frequent finding, particularly in the 6 months following discharge.
- Post-discharge longitudinal trajectories of potassium were predictors of all-cause mortality. The effect of transitioning from hyperkalemia to normokalemia after the acute episode was significant, and inversely associated with mortality risk.

Intensive Blood Pressure Treatment and Brain Perfusion in CKD

Approximately 25 million adults in the United States are affected by chronic kidney disease (CKD), characterized by a reduction in estimated glomerular filtration rate (GFR) or the presence of excess albumin in the urine. Individuals with CKD are at 2- to 7-fold increased risk for stroke and dementia; the risk varies by level of estimated GFR (eGFR) and albuminuria. There is a high prevalence of cerebral small-vessel ischemic disease in those with CKD, which is a major contributor to strike and dementia in that population.

Individuals with CKD also have a high prevalence of hypertension, which is a modifiable risk factor for stroke, dementia, and cerebral small-vessel ischemic disease in the general population. Previous cohort studies have identified a J-shaped association between blood pressure and stroke risk in participants with CKD. Other studies among patients on maintenance dialysis have demonstrated an association between blood pressure instability and white matter injury and cognitive impairment. Those observations have resulted in concerns about the safety of blood pressure treatment targets in the CKD population.

Manjula Kurella Tamura, MD, MPH, and colleagues conducted a neuroimaging substudy of a randomized trial to characterize the effect of intensive blood pressure treatment on global cerebral blood flow (CBF), white matter lesions (WMLs) volume, and total brain volume (TBV) according to eGFR and urinary albumin-creatinine ratio (UACR) at study entry. The researchers also sought to evaluate the independent association between baseline eGFR and UACR with longitudinal changes in cerebral perfusion and structure. Results were reported in the *American Journal of Kidney Diseases* [2022;79(5):677-687].

Print-only Content

The substudy included participants in the SPRINT (Systolic Blood Pressure Intervention Trial) who underwent brain magnetic resonance imaging (MRI) studies. The presence of CKD was identified by eGFR and UACR. Participants were randomly assigned to intensive (systolic blood pressure <120 mm Hg) or standard (systolic blood pressure <140 mm Hg) blood pressure lowering. The MRI outcome measures were the 4-year change in global CBF, WML volume, and TBV.

Of the 718 participants who completed a baseline or follow-up MRI study that met quality control requirements, 716 had baseline eGFR and 690 had baseline UACR assessments. A total of 223 participants did not complete a follow-up scan, including 88 who were unwilling to participate, 32 who withdrew or were lost to follow-up, 32 who died, and 71 who had missing scans for other reasons. Those who did not have follow-up MRI had similar eGFR and higher UACR levels compared with participants who completed follow-up. Participants in the MRI substudy were well balanced by treatment arm in baseline characteristics. At baseline, 32.8% of participants (n=234) had an eGFR <60 mL/min/1.73 m^2 and 22.0% (n=151) had albuminuria.

Through the end of the active intervention phase of the trial, mean

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systolic blood pressure among those in the MRI substudy was 122.3 mm Hg in the intensive treatment group, compared with 135.2 mm Hg in the standard treatment group. There was no difference by eGFR in achieved systolic blood pressure in the intervention phase in either treatment group or by UACR in the standard group. However, in the intensive treatment group, systolic blood pressure was 4.6 mm Hg higher in the subgroup with UACR ≥30 mg/g than in those with UACR <30 mg/g.

Following the termination of the trial intervention, patients were managed by their primary care provider. During the transition period, mean systolic blood pressure increased in both groups. The between-group difference in systolic blood pressure was sustained across eGFR and UACR strata.

Among participants with eGFR <60 mL/min/1.73 m^2, the effects of intensive versus standard blood pressure treatment on change in global CBF, WMLs, and TBV were 3.38 (95% CI, 0.32 to 6.44) mL/100 g/min, –0.06 (95% CI, –0.16 to 0.04) cm^3 (inverse hyperbolic sine-transformed), and –3.8 (95% CI, –8.3 to 0.7) cm^3, respectively.

Among those with UACR >30 mg/g, the effects of intensive versus standard blood pressure treatment on change in global CBF, WMLs, and TBV were 1.91 (95% CI, –3.01 to

6.82) mL/100 g/min, 0.003 (95% CI, −0.13 to 0.13) cm^3 (inverse hyperbolic sine-transformed), and −7.0 (95% CI, −13.3 to −0.3) cm^3, respectively.

The overall treatment effects on CBF and TBV were not modified by baseline eGFR or UACR. However, the effect on WMLs was attenuated in participants with albuminuria (*P*=.04 for interaction). In models adjusted for blood pressure treatment group, intracranial volume, age, sex, race, history of cardiovascular disease, smoking, MRI scanner, and baseline MRI value, there was no significant association between baseline eGFR and longitudinal changes in global CBF, WML volume, or TBV. There was also no significant association between longitudinal changes in global CBF, WML volume, or TBV and baseline UACR.

The overall treatment effects on CBF and TBV were not modified by baseline eGFR or UACR. However, the effect on WMLs was attenuated in participants with albuminuria (*P*=.04 for interaction).

Citing limitations to the study findings, the researchers noted the MRI substudy sample being less than 10% of SPRINT participants and perhaps not representative of the overall trial population. Other limitations included the lower than expected MRI completion rate, and the use of multiple MRI scanners as a result of the multisite design that may have increased variability in measurements. In addition, the study was designed to examine longer-term changes in cerebral perfusion and structure and did not capture short-term changes that may have occurred during intensification of blood pressure treatment.

In summary, the researchers said, "Among adults with hypertension, intensive versus standard blood pressure treatment increased global CBF and led to a small decrease in TBV; these effects were similar in participants with primarily mild to moderate CKD. There was no evidence that intensive treatment accelerated the accumulation of WMLs. The results support the safety of more intensive blood pressure treatment targets on brain health in the high-risk CKD population." ■

TAKEAWAY POINTS

- Researchers reported results of a substudy of participants in SPRINT (Systolic Blood Pressure Intervention Trial) to evaluate the effects of intensive hypertension treatment on cerebral perfusion and structure in patients with and without CKD.
- In patients with primarily early kidney disease, intensive versus standard blood pressure treatment did not appear to have a detrimental effect on brain perfusion or structure.
- The findings support the safety of intensive blood pressure targets on brain health in patients with early kidney disease.

Conference Coverage

Boston, Massachusetts | June 4-8, 2022

AMERICAN TRANSPLANT CONGRESS 2022

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.

Conversion to Belatacept in Pediatric Transplant Recipients

Belatacept (CTLA-Ig) is a selective co-stimulation blocker. Compared with regimens based on calcineurin inhibitors (CNI), belatacept is associated with reduced de novo donor specific antibodies (dnDSA), improved renal function, and increased allograft survival in adult transplant recipients. The use of belatacept in older children and young adults is limited.

During a poster session at the 2022 American Transplant Congress, **C. Duneton** and colleagues in the pediatric nephrology department at the Robert Debré Hospital, APHP, Paris, France, reported outcomes for pediatric transplant patients who were converted to belatacept. The poster was titled *Outcomes After Conversion to Belatacept in Pediatric Kidney Transplantation.*

The report included 13 patients who were converted to belatacept therapy between May 2018 and January 2021. Eight patients received an induction with basiliximab and five with antithymocyte globulin. Maintenance immunosuppression included CNI, antimetabolite, and steroids. Patients' viral status was monitored monthly (Epstein-Barr virus and cytomegalovirus). Prior to conversion, allograft biopsy was performed; it was repeated 6 months after conversion.

The first five belatacept injections were administered at 5m/kg/dose every 2 weeks and then monthly. At each infusion, CNI doses were decreased by 25% and stopped after 2 months. At CNI withdrawal, antimetabolite doses were increased. At the time of conversion, six of the 13 patients were steroid free.

Median age at conversion was 17.6 years and median time since transplant was 3.9 years. In 11 patients, conversion to belatacept was based on medical need for long-term avoidance of CNI (side effect or histologic evidence of CNI toxicity) and in two patients, conversion was indicated to improve adherence.

By a median of 42 days after initiating belatacept, CNI was withdrawn in all patients. Over a median follow-up of 12.1 months, glomerular filtration rate was stable or improved. Rejection episodes were observed in four of the 13 patients: two patients had chronic active t-cell mediated rejection (TCMR) 1A, one had mixed acute rejection (TCMR IB and antibody-mediated rejection (AMB]), and one had ABMR (both were donor specific antibody negative).

Among the four patients with rejection episodes, two had prior history of rejection (with normal pre-belatacept biopsies), one showed minimal interstitial inflammation without tubulitis (and was off steroids) prior to starting belatacept, and one had been converted for adherence problems, which subsequently persisted. In all four patients, the rejection episodes demonstrated good evolution after treatment; CNI was reintroduced in two of the four.

In all of the other patients, there were no severe viral complications or development of dnDSA. Four patients had pre-existing DSA that remained stable.

In conclusion, the authors said, "Selected pediatric kidney recipients may benefit from long-term CNI toxicity avoidance, but selection criteria need to be refined to avoid rejection episodes under co-stimulation blockade."

Source: Duneton C, Maison A, Cheyssac E, Dahdouh H, Baudouin V, Hogan J. Outcomes after conversion to belatacept in pediatric kidney transplantation. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 828), Boston, Massachusetts, June 4, 2022.

Donor-Derived Cell-Free DNA and Acute Rejection in Pediatric Transplantation

Donor-derived cell-free DNA (dd-cfDNA) is a dynamic plasma biomarker for allograft rejection in transplant recipients. According to **K. A. Klein** and colleagues, there are limited data on dd-cfDNA in pediatric kidney transplant recipients and few reports on dd-cfDNA behavior throughout an episode of rejection, from time of biopsy to completion of therapy.

The researchers conducted a study designed to examine changes in dd-cfDNA prior to biopsy-proven acute rejection (BPAR) and following treatment of rejection. Results were reported during an oral presentation at the 2022 American Transplant Congress in a presentation titled *Surveillance of Donor-Derived Cell-Free DNA Throughout Treatment of Acute Rejection in Pediatric Renal Transplant Recipients.*

Prior to and at the time of biopsy as well as prior to each treatment throughout the BPAR therapy course, dd-cfDNA (AlloSure®) levels were drawn. Surveillance and for-cause biopsies were performed with dd-cfDNA levels collected per institutional protocol.

A total of 42 patients had dd-cfDNA testing and biopsy. Thirteen patients had more than one biopsy: 56 biopsies total, 37 for cause and 19 surveillance. There were 32 episodes of BPAR in 23 patients (21 T-cell mediated rejection [TCMR] or borderline; 11 antibody-mediated rejection [AMR] or mixed). In the overall cohort, receiver operator curves for dd-cfDNA predicted BPAR (AUC, 0.795) and de novo donor-specific antibodies (DSA) (AUC, 0.75).

Complete data were available for 23 biopsies with BPAR and 15 biopsies without BPAR. In the cohort with BPAR, 13 of the 23 episodes had dd-cfDNA >1% at biopsy, and eight of those patients had dd-cfDNA decline to <1% after treatment. There was no significant difference in median change in patients with TCMR and in patients with AMR (-0.2% vs -0.94%; P=.77). Creatinine clearance (CrCl) in the BPAR group was not significantly different pre- and post-treatment (median 55.5 vs 59.1; P=.80).

Two patients had repeat biopsies for persistently high dd-cfDNA following rejection treatment: one had persistent TCMR and dd-cfDNA levels decreased to <1% after repeat treatment; the other patient showed persistent biopsy-proven AMR and dd-cfDNA levels remained >1% despite ongoing treatment.

In conclusion, the researchers said, "Consistent with previous studies, all pediatric renal transplant recipients with dd-cfDNA >1% had BPAR that correlated with de novo DSA development. Patients treated for BPAR demonstrated a significant dd-cfDNA decrease associated with stable CrCl. Persistently elevated dd-cfDNA levels suggest ongoing graft injury, indicating the need for re-evaluation and biopsy. Ongoing investigation is warranted to support dd-cfDNA utility in the management of acute rejection for pediatric renal transplant recipients."

Source: Klein KA, Kincaide EL, Fei M, Bell AM, Arar MY, Ranch D. Surveillance of donor-derived cell-free DNA throughout treatment of acute rejection in pediatric renal transplant recipients. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 373), Boston, Massachusetts, June 6, 2022.

HLA Mismatch in First Deceased-Donor Kidney Transplant and Outcomes

Analysis of current data in the United States suggests that Black patients awaiting kidney re-transplantation are more likely to be highly sensitized compared with other races. A possible contributor may be the degree of human leukocyte antigen (HLA) mismatching in the first transplant.

K. Atiemo at Tulane University, New Orleans, Louisiana, conducted a study to assess the association between race, number of HLA mismatches, and death-censored graft failure in a contemporary era. Results were reported during an oral presentation at the 2022 American Transplant Congress in a presentation titled *Does Black Race Modify the Risk of Transplant Failure Associated With HLA Mismatch in First Adult Kidney Allografts From Deceased Donors?*

The study utilized data from the United Network for Organ Sharing to identify first deceased-donor kidney transplants between January 1, 2015, and June 1, 2019, with follow-up to September 1. 2020. Recipients were classified by number of HLA mismatches and race (non-Hispanic White vs Black). The analysis utilized Cox multivariate regression, including terms for race and number of HLA mismatches and adjustments for age, sex, cause of renal failure, education level, insurance status, employment status, body mass index, kidney donor risk index, and cold ischemia time.

A total of 33,234 adult kidney transplant recipients met inclusion criteria. Of those, 49% (n=16,400) were non-Hispanic White and 51% (n=16,834) were Black. Compared with the non-Hispanic White patients, Black patients had greater proportions of HLA mismatch.

Kaplan Meier estimates of death-censored graft failure were greater for Black patients, For non-Hispanic White patients, graft failure at 1 year, 3 years, and 5 years, was 3%, 6%, and 12%, respectively. For Black patients, the corresponding rates were 3%, 9%, and 18%, respectively (P=.001).

With zero mismatches as reference, there was increased risk of graft failure for five HLA mismatches (hazard ratio [HR], 1.41; 95% CI, 1.08-1.85), six HLA mismatches (HR, 1.38; 95% CI, 1.04-1.83), and Black race (HR, 1.26; 95% CI, 1.15-1.39). When the effect modification was assessed, Black race did not modify the effect of HLA mismatches on graft failure.

In summary, the author said, "While an increasing number of HLA mismatches and Black race are associated with a higher risk of graft failure, for each number of HLA mismatches (zero to six), Blacks do not have poorer outcomes compared to non-Hispanic Whites. The greater proportion of highly sensitized Black patients awaiting re-transplantation is more likely due to a greater proportion having been transplanted with greater mismatch than a unique effect specifically related to race."

Source: Atiemo K. Does Black race modify the risk of transplant failure associated with HLA mismatch in first adult kidney allografts from deceased donors? Abstract of a presentation at the 2022 American Transplant Congress (Abstract 509), Boston, Massachusetts, June 7, 2022.

Conference Coverage

Boston, Massachusetts | June 4-8, 2022

Risk Factors for 30-Day Readmission After Kidney Transplant

Following kidney transplantation, the 30-day readmission rate serves as a surrogate metric of quality of care and mortality following transplantation. In the general population, diabetes mellitus and variability in blood glucose are independent risk factors for 30-day readmission. It is unknown whether those metrics apply among kidney transplant recipients.

H. Chakkera and colleagues conducted a retrospective study to analyze the 30-day readmission rate among kidney transplant recipients at a single center between July 1, 2105, and December 31, 2018. The researchers sought to determine whether there were associations between diabetes mellitus prior to transplantation and variability in glucose measurements during hospitalization after kidney transplantation and hospital readmission within 30 days of discharge.

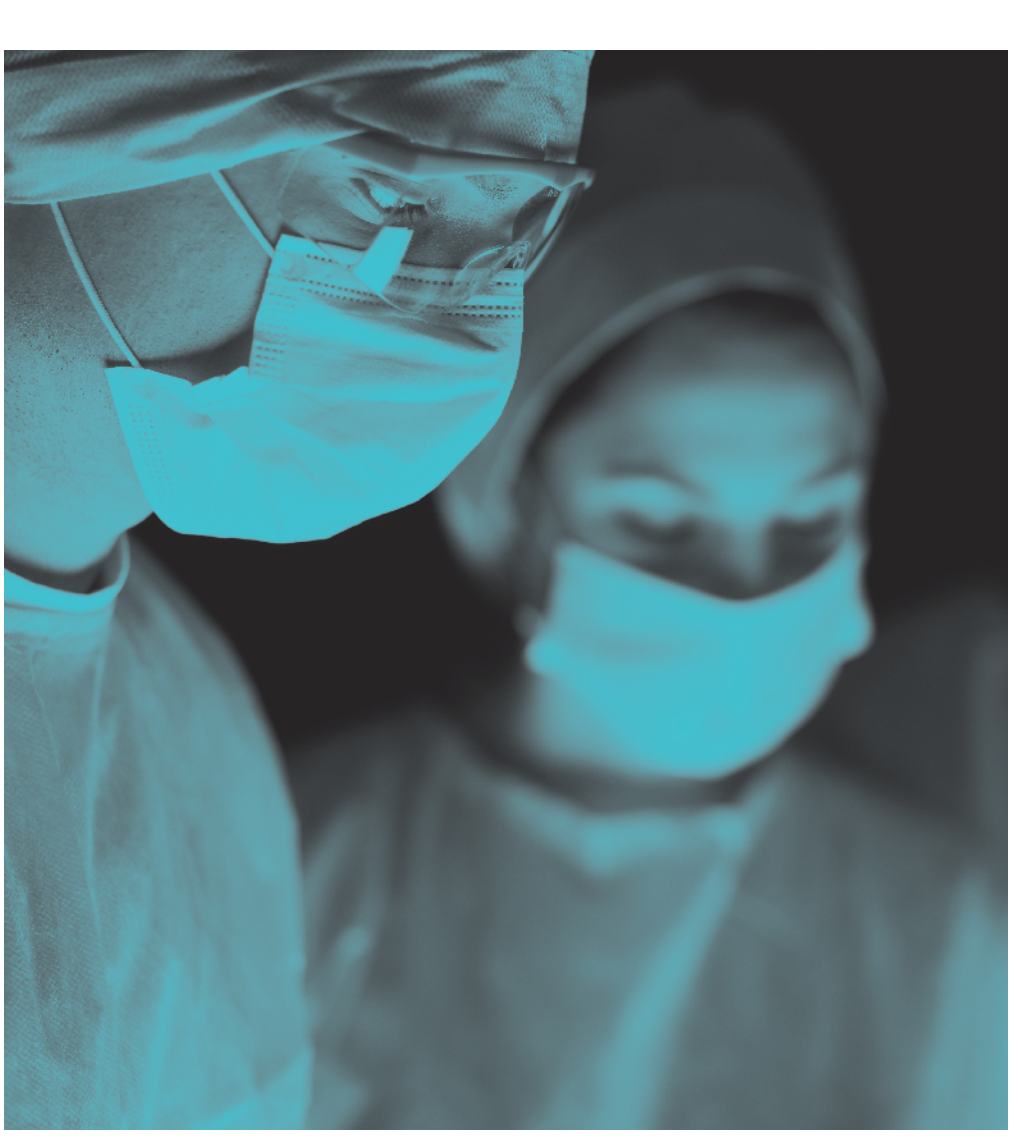
Results of the study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Diabetes Mellitus and Blood Glucose Variability Increases 30-Day Readmission Rate After Kidney Transplantation.*

The study cohort included 1036 patients who underwent kidney transplantation. Of those, 42.2% (n=437) had diabetes prior to transplant. Median hospital stay after transplant was 3 days. A total of 224 (21.6%) patients had readmissions within 30 days.

The readmission rate was higher among patients with diabetes prior to transplant than among those without diabetes prior to transplant (28.4% vs 16.7%, $P<.001$). The presence of hypoglycemia and hyperglycemia was also associated with higher rates of readmission.

"Our findings highlight the importance of the following risk factors for 30-day readmission," the researchers said. "1. Presence of diabetes prior to kidney transplantation. 2. Presence of hypoglycemia and hyperglycemia after kidney transplantation. This analysis suggests that better blood glucose management after kidney transplantation, a modifiable factor, could result in reducing the incidence of 30-day readmission."

Source: Chakkera H, Cook C, Saghafian S, Orfanoudaki A. Diabetes mellitus and blood glucose variability increases the 30-day readmission rate after kidney transplantation. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 777), Boston, Massachusetts, June 4, 2022.



Live Viral Vaccination After Pediatric Liver and Kidney Transplantation

New recommendations regarding use of live viral vaccination in certain non-immune pediatric transplant recipients suggest that the measles-mumps-rubella vaccine (MMR-vx) and varicella vaccine (VZV-vx) may be administered in that patient population. **A. Feldman** and colleagues conducted a study designed to assess the safety and immunogenicity of MMR and VZV-vx in a cohort of pediatric transplant patients.

Results of the study were reported during an oral presentation at the 2022 American Transplant Congress. The presentation was titled *Safety and Immunogenicity of Live Viral Vaccination After Pediatric Liver and Kidney Transplantation.*

Eligible pediatric liver and kidney transplant recipients across the United States received MMR and/or VZV-vx according to the guidelines at the individual centers. Data on demographics, and clinical and laboratory data were collected pre- and post-vaccination.

The study cohort included 147 children (141 liver, 5 kidney, 1 liver-kidney recipient) from 13 centers, representing 295 doses of live vaccine (155 VZV, 140 MMR). Median age at transplant was 0.9 years and median age at receipt of the first post-transplant vaccine was 8.3 years. Immunosuppression at the time of the first post-transplant vaccine included tacrolimus (n=180, 97% with trough <8), cellcept (n=12), sirolimus (n=6), steroids (n=6), azathioprine (n=4), everolimus (n=2), or none (n=1).

Pre-transplant, 40 participants received MMR-vx and 40 received VZV-vx (23 received both). Of those who received either MMR or VZV-vx pre-transplant and had subsequent pre-transplant antibodies checked, 50% (n=15/30) had positive VZV antibodies, 71% (n=5/7) had positive measles antibodies, 60% (n=3/5) had positive mumps antibodies, and 62% (n=8/13) had positive rubella antibodies.

Of those who received at least one post-transplant VZV-vx (n=111), 81% (n=42/52) had antibodies checked and mounted a positive varicella immunoglobulin G (IgG). Of the 103 who received at least one post-transplant MMR-vx, antibodies were checked and an IgG response mounted in 81% (n=46/57) for measles, 82% (n=31/38), for mumps, and 82% (n=31/38) for rubella. At 1 year post-transplant, 78% of children with follow-up laboratory values (n=7/9) had positive VZV IgG, 80% (n=8/9) had positive rubeola IgG, 100% (n=9/9) had positive rubella IgG, and 89% (n=8/9) had positive mumps IgG.

Following vaccination, three children developed clinical varicella (all more than 10 days post vaccine) that resolved within a week of starting oral or intravenous antiviral therapy. No child developed measles. No child developed acute cellular rejection within the first month after vaccination.

In summary, the researchers said, "Live vaccines can be safe and immunogenic in certain transplant recipients. Further studies are ongoing to correlate demographics and immunosuppression with antibody response. Similarly, longitudinal assessment is ongoing to understand ideal timing of vaccination, length that immunity persists, and need for boosters."

Source: Feldman A, Beath B, Ebel N, et al. Safety and immunogenicity of live viral vaccination after pediatric liver and kidney transplantation. Abstract of a presentation at the 2022 American Transplant Congress (Abstract 328), Boston, Massachusetts, June 6, 2022.

Immunosuppression and Mortality in Kidney Transplant Recipients With COVID-19

The mortality risk from COVID-19 is increased in kidney transplant recipients. **A. O. Gérard** and colleague conducted a study to examine the association between maintenance immunosuppressive drugs and 60-day mortality in kidney transplant recipients with COVID-19.

Results of the study were reported during an oral presentation at the 2022 American Transplant Congress. The presentation was titled *Association Between Maintenance Immunosuppressive Regimens and COVID-19 Mortality in Kidney Transplant Recipients*.

Data from all kidney transplant recipients with COVID-19 in the French Solid Organ Transplant COVID-19 registry from February 28, 2020, to December 30, 2020, were retrieved. Patients with missing data on immunosuppressive therapy were excluded (n=116). Logistic regression was used to assess associations between immunosuppressive drugs and death within 60 days of COVID-19 symptom onset, with all baseline characteristics considered to influence outcome or immunosuppressive regimen. False positive rate was controlled for using Benjamini-Hochberg correction; 40 multiple imputations were performed. An adjusted *P* value of <.05 was considered statistically significant.

The cohort included 1451 kidney transplant recipients with COVID-19. Median age was 58 years, and 66.4% (n=963) were female. The most common comorbidities were hypertension (81.9%, n=1188), diabetes (34.5%, n=501), and cardiovascular disease (29.5%, n=428). Median time since transplant was 71 months. Maintenance immunosuppression regimen included calcineurin inhibitors (89.2%, n=1295), antimetabolites (83%, n=1205), corticosteroids (75.4%, n=1094), mammalian target of rapamycin inhibitors (9.9%, n=144), and belatacept (4.0%, n=58).

Of the 1451 patients, 13.9% (n=201) died within 60 days of COVID-19 symptom onset. Older age and baseline creatininemia were associated with mortality (odds ratio [OR], 1.09; 95% CI, 1.07-1.11 and OR, 1.01; 95% CI, 1.005-1.009, respectively; *P*<.001). There was an association between corticosteroid-free regimens and a significantly lower risk of death (OR, 0.48; 95% CI, 0.31-0.76; *P*=.011). There were no significant *P* values with all other variables.

"Corticosteroid-free regimens were associated with a lower risk of death in kidney transplant recipients with COVID-19," the authors said. "While a short course of high-dose corticosteroids is beneficial in severely ill COVID-19 patients, prolonged maintenance corticosteroids expose to chronic immune disorders that may predispose kidney transplant recipients to severe forms of COVID-19."

Source: Gérard AO., Barbosa S, Anglicheau D, et al. Association between maintenance immunosuppressive regimens and COVID-19 mortality in kidney transplant recipients. Abstract of an oral presentation at the 2022 American Transplant Congress (Abstract 9026), Boston, Massachusetts, June 6, 2022.

Baseline Blood Pressure and Early Graft Function in Kidney Transplantation

Proper graft function in kidney transplantation is associated with adequate perfusion pressure to the graft, particularly in deceased-donor kidney transplantation. Analysis of intraoperative mean arterial pressure (MAP) is key to avoid inadequate perfusion and to identity which anesthetic period can affect more significantly on early graft function.

B. Jun Bae and colleagues conducted a study to examine the relationship between intra-operative MAP and early graft function in deceased-donor kidney transplantation. Results of the study were reported during a poster session at the 2022 American Transplant Congress in a poster titled *The Effect of Baseline Blood Pressure on Early Graft Function in Deceased Donor Kidney Transplantation*.

The retrospective analysis included 363 kidney transplant recipients who underwent deceased-donor kidney transplantation from March 2010 to December 2020. The researchers analyzed data on anesthetic monitoring during the intraoperative period and compared basic clinical parameters. Following initial analysis, patients were divided into two groups based on median value of baseline MAP (124 mm Hg), and the two groups were analyzed and compared.

Mean recipient age was 48.9 years and mean donor age was 48.2 years. Anesthetic time was mean 285.9 minutes and operation time was 226.4 minutes. Median values of baseline MAP and MAP at reperfusion were 124 mm Hg and 88 mm Hg.

During the immediate postoperative period (1 week), estimated glomerular filtration rate (eGFR) and urine output in the group with high baseline MAP were higher compared with patients in the group with low baseline MAP. At postoperative day 5, eGFRs were 43.4 mL/min/1.73 m^2 in the group with high baseline MAP compared with 24.2 mL/min/1.73 m^2 in the group with low baseline MAP (*P*=.022). Urine outputs in the two groups were 2942.6 mL in the group with high baseline MAP and 2474.3 mL in the group with low baseline MAP (*P*=.001).

Results of analysis of the effect of MAP at reperfusion did not show any significant relationship between MAP at reperfusion and early graft function.

In conclusion, the authors said, "In this retrospective study, MAP at reperfusion was not significantly related to early graft functions and incidence of delayed graft function. In baseline MAP analysis, high baseline MAP group showed early recovery of eGFR and more urine output than low baseline MAP group. As a result, high baseline MAP was related to early recovery of graft function in deceased donor kidney transplantation."

Source: Jun Bae B, Oh C, Ahn H. The effect of baseline blood pressure on early graft function in deceased donor kidney transplantation. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 763), Boston, Massachusetts, June 4, 2022.

Outcomes of Living and Deceased Kidney Donor Transplants in Philippines

A. B. Burog and A. Parayno, researchers in the Philippines, conducted a retrospective cohort study designed to compare graft and patient survival in living and deceased donor kidney transplantation and to identify the factors that affect graft survival. Results of the study were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Outcome of Living Donor Kidney Transplant and Deceased Donor Kidney Transplant: A Retrospective Cohort Study at National Kidney and Transplant Institute.*

The researchers utilized data from the National Kidney and Transplant Institute, Quezon City, Philippines, from January 2013 to December 2017. Graft and patient survival were determined using the Kaplan-Meier method; logistic regression was used to establish correlation between factors and survival.

A total of 787 kidney transplants were included in the analysis. Of those, 154 were deceased donor transplants and 633 were living donor transplants. The incidence of delayed graft function was higher in deceased donor transplant; the incidence of acute rejection was comparable between the two groups.

Graft survival was higher in the living donor group than in the deceased donor group at 6 months (99.2% vs 91.5%), at 1 year (98.4% vs 89.6%), at 2 years (96.5% vs 88.3%), and at 3 years (94.8% vs 87%). Patient survival was higher in the living donor group compared with the deceased donor group at 6 months (99.5% vs 92.2%), at 1 year (98.7% vs 90.9%), at 2 years (97.8% vs 90.3%), and at 3 years (96.8% vs 89.6%).

Donor's older age and female sex, incidence of delayed graft function, acute tubular necrosis, and acute rejection were associated with adverse effects on graft survival.

In conclusion, the researchers said, "Outcome of kidney transplant in this institution continued to improver; however, graft survival and patient survival of deceased donor kidney transplant were lower. Factors that negatively affect graft survival were identified."

Source: Burog AB, Parayno A. Outcome of living donor kidney transplant and deceased donor kidney transplant: a retrospective cohort study at National Kidney and Transplant Institute. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1037), Boston, Massachusetts, June 5, 2022.

Early Steroid Withdrawal and de novo Donor-Specific Antibodies

In kidney transplant recipients, regimens that included early steroid withdrawal (ESW) may lead to the formation of de novo donor-specific antibodies (dnDSA) following transplant, increasing the risk of antibody-mediated rejection. **D. Majmundar** and colleagues at Temple University Hospital, Philadelphia, Pennsylvania, conducted a study designed to examine the incidence of dnDSA post-kidney transplant in patients receiving ESW regimens versus regimens that include steroids.

Results of the study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Incidence of de novo Donor-Specific Antibodies After Early Steroid Withdrawal in Kidney Transplant Recipients.*

The retrospective, single-center, cohort study included all patients who received a kidney transplant at Temple University Hospital between August 6, 2016, and October 30, 2020. The control cohort (CC) included patients who received steroid-containing regimens and were considered high immunologic risk, defined as the presence of at least one of the following: calculated panel-reactive antibody (cPRA) >30%, pre-existing DSA, positive crossmatch, retransplant, HIV positive, or delayed graft function. The patients who did not meet those criteria were considered low immunologic risk and received ESW regimens. Patients who received a multi-organ transplant were excluded.

The primary and secondary end points were to identify the incidence of dnDSA, biopsy proven acute rejection (BPAR), graft failure, graft function, patient survival, and occurrence of common steroid-related adverse events at 12 months post-transplant (hemoglobin A1c, total cholesterol, low density lipoprotein, and change in weight).

The cohort included 156 patients (ESW, n=59; CC, n=97); mean follow-up was 12 months. Mean weight-based rabbit-derived antihymocyte globulin doses were 4.2 mg/kg in the ESW group and 5.1 mg/kg in the CC group (P=.03). There was a lower incidence of deceased donor transplants in the ESW group compared with the CC group (76% vs 93%; P=.006).

In the CC group, 39% of patients had cPRA >30%, mean cPRA was 83%, and 43% experienced delayed graft function. The two groups were similar in the formation of dnDSA within 12 months following kidney transplant (10% vs 14%; P=.62). There were no statistically significant differences between the two groups in graft function, graft failure, patient survival, biopsy proven acute rejection, or steroid-related adverse events within 12 months after transplant.

In conclusion, the authors said, "Kidney transplant patients receiving ESW regimens were not at higher risk of developing dnDSA compared to patients receiving chronic steroids. However, given the majority of patients meeting criteria for high immunologic risk, this favors using chronic steroids in the high-risk population to avoid formation of dnDSA without an increased risk of steroid-related adverse events."

Source: Majmundar D, Karhadkar S, Diamond A, Au J, Ruggia-Check C. Incidence of de novo Donor Specific Antibodies after Early Steroid Withdrawal in Kidney Transplant Recipients. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1058), Boston, Massachusetts, June 5, 2022.

Graft and Patient Survival Following Simultaneous Pancreas-Kidney Transplant

For patients with diabetes and end-stage kidney disease, the only persistently successful treatment is simultaneous pancreas-kidney transplant (SPK). However, according to **M. Ji** and colleagues, SPK has a technical failure rate of 7% to 22%. Technical failure is defined as a graft loss within 3 months of transplantation.

The researchers conducted a study designed to quantify the impact of 3-month pancreas function on kidney graft failure and patient survival following SPK in patients with type 1 diabetes. Results of the study were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Three-Month Pancreas Graft Function Significantly Influences Survival Following Simultaneous Pancreas-Kidney Transplantation in Type 1 Diabetes Patients*.

The researchers utilized data from a national transplant registry to identify patients with type 1 diabetes who received a transplant between 2000 and 2021 and who survived the first 3 months following the transplant with a functioning kidney. Eligible patients were categorized as: (1) deceased-donor kidney transplant alone (DDKA); (2) living-donor kidney transplant alone (LDKA); (3) SPK recipients with a functioning pancreas graft 3 months post-transplant (SPK, P+); or (4) SPK recipients with a pancreas graft failure within 3 months post-transplant (SPK, P-).

Multivariable inverse probability of treatment weighted accelerated failure-time (AFT) models, with weights estimated using generalized boosted regression, was used to estimate associations of transplant type with kidney failure and patient survival through September 2021.

The study cohort included 22,258 patients. The AFT model coefficients were exponentiated to calculate time ratio (TR), $_{95\%LCL}TR_{95\%UCL}$, which was interpreted as the expected time to graft failure or patient death in one category relative to the referent group. Compared with the recipients in the SPK, P+ group, LDKA had 18% less graft survival time (TR:$_{0.73}0.82_{0.92}$) and 18% less patient survival time (TR:$_{0.72}0.82_{0.93}$), patients in the DDKA group had 23% less graft survival time (TR: $_{0.71}0.77_{0.85}$) and 29% less patient survival time (TR: $_{0.64}0.71_{0.79}$), and patients in the SPK,P- group had 34% less graft survival time (TR: $_{0.59}0.66_{0.75}$) and 34% less patient survival time (TR: $_{0.58}0.66_{0.75}$).

In summary, the authors said, "SPK recipients with functioning pancreas grafts within 3 months post-transplant have better kidney allograft and patient survival compared with LDKA and DDKA. Early pancreas graft failure results in kidney and patient survival time similar to kidney transplant alone. Our findings provide insights into the decision-making of SPK versus KA transplant options for patients and providers."

Source: Ji M, Chang S, Wang M, et al. Three-month pancreas graft function significantly influences survival following simultaneous pancreas-kidney transplantation in type 1 diabetes patients. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1150), Boston, Massachusetts. June 5, 2022.

Pharmacokinetics and Tolerability of New Tacrolimus Tablet Formulation

Previous formulations of twice-a-day tacrolimus were capsular and of limited dose formulations (0.5 mg and 1 mg). The Chung Kun Dang Pharmaceutical Corp. has released a new tablet formulation of tacrolimus, with more diverse dose formulations. **A. Han** and colleagues conducted a study to compare the pharmacokinetics and tolerability profiles of the new Tacrobell tablet formulation with the innovator drug Prograf® (Astellas) in kidney transplant recipients.

Results of the parallel, randomized, single-center, open-label, phase 4 study (PK-TACT) were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *Randomized, Phase 4 Study Evaluating the Pharmacokinetics and Tolerability of the New Tacrolimus Tablet Formulation (Tacrobell Tab) in Kidney Transplant Recipients*.

The study drugs were administered as the primary immunosuppressant for 6 months, starting from the peri-operative period. Study participants were stratified by donor type (living vs deceased) and by expression of CYP3A5. Pharmacokinetic analysis was performed at 2 and 24 weeks post-transplant. The bioequivalence of the two study drugs was assessed based on Cmax (maximum observed concentration), AUCt (area under the curve from zero to t hour), Tmax (time of Cmax), and AUC∞ (AUC from zero to infinite) at 2 and 24 weeks. Graft outcome (renal function, survival, biopsy proven acute rejection) and adverse events were used to evaluate tolerability.

The study enrolled 1331 patients. A total of 117 patients (Tacrobell tab, n=57; Prograf, n=60) completed the 2-week post-transplant pharmacokinetic analysis. Mean Cmax was 31.281 µg/L in the Tacrobell group and 28.119 µg/L in the Prograft group; mean AUCt was 218.028 µg·h/L and 202.713 µg·h/L. The geometric ratio of Cmax and AUCt at 2 weeks was 1.08 (90% CI, 0.96-1.22) and 1.07 (90%C CI, 0.98-1.16), meeting the conventional bioequivalence criteria.

The dose-normalized Cmax and AUCt were also comparable at both 2 and 24 weeks post-transplant. The two groups were similar in graft function at 2, 4, 14, and 24 weeks post-transplant. In the Tacrobell tab group , there were 10 participants (17.5%) with biopsy proven rejection, compared with eight (13.3%) in the Prograf group. During the study period, there was one graft loss in the Tacrobell group and one patient death in the Prograf group due to fulminant hepatitis of unknown origin.

"The new Tacrobell tablet formulation was shown to be bioequivalent and of comparable clinical efficacy to the innovator drug Prograf following current FDA bioequivalence metrics," the researchers said.

Source: Han A, Cho E, Woo HY, et al. Randomized, phase 4 study evaluating the pharmacokinetics and tolerability of the new tacrolimus tablet formulation (Tacrobell tab) in kidney transplant recipients. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1709), Boston, Massachusetts, June 7, 2022.

Diabetes and Obesity and Outcomes of Kidney Transplant

The most common cause of kidney failure in patients undergoing kidney transplantation is type 2 diabetes, which is highly correlated with obesity. **V. Rohan** and colleagues conducted a study designed to examine the interplay between type 2 diabetes mellitus and obesity on long-term outcomes following kidney transplantation.

Results of the study were reported during a poster session at the 2022 American Transplant Congress. The poster was titled *A Large-Scale National Cohort Study Assessing the Impact of Diabetes and Obesity on Kidney Transplant Outcomes*.

The longitudinal cohort study utilized data from the Scientific Registry of Transplant Recipients, 2002-2018. The primary outcomes of interest were graft loss and death. Multivariable Cox regression with obesity and type 2 diabetes mellitus as interaction terms was used to examine the outcomes.

A total of 233,703 recipients were included. Of those, 23% (n=53,725) had type 2 diabetes mellitus. Kidney transplant recipients with diabetes tended to be older (mean age 58.8 years vs 48.4 years), male (67.3% vs 57.6%), and had higher body mass index (BMI) (30.2 vs 27.4 kg/m^2) compared with those without diabetes.

There was no significant association between the risk of death-censored graft loss and type 2 diabetes mellitus status. However, the risk of death following kidney transplant was significantly higher among those with type 2 diabetes mellitus: the adjusted hazard ratio for death with BMI of 18.5 to 30 was 1.51 (95% CI, 1.47-1.55; $P<.001$); for BMI of 30 to 35, 1.53 (95% CI, 1.48-1.58; $P<.001$), and for BMI >35, 1.58 (95%CI, 1.51-1.65; $P<.001$). After correcting for age, the increased risk persisted. There was no significant variation by BMI ($P>.05$ for type 2 diabetes mellitus*BMI interaction term).

In conclusion, the authors said, "Type 2 diabetes mellitus substantially increases the risk of overall graft loss, driven by death with a functioning graft. The impact of type 2 diabetes mellitus is independent and does not vary based on BMI. These findings highlight the importance of reducing mortality risk in those with type 2 diabetes mellitus to improve overall graft survival."

Source: Rohan V, Casey M, Zemin S, Baliga P, Taber D. A large-scale national cohort study assessing the impact of diabetes and obesity on kidney transplant outcomes. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 785), Boston, Massachusetts, June 4, 2022.

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.

Collaborative Approach to Hemodialysis During Liver Transplant

The kidney transplant program at Keck Medicine of the University of Southern California, Los Angeles, is part of the center's multiorgan transplant program and is ranked in the top 10% of all transplant centers nationwide for quality. In a presentation at the ANNA 2022 National Symposium, **Isagani I. Marquez Jr, MSN, RN, QIA,** and colleagues described the center's protocols related to liver transplantation with or without simultaneous kidney transplantation. The presentation was titled *A Collaborative Approach to Intraoperative Hemodialysis at Keck Hospital of USC.*

Patients undergoing liver transplantation (with or without simultaneous kidney transplantation) present complicated cases that involve major fluid shifts, electrolyte imbalances, and coagulative abnormalities during the perioperative phase. Patients undergoing liver transplant who have renal dysfunction commonly experience metabolic acidosis, a life-threatening electrolyte abnormality; acute treatment for metabolic acidosis may include intraoperative hemodialysis (IOHD).

Since the late 1990s, hemodialysis during liver transplantation has been the preferred renal replacement therapy at the center. Dialysis nurses play a major role in the multiservice team charged with caring for patients undergoing liver and kidney transplant. The team works closely in collaboration to manage the stability of the renal function during the extended surgery.

The renal fellow writes the orders that are called in by the nursing supervisor and/or the surgery team. The dialysis nurses review and confirm the orders, current results of laboratory test, and consents. To ensure accommodation of the dialysis machine for accessibility in the event of circuit change or problems with access, designated surgical rooms are used for IOHD.

As part of the IOHD performance quality project, the center's dialysis machine setup and pretreatment alarms, pressure test, and water checks are completed and passed. The dialysis nurse and the anesthesiologist confer regarding recent laboratory results, ultrafiltration, and the timing of initiation of hemodialysis.

Vital signs are taken at a minimum of 15-minute intervals. Changes on dialysate parameters are made per ordered the standing IOHD sliding scale or via communication with the covering nephrology fellow. Adjustments in ultrafiltration are ordered by the anesthesiologist.

In summary, the authors said, "The implementation of OPHD during liver transplant and simultaneous liver and kidney transplant has been used safely and effectively in critical patients with high model of end-stage liver disease scores and renal dysfunction. It adequately allows adjustments of the acid/base balance, electrolyte management, and intravascular volume adjustments during liver and kidney transplantation surgery. It is best achieved by the collaborative approach of the nephrologist, hepatobiliary surgeon, anesthesiologist, renal transplant surgeon, the surgery team, and the dialysis team. At our facility the 1-year survival rate of kidney transplant recipients is approximately 98.5%. Graft survival after 1 year is approximately 97.5%."

Source: Marquez II, Aquino-Tan L, Casagrande Y, et al. A collaborative approach to intraoperative hemodialysis at Keck Hospital of USC. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

Avoiding BSIs Related to Buttonhole Cannulation

Over the past 40+ years, same site cannulation with blunt needles of the arterio-venous fistula (AVF), known as buttonhole cannulation, has garnered both positive and negative assessments. On one hand, it is considered a method with the potential to preserve the life of the AVF, while decreasing pain and trauma associated with sharp needle cannulation. On the other hand, buttonhole cannulation has been associated with an increase in access-related blood stream infections (BSIs).

At the ANNA 2022 National Symposium, **Peggy Bushey, BSN, RN, CDN,** University of Vermont Medical Center, Fairfax, and **Adam Locke, CCHT,** University of Vermont Medical Center, Waterville, presented the process used at the centers to address BSIs in the home dialysis programs. The presentation was titled *Buttonhole Cannulation Revisited; Utilizing an Updated Skin Prep Procedure, it is Possible to Minimize Access Related BSIs With the Buttonhole Cannulation Method.*

An assessment of the underlying source of the BSIs revealed incomplete scab removal and/or tears in the skin at the canulation site secondary to pulling off the scabs with tweezers or pickers (supplied by some needle manufacturers). Because scabs are colonized with staph aureus, a break in skin integrity decreases skin's protective mechanisms, resulting in the introduction of bacteria at the cannulation site and the development of a BSI.

At the University of Vermont Medical Centers, using an updated approach to scab removal has resulted in a zero BSI rate in home dialysis patients for the past 7 years. The approach includes soaking the scab site and gently scrubbing off an residual scab particles, eliminating the introduction of particles laden with bacteria into the blood stream. Any tearing or excoriation of skin at the cannulation site is also avoided.

In summary, the authors said, "In light of the escalating goal of patients choosing a home modality or taking on a more active role in their in-center dialysis care, we are asking practitioners to revisit and reconsider the buttonhole method using a modified method of pretreatment scab removal as described, thus minimizing the risk of cannulation related infections in this patient population. These data have not been collected in a structured study, but rather are a result of an observational cohort report. However, we feel [the findings] are adequate for consideration, and can serve as a means to invoke future research."

Source: Bushey P, Locke A. Buttonhole cannulation revisited; utilizing an updated skin prep procedure, it is possible to minimize access related BSIs with the buttonhole cannulation method. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

ILLUMINATE-C Study 6-Month Primary Analysis Results

ILLUMINATE-C was a single-arm, phase 3 study examining lumasiran, an RNA interference (RNAi) therapeutic. The agent inhibits oxalate production in patients with primary hyperoxaluria type 1 (PH1) and impaired kidney function.

At the ANNA 2022 National Symposium, **Philip Arnold, MSN, RN,** and colleagues presented 6-month primary analysis ILLUMINATE-C data in a session titled *ILLUMINATE-C, a Single-Arm, Phase 3 Study of Lumasiran in Patients With Primary Hyperoxaluria Type 1 and CKD 3b-5, Including Those on Hemodialysis.*

Inclusion criteria were genetically confirmed PH1 diagnosis, estimated glomerular filtration rate ≤45 mL/min/1.73 m^2, and plasma oxalate (POx) ≥20 mmol/L (upper limit of normal = 12 mmol). Patients who did not require dialysis or kidney transplantation at the start of the study were cohort A (n=6) and patients receiving hemodialysis were cohort B (n=15). The primary end points of interest were percent change in POx from baseline to month 6 (cohort A) and percent change in predialysis POx from baseline to month 6 (cohort B).

Baseline mean POx was 64.7 mmol/L in cohort A and 108.4 mmol/L in cohort B. Lumasiran led to 33.33% (95% CI -15.16% to 81.82%) least-square mean reduction in POx from baseline to month 6 (averaged across months 3-6) in cohort A and 42.43% least-square mean reduction (95% CI, 34.15% to 50.781%0 in cohort B.

The most common adverse events related to the study drug were injection-site reactions (all mild).

In summary, the authors said, "Lumasiran resulted in substantial reductions in POx in PH1 patients with CKD 3b-5, with an acceptable safety profile through month 6."

Source: Arnold P, Michael M, Groothoff J, et al. ILLUMINATE-C, a single-arm, phase 3 study of lumasiran in patients with primary hyperoxaluria type 1 and CKD 3b-5, including those on hemodialysis. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

The primary end points of interest were percent change in plasma oxalate (POx) from baseline to month 6 (cohort A) and percent change in predialysis POx from baseline to month 6 (cohort B).

Conference Coverage

Fort Worth, Texas | May 22-25, 2022

Preventing CLASBIs in Hemodialysis Patients

During a presentation at the ANNA 2022 National Symposium, **Kim Arthur, MSN, APRN, ACNS-BC, CMSRN,** and **Kat Persell, BSN, RN, PCCN,** reported results of a 6-month review of an inpatient dialysis unit. The review, conducted by a vascular access clinical nurse specialist, identified seven central line-associated bloodstream infections (CLABSI) in the unit, promoting investigation, assessment, and intervention. The presentation was titled *EBP strategies to Prevent CLABSI in Hemodialysis Patients.*

The goal of the investigation and subsequent intervention was zero patient harm. Standards of care were identified after a literature review was performed, and recommendations regarding care of hemodialysis patients' central lines were gathered. The review included the Centers for Disease Control and Prevention Guidelines, Recommendations, and Resources, the National Kidney Foundation Kidney Disease Outcomes Quality Initiatives, and the instructions for use for central lines. Assessment also occurred in the unit via observations of practice, review of skills checklists, and evaluation of staff knowledge.

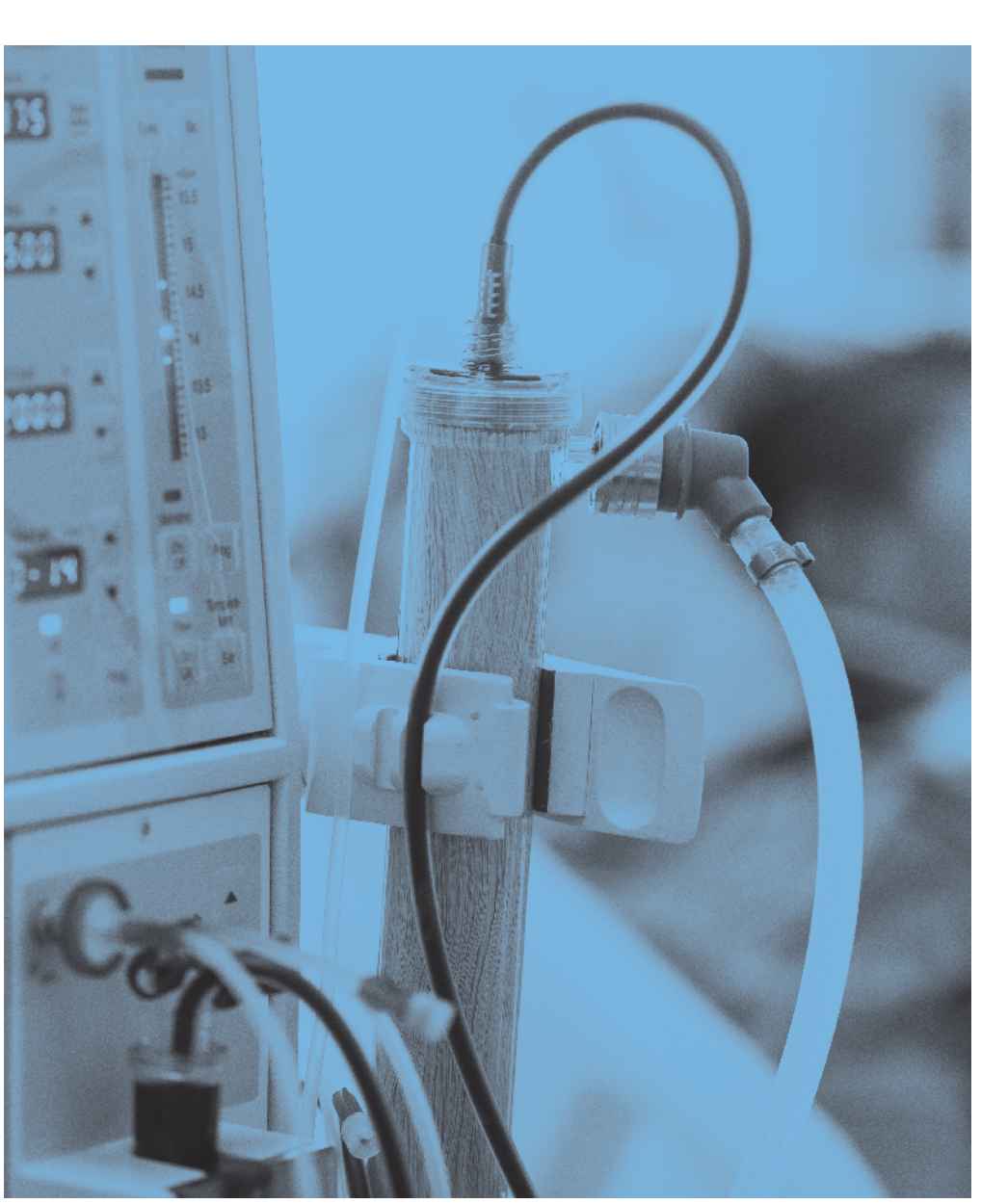
A new process that incorporated evidence-based practices such as chlorhexidine (CHG) care prior to access was developed. The use of CHG and 70% alcohol was implemented to scrub the hub, and a clean pad is placed under the central like to prevent contamination.

A one-on-one demonstration was used for education to enhance staff knowledge, followed by a return demonstration. To ensure accuracy of documentation and communication of completed line care to inpatient nurses, changes were made to the process for electronic health records.

Following completion of the investigation and the education phase, auditing was initiated and continued for 6 months. Observations for compliance with hand hygiene protocols and catheter access care are ongoing. In 6 months following implementation of the initiative, there have been zero CLABSIs in patients treated in the inpatient dialysis unit, showing a 100% reduction in infections and zero harm to patients.

In conclusion, the authors said, "Dialysis patients are at high risk of infection, so meticulous care must be maintained in the care of the central line. The use of current best evidence is necessary to provide safe care and prevent harm. The relationship and roles of clinical nurse specialists and unit educators to ensure excellent care cannot be overstated."

Source: Arthur K, Persell K. EBP strategies to prevent CLABSI in hemodialysis patients. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.



CKD Education Program and Modality Decisions

Patients with chronic kidney disease (CKD) commonly experience multiple comorbidities, resulting in the need for complex care decisions. Patients with inadequate health literacy are ill equipped to participate in making those decisions. Structured CKD education has been shown to improve disease awareness, and to provide adequate preparation for the need for renal replacement therapy and primary choice of dialysis modality.

Recent federal policy includes an emphasis on utilization of home dialysis, contributing to the need for structured CKD education to aid patients as they make the choice of dialysis modality. **Laura Siegle, RN,** and colleagues at the Minneapolis VA Health Care System, Minneapolis, Minnesota, reviewed the effect of a nursing-led, structured CKD education program focusing on dialysis modality selection.

Results of the analysis were reported during the ANNA 2022 National Symposium. The presentation was titled *Structured Chronic Kidney Disease (CKD) Education and Choice of Dialysis.*

The team developed a structured multidisciplinary CKD educational program within two large medical centers. The program was designed for patients with advanced CKD (stage 4, estimated glomerular filtration rate [EGFR] 15-30 mL/min/1.73m^2 and stage 5, eGFR <15 mL/min/1.73 m^2). Selection was computerized and participation was voluntary.

To broaden participation and extend reach to patients in rural areas, multiple forms of media were used to deliver content. Classes were offered in a group setting, via video visit, or 1:1 if needed. Patients received handouts designed to assess their health knowledge, a survey measuring mental health, and an outline of care plans. Two weeks following attendance, follow-up phone calls were made to provide answers to any further questions.

A total of 524 patients across the two sites were identified for inclusion between January 8, 2021, and December 1, 2021. Of the 524 patients, 91% (n=478) were screened and contacted for inclusion in the education program.

Of those who completed the program, 62.5% opted for peritoneal dialysis as their primary dialysis modality and 11.7% opted for conventional care. Nineteen patients had surgical referral and 12 patients had peritoneal catheter placement, which compared with only two peritoneal catheter placements total over the 2 years prior to the educational program.

In summary, the authors said, "A structured, nursing-led, multidisciplinary approach to CKD education resulted in substantial increases in participation, interest, and ultimately transition to a home dialysis modality. This approach may provide a scalable model for home dialysis growth."

Source: Siegle L, Barbot T, Foley R, Reule S. Structured chronic kidney disease (CKD) education and choice of dialysis. Abstract of a presentation at the American Nephrology Nurses Association 2022 National Symposium, Fort Worth, Texas, May 22-25, 2022.

IGAN Foundation Forms Advisory Board

The IgA Nephropathy Foundation (IGAN Foundation) is a nonprofit organization supporting patients with IgA nephropathy, a rare autoimmune kidney disease. In a recent press release, the foundation announced the formation of a Medical and Scientific Advisory Board. The board will help inform and enhance the work of the Foundation in supporting patients with IgA nephropathy and their families.

Currently, the board includes seven members, including medical professionals, researchers, and experts in IgA nephropathy. Plans call for expansion of the board to 20 members who will help the Foundation work to find a cure, fund research, empower patients, and build a strong support network for patients.

Bonnie Schneider, co-founder and director of the IGAN Foundation, said, "At the Foundation, we strive to provide our community with the most up-to-date resources and support they need to navigate their condition. With the Advisory Board's support, we can ensure we continue to bring medically and scientifically sound advice and resources to our members. I am so grateful to this committed team of experts for their support in driving our work forward."

Jonathan Barratt, MD, is chairman of the Advisory Board and Mayer Professor of Renal Medicine at the University of Leicester, England. He said, "It is very encouraging to see the marked increase in clinical research on IgA nephropathy, which has had no treatment until the approval of the first-ever treatment for IgA nephropathy in late 2021. Accurate understanding of this rare condition by both patients and clinicians is critical as the medical community unites to research a cure. I am proud to partner with my fellow Advisory Board members to lend our shared knowledge and expertise to the IGAN Foundation to enhance patients' understanding of this disease and how to best manage their condition."

AOPO Announces 2022–2023 President and President-Elect

In a recent press release, the Association of Organ Procurement Organizations (AOPO) announced the president and newly elected members of the Executive Committee whose terms took effect in July. AOPO is the nonprofit organization representing federally designated organ procurement organizations (OPOs) in the United States.

Barry Massa, executive director at LifeCenter Organ Donor Network, is the incoming AOPO president. As president, he will serve as spokesman for AOPO and as chair of the Board of Directors. He plans to focus on collaborating with other stakeholders to increase organ donation.

"I am looking forward to my tenure as AOPO's president as this crucial time in our community," Mr. Massa said. "We will continue to work collaboratively with OPOs and stakeholders to improve the organ donation and transplantation system. Our focus is on performance improvement to optimize every donation opportunity, AOPO is committed to saving more lives through collaborations that will reduce health inequities, maximize organ utilization, and drive innovation."

Colleen McCarthy has been named president-elect of AOPO. She is vice president of organ and tissue donation at Versiti Wisconsin. She will lead AOPO's strategic planning process, collaborate with AOPO committees, and serve as a national advocate for issues that impact donation and transplantation. She will serve as the AOPO president of the 2023-2024 Executive Committee.

New Executive Committee members confirmed during this election cycle include **Tasha Flowers,** director of finance at ARORA, as the secretary/treasurer, and **Luke Y. Shen,** medical director at Texas Organ Sharing Alliance, as the medical advisor-elect.

NKF's Voices for Kidney Health Celebrates Successful Year

The National Kidney Foundation (NKF) issued a press release highlighting the success of the Voices for Kidney Health program launched in spring 2021. The program has gained significant increases in congressional support and funding for kidney-based related research and prevention.

Voices for Kidney Health is a nationwide community of advocates committed to improving the lives of individuals living with kidney disease through meaningful policy change. The advocates work to advance policies that expand access to home dialysis, work toward transplants for all, protect living organ donors, promote health equity, and accelerate investment in kidney disease prevention and research.

Kevin Longino, CEO of the NKF, said, "As we celebrate the achievements of the past year, we must also acknowledge that there is still much work to be done. Racial and ethnic disparities in the awareness, diagnosis, and treatment of kidney disease lead to worse outcomes for kidney patients in communities of color. Patients face unequal access to kidney transplant, the optimal treatment for kidney failure. Life, long-term care, and disability insurers can still discriminate against living organ donors in almost half of US states. These are just a few of the issues we're addressing as Voices for Kidney Health enters its second year."

He added, "NKF's gratitude to our Voices advocates cannot be overstated. We are continually impressed by their commitment to improving the lives of their fellow kidney patients, and it is a privilege to work with each and every one of them. Thanks to their continued dedication, Voices for Kidney Health will continue to represent the sound of positive changed for kidney patients nationwide."

Reference Tissue Atlas for the Human Kidney

Researchers at the Icahn School of Medicine at Mount Sinai have joined forces with the University of Michigan, University of Washington, Princeton University, Washington University, Harvard Medical School, University of Texas, Duke University, University of California San Diego, University of California San Francisco, Indiana University, and Ohio State University to build a spatially specified human kidney tissue atlas, an integrated reference map of cells, pathways, and genes using undiseased biopsies from 56 adult subjects.

In a recent press release, **Ravi Iyengar, PhD,** principal investigator, said, "This study, which is focused on undiseased (reference) tissue, provides the framework for a molecular classification of kidney disease in a data-driven manner by analyses of biopsies of patients with kidney disease. This new classification identifies which cell types in the kidney are affected by disease at various stages and provides drug targets to repurpose or develop new drugs to halt progression. It is the first step in revolutionizing the treatment of kidney disease."

Dr. Iyengar collaborated with **John Cijiang He, MD, PhD,** division chief of nephrology at the Icahn School of Medicine. Dr. He said, "Kidney disease is a great health burden that is most pronounced among communities of color. To halt the progression of kidney disease, which ultimately leads to dialysis and, in some cases, kidney transplants, we need this greater level of understanding of kidney function. The atlas provides an excellent first step in this direction."

AKF Launches Pruritus Awareness Campaign

Pruritus is common among patients on dialysis and is often disruptive, affecting quality of life and sleep. The American Kidney Fund (AKF) has launched an education and awareness campaign to focus attention on pruritus to help patients with chronic kidney disease who develop pruritus understand and deal with the condition. According to a recent press release from AKF, the initiative has bene developed with support from Vifor Pharma. The campaign is the first large-scale effort to provide resources for people with CKD who are experiencing pruritus.

LaVarne A. Burton, president and CEO of

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AKF, said, "Far too many people on dialysis are suffering from pruritus, which can be unrelenting and debilitating in its most severe form. Our new, evidence-based educational materials will help those who are affected better understand pruritus and empower them to seek help from their kidney care team so that they are not suffering in silence. We are grateful to Vifor Parma for their support of this important work."

The campaign provides an online hub of information about pruritus as well as a free downloadable guide to aid patients in speaking with their clinician about the condition. There will be a webinar for patients with CKD affected by pruritus later in the year.

Molly Painter, US president for Vifor Pharma Inc., said, "Chronic kidney disease-associated itching is a condition that is often underreported and misunderstood. Easily accessible resources and guidance are important for both patients and health care providers, and that is why we are delighted to support the American Kidney Fund's pruritus education campaign."

Patient Enrollment Completed in ORIGIN Trial

In a recent press release, Vera Therapeutics, Inc. announced completion of patient enrollment in the phase 2b ORIGIN trial of atacicept. The multinational, dose-ranging study is designed to evaluate the efficacy and safety of atacicept in patients with IgA nephropathy (IgAN) who continue to have persistent proteinuria and are at high risk for disease progression despite a stable regimen of renin-angiotensin-aldosterone system inhibition with an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker.

Richard Lafayette, MD, of Stanford University School of Medicine and a clinical investigator in the trial, said, "We have been seeking a disease modifying therapy for IgAN to potentially slow or reverse disease progression. Recently, new data analysis from the phase 2a JANUS clinical trial in patients with IgAN sowed atacicept is the first known investigational therapeutic to reduce IgG autoantibodies as well as its autoantigen, Gd-IgA1, the source of immune complexes that causer disease. This builds on the already compelling disease-modifying dose-dependent activity and well tolerated safety profile for atacicept. We look forward to the results of the ORIGIN trial which will be a first for the filed."

Celia Lin, MD, chief medical officer at Vera Therapeutics, said, "We are excited to complete enrollment in the phase 2b ORIGIN trial and reach this significant milestone for atacicept as we work diligently amidst a global pandemic and geopolitical crises to provide a much-needed treatment option for patients with IgAN. IgAN represents a high unmet medical need in the world, with an estimated 400,000 patients in the US, the European Union, and Japan—up to half of whom will develop end-stage renal disease within 20 years from initial diagnosis, requiring dialysis or kidney transplant. We believe atacicept could have a profound benefit for patients with IgAN and look forward to topline results of this study expected to be announced later this year."

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Calyxo Raises Series C Funding for Kidney Stone Treatment

The medical device company Calyxo, Inc. has announced the closing of a $32.7 million Series C financing round led by Questa Capital and CRG. Calyxo has developed the CVAC Aspiration System that utilizes irrigation and aspiration to remove kidney stones, with the goal of a surgically stone-free outcome.

In a press release, **Joe Catanese,** president and CEO of Calyxo, said. "We are excited to be moving into the next step of our evolution. Kidney stone disease is a painful problem for patients, and it consumes vast amounts of health care resources each year. We believe our solutions will better meet the needs of kidney stone patients and transform the care of this condition. We look forward to applying this latest financing round toward further product development and the expansion of our team."

AOPO Washington, DC Advocacy Day

Earlier in 2022, the Association of Organ Procurement Organization (AOPO) held an Advocacy Day in Washington, DC. Organ procurement organizations (OPOs) met with members of Congress to provide information on the need for system-wide changes to the organ donation and transplantation system.

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Jan Finn, RN, MSN, president of AOPO and president and CEO of Midwest Transplant Network, said, "OPO representatives descended onto Capitol Hill to meet with legislators and their staff to discuss the recommendations in the NASEM (National Academy of Sciences, Engineering, and Medicine) report and urge members of Congress to sign a congressional letter to the Department of Health and Human Services to adopt standardized metrics and establish national performance goals to improve donation and transplantation rates among minority an disadvantaged populations. In addition, we encouraged Congress to support modernizing the organ IT infrastructure and better engage patients in their own care decisions. We also emphasized the need to reduce the number of organs recovered but not accepted for transplant, increase the number of medically complex donors, and increase the number of transplants to at least 50,000 in 2026."

Other issues raised included the shortage of organ preservation solution, and the CARE for All Kidneys Act, which creates a national health plan bringing together key stakeholders such as the National Institutes of Health (NIH), the National Institute of Diabetes and Digestive and Kidney Diseases at NIH, and the Centers for Disease Control and Prevention.

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University of Michigan and Walden Biosciences Research Collaboration

Walden Biosciences, Inc. has announced a research collaboration with the University of Michigan at Ann Arbor to advance research in the area of the genetics of soluble urokinase plasminogen activating receptor (suPAR). Walden is a biotechnology company that focuses on transforming the treatment of kidney disease.

The research will be conducted in collaboration with **Salim Hayek, MD,** a National Institute of Health-funded physician-scientist with expertise in renal disease, cardiovascular disease, and biomarker and risk prediction research. Dr. Hayek has characterized suPAR as a pathogenic factor, causative agent, and a "druggable target in kidney disease," according to a recent press release.

Walden will provide materials, consultative support, data analysis, and may perform experiments to support Dr. Hayek's ongoing research in suPAR.

Alex Duncan, PhD, Walden Bioscience's chief scientific officer, said, "We are delighted to be

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working with Dr. Hayek's lab to advance suPAR science in order to demonstrate its causality in chronic kidney disease and other important disease indications where suPAR may play a role. The data generated to date are compelling, and we look forward to using genetic tools to further validate and support the strong correlation between suPAR and its effects on chronic kidney disease."

Diality, Inc. Joins IKC Campaign

The Innovative Kidney Care (IKC) campaign is an initiative undertaken by a collaborative group of industry representatives as well as patient and provider advocates in an effort to remove barriers to choice for kidney patients and increase access to home dialysis. In a recent press release, Diality, Inc. announced it is joining IKC in that effort.

More than 800,000 patients annually are affected by kidney failure in the United States, and approximately 550,000 of those patients are Medicare enrollees.

Osman Khawar, MD, Diality CEO, said, "Evidence suggests that home dialysis can improve patient outcomes and quality of life, but in 2019 only about 13% of prevalent dialysis patients received either hemodialysis or peritoneal dialysis

at home, and 45% of Medicare-certified dialysis facilities still were not certified to offer either home dialysis modality. Clearly there is room for improvement, and this will require more than technology and care advancements. The IKC campaign is designed to encourage the Centers for Medicare & Medicaid Services (CMS) to improve access to home dialysis, which will require fundamental changes to provider certification and payment models for home treatment, including home dialysis."

IKC brings together a diverse group of organizations who work together to advocate for CMS to modernize the ESRD Conditions for Coverage and related guidance for better patient outcomes, improved patient experiences, improved clinical experiences, and lower costs of care.

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AOPO Holds Annual Meeting

At the 39th Annual Meeting of the Association of Organ Procurement Organizations (AOPO) in July, the organ procurement organization (OPO) community shared information on new technologies and successful practices aimed at reaching the goal of 50,000 annual organ transplants in 2026.

Barry Massa, executive director of LifeCenter Organ Donor Network, began his term as AOPO president, and outlined his commitment to transparency; collaboration; initiatives of diversity, equity, and inclusion; and the passion to pursue AOPO's mission. He said, "The collaboration I saw at the meeting among OPOs and our other community partners was impressive and illustrated what we can achieve when we work together and share information. We will continue to work with our stakeholders and help guide improvements that help OPOs to build on their efforts to improve their outcome sand move to higher performance tiers."

Key initiatives include programs to optimize kidneys for transplant, working to create a more unbiased donation system, strategies to increase donation after circulatory determination of death, and models of donor care units. The meeting also introduced the IMPACT Program that will assess OPOs in the areas of operations, donation derivers, donation system, and transplant rate, in order to provide recommendations for performance improvement.

Milken Institute Issues Report on CKD

The Milken Institute has issued a report titled *Chronic Kidney Disease: Finding a Path to Prevention, Earlier Detection, and Management.* According to a recent press release, the report examines the current landscape of chronic kidney disease (CKD) and identifies ways to manage this urgent public health issue.

The report includes sections on emerging trends in CKD, including ways in which climate change has become a risk factor for the development of CKD; the roles of various stakeholders, including government agencies, policymakers, payers, providers, and community-based organizations, in earlier detection and diagnosis of CKD; and ways to drive system-level change for the prevention, earlier detection, and management of CKD. ■

COVID-19

Telehealth for Dialysis Patients During COVID-19 Pandemic

Journal of Renal Nutrition. 2022;32(3):319-325

Ana Valente, MSc, and colleagues conducted a multicenter, observational, prospective longitudinal study to examine the effect of a telehealth-delivered nutritional intervention via telephone in maintenance hemodialysis patients during the COVID-19 pandemic. The study cohort included data collected during the COVID-19 pandemic on 156 patients undergoing maintenance hemodialysis at 15 dialysis units

According to individual biochemical and nutritional parameters, participating patients were assigned to receive dietary counseling during a phone call. Factors recorded at baseline and 1 month following nutritional counseling were dry weight, intradialytic weight gain percentage (%IDWG), body mass index, potassium, phosphorus, calcium, calcium/phosphorus product, normalized protein catabolic rate, albumin, and hemoglobin.

Following dietary advice, there were significant decreases in the prevalence of hyperkalemia and hyperphosphatemia. Following counseling targeted to hyperkalemia and hyperphosphatemia, there were statistically significant reductions in serum potassium and phosphorous levels. There was also a statistically significant decrease in the prevalence of hypophosphatemia.

There was a significant decrease in %IDWG, although there were no statistically significant differences detected in patients with high %IDWG.

When the participant receiving the phone contact was the patient or the caregiver, there were significant differences in both potassium and phosphorus values. Differences in hypophosphatemia and %IDWG were only observed when the contact was made directly with the patient. When the contact was made through a nursing home, there were no statistically significant differences observed.

"Our results suggest that telehealth-delivered dietary interventions can improve the clinical and nutritional parameters of hemodialysis patients. Consequently, this strategy may be effective for promoting continuous nutritional monitoring in these patients, in particular when conducting a face-to-face option is not crucial," the researchers said.

CHRONIC KIDNEY DISEASE

Hypervitaminosis A in Pediatric Patients With CKD

Journal of Renal Nutrition. 2022;32(3):275-281

According to **Meredith Harris, MD,** and colleagues, hypervitaminosis A, often overlooked in chronic kidney disease (CKD), has been shown to be associated with hypercalcemia, contributing to mineral bone disease. The researchers performed a retrospective review to identify the prevalence of hypervitaminosis A and its association with bone health in a population of pediatric patients with advanced CKD.

The review included 58 children with CKD stage 4-5. The researchers sought to examine the association between vitamin A levels and bone health. Those values were then compared between a primarily formula-fed (FF) cohort and a nonprimarily formula-fed (NFF) cohort.

Of the 58 patients, 56 (97%) had hypervitaminosis A, with a mean vitamin A level of 1475 mcg/dL. The vitamin A level in the FF group was 2.9 times the upper limit of normal vitamin A level; the vitamin A level in the NFF group was 2.2 times the upper level of normal (*P*=.02). In the FF group, mean calcium level was 10.3 mg/dL compared with 9.8 mg/dL in the NFF group (*P*=.057).

Fifteen of the patients in the FF group (62%) were below the goal parathyroid hormone range compared with 16 (72%) of patients in the NFF group at greater than goal (*P*=.006).

"We concluded vitamin A and calcium levels are higher in the FF versus the NFF population," the researchers said. "FF patients are more likely to have parathyroid hormone levels lower than the goal range, placing them at risk for adynamic bone disease. We recommend monitoring vitamin A levels as part of routine nutritional assessments and dietary interventions to prevent hypervitaminosis A to improve bone health in late CKD."

Serum Irisin Level and Cardiovascular Risk in CKD

Journal of Renal Nutrition. 2022;32(3):282-291

During the course of chronic kidney disease (CKD), the production of irisin, a circulating myokine released from skeletal muscles following physical exercise, decreases. The decrease in irisin may be related to sarcopenia and physical inactivity. **Teresa Arcidiacono, MD,** and colleagues reported results of an observational study designed to examine the relationship of serum irisin with cardiovascular outcomes in patients with stage 3-5 CKD.

Serum irisin was significantly higher in healthy subjects (n=20) than in patients with CKD (7 vs 3.1 µg/mL; *P*=.0001), and was higher in patients with CKD stage 3 (3.2 µg/mL) compared with patients at stage 4 and 5 taken together (n=36; 2.8 µg/mL; *P*=.05). Patients in the lowest serum irisin tertile had lower serum 1,25(OH)2D levels (21 pg/mL) compared with patients in the middle tertile (30 pg/mL; *P*=.005) and those in the highest tertile (27 pg/mL; *P*=.047). Patients in the highest tertile had lower Kauppila scores than patients in the middle and lowest tertiles (10.6 vs 11.8 [*P*=.007] and 6.9 [*P*=.043]), respectively.

During a 3-year follow-up period, 20 patients experienced cardiovascular events. The researchers performed an analysis with a Cox regression model that used age, body weight, presence of diabetes mellitus, sex, Kauppila calcification score, serum values of FGF23 (as logarithm), phosphate, sclerostin, albumin, and cholesterol, estimated glomerular filtration rate, and serum irisin tertiles as covariates. Results demonstrated that cardiovascular risk was lower in patients in the highest tertile of serum irisin compared with patients in the middle tertile (B, 2.38; odds ratio [OR], 10.8; 95% CI, 1.65-58.13; *P*=.013) or with those in the lowest tertile (B, 1.61; OR, 5.0; 95% CI, 1.09-22.83; *P*=.038).

In summary, the researchers said, "These findings suggest that serum irisin may be a marker of cardiovascular outcome in patients with CKD."

RENAL NUTRITION

Dietary Restriction of Phosphorus in Patients With Proteinuria

Journal of Renal Nutrition. 2022;32(2):189-198

Negar Mozaffari-Rad, MS, and colleagues reported results of a study designed to determine the effect of dietary phosphorus restriction, independent of protein intake, on the urinary protein excretion in patients with proteinuria.

The parallel randomized controlled trial enrolled 71 patients with proteinuria. Participants were randomly allocated to receive either a recommended phosphorus-restricted diet (n=36) or a recommended control diet (n=35). The diets were designed and recommended to participants in a way that both groups would receive the same amount of energy and protein; the only significant difference between the diets was the amount of phosphorus intake. The primary outcomes of interest were changes in spot urine protein-to-creatinine ration, changes in serum and urine levels of phosphorus, and changes in estimated glomerular filtration rate (eGFR).

Mean age of the participants was 59 years, mean body mass index was 29 kg/m^2, and mean eGFR was 56.1 mL/min/1.73 m^2. In the phosphorus-restricted group, the amount of phosphorus intake decreased significantly compared with the control group (–709 mg/day vs –369 mg/day; *P*<.001). The decrease was accompanied by a significant reduction in urine protein-to-creatinine ratio in the phosphorus-restricted group; when the change was compared with the control group, the change did not reach statistical significance (mean change, –75.78 mg/g vs –55.25 mg/d; *P*=.539).

Limiting phosphorus intake did not result in change in serum and urine values or in eGFR at the end of the trial.

In conclusion, the authors said, "Although adherence to a phosphorus-restricted diet by patients with proteinuria led to a significant decrease in urinary protein excretion, this change was not significantly different

from that of the control diet. Further studies with larger sample sizes and different designs will reveal more evidence for a link between phosphorus intake and proteinuria."

TRANSPLANTATION

ABO-Incompatible Kidney Transplant

Journal of Inflammation Research. 2022;15:3095-3101

In patients with end-stage kidney disease, kidney transplantation offers substantial survival advantage over hemodialysis. While the demand for donor organs increases, there is a considerable gap between availability of kidneys and the number of patients on the transplant wait list. The pool of deceased donors has been successfully expanded with donation following circulatory death or kidneys from extended criteria donors.

Living-donor kidney transplant is associated with superior survival of both patient and graft compared with transplant from a deceased donor, and has resulted in expansion of the donor pool. However, according to **Federica Maritati, MD,** and colleagues at the Nephrology, Dialysis, and Renal Transplant Unit at the University of Bologna, Italy, immunologic barriers often create limitations to living-donor transplant. The barriers are mainly associated with performed anti-human leukocyte antigen (HLA) antibodies and ABO system antibodies, which can cause hyperacute rejection.

For many years, ABO incompatible (ABOi) living-donor kidney transplantation was contraindicated, due to the immunological impediment based on the presence of isohemagglutinins, natural antibodies reacting with non-self ABO antigens. More recently, as the demand for kidney transplantation has increased, development of methods to expand the donor pool has gained importance.

Specific desensitization strategies for ABOi transplantation have been developed, and outcomes in ABOi kidney transplantation have shown marked improvement. Previous studies have demonstrated that there is no difference in terms of graft failure, biopsy-proven acute rejection, and patient survival in ABOi kidney transplant versus ABO compatible kidney transplant.

Dr. Maritati et al conducted a review summarizing the primary aspects of ABOi kidney transplantation and the techniques and strategies used to treat recipients to overcome the barrier.

Outcomes Among Obese Kidney Transplant Recipients

Nephrology Dialysis Transplantation. 2022;37(3):584-594

Results of several previous studies have suggested that obese kidney transplant recipients have better survival rates compared with those undergoing dialysis. However, according to **Clarisse Grèze, MD,** and colleagues, access to kidney transplantation is limited among patients with obesity. The researchers conducted a study comparing patient and graft survival rates and post-renal transplant complications between obese recipients and nonobese recipients. The researchers also sought to examine the effect of pretransplant weight loss in obese patients on transplant outcomes.

The prospective cohort study utilized data from two French registries, the Renal Epidemiology and Information Network and CRISTAL, on 7270 kidney transplant recipients between 2008 and 2014 in France.

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Outcomes among obese patients were compared with outcomes among nonobese patients and among obese patients who lost more than 10% of weight prior to the transplant (obese WL and obese nWL).

Among the obese patients, mean body mass index was 32 kg/m^2. Graft survival was lower in obese patients than in nonobese patients (hazard ratio [HR], 1.40; 95% CI, 1.09-1.78; *P*=.007). Patient survival was similar between the two groups (HR, 0.94; 95% CI, 0.73-1.23; *P*=.66).

In comparisons between obese WL and obese nWL, graft survival was significantly lower in obese WL than in obese nWL (HR, 2.17; 95% CI, 1.02-4.63; *P*=.045). The two groups were similar in patient survival (HR, 0.79; 95% CI, 0.35-1.77; *P*=.56).

In conclusion, the researchers said, "Grade 1 obesity does not seem to be a risk factor for excess mortality after kidney transplantation and should not be an obstacle to having access to a graft. Weight loss before a kidney transplant in these patients should not be essential for registration on the waiting list."

Weight Loss Prior to Kidney Transplantation

Journal of Renal Nutrition. 2022;32(3):347-353

There is an association between obesity, a common comorbidity of chronic kidney disease (CKD), and complications following kidney transplantation. While most transplant programs use a body mass index (BMI) limit, there are few data available on the effect of conservative weight loss in kidney transplant candidates. **Roy Hajjar, MD,** and colleagues conducted a retrospective study to examine the efficacy of a basic conservative weight management program in morbidly obese kidney transplant candidates. The researchers also performed a comprehensive nutritional evaluation in a subset of participants.

Eligible patients had BMI >35 kg/m^2 and stage 4 or 5 CKD. The study intervention consisted of anthropometric measurement every 3 months, consultation with a nutritionist, daily exercise, and counseling to encourage healthier eating habits. Quarterly and overall BMI targets were defined at study initiation. In a subset of participants, the researchers conducted a comprehensive nutritional evaluation designed to measure socioeconomic characteristics, food intake behavior, motivation for change, and a 4-day food diary.

A total of 80 patients were observed for a mean duration of 24 months. Approximately 26% of the cohort achieved successful weight loss (BMI <35 kg/m^2). There were associations between female sex and being close to the target at baseline and successful weight loss. At 1 year, the mean excess body weight loss was 84%. None of the patients with baseline BML >40 kg/m^2 were successful at meeting the study target.

A total of 44 patients were included in the comprehensive nutritional evaluation; of those, only 14.6% had previously received nutritional counseling for weight loss. On the food-intake behavior scale, cognitive restraint scored the highest. Most of the patients were motivated to lose weight, with 66% in the action phase. There was little evidence of overeating, with a recommended mean calculated caloric intake of 82.9%

"The conservative weight loss program can have limited but non-negligible success," the researchers said. "Future successful nutritional interventions should take into consideration this surprising comprehensive profile of morbidly obese kidney transplant candidates." ■

Sarah Tolson

Implications of the 2023 ESRD PPS Proposed Rule

When I started my journey in the renal billing field in 2008, I was excited about the opportunity to make a difference in the lives of dialysis patients and to help dialysis facilities. I learned about the long history of Medicare reimbursement of dialysis treatments and how the fundamental principle behind Medicare's coverage and reimbursement of dialysis is for Medicare to provide access to dialysis for people with ESRD. Access to coverage is critical in ensuring there is never a need to bring back committees that decide who gets dialysis.

In addition to learning about dialysis death committees from the 1960s, I also learned how small the gap is between the cost to provide treatment and the amount Medicare reimburses. This gap narrowed further in 2011 with the implementation of the ESRD Prospective Payment System (ESRD PPS). In the years following the rollout of the ESRD PPS, CMS has adjusted the rate at which they reimburse dialysis based on many different factors, one of which is the wage index.

CMS recently released the CY 2023 ESRD PPS Proposed Rule, which includes a proposed increase of 3.1% to the base rate. However, the facility impact file indicates there are facilities that will receive a decrease in reimbursement under the proposed rule. The response I have observed in renal industry forums is a cry to CMS to consider the significant increase in labor costs since the beginning of the Public Health Emergency (PHE) in 2020 in the calculation for the 2023 ESRD PPS base rate. As labor costs are commonly cited as a main contributor to the need for a larger increase in the ESRD PPS, I thought it would be helpful to look at some data related to labor costs.

Using Bureau of Labor Statistics (BLS) data, I compared the national average annual wage per employee for a privately owned kidney dialysis center from 2017 through 2021. Based on this information from the BLS, before the PHE (2017 through 2019) the average annual wage for an employee of a privately held kidney dialysis center was $57,943.33. During the PHE (2020-2021) the average wage increased to $65,052.50, which is an increase of 12.27%. These data are somewhat limited as only privately owned dialysis centers are included; however, it does give us some insight into the changes in labor costs during the PHE.

I was also curious about how the ESRD PPS base rate changed during this same period. During this period, CMS began reimbursing separately for calcimimetics under TDAPA, and in 2021 CMS increased the ESRD PPS base rate by $9.93 to account for the increase in cost of dialysis treatments due to the utilization of calcimimetics. The average base rate from 2017 through 2019 was $233.06. The average base rate for 2020 and 2021, excluding the calcimimetics add-on of $9.93 for the 2021 base rate, was $241.27, an increase of 3.52%.

Considering the disparity in costs and reimbursement, I have been reaching out to the dialysis facilities my company works with to make sure they are aware of the proposed changes and the opportunity to voice their concerns to CMS before the end of the comment period for the 2023 ESRD PPS. In my conversations with the leaders of these dialysis programs, they have highlighted additional financial challenges they have been navigating since the beginning of 2020, such as exacerbated training costs due to increased turnover, costs associated with coverage for staff that are out sick due to COVID-19, and supply costs that increased during the PHE and have not reverted to pre-PHE rates. Supply issues hit smaller facilities the hardest as they don't have the same purchasing power as large dialysis organizations.

To recap, because the PHE and annual wages of privately owned kidney dialysis centers have increased more than 12%, CMS has increased the ESRD PPS base rate by 3.52%. In addition to increases in wages, dialysis facilities are struggling with other cost increases. When costs exceed reimbursement, dialysis facilities are at risk of closing—which would decrease access to care for those with ESRD that are on dialysis. Access to care for this medically fragile and vulnerable population must be preserved. ■

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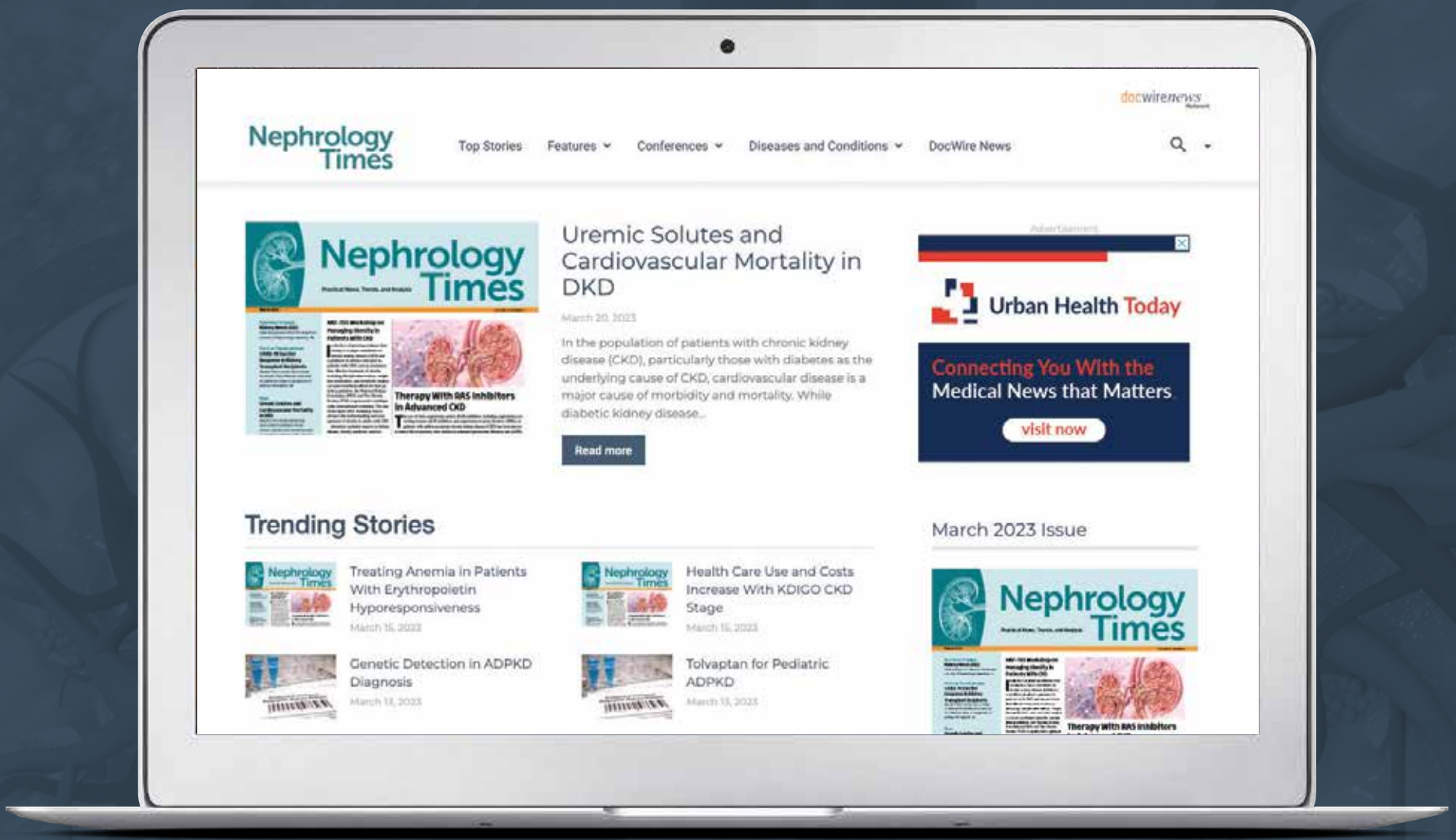

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