Zinc and Kidney Disease: A Review

Ashkan Abdollahi,[1] Aria Ghahramani,[2] Nasrollah Ghahramani[2]

[1]Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Pennsylvania State University College of Medicine, USA

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Zinc is the second most abundant essential trace element in the human body with important regulatory functions in cellular and subcellular levels in several tissues. Zinc deficiency is associated with the development and progression of chronic kidney disease (CKD) and its complications. With the progression of CKD to end-stage kidney disease (ESKD) and initiation of dialysis, zinc is further removed from the body, potentiating the zinc deficiency. Dietary intake plays a major role in zinc-deficiency-related risks and progression of CKD. By taking into account the evidence from clinical studies depicting the mutual correlations between zinc and CKD, and the plausibility based on animal studies, it can be deduced that zinc deficiency has a causative role in CKD and its progression. This review highlights the role of zinc deficiency in kidney disease and the possible indication for supplementation of zinc at various stages of CKD.

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Review

INTRODUCTION

Zinc is an essential trace element, the second most abundant trace element in the human body. The human body normally contains 2 to 3 grams of zinc (80 to 130 mcg/dL), of which more than 90% is stored in muscles and bones, and only 0.1% in plasma.[1-3] Zinc is actively absorbed through the small bowel and circulates bounded to albumin (exchangeable pool), α2-macroglobulin (non-exchangeable pool), and transferrin.[4-6] The amount of zinc absorbed by the body highly depends on dietary intake and bioavailability. Red meat, legumes, cereal, and dairy products are among the most important dietary sources of zinc, whereas fibers, calcium, ferrous sulfate, and folic acid will decrease the bioavailability of zinc and interfere with its absorption.[7,8] The major route of zinc excretion in healthy individuals is through the gastrointestinal tract.[9] Renal handling of zinc, on the other hand, has not been fully elucidated yet. Studies indicate that approximately 70% of zinc is reabsorbed in the proximal convoluted tubule and since it is bound to plasma proteins, its glomerular filtration and urinary excretion are limited.[10,11]

Zinc is a major regulator of many cellular and subcellular functions in various tissues and acts as a cofactor for the catalytic activity of several enzymes involved in DNA replication, cell division, energy metabolism, and growth.[12-16] It is also significant in maintaining protein structure and stability, as well as the structure and function of cell membrane.[17,18] Recent studies have identified zinc as an antioxidant agent with anti-inflammatory characteristics and a key regulator of leptin and insulin signaling, as well as innate and adaptive immunity.[19-22] Dysregulation of zinc homeostasis is associated with numerous disease conditions including impairments in immune function, growth, cognitive performance, and glucose homeostasis.[5,23,24] Zinc deficiency is known to contribute to organ fibrosis, and zinc supplementation has been shown to protect against fibrosis,[25] including in nephrotoxin-induced kidney fibrosis, Balkan endemic nephropathy[28] and diabetic nephropathy.[25-29]

Anemia is common among patients with chronic

kidney disease (CKD) and increases morbidity and mortality, regardless of the stage of the disease.[30-32] Most patients starting dialysis have a hemoglobin concentration below the standard range.[33] Zinc supplementation has shown promising results in increasing hemoglobin concentrations in these patients.[34]

In recent years, there has been growing interest in zinc within the nephrology community; some studies have indicated that plasma zinc levels decrease with the progression of CKD.[35-37] Increased oxidative stress, cardiovascular complications and the development of atherosclerosis, which play significant roles in the progression of CKD, can all arise from decreased plasma concentration of zinc.[38-41]

Considering the fact that CKD is a progressive condition, it is important to identify modifiable risk factors, including zinc deficiency to reduce CKD-related morbidity and mortality.[42] In this review we have discussed the mutual interactions between zinc and CKD.

DIET, ZINC, AND CKD

Dietary factors play a significant role in zinc-deficiency related risks and progression of CKD. In a cross-sectional study of 159,711 participants, Kim *et al* showed that dietary intake of zinc ≤ 5.86 mg/d is associated with higher odds for advanced CKD (OR = 1.52, 95% CI: 1.02 to 2.26).[43] Joo *et al*, in a cohort study of 7735 participants with preserved kidney function who were followed for 11.5 years, found that participants with the lowest zinc consumption were significantly more susceptible to development of CKD than those with high zinc consumption. This held true after adjusting for clinical, anthropometric, and laboratory confounding factors (HR = 1.20, 95% CI: 1.04 to 1.40, P = .02).[42,44] In a retrospective cohort study of 210 patients with end-stage kidney disease (ESKD) attending a pre-dialysis clinic, it was reported that the dietary zinc intake was below the recommended daily intake in 64.2% of the patients.[45] Joyce *et al*, in a cross-sectional study of infants and children with chronic kidney disease managed without dialysis, reported below normal plasma zinc concentrations in 34% of the study participants who were taking diet without any nutritional supplementation. Also, 44% of participants who had some or all of their nutrition via nasogastric or gastrostomy tubes were zinc deficient. Conversely, plasma zinc levels were within normal range in patients taking oral nutritional supplementation.[46] These results were supplementary to the previous articles about lower dietary intake of zinc in adult uremic patients.[47] In a study on high fat diet fed mice, Luo *et al* found that zinc deficiency worsens the pathological progression of obesity-related kidney disease as well as kidney inflammation, whereas zinc supplementation had a protective effect.[16] They concluded that zinc plays a key role in ameliorating obesity-induced kidney inflammation and hypertrophy by down-regulating P38 mitogen-activated protein kinase.

Another study on IgA nephropathy-prone mice by Maiguma *et al* showed that high zinc diet suppresses serum levels of IgA (P < .05) as well as IgA-IgG immune complexes (P < .05). Also, the intensity of glomerular deposition of IgA was significantly reduced in high zinc diet group as compared with normal (P < .01) and low zinc diet (P < .01) mice. Furthermore, urinary albumin levels were significantly higher in low zinc diet and high zinc diet mice than the normal group (P < .05 and P < .01, respectively) and it was more pronounced after nasal lipopolysaccharide (LPS) challenge (P < .05). The *in vitro* study demonstrated that splenic cells produced more IgA in low zinc (P < .001) and high zinc (P < .001) conditions than normal. Similarly, the expression of TLR4 in dendritic cells significantly increased after LPS stimulation under low (P < .05) and normal (P < .01) zinc conditions; however, this was attenuated under high zinc condition as compared with low (P < .05) and normal (P < .05) zinc condition. The expression of TIR-domain-containing adapter-inducing interferon-β (TRIF), was significantly upregulated in low zinc condition in comparison with normal (P < .05) and high (P < .05) zinc conditions. They concluded that zinc modulates production of IgA by its effects on the activity of dendritic cells especially via TLR4/TRIF, so that it can alter nephrogenic IgA production following mucosal infections.[48]

In a study of 100 pre-dialysis CKD patients Sahni *et al* found significantly lower zinc and nutritional status in CKD patients compared with healthy controls (P ≤ .001). Additionally, zinc supplementation alone failed to improve dietary intake, as the patients were scared to eat more

kidney unfriendly food in the absence of clear dietary guidelines. By contrast, desired results in terms of nutritional intake were observed when zinc supplementation was accompanied with parametric, individualized dietary counseling. Thus, there is an essential need for implementation of effective nutritional management and diet counseling in addition to proper zinc supplementation for correcting missunderstandings of diet and making the treatment effective.[49]

CKD AND ZINC

Compared with individuals without CKD, patients with CKD have significantly lower plasma zinc levels, and higher urinary excretion of zinc. In a cohort study of 189 individuals followed for three years, Damianaki *et al.* reported lower circulating zinc levels in CKD patients as compared with a non-CKD control group, and a higher 24-h urinary excretion of zinc among the CKD group (612.4 ± 425.9 vs. 479.2 ± 293.0 µg/d, $P = .02$). Moreover, fractional excretion (FE) of zinc was higher in CKD patients with a significantly increasing trend in more advanced stages. The FE of zinc was negatively correlated with 24-h uromodulin excretion (r = -0.29, $P < .01$), suggesting that the possibly impaired tubular activity contributes to zinc imbalance in CKD. They also observed that lower plasma zinc levels correlated with faster decline in annual kidney function. Finally, they found that hypertensive participants had a higher 24-h urinary excretion of zinc than normotensive controls.[50] In a cross-sectional study, Shen *et al.* demonstrated that in elderly population, plasma zinc levels were significantly higher among non-CKD participants than CKD patients.[51] A cohort study of 3057 participant also showed that CKD patients had significantly lower plasma zinc concentrations than non-CKD participants ($P < .0001$).[52]

Plasma zinc levels have a positive correlation with kidney function, and a negative correlation with proteinuria, as well as the risk and progression of CKD. In a cross-sectional study of 104 pre-dialysis CKD patients, Kim *et al* found that serum zinc levels were positively correlated with eGFR (r = 0.202, $P = .039$).[53] Similarly, Hung *et al.* showed a positive correlation between plasma zinc levels and eGFR in patients with morbid obesity who had undergone laparoscopic sleeve gastrectomy after 6 (r = 0.252, $P = .037$) and 12 months (r = 0.41, $P = .001$).[54] Among the CKD population, Kim *et al* found that serum zinc level had a negative correlation with proteinuria (r = -0.316, $P = .001$).[53] Proteinuria has been associated with progression of CKD, and the range of proteinuria is strongly associated with loss of kidney function; this has been well-documented in various settings, including in the post-acute kidney injury (AKI) period, among diabetics and non-diabetics, and in the hypertensive population.[55-62] Shen *et al.* demonstrated a non-linear negative correlation between plasma zinc levels and CKD risk among elderly patients (90-years of age or older) with CKD (adjusted OR = 0.50, 95% CI: 0.28 to 0.89 for the fourth vs. first quartiles), leading them to propose that plasma zinc levels protect against CKD in elderly populations.[51] In a study on194 CKD patients Kung *et al* showed that zinc levels decrease as CKD progresses to more advanced levels after adjustments for age, sex, smoking habits, education, diabetes, hypertension, and body mass index (BMI) ($P = .002$).[10] Another study of 145 CKD patients at stages 1 to 4 supported the aforementioned results. Shih *et al.* observed that serum levels of zinc were significantly different at various stages of CKD ($P = .005$) with a statistically significant decrease in late-stage CKD subjects.[63]

DIALYSIS AND ZINC

Patients on dialysis have lower plasma zinc levels. Esfahani *et al.* studied zinc levels in pediatrics and demonstrated that patients with CKD on hemodialysis had lower levels of plasma zinc than those with CKD on conservative management or than healthy controls. They also showed that ESKD patients who were on hemodialysis for more than 18 months had lower plasma zinc levels than those who were on hemodialysis for less than 18 months ($P < .001$).[64] Plasma zinc levels did not significantly differ between ESKD patients on hemodialysis and patients on continuous ambulatory peritoneal dialysis (CAPD). Patients on cAPD had lower zinc levels than healthy participants ($P < .05$) and than ESKD patients managed conservatively ($P < .001$).[65] In a case-control study of 50 children there was no difference between plasma zinc concentrations in patients with stage 5 CKD on routine hemodialysis and those with stage 3 or 4 of CKD who were

on conservative management; nevertheless, both groups had lower zinc levels as compared with healthy controls.[66] A double-blind clinical trial of zinc supplementation in 20 patients who were on hemodialysis for at least 6 months, showed that initial concentrations of plasma zinc were below the normal range in both zinc-supplemented and control groups. Nevertheless, after 90 days of daily administration of 50 mg elemental zinc, subjects in the zinc-supplemented group showed significant increase in serum zinc concentrations as opposed to the control group.[67]

Zinc is partially removed by hemodialysis. The binding affinity of trace elements to plasma proteins is an important factor in their removal by conventional hemodialysis and peritoneal dialysis.[68] Sotogaku *et al.* reported that plasma protein binding of zinc is only 12 to 17%, which makes it prone to removal during dialysis.[69] Other studies supported this hypothesis; a meta-analysis of 128 studies showed that zinc levels were lower in hemodialysis patients compared with healthy controls.[70] Pasko *et al.* also reported trans-membrane loss of zinc in a case-series of five pediatric patients on continuous kideny replacement therapy.[71] In a 6-month longitudinal study of 48 hemodialysis patients, Navarro-Alarcon *et al.* claimed that zinc deficiency is a consequence of the significant loss of this trace element in hemodialysis. They hypothesized that although albumin acts as the main carrier of zinc in plasma, low zinc levels found in hemodialysis patients are probably more related to the element deficiency itself rather than albumin deficiency.[72] The low zinc levels among patients with ESKD on hemodialysis persists up to 12 months after kidney transplant, possibly related to increased urinary loss of zinc.[73] Although in a cohort study of 152 stable patients on chronic peritoneal dialysis the incidence of zinc deficiency was reported to be as high as 57.2%,[74] it has been reported that in apposition to hemodialysis, ESKD patients undergoing continues ambulatory peritoneal dialysis have no significant zinc loss.[75]

Infectious complications are higher among zinc-deficient dialysis patients. Several studies have suggested that zinc deficiency leads to poor immunity in hemodialysis patients.[76-78] In two years follow up of ESKD patients on dialysis, for each 1 µg/dL decrease in serum levels of zinc, a 2.0% increase in risk of hospitalization for infection and a 2.8% increase in mortality, has been shown.[79]

In a multi-center study of 265 patients with ESKD on routine hemodialysis, Skarupskiene *et al.* showed that infectious complications were associated with zinc deficiency and that hemodialysis patients with infectious complications had significantly lower plasma levels of zinc ($P < .005$).[80] Yang *et al.*, in a 2-year prospective cohort study of 111 ESKD patients under dialysis for a mean duration of 6.5 years, offered a reference value for serum zinc associated with adverse clinical outcomes in dialysis patients. In their study, patients with serum zinc more than 72.2 µg/dL had a significantly greater event-free survival in the case of hospitalization for infection, as well as a significantly higher overall survival than those with concentrations less than 72.2 µg/dL ($P = .001$, .027; respectively). After a multivariate Cox regression analysis, zinc deficiency was found to be an independent predictor of infectious diseases requiring hospitalization (HR = 0.980, 95% CI: 0.967 to 0.993; $P = .002$), as well as an independent predictor of 2-years mortality (HR = 0.973, 95% CI: 0.948 to 0.999; $P = .046$). They also showed that patients with both hypoalbuminemia and zinc deficiency had the worst prognosis with regard to event-free survival in the case of hospitalization for infection than those with hypoalbuminemia but normal to high level of zinc ($P = .024$) and those with neither hypoalbuminemia nor zinc deficiency ($P < .001$). Also, patients with both hypoalbuminemia and zinc deficiency were at the greatest risk for mortality compared with those with neither hypoalbuminemia nor zinc deficiency.[79] It is worth noting that the vast majority of zinc is albumin-bounded and there is a positive correlation between zinc and albumin levels.[81-83] Low serum albumin leads to a reduction in the circulating levels of albumin-bound zinc, resulting in increased zinc excretion.[84] Thus, hypoalbuminemia is a potentially significant contributor to zinc deficiency among patients with CKD.

Zinc supplementation reduces inflammatory markers in hemodialysis patients. In a randomized clinical trial of zinc supplementation in ESKD patients with low plasma zinc concentrations who were on regular hemodialysis, Guo *et al.* showed that after zinc supplementation, plasma

levels of CRP, TNF-α, and IL-1β significantly decreased in zinc-supplemented patients compared with the control group.[22] Another study by Roozbeh *et al.* also demonstrated that serum CRP levels decreased significantly after 6 weeks of oral zinc supplementation in 41 ESKD patients with low serum zinc levels who were on routine hemodialysis.[85] A systematic review and meta-analysis of 8 randomized controlled trials confirmed these results and concluded that zinc supplementation markedly reduces plasma CRP concentrations, particularly at high doses (50 mg elemental zinc daily) and in patients with kidney dysfunction.[86]

Zinc supplementation increases hemoglobin concentrations in dialysis patients. Fukushima *et al.* treated maintenance hemodialysis patients who had zinc levels below the normal range with adjuvant zinc therapy and found that zinc supplementation was associated with significant increase in hemoglobin levels within a month ($P < .01$) as well as with significant increases in other hematological parameters, including red blood cell count and hematocrit levels.[87] Yasuhiro *et al.* reported an 82-years-old woman with ESKD on routine hemodialysis, who presented with fatigue and loss of appetite with hemoglobin and zinc levels of 6.3 g/dL and 54 μg/dL, respectively. The patient was put on zinc replacement therapy (34 mg of elemental zinc daily) with the diagnosis of zinc deficiency anemia and after 3 weeks of therapy her hemoglobin levels increased to 11.0 g/dL.[88] A cohort study of 3057 participants showed that CKD patients with above normal levels of zinc had significantly higher levels of hemoglobin ($P < .0001$).[52] In a randomized controlled trial of zinc supplementation on 70 hemodialysis patients with zinc deficiency, Kobayashi *et al.* reported that zinc supplementation increases erythropoietin responsiveness index, measured as weekly erythropoietin dose (units)/ dry weight (Kg)/ hemoglobin (g/dL).[89]

SUMMARY AND CONCLUSION

Zinc is an essential trace element, which plays a major role in maintaining cell membrane structure and function. It possesses antioxidant and anti-inflammatory properties, and its imbalances are associated with impaired immune function. The amount of zinc absorbed by body depends largely on its dietary intake and bioavailability. Compared with individuals without CKD, patients with CKD have significantly lower plasma zinc levels, and higher urinary excretion of zinc. Zinc deficiency is associated with tissue fibrosis, increased risk of CKD progression and proteinuria. Since patients with CKD have increased urinary excretion of zinc, it might be hypothesized that decreased zinc in CKD is secondary to its increased urinary excretion. However, there are several factors favoring the hypothesis that zinc deficiency contributes to CKD, rather than being its result. Zinc deficiency is associated with proteinuria, and zinc supplementation in animal models leads to amelioration of kidney injury; the pathogenic role of inflammation in CKD, and the anti-inflammatory role of zinc have been well established. Given the evidence from clinical studies of correlation between zinc deficiency and CKD and the biological plausibility based on animal studies, it is safe to say that zinc deficiency plays a causative role in CKD and its progression. It is likely that dietary restrictions (such as restrictions of meat and dairy) in CKD, combined with supplements such as calcium, iron, and folic acid which are often prescribed for CKD patients, contribute to zinc deficiency. With the progression of CKD towards ESKD and initiation of dialysis, zinc is partially removed by dialysis, leading to worsening of zinc deficiency, and higher risk of infectious complications. Furthermore, zinc supplementation leads to increased hemoglobin concentrations in dialysis patients.

This review underscores the need to be cognizant of the role of zinc deficiency in kidneydiseases and the possible need for attentiveness on supplementing of zinc at various stages of CKD. Prevention and correction of zinc deficiency will likely lead to mitigation of complications such as infections and anemia among patients with CKD and ESKD.

CONFLICT OF INTEREST

None.

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Correspondence to:
Ashkan Abdollahi, MD
Nephro-Urology Research Center, Shiraz University of Medical Sciences, Khalili St, Shiraz, Iran
E-mail: ashkan.abdollahi@gmail.com

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