



Open Your Mind in Nephroprotection: Controversies and Perspectives

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AT THE 63rd Congress of the European Renal Association (ERA), experts from across the globe gathered to spotlight major advances and discuss pressing issues in the field of nephrology. This educational session, chaired by Samar Abd ElHafeez and Marcin Adamczak, Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, featured three insightful talks centred around nephroprotection in chronic kidney disease (CKD).

FRUIT- AND VEGETABLE-RICH DIET IN PATIENTS WITH CKD

Juan-Jesus Carrero, Professor of Kidney Epidemiology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, opened the session by discussing the impact of a fruit- and vegetable-rich diet in patients with CKD. His talk assessed the evidence supporting the inclusion of dietary recommendations in recent clinical guidelines.^{1,2}

A plant-based diet is a broad term encompassing any eating pattern in which animal-based foods are consumed in moderation, and a greater proportion of food choices are plant-based. As explained by Carrero, this umbrella term includes vegan, vegetarian, dietary approaches to stop hypertension (DASH), Mediterranean, healthy eating, and Okinawan diets. Carrero subsequently debunked several widespread myths, including that plant-based diets cause nutrient deficiencies, hyperphosphatemia, and hyperkalaemia.

Firstly, several studies have confirmed that vegetarian and vegan diets do not contribute to amino acid deficiencies,³ and this has also been demonstrated specifically in CKD in both clinical trials⁴ and observational studies.⁵ Regarding the second myth, that plant-based diets cause hyperphosphatemia, this has likewise been disproven. For example, in patients with Stage 4 CKD, plant-based diets resulted in lower serum phosphate concentrations and lower urinary phosphate excretion.⁶ Finally, Carrero cited several studies demonstrating a weak, if any, association between dietary and circulating potassium levels, reaffirming that diet is only one contributing factor to serum potassium concentrations.⁷

Carrero went on to emphasise that restricting organic potassium (K⁺) sources fails to recognise that potassium absorption and distribution are influenced by the intake of other nutrients. For example, in patients with CKD, consuming potassium together with glucose favours intracellular potassium deposition, whilst alkali promotes both intracellular potassium



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deposition and renal potassium excretion. In addition, fibre improves faecal potassium excretion by increasing stool volume and alleviating constipation.

So, what can be done? Firstly, as noted by Carrero, increasing plant protein intake has been shown to improve renal plasma flow and reduce the fractional clearance of albumin.⁸ Secondly, he advocated for greater fibre consumption because of its well-established benefits in lowering cardiovascular risk and regulating blood glucose levels. Finally, greater consumption of plant foods increases dietary alkali intake, which has been shown to preserve glomerular filtration rate, decrease bone resorption, improve insulin sensitivity, and reduce sarcopenia.⁹

SHOULD WE TREAT MILD METABOLIC ACIDOSIS IN PATIENTS WITH CKD?

Marcin Adamczak, subsequently took the stage to discuss the controversial issue of treating mild metabolic acidosis in patients with CKD.

Metabolic acidosis in CKD is defined as an acid-base disorder diagnosed when the venous plasma or blood bicarbonate concentration is lower than 22 mmol/L in the absence of signs of respiratory alkalosis, and occurs in nearly 20% of patients with CKD.¹⁰

3%

Each 1 mEq/L increase in bicarbonate was associated with a 3% reduction in the risk of reaching a renal endpoint, with the strongest association observed in patients with better-preserved kidney function

The main causes of metabolic acidosis are decreased tubular HCO_3^- reabsorption and insufficient HCO_3^- production during ammoniogenesis in the distal tubule.



As highlighted by Adamczak, metabolic acidosis can directly impair quality of life through reductions in skeletal muscle mass and strength, cognitive impairment, and sexual dysfunction in men.

Adamczak then discussed the association between metabolic acidosis and CKD progression, highlighting a prominent observational study.¹¹ This study evaluated serum bicarbonate levels as a risk factor for renal outcomes, cardiovascular events, and mortality in 3,939 participants with CKD Stages 2–4. Over a median follow-up of 3.9 years, lower serum bicarbonate levels were independently associated with a higher risk of CKD progression. Each 1 mEq/L increase in bicarbonate was associated with a 3% reduction in the risk of reaching a renal endpoint, with the strongest association observed in patients with better-preserved kidney function (estimated glomerular filtration rate: >45 mL/min/1.73 m²). Similar associations have also been reported in adolescents.¹²

How Do We Treat Metabolic Acidosis in Patients with CKD?

Several studies have found that fruit- and vegetable-enriched diets increase plasma bicarbonate concentrations and possess

nephroprotective properties.^{13,14} Examples include apples, apricots, oranges, peaches, pears, raisins, strawberries, and carrots.

The second treatment option is oral sodium bicarbonate supplementation; however, this remains somewhat controversial. Adamczak discussed two key studies: the UBI study¹⁵ and the BICARB study.¹⁶ The UBI study was a randomised trial in patients with CKD Stages 3–5 and metabolic acidosis that found oral sodium bicarbonate significantly reduced kidney disease progression, dialysis initiation, and all-cause mortality compared with standard care. Sodium bicarbonate was generally well tolerated and did not significantly increase blood pressure, body weight, or hospitalisation rates. In contrast, the BICARB study found that oral sodium bicarbonate did not improve physical function, kidney function, or quality of life in older adults with advanced CKD and metabolic acidosis compared with placebo. Furthermore, bicarbonate treatment was associated with more adverse events and higher healthcare costs, suggesting that it is unlikely to be a cost-effective intervention in this population.

Due to the conflicting results of these pivotal studies, the question remains unresolved. Adamczak therefore advocated for more high-quality data, citing a 2024 meta-analysis of eight RCTs involving 2,037 patients with CKD.¹⁷ The analysis concluded that sodium bicarbonate treatment significantly improved estimated glomerular filtration rate.

Finally, Adamczak discussed sodium zirconium cyclosilicate for patients with hyperkalaemia. This selective, non-absorbed potassium binder promotes potassium elimination through the gastrointestinal tract. Studies have shown that it can also reduce the incidence of metabolic acidosis.¹⁸

In conclusion, as noted by Adamczak, the treatment of mild metabolic acidosis (serum bicarbonate 18.0–21.9 mmol/L) in patients with CKD remains controversial due to the lack of definitive placebo-controlled clinical trial data.

ALDOSTERONE ACTIVITY REDUCTION IN PATIENTS WITH CKD

Katherine R. Tuttle, Executive Director for Research at Providence Inland Northwest Health and Professor of Medicine at the University of Washington, Spokane, USA, delivered the final presentation of the session, focusing on the role of aldosterone activity reduction in patients with CKD. Tuttle explored the growing recognition of aldosterone as a key driver of kidney and cardiovascular disease progression and discussed emerging therapeutic strategies aimed at mitigating its harmful effects. The presentation highlighted the increasing importance of targeting mineralocorticoid receptor overactivation as part of a comprehensive nephroprotective approach.

“Several studies have found that fruit- and vegetable-enriched diets increase plasma bicarbonate concentrations and possess nephroprotective properties”

She opened her talk by discussing baxdrostat, a first-in-class aldosterone synthase inhibitor used in combination with other therapies to treat treatment-resistant hypertension. In a pivotal 2023 study, patients with treatment-resistant hypertension, defined as having blood pressure $\geq 130/80$ mmHg despite treatment with three or more blood pressure-lowering agents, including a diuretic, experienced significant reductions in blood pressure when baxdrostat was added to standard-of-care therapy.¹⁹ In the Phase 2 Advance-HTN trial, the aldosterone synthase inhibitor lorundrostat significantly reduced 24-hour ambulatory systolic blood pressure compared with placebo in patients with uncontrolled or treatment-resistant hypertension despite receiving multiple antihypertensive medications. After 12 weeks, lorundrostat lowered systolic blood pressure by an additional 6.5–7.9 mmHg versus placebo, although treatment was associated with an increased incidence of hyperkalaemia, with potassium levels exceeding 6.0 mmol/L in 5–7% of treated participants.²⁰

Tuttle highlighted a Phase 2 trial evaluating the aldosterone synthase inhibitor vicaurostat (BI 690517) in 714 adults with CKD, with or without Type 2 diabetes, receiving stable ACE inhibitor or ARB therapy.²¹ Participants were randomised to receive varying doses of vicaurostat alone or in combination with empagliflozin, with the primary endpoint being the change in urinary albumin-to-creatinine ratio at 14 weeks. The study demonstrated dose-dependent reductions in albuminuria, supporting aldosterone synthase inhibition as a promising strategy for reducing residual cardiorenal risk in patients with CKD.

Tuttle then discussed emerging data for vicaurostat, highlighting a Phase 2 study showing dose-dependent suppression of plasma aldosterone levels in patients with CKD and proteinuria.²² Maximal aldosterone suppression was observed at Week 14 and was sustained after treatment cessation, while cortisol levels remained unchanged, demonstrating selective inhibition of CYP11B2 without affecting glucocorticoid production. These findings further support vicaurostat as a promising strategy for reducing aldosterone-mediated kidney damage.

Additionally, she discussed the reported lower risks of oedema and hyperkalaemia with empagliflozin in patients with Type 2 diabetes and CKD.²³

Finally, looking to the future, Tuttle highlighted the EXPLORE-CKD Phase 2b crossover trial, which met its primary endpoint. Lorundrostat 25 mg once daily achieved a 9.3 mmHg reduction in systolic blood pressure and a 7.5 mmHg placebo-adjusted reduction at 4 weeks ($p=0.0024$).

CONCLUSION

The session highlighted both the progress made and the ongoing debates in nephroprotection, from challenging longstanding dietary restrictions to refining the management of metabolic acidosis and targeting aldosterone-driven kidney injury. Together, these discussions underscored a growing shift towards more personalised, evidence-based strategies aimed at slowing CKD progression and improving long-term patient outcomes.

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