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Zinc Deficiency: A Potential Hidden Driver of the Detrimental Cycle of Chronic Kidney Disease and Hypertension

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Abstract

Globally, over 103 million individuals are afflicted by CKD, a silent killer claiming the lives of 1.2 million people annually. CKD is characterized by five progressive stages, in which dialysis and kidney transplant are life-saving routes for patients with end stage kidney failure. While kidney damage impairs kidney function and derails BP regulation, uncontrolled hypertension accelerates the development and progression of CKD. Zinc (Zn) deficiency has emerged as a potential hidden driver within this detrimental cycle of CKD and hypertension. This review article will (*1*) highlight mechanisms of Zn procurement and trafficking, (*2*) provide evidence that urinary Zn wasting can fuel Zn deficiency in CKD, (*3*) discuss how Zn deficiency can accelerate the progression of hypertension and kidney damage in CKD, and (*4*) consider Zn supplementation as an exit strategy with the potential to rectify the course of hypertension and CKD progression.

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Introduction

Globally, an estimated 103 million individuals (1 in 10) are burdened with CKD,[1] a life-threatening condition that has catapulted to the 11th leading cause of global deaths.[2] CKD is commonly diagnosed by an estimated GFR of <60 ml/minute per 1.73 m^2 or albuminuria lasting for ≥ 3 months. While CKD progressively worsens in five stages, the National Institute of Diabetes and Digestive and Kidney Diseases reports that approximately 90% of people in stages 1–3 are unaware of their condition,[3] earning CKD the grave moniker of being a silent killer.[4] In addition to a host of comorbidities, the looming risk of CKD-related deaths and adverse cardiovascular events increases greatly with each stage.[4] By stage 5, patients with kidney failure require renal replacement therapy (dialysis or kidney transplant) for life support. Of note, 85% of US patients on the transplant waiting list require a kidney,[5] further highlighting an urgent need for effective therapeutic strategies to halt the progression of CKD to end stage kidney failure.

A major risk factor of the development of CKD is uncontrolled hypertension.[6,7] Chronically elevated BP damages the kidneys; meanwhile, kidney damage impairs kidney function and derails BP control. This self-perpetuating cycle of kidney damage and hypertension accelerates CKD progression. Despite the clinical use of potent antihypertensive drugs, uncontrolled BP persists in up to 90% of patients with CKD[6-9]. As an alternative strategy to address this critical demand, the National Institutes of Health Joint National Committee recommended a concurrent dietary approach to lower BP[10] in hopes of improving both cardiovascular and kidney health.

CKD is commonly accompanied by a deficiency in the essential dietary micronutrient, zinc (Zn). Several factors contribute to reduced serum Zn levels in patients with CKD[11-18] including (*1*) dietary protein restriction, (*2*) decreased caloric intake, (*3*) intestinal malabsorption, (*4*) hyperuricemia, (*5*) impaired kidney reabsorption and subsequent urinary wasting, (*6*) elevated fecal excretion, and (*7*) hemodialysis. It is worth noting that patients with CKD are often in the elderly population[19] and are on multiple medication regimens that alter taste sensation,[20] thus contributing to Zn deficiency through decreased caloric intake. In addition to the mechanisms noted above, Zn redistribution can also contribute to Zn deficiency in CKD. Specifically, a study noted recruitment of Zn from both bone and plasma into the bone marrow to stimulate the production of new blood cells in animal models of CKD.[21]

As the impact of Zn in CKD onset and progression is now being more investigated, Zn supplementation may be recognized as an effective therapeutic strategy. However, progress in integrating Zn supplementation into clinical practice will remain difficult until the interplay between Zn homeostasis, kidney function, and BP regulation is better defined. This review article will (*1*) highlight mechanisms of Zn procurement and trafficking, (*2*) provide evidence that urinary Zn wasting can fuel Zn deficiency in CKD, (*3*) discuss how Zn deficiency can accelerate the progression of hypertension and kidney damage in CKD, and (*4*) consider Zn supplementation as an

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exit strategy with the potential to rectify the course of hypertension and CKD progression.

Mechanisms of Zn Procurement and Trafficking

The human body contains 2–3 g of Zn, with the largest fractions found in the skeletal muscle (approximately 50%) and bone (approximately 30%)[13,16,22] (Figure 1). Lower Zn fractions are also present in the following tissues: kidney, prostate, liver, gastrointestinal (GI) tract, skin, lung, brain, heart, and pancreas[16,23,24] (Figure 1). Three major routes enable Zn entry into the human body[12,25,26]: (*1*) inhalation through the lungs, (*2*) penetrance through the skin, and (*3*) ingestion through the GI tract. Notably, these organ systems are also responsible for Zn loss. Approximately 0.8–2.7 mg Zn/day are excreted in the feces[23] while 500–600 μg Zn/day are excreted in sweat.[27] The kidneys also regulate Zn excretion as urinary losses amount to 500–800 μg/day.[28]

While the amount required to replenish lost Zn is primarily obtained by adequate dietary intake and proper intestinal absorption, kidney reabsorption is also critical for Zn procurement[14,29,30] (Figure 2). Zn trafficking to target organs subsequently occurs through the serum, where it primarily circulates bound to plasma proteins such as albumin, macroglobulins, and transferrin[31] (Figure 2). Serum Zn levels in healthy individuals vary from 12 to 16 μM, which corresponds to $<$ 0.1% of total body Zn.[32] However, caution is advised when interpreting serum Zn levels because many factors affect plasma Zn concentration[32-38]—including sex, age, time of the day, meal consumption, medications (thiazides, oral contraceptive use), pregnancy, and inflammation.

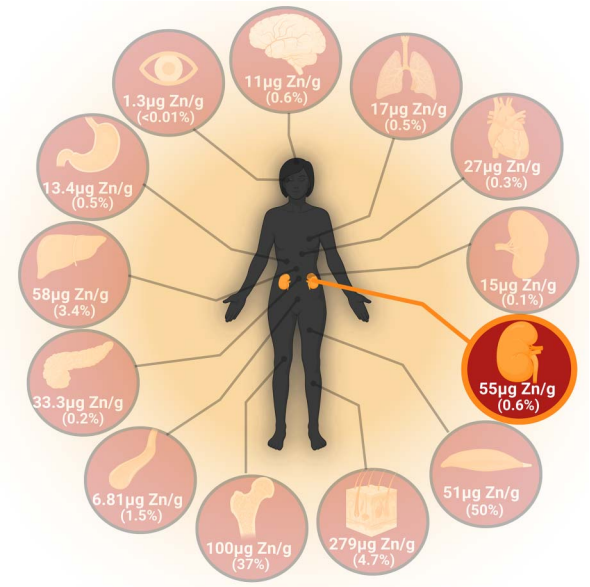

Figure 1. Zinc distribution in organs (clockwise). Brain (11 μgZn/gram, 0.6%), lungs (17 μg Zn/gram, 0.5%), heart (27 μg Zn/gram, 0.3%), spleen (15 μg Zn/gram, 0.1%), kidneys (55 μg Zn/gram, 0.6%), skeletal muscles (51 μg Zn/gram, 50%), hair/skin/nails (279 μg Zn/gram, 4.7%), bone (100 μg Zn/gram, 37%), blood vessels (6.81 μg Zn/gram, 1.5%), pancreas (33.3 μg Zn/gram, 0.2%), liver (58 μg Zn/gram, 3.4%), stomach (13.4 μg Zn/gram, 0.5%), and eyes (1.3 μg Zn/gram, $<$0.01%).

Cellular uptake of Zn constitutes an efficient homeostatic control mechanism that prevents excess serum Zn levels.[12,16,23] Cellular Zn homeostasis is mediated by three main families of Zn transport proteins (Figure 2). The Zrt-, Irt-like protein family facilitates entry of Zn into the cytosol while Zn-binding metallothioneins bind intracellular Zn. Intracellular Zn serves as a cofactor for the catalytic activity and structural integrity of over 300 proteins, including those involved in macromolecule synthesis and cell division[39-41]. Finally, Zn transporters facilitate exit of unbound, cytosolic Zn into organelles.

Evidence That Urinary Zinc Wasting Can Fuel Zinc Deficiency in CKD

The World Health Organization has deemed Zn deficiency a global health crisis, affecting 31% of the population.[42,43] While Zn deficiency is well-documented in patients with CKD,[14,17,44-48] it is worth acknowledging that the following factors are associated with Zn deficiency: vegetarian diets, older age, diabetes, diuretics, inflammatory diseases, and digestive disorders. Thus, parsing out whether Zn deficiency is a cause or consequence of CKD is quite complicated given the aforementioned confounding factors in patients with CKD. Multiple mechanisms can contribute to Zn deficiency in patients with CKD, including low dietary intake and increased Zn excretion.[18,49,50] A cross-sectional study examining 145 patients at different stages of CKD (stages 1–4) found that serum Zn levels decreased with CKD progression, whereas serum levels of copper, iron, and selenium did not.[48] In a case-control study of patients on maintenance hemodialysis, average serum Zn levels were significantly lower (69.2 μg/dl$\pm$17.29) than those in healthy controls (82.9 μg/dl$\pm$14.75).[44] Although dialysis may contribute to Zn deficiency,[51] it should be noted that abnormalities in Zn metabolism develop before end stage kidney failure and the initiation of dialysis.[47]

The progressive decline in serum Zn levels observed in patients with CKD is partially fueled by a newly uncovered phenomenon—*urinary Zn wasting* (Figure 3). In a cohort study, patients with CKD (regardless of stage) exhibited lower plasma Zn levels (606 μg/L$\pm$106.3 versus 664.1 μg/L$\pm$101.2), accompanied by higher urinary Zn excretion (612.4 μg/day$\pm$425.9 versus 479.2 μg/day$\pm$293) than patients without CKD.[14] A decline in GFR correlated with enhanced urinary Zn wasting. A sharp increase in urinary Zn was observed at stage 3, when most patients receive a CKD diagnosis. Although hypertension contributes to CKD, hypertensive patients without CKD also had higher urinary Zn excretion than normotensive controls. This indicates that hypertension, in the absence of CKD, can independently promote urinary Zn excretion. Interestingly, these patients were at *greater* risk of experiencing CKD development within 3 years.[14] Taken together, these critical findings indicate that Zn deficiency, accelerated by urinary Zn wasting, is both an early warning sign for the decline in kidney function and a hidden driver of CKD progression.

Does Zinc Deficiency Accelerate the Detrimental Cycle of Hypertension and Kidney Damage in CKD?

The kidneys are essential in the maintenance of salt-water balance and, subsequently, BP control. Because this critical

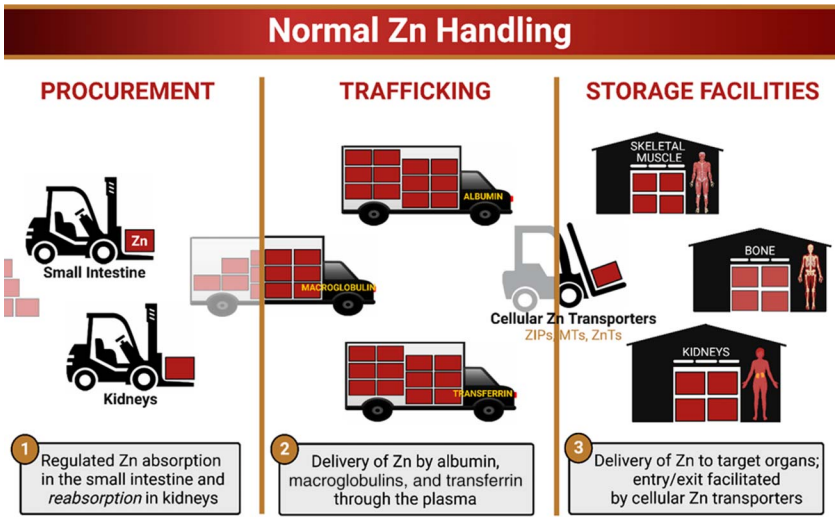

Figure 2. Normal zinc handling. MTs, metallothioneins; ZIPs, Zrt-, Irt-like proteins; ZnTs, Zn transporters.

homeostatic function is impaired in the setting of CKD, up to 90% of patients experience comorbid hypertension.[6-9] Notably, resistant hypertension is a common clinical problem, and CKD poses one of the greatest risks of developing treatment-resistant hypertension.[52] The prevalence of hypertension increases with advanced CKD stages, with nearly 100% of patients experiencing hypertension in stage 5.[53] This stark reality creates a detrimental cycle in which kidney damage causes hypertension, thus further worsening damage to the kidneys. Hypertension in patients with CKD has many etiologies including a hyperactive renin-angiotensin-aldosterone system, reduced GFR, altered vascular reactivity, overactivity of the sympathetic nervous system, and increased Na^+ retention.[6] As CKD progresses, BP becomes increasingly Na^+-sensitive due to the fluid retention caused by salt intake. We present that the disruption of renal Na^+ excretory function that causes Na^+ retention is fueled by Zn deficiency[54] (Figure 3). This overlooked culprit may consequently promote the self-perpetuating cycle of hypertension and kidney damage (Figure 3) that accelerates CKD progression to end stage kidney failure.

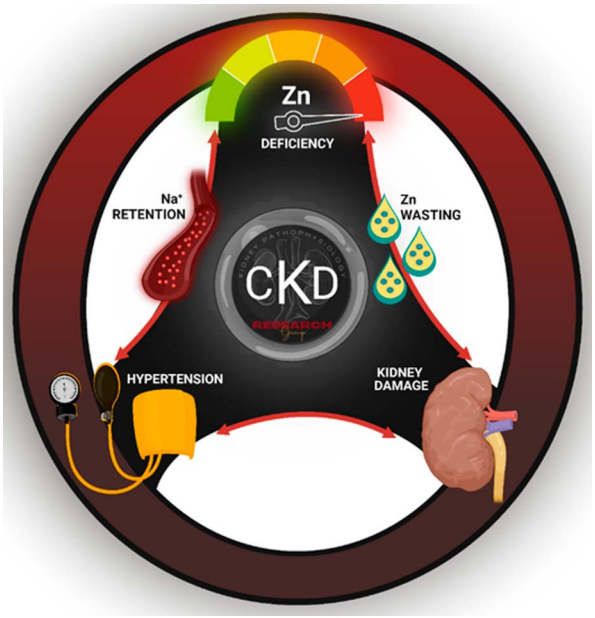

Figure 3. Zinc deficiency can accelerate the detrimental cycle of hypertension and kidney damage in CKD. Zn deficiency is partially fueled by a newly uncovered phenomenon—*urinary Zn wasting*. Zn deficiency *alone* causes kidney damage and is also sufficient to induce hypertension. This overlooked culprit drives renal Na^+ retention and can consequently promote the self-perpetuating cycle of hypertension and kidney damage that accelerates CKD progression to end stage kidney failure.

Zn is an essential micronutrient present in the diet and readily available as a supplement. The recommended dietary allowance of Zn is approximately 11 mg/day for men and approximately 8 mg/day for women,[55] with an increased Zn demand (approximately 10–15 mg) during physiological states of growth such as pregnancy or puberty.[31,55] Zn supports numerous aspects of cellular metabolism, and the coronavirus disease 2019 pandemic has highlighted the utility of Zn in immune function.[56,57] While Zn's role in both vascular[58,59] and cardiac functions[31,60] is well established, its impact on kidney function is *less* known.[31] Our laboratory recently established a regulatory role for Zn in renal Na^+ reabsorption by the distal nephron.[54] Although most of Na^+ is reabsorbed in the proximal tubule, renal Na^+ handling is fine-tuned in the distal nephron. Specifically, this nephron segment precisely integrates local changes in urinary Na^+ with hormonal signals to modulate Na^+ excretion, thus maintaining salt-water balance. This sequence of physiological events culminates in BP control.

In CKD, however, distal nephron function is impaired,[61] resulting in three of five patients with salt-water retention, thereby fueling the initiation and persistence of hypertension.[62] Our preclinical findings provide evidence that Zn deficiency *alone* causes kidney damage[63] and is sufficient to induce hypertension as a direct consequence of impaired

Figure 4. Zinc supplementation: A possible offramp from the road to end stage kidney failure.

renal Na^+ excretory function.[54] Specifically, mice fed a Zn-deficient diet exhibited hypertension with a concurrent reduction in urinary Na^+ excretion.[54] Consistent with higher Na^+ reabsorption activity in the distal nephron, thiazide treatment promoted natriuresis and importantly restored BP control.[54] Mice fed a Zn-deficient diet also exhibited multiple markers of kidney damage including oxidative stress, renal fibrosis, and albuminuria.[63,64] These same pathological events likely occur in the context of CKD. However, future studies are necessary to (*1*) identify renal Zn-sensitive pathways that drive hypertension and accelerate CKD progression and (*2*) explore strategies using Zn supplementation to provide an offramp from this detrimental cycle of hypertension and kidney damage.

Can Zinc Supplementation Provide an Exit Strategy to Rectify the Course of Chronic Kidney Disease and Hypertension?

Current treatment strategies for hypertension in the CKD population attempt to restore salt balance to lower BP. Particularly, (*1*) low-salt diets are often recommended to enhance the effects of ACE inhibitors and angiotensin receptor blockers[9,65]; (*2*) thiazide diuretics inhibit the distal nephron Na^+ reabsorption pathway to reduce Na^+ retention mediated by the kidneys[9]; and (*3*) mineralocorticoid receptor antagonists block aldosterone-stimulated reabsorption of Na^+ by the distal nephron.[9,66] Although these treatment strategies exist as monotherapies to exploit renal Na^+ excretory function, even their use as combination therapies (three or more antihypertensive drugs) often fail to control BP in patients with CKD.[52,62] Notably, these antihypertensives also alter Zn homeostasis.[67,68] A systematic review of eight clinical studies, which included patients on antihypertensive therapy, reported reduced serum Zn levels with daily doses of captopril (50–150 mg), hydrochlorothiazide (12.5 mg), and losartan (50 mg). Moreover, urinary Zn wasting was reported with the use of captopril (50–75 mg), enalapril (20 mg), hydrochlorothiazide (12.5–25 mg), furosemide (40 mg), and losartan (50 mg). Further investigation is necessary to determine the extent of this influence because study limitations include small patient sample sizes and a lack of dietary Zn intake reporting.

Zn supplementation is a potential therapeutic strategy for many conditions because of its anti-inflammatory, antifibrotic, and antioxidative properties in the body[69-71]. Our findings reveal that Zn also exhibits *anti-hypertensive* and *reno-protective* properties because of its critical role in renal Na^+ excretory function and BP regulation.[54,63] There is also evidence that Zn plays a protective role in other organ systems relevant to BP, such as the vasculature and heart. Specifically, the protective effects of Zn include promoting cardiomyocyte redox balance and vascular integrity.[31] Interestingly, Zn supplementation *in vitro* led to the complete restoration of the endothelial cell barrier,[58,59,72] an effect not achieved with either calcium or magnesium supplementation.

Collectively, our findings and others support future studies exploring Zn supplementation to disrupt the detrimental cycle of hypertension and kidney damage burdening patients with CKD. Although clinical trial evidence in support of Zn supplementation in patients with CKD is limited, multiple preclinical studies have shown Zn to possess beneficial renal and cardiovascular effects. In rodent models of CKD, Zn supplementation slowed the progression of diabetic nephropathy,[73,74] with the antifibrotic effects of Zn reducing renal morphologic changes. These positive outcomes attenuated diabetes-induced proteinuria, a well-known feature of CKD. Furthermore, the antioxidative effects of Zn also protected against diabetes-induced aortic damage and endothelial dysfunction.[75] In the same manner that Zn is cardio- and renoprotective in preclinical studies, Zn supplementation likely exerts similar effects in patients with CKD. However, insights from clinical investigation are greatly needed.

In patients with CKD and low serum Zn levels, Zn supplementation may be an effective therapeutic strategy to prevent disease progression. While urinary Zn wasting occurs in CKD, oral Zn supplementation is sufficient to increase serum Zn levels, even in patients on hemodialysis.[76] Notably, in patients with CKD and low serum Zn, drugs containing Zn were *more* renoprotective, leading to a reduction in the risk of disease progression or death by 62%.[11] The authors credit these outcomes to the anti-inflammatory and antioxidative benefits of Zn. Although these findings seem encouraging, there is a paucity of evidence *directly* demonstrating the beneficial effects of Zn supplementation in the CKD population. However, the therapeutic index of Zn supplementation should also be investigated because acute symptoms after uptake of high doses of Zn include abdominal pain, nausea, and vomiting. Additional effects include lethargy, anemia, and neurologic disturbances such as dizziness.[12] However, acute Zn intoxication is considered a rare event.[12] Long-term, high-dose Zn supplementation interferes with the uptake of copper. Hence, many of the toxic effects of Zn uptake are in fact attributed to copper deficiency.[12] Until large-scale clinical trials are conducted, the fate of Zn supplementation remains unknown in the vulnerable CKD population. As such, future studies would provide data *directly* examining Zn supplementation as a therapeutic intervention—serving as an offramp from the road to end stage kidney failure (Figure 4).

Disclosures

The authors have nothing to disclose.

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