Nephrology Times

Practical News, Trends, and Analysis

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Conference Coverage
Selected presentations from the National Kidney Foundation 2020 Spring Clinical Meetings. **8**

Changes in Parathyroid Hormone Levels and Severity of Hyperparathyroidism Symptoms
Larger changes in PTH levels were associated with more pronounced effects. **14**

Focus on Transplantation
Risk of ESRD in Living Kidney Donors by Donor-Recipient Relationship and Across Racial Groups
There were substantial variations in ESRD risk across race and donor-recipient relationship. **20**

PLUS....

From the Field
Chronic Care Management, Part Two
The Chronic Care Management codes and answers to frequently asked questions about CCM. **26**

Renin-Angiotensin System Blockade Therapy in Patients with Low eGFR: Benefits and Risks

Use of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) is the gold standard for the treatment of hypertension, albuminuric chronic kidney disease (CKD), heart failure with reduced ejection fraction, and coronary artery disease. However, along with the benefits of treatment with ACE-Is and ARBs, there are also potential risks, including acute, largely hemodynamic reductions in estimated glomerular filtration rate (eGFR), hyperkalemia, and acute kidney injury (AKI).

Among individuals with lower eGFR, the risks of those adverse events are particularly relevant. Results of previous real-world studies have suggested that more than half of patients who initiated therapy with an ACE-I or an ARB discontinued within 5 years of the initial prescription; discontinuations were increasingly common among patients with more advanced CKD stage.

Guidelines from Kidney Disease Improving Global Outcomes call for temporary discontinuation of ACE-I or ARB therapy in patients with eGFR <60 mL/min/1.83 m^2 "who have serious intercurrent illnesses that increases the risk of AKI." However, the guidelines also emphasize to "not routinely discontinue [ACE-I/ARB] in people with eGFR <30 mL/min/1.73 m^2 as they remain neuroprotective."

continued on page 5

Focus on Transplantation

Kidney Transplant Improves Cardiovascular Functional Reserve

Among patients with chronic kidney disease (CKD), the leading cause of death is cardiovascular disease. In patients receiving maintenance dialysis, left ventricular hypertrophy and systolic and diastolic dysfunction are predictors of worse cardiovascular outcomes. In patients with advanced CKD, the myocardium is exposed to complex metabolic stressors resulting from uremia-related inflammation, oxidative stress, renin-angiotensin-aldosterone system activation, calcitriol

continued on page 4

Effects of Exercise Added to Oral Nutritional Supplementation Physical Function in Dialysis Patients

One of the late consequences of chronic kidney disease (CKD) is protein energy wasting (PEW); PEW is seen in approximately 18% to 75% of patients on maintenance dialysis. PEW adversely affects muscle mass, nutritional status, and physical function in that patient population. CKD-related PEW is associated with decreases in physical function and leads to reductions in quality of life, frailty, disability, and increased risk of mortality.

Anabolic interventions to improve the nutritional status and physical function of patients on dialysis include oral nutritional supplementation, resistance exercise, and aerobic exercise. There are few data available on the effectiveness of a combination of oral nutritional supplementation and anabolic exercise.

Geovana Martin-Alemañy, MSc, and colleagues conducted a study to test the hypothesis that the combination of oral nutritional supplementation with any exercise program would enhance physical function and nutritional status compared with exercise without supplementation. The trial assessed the effect of exercise combined with oral nutritional supplementation versus oral nutritional supplementation without exercise during hemodialysis sessions on physical function and nutritional status. Results were reported in the *Journal of Renal Nutrition* [2020;30(2):126-136].

continued on page 6

Print-only Content

COVID-19 and Acute Kidney Injury

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COVID-19 is essentially an acute respiratory illness that in some patients, especially vulnerable groups, can be fatal. High-risk patients include the elderly and the immunocompromised or immunosuppressed, as well as those with a history of chronic pulmonary disease, asthma, and diabetes. Recent reports in the media suggest a spike in kidney failure, placing a significant strain on the availability of dialysis spots and dialysis machines in the midst of the COVD-19 pandemic. How common is kidney failure and what causes it?

Recent reports from China indicate that acute kidney injury (AKI) occurs in about 25% of critically ill COVID-19 patients.[1,2] The one exception is a study by Wang et al who report on 116 COVID-19-confirmed patients hospitalized at Renmin Hospital in Wuhan University from January 14, 2020, to February 13, 2020.[3] In their study the incidence was less than 5%.

Italian data in more than 2000 patients published in *Critical Care* reinforces an AKI incidence of 27.8% among hospitalized COVID-19 patients.[4] AKI develops approximately 9 days after admission and is accompanied by cardiac complications and secondary infections. The risk factors for AKI include age, severity of illness, and the presence of diabetes.

In the US, very limited published data are available. However, anecdotal reports indicate that AKI is not an uncommon finding and the prevalence numbers are in the 25% range. AKI seems to accompany acute respiratory distress syndrome (ARDS) and is thought to result from the cytokine storm that also causes a coagulopathy, cardiac injury, and hemodynamic compromise. However, while there is a fairly large amount of literature on viral infections causing kidney disease, whether SARS-CoV-2 binding to kidney epithelial cells results in direct nephrotoxicity remains elusive.

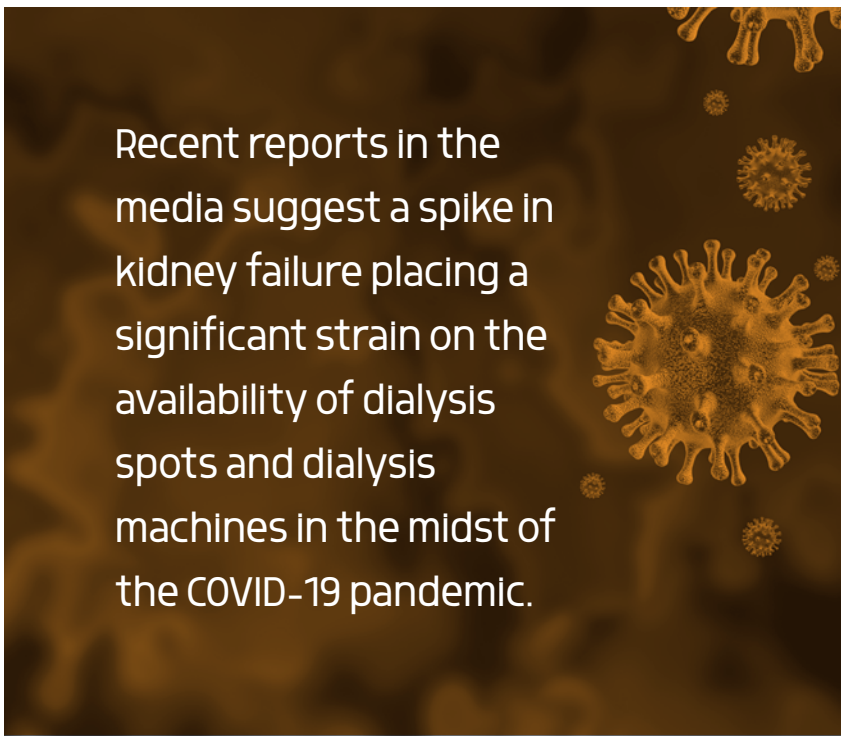
Not all coronavirus infections are associated with AKI; for example, the common cold is not. However, both the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) do appear to be associated with AKI, but through distinct pathways and with a different natural history.[5] MERS-CoV enters cells via binding to dipeptidyl-peptidase 4 (DPP-4), whereas the SARS-CoV via the angiotensin-converting-enzyme-2 (ACE-2) receptor (SARS-CoV-2 also binds via ACE-2). Both DPP-4 and ACE-2 are expressed in several human tissues, including the kidney.

Eckerle et al in 2003 in the *Virology Journal*[5] report that AKI occurs relatively early in MERS-CoV patients (at 11 days), whereas it occurs later in SARS-CoV, at around 20 days. With COVID-19, AKI is observed generally earlier (7-10 days) rather than later.

A recent unpublished study of 85 patients from Wuhan China[6] with laboratory-confirmed COVID-19 confirms an AKI incidence rate of 27.06%. The study included postmortem analysis in six patients. On light microscopy there was severe acute tubular necrosis and lymphocyte infiltration. The infiltration contained CD68+ macrophages. Immunohistochemistry of kidney epithelial cells stained positive for SARS-CoV-2 NP antigen. Immunofluorescence showed complement C5b-9 deposition in tubules, and virus like particles were observed by electron microscopy in the renal epithelial cells.

Earlier reports do point to direct nephrotoxicity from the coronavirus.[7,8] Comparative infection experiments with SARS- and MERS-CoV in primary human kidney cells versus primary human bronchial epithelial cells showed cytopathogenic infection only in kidney cells. MERS-CoV appears particularly nephrotoxic and seems to have a predilection to kidney over bronchial epithelial cells. In this regard, SARS CoV-2 seems to be behaving more like MERS-CoV rather than SARS-CoV.

In summary, from what we know so far, there are likely to be two causes of AKI; one is related to a systemic syndrome with origins in the cytokine storm and the second is direct nephrotoxicity from SARS CoV-2 binding the ACE-2 receptor on kidney epithelial cells. Management of the nephrotoxic effects of SARS CoV-2 will likely require antiviral agents, which at least thus far, has only been possible in the context of clinical trials.



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Kidney Transplant

continued from page 1

and klotho deficiency, increased fibroblast growth factor 23 (FGF 23), and changes in mineral metabolism. This leads to myocyte hypertrophy, reduced myocardial capillarization, and nonvascularized interstitial fibrosis, and arteriosclerosis and arterial stiffening. Combined, the changes reduce pump efficiency and increase cardiac energy expenditure and consumption of myocardial oxygen.

The optimal treatment for end-stage renal disease (ESRD) is kidney transplant; restitution of kidney function is associated with reduced cardiovascular morbidity and improved quality of life and survival. Previous studies of the mechanisms involved with improved cardiovascular survival have relied in most part on static measures from echocardiography or cardiac magnetic resonance imaging; to date, results from those studies have been conflicting.

Kenneth Lim, MD, PhD, and colleagues conducted a prospective, nonrandomized, single-center, three-arm, controlled cohort study to examine cardiovascular functional reserve in patients with ESRD prior to and following kidney transplant. The researchers also sought to examine the functional and morphologic alterations of structural-functional dynamics in that patient population. Results were reported online in *JAMA Cardiology* [doi:10.1001/jamacardio.2019.5738].

The cohort included patients with ESRD who underwent kidney transplant (KTR group), patients with ESRD on the transplant wait-list who did not undergo kidney transplant (NTWC group), and a control group of patients with hypertension but without CKD, cardiovascular disease (heart failure, ischemic heart disease, or cerebrovascular disease), or diabetes (HTC group). Baseline data were gathered from April 2, 2010, to January 1, 2103. Patients were followed up longitudinally for up to 1 year. Patients were assessed at baseline, 2 months, and 1 year.

The total study cohort included 253 participants; mean age was 48.5 years, 55.7% (n=141) were men, 81 were in the KTR group, 85 were in the NTWC group, and 87 were in the HTC group. Of the patients in the KTR group, 91.4% (n=74) received a living donor kidney transplant. Following transplant, the patients received a maintenance immunosuppression regimen consisting of combination treatment with corticosteroids (97.5%, n=79), tacrolimus (93.6%, n=96), or cyclosporine (1.2%, n=1), and azathioprine (50.6%, n=41) or mycophenolate mofetil (44.4%, n=36).

Seventy-three patients (90.1%) in the KTR group completed assessments at two-months post baseline, compared with 81 (95.3%) of those in the NTWC group. Assessments at 12 months were completed by 68 patients (84.0%) in the TKR group, 61 patients (71.8%) in the NTWC group, and 71 patients (81.6%) in the HTC group. None of the 81 patients in the KTR group had serious infectious complications that would have required exclusion from the study. During the 12-month study period, 27 in the KTR group required treatment for acute graft rejection episodes, but were not excluded from the study. Mean estimated glomerular filtration rate (eGFR) of all patients in the KTR group was 55.3 mL/min/1.73 m^2 at 2 months and 59.1 mL/min/1.73 m^2 at 12 months.

Mean age of the patients in the KTR group was 43.1 years, compared with 49.7 years in the NTWC group (P=.002) and 53.6 years in the HTC group (P<.001). Patients in the KTR group had significantly lower mean body mass index compared with the other two groups. There were no significant differences in sex, race/ethnicity, prevalence of hypertension, duration of antihypertensive use, and tobacco smoking status among the three groups. In the two CKD groups (KTR and NTWC), there were no significant differences in the antihypertensives used, prevalence of diabetes or cardiovascular disease, dialysis vintage, or levels of hemoglobin, highly sensitive C-reactive protein, serum calcium, or albumin.

At baseline, mean maximum oxygen consumption (VO_2max) was significantly lower in the two CKD groups (KTR group, 20.7 mL · min^{-1} · kg^{-1}; NTWC group, 18.9 mL · min^{-1} · kg^{-1}; P=.03) compared with the HTC group (24.9 mL · min^{-1} · kg^{-1}) (P<.001). Mean cardiac left ventricular mass index was higher in patients with CKD (KTR group, 104.9 g/m^2; NTWC group, 113.8 g/m^2) compared with the HTC group (878. g/m^2) (P<.001). Mean left ventricular ejection fraction was significantly lower in patients with CKD (KTR group, 60.1%; NTWC group, 61.4%) compared with the HTC group (66.1%) (P<.001).

At 12 months, there was a significant improvement in VO_2max in the kidney transplant group (22.5 mL · min^{-1} · kg^{-1}; P<.001); the value did not reach the VO_2max in the HTC group (26.0 mL · min^{-1} · kg^{-1}). Compared with baseline, at 12 months VO_2max decreased in the NTWC group (17.7 mL · min^{-1} · kg^{-1}; P<.001).

Compared with the KTR group (63.2%, P=.02) or the NTWEC group (59.3%, P=.003) at baseline, there was a significant association between transplant and improved left ventricular ejection fraction at 12 months. There was no association between transplant and improved left ventricular mass index.

The researchers cited some limitations to the study, including lack of randomization and significant baseline differences in known variables associated with cardiovascular risk; the use of echocardiography to assess structural cardiac changes rather than cardiac magnetic resonance imaging; and the lack of assessment of noninvasive measures of cardiac output.

In conclusion, the researchers said, "Our study found that partial restoration of kidney function by transplant was significantly associated with improved cardiovascular functional reserve as assessed by CPET [cardiopulmonary exercise testing], without major change in ventricular structural morphologic features. The CPET-derived indexes were also sensitive enough to detect a decrease in cardiovascular functional reserve in wait-listed patients with CKD who did not receive transplants. The study appears to provide insight on cardiovascular structural-functional dynamics and the association of kidney function restoration with cardiovascular physiologic findings. The data presented indicate that VO_2max may be a sensitive index for assessing cardiovascular function and stratifying risk in patients with renal impairment." ■

TAKEAWAY POINTS

- Researchers conducted a prospective, nonrandomized, single-center, three-arm, controlled cohort study to examine cardiovascular functional reserve in patients with end-stage renal disease prior to and after kidney transplantation.
- At 12 months post-transplantation, there was an association between kidney transplant and improved cardiovascular functional reserve.
- There was no association between kidney transplant and left ventricular mass index.

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Renin-Angiotensin System Blockade Therapy

continued from page 1

Current evaluations of the risks and benefits of ACE-I/ARB therapy in patients with advanced CKD offer conflicting results. **Yao Qiao, MPH,** and colleagues conducted a retrospective, propensity score-martched cohort study to examine the association of ACE-I or ARB therapy discontinuation after decrease in eGFR to below 30 mL/min/1.73 m^2 with the risk of mortality, major adverse cardiovascular events (MACE), and end-stage renal disease (ESRD). A secondary objective of the study was an evaluation of the association of ACE-I or ARB therapy discontinuation with the same end points among users who experienced a decrease in eGFR by ≥40% within 1 year, a surrogate end point for kidney failure used by the US FDA. Results of the study were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2020.0193].

The researchers utilized data from the Geisinger Health System that serves 45 counties in central and northeastern Pennsylvania. A total of 162,654 individuals who initiated therapy with an ACE-I or ARB between January 1, 2004, and December 31, 2018 were identified. Of those, 10,810 had decreases in outpatient eGFR to below 30 mL/min/1.73 m^2 following therapy initiation. Following application of inclusion and exclusion criteria, the final study cohort included 3909 participants.

Of the 3909 study participants, mean age was 73.7 years, and 61.6% (n=2406) were female; 1235 discontinued ACE-I or ARB therapy within 6 months following a decline in eGFR to below 30 mL/min/1.73 m^2, and 2674 did not discontinue therapy. Compared with the group that did not discontinue therapy, those who did were more often male, had lower eGFR, had higher serum potassium levels, had a higher prevalence of congestive heart failure, and were more likely to be receiving antiplatelet agents at the time of the decrease in eGFR. They were also less likely to have diabetes or to be taking statins and beta-blockers.

A total of 1205 participants in the discontinuation group were successfully matched to controls, for a total of 2410 individuals in the propensity score-matched sample. At baseline, the two treatment groups were well balanced on all covariates; the absolute standardized mean differences was below 0.1 for all covariates.

Follow-up continued for a mean of 2.9 years. During follow-up, 35.1% (n=434) of the 1235 participants who discontinued ACE-I or ARB therapy following a decline in eGFR to below 30 mL/min/1.73 m^2 and 29.4% (n=786) of the 2674 who did not discontinue therapy died within 5 years after the baseline date of follow-up. Twenty-eight percent (n=347) of the 1235 patients who discontinued therapy following the decrease in eGFR restarted therapy during the follow-up period. In the propensity score-matched sample, following adjustment for baseline covariates, the association between discontinuation of ACE-I or ARB therapy and a higher risk of mortality remained (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.20-1.60).

During a median follow-up of 2.7 years, the risk of MACE during the 5-year period among the group who discontinued ACE-I or ARB therapy was higher than among those who did not discontinue therapy (40.0% [n=494] vs 34.0%, [901], respectively). The association between discontinuation of ACE-I or ARB therapy and the increased risk of MACE remained in the propensity score-matched sample (HR, 1.37; 95% CI, 1.20-1.56).

Seven percent (n=87) of participants in the group that discontinued ACE-I or ARB therapy with 6 months following an eGFR decline to below 30 mL/min/1.73 m^2 developed ESRD within 5 years compared with 6.6% (n=176) of the group that did not discontinue therapy. In adjusted analysis within the propensity score-matched sample, there was no significant association between discontinuation of ACE-I or ARB therapy and the risk of ESRD (HR, 1.19; 95% CI, 0.86-1.65).

In analyses of additional outcomes, a lower proportion of those who discontinued ACE-I or ARB therapy within 6 months after decrease in eGFR to below 30 mL/min/.73 m^2 experienced hyperkalemia compared with those who did not discontinue therapy (15.6% vs 22.2%). In the propensity score-matched sample, there was an association between discontinuation of ACE-I or ARB therapy and a lower risk of hyperkalemia (HR, 0.65; 95% CI, 0.54-0.79). The risk of developing AKI was slightly lower among those who discontinued therapy, however, after accounting for baseline covariates in the propensity score-matched sample, the risk was not significantly different between the two groups.

The researchers cited some limitations to the study findings, including identifying ACE-I or ARB use via prescription records, preventing verification of actual medication dispensation or intake; the observational design of the study, creating the possibility of confounding; and most of the study population being white.

In summary, the authors said, "We found a higher risk of mortality and MACE associated with ACE-I or ARB therapy discontinuation after an eGFR decrease to below 30 mL/min/1.73 m^2 but no significant differences in the risk of ESRD. Similar patterns held for individuals with a 40% or greater decrease in eGFR. Our findings suggest that continuing ACE-I or ARB therapy in patients with declining kidney function may provide cardiovascular and survival benefits without excess risks of ESRD." ■

TAKEAWAY POINTS

- Researchers investigated the association of discontinuation of renin-angiotensin system blockade (ACE-I/ARB) therapy after decrease in estimated glomerular filtration rate (eGFR) and the risk of mortality, major adverse cardiovascular events (MACE), and end-stage renal disease (ESRD).
- There was a higher risk of morality and MACE associated with discontinuation of ACE-I or ARB therapy after a decrease in eGFR to below 30 mL/min/1.73 m^2.
- There were no significant differences in the risk of ESRD, suggesting that ACE-I/ARB therapy may provide cardiovascular and survival benefits with no excess risk of ESRD.

Effects of Exercise

continued from page 1

The parallel controlled trial included young hemodialysis patients with predominately unknown causes of renal disease. Study participants were categorized into one of three groups: (1) oral nutritional supplementation (n=15); (2) oral nutritional supplementation + resistance exercise; and (3) oral nutritional supplementation + aerobic exercise.

Anthropometric, biochemical, physical function, and quality of life measurements were recorded at baseline and after 3 months. The effect of exercise and nutrition were assessed using repeated measures analysis of variance and effect sizes (Cohen's *d*). The primary outcomes of interest were physical function and muscle strength. Secondary outcomes included assessments of body composition, physical activity, quality of life, and laboratory parameters.

During hemodialysis sessions, study participants received a can of a specialized oral nutritional supplement for maintenance dialysis that consisted of 480 kcal, 20 g protein, 20 g lipids, and 56 g carbohydrates (Enterex® RNL; Victus Laboratories). Enterex RNL contains water, maltodextrin, canola oil, lactalbumin, ascorbic acid, and citric acid as an antioxidant. For participants in the supplementation + aerobic exercise group, half of the can was given during the first hour of the hemodialysis session and the other half after the aerobic exercise routine. The exercise consisted of pedaling a stationary bike and was completed during the first 2 hours of the hemodialysis session. For those in the supplementation + resistance exercise group, half of the can of supplement was also given during the first hour of the session and the other half after the exercise routine. The routine included four types of resistance exercise performed during the first 2 hours of hemodialysis.

A total of 71 patients were assessed for eligibility by a nephrologist; following application of inclusion and exclusion criteria, 45 patients were deemed eligible and were randomized to one of the three study groups. During the study period, 11 patients discontinued the study: six received a kidney transplant, one changed hemodialysis units, one presented parapneumonic pleural effusion, one had postinfectious pericardial effusion, and one patient died due to metabolic derangement associated with dietary transgression.

A total of 34 patients were analyzed; none recorded infection, cardiovascular complication, hospitalization, or death associated with the exercise. Of those 34, 13 were in the supplementation alone group, 12 were in the supplement + aerobic exercise group, and nine were in the supplement + resistance exercise group.

At baseline, with the exception of body mass index, triceps, and skinfold thickness, there were no significant differences among the three groups in any of the study variables. Overall, median age was 29 years, 46.7% (n=21) were male, and the cause of CKD was unknown in 80% of the participants. Most of the study population (86.7%) received two hemodialysis sessions per week. Participants in the supplement alone group had lower percent fat mass and lower body mass index than those in the other two groups. There were no differences in physical function at baseline.

In the two exercise groups, there were statistically significant improvements in the times up and go (TUG) test, 6-minute walk test (6-MWT), sit-to-stand (STS) test, and in handgrip strength. Participants in the supplement alone group showed statistically significant increases in the 6-MWT (P=.003), TUG test (P=.013), and muscle strength (P=.000).

In the distance walked in 6 minutes, the group without exercise had an increase of 11m; the group with resistance exercise had an increase of 43 m and the group with aerobic exercise had an increase of 42 m. There were no statistically significant differences in the time × group interaction of the physical function tests and muscular strength among the groups; however, according to the magnitude of effect sizes (Cohen's d), groups with exercise reported larger effects in comparison with the nonexercise group in the 6-MWT, STS test, TUG test, and in muscle strength.

The oral supplementation + resistance exercise group had more areas of improvement in quality of life at the end of the study, followed by the supplementation + aerobic exercise group.

The researchers did cite some limitations to the findings, including the lack of follow-up time to observe the anabolic impact of the combination of exercise and oral nutritional supplementation, and the age of the patients, with a bias toward relatively young patients who are generally more active and physically functional.

"In conclusion, our findings indicate that neither 12 weeks of aerobic exercise or resistance exercise training significantly improves physical function in hemodialysis patients more than oral nutritional supplementation alone. This may have been due to a number of factors, including the relatively short intervention period, the modest dose and intensity of the exercise intervention, and the small sample size in this pilot study. Indeed, we did observe larger effect sizes for physical function outcomes in the exercise groups, suggesting a modest improvement in the indices when oral nutritional supplementation and exercise are combined. Future studies should consider strategies that include more robust exercise interventions that may enhance the effects seen here and in other similar studies," the researchers said. ■

TAKEAWAY POINTS

- Results of a parallel controlled trial designed to compare the effect of aerobic exercise and resistance exercise programs both combined with oral nutritional supplementation versus oral nutritional supplementation alone in a cohort of patients on maintenance hemodialysis.
- Outcomes of interest were physical function, muscle strength, quality of life, and indicators of nutritional status.
- The combination of exercise with oral nutritional supplementation had larger effects on physical function than oral nutritional supplementation alone.

CONFERENCE COVERAGE KIDNEY WEEK 2019

Reloxaliase: Pro Tem Results from Study ALLN-177-206

Washington, DC–Increased excretion of urinary oxalate, enteric hyperoxaluria, can occur as a complication of fat malabsorption associated with gastrointestinal surgery or other gastrointestinal conditions. Hyperoxaluria is also a major risk factor for kidney stones and can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Levels of plasma oxalate can rise subsequent to decreasing kidney function, resulting in oxalate deposition in the kidneys and other tissues.

Reloxaliase is an oral enzyme that degrades oxalate in the gastrointestinal tract. Researchers, led by **Felix Knauf, MD,** are enrolling patients with enteric hyperoxaluria and CKD in a pilot study to examine the efficacy of reloxaliase in reducing urinary oxalate excretion and plasma oxalate. The study was described during a poster session at Kidney Week 2019 in a poster titled *Pilot Study of Reloxaliase in Subjects with Severe Enteric Hyperoxaluria and Hyperoxalemia: A Pro Tem Analysis of Study ALLN-177-206.*

Inclusion criteria for the open label study are diagnosis of enteric hyperoxaluria, CKD, and hyperoxalemia (defined as urinary oxalate 40 mg/24 hours; estimated glomerular filtration rate <45 mL/min/1.73 m^2, and plasma oxalate >5 mmol/L, respectively). Participants receive reloxaliase 7500IU orally five time per day for 12 weeks. Measurements of plasma oxalate levels and 24 hour urinary oxalate excretion are obtained monthly; in participants receiving dialysis, plasma oxalate level is collected immediately prior to the dialysis session following the longest weekly interval between sessions. The change from baseline to the on-treatment average plasma oxalate level and urinary oxalate excretion were utilized to assess efficacy of reloxaliase.

To date, four participants with enteric hyperoxaluria have completed the study: two have stage 3 and 3bT CKD (short bowel syndrome, fat malabsorption status post-kidney transplant) and two receive hemodialysis (Crohn's disease, pancreatic insufficiency). On average, treatment compliance was 90%, and the therapy was well tolerated. Twenty-four hour urinary oxalate excretion (normalized to creatinine) was reduced by 29% to 42%, and plasma oxalate level was reduced by 16% to 49%.

In conclusion, the researchers said, "In this population, reloxaliase was well tolerated and reduced both urinary oxalate and plasma oxalate level, suggesting the potential for reducing systemic oxalate deposition with chronic therapy. These preliminary data support further testing of reloxaliase in patients with severe enteric hyperoxaluria. To our knowledge, this is the first therapeutic reduction in plasma oxalate in patients with enteric hyperoxaluria and CKD with oxalosis."

Source: Knauf F, Lieske JC, Pfau AC, Grujic D, Bernard KE, Kausz AT. Pilot study of reloxaliase in subjects with severe enteric hyperoxaluria and hyperoxalemia: A pro tem analysis of study ALLN-177-206. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2019 (Abstract FR-P0316), November 8, 2019, Washington, DC.

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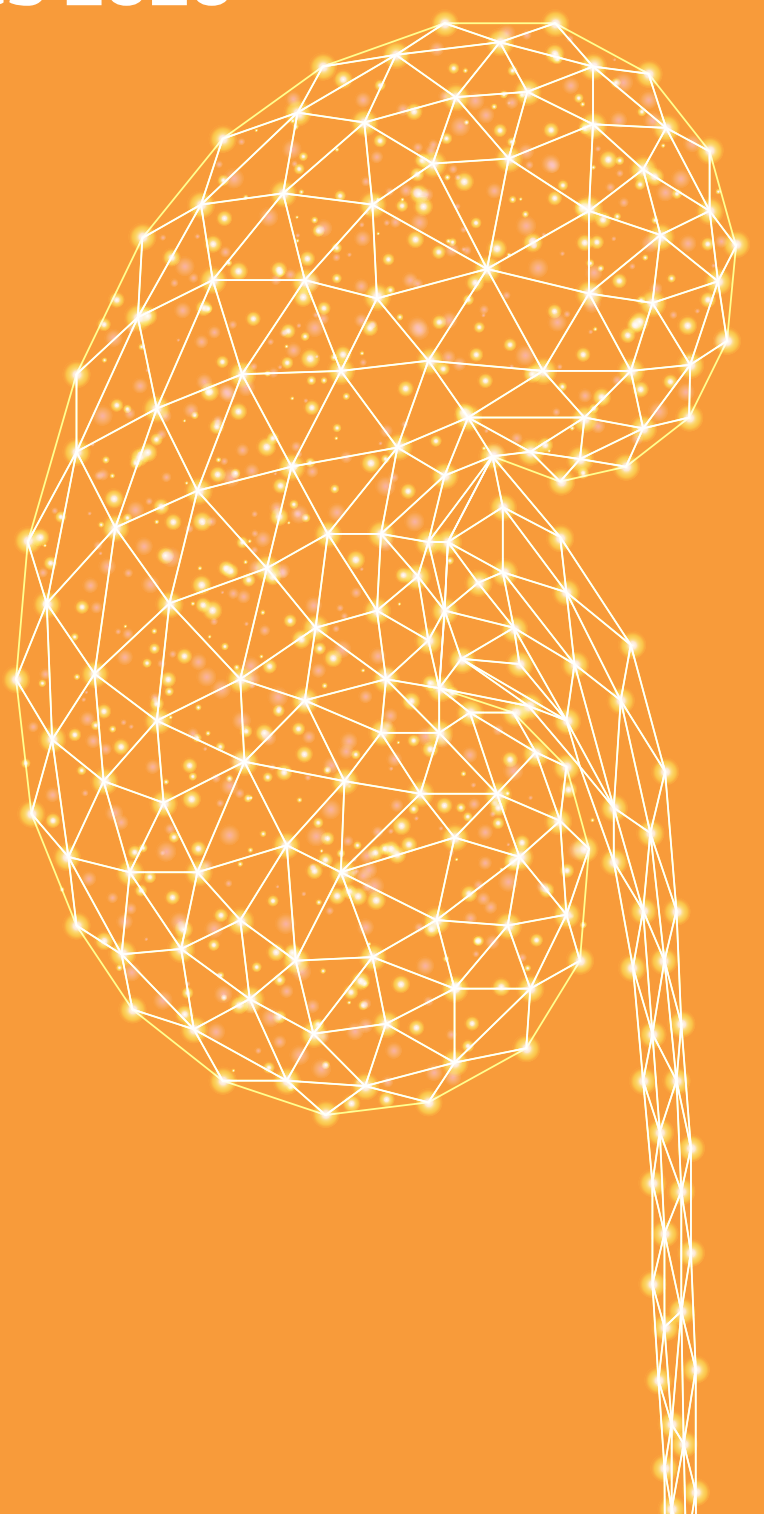
NATIONAL KIDNEY FOUNDATION

SPRING CLINICAL MEETINGS 2020

March 25-29, 2020



Nephrologists, fellows and residents with a special interest in kidney disease, general internists, pharmacists, physician assistants, nurse practitioners, nurses and technicians, social workers, and renal and clinical dietitians all benefit from the NKF Spring Clinical Meetings.

Presenters reported the latest insights into chronic kidney disease care and participants were informed about new and evolving concepts related to kidney disease.

Investigational Interventions May Improve Physical Function in Patients with CKD

In patients with chronic kidney disease (CKD), complications associated with aging occur at younger ages compared with the general population. **Matthew Abramowitz, MD,** and colleagues conducted a recent analysis to examine impaired physical function (a common complication of aging) in the context of a recent trial of the investigational product veverimer in patients with CKD. Results of the analysis were reported in a presentation at the NKF Spring Clinical Meetings. The presentation was titled *CKD as a Model of Accelerated Aging and Improvement in Physical Function with Investigational Product Veverimer.*

The randomized, placebo-controlled trial included patients with estimated glomerular filtration rate 20 to 40 mL/min/1.73 m^2; results found an association between veverimer and a statistically significant improvement at 52 weeks in the time required to complete a 5-repetition chair stand test (STS time). The current analysis examined those results in the context of accelerated aging using population-based reports of mean STS time by age group, as well as STS time scored as a component of the Short Physical Performance Battery (SPPB). The treatment × time interaction was assessed using generalized estimating.

Mean age of the cohort was 62 years. At baseline, only 27% of the cohort had STS times at least as fast as the average patient 60 to 69 years of age; 45% were slower than the average patient 80 to 89 years of age. The median SPPB chair stand time score was 2. Following 52 weeks of treatment, both proportions improved in the veverimer group but not in the placebo group (P=.02 for functionally 60-69-year olds; P=.06 for functionally 80-89-year olds).

In the veverimer group, between baseline and week 52, STS time decreased by 4.3 seconds; the difference was larger than the 3.4 second difference in mean expected performance in patients between 80 and 89 years of age and those between 60 and 69 years of age (i.e., -20-year age difference). In the veverimer arm, the placebo-corrected improvement in STS time (2.9 seconds) was larger than the 2.2 second mean expected performance in patients between 80 and 89 years of age and those between 70 and 79 years of age (i.e., -10-year age difference). More patients in the veverimer group had a ≥1-point improvement in SPPB chair stand score than in the placebo group: 41% versus 16%; P<.001.

In conclusion, the researchers said, "CKD patients have markedly reduced physical function compared to adult populations of the same age. Interventions that improve physical function in patients with CKD have the potential to restore a substantial proportion of age-predicted loss of performance."

Source: Abramowitz M, Mathur V. CKD as a model of accelerating aging and improvement in physical function with investigational product veverimer. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #219.

Persistent AKI as Predictor of In-Hospital Mortality in Abdominal Surgery

Surgical patients frequently experience acute kidney injury (AKI). AKI is associated with adverse effects on both short-term and long-term outcomes. **Ioana Gameiro, MD,** and colleagues in Portugal conducted a study designed to examine the incidence and predictive factors of transient and persistent postoperative AKI in patients undergoing major abdominal surgery. The researchers also sought to characterize the impact of AKI on in-hospital mortality.

Results were reported online in a NKF 2020 Spring Clinical Meetings abstract. The abstract was titled *Postoperative AKI Duration and Outcome in Patients Undergoing Major Abdominal Surgery.*

The current study was a cross-examination of a retrospective analysis of clinical data of 450 patients who underwent major abdominal surgery form January 2010 to February 2011. The analysis included only AKI developing in the first 48 hours following surgery.

The Kidney Disease Improving Global Outcomes classification was used to define AKI based on both serum creatinine and urine output criteria. Persistent and transient AKI were defined using definitions from the Acute Disease Quality Initiative workgroup.

In the first 48 hours following surgery, 22.4% of patients developed AKI (n=101); of those, 48% (n=49) had persistent AKI, defined as postoperative AKI with a duration of more than 48 hours. Independent predictors of persistent AKI were older age (adjusted odds ratio [aOR], 1.06; 95% confidence interval [CI], 1.00-1.11; P=.039); hypertension (aOR, 4.60; 95% CI, 1.17-18.11; P=.029); and higher preoperative serum creatinine (aOR, 22.67; 95% CI, 4.00-128.46; P<.001).

Overall in-hospital mortality was 6.4% (n=29). There was an association between persistent AKI and higher mortality compared with transient AKI (51.9% vs 20.7%; unadjusted OR, 13.03, 95% CI, 5.78-29.36; P<.001; aOR, 4.20, 95% CI, 1.02-17.27, P=.047).

In summary, the researchers said, "In this cohort of patients submitted to major abdominal surgery, persistent AKI was an independent predictor of in-hospital mortality in contrast to transient AKI."

Source: Gameiro I, Duarte I, Marques F, et al. Postoperative AKI duration and outcome in patients undergoing major abdominal surgery. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #3.

Diabetes Associated with Higher Proteinuria in Patients with Glomerular Diseases

The Cure Glomerulopathy Network (CureGN) is a multi-center, prospective, observational study of patients with primary glomerular disease. According to **Natasha Freeman, MD,** and colleagues at the Columbia University Roy and Diana Vagelos College of Physicians and Surgeons, New York, New York, the exclusion from CureGN of patients with a prior history of diabetes "disadvantages a rising proportion of patients with glomerular disease."

The researchers conducted a study to examine the presentation and outcomes of excluded diabetic patients at the Columbia University site with focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) versus enrolled CureGN patients. Results of the study were reported online in a National Kidney Foundation 2020 Spring Clinical Meetings abstract. The abstract was titled *Presentation and Outcomes of Primary Glomerular Diseases in Patients with and without Diabetes Mellitus.*

The study matched 48 diabetic subjects with FSGS (n=16) or MN (n=10) treated at Columbia University to 96 age- and disease-matched CureGN controls at the same site. ANOVA, two-sample T-test, and Fischer's exact test were used to analyze clinical and histopathologic data at presentation; the researchers also examined the rates of progression to end-stage renal disease (ESRD) at 5 years.

At presentation, there was no significant difference in renal function among all groups; in diabetic patients with both FSGS and MN, proteinuria was greater than in the non-diabetic patients. Diabetic patients with MN also had more hematuria (P=.005) and anti-PLA2R negative disease (P=.01).

The presence of diabetic glomerulosclerosis on biopsy among diabetic patients with MN was associated with lower estimated glomerular filtration rate (eGFR) and more chronicity histologically. However, the differences were not seen in diabetic patients with FSGS. Regardless of diagnosis, there was a trend toward higher rates of ESRD in the presence of diabetic glomerulosclerosis (22.7% vs 7.9%; P=.1).

"A history of diabetes is associated with a higher degree of proteinuria at presentation in both FSGS and MN. The presence of concomitant diabetic glomerulosclerosis may be associated with reduced eGFR, more chronicity histologically, and higher rates of ESRD in glomerular disease patients," the researchers said.

Source: Freeman N, Canetta P, Bomback A. Presentation and outcomes of primary glomerular diseases in patients with and without diabetes mellitus. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #345.

AMBER Trial Results by Patient Age: Patiromer vs Placebo

In patients with resistant hypertension, use of spironolactone reduces blood pressure. However, in patients with chronic kidney disease (CKD), hyperkalemia may limit the use of spironolactone. Results of the AMBER study demonstrated that the addition of patiromer enabled more persistent use of spironolactone in patients with resistant hypertension and advanced CKD.

Older patients may be at increased risk for hypertension. In a presentation during the NKF Spring Clinical Meetings, **Rajiv Agarwal, MBBS,** and colleagues reported AMBER results stratified by age. The presentation was titled *Patiromer vs Placebo to Enable Spironolactone in Patients with Resistant Hypertension and CKD According to Patient Age (AMBER Trial).*

AMBER, a randomized, double-blind, placebo-controlled randomized clinical trial, included adults with estimated glomerular filtration rate 25 to ≤45 mL/min/1.73 m^2, and uncontrolled resistant hypertension. Patients were randomly assigned 1:1 to spironolactone plus placebo or to spironolactone plus patiromer. The primary end point was the between group difference at week 12 in the percentage of patients on spironolactone. In the current analysis, the end point was assessed prospectively by age (<65 years and ≥65 years).

A total of 295 patients were randomized; of those, 31.5% (n=93) were <65 years of age and 68.5% (n=202) were ≥65 years of age. At baseline, mean automated office systolic blood pressure was 145.4 mmHg and 143.5 mmHg, respectively. Mean baseline serum potassium level was 4.71 mEq/L and 4.72 mEq/L, respectively.

In both subgroups, significantly more patients treated with patiromer than those in the placebo group remained on spironolactone at week 12 (between group difference: <65 years, 21.6%; *P*=.0137; ≥65 years, 18.3%; *P*=.0037). The mean cumulative spironolactone dose was higher with patiromer than with placebo by 332 mg and 398 mg in patients <65 years of age and patients ≥65 years of age, respectively.

Among patients <65 years of age, adverse events occurred in 52% of the placebo group and 65% of the patiromer group. Among patients ≥65 years of age, the percentages of adverse events were 54% (placebo) and 51% (patiromer). A total of four patients (one in the placebo group and three in the patiromer group) had serum magnesium 1.2 to <1.4 mg/dL.

In conclusion, the researchers said, "Patiromer enabled more patients with advanced CKD and resistant hypertension to continue spironolactone treatment, including those aged ≥65 years."

Source: Agarwal R, Rossingnol P, Mayo MR, et al. Patiromer vs placebo to enable spironolactone in patients with resistant hypertension and CKD according to patient age (AMBER trial). Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #401.

Higher Glycemic Control Associated with Lower Albuminuria

Worldwide, the leading cause of chronic kidney disease (CKD) is diabetes mellitus. According to data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of kidney disease in patients with diabetes overall has not changed over time. However, there have been changes in the prevalence of the independent defining features of kidney disease.

Albuminuria (albumin creatinine ratio [ACR], ≥30 mg/g) has declined over time, while the prevalence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 has increased. There are few available data on whether the prevalence of those features is associated with glycemic control (defined by hemoglobin A1c).

Mitra Mosslemi and colleagues at the University of California, Irvine, conducted a study to examine the association of glycemic control level with clinical manifestation of CKD among patients with diagnosed diabetes. The researchers reported results in a presentation during the NKF Spring Clinical Meetings. The presentation was titled *Association of Glycemic Control Level with the Clinical Manifestation of Kidney Injury among Patients with Diagnosed Diabetes.*

The cross-sectional study analyzed NHANES data from 1999 through 2016. Diagnosed diabetes cases where those who reported being diagnosed by a physician or using glucose-lowering medications (n=5647). The researchers characterized the proportion of any CKD (ACR ≥30 or eGFR <60), albuminuria only (ACR ≥30 and eGFR ≥60), reduced eGFR only (ACR <30 and eGFR <60), and both albuminuria and reduced eGFR (ACR ≥30 and eGFR <60) among patients with diagnosed diabetes with good (a1c <7%), intermediate (7% ≤ A1c <9%), and poor glycemic control (A1c >9%).

The study also examined the prevalence of patients with hyperfiltration (defined by eGFR >120) across glycemic control groups. The association between eGFR and ACR with A1c was assessed using univariate and multivariable linear regression models.

Proportions of any CKD in the study population were similar across glycemic control groups: good, 51%; intermediate, 50%; and poor, 54%. The proportion of patients with reduced eGFR only was highest in the good glycemic control group, and the albuminuria only status was highest in the group with poor glycemic control.

In univariate analyses, there were significant associations between A1c and ACR and between A1c and eGFR. Following adjustment for age, sex, race, and age at diagnosis of diabetes, the association remained significant only for ACR. In the poor glycemic control group compared with the other two groups, the percentage of hyperfiltration (relatively higher eGFR) was higher: 8.5% versus intermediate, 4% and good, 3.2%.

"This study demonstrated that among patients with diabetes, better glycemic control is associated with lower albuminuria, but not higher eGFR level. Further studies should examine the risk factors of eGFR decline in patients with diabetes," the researchers said.

Source: Mosslemi M, Wenziger C, Hsiung J-T, et al. Association of glycemic control level with the clinical manifestation of kidney injury among patients with diagnosed diabetes. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #311.

Multidisciplinary Team Model Improves Anemia Management in Patients On Peritoneal Dialysis

Management of anemia in patients receiving peritoneal dialysis carries more challenges compared with anemia management in patients receiving hemodialysis. Peritoneal dialysis patients are seen infrequently and, due to factors related to finances, social life, and work life, noncompliance with anemia regimens is more common among peritoneal dialysis patients than among hemodialysis patients. The limited time and interaction between patient and clinician contribute to limited success in anemia management in peritoneal dialysis patients.

At Hamad General Hospital, Doha, NA, Qatar, anemia management in peritoneal dialysis was transferred to a multidisciplinary team led by a trained peritoneal dialysis nurse. **Abdullah Hamad, MD,** and colleagues conducted a retrospective cohort study to examine the impact of the new model to achieve anemia targets. Results of the study were reported online in an abstract from the NKF 2020 Spring Clinical Meetings.

The study included all patients on chronic peritoneal dialysis for more than 1 month in Qatar. The researchers reviewed data from June 2017 to July 2018; the multidisciplinary team model was initiated in August 2017. Patient characteristics, laboratory test results, and medications were identified via electronic medical records and quality data.

The mean census during the study period was 180 (range, 177-184). Throughout the study period, an average of 76% of patients were treated with erythropoietin stimulating agents (ESA) (range, 67% to 82%). Following initiation of the multidisciplinary team model, the number of patients with monthly office visits and measured hemoglobin (Hb) improved from 73% to 83%, and the number of patients requiring a monthly Hb recheck decreased from 30% to 17% (*P*=.01).

The percentage of patients in the target Hb range of 10 to 12 g/dL improved from 52% in June 2017 to 68% in July 2018 (*P*=.009). Extreme Hb, defined as <9 or >13 d/dL, also improved, from 13% to 8% during the same time period; there were no changes in ferritin and iron saturation levels.

A third of the patients received financial aid for their ESA regimen. Noncompliance with monthly visits and ESA adherence was reduced from 20.5% to 10% (*P*=.03) following the multidisciplinary team model initiation. The ESA dose was reduced by 6%, with an estimated cost savings of $30,000 annually.

"Anemia management in peritoneal dialysis was shifted to a multidisciplinary team model. The new model achieved better target Hb and decreased extreme Hb levels. It also improved compliance, efficiency, and cost benefit. A multidisciplinary team model should be considered more in peritoneal dialysis management," the researchers said.

Source: Hamad A, Ezzat H, Futotana M, et al. Effect of multidisciplinary team on anemia management in peritoneal dialysis patients. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #187.

Mortality Risk Higher in Patients with Post-Dialysis MAP 107 mm Hg or Less

Among patients receiving hemodialysis, blood pressure control presents challenges requiring multiple medications and aggressive control of fluid gain. Lacking robust guidelines regarding patients on hemodialysis, nephrologists commonly rely on blood pressure targets derived from non-hemodialysis patients. **Manasi Tannu, MD,** and **Jose Navarrete, MD,** at the Emory University School of Medicine, Atlanta, Georgia, conducted a retrospective cohort study to examine whether achieving a normal blood pressure post dialysis is associated with better survival.

The researchers reported results of the study in a presentation during the NKF Spring Clinical meetings. The presentation was titled *Post-Hemodialysis Blood Pressure and Risk of Death*.

The study included 855 incident hemodialysis patients admitted to Emory Dialysis from January 2011 to December 2015; follow-up continued until December 2018.

Following adjustment for age, weight, diabetes, Kt/V, and ultrafiltration rate (UFR), there was an association between a post-dialysis mean arterial pressure (MAP) of 107 mmHg or less (equivalent to blood pressure 140/90) and a significant increase in the risk of death (hazard ratio, 1.53; 95% confidence interval, 1.1-2.1). Patients with MAP of 107 mmHg or less were older (60 vs 57 years) with similar UF (1.8 vs 1.9 L), UFR (6.4 vs 7.2 mL/h/kg), and prevalence of diabetes (40%) and congestive heart failure (20%) than those with higher post-dialysis MAP. In patients with post-dialysis MAP of 107 mmHg or less, the risk of severe hypotension (MAP <60 mmHg) was more common than in patients with higher post-dialysis MAP (5.4% vs 1.5%).

In summary, the researchers said, "A post-hemodialysis MAP of 107 mmHg or less was associated with a higher risk of death as well as a higher risk of hypotensive episodes during dialysis. These data suggest that blood pressure goals for the non-dialysis population should not be used in hemodialysis patients. Further, aggressive blood pressure control increases the risk of hypotension during dialysis, perhaps contributing to the higher mortality observed in patients with post-hemodialysis MAP of 107 mmHg or less."

Source: Tannu M, Navarrette J. Post-hemodialysis blood pressure and risk of death. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #203.

Healthcare Costs Higher in Patients with ADPKD and Advanced Renal Dysfunction

In patients with autosomal dominant polycystic kidney disease (ADPKD), the progressive nature of declining kidney function is associated with increased risk of cardiovascular events and mortality. **Patrick Gagnon-Sanschagrin, BSc,** and colleagues recently conducted an analysis to examine the use of healthcare resources and costs associated with increasing renal dysfunction in patients with ADPKD. Results were reported online at the NKF Spring Clinical Meetings. The report was titled *Substantial Excess Healthcare Costs in Commercial and Medicare Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) with Advanced Renal Dysfunction*.

The researchers utilized IBM MarketScan® Commercial and Medicare Advantage Supplemental Databases from January 1, 2015, to December 31, 2107, to conduct a retrospective matched cohort claims analysis. Patients with ADPKD were eligible for the analysis if they had continuous enrollment and two *International Classification of Diseases, Tenth Edition, Clinical Modification* diagnosis codes for ADPKD.

Each patient with ADPKD was matched with up to three different patients without ADPKD (controls) by age, sex, region of residence, insurance plan, and calendar year. Differences in costs per patient per year (PPPY) between cohorts were estimated using index renal function stage.

The analysis included 7861 eligible patients with ADPKD and 22,928 controls in the commercial cohorts and 1366 eligible patients with ADPKD and 3922 controls in the Medicare Advantage cohorts. Costs in the ADPKD cohorts were higher than in the control cohorts.

There were significant variations in costs by index renal function stage. Total cost differences incurred among patients receiving dialysis were 34 to 37 times greater compared with patients with CKD stage 1 (commercial: $205,073 PPPY vs $6024 PPPY; Medicare: $259,974 PPPY vs $6984 PPPY).

In conclusion, the researchers said, "This study supports previous estimates of the excess economic burden among patients with ADPKD. Compared with controls, patients with ADPKD incur higher costs in both commercial and Medicare plans and the costs increase with renal impairment. Interventions to prevent loss of renal function early in the disease process have the potential to reduce substantial healthcare charges."

Source: Gagnon-Sanschagrin P, Liang Y, Sanon M, Oberdhan D, Cloutier M. Substantial excess healthcare costs in commercial and Medicare patients with autosomal dominant polycystic kidney disease (ADPKD) with advanced renal dysfunction. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #378.

Renal Outcomes in Simultaneous Kidney-Heart Transplant Recipients

Patients with both end-stage heart failure and severely impaired kidney function are candidates for simultaneous kidney-heart transplants (SKHT). There are limited data on renal outcomes in patients undergoing SKHT, obtained primarily from single-center studies. **Krishna Agarwal, MD,** and colleagues conducted an analysis of data from the United Network for Organ Sharing (UNOS) dataset on 1706 recipients of SKHT.

Results of the retrospective cohort analysis were reported in a presentation during the NKF Spring Clinical Meetings. The presentation was titled *Factors Associated with Renal Graft Loss in Simultaneous Kidney-Heart Transplant Recipients in the UNOS Cohort*.

The analyzed data included patients who received their transplants between October 1987 and December 2018. The researchers compared the incidence and risk factors of renal allograft loss in SKHT recipients with failed renal allograft with those with a functioning renal allograft at 3-year follow-up. Continuous variables were compared using the Student t-test or the Kruskal Wallis test; categorical variables between groups were compared using the Chi-2 test. Cox regression hazard models were used to examine the factors associated with graft failure.

The analysis included 1706 SHKT recipients. Over 3 years of follow-up, 94.3% (n=1608) had functioning renal allografts and 5.7% (n=98) had failed renal allograft. Compared with the group with functioning renal allograft, those with failed renal allograft were more likely to have high-risk cytomegalovirus status, expanded-criteria donor, delayed graft function, and higher creatinine at discharge. In the group with functioning renal allograft, use of tacrolimus at discharge was higher than among patients with nonfunctioning renal allograft.

Causes of renal allograft failure were primary failure (16%), chronic rejection (12%), acute rejection (11%), cardiorenal (8%), infection (7%), and other causes in the remainder.

The researchers said, "The number of simultaneous kidney-heart transplants has been gradually increasing in the United States over the past two decades from 11 before 1990 to 208 in 2018. Single-center studies have previously described renal outcomes in SKHT recipients at their respective centers. Our study describing the factors associated with renal graft loss in SKHT recipients in the UNOS database is the largest to date."

Source: Agarwal K, Almonte K, Patel H, Cardarelli F, Agarwal N. Factors associated with renal graft loss in simultaneous kidney-heart transplant recipients in the UNOS cohort. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #453.

Metabolic Acidosis in Patients with CKD and Hyperkalemia

Patients with chronic kidney disease (CKD) may experience both hyperkalemia and metabolic acidosis. **Erin Cook, MD,** and colleagues conducted a study designed to determine the prevalence of metabolic acidosis among patients with CKD and hyperkalemia. Results were reported in a presentation at the NKF Spring Clinical Meetings in a session titled *Prevalence of Metabolic Acidosis among Patients with CKD and Hyperkalemia*.

Electronic medical records from the Research Action for Health Network were utilized to estimate the annual prevalence of metabolic acidosis among patients with CKD and hyperkalemia from 2014 to 2017. For each calendar year, adult patients eligible for participation in the study had CKD stage 3-5 (≥2 estimated glomerular filtration rate values <60 mL/min/1.73 m^2 or ≥1 CKD diagnosis code) and ≥1 bicarbonate laboratory value available. Exclusion criteria were end-stage renal disease (CKD stage 5 and the need for dialysis in the prior year).

Metabolic acidosis was defined in the primary analysis as bicarbonate <22 mEq/L for potassium >5.0 and >5.5 mEq/L. The prevalence of metabolic acidosis defined as bicarbonate <18 mEq/L with both hyperkalemia cutoffs was also calculated.

During the study period, the prevalence of metabolic acidosis, (bicarbonate <22), ranged from 24.5% to 29.4% for potassium >5.0 and from 33.1% to 39.1% for potassium >5.5. Of the patients with CKD and potassium >5.0, those with metabolic acidosis (bicarbonate <22) were younger (mean age 68.7 years vs 74.0 years), more likely to have CKD stage 5 (34.8% vs 13.4%) or type 2 diabetes (62.6% vs 56.3%), less likely to receive renin-angiotensin, aldosterone system inhibitors (54.3% vs 59.8%), and more likely to receive potassium-binding treatments (32.1% vs 10.5%), diuretics (61.2% vs 52.0%), or oral sodium bicarbonate (20.9% vs 4.0%), compared with those without metabolic acidosis.

In conclusion, the authors said, "From 2014-2017, metabolic acidosis prevalence (bicarbonate <22 mEq/L) ranged from 24.5% to 29.4% for potassium >5.0 mEq/L and 33.1% to 39.1% for potassium >5.5 mEq/L among patients with CKD and hyperkalemia and was sensitive to the definition of metabolic acidosis utilized. Metabolic acidosis is commonly seen in conjunction with hyperkalemia in patients with CKD stage 3-5, as the kidney's ability to maintain electrolyte and acid-balance is compromised."

Source: Cook E, Davis K, Israni R, et al. Prevalence of metabolic acidosis among patients with CKD and hyperkalemia. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #316.

Subanalysis of NCT 03536663: Optiflux® F160NR Dialyzer Safe and Effective

Jill Meyer, MD, of the California Institute of Renal Research, Chula Vista, California, presented results of a subanalysis of data from the clinical trial, An Open-Label Clinical Study to Assess the Performance of the Dialyzer with Endexo™ in End-Stage Renal Disease Subjects (NCT # 03536663) during the NKF 2020 Spring Clinical Meetings. Participants in the study were dialyzed with the Optiflux® F160NR dialyzer, followed by the new dialyzer with Endexo.

The presentation was titled *Clinical Performance of the Optiflux F160NR Dialyzer.* The subanalysis examined the safety and performance of the Optiflux F160NR dialyzer.

Study participants were patients who were prescribed hemodialysis three times per week for a minimum of 30 days at three study sites in the United States. The study period that included the Optiflux F160NR dialyzer included 12 hemodialysis treatments. Assessments of performance and safety in the subanalysis included urea reduction ratio (URR), single-pool Kt/V (spKt/V), serum albumin, and ß-2-microglobulin levels. Also included were removal rates measured prior to and following hemodialysis, complement activation, and adverse events.

A total of 26 patients were screened; of those, 23 were enrolled in the study. Median age was 64 years, 73.9% were female, and 73.9% were white. Overall, the study participants completed 268 hemodialysis treatments with the Optiflux F160NR dialyzer.

Of the 23 study participants, four discontinued the study, due to missed visits not related to adverse events. The remaining 19 participants completed all 12 hemodialysis treatments per study protocol (n=228 dialysis sessions). The mean duration of dialysis was 205.2 minutes, mean blood flow rate was 445.6 mL/min, mean dialysate flow rate was 695.0 mL/min, mean blood volume processed was 82.2 L, and mean ultrafiltration volume was 2255.8 mL.

There were no serious adverse events reported during the study period. Four participants reported at least one adverse event not related to the device.

For the measurements of interest, mean reported values were: 80.5% for URR; 1.9 for spKt/V; 47.1% for corrected ß-2-microblobulin removal rate; and a post-dialysis increase of 8.3% for serum albumin. Complement activation was measured prior to and 30 minutes after hemodialysis start and showed no overt activation for C_3a, C_5a, and sC_5b-9.

In conclusion, the researchers said, "Hemodialysis treatments were well tolerated and URR and spKt/V were high with Optiflux F160NR dialyzer. Serum albumin levels increased post hemodialysis. Complements showed no overt activation."

Source: Meyer J, Steer D, Weber D, et al. Clinical performance of the Optiflux® F160NR dialyzer. Abstract (#249) of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #249.

In-Patient Admissions Reduced with Participation in a CKD Management Program

Rahul Dhawan, MD, and colleagues at Optum®, part of United Healthcare, Eden Prairie, Minnesota, conducted a study to assess the association between access to and participation in a program for management of kidney disease and patient outcomes, including utilization of the emergency department, in-patient hospital admission, and costs of care. Results of the study were reported online in an abstract from the NKF 2020 Spring Clinical Meetings.

The program is part of an established product of Optum; the current study was designed to illustrate quality improvement in CKD patients as a result of patient engagement.

The study population included fully insured commercial patients identified as having chronic kidney disease (CKD) stage 4 or 5 from July 2017 to July 2018. The researchers sought to examine the reduction in utilization of in-patient care as well as the total cost of care. The study compared data from program participants with data from nonprogram participants. The study included a subanalysis of patients who transitioned to end-stage renal disease (ESRD) during the study period. Outcomes measured included all-cause medical allowed amount per participant and all-cause in-patient admissions per participant.

The treatment group included 805 unique members; the control group included 2714 unique members. Eligible patients had at least one claim with a diagnosis code for CKD 4 or 5 in the previous 24 months, or at least two laboratory claims at least 7 days apart with an estimated glomerular filtration rate result ≤30 mL/min/1.73 m^2 in the previous 24 months.

Utilization for each member was measured starting from the date of CKD identification or at the beginning of the study period, whichever was later. Program participant was defined as a patient engaged in three or more outreach calls from a case manager. Nonparticipants were defined as patients with CKD but who were not contacted.

Among patients who did not transition to ESRD during the study period, there was an 11% cost reduction between the control and treatment groups during the study period. There was also a 52% reduction in in-patient admissions between the control and treatment groups, which equated to $2.6 million annual savings.

Among patients who did transition to ESRD, there was a 6% reduction in costs for those who participated in the program. In addition, there was a 36% reduction in in-patient admissions. Program participants were seen more often by a nephrologist compared with nonparticipants.

"This study highlights the benefits of patient participation in a kidney disease specific management program. Participation increases patient engagement in the disease process, reduces hospitalizations, and therefore improves quality of life," the researchers said.

Source: Dhawan R, Friedman J, Bannister W, et al. Impact of a kidney disease management program on ER utilization in patient utilization and total cost of care. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #288.

Risk of Red Blood Cell Transfusion Lowered with Roxadustat in Patients with CKD Anemia

Patients requiring red blood cell transfusions may experience reactions leading to allo-sensitization, or rarely transmit infections; thus, treatments that reduce the need for transfusions are desirable. Researchers, led by **Stephen Fishbane, MD,** conducted an analysis to determine whether roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, reduced the need for red blood cell transfusions in patients with non-dialysis-dependent (NDD) and dialysis-dependent (DD) chronic kidney disease (CKD) and anemia. Results were reported at the NKF Spring Clinical Meetings online. The report was titled *Roxadustat Lowers Risk of RBC Transfusion in Patients with Anemia of CKD.*

The analysis included data from six completed randomized phase 3 studies with up to 4-year duration. The studies included patients with stage 3-5 CKD. The studies compared roxadustat with placebo among patients with NDD CKD and roxadustat with epoetin alfa among patients with DD CKD. Individual studies assessed the risk of first red blood cell transfusion; the risk was also assessed within pooled NDD and DD populations.

A total of 4277 patients with NDD CKD were included in the analysis: 2391 in the roxadustat arm and 1886 in the placebo arm. At baseline, mean hemoglobin was 9.10 g/dL in the roxadustat arm and 9.10 g/dL in the placebo arm. In the DD-CKD cohort (n=3857; 1929 roxadustat/1928 epoetin alfa), mean baseline hemoglobin was 9.63 g/dL in the roxadustat arm and 9.67 in the epoetin alfa arm. In the NDD-CKD cohort, roxadustat reduced the risk of red blood cell transfusion by 74% versus placebo; in the DD-CKD cohort, roxadustat reduced the risk of red blood cell transfusion by 18% versus epoetin alfa.

In conclusion, the researchers said, "Roxadustat markedly and significantly reduced the risk of red blood cell transfusion during anemia treatment compared with placebo in NDD CKD and, versus epoetin alfa in DD CKD in the pooled patient populations."

Source: Fishbane S, Provenzano R, Rastoki A, et al. Roxadustat lowers risk of RBC transfusion in patients with anemia of CKD. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #186.

Case Report: Concomitant Steal Syndrome and PAD in a Dialysis Patient

In patients on hemodialysis using arteriovenous (AV) access on the ipsilateral side, hand ischemia is recognized as steal syndrome. In addition, peripheral arterial disease (PAD) is often seen in patients with end-stage renal disease (ESRD). In this patient population, there is an association between the presence of both PAD and steal syndrome and significant mortality. Online at the NKF Spring Clinical Meetings, **Jenna Alkhatib, MD,** and colleagues presented a case of a dialysis patients with known history of PAD who presented with ischemic hand distal to the ipsilateral dialysis access.

The African American patient is 53 years of age with a history of hypertension, HIV, PAD, and ESRD. He has been on hemodialysis via a left upper arm AV fistula since 2003. He presented with a left index finger non-healing non-traumatic ulcer and left arm pain during dialysis for the last few weeks.

The physical exam was remarkable for left upper arm AV fistula with large aneurysmal formations and weak left radial pulse, absent bilateral distal pedal dorsalis pulse and left second toe amputation. The findings raised the suspicion for steal syndrome.

The patient underwent fistulogram and arteriogram of the left upper extremity that showed large aneurysmal formations of the fistula body and severe arterial calcification. The arteriogram without occluding the AV fistula showed an excellent flow to the AV fistula and a minimal flow into the left radial and ulnar arteries. Fistula occlusion markedly improved the arterial flow, confirming the steal syndrome diagnosis. The patient was referred to vascular surgery for banding procedure and aneurysmal repair.

"Our case showed the ESRD with large AV fistula can cause the shunting of blood into the venous circulation away from the distal extremity. The compromised blood flow to the distal extremity is exacerbated by the presence of PAD. This case highlights the challenges encountered in managing dialysis patients with concomitant PAD and steal syndrome," the authors said.

Source: Alkhatib A, Hamwyeh B, Al-Balas A, Almehmi A. Concomitant steal syndrome and peripheral arterial disease in a dialysis patient. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings, abstract #301.

Supervised Walking Program Improves Fitness and Quality of Life in Renal Patients

Physical exercise can improve symptoms, function, and mental health. However, many patients with renal disease do not meet physical activity guidelines. Exercise programs affiliated with hospitals may be able to reduce fears and improve exercise levels in that patient population. **Leonora Chao, RD,** and colleagues conducted a study to assess the effects of a 3-month supervised renal Nordic walking (NW) program on the fitness and quality of life of renal outpatients.

Results of the study were reported online during the NKF Spring Clinical Meetings. The presentation was titled *Effects of a Renal Nordic Walking Program on Quality of Life and Fitness in Renal Patients: A Randomized Controlled Trial.*

The study included 30 participants 45 to 84 years of age. Patients were randomized to one of two groups: NW (n=15) or non-NW (n=15). The NW group was offered two supervised NW sessions per week; the non-NW group continued their usual activities.

Outcomes of interest were: weight, handgrip strength, 30-second sit-to-stand test (30-STS), 6-minute-walk test (6MWT), and Kidney Disease and Quality of Life questionnaire (KDQOL-36). Outcome measurements were taken at baseline and at 3-months. During the 3-month study period, daily steps were recorded using a Fitbit tracker. Using the intention-to-treat principle, the researchers calculated median changes in outcomes from baseline to 3 months between the two groups, and tested with a Brown-Mood median test.

Of the 30 participants, ten were kidney transplant recipients, 14 were pre-dialysis, three were receiving hemodialysis, and three were receiving peritoneal dialysis. Two patients in the non-NW group were lost to follow-up; missing data were minimal.

At 3 months, compared with the non-NW group, participants in the NW group had a median increase in body mass index (+0.3 kg/m^2), handgrip strength (+2.1 kg), 30-STS (+1), 6MWT (+31.5 m), and several domains of the KDQOL-36 (effect of kidney disease; burden of kidney disease; and symptoms and problems). There were no significant differences in the median average daily steps between the two groups (NW, 7857 steps; non-NW, 8083 steps).

In summary, the researchers said, "The NW group had greater improvements in handgrip strength (1.1 kg), KDQOL-36 scores, and exceeded the minimal clinically important difference of 14.0-30.5 m for 6MWT (41.5 m). Post-study comments from participants were consistent with perceptions of improvements in quality of life. A group-based supervised renal NW program may provide benefits to renal patients as part of their clinical care."

Source: Chao L, Neufeld S, Ngo V, et al. Effects of a renal Nordic walking program on quality of life and fitness in renal patients: a randomized controlled trial. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #228.

Changes in Parathyroid Hormone Levels and Severity of Hyperparathyroidism Symptoms

In patients with kidney failure, improved health-related quality of life (HRQoL) is seen as a touchstone of quality of care. Yet, according to **Adrian R. Levy, PhD,** and colleagues, the many aspects of care in that patient population are largely based on biomarkers. The initiation and treatment of kidney replacement therapy among patients with chronic kidney disease is guided by estimated glomerular filtration rate and other biochemical values.

Larger changes in PTH levels were associated with more pronounced effects.

TAKEAWAY POINTS

- Researchers conducted a prospective cohort study to determine whether changes in parathyroid hormone (PTH) are associated with changes in symptoms in patients with kidney failure on hemodialysis.
- Generalized additive models were used to assess longitudinal associations between changes in PTH levels and symptom severity.
- There was an association between increases in PTH level over time and worsening of bone aches and stiffness, joint aches, muscle soreness, overall pain, itchy skin, and tiredness.

Biochemical markers are inadequate proxies for direct measures of HRQoL. The Centers for Medicare & Medicaid Services require routine assessment of HRQoL with the completion of the Kidney Disease Quality of Life 36 (KDQOL-36) each year. The KDQOL-36 is designed to quantify the overall burden of disease; more than 50% of patients on maintenance dialysis report fatigue, pain, cramps, pruritis, sleep disorders, or sexual dysfunction.

Treatment for metabolic complications of kidney failure is common and well understood; however, less is known about the effect of metabolic complications on symptoms such as secondary hyperparathyroidism. More than half of patients with kidney failure receiving kidney replacement therapy experience hyperparathyroidism, characterized by elevated parathyroid hormone (PTH) level and associated with dysregulation of calcium and phosphorus metabolism.

It is unclear whether patients can detect symptoms associated with hyperparathyroidism. Dr. Levy et al. conducted a prospective cohort study designed to examine whether changes in PTH levels are associated with changes in symptoms in patients with kidney failure receiving hemodialysis. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;73(3):373-383].

The outcomes of interest were changes in 19 symptoms measured up to four times using a self-administered questionnaire that assessed severity on a five-level scale. The 19 symptoms of interest were: tiredness, overall weakness, shortness of breath, diarrhea, vomiting, nausea, loss of appetite, joint aches, joint stiffness, bone aches, bone stiffness, muscle soreness, muscle pain, headaches, back pain, overall pain, itchy skin, skin problems, and difficulty sleeping.

Eligible patients were ≥18 years of age, had been receiving maintenance hemodialysis three times a week for at least four months, had been diagnosed with or treated for secondary hyperparathyroidism for at least 4 months, and were able to complete the English informed consent form and the symptom assessment questionnaire. Exclusion criteria were participation in another study involving an investigational device or drug within 4 months of screening, pregnancy or lactation, inability to sign the informed consent form, or unlikely to be able to complete the symptom assessment questionnaire.

A total of 204 patients were enrolled in the study; of those, 165 (80.8%) had complete data at baseline and at least one follow-up visit. Of the 165 in the final cohort, mean age was 56.0 years and 54.5% were women. A total of 80 participants (89%) had PTH level <600 pg/mL and 40 (24.2%) had PTH level >1000 pg/mL. Nearly all (92.7%) were being treated with vitamin D and phosphate-binder therapy (92.1%); 49.1% of participants were using cinacalcet. The proportions of patients on those therapies remained largely stable over time during follow-up visits at week 4, 12, and 24.

There were 646 PTH measurements gathered for the 165 participants followed up over four visits: 14 participants were missing laboratory values over a total of 660 possible measurements; 151 participants had all four measurements, 11 had three, and three had two. For all measurements, the mean number of days between measurement of PTH and symptoms was 24.0.

In analyses of the pattern between change in PTH levels and the probability of at least one increase in symptom severity (none to mild, mild to moderate, moderate to severe, or severe to very severe), there was a monotonically increasing curve, indicating a trend for worsening of symptoms with increased in PTH levels from 0 to 2000 pg/mL between visits for bone aches, joint aches, and overall pain. A U-shaped curve for bone stiffness and nausea indicated symptom worsening with greater values of absolute difference in PTH levels.

Increases in PTH levels over time were associated with worsening of bone aches and stiffness, joint aches, muscle soreness, overall pain, itchy skin, and tiredness ($P<.01$). Larger changes in PTH levels were associated with more pronounced effects.

The researchers cited some limitations to the study findings, including possible confounding due to unmeasured comorbid conditions, concomitant medications, and multiple testing coupled with a *P* value threshold of 0.10.

In summary, the researchers said, "The findings reported here suggest that worsening of secondary hyperparathyroidism may be associated with one or more clusters of symptoms, including aches/soreness/pain, itchy skin, and tiredness. Given that this study aimed to generate hypotheses, not test them, any meaningful relationships observed in this study require further confirmation before they can be used by patients and clinicians to determine treatment approaches. If validated, these findings may be useful for the development of a disease-specific patient-reported outcome measure that enables patients and clinicians to determine a treatment approach based on symptom reduction and PTH biomarkers." ■

Creatinine Supplementation Not Associated with Renal Damage

Creatinine, a compound formed by the amino acids methionine, glycine, and arginine, has been shown to increase athletic performance during short duration and high intensity exercise. Creatinine supplementation is usually consumed by professional and amateur athletes. Creatinine supplementation has been shown to increase muscle creatinine and phosphocreatine, and there is evidence of therapeutic benefits in patients with type 2 diabetes, including improved insulin sensitivity and glucose tolerance.

However, there are concerns regarding the safety of indiscriminate use of creatinine supplementation, particularly in terms of changes in the liver and kidneys. **Alexandre de Souza e Silva, PhD,** and colleagues recently conducted a systemic review and meta-analysis to examine whether creatinine supplementation is associated with renal damage. Results were reported in the *Journal of Renal Nutrition* [2019;29(6):480-488].

The search was conducted in four electronic databases: PubMed, Web of Science, SciELO, and Cochrane. The terms searched were creatinine supplementation AND function renal (creatinine supplementation) AND kidney, (creatinine supplementation) AND renal insufficiency. Two investigators independently screened the titles and abstracts to select relevant articles.

Eligibility criteria included: (1) randomized controlled trials; (2) published in peer-reviewed scientific journals; (3) case studies; and (4) studies assessing creatinine supplements and kidney effects. Exclusion criteria were (1) animal studies; (2) review articles; (3) abstracts from conferences and unpublished studies; (4) lack of creatinine supplementation; (5) no evaluation of renal damage following supplementation; and (6) prior renal damage before supplementation.

The initial search yielded 509 records. Of those, 28 were selected for full-text review and, after application of inclusion and exclusion criteria, 15 studies were eligible. The 15 studies were published from 1997 to 2003 and included a total of 497 subjects. The included studies were conducted in Brazil, England, the United States, the Netherlands, Uruguay, Belgium, Turkey, and Austria.

The studies included creatinine supplementation groups (creatine intake of 4 to 20 g/day) and control groups (no creatine intake). Participants in the control groups received placebo solutions of 500 mL of carbohydrates, dextrose, maltodextrin, glucose polymer, and Gatorade powder. Follow-up intervals from the pre- to post-supplementation period ranged from 5 days to 132 weeks in the longitudinal studies; follow-up in case studies ranged from 6 weeks to 112 weeks.

The randomized controlled trials were evaluated using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale includes 11 items; however, the first item is not included in the final score, thus the scores ranges from one to ten. The non-randomized trials, case studies, and cross-sectional studies were evaluated using criteria developed by the Joanna Briggs Institute (JBI), using varying assessment tools for each study design in question.

In the evaluation of the randomized trials by the PEDro scale, the average score was six points. One study scored four points, four scored six points, two scored seven points, and one scored eight points. Using the JKBI critical evaluation tool to assess the non-randomized studies resulted in one score of five points and one of six points; the cross-sectional study obtained a score of four points; and the case reports presented an average of seven points.

The meta-analysis included five studies that evaluated serum creatinine levels before and after subjects received either creatinine supplementation or placebo, representing eight outcome measures in 220 subjects. The period of supplementation varied between 5 days and 112 weeks.

Using the fixed-effects model, results of the meta-analysis suggested that there was no association between creatinine supplementation and creatinine levels. In addition, supplementation did not induce renal damage.

Three studies that evaluated the glomerular filtration rate through creatinine clearance prior to and following creatinine supplementation or placebo were included in the meta-analysis, representing five outcome measures in 136 individuals. In general, supplementation with creatinine did not induce renal damage in those studies.

Six studies that examined plasma urea concentrations prior to and following creatinine supplementation were included in the meta-analysis, representing 14 outcome measures in 382 participants. In general, the study results indicated no alteration in plasma urea levels with creatinine supplementation.

Limitations to the current review and meta-analyses cited by the authors included lack of inclusion of additional variables related to renal damage, such as total protein, albumin, and globulin, as well as limiting the review to studies published in English or Portuguese.

In summary, the researchers said, "The findings indicate that creatinine supplementation does not induce renal damage. Thus, creatinine supplementation is relevant to clinicians in renal nutrition and/or working with interested populations, such as athletes of strength and bodybuilding." ■

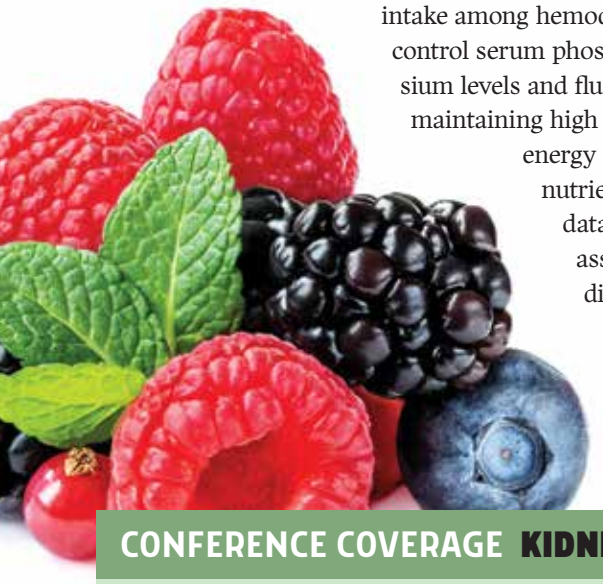
TAKEAWAY POINTS

- Researchers in Brazil conducted a systematic review and meta-analysis to determine whether creatinine supplementation was associated with renal damage.
- Fifteen studies were included in the qualitative analysis and six were included in the quantitative analysis.
- Results suggested that creatinine supplementation does not induce renal damage in the studied amounts and durations.

Mortality and Dietary Patterns in Patients on Hemodialysis

Patients with end-stage renal disease are at high risk for premature death. On average, life expectancy among patients who initiate long-term hemodialysis therapy is 3 to 4 years; cardiovascular disease is responsible for approximately 40% of those deaths. Compared with findings in the general population, there are only minimal or no survival benefits associated with interventions designed to lower lipid levels, control blood pressure and glucose levels, and prevent thrombosis in patients in maintenance dialysis therapy. Identification of strategies to prevent cardiovascular death is a priority for patients, caregivers, and clinicians.

Clinical practice guidelines for dietary intake among hemodialysis patients to control serum phosphate and potassium levels and fluid overload while maintaining high intake of protein and energy focus on individual nutrients. There are few data available on the association between dietary patterns and cardiovascular and all-cause mortality in adults treated by hemodialysis.



Valeria M. Saglimbene, MScMed, and colleagues conducted a secondary analysis of data from the DIET-HD (Dietary Intake Death and Hospitalization in Adults with End-State Kidney Dieseae Treated with Hemodialysis) study to generate data-driven patterns reflecting the eating behavior of patients in the DIET-HD hemodialysis cohort. The researchers sought to examine the association between commonly practiced dietary patterns and cardiovascular and all-cause mortality in that patient population. Results of the prospective cohort study were reported in the *American Journal of Kidney Diseases* [2020;75(3):361-372].

Eligible patients completed the Global Allergy and Asthma European Network food frequency questionnaire (FFQ) during a routine hemodialysis treatment, either independently or assisted by an interviewer in the case of severe clinical conditions or limited literacy. The FFQ is an internationally validated instrument to ascertain dietary intake to facilitate international comparisons. The FFQ records the consumption of 210 foods during the previous 12 months, at frequencies ranging from never to four or more times per day; FFQ responses were converted into average servings per week.

Energy intake was estimated from food intake considering standard portion size and using the latest available McCance & Widdowson's Food Composition Tables. Patients with more than 20% missing answers or implausible responses were excluded from the data analyses.

A total of 9757 hemodialysis patients completed the FFQ between January 2014 and January 2015. Of those, 8110 had complete and plausible dietary data and were followed-up through June 27, 2017. At baseline, mean age of the cohort was 63 years, 58% were men, 68% had a life partner, 44% had secondary education; 15% reported daily physical activity, and 18% were wait-listed for a kidney transplant. Thirty-three percent were current or former smokers, 5% were underweight, 42% had normal weight, 34% were preobese, and 20% were obese; 85% had hypertension, 32% had diabetes, 12% had experienced a myocardial infarction, and 9% had experienced stroke.

Of the 210 food items in the FFQ, 179 were included in the principal component analysis; exclusion of the 31 food items was due to infrequent consumption. The first dietary pattern identified was characterized by higher intake of fruit (including stone, citrus, and pome [pears and apples]

CONFERENCE COVERAGE KIDNEY WEEK 2019

Cardio-Renal Risk Tool: Diagnosis and Management of CKD Complications

Washington, DC–Worldwide, the prevalence of chronic kidney disease (CKD) is on the rise. In the United States, approximately 15% of the population is affected by CKD. Patients with CKD often have comorbidities complicating their condition. Complications associated with CKD are common and represent an important component in the associated disease burden. **Eirini Palaka, MSc,** and colleagues conducted a study that sought to synthesize evidence reporting associations between two common complications of CKD, hyperkalemia and anemia, and the risk of adverse outcomes, including death and cardiovascular events.

The researchers developed a novel risk tool to encourage a holistic approach to evaluating the disease burden of CKD complicated by hyperkalemia or anemia. Results of the study evaluating the tool were reported during a poster session at Kidney Week 2019 in a poster titled *Clinical Burden of Complications Associated with CKD: A Novel Cardio-Renal Risk Tool*.

Studies reporting risk of either hyperkalemia or anemia in patients with CKD, including those receiving hemodialysis, were identified using systematic literature review. The review also included studies associating the incidence of hyperkalemia or anemia with clinical outcomes, including mortality, hospitalization, and cardiovascular events. To characterize the risk of hyperkalemia, anemia, and associated adverse outcomes in patients with CKD, the reported evidence was then incorporated in a Cardio-Renal Risk Awareness and Impact Tool developed in Excel.

The review identified a total of 314 studies that reported the risk of hyperkalemia (n=123) or anemia (n=191), or the association between each complication and patient outcomes. Among male patients ≥65 years of age with CKD stage 3b, the estimated 5-year risk of a hyperkalemia event, defined as potassium ≥5.5 mmol/L, was 11.9%. Separately, the prevalence of anemia, defined as Hb <11 g/dL, was 35.0%.

For a patient with hyperkalemia, the estimated relative risks of death, hospitalization, and cardiovascular events were 1.50, 1.20, and 1.08, respectively. For a patient with anemia, the corresponding relative risks were 1.13, 1.47, and 1.12.

In addition, the estimated relative risks increased with the severity of each complication. For a patient with potassium ≥6.0 mmol/L, the relative risks of death, hospitalization, and cardiovascular events were 2.19, 1.73, and 1.14, respectively. For a patient with Hb ≤10 g/dL, the corresponding relative risks were 1.13, 1.72, and 1.24.

In conclusion, the authors said, "Hyperkalemia and anemia are both consistently and independently associated with increased risk of adverse outcomes in CKD patients. This study uniquely synthesizes the growing body of evidence on the epidemiology and impact of complications such as hyperkalemia and anemia in CKD patients. This novel risk tool can be used to communicate the importance of timely diagnosis and management of these conditions to reduce the burden of disease in this population."

Source: Palaka E, Darlington OT, McEwan P, Grandy S. Clinical burden of complications associated with CKD: A novel cardio-renal risk tool. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2019 (Abstract SA-P0930), November 9, 2019, Washington, DC.

Funding for this study was provided by AstraZeneca.

fruit) and vegetables (including cruciferous and green leafy vegetables). The second pattern was characterized by higher intake of Western-style foods, such as French fries, other potato meals, eggs, desserts, red and processed meat (including bacon, sausages, beef burger, and meat pie), fish (mostly cured, smoked, or tinned), and pizza. Higher levels of both dietary pattern scores in quartiles were associated with higher total energy intake. Both dietary patterns were consistently seen across the 11 countries in the study. The patterns were identified as (1) fruit and vegetables and (2) Western.

Participants received a score for each identified pattern, with higher scores indicating closer resemblance of their diet to the identified pattern. Quartiles of standardized pattern scores were used as primary exposures.

Median follow-up was 2.7 years (18,666 person-years). During the follow-up period, there were 2087 deaths; 958 of those were attributable to cardiovascular diseases.

In multivariable analyses, compared with patients in the lowest quartile of the fruit and vegetable dietary pattern score, adjusted hazard ratios for cardiovascular mortality in the other quartiles, in ascending order, were 0.94 (95% confidence interval [CI], 0.76-1.15), 0.83 (95% CI, 0.66-1.06), and 0.91 (95% CI, 0.69-1.21). For the Western dietary pattern, the corresponding estimates were 1.10 (95% CI, 0.90-1.35), 1.11 (95% CI, 0.87-1.41), and 1.09 (95% CI, 0.80-1.49). Findings were similar in case-complete analyses. The results of continuous dietary patterns scores agreed with those of quartiles.

In adjusted analyses of all-cause mortality, compared with patients in the lowest quartile of the fruit and vegetable dietary pattern score, hazard ratios among patients in the other quartiles, in ascending order, were 0.95 (95% CI, 0.83-1.09), 0.84 (95% CI, 0.71-0.99). and 0.87 (95% CI, 0.72-1.05). For the Western dietary pattern, corresponding estimates were 1.01 (95% CI, 0.88-1.16), 1.00 (95% CI, 0.85-1.18), and 1.14 (95% CI, 0.93-1.41). Results of case-complete analyses were similar. With the exception of a significant association between higher fruit and vegetables dietary pattern score and lower all-cause mortality in case-complete analysis, results of continuous dietary patterns scores agreed with those of quartiles.

Study limitations cited by the authors included the use of the self-reported food frequency questionnaire and the possibility that the data-driven approach could limit the generalizability of the findings to patients living outside of Europe and Argentina.

"In conclusion, our findings did not confirm an association between mortality among patients receiving long-term hemodialysis and the extent to which dietary patterns were either high in fruit and vegetables or consistent with a Western diet. Trials investigating the benefits and harms of more inclusive diets are warranted," the researchers said. ■

TAKEAWAY POINTS

- Researchers conducted an analysis of data from the DIET-HD study to examine the associations between dietary patterns and cardiovascular and all-cause mortality in a cohort of adults on long-term hemodialysis.
- The prospective cohort study included 8100 patients on hemodialysis from January 2014 to January 2015; follow-up continued until June 27, 2017.
- There was no association between mortality in the patient population and the extent to which dietary patterns were either high in fruit and vegetables or consistent with a Western diet.

Defining Hourly Urine Output to Report Incidence of AKI

Acute kidney injury (AKI) is identified as a rise in serum creatinine and/or reduction in urine output as surrogate markers of reduced glomerular filtration rate. Beginning in 2012, criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury have been the standard for defining and staging of AKI. The KDIGO definition includes oliguria, defined as urine volume <0.5 mL/kg per hour for 6 hours.

Because it is possible to detect AKI earlier using urine output (UO), results from a previous study suggested that UO can detect AKI 11 hours earlier than serum creatinine. There is no clear consensus on whether UO should be measured using consecutive hourly readings or mean output, making the KDIGO UO definition and AKI staging potentially inconsistent. **Jennifer C. Allen** and colleagues conducted a study to determine whether the incidence and staging of AKI is affected by the way in which UO is defined. Study results were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-019-1678-2].

The researchers conducted a retrospective analysis of two single-center observational studies to investigate novel urinary biomarkers. The analysis included patients admitted to the cardiac intensive care unit following cardiac surgery or to a general intensive care unit (ICU) to determine whether differing methods of measuring UO affected the reported incidence of AKI, stratified by stage (stage 1-3). Serum creatinine was used as the gold standard of categorizing AKI.

The researchers analyzed data from 151 patients undergoing cardiac surgery and 150 patients admitted to the ICU. The cardiac surgery procedures were valve surgery (45%), coronary artery bypass graft (CABG; 30%), off-pump CABG (11%), combined valve and CABG (11%), aortic root surgery (2%), and other surgeries (1%). Of the 151 procedures, 62% were routine and 38% were urgent.

Of the 150 ICU admissions, 34% were medical, 21% were neurosurgical, 17% were trauma, 15% were elective surgical, and 14% were emergency surgical. Compared with patients admitted to the ICU, those in the cardiac surgery group were older ($P<.001$) and had a higher incidence of chronic kidney disease ($P<.001$) and other comorbidities. Smoking was common in both groups and approximately 50% had smoked at some time. The incidence of sepsis was significantly higher in patients in the ICU compared with those in the cardiac surgery group (27.3% vs 1.3%; $P<.001$).

There was significant variation in the incidence of AKI according to the definition of AKI used. Based only on serum

continued on page 18

continued from page 17

creatinine/renal replacement therapy, 23.8% of the cardiac surgery patients developed AKI (all stages). In the ICU, using the same definition, 32% of the patients developed AKI. When the diagnosis included UO as well as serum creatinine, the AKI incidence increased significantly.

The largest effect was seen among the patients in the cardiac surgery group. The incidence of AKI in the cardiac surgery patients rose from 23.8% using serum creatinine alone to 39.8% using UO^{cons} (hourly urine output where each consecutive hour met KDIGO criteria), and to 72.9% using UO^{mean} (mean hourly output measured for every 6-, 12-, and 24-hour period). Among the patients in the ICU, there was a similar inflation of incidence of AKI, rising from 32% to 51.4% using UO^{cons} and to 69.3% using UO^{mean}.

When UO was used in combination with serum creatinine/renal replacement therapy to stratify AKI by severity, there was considerable change in the proportion of patients allocated to each stage among patients in the cardiac surgery group compared with the ICU group. In both clinical settings, using serum creatinine alone, stage 1 AKI was the most common category (15.9% in cardiac surgery vs 14.6% in ICU). When UO was added to the diagnostic criteria using UO^{cons}, the incidence of stage 1 AKI doubled in both groups.

There was no difference in the cardiac surgery group in the incidence of stage 1 AKI between UO^{cons} and UO^{mean}. In the ICU, the incidence of AKI stage 1 was reduced with use of UO^{mean} (UO^{mean} 19.3% vs UO^{cons} 28%).

In both groups, the incidence of stage 2 AKI was low using serum creatinine (1.9% in cardiac surgery vs 7.3% in ICU). When UO^{cons} was applied, there was a modest increase in the incidence of stage 2 AKI (3.3% in cardiac surgery, 12.7% in ICU). There was a dramatic increase in the incidence of stage 2 AKI using UO^{mean}: an increase of 33.8% in cardiac surgery and 29.4% in ICU. There was no difference in incidence of stage 3 AKI in cardiac surgery using either UO measurement method; in ICU, there was a small rise in stage 3 AKI (2.6%) when UO^{mean} was used.

The researchers cited some limitations to the study, including the retrospective and single-center design, the use of serum creatinine as the gold standard to define AKI, and the relatively high use of diuretics among the cardiac surgery group.

In summary, the researchers said, "Our study demonstrates that reported incidence of AKI differs according to the method used to document UO and that the extent of this effect varies between different clinical groups. Clarification of method in UO calculation is important in both clinical and research settings. This single-center study provides justification for conducting a larger multi-center study in order to establish more specific criteria for AKI definition." ■

TAKEAWAY POINTS

- Researchers conducted a single-center retrospective analysis of two single-center observational studies to examine whether the way urine output is measured affects the incidence and staging of acute kidney injury (AKI).
- Using serum creatinine alone, the incidence of AKI was 23.8% among patients undergoing cardiac surgery and 32% among patients in the intensive care unit (ICU).
- When urine output was considered, the incidence of AKI increased in both groups.

CONFERENCE COVERAGE KIDNEY WEEK 2019

Predicting Progression of CKD to Kidney Failure

Washington, DC–Researchers, led by **Ajay Sharma,** conducted a study designed to develop and validate a predictive model to identify patients with chronic kidney disease (CKD) stage 3 or 4 at high risk for progression to kidney failure over a 24-month period. Results were reported during a poster session at Kidney Week 2019 in a poster titled *A Predictive Model for Progression of CKD to Kidney Failure Using an Administrative Claims Database*.

The model was developed and validated using data from a retrospective claims database from a large US payer of patients with CKD stage 3 or 4. The study included a 12-month baseline period (2015) and a 24-month prediction period (2016-2017). Inclusion criteria were ≥18 years of age without dialysis or kidney transplant and enrollment for at least 36 months.

Kidney failure was defined as estimated glomerular filtration rate of <15 mL/min/1.73 m^2, or dialysis or kidney transplant; or one diagnosis according to International Classification of Diseases, Tenth Revision, Clinical Modification codes during the prediction period. A model to estimate the 2-year probability of kidney function was developed using multivariate logistic regression as a function of baseline covariates. The performance of the predictive model was assessed using area under receiver operating characteristic (ROC) curve (AUC), calibration, gain, and lift charts.

A total of 74,114 patients were included. Of those, 3.34% (n=2476) had incident kidney failure during the prediction period. Variables included in the predictive model were age, sex, CKD stage, hypertension, diabetes mellitus, congestive heart failure, peripheral vascular disease, anemia, hyperkalemia, and poor adherence to renin-angiotensin-aldosterone system inhibitors. The strongest predictors were CKD stage (4 vs 3), hypertension, diabetes mellitus, and hyperkalemia. The ROC curve and calibration analyses in the validation sample showed good predictive accuracy (AUC=.834) and good calibration.

In conclusion, the researchers said, "This predictive model provides a good level of accuracy in identifying CKD patients at high risk of progressing to kidney failure up to 2 years in advance in a national health plan with over 10 million lives. Early identification using this model could potentially lead to improved health outcomes and reduce healthcare expenditures."

Source: Sharma A, Alvarez PJ, Woods SP, Fogli J, Dal D. A predictive model for progression of CKD to kidney failure using an administrative claims database. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2019 (Abstract TH-P0382), November 7, 2019, Washington, DC.

CONFERENCE COVERAGE KIDNEY WEEK 2019

OLYMPUS: Roxadustat Meets US and EU Endpoints in Patients with NDD CKD

Washington, DC–In the OLYMPUS trial, researchers examined the efficacy of roxadustat for the treatment of anemia in patients with non-dialysis dependent chronic kidney disease (NDD CKD). Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves absorption and utilization of iron. Efficacy results of the OLYMPUS trial, one of three trials for US and EU applications, were reported during an oral presentation at Kidney Week 2019. Safety results will be reported separately. The research team was led by **Steven Fishbane, MD,** of Northwell Health, Great Neck, New York.

The study population included patients with NDD CKD stages 3 to 5 and anemia, defined as hemoglobin (Hb) <10.0 g/L. Patients were randomized 1:1 to receive 70 mg oral roxadustat or placebo three times weekly. A dose adjustment algorithm was used to achieve and maintain Hb values of 10 to 12 g/L. The primary efficacy endpoint of interest for the US (FDA) submission was mean change from baseline Hb to average Hb over weeks 28 to 52; for the EU (EMA) submission, the primary efficacy endpoint was the proportion of patients with Hb response at two consecutive visits during the first 24 weeks of therapy without anemia rescue therapy.

A total of 2781 patients were randomized: 1393 to the roxadustat arm and 1388 to the placebo arm. Mean age of the total cohort was 61.7 years, 42% were male, 45% were white, and 55% had type 2 diabetes. At baseline, mean Hb was 9.1 g/dL and mean estimated glomerular filtration rate was 19.8 mL/min/1.73 m^2. In the roxadustat arm, mean study drug exposure was 19.6 months versus 15.2 months in the placebo arm.

In the roxadustat arm, the mean change in Hb from baseline to the average over weeks 28 to 52 was +1.75 g/L versus +0.40 g/L in the placebo arm (P<.001). In a subgroup of patients with baseline elevated high-sensitivity C-reactive protein (hsCRP) (n=411), changes in Hb from baseline were +1.75 g/L in the roxadustat arm and +0.62 g/L in the placebo arm (P<.001).

Among patients in the roxadustat arm, the proportion of patients achieving Hb response at two consecutive visits without anemia rescue therapy during the first 24 weeks was 77.0%, compared with 8.5% in the placebo arm (P<.001). The percentage of total time with interpolated Hb values ≥10 g/L for weeks 28 to 52 was 82% in the roxadustat arm versus 33% in the placebo arm (P<.001). The risk of rescue therapy was reduced by 74% with roxadustat, including red blood cell transfusion by 63%, intravenous iron by 59%, and erythropoietin by 87% (all P<.001).

In conclusion, the researchers said, "Roxadustat achieved prespecified primary endpoints for US and EU submissions, effectively increased Hb in the subgroup of patients with elevated hsCRP, and reduced rescue therapy use in patients with NDD CKD and anemia."

Source: Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. OLYMPUS: A phase 3, randomized, double-blind, placebo-controlled, international study of roxadustat efficacy in patients with non-dialysis dependent (NDD) CVD and anemia. Abstract of an oral presentation at American Society of Nephrology Kidney Week 2019 (Abstract TH-OR023), November 7, 2019, Washington, DC.

Funding for the OLYMPUS study was provided by AstraZeneca.

Evolution of Markers of Mineral Metabolism in Patients with CKD Stage 3b

Patients with chronic kidney disease (CKD) commonly experience disordered mineral metabolism, a complication that is associated with increased risk for cardiovascular disease events, progression to end-stage renal disease (ESRD), and mortality. Changes in levels of markers of mineral metabolism evolve over time and understanding those changes will provide insights into the pathogenesis of the condition in CKD, enable epidemiologic analyses that relate temporal trends to the risk for adverse events, and facilitate identification of high-risk patterns of changes that can be targeted for interventions.

To date, the pathogenesis of disordered mineral metabolism in CKD has been informed by cross-sectional studies in humans and longitudinal studies in animals. **Tamara Isakova, MD, MMSc,** and colleagues recently conducted a retrospective analysis nested in a cohort study to characterize the longitudinal evolution of the condition during the course of CKD. Results of the analysis were reported in the *American Journal of Kidney Diseases* [2020;75(2):235-244].

> Overall, there was a steeper increase in FGF-23 levels over time compared with more modest elevations in parathyroid hormone (PTH) and phosphate levels.

Cross-sectional data from the CRIC (Chronic Renal Insufficiency Cohort) Study reported that elevated levels of fibroblast growth factor 23 (FGF-23) were more prevalent at higher estimated glomerular filtration rates (eGFR) than secondary hyperparathyroidism or hyperphosphatemia. The findings suggested that FGF-23 excess preceded the onset of secondary hyperparathyroidism or hyperphosphatemia in patients with CKD. For the current analysis, the researchers examined a subset of CRIC participants who developed ESRD to test the hypothesis that in the prelude to ESRD, FGF-23 levels would increase more rapidly compared with changes in levels of other mineral metabolites.

The study population included 847 individuals who progressed to ESRD during CRIC follow-up. Participants had advanced CKD (identified by low eGFR and high urinary albumin-creatinine ratio) and a high prevalence of comorbidities and risk factors for progression of CKD. Fewer than 10% of participants were prescribed nutritional vitamin D (7.7%), phosphate binders (8.0%), or active vitamin D (5.2%) at enrollment.

The mean age of the cohort was 55.5 years, 40% were women, 52.3% were black, 17.4% were Hispanic, and 16.3% were current smokers. Overall, 93.7% had hypertension, 65.4% had diabetes, 12.9% had heart failure, 9.8% had peripheral vascular disease, and 23.9% had coronary artery disease.

In the longitudinal analyses, time was expressed as years before ESRD onset rather than being anchored to the CRIC Study annual visits in order to assess levels of mineral metabolites spanning 8 years of CKD progression prior to development of ESRD. The analyses revealed the rates of change in the levels, provided an assessment of how rapidly the changes developed during a time frame when eGFR declined progressively, and identified when change points occurred in relation to years before ESRD.

Overall, there was a steeper increase in FGF-23 levels over time compared with more modest elevations in parathyroid hormone (PTH) and phosphate levels. Levels of calcium were predominately stable; as ESRD neared, calcitriol levels steadily declined.

To estimate rates of change of concentrations of FGF-23, PTH, phosphate, and calcium, the researchers calculated the first and second derivatives of the longitudinal functions over time as CKD progressed to ESRD: (1) velocity and (2) magnitude of acceleration.

Compared with the other metabolites, levels of FGF-23 demonstrated the highest rate of change (first derivative) and magnitude of acceleration (second derivative). The changes became apparent approximately 5 years prior to ESRD and persisted without deceleration through onset of ESRD. At approximately the same time, there were modest increases in levels of PTH and phosphate, with modest deceleration immediately prior to ESRD when use of Vitamin D and phosphate binders increased.

The researchers cited some limitations to the study findings, including the inability to assess changes in levels of a-klotho and intake FGF-23 because those measurements were not available in the CRIC Study; the lack of measurements of serial levels of urinary phosphate excretion, dietary phosphate intake, 25-hydroxyvitamin D, and iron status; and lack of data on the heterogeneity by CKD subtype. In addition, the study included only participants who progressed to ESRD during follow-up, excluding participants who entered the CRIC Study at early stages of CKD who did not progress to ESRD during follow-up.

In summary, the researchers said, "Disordered mineral metabolism is a progressive disorder that develops early in the course of CKD, continues through the period of ESRD, and often persists into the post-transplantation period. Based on a cross-sectional analysis of the CRIC Study, we previously concluded that patients with eGFR <60 mL/min/1.73 m^2 could be targeted for clinical trials testing interventions for disordered mineral metabolism. Our findings from ESRD-anchored longitudinal analyses suggest that a critical period in the pathogenesis is approximately 5 years before ESRD, or at CKD stage 3b. Although the necessity to intervene is debated by guideline groups, our current results would suggest that it is prudent to consider close surveillance of disordered mineral metabolism in patients with CKD stage 3b. Because this population is likely to experience dynamic changes in levels of markers of mineral metabolism over time, clinical investigators may opt to target patients with CKD stage 3b for future trials aimed at testing novel interventions for disordered mineral metabolism." ■

TAKEAWAY POINTS

- Researchers analyzed data from the CRIC Study to characterize the longitudinal evolution of disordered mineral metabolism during the course of chronic kidney disease.
- There was a marked increase in mean levels of fibroblast growth factor 23 (FGF-23) as time to end-stage renal disease (ESRD) decreased; there was a modest increase in levels of parathyroid hormone and phosphate and a minimal decrease in calcium.
- Compared with the other markers, FGF-23 levels showed the highest rate of change and magnitude of acceleration of disordered mineral metabolism; the changes were evident ~5 years prior to the onset of ESRD.

Risk of ESRD in Living Kidney Donors by Donor–Recipient Relationship and Across Racial Groups

A key component in the evaluation of live kidney donor candidates is the risk factor of subsequent kidney failure in the candidate. At present, standard donor evaluation relies on exclusion of candidates at high risk for end-stage renal disease (ESRD) based on clinical risk factors that include hyperglycemia, high blood pressure, and proteinuria.

Previous studies designed to characterize risk for ESRD in related donors had limitations such as limited follow-up and limited statistical power that allowed for only a single estimate of ESRD risk for related versus unrelated donors (1.7-fold greater risk for related donors). However, according to **Abimereki D. Muzaale, MD, MPH,** and colleagues, a single risk estimate does not account for the substantial variation in risk by ancestry or the potential gradient of risk within more closely related donors.

The researchers recently conducted a retrospective cohort study designed to better quantify risk for ESRD among donors biologically related to the recipient. The study utilized national registry data from the United States to examine the risk along the gradients of biological relationships between donor and recipient. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;75(3):333-341].

National dialysis and transplantation registries were linked to donors' records to determine ESRD in the study cohort. The study included all adult living donors between October 1, 1987, and December 31, 2017, including adults who donated to children. ESRD outcomes were ascertained by linkage of the Scientific Registry of Transplant Recipients database to Centers for Medicare & Medicaid Services medical evidence form 2728.

The outcome of interest was development of ESRD, defined as the initiation of maintenance dialysis or receipt of a living or deceased donor kidney transplant. Time zero for all donors was the date of the donation. Death prior to ESRD was a competing event. The 20-year risk for ESRD was estimated using cumulative incidence functions, with a time scale of years since time zero.

Of 143,750 live kidney donors, median age at donation was 40 years, 59% were female, 71% were white, 12% were Hispanic, 12% were black, and 3% were Asian. At baseline, none of the donors had diabetes, but 2% had hypertension. Median estimated glomerular filtration rate was 97 mL/min/1.73 m^2, mean systolic/diastolic blood pressure was 121/74 mm Hg, median body mass index was 27 kg/m^2, 25% had a history of smoking, 26% had a college degree, and 11% had postgraduate education. Overall, 35% were unrelated to the recipient (including 11% who were spousal relations), 8% were half-sibling or other biological relatives, 13% were parents, 16% were offspring, 29% were full siblings, and 0.2% were identical twins. There were variations in those characteristics by race.

There were also variations in the relative frequency of recipient causes of kidney failure by race. Among white donors, the most frequent cause of kidney failure was glomerulonephritis (GN) (30%), followed by diabetes (21%) and hypertension (12%) and cystic

CONFERENCE COVERAGE KIDNEY WEEK 2019

Efficacy of Allocation Decision-Making Based on Preimplantation Biopsy Results

Washington, DC–Worldwide, a significant number of kidneys are discarded due, in large part, to results from the preimplantation biopsy. **Olivier Aubert, MD, PhD,** and colleagues at the Paris Translational Research Center for Organ Transplantation, Paris, France, conducted a study to examine the value of preimplantation biopsies to predict long-term allograft outcome. Results were reported during an oral presentation session at Kidney Week 2019 in a presentation titled *Absence of Additional Predictive Ability Value of Preimplantation Biopsies for Long-Term Allograft Outcome*.

The development cohort included patients who underwent kidney transplantation from a deceased donor in two French referral centers between 2004 and 2014; the donor organs had preimplantation biopsy results. The study also included two validation cohorts: 1107 deceased donors from Belgium and 1103 discarded kidneys based on biopsy results from the United States.

There were 1629 patients in the development cohort. Preimplantation biopsy findings included interstitial fibrosis and tubular atrophy (IFTA), Banff cv and ah scores, and glomerulosclerosis percentage. Following adjustment for donor, recipient, and transplant characteristics, as well as for preimplantation biopsy findings and baseline immunological parameters, Kidney Donor Risk Index score (hazard ratio [HR], 2.50; 95% confidence interval [CI], 1.38-3.40; $P<.001$), the presence of circulating donor-specific antibodies on the day of transplantation (HR, 1.76; 95% CI, 1.36-2.28; $P<.001$), prior kidney transplantation (HR, 1.34; 95% CI, 1.01-1.78; $P=.045$), and the IFTA score (HR, 1.51; 95% CI, 1.00-2.26; $P=.048$) were identified as the main independent determinants of long-term allograft loss.

However, there was no additional value in the biopsy results for the prediction of long-term allograft outcome compared with the model with no biopsy results. In the Belgium validation cohort, there were no associations with allograft loss with any of the biopsy results. Kidneys discarded based on histology results in the United States were matched with transplanted kidneys in France. The French kidneys with histologic results similar to those of discarded US kidneys did not have worse allograft survival compared with the unmatched transplanted kidneys ($P=.156$).

In conclusion, the authors said, "Given this result and the fact that preimplantation biopsies increase the cold ischemia time, the current practice of discarding kidneys based on preimplantation biopsy results may not be optimal for allocation decision-making."

Source: Aubert O, Raynaud M, Divard G, et al. Absence of additional predictive ability value of preimplantation biopsies for long-term allograft outcome. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2019 (Abstract TH-OR129), November 7, 2019, Washington, DC.

kidney disease (12%). Among black donors, the three most common recipient causes of kidney failure were hypertension (32%), GN (30%), and diabetes (21%). For Hispanic donors, the recipient causes of kidney failure were GN (32%), diabetes (23%), and hypertension (19%). For Asian donors, the recipient causes of kidney failure were GN (42%), hypertension (18%), and diabetes (17%).

Median follow-up of donors was 12 years, a total of 1,824,825 person-years. During the follow-up period, 407 donors developed ESRD. The researchers estimated the incidence of ESRD by race and donor-recipient biological relationship.

For Asian donors, the 20-year risk of ESRD (per 10,000 donors) was 10 (95% confidence interval [CI], 1-70) for full siblings; 32 (95% CI, 4-222) for offspring; 0 for parents; 0 for half-sibling/other biological relatives; and 0 for biologically related donors. For black donors, the risk was 170 (95% CI, 126-230) for full siblings; 130 (95% CI, 86-195) for offspring; 83 (95% CI, 42-164) for parents; 62 (95% CI, 27-144) for half-sibling/other biological relatives; and 30 (95% CI, 10-95) for biologically unrelated donors.

For Hispanic donors, the 20-year risk of ESRD per 10,000 donors was 35 (95% CI, 19-64) for full siblings; 35 (95% CI, 12-100) for offspring; 39 (95% CI 17-91) for parents; 52 (95% CI, 17-165) for half-sibling/other biological relatives; and 22 (95% CI, 6-79) for biologically unrelated donors. For white donors, the risk was 35 (95% CI, 27-46) for full siblings; 23 (95% CI, 12-44) for offspring; 53 (95% CI, 38-72) for parents; 22 (95% CI, 8-58) for half-sibling/other biological relatives; and 25 (95% CIO, 14-144) for biologically unrelated donors.

Following adjustment for age and sex, the odds ratio risk for ESRD varied by orders of magnitude across race. For Asian donors, the risks compared with unrelated donors were elevated 259.4-fold for identical twins, 4.7-fold for full siblings, 3.5-fold for offspring, 1.0-fold for parents, and 1.0-fold for half-sibling or other biological relatives. For black donors, the risks compared with unrelated donors were 22.5-fold for identical twins, 4.1-fold for full siblings, 2.7-fold for offspring, 3.0-fold for parents, and 1.3-fold for half sibling or other biological relatives.

For Hispanic donors, the risks compared with unrelated donors were undefined for identical twins, elevated 1.4-fold for full siblings, 1.5-fold for offspring, 1.5-fold for parents, and 1.0-fold for biologically unrelated donors. For white donors, the 20-year risks compared with unrelated donors were elevated 3.5-fold for identical twins, 2.0-fold for full siblings, 1.4-fold for offspring, 2.9-fold for parents, and 0.8-fold for half sibling or other biological relatives.

There were some limitations to the study, including the lack of information on family members other than the recipient; the lack of sufficient statistical power to investigate the risk in various racial and ethnic groups; the registry-based observational design of the study; the inability to adjust for confounders other than age and sex; and not examining nonbiological factors such as psycho-social factors, income, education level, and environment that may contribute to the risk for ESRD.

"In conclusion," the researchers said, "substantial variations in risks for ESRD were observed across race and donor-recipient relationship. Whether counseling and screening guidelines for donor candidates should reflect these race- and relationship-specific risks is debatable. However, our findings point to signals that warrant further validation with more robust data." ■

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to quantify the risk for end-stage renal disease (ESRD) among living kidney donors biologically related to the recipient of a kidney transplant.
- The risks for ESRD varied by orders of magnitude across donor-recipient categories.
- There were marked differences across types of donor-recipient relationships for Asian, black, Hispanic, and white donors.

CONFERENCE COVERAGE KIDNEY WEEK 2019

Extending Medicare Coverage for Immunosuppressive Drugs Cost-Effective

Washington, DC–Medicare coverage for kidney transplant recipients ceases 36 months following transplantation. The 36-month removal policy cancels coverage for the immunosuppressive medications that are essential to prevent rejection and maintain transplant function.

There are no contemporary data regarding the economic impact of extending Medicare coverage for the duration of transplant survival using mean cost of immunosuppressive medications in the era of generic equivalents. Many transplant recipients currently continue to receive Medicare coverage beyond the 36 months cutoff due to medical disability benefits.

Matthew J. Kadatz, MD, and colleagues used a Markov model to determine the incremental cost and effectiveness of extending Medicare coverage for immunosuppressive drugs for the duration of transplant survival versus the current policy from the perspective of the Medicare payer. Results of the analysis were reported during an oral presentation at Kidney Week 2019 in a presentation titled *Economic Evaluation of Lifelong Medicare Immunosuppressive Drug Coverage for Kidney Transplant Recipients*.

The analysis used contemporary mean costs of immunosuppressive medications and incorporated assessment of continuation of Medicare coverage beyond the current 36 months in patients who have been designated medically disabled. Data from a cohort of privately insured recipients derived using multivariable survival analysis were used to estimate the expected graft survival of extending immunosuppressive drug coverage.

Results of the analysis demonstrated that extension of immunosuppression coverage under Medicare for kidney transplant recipients led to lower costs of approximately $3163 as well as 0.18 additional quality adjusted life years. Following the reduction of the improvement in transplant survival associated with extended immunosuppressive coverage to 50% of that seen in privately insured patients, the strategy of extending drug coverage had an incremental cost-utility ratio of $77,613 per quality adjusted life year gained.

"Extending immunosuppressive drug coverage under Medicare from the current 36 months to the duration of transplant survival will result in better patient outcomes and cost savings, and remains cost-effective if only a fraction of anticipated benefit is realized," the researchers said.

Source: Kadatz MJ, Gill JS, Formica RN, Klarenbach S. Economic evaluation of lifelong Medicare immunosuppressive drug coverage for kidney transplant recipients. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2019 (Abstract TH-OR128), November 7, 2019, Washington, DC.

Nephrology Fellows Named AKF Recipients

The American Kidney Fund (AKF) has announced two recipients of the Clinical Scientist in Nephrology Program. The program is funded by the Hearst Foundation.

Anika Lucas, MD
Dr. Lucas is a nephology fellow at Duke University (Durham, North Carolina). Her patient-centered research on pregnancy and kidney disease will focus on understanding and addressing racial differences and health disparities. The goal of Dr. Lucas' research is to more accurately identify women who are at particularly high risk for adverse events.

Maria Clarissa Tio, MD
Dr. Tio is a fellow at Brigham and Women's Hospital/Massachusetts General Hospital Joint Nephrology Program. Her research will focus on several emerging risk factors for progression of chronic kidney disease (CKD).

The AKF Clinical Scientist in Nephrology Program is designed to fund promising young nephrology researchers whose work is designed to improve diagnosis, treatment, and outcomes for patients living with CKD. The Hearst Foundation provided a grant of $100,000 to support the program.

Virtual Care Program Improves Patient Knowledge

Cricket Health has released results of a study evaluating Cricket's virtual care program. The study was conducted by Samaritan Health Services; results were reported in the *Journal of Medical Internet Research*. The study found that the virtual care program resulted in improved patient knowledge regarding chronic kidney disease (CKD), increased interest in home dialysis, and possibly increased the proportion of dialysis starts in the out-patient setting.

In a press release from Cricket Health, **Carmen Peralta, MD, MAS,** chief medical officer at Cricket and co-author of the study said, "In this study, Samaritan researchers found that our virtual program can effectively educate patients on their condition, help them understand their treatment options, and, in some cases, help them avoid starting dialysis in the hospital. That's exactly what's needed to change the status quo in kidney care. People live with chronic kidney disease every day, not just when they're visiting a doctor's office. Better engaging patients through digital tools will help them manage their condition beyond the four walls of a clinic."

Patients in the program have access to online education materials as well as a multidisciplinary team that includes a nurse, pharmacist, social worker, and dietician, as well as patient mentors. The team works in concert with nephrologists and primary care providers to engage patients to better manage their condition.

Following the pre-specified 9 month study period as well as extended follow-up periods, program participants who initiated dialysis did so in an outpatient setting, compared with 20% of the control group at the end of the 9-month period and 22% after the extended follow-up periods.

Arvind Rajan, Cricket Health CEO, said, "Our current kidney system too often takes a one-size-fits-all approach, but we're working to change that. Cricket's virtual program is part of our patient-centered, personalized approach that empowers patients to make informed decisions and remain engaged throughout their journey with a team that is accessible online, at-home, or at their local clinic."

NDA Submitted for Hepatorenal Syndrome Treatment

Mallinckrodt has announced their complete submission of a New Drug Application (NDA) to the US FDA for terlipressin. The agent is being studied for the treatment of hepatorenal syndrome type 1 (HRS-1). Upon approval, terlipressin will be the first FDA-approved treatment for HRS-1 in the United States.

HRS-1, a life-threatening syndrome associated with rapid kidney failure and an overproduction of creatinine typically found in patients with cirrhosis, affects up to 40,000 Americans annually. As the kidneys stop functioning, toxin build up in the body, resulting in a median survival time of <2 weeks and >80% mortality within 3 months in untreated patients.

The NDA is based, in part, on results from the CONFIRM trial, a phase 3 prospective study conducted in patients with HRS-1. Results were reported at The Liver Meeting in 2019. Terlipressin is an investigational product and its safety and efficacy have not been established.

Target Serum Phosphorus Levels Achieved with Velphoro®

In a recent press release, Fresenius Medical Care North America announced results of a new analysis of retrospective data on patients on hemodialysis treated with the phosphate binder Velphoro® (sucroferric oxyhydroxide chewable tablets). Study results were reported in *Kidney Medicine*.

Patients in the sucroferric oxyhydroxide group were compared with patients who switched from Velphoro to another phosphate binder. A higher percentage of patients who remained on Velphoro maintenance therapy for two years (n=222) achieved target serum phosphorous levels of ≤5.5 mg/dL compared with patients who discontinued the drug within 90 days and switched to another phosphate binder.

Michael Anger, MD, chief medical officer, Renal Therapies Group at Fresenius Medical Care North America, said, "This novel analysis is giving us more evidence that the use of Velphoro has several benefits for our dialysis patients by increasing the number of patients that achieve target serum phosphate levels and lowering the pill burden compared to other prescribed phosphate binders."

Daniel Coyne, MD, professor of medicine at Washington University School of Medicine St. Louis, said, "Previous real-world studies have shown similar results with Velphoro, but lacked a control group. This two-year analysis addresses that problem, and shows marked improvements with Velphoro that are not achieved using other phosphorus binders."

Myles Wolf, MD, MMSc, Named to Akebia Therapeutics Board

Akebia Therapeutics, Inc. has announced the appointment of **Myles Wolf, MD, MMSc,** to the company's board of directors. Akebia Therapeutics is a biopharmaceutical company dedicated to the development and commercialization of therapeutics for people living with kidney disease. Dr. Wolf is a leading clinical nephrologist and physician-scientist, with special expertise in disordered mineral metabolism and cardiovascular disease in patients with chronic kidney disease. He is chief of the division of nephrology and a professor of medicine at the Duke University School of Medicine, Durham, North Carolina.

In a recent press release, **Adrian Adams,** chairperson of the board of directors at Akebia said, "We are thrilled to welcome Dr. Myles Wolf as a member of the Akebia board of directors. Given his extensive knowledge and experience with kidney and cardiovascular diseases, Myles brings valuable healthcare provider and patient perspectives to Akebia."

"I look forward to working with the other members of the board and the management team to deliver on Akebia's purpose to improve the lives of people living with kidney disease," Dr. Wolf said. ■

ACUTE KIDNEY INJURY

AKI Outcomes Following High-Dose Chemotherapy

Clinical Genitourinary Cancer. doi.org/10.1016/j.clgc.2020.01.008

Kevin Juan Zhang, MD, and colleagues recently conducted a study to examine the risk factors and outcomes of patients who developed acute kidney injury (AKI) during high-dose chemotherapy for relapsed germ cell tumors (GCTs). All eligible patients were scheduled to receive two consecutive courses of high-dose chemotherapy (HDCT). Characteristics and outcomes of the patients with stage ≥3 AKI were compared with those in patients without stage ≥3 AKI.

The study included 462 patients; of those, 4.5% (n=21) developed stage ≥3 AKI. Of the 21 patients, 18 required hemodialysis during HDCT and six died during HDCT. Of the 15 patients who survived during HDCT, 10 experienced recovery of renal function to baseline.

AKI occurred in the first cycle of HDCT in 18 patients. Those patients were also more likely to have received HDCT in a third-line setting and/or to have Eastern Cooperative Oncology Group performance status of 1 or 2 and to have experienced gastrointestinal, hepatic, pulmonary, and infectious grade ≥3 toxicities.

At a median follow-up of 10 months after HDCT, four patients had no evidence of disease, three were alive with disease, six had died of disease, seven had died of complications from HDCT, and one had been lost to follow-up.

In conclusion, the researchers said, "Irreversible AKI during HDCT for relapsed GCT is uncommon but is associated with greater rates of infectious, gastrointestinal, hepatic, and pulmonary complications, and treatment-related deaths. These patients were also more heavily pretreated and had a lower baseline performance status, However, most surviving patients had recovered their renal function and five of the 21 were alive with no evidence of disease."

ADPKD

Anemia as Factor for Poor Renal Prognosis

Clinical and Experimental Nephrology. doi.org/10.1007/s10157-020-01856-1

In patients with chronic kidney disease (CKD), anemia is an indicator of poor renal prognosis. However, hemoglobin (Hb) levels are typically higher in autosomal dominant kidney disease (ADPKD) compared with other kidney diseases. There are few data available on anemia as a potential prognosticator in patients with ADPKD. **Yusuke Ushio, MD,** and colleagues conducted a study to examine anemia as a factor for renal prognosis in ADPKD.

The analysis included 115 non-dialysis patients with ADPKD; of those 48 were men and 67 were women. The outcome of interest was a 50% reduction in the estimated glomerular filtration rate or the need for renal replacement therapy. Cox regression analysis and Kaplan-Meier analyses were used to assess the outcome.

Fifty patients reached the end point during a median follow-up of 5.5 years. At the first visit, the mean age of the patients was 49.9 years, the overall mean Hb was 12.90 g/dL, and the mean Hb in men was 13.82 g/dL and 12.25 g/dL in women. Hb levels and uric protein content were

continued on page 24

Print-only Content

Abstract Roundup

continued from page 23

statistically significant factors for poor renal prognosis; hypertension and genetic mutations did not reach statistical significance as factors for poor renal prognosis. Statistical significance was seen in men with Hb <12 g/dL and in women with Hb <11 g/dL. There was a significant association between anemia and progression of kidney disease in patients with ADPKD.

"We found that anemia might be a factor for poor renal prognosis in ADPKD. Furthermore, a sex difference was found, wherein men with Hb <12 g/dL and women with Hb <11 g/dL were at risk of renal disease progression," the researchers said.

Print-only Content

ANEMIA

Novel Iron Therapies for IDA in CKD

Advances in Chronic Kidney Disease. 2019;26(4):272-291

Patients with chronic kidney disease (CKD) frequently experience iron deficiency anemia (IDA); there is an association between IDA and adverse outcomes in this patient population. Patients with IDA and CKD are commonly undertreated. Poor absorption of conventional iron agents as well as gastrointestinal side effects result in insufficient effectiveness of those agents, creating a need for novel oral iron preparations. **Pablo E. Pergola, MD,** and colleagues reviewed current treatment guidelines for patients with anemia and CKD. The review included clinical trial data for iron-repletion agents being used currently, as well as novel oral iron therapies in development.

Ferric citrate is a novel iron-repletion agent approved for use in patients with non–dialysis-dependent CKD and IDA; results of trials found improvements in hemoglobin levels and iron parameters, with good tolerability in that patient population. When used as a phosphate binder in patients with dialysis-dependent CKD, ferric citrate also improved hemoglobin and iron parameters; additional trials are needed to assess efficacy as an iron repletion agent.

There are other novel iron preparations in development, including ferric maltol (approved in Europe and the United States for IDA in adults) and Sucrosomial® iron that has been evaluated in IDA associated with CKD and several other clinical settings.

Pathophysiology, Diagnosis, and Treatment of Iron Deficiency in CKD

Journal of the American Society of Nephrology. doi.org/10.1681/ASN.2019020213

A majority of patients with advanced chronic kidney disease (CKD) develop anemia. Relative deficiency of erythropoietin is a major driver of anemia in CKD; however, iron deficiency is a key mechanism associated with impaired erythropoiesis in patients with reduced kidney function. Iron deficiency plays a crucial role in anemia in CKD due to absolute iron deficiency (a true paucity of iron stores) or a functional (relative) deficiency that prevents the use of available iron stores.

Both absolute and functional iron deficiency in CKD are associated with risk factors such as blood losses, impaired iron absorption, and chronic inflammation. There are limitations to the traditional biomarkers used to diagnose iron deficiency anemia (IDA) in patients

with CKD, creating challenges in the detection and management of patients with CKD and IDA. **Elizabeth Katherine Batchelor, MD,** and colleagues reviewed the pathophysiology and available diagnostic tests for IDA in CKD and highlighted the literature that has informed current practice guidelines for the treatment of IDA in CKD.

The article addresses the potential risks of a more liberal approach to iron supplementation and the potential risks and benefits of intravenous versus oral iron supplementation in this patient population.

CHRONIC KIDNEY DISEASE

Racial Differences in Progression of Aortic Stenosis in CKD

Cardiovascular Diagnosis & Therapy
2020;10(1):24-30

In patients with advanced chronic kidney disease (CKD) and European ancestry, there is a high prevalence of aortic stenosis. There are few data available on a comparison of progression of aortic stenosis in white and black patients in an advanced CKD population.

Aamir Husain, MD, and colleagues conducted a study to compare the progression of aortic stenosis between white and black patients in a CKD-specific population and determine whether the genetic link between white adults and aortic progression prevails in a CKD population. The cohort included 1283 patients with CKD stage 4-5 who were referred to the University of North Carolina Cardiorenal Clinic for preoperative kidney transplant evaluation.

Of the 1283 patients, 140 (34% white; 66% black) developed or had baseline aortic stenosis. Initially, 81% had no aortic stenosis, 13% had mild, and 6% had moderate aortic stenosis. White patients were more likely to be male and less likely to be on hemodialysis compared with black patients. There were no differences in severity of aortic stenosis or age at baseline.

In white versus black patients, mean gradient increased at 1.90 (95% confidence interval [CI], 0.79 to 3.01) mmHg per year versus 1.46 (95% CI, 0.79 to 2.14) mmHg per year (*P*=.20); aortic valve area decreased at -0.10 (95% CI, -0.15 to -0.05) m^2 per year versus –0.08 (95% CI, -0.11 to -0.05) m^2 per year (*P*=.13); and transvalvular velocity increased at 0.11 (95% CI, 0.04 to 0.18) meters per second (m/s) per year versus 0.07 (95% CI, 0.03 to 0.11) m/s per year (*P*=.09).

In conclusion, the researchers said, "Compared to black patients, white patients in an advanced CKD cohort may have exhibited more rapid progression of aortic stenosis. Ours is the first study to analyze racial differences in such a population. A study with a larger sample size is needed to confirm our findings."

DIABETES

Nutritional Needs in Patients with Diabetes and CKD

Current Diabetes Reviews. doi:10.2174/1573399816666200211120402

Up to 40% of patients with diabetes are diagnosed with chronic kidney disease (CKD) as a direct result of diabetes-related complications. Due to the need for disease-specific diets for patients with diabetes, management of patients with diabetes and CKD presents challenges; there are also increased risks for malnutrition in this patient population.

Researchers led by **Nourhan Khaled Hassan, MD,** recently conducted a systematic review to examine nutritional requirements for patients with type 2 diabetes and chronic renal failure. The researchers screened 85 articles; of those, 22 were analyzed and included as per the study criteria. The data search included PubMed using medical subject headings terms, and a literature review through the Cochrane library and the *British Medical Journal*.

The review highlighted nutrients and minerals needed to be maintained within a specified range defined by a patient's needs and conditions. Dietary restrictions to prevent disease progression were also necessary. Patients receiving hemodialysis required vigorous monitoring of blood glucose levels as well as strict management of dietary intake. Risk-to-benefit ratios were utilized to determine optimal protein intake in patients on hemodialysis.

"Dietary requirements should be individualized based on the patient's disease severity and progression. Assessment of the patient's previous and current diet, as well as matching it with their dietary requirements and preferences is crucial," the researchers said.

HYPERKALEMIA

Economic Impact of Hyperkalemia in a Managed Care Population

American Health & Drug Benefits.
2019.12(7):352-361

Hyperkalemia, serum potassium level >5 mEq/L, can lead to life-threatening arrhythmias and sudden cardiac death. The complexity of care is significantly increased in patients with coexisting cardiac and renal disease (cardiorenal syndrome). There are few data available of the economic impact of hyperkalemia in patients with cardiorenal syndrome in patients in the Medicaid managed care population.

Nihar R. Desai, MD, MPH, and colleagues conducted a retrospective cohort study using real-world data to calculate the economic impact of hyperkalemia in patients with cardiorenal syndrome in a Medicaid managed care population in the United States.

The data were from a proprietary Medicaid managed care database from a southern state. The total study cohort included 3563 patients: 973 patients with hyperkalemia and 2590 without hyperkalemia (controls). Patients and controls were matched based on age, comorbidities, and Medicaid eligibility status between 2013 and 2016.

For the patients with hyperkalemia, mean healthcare costs (medical and pharmacy per member per year [PMPY]) were higher than for patients in the control cohort: $56,002 versus $23,653, respectively. The cost differences were driven by medical costs accrued in the hyperkalemia and in the control cohorts: $49,648 and $18,399 PMPY, respectively. Inpatient costs ($33,116 vs $10,629 PMPY for the hyperkalemia cohort vs the controls, respectively) and dialysis costs ($2716 vs $810 PMPY, respectively) were two of the largest drivers of the variance in medical costs. Both cohorts had revenue deficits to the health plan, but the hyperkalemia cohort had double the medical loss ratio compared with controls.

In conclusion, the researchers said, "The findings from this Medicaid managed care population suggest that hyperkalemia increased healthcare utilization and costs, which were primarily driven by the costs associated with inpatient care and dialysis. Our findings demonstrate that the Medicaid beneficiaries who have cardiorenal comorbidities accrue high costs to the Medicaid health plan, and these costs are even higher if a hyperkalemia diagnosis is present. The very high medical loss ratio for the hyperkalemia cohort in our analysis indicates that enhanced monitoring and management of patients with hyperkalemia should be considered." ■

Sarah Tolson

These are strange and unprecedented times we are living in. At the time of this writing, plans for reopening the US economy during the COVID-19 pandemic are still being discussed. Many businesses that have been deemed nonessential are closed, and many healthcare providers have made changes to provide only essential and emergent care to patients to slow the spread of the pandemic in the US. Many payers have made drastic policy changes to allow providers the flexibility to continue to provide care via telephone or video calls and still obtain reimbursement.

Payer reimbursement policies changed so rapidly from mid-March to mid-April that billing departments and providers across the nation have struggled to keep up with the latest information about which services are covered and how to bill for them. It's impossible to predict what our healthcare system will look like on the other side of this pandemic, but it is inspiring to see the ingenuity and creativity behind efforts to keep the people of our nation safe.

Chronic Care Management Part Two

In the last edition of From the Field, we discussed the basic elements of Chronic Care Management (CCM) services. In this edition, we will discuss the codes that represent CCM services as well as several CCM frequently asked questions. There are procedure codes for three separate levels of CCM services and one add-on procedure to reflect extra time spent on an individual patient's CCM services. Below are descriptions of the three code levels and the add-on code.

Level 1 (CPT 99490) encompasses at least 20 minutes of clinical staff time directed by a physician or other qualified healthcare professional per month spent on CCM services when the following are present:

- Two or more chronic conditions that will last at least 12 months and place the patient at significant risk of death, functional decline, etc.
- Comprehensive care plan established, implemented, revised, or monitored.

Level 2 (CPT 99491) encompasses 30 minutes of CCM services provided personally by a physician or other qualified healthcare professional per month when the following are present:

- Two or more chronic conditions that will last at least 12 months and place the patient at significant risk of death, functional decline, etc.
- Comprehensive care plan established, implemented, revised, or monitored.

Level 3 (99487) Complex CCM services encompasses 60 minutes of clinical staff time directed by a physician or other qualified healthcare professional, per month.

Complex CCM services include the following elements:

- Two or more chronic conditions that will last at least 12 months and place the patient at significant risk of death, functional decline, etc.
- Establishment or substantial revision of a comprehensive care plan.
- Moderate or high complexity medical decision making.

For each additional 30 minutes of clinical staff time directed by a physician or other qualified healthcare practitioner per calendar month, there is an add-on code (CPT 99489) that can be reported to represent the additional time spent on a patient's CCM services.

CCM FREQUENTLY ASKED QUESTIONS

Below are just a few of the questions that I have received in recent months regarding CCM services. There are many online resources readers may find helpful, and as always, I welcome reader questions.

Q: Are there services that cannot be billed under the Medicare physician fee schedule during the same calendar month as CCM?
A: Yes, Transitional Care Management (TCM), Home Health Care Supervision, Hospice Care Supervision, and ESRD Monthly Capitation Payment services may not be billed by the same provider in the same service period as CCM services. While nephrologists may not bill for CCM services for their ESRD patients, they may have stage 4 kidney failure patients that have qualifying chronic conditions that would benefit from CCM services.

Q: Is a new patient consent required each calendar month or annually?
A: A new consent is only required if the patient changes billing practitioners.

Q: In the event the patient dies during the service period, can CCM services still be billed?
A: CCM services can be billed if the patient dies during the service period, as long as the required service time for the code and all other requirements were met. ■

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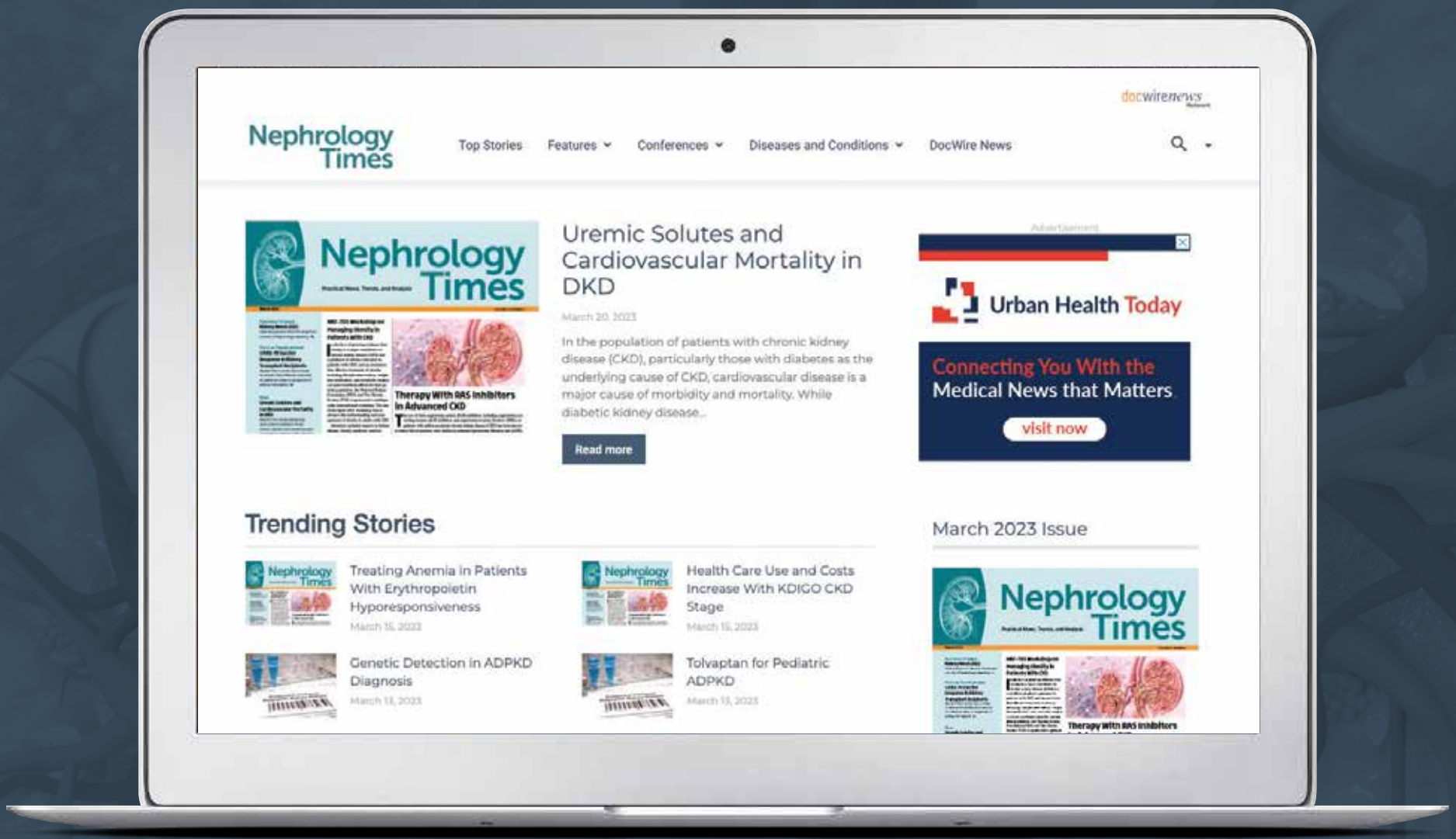

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