

Micronutrients and kidney health

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Chronic kidney disease (CKD) is a structural and functional disorder of the kidney caused by many diseases, such as diabetes, hypertension and glomerular disease.¹ There are many factors that contribute to the development and progression of CKD, and often, we do not look at the exposure of heavy metals as a risk factor for the development and accelerant of CKD.² Heavy metals, such as cadmium, mercury, arsenic and lead, can enter the body through various sources, including contaminated water, food, air pollution, occupational exposure and certain medications. Prolonged or excessive exposure to these metals can lead to their accumulation in the kidneys and cause nephrotoxicity. The kidney has the ability to reabsorb and concentrate divalent ions and metals. The renal proximal tubules are responsible for the reabsorption of essential substances from the glomerular filtrate. Heavy metals in the blood can bind to metallothionein and glutathione in inert forms, and the conjugates are then released into the blood through the liver and kidneys. These substances are then reabsorbed through the endocytic process in the S1 segment of the proximal tubule, which may eventually lead to chronic inflammation, renal fibrosis and renal failure.

Trace elements and vitamins, collectively known as micronutrients, are essential for maintaining normal human physiology.³⁻⁵ Adequate intake of these micronutrients is vital for the proper functioning of various biological processes, including metabolism, immune function, antioxidant defence and enzymatic reactions. Selenium and zinc are essential micronutrients for maintaining human health. Selenium contributes to the regulation of gastrointestinal function, improvement of human immunity, antioxidant activity and cell repair. Zinc is involved in regulating appetite, supporting a healthy immune system, wound healing, vitamin A absorption and enzymatic functions. In diabetic patients, zinc has several positive effects and CKD is associated with lower zinc concentrations.³ Deficiency of micronutrients is associated with more rapid progression

of CKD.⁴ Lower blood selenium is associated with an increased incidence of CKD and increased mortality in haemodialysis-dependent CKD patients.^{5,6} Zinc supplementation may protect the kidney by reducing blood glucose levels, microalbuminuria and alleviating glomerular damage.³

In this issue of the *Annals*, Lin et al. explored associations between CKD and heavy metal exposures measured in blood or urine among the community-dwelling population, and whether and how selenium and zinc modify the associations.⁷ Data for this cross-sectional retrospective cohort study were extracted from the National Health and Nutrition Examination Survey (NHANES) database of the US Centers for Disease Control and Prevention's National Center for Health Statistics. Adults aged 18 years or older, who had complete information for the variables of interest, were included but subjects with end-stage renal disease (ESRD), defined as a glomerular filtration rate (GFR) of <15 mL/min/1.73 m², were excluded. The study population was divided into subjects with or without CKD, defined as having a GFR <60 mL/min/1.73 m² for further comparisons. Three types of associations were evaluated: (1) roughly linear associations between log10 GFR and blood lead, cadmium, mercury, urinary arsenic, plasma selenium, serum zinc, and serum and red blood cell (RBC) folate; (2) crude and adjusted associations between the presence of CKD and quartiles of blood metals, urinary arsenic, plasma selenium, serum zinc, and serum and RBC folate; (3) combined effects of blood metals, urinary arsenic, and plasma selenium or serum zinc on CKD. In this large population-based study, the authors found that micronutrients had a protective effect in CKD patients with high blood heavy metals. Individuals with elevated blood levels of toxic heavy metals had an increased likelihood of CKD, which decreased with higher plasma selenium and serum zinc concentrations. There appears to be interactions between high levels of zinc and toxic heavy metals that reduce the risk of CKD.

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These results suggest that increasing the levels of zinc and selenium in the body and avoiding exposure to heavy metals may prevent CKD.

While these findings are intriguing, the study is limited by its observational, cross-sectional, retrospective design and non-standard collection time points of urine and blood. Thus, the inferences of causality are also limited. The results may not be generalisable to other populations, and single measurements of nephrotoxic metals may not reflect cumulative exposure. More comprehensive, observational and interventional studies are needed to determine whether clinical supplementation with selenium and zinc reduces CKD risk in people exposed to heavy metals.

Current clinical practice does not fully evaluate the micronutrient status of pre-dialysis and dialysis-dependent CKD patients due to lack of data and intervention studies.⁸ The most common causes of CKD and ESRD in Singapore are diabetes and hypertension, both of which are lifestyle-related and non-communicable diseases.¹ The micronutrient status of diabetic CKD patients in Singapore and the general population is unclear. Further studies are needed to identify CKD patients with micronutrient deficiencies and perform trials to determine if supplementation for diagnosed CKD patients can improve clinical outcomes; or if fortifying food with zinc and selenium may protect the public at large from CKD. While selenium and zinc are essential for health, excessive intake can have adverse effects. It is generally recommended to obtain these micronutrients through a balanced diet or based on recommend daily allowances.⁸ Supplementation should

be considered under the guidance of a healthcare professional if deficiencies are identified, especially in CKD patients who are prescribed restrictive diets as part of the nutritional management of CKD.⁹

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