Welcome to the latest issue of Nephrology Research Review.

In this issue, Israeli investigators report that hypertension doubles the risk of future ESKD in an otherwise healthy adolescent population, an analysis of the CRIC study finds that elevated 24-hour urinary oxalate excretion is an independent risk factor for CKD progression, and researchers report that ESKD is a substantial public health problem in Fiji. The novel acid binder veverimer is shown to be an effective treatment for metabolic acidosis in patients with CKD, the antiviral combination glecaprevir/pibrentasvir appears to be effective and safe in patients with chronic hepatitis C and severe renal impairment, and an analysis from Taiwan shows that patients with CKD are at increased risk for developing new-onset type 2 diabetes.

We hope you find these and the other selected studies interesting and look forward to any feedback you may have.

Kind Regards,

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Association of adolescent hypertension with future end-stage renal disease

Authors: Leiba A et al.

Summary: This retrospective cohort study evaluated the association between hypertension and future ESKD in otherwise healthy adolescents. Data were reviewed for 2,658,238 adolescents aged 16–19 years entering military service in the Israeli Defense Forces in 1967–2013 (individuals with evidence of renal damage or kidney-related risk factors prior to military service were excluded). 7997 (0.3%) participants had an established hypertension diagnosis at inclusion; almost 50% of these individuals were overweight or obese, and most were male. During a median follow-up of 19.6 years, 2189 individuals developed ESKD (incidence rate 3.9 per 100,000 person-years). In a multivariable model adjusted for confounding factors, adolescent hypertension was found to be associated with future ESKD (HR, 1.98). The association remained significant after exclusion of individuals with severe hypertension (HR, 1.93).

Comment: This large cohort of apparently healthy army recruits had the expected low risk of ESKD over a median of almost 20 years, but it was substantially more common in those with hypertension. As most current guidelines focus treatment on people at high cardiovascular risk, they are unlikely to capture these individuals, highlighting the potential importance of checking renal function and/or medical follow-up of adolescents with hypertension.

Reference: JAMA Intern Med 2019; published online Feb 25

Abstract
**Association of urinary oxalate excretion with the risk of chronic kidney disease progression**

**Authors:** Waikar S et al., for the Chronic Renal Insufficiency Cohort study investigators

**Summary:** This analysis of the prospective CRIC study assessed whether urinary oxalate excretion is a risk factor for faster progression of CKD. 3123 patients with stage 2–4 CKD who enrolled in the CRIC study in 2003–2006 were included. During 22,318 person-years of follow-up, 752 patients developed ESKD, and 940 reached the composite end-point of ESKD or 50% decline in eGFR (CKD progression). Higher oxalate excretion at baseline was independently associated with greater risks of both CKD progression and ESKD: compared with quintile 1 (oxalate excretion <11.5 mg/24h) patients in quintile 5 (≥27.8 mg/24h) had a 33% higher risk of CKD progression and a 45% higher risk of ESKD.

**Comment:** Urinary oxalate excretion is often studied in the context of renal stones, but is not a well-known risk factor for CKD progression. This analysis from CRIC suggests that it is an independent risk factor for CKD progression as well as ESKD. Whether this is clinically useful or modifiable remains to be demonstrated.

**Reference:** JAMA Intern Med 2019; published online Mar 4

**End-stage kidney disease in Fiji**

**Authors:** Krishnan A et al.

**Summary:** CKD is a leading cause of mortality in Fiji. This retrospective cohort study estimated the incidence and characteristics of ESKD in Fijian adults. A review of patients admitted to Colonial War Memorial Hospital in Suva in 2012 identified 159 cases of confirmed ESKD (median age, 57 years). Crude and age-adjusted ESKD incidence rates were 753 and 793 per million population, respectively. Diabetic nephropathy was the most common cause of ESKD (65.4%).

**Comment:** The Pacific Islands have some of the highest rates of diabetes in the world, but little has been known about the prevalence of kidney failure. This analysis demonstrates extremely high rates of ESKD, mostly due to diabetes, and suggests this should be a health priority. We need more work to reliably understand the burden of kidney disease in our region, in order to develop and implement affordable solutions.

**Reference:** Intern Med J 2019;49(4):461-6

**Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease**

**Authors:** Wesson D et al.

**Summary:** Veverimer is a non-absorbed, counterion-free, polymeric drug that selectively binds and removes hydrochloric acid from the gastrointestinal lumen. This multicentre study investigated the efficacy and safety of veverimer as a treatment for metabolic acidosis in patients with CKD. 217 patients aged 18–85 years with non-dialysis-dependent CKD (eGFR 20–40 ml/min/1.73m²) and metabolic acidosis (serum bicarbonate level 12–20 mmol/L) were randomised 4:3 to veverimer 6 g/day or placebo for 12 weeks. Both drugs were taken as oral suspensions in water with lunch. The primary composite end-point was the proportion of patients achieving either a ≥4 mmol/L increase from baseline in serum bicarbonate levels, or serum bicarbonate in the range 22–29 mmol/L (normal). 59% of patients in the veverimer group and 22% in the placebo group achieved the composite end-point at week 12 (p<0.0001). Gastrointestinal adverse events included diarrhoea, flatulence, nausea, and constipation, and occurred in 13% and 5% of veverimer and placebo recipients, respectively.

**Comment:** Acidosis is common in advanced CKD, and a growing body of literature suggests that oral sodium bicarbonate might reduce the risk of kidney disease progression, as well as other complications. It has not been able to tell whether this is due to the bicarbonate, or volume changes due to sodium administration. This novel acid binder improved acidosis in this phase 2 trial in CKD patients, with some intriguing suggestions of possible additional benefits. More data will come from the phase 3 trial which is currently recruiting.

**Reference:** Lancet 2019;393(10179):1417-27

**The efficacy and safety of glecaprevir plus pibrentasvir in 141 patients with severe renal impairment**

**Authors:** Atsukawa M et al.

**Summary:** This prospective, multicentre study investigated the efficacy and safety of glecaprevir/pibrentasvir in patients with hepatitis C and severe renal impairment. 141 patients with hepatitis C genotype 1–3 and CKD stage 4–5 were included, of whom 100 were undergoing haemodialysis. All but one stage 5 CKD patient undergoing haemodialysis achieved a sustained virologic response with glecaprevir/pibrentasvir (99.3%), 39.7% of patients reported adverse events, with pruritus being the most common (30.5%).

**Comment:** Hepatitis C is common in people with kidney disease, and this observational study shows extremely high success rates for sustained viral suppression with the combination of glecaprevir and pibrentasvir. Given that virologic response was over 99% with treatment, and is unlikely without treatment, a randomised trial is not necessary here to prove the treatment is effective. It is more difficult to interpret the adverse event profile without a randomised control group.

**Reference:** Aliment Pharmacol Ther 2019;49(9):1230-41

**Increased risk of new-onset type 2 diabetes in people with chronic kidney disease**

**Authors:** Wang I-K et al.

**Summary:** This study determined the risk of new-onset type 2 diabetes in patients with CKD. 16,624 nondiabetic patients with CKD and 66,496 age- and sex-matched controls without diabetes or kidney disease were identified from the Taiwan National Health Insurance Database in 2000–2010. Both cohorts were followed-up until 2011 to evaluate the risk of developing new-onset type 2 diabetes. The incidence of type 2 diabetes during follow-up was 1.51-fold higher in the CKD cohort than in the control cohort (16.9 vs 11.2 per 1000 person-years; adjusted HR, 1.17).

**Comment:** Nobody would be surprised to hear that CKD is more common in people with diabetes, but the analysis from Taiwan shows that this relationship is bi-directional: people with existing CKD had an increased risk of developing diabetes. The continuous relationship between glucose metabolism and kidney damage is likely to play a role, but exploration of other potential mechanisms might provide important insights.

**Reference:** Int Urol Nephrol 2019;51(4):707-12
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References:

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Long-term efficacy and safety of molidustat for anemia in chronic kidney disease: DIALOGUE extension studies

Authors: Akiwa Z. T et al.

Summary: Molidustat is a novel hypoxia-inducible factor prolyl hydroxylase inhibitor that is being investigated for the treatment of anemia associated with CKD. This report presented the results of two long-term extension studies of molidustat in patients with anemia due to CKD. Both were open-label studies of ≤36 months' duration, and used an erythropoiesis-stimulating agent as an active control. One study included 164 non-dialysis patients, and the other enrolled 98 haemodialysis patients. The primary efficacy end-point in both studies was change in blood haemoglobin (Hb) level from baseline to each post-baseline visit. In non-dialysis patients, mean Hb levels at baseline were 11.28 and 11.08 g/dl for molidustat and darbepoetin, respectively. Mean Hb levels throughout the study were 11.10 and 10.98 g/dl in the respective groups. In haemodialysis patients, mean Hb levels at baseline were 10.40 g/dl in the molidustat group and 10.52 g/dl in the epoetin group. Mean Hb levels during the study were 10.37 and 10.52 g/dl, in the respective groups. The percentage of patients reporting at least one adverse event did not differ significantly between molidustat, darbepoetin and epoetin groups.

Comment: A number of prolyl hydroxylase inhibitors are under development as alternatives to erythropoietin for the treatment of renal anemia. This extension study is not very exciting in itself, given that it mostly focuses on tolerability and Hb response, but recent press releases relating to roxadustat suggest that they might have an important role going forward, and possibly some advantages to erythropoietin. We should learn more later this year.


Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis

Authors: Block G et al.

Summary: Tenapanor reduces paracellular phosphate transport via inhibition of gastrointestinal sodium/hydrogen exchanger 3. This phase 3 study evaluated the effects of tenapanor on elevated serum phosphate levels in patients with CKD. 219 patients with hyperphosphataemia receiving maintenance haemodialysis were randomised to receive oral tenapanor 3, 10, or 30mg twice daily for 8 weeks. They were then re-randomised 1:1 to receive either their previously assigned dosage or placebo for a 4-week 'withdrawal' period. 152 patients completed both study phases. During the initial 8-week treatment period, mean serum phosphate levels decreased significantly with all 3 dosages (by 1.00, 1.02, and 1.19 mg/dl, respectively). Tenapanor also had a significant benefit during the withdrawal period, with a mean increase of only 0.02 mg/dl in the pooled tenapanor group compared with 0.85 mg/dl in the placebo group. Adverse events were mostly due to softened stool and an increase in bowel movement frequency.

Comment: An interesting new approach to phosphate control has been proposed here. Tenapanor indirectly increases phosphate excretion, as well as increasing sodium and water excretion in the stool. It clearly reduces phosphate levels, but may also have an impact on sodium and water balance as well as blood pressure. Given that the gastrointestinal side effects appear likely to be tolerable, further study would be of interest.


Improving CKD-specific patient-reported measures of health-related quality of life

Authors: Ware J et al.

Summary: This study compared a new CKD-specific quality-of-life impact scale (CKD-QOL) with currently used measures (Kidney Disease Quality of Life-36 [KDQOL-36] and the generic SF-12 Health Survey). 485 patients in different treatment stages (nondialysis stages 3–5, on dialysis, or post-transplant) completed the kidney-specific CKD-QOL and KDQOL-36 forms and the generic SF-12 Health Survey at baseline and 3 months. KDQOL-36 and CKD-QOL measures generally discriminated better than generic SF-12 Health Survey measures. Validity tests compared the CKD-QOL, KDQOL-36 (Burden, Effects, and Symptoms/Problems subscales), and generic SF-12 measures across groups in four tests of clinical status and clinician assessment of CKD. The pattern of variances across CKD-specific tests favoured CKD-QOL over KDQOL-36.

Comment: Quality of life is perhaps even more important than mortality risk for many people with CKD but study has been limited by the relatively blunt nature of tools developed for the general population, and the relative complexity of kidney disease-specific measures. This new tool may address these issues with promising initial data reported here, but further studies will be important, including the assessment of responsiveness to intervention.


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