Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

Biological importance of Zinc for Chronic Kidney Disease Patients

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Abstract

Background: Trace element metabolism change frequently in patients with Chronic Kidney Disease (CKD) who undergo HD.Zn deficiency in CKD patients may be due to fecal excretion or decrease in its absorption.Zn deficiency may be associated with some of the uremic symptoms such as anorexia, hypogeusia, sexual dysfunction or decreased immunologic function.Many studies have shown a high prevalence of Zn deficiency in CKD patients who were under either conservative or dialytic treatment. Zinc deficiency is a common consequence of, or contribution to human inflammatory disease.

Keywords: Zinc, Chronic Kidney Disease

Introduction

Total zinc content of body is about 2 g, out of which 60% is in skeletal muscles and 30% in bones. Highest concentration of zinc is seen in hippocampus area of brain and prostatic secretion. Rich dietary sources are grains, beans, nuts, cheese, meat and shellfish. Copper, calcium, cadmium, iron and phytate will interfere with the absorption of zinc. Zinc and copper will competitively inhibit each other's absorption. So, zinc is therapeutically useful to reduce copper absorption in Wilson's disease. In liver, zinc is stored in combination with a specific protein, metallothionein. Zinc is excreted through pancreatic juice and to a lesser extent through sweat **(2)**.

More than 300 enzymes are zinc dependent. Some important ones are carboxypeptidase, carbonic anhydrase, alkaline phosphatase, lactate dehydrogenase, ethanol dehydrogenase and glutamate dehydrogenase. RNA polymerase contains zinc and so it is required for protein biosynthesis. Extracellular superoxide dismutase is zinc dependent and so, zinc is an anti-oxidant. Insulin when stored in the beta cells of pancreas contains zinc, which stabilizes the hormone molecule. But the insulin released into the blood does not contain zinc. The commercially available preparation, protamin-zinc-insulinate (PZI) also contains zinc. Zinc containing protein, Gusten, in saliva is important for taste sensation. The requirement of Zinc for adults is 10 mg/day; children 10 mg/day; in pregnancy and lactation 15‑20 mg/day. Since iron inhibits absorption of zinc, when iron is supplemented, zinc is also given to prevent any deficiency **(2)**.

The second most common nutrient in the body after iron, zinc is a micronutrient to which 10% of the proteins in the body bind. Zinc is found in its free form as Zn^{+2} in the body, but by binding to various structures, it endows these structures with attributes that will enable them to fulfill their duties. A total of 7200 enzymes including DNA polymerase and RNA polymerase **(3)**, many finger proteins such as Transcription factor IIIA (TFIIIA), and GATA binding protein 6 (GATA6), and numerous hormones like human prolactin (hPRL) and growth hormone (gGH) bind zinc to assume features to serve their proper functions **(4)**.

Zinc is necessary for the development of bones, muscles, and cartilage tissue. Zinc increases the activity of osteoblasts and inhibits the activity of osteoclasts among the bone cells. In osteoblastic cells, zinc can improve cell proliferation, alkaline phosphatase activity, and osteogenic effect **(5).** In the case of zinc deficiency, however, significant impairments are observed in these tissues whose development is then curbed. Diseases involving the connective tissue such as myotonic dystrophy type II and Ehlers-Danlos syndrome are associated with zinc disturbance **(6)**.

Zinc also functions in neuromodulator and neurotransmitter capacities. Released from the presynaptic area, it acts in the postsynaptic area in neurons. Therefore, zinc is also linked to learning and memory **(7)**. In relation to the nervous system, zinc deficiency leads to learning impairment, memory loss, and depression. Zinc uncovers significant effects on the immune system. Zinc deficiency causes a decrease in the percentage of T cells and the lytic activity of natural killer (NK) cells (Natural Killer cells). Interleukin (IL)-6 level was reported to fall significantly in ZIP14 KO mice (whose ZIP14 gene was suppressed) **(8)**.

Zinc serves in the regulation of the oxidative stress induced by oxidant production and metals. The relation of zinc and sulfur in the cysteine part of proteins is important, as zinc is released from this part of proteins by metals, nitric oxide, peroxides, oxidized glutathione, and other thiol oxidant species, causing these proteins to function less **(9)**.

One of the molecules' containing zinc is NOS (nitric oxide synthase). Zinc in the structure of NOS is released by peroxynitrite ($ONOO^-$) produced during sepsis, inflammation, ischemia-reperfusion, and atherosclerosis, and this causes an increase in superoxide anions. Deficiency in Cu, Zn-superoxide dismutase (Sod1) (Sod1 transgenic mice) has elevated oxidative stress and decreased muscle mass and strength compared to wild-type (WT) mice and appears to have an accelerated muscle-aging phenotype **(10)**.

The decrease in extracellular zinc leads to an increase in neuronal oxidants through the activation of N-methyl-D-aspartate (NMDA) receptor, which causes calcium absorption and calcium-dependent activation of protein kinase C/NADPH oxidase and NOS **(11)**. Brain-derived neurotrophic factor (BDNF) and neurotrophin (NT) 4 or 5 raise the level of

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

NADPH oxidation. NAPDH oxidase inhibitor, 4-(2- aminoethyl) benzenesulfonyl fluoride (AEBSF), scales down the increase in free oxygen radicals. Consequently, NAPDH oxidase mediates the increase in free oxygen species **(12)**.

Apoptosis proteins such as Fas, Fas ligand (FasL), apoptosis-inducing factor, and caspase 3 are activated in the hippocampus of mice fed on a zinc-deficient diet. Reduced extracellular zinc leads to the activation of NMDA receptors, which in turn causes caspase 3 activation and apoptosis. Zinc deficiency in human neuronal precursor cells (NT-2) causes a buildup of reactive oxygen species through a chain of signals involving p53, and upon expulsion of apoptosis-inducing factor outside the mitochondria, it impairs the mitochondrial integrity, with a 24% decrease in the potential of the mitochondrial membrane, and also causes apoptosis, leading to an increase in pro-apoptotic mitochondrial protein BAX. While zinc deficiency stimulates apoptosis in many cells, zinc supplementation inhibits apoptosis. Supplementation of 8 μM zinc in cultured Sertoli cells reduced caspase 3 expression and curbed apoptosis **(13,14)**

Although there are some studies indicating that zinc inhibits apoptosis, others suggest that zinc induces apoptosis. What is important in this context is the concentration of supplemented zinc, duration of supplementation, cell type, agent administered before zinc, and way of supplementation. Zinc oxide nanoparticles induced apoptosis through PI3K/Akt/caspase3/7 and necrosis through LOX-mediated ROS production. Exposure to zinc in human prostate cancer cells led to an increase in intracellular zinc and step-up of cells undergoing apoptosis. This has been attributed to elevated Bax level or reduced Bcl-2 and survivin expression, as survivin directly inhibits caspases and prevents apoptosis, while survivin suppression induces apoptosis **(15)**.

Zinc deficiency in CDK:

Many studies have shown a high prevalence of Zn deficiency in CKD patients who were under either conservative or dialytic treatment. Zinc deficiency is a common consequence of, or contribution to human inflammatory disease. However, the molecular mechanisms through which zinc contributes to inflammatory disease remain largely unknown due to zinc's widespread action on different enzymes, peptides, transcriptional factors, and cytokines involved in the various physiological steps of immune development **(16)**.

Bozalioğlu et al. showed that patients on maintenance hemodialysis exhibit zinc deficiency and disturbed immune response **(17)**. Ribeiro et al. observed that zinc therapy improved in vivo and in vitro hypersensitivity skin tests and lymphocyte function of hemodialysis patients, and that its discontinuation suppressed all of the benefits observed **(18)**. Lobo et al. proposed that zinc supplementation induces the activation of T lymphocytes and T-cell-dependent B lymphocytes in chronic uremic patients. Besides decreasing lymphocyte levels, zinc deficiency causes anorexia in CKD patients. The

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

mechanisms by which zinc deficiency induces anorexia are unclear, but hormone leptin provides a tool for elucidating the physiology of zinc deficiency-induced anorexia **(19)**.

Increased fat mass, food intake, and elevated concentrations of insulin and glucocorticoid produce increases in obese (ob) mRNA and circulating leptin. Conversely, lower body fat, fasting, and decreased serum insulin concentrations are correlated with lower concentrations of leptin. leptin was reduced in the serum of zinc-deficient rats, which was not surprising, since anorexic rats have less body fat compared with controls **(19)**.

Zinc is essential for insulin synthesis and release, and zinc deficiency seems to impair release of insulin. Additionally, leptin secretion and gene expression are induced by insulin. Therefore, reduced insulin action in hypozincemia may be partially responsible for decreased expression of the ob gene **(20)**.

Other authors have suggested that changes in circulating interleukin (IL-2) and tumor necrosis factor-α (TNF-α) are an important part of the physiology of zinc deficiency. Therefore, hypozincemia negatively affects also the leptin secretion, possibly depending on a decreased secretion of adipocyte-derived TNF-α and IL-2. According to experimental data, zinc deficiency decreases leptin levels whereas zinc supplementation increases it. Adipose tissue obtained from zinc-adequate rats secreted more leptin than similar tissue obtained from zinc deficiency rats. It seems that the reduction in serum leptin observed in zinc deficiency rats depends on the amount of adipose tissue **(19,21)**.

Several factors may contribute to and explain zinc deficiency seen in association with CKD. Some studies have demonstrated a negative zinc balance in CKD patients. This may be due to decreased intestinal absorption, decreased food intake, uremic toxicity, bioavailability, and/or increased loss, such as through the face, urine, or hemodialysis. It is also important to note that many CKD patients are elderly and using multiple medications that can affect taste sensation and increase zinc deficiency **(22)**.

In a recent study 5/6 nephrectomized rats as well as phenylhydrazine-induced anemic mice were found to have zinc redistributed to bone marrow from bone and plasma, causing the zinc level in plasma to decrease, which produced reticulocytes. Their novel findings of pools of zinc in plasma and bone redistributed to bone marrow in the majority of those nephrectomized rats indicate the mechanism of zinc deficiency in CKD **(22)**.

Urinary Zinc excretion in CKD:

Due to the fact that zinc is bound to proteins in plasma, it is generally believed that glomerular filtration of zinc and consecutive urinary zinc excretion are limited. However, Damianaki et al. recently found that urinary zinc excretion was significantly higher in CKD patients (612.4±425.9 g/24 h) (n = 108) as compared with non-CKD patients with preserved kidney function (479.2±293.0 _g/24 h) (n = 81) (p = 0.02) **(23)**.

That study also noted that zinc fractional excretion was stable in the early stage of CKD, then a sudden and strong increase was seen in stage 3 patients, while that was correlated negatively and linearly with estimated glomerular filtration rate (eGFR). Although the mechanism related to increased fractional excretion of zinc in CKD patients remains unclear, increased urinary zinc excretion has been shown to be linked to tubular dysfunction in patients with cancer, type 1 diabetes mellitus, and type 2 diabetes mellitus, possibly due to impaired tubular activity **(22)**.

In the study presented by Damianaki et al., zinc fractional excretion was correlated negatively with 24 h urinary uromodulin excretion ($r = 0.29$; $p < 0.01$). Uromodulin, a protein produced by tubular cells of the ascending loops of Henle, was recently identified as a marker of tubular mass and function in the general population. The negative correlation between urinary uromodulin excretion and fractional excretion of zinc suggests that urinary zinc loss may be linked to the low number of functional tubules associated with CKD **(23)**.

Taste change associated with CKD:

Many CKD patients are elderly and using multiple medications that can affect taste sensations and increase zinc deficiency. Taste change has been reported by 40–60% of pre-dialysis CKD and hemodialysis patients, with taste changes of "bland" and "bitter" found to be associated with upper gastrointestinal symptoms, including nausea, vomiting, anorexia, and malnutrition. In addition, taste change is one of the major symptoms of zinc deficiency **(24)**.

There are roughly 7000 taste buds, peripheral receptors of taste, present in the oral cavity, pharynx, and larynx, with a particularly high concentration in lingual papillae on the tongue surface **(24)**. In findings obtained with an in vivo zinc-deficient model, microstructural abnormalities including microvilli rupture and vacuolation were shown in taste cells **(22)**.

Taste cell differentiation from basal cells is also impaired when zinc deficiency is present, and an in vitro study demonstrated that reduced expression of bitter taste receptors was the result of that deficiency. Furthermore, several reports have noted recovery of taste change by treatment with various forms of zinc, such as zinc gluconate, zinc picolinate, and polaprezinc. Additional studies are needed to investigate whether recovery of taste change by use of these medications has effects on clinical hard endpoints such as CVD events or mortality **(25)**.

Albumin and Zinc in CKD:

Zinc is actively absorbed throughout the small intestine, and in circulation, zinc is present predominantly as being bound to proteins such as albumin, macroglobulin, and transferrin, with approximately 60–80% of zinc in serum bound to albumin. Patients

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

undergoing hemodialysis often show low serum albumin along with chronic malnutrition. Because albumin is the primary carrier protein for circulating zinc, hypoalbuminemia should be considered as another confounding factor in interpreting plasma zinc concentration **(22,26)**.

Zinc and progression of CKD:

Damianaki et al. assessed the relationship between baseline plasma zinc level and yearly kidney function decline in a cohort with 3-year follow-up data and found a significant association of a lower baseline zinc level with a large decline of kidney function. Furthermore, the association remained statistically significant in multivariable models adjusted for age, gender, diabetes, and arterial hypertension, while it was no longer significant when baseline eGFR or proteinuria were introduced into the model **(23)**.

Unfortunately, the number of subjects was relatively small (n = 108); thus, additional large scale longitudinal observational studies are necessary to clarify the association between blood zinc level and progression of CKD. Additionally, randomized controlled trials (RCTs) are needed to determine the effect of zinc supplementation on kidney function in pre-dialysis CKD patients **(22)**.

2.1.1. Zinc supplementation in patients with CKD:

Although the median intervention period was 60 days and the daily dose ~45 mg, zinc supplementation resulted in higher serum zinc, SOD, and dietary protein intake levels and lower levels of CRP and malondialdehyde **(27)**. In consideration of previously presented RCTs, zinc supplementation greater than 45 mg/day may be necessary to increase the serum zinc level in hemodialysis patients. In children with CKD, adequate nutritional status is important for normal growth and development; thus, careful monitoring is essential. The Chronic Kidney Disease in Children study revealed that 7–20% of pediatric CKD patients showed protein-energy wasting **(28)**.

An RCT was conducted with 48 CKD patients including 33 undergoing hemodialysis to compare the effects of two different doses of zinc supplementation (15 and 30 mg/day) given for 12 months. There was no significant change in mean serum zinc level in children in either group. On the other hand, a small but positive and significant change in body mass as well as normalization of body mass index (BMI) Z-score, hypoalbuminemia, hypozincemia, and high CRP was noted, especially with a dose of 30 mg/day, which suggested that zinc supplementation could be beneficial for nutritional status in children with CKD **(22)**. Another interventional study of 40 hemodialysis patients aged between 5 and 18 years old and given daily zinc supplementation of 50–100 mg for 90 days found that serum zinc was significantly increased from 53.2±8.15 to 90.75±12.2 g/dL ($p = 0.001$) **(29)**.

Zinc supplementation and renal ischemia/reperfusion injury:

ischemia/reperfusion (I/R) is a major etiology of acute kidney tissue-destructive and renal chronic problems **(30)**. It is an inevitable phenomenon in renal transplantation. Besides, acute renal failure (ARF) is one of the most important complications of renal I/R which is associated with tubular cell damage. Overproduction of reactive oxygen species (ROS), neutrophil infiltration, vasoactive peptides, and adenosine triphosphate (ATP) depletion are involved in pathogenesis of I/ R-induced injuries **(31)**. In addition, intracellular Ca^{+2} accumulation, activation of intrarenal adenosine, and superoxide-induced membrane alterations are determinants of ischemic insult. These agents aggravate kidney damage through lipid peroxidation, proteins, and DNA oxidative insult **(32)**

Role of Zn in the activation of phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway to protect against renal I/R injury has been shown. It has been observed that I/R injury results in significant increase in the serum levels of blood urea nitrogen (BUN) and creatinine (Cr) and increase in the fractional excretion of sodium (FENa) which is decreased by zinc chloride (ZnCl2) supplementation. Zn also improved glomerular filtration rate (GFR) value **(31)**, Cr-clearance, and urine flow (UF) rate beyond renal I/R-induced damage. Furthermore, Zn downregulates the expression of hypoxia-inducible factor 1α (HIF1α) and its downstream target vascular endothelial growth factor (VEGF) both in vivo and in vitro in renal cancer cells **(33)**.

Additionally, Zn induces the expression of HIF1α and HIF2α in the papillary renal cell carcinoma cell lines (ACHN) and the immortalized normal proximal tubular cell lines (HK-2). Major antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione (GSH) decreased after renal I/R-induced injury. It has been suggested that Zn supplementation stimulates the activity of these enzymes. Indeed, I/R injury increases the concentrations of carbonylated proteins and decreases the protein sulfhydryl (P-SH) group. These agents return to normal level following Zn administration. The potential antioxidant activity of Zn may be attributed to induction of MTs **(34)**.

Metalloproteinases (MTs) contribute in maintaining Zn level. Furthermore, Zn is a well-known inducer of MTs. Renal I/R is associated with enhancement of endoplasmic reticulum (ER) stress as reflected by phosphorylated positive energy rejuvenates kin (p-PERK), glucose-regulated protein 78 (GRP78), activating transcription factor-4 (ATF-4), ATF-6, X-box binding protein- 1 (XPB-1), and C/EBP (CCAAT/enhancer-binding protein alpha) homologous protein (CHOP). These parameters decrease by ZnCl2 pretreatment **(32)**.

Furthermore, an increase in malondialdehyde (MDA), conjugated diene (CD) as lipid peroxidation markers, as well as the activity of lactate dehydrogenase (LDH) and histopathological alterations including brush border loss, nuclear condensation, cell

swelling, a consistent loss of nuclei, and hemorrhage, occurred beyond renal I/R damage that is relieved by ZnCl2 pretreatment. A significant decrease in lipid peroxidation following Zn administration results in consolidation of cytoplasm and mitochondrial membranes and reduction of cytolysis which eventually leads to maintenance of the kidney architecture **(35)**.

Beclin-1 and lysosome-associated membrane protein (LAMP-2) are two autophagosome parameters which increased after renal I/R injury. It is indicated that exogenous Zn administration downregulates their protein expression **(36)**. Furthermore, pro-apoptotic factors of caspase-9, caspase-3, and phosphorylated-Jun amino terminal kinase (p-JNK) upregulate following kidney I/R damage that downregulates following Zn supplementation. In addition, renal I/R insult significantly increased mRNA expression of cytokines including interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1) **(32)**.

ZnCl2 attenuates the expression of these proinflammatory cytokines. Besides it was supported that Zn decreased the levels of IL-6 and MCP-1. Moreover, renal I/R also decreased expression of phosphorylated voltage-dependent anion channel- 1 (p-VDAC-1) and the translocase of the mitochondrial outer membrane (TOM)-20 mitochondrial proteins that reverse by ZnCl2 administration **(32;35)**.

2.2. Zn supplementation prevents diabetic nephropathy with an increased expression of renal MT:

Zn supplementation also protected the kidney from diabetic damage. Diabetic and age-matched control rats were given Zn sulfate at 5 mg/kg of rat body weight in drinking water for 3 months. Zn supplementation could significantly prevent diabetes-induced renal dysfunction, measured by 24-hour urine proteins. The improvement of renal function by Zn supplementation in diabetic rats was also accompanied with a partial prevention of diabetes-induced renal inflammation, measured by renal expression of plasminogen activator inhibitor-1 (PAI-1), and fibrosis, measured by renal expression of connective tissue growth factor (CTGF) **(37;38)**.

Renal MT expression was also significantly increased, particularly in the renal tubules of Zn-treated non-diabetic and diabetic rats. To further explore the protective role of MT in diabetic renal damage, human renal tubular cells (HK11) were used to mimic diabetic damage in vitro and exposed to high glucose (HG) (27.5 μM) for 24 h with or without pre-treatment of Zn at 50 μM. The exposure of HKB11 cells to HG for 24 h caused a significant increase in CTGF expression, which could be significantly prevented by Zn pretreatment along with an induction of MT expression at mRNA and protein levels **(38)**.

2.3. Zn deficiency exacerbates diabetes-induced renal damage:

Previous study had investigated the effect of Zn deficiency on the diabetic kidney. They used streptozotocin (STZ) to induce a type 1 diabetic model, and then diabetic and age-matched rats were fed with food containing either low-level Zn or normal Zn level (standard chow). The pathogenic changes in the kidney of diabetic rats fed with low-Zn diet were observed, shown by calcium deposits from the 2nd to the 8th week. No change was detected in the control for the low-Zn diet or in the diabetic group fed with standard diet **(39)**.

However, urinary N-acetyl-beta-D-glucosaminidase activity of the low-Zn-diabetic group at the 8th week was significantly higher than that of the normal Zn-diabetic group. These findings suggested that low-Zn diet accelerates renal damages in diabetic rats. The above studies have demonstrated the protection by Zn supplementation against diabetes-induced cardiac and renal damage, suggesting that Zn is required for the tissue to reduce diabetes-induced damage. Whether Zn deficiency can make the individuals more susceptibility to diabetes-induced cardiac or renal damage was explored recently. Diabetic mouse model was induced by multiple low-dose STZ. Diabetic and age-matched mice were treated with N,N,N′,N′-tetrakis (2-pyridylemethyl) ethylenediamine (TPEN) at 5 mg/kg of mouse body weight daily for 4 months to induce systemic Zn deficiency **(37)**.

Chronic treatment with TPEN significantly reduced renal Zn level in diabetic mice compared to TPEN or diabetes alone. Renal oxidative damage was significantly evident in diabetes with Zn deficiency compared to diabetes without Zn deficiency, examined by Western blotting of protein nitration with 3-nitrotoluene (3-NT) and lipid peroxidation with 4-hydroxynonenal (4-HNE). Compared to diabetes group, diabetic mice with Zn deficiency also showed significant increases in renal inflammation, reflected by increased infiltrated inflammatory cells and inflammatory mediators' intercellular adhesion molecule – 1 (ICAM-1) and PAI-1 protein expressions, and renal fibrosis, mirrored by increased CTGF expression, collagen accumulation and Sirius-red materials in the kidney **(39)**.

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