



Benefits and risks of essential trace elements in chronic kidney disease: a narrative review

Yi Xie, Fei Liu, Xiaojing Zhang, Yanyan Jin, Qiuyu Li, Huijun Shen, Haidong Fu, Jianhua Mao

Department of Nephrology, the Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

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Correspondence to: Jianhua Mao. Department of Nephrology, the Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou 310000, China. Email: maojh88@zju.edu.cn.

Background and Objective: Chronic kidney disease (CKD) is an important public health concern. With the decline of renal function, CKD patients gradually progress to end-stage kidney disease and need to undergo dialysis or kidney transplantation to maintain life, bringing a heavy economic burden to the family and society. Therefore, it is necessary to effectively prevent and delay the progression of CKD. Essential trace elements play an indispensable role in CKD, and the objective of this study is to systematically review their benefits in the disease and summarize the risks of their excess.

Methods: The keywords “trace elements”, “chronic kidney disease”, “dialysis”, “inflammation”, and “fibrosis” and their combinations were used to search for relevant literature published in the PubMed database and Web of Science. We then summarized the role of trace element abnormalities in CKD patients in anemia, oxidative stress, inflammation, and chronic fibrosis, and the risk of their excess.

Key Content and Findings: Imbalance of essential trace elements is a common complication of CKD and a risk factor for CKD progression, cardiovascular events, and death. This article reviews the effects of essential trace elements (iron, zinc, selenium, copper, iodine, and manganese) on CKD. We analyze literature and discuss the advantages and disadvantages of various essential trace elements.

Conclusions: Research shows CKD patients have an imbalance of essential trace elements, and treatment based on these is an important direction for future exploration. A knowledge of the homeostasis of trace elements is important to improving the prognosis of CKD patients and delaying the progression of the disease.

Keywords: Trace elements; chronic kidney disease (CKD); dialysis

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Introduction

The current global prevalence of chronic kidney disease (CKD) is estimated at 13% and is rising quickly against a background of increasing obesity, diabetes mellitus, and hypertension (1). Current international guidelines define this condition as decreased kidney function shown by a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m²,

and/or markers of kidney damage of at least 3 months duration, regardless of the underlying cause. The classification of CKD is in five stages according to the decline in GFR from early disease to kidney failure (2). The causes of CKD are varied. Diabetes and hypertension are the main causes in middle-income and high-income countries. The use of herbs can produce renal toxicity. Environmental pollution of heavy metals and organic

Table 1 Essential trace elements: physiological functions, symptoms of deficiency, and excess intake in humans

Element	Physiological function(s)	Symptoms of deficiency	Excess intake
Iron (Fe)	Component of several important biochemical processes (redox reactions, mitochondrial respiration, nucleic acid production, and protein transport)	Anemia, susceptibility to infection, immune dysregulation, cognitive decline, impaired growth and development	Oxidative damage and organ dysfunction
Zinc (Zn)	As a component of various zinc enzymes, regulation of cellular and subcellular levels and has antioxidant and anti-inflammatory effects	Appetite loss, growth retardation, decreased immune function, delayed sexual maturation, diarrhea, dermatitis, behavioral changes, hair loss, delayed wound healing	Digestive tract symptoms, lethargy, fatigue, reproductive dysfunction, taste disorders, visual disorders, copper deficiency, impaired immune function
Selenium (Se)	Acts as an essential cofactor for selenoproteins and is involved in redox signaling, the antioxidant defence system, thyroid hormone metabolism, and immune response	Immune dysfunction, infection, oxidative stress, cardiovascular disease, chronic osteoarthritis, brain damage, increased risk of autoimmune thyroid disease impaired reproductive ability	Digestive tract discomfort, peripheral neuropathy, fatigue, irritability, skeletal myopathy, cardiomyopathy, hair and nail changes
Copper (Cu)	Component of oxidase enzymes, responsible for bone and connective tissue metabolism, electron transport, oxygen transport, and hemopoiesis	Peripheral neuropathy, anemia, leukopenia, skeletal abnormalities, poor blood pressure control, decreased immunity, reduced skin and hair pigmentation	Gastrointestinal symptoms, hemolytic anemia, neurodegeneration, liver and kidney failure, as well as death may occur
Iodine (I)	Essential for thyroid hormone biosynthesis, regulates resting energy expenditure, and plays an important role in growth and development	Endemic goiter, mental retardation (cretinism), teratogenic effects	Various thyroid disorders, thyroid cancer, radioactive iodine exposure induced cancer
Manganese (Mn)	Cofactor for the activity of many metalloenzymes involved in antioxidant protection and amino acid, lipid, protein, and carbohydrate metabolism	Impaired growth, skeletal defects, reduced reproductive function, birth defects, abnormal metabolism	Neurotoxicity and neurodegenerative diseases, respiratory inflammation and hepatotoxicity

compounds is also one of the causes of CKD (3). CKD has become one of the major diseases threatening worldwide public health and has a significant negative impact on mortality and quality of life, which increases with age. According to WHO global health estimates, 864,226 deaths were attributable to CKD in 2012 and the condition ranked fourteenth in the list of leading causes of death, accounting for 12.2 deaths per 100,000. Projections from the Global Health Observatory suggest the death rate from CKD will continue to increase to reach 14 per 100,000 by 2030 (3,4).

Trace elements are essential micronutrients required for normal body function and include iron (Fe), zinc (Zn), selenium (Se), copper (Cu), iodine (I), and manganese (Mn) in amounts ranging from 50 micrograms to 18 milligrams per day. In CKD patients this may be abnormal as a result of poor dietary intake, uremia-induced hypercatabolism, persistent inflammation, or the dialysis procedure itself (4). Optimal

trace element status can help support optimal immune function, reducing the impact of infections and improving the life quality of patients with CKD. Previous study has shown the homeostasis of trace elements can help regulate immune disorders, enhance growth and development, and reduce infections, cardiovascular complications, anemia, and mineral and bone diseases (5). Additionally, the loss of trace element homeostasis in end-stage kidney disease (ESKD) patients significantly contributes to increased morbidity and mortality. Therefore, homeostasis of trace elements should be considered during all stages of CKD, and all physicians caring for patients should be aware of trace elements requirements. This review summarizes the benefits and risks of trace elements in CKD patients (*Table 1*). We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5969/rc>).

Table 2 Search strategy summary

Items	Specification
Date of search	2021-11-01 to 2022-06-01
Databases and other sources searched	PubMed and Web of Science
Search terms used	“trace elements”, “chronic kidney disease”, “dialysis”, “anemia”, “oxidative stress”, “inflammation”, “fibrosis”
Timeframe	1989-01-01 to 2022-05-01
Inclusion and exclusion criteria	Articles in English and Chinese were included. Association studies and articles before 1989 were excluded
Selection process	Yi Xie and Fei Liu collected and assembled the data. Finally, all authors reached an agreement on the manuscript

Methods

We searched the PubMed and Web of Science databases for original researches and review articles up to May 2022. Articles in English and Chinese languages were included. The following terms were employed in different combinations: “trace elements”, “chronic kidney disease”, “dialysis”, “inflammation”, and “fibrosis”. The references cited in relevant articles were also reviewed to obtain more information. *Table 2* describes the study sequence and details.

Discussion

Role of trace elements in CKD

Fe

Fe is essential to most living organisms and is a co-factor for vital proteins and enzymes. Humans have a daily requirement for 25 mg of Fe, nearly 80% of which is used for erythropoiesis. While a small fraction of Fe is absorbed in the gastrointestinal tract (1–2 mg) and bound to serum transferrin, the majority is provided by recycling Fe from senescent erythrocytes via macrophages in the liver, spleen, and bone marrow. Fe is stored both in an inactive Fe³⁺ form in ferritin and in the bone marrow to make red blood cells (6) (*Figure 1*).

Fe and anemia

Anemia is a frequent comorbidity of CKD, as Fe combines with porphyrins to form heme, a component of hemoglobin. Fe imbalance is highly prevalent in CKD patients and is associated with an increased risk of morbidity and mortality.

Anemia is defined as a low level of hemoglobin (Hb): <12 g/dL in female patients and <13 g/dL in male patients with CKD (7), and there are many reasons it occurs in these patients. Erythropoietin (EPO) is an endogenous glycoprotein hormone that stimulates red blood cell production and is mainly synthesized in the kidney. When CKD progresses, insufficient EPO production leads to increased anemia (8), and most CKD patients with anemia are treated with erythropoiesis-stimulating agents (ESA), as the optimal hematopoietic response to ESA requires an adequate supply of Fe. In addition to the decrease in erythrocyte production, patients with CKD also have shortened survival of red blood cells, which may be due to Fe deficiency, inflammation, hemolysis, blood loss, nutritional deficiency, and other factors (9). Absolute Fe deficiency is characterized by insufficient Fe intake or excessive loss, such as seen in reduced dietary absorption or loss of blood, which result in a decrease in red blood cell production. Functional Fe deficiency has been defined as a deficiency in circulating Fe that limits erythropoiesis despite normal or elevated Fe stores and is mainly caused by infection or EPO deficiency (10). A combination of these features may also be present.

Bone marrow biopsy is the gold standard for diagnosing iron-deficiency anemia. However, bone marrow reports with unstainable Fe cannot be equated to Fe deficiency, and invasive procedures also limit the clinical use of bone biopsies (11). Biomarkers for Fe deficiency include ferritin, serum Fe, total Fe-binding capacity, and transferrin saturation (TSAT = plasma Fe divided by the total Fe-binding capacity ×100) (12). Fe deficiency anemia is usually defined as a serum ferritin concentration <30 ng/mL in

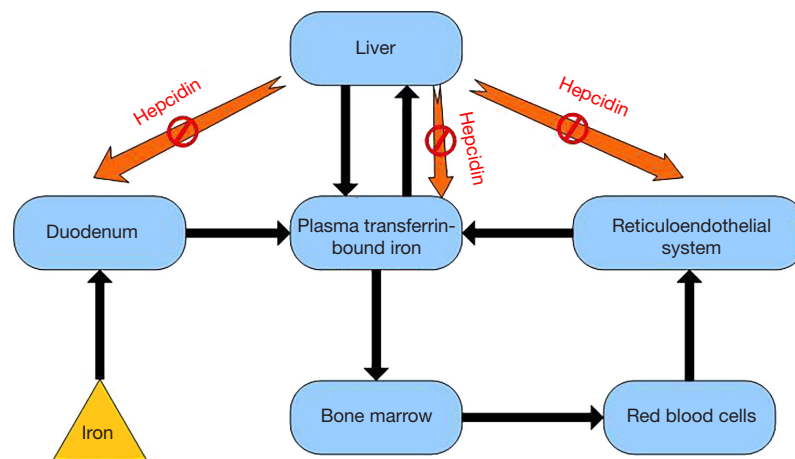


Figure 1 Iron absorption and recycling: Dietary iron is absorbed through the duodenum, stored primarily in enterocytes as ferritin, and transported in plasma by transferrin. Most iron is transported to the liver and bone marrow for storage and metabolism. Senescent red blood cells are phagocytosed by reticuloendothelial macrophages, and iron is also recycled. Hepcidin prevents iron transport by binding to the iron transporter ferroportin located on the basal membrane of enterocytes, reticuloendothelial cells, and hepatocytes. Hepcidin binding causes internalization of ferroportin from the plasma membrane into the cell and its ultimate degradation.

normal renal function. In CKD, absolute Fe deficiency has been defined as TSAT <20% and ferritin <100 µg/L in patients who are not on hemodialysis (HD) therapy or <200 µg/L in HDCKD patients. Functional Fe deficiency has been defined as TSAT <20% and ferritin >100 µg/L in not on dialysis therapy (NDCKD) patients or >200 µg/L in HDCKD patients (10,12). However, ferritin is an acute phase reactant that is elevated by an inflammatory response, regardless of whether Fe deficiency is present in CKD. As kidney disease progresses, liver transferrin production is reduced, and in the late stages of CKD transferrin levels are reduced by 30%, leading to elevated TSAT levels, independent of Fe status. The disadvantage of traditional threshold values is that they are insensitive to Fe deficiency detection and cannot distinguish absolute and functional Fe deficiency, making it impossible to predict Fe stores and treatment response. In the last two decades, several new biomarkers of Fe status in CKD have been discovered, including the hepcidin-ferroportin axis, erythroferrone, hypoxia-inducible factors (HIFs), soluble transferrin receptor, reticulocyte hemoglobin content, and percentage of hypochromic red blood cells (13). However, many of these are influenced by renal failure alone and concomitant inflammation, and because of these confounding effects on the interpretation of most of the biomarkers, the assessment of Fe status in CKD remains a challenge (14).

Fe and inflammation

As Fe is essential to almost all infectious microorganisms, there is concern that giving it to patients with CKD may increase the risk of infection. When Fe is used to treat CKD anemia, microbial proliferation and secondary infections may occur due to excessive Fe storage, while increased hepcidin production may accelerate Fe absorption. At the same time, chronic inflammation in CKD can lead to Fe metabolism disorders. Fe also alters cellular homeostasis (15-17) by impairing monocyte immune responses which increases the risk of infection (18), and *in vitro* study suggested the serum of HD patients without Fe supplementation could inhibit growth of the multiple drug-resistant *Staphylococcus epidermidis* strain, and that bacterial growth was positively correlated with transferrin saturation after intravenous (IV) Fe supplementation (19). A prospective cohort study found Fe overload, prior bacterial infection, and the use of dialysis catheters were important independent risk factors for infection in HD patients (20). A retrospective cohort study compared the safety of bolus dosing, which provides a large amount of Fe over a short period of time, with maintenance dosing, which provides smaller amounts on a regular schedule to maintain Fe repletion. The result showed patients receiving bolus versus maintenance Fe were at increased risk of infection-related hospitalization, particularly among patients with a catheter

(21). A prospective multicenter study in Japan also found HD patients with higher ferritin levels had an increased risk of infectious disease. There was a high risk of death and/or adverse events in patients with hemoglobin levels outside the target range, high-amplitude hemoglobin fluctuations, consistently high serum ferritin levels, and high-amplitude ferritin fluctuations (22). Current studies have also found oral Fe supplementation may adversely affect intestinal microbiome composition, intestinal and systemic metabolites, host immunity, and infection in Fe-deficient CKD patients, although there are many clinical benefits of oral Fe supplementation in patients with CKD, and further studies are needed to clarify the benefits and disadvantages (23,24).

Since IV Fe supplementation bypasses the normal physiological process of intestinal Fe absorption, iatrogenic Fe overload may occur, increasing the risk of infection. In a meta-analysis of data from eight observational trials, the risk for infection was comparable between higher-dose IV Fe and lower-dose IV Fe/oral Fe/no Fe (25). A large US cohort study (N=22,820) showed an increased risk of infection-related events and infection-related mortality with high IV doses of Fe in HD (26), and a meta-analysis by Litton suggested IV Fe was associated with a significantly higher incidence of infection compared with either oral Fe or no Fe supplementation (27). A retrospective study analyzed the longitudinal Fe parameters of peritoneal dialysis (PD) patients and proposed Fe excess was associated with the onset of peritonitis and poor prognosis (28). There are also recent conflicting reports of randomized controlled trials concerning the association between IV Fe administration and infections. The PIVOTAL trial (29,30) randomized 2,141 patients undergoing maintenance HD for ESKD to a high-dose or a low-dose IV Fe regimen and found both had identical infection rates. FIND-CKD was a 1-year, randomized, multicenter trial of Fe therapy in patients with nondialysis-dependent CKD (ND-CKD), anemia, and Fe deficiency which revealed the incidence of infection was similar between treatment groups (31). A retrospective study of PD showed a nonstatistically significant increase in the incidence of peritonitis 6 months after IV Fe injection (30), although the DEcIDE-ESRD study showed a higher cumulative dose of IV Fe may not be associated with increased risk of hospitalization in HD patients (32), and a Taiwanese trial also showed IV Fe supplementation did not increase short-term infection risk among HD patients (33). There is a scarcity of studies investigating the effects of different Fe formulations on infection risk, and the few available studies

are inconclusive as they show conflicting results. The different results from each study may be due to differences in the dosage of Fe treatment, methods of administration, and the study population, and that some studies were not specifically designed to assess the risk of IV Fe infection.

Although the current clinical data cannot prove IV Fe injection is associated with infection in patients with CKD, it is still necessary to evaluate the benefits and risks individually, weigh the advantages and disadvantages, and minimize the risks. KDIGO guidelines suggest IV Fe should not be administered during active systemic infections (34). Two possible mechanisms causing susceptibility to infection in CKD patients should be managed: (I) the prevention of excessive Fe administration for the treatment of renal anemia, and (II) the attenuation of inflammation associated with dysregulated Fe metabolism (16).

Ferroptosis in CKD

Unlike traditional cell death, ferroptosis is an iron-dependent non-apoptotic cell death characterized by the intracellular glutathione depletion and decreased glutathione peroxidase 4 (GPX4) activity, abnormal iron metabolism could induce iron overload resulting in accumulation of lipid reactive oxygen species (ROS) via the Fenton reaction. Ferroptosis mainly manifests as obvious shrinkage of mitochondria with increased membrane density and reduction in or vanishing of mitochondrial cristae (35). The rich mitochondrial structure of the kidney is more vulnerable to oxidative stress. Recent studies have shown that ferroptosis plays an important regulatory role in the CKD (36,37).

Ferroptosis has been certified to be a potential mechanism in the progression of CKD, such as diabetic nephropathy (DN). DN has severe microvascular lesions, decreased antioxidant capacity, ROS accumulation, resulting in cell and tissue destruction. Iron overload was found in DN mice, leading to ferroptosis. A study showed ferroptosis occurred in high glucose-treated podocytes and that regulation of peroxiredoxin 6 expression interfered with ferroptosis and thus ameliorated podocyte injury (36). Expression of the cystine/glutamate antiporter system Xc and GPX4 mRNA was reduced in kidney biopsy samples from diabetic patients compared with non-diabetic samples. In transforming growth factor- β 1-stimulated tubular cells, intracellular glutathione concentration was reduced and lipid peroxidation was enhanced, both of which are related to ferroptosis-related cell death (37). Ferroptosis is related to the action of active iron, lipid peroxidation, and weakened

antioxidant capacity, and intervention of these processes may inhibit ferroptosis for therapeutic purposes (36).

The most common pathological manifestation of CKD is renal fibrosis. Chronic inflammation and cell death can lead to increased fibrosis and eventually kidney failure. Ferroptosis is thought to play an adverse role in renal fibrosis, mediating renal cell death (38). Unlike necroptosis, which depends on an outside-in signal, the independence of an outside-in signal renders ferroptosis a candidate pathway that could cause the initial necrosis which begins the auto-amplification loop (39). Currently, ferroptosis has been found in unilateral ureteral obstruction and 5/6 nephrectomy rodent model of renal fibrosis (40,41). These studies uncover that tubular epithelial cell ferroptosis may promote interstitial fibrosis and inflammation, and targeting ferroptosis may shine a light on protecting against kidney fibrosis in patients with CKD.

Ferroptosis can be inhibited by reducing unstable iron, inhibiting lipid peroxidation and eliminating lipid peroxides. Among these approaches, lipophilic antioxidants and iron chelators are well-recognized inhibitors against ferroptosis. Many investigated substances against ferroptosis including clinical drugs, herbal medicines and microRNAs, and even intrinsic components of kidney have been shown to protect kidney from ferroptosis (42). Although ferroptosis has been confirmed to be involved in the process of CKD, there are still many basic problems that need to be further explored.

Fe therapy

Currently, ESA combined with Fe therapy is the main treatment for CKD anemia, and good Fe metabolism is essential for the efficacy of ESA (10). Multiple guidelines recommend the initiation of IV Fe therapy prior to commencing ESA therapy and in combination with it, provided TSAT and ferritin levels are below the proposed thresholds. Use of ESA when the Hb target is 10–12 g/dL can improve anemia and reduce transfusion adverse reactions. However, when the Hb target is >13 g/dL, the application of ESA increased adverse reactions (43,44). KDIGO guidelines suggest addressing all correctable causes of anemia prior to ESA use and considering its use only if Hb ≤10.0 g/dL (10).

Fe balance involves ensuring there is sufficient Fe to produce red blood cells while avoiding the side effects of excess, and Fe therapy aims to replenish stores and raise Hb levels to desired levels. Compared with IV Fe injection, oral Fe is less effective in improving Hb, ferritin and TSAT,

and adverse gastrointestinal reactions, malabsorption, and intestinal flora disorders may also occur (45). In CKD, different degrees of inflammation lead to increased hepcidin and reduced Fe absorption in the gastrointestinal tract, which leads to a decreased effect of oral Fe (46). However, IV Fe therapy effectively circumvents the hepcidin pathway and leads to more rapid repletion of Fe stores (47). Several clinical studies have shown IV Fe produces a greater increase in Hb than oral Fe, and KDIGO recommends using IV Fe instead of oral Fe in dialysis-dependent CKD (DD-CKD) patients (34). In the short term, mild infusion reactions may include flushing, mild chest discomfort, dizziness, lightheadedness, nausea, or itching, which can be relieved by stopping or slowing infusion, while severe to life-threatening allergic reactions are rare (48). The longer-term effects include effects of oxidative stress, possible increased risk of infections, and risk of Fe overload (49). In contrast, there have been very few randomized controlled trials using IV Fe in PD patients (50), and current guidelines (10,44,51) recommend a more conservative strategy, with oral Fe as first-line treatment, for PD patients with less severe Fe deficiency (52).

Guidelines also recommend (I) anemic CKD patients not receiving ESA therapy and not receiving HD should first be offered a trial of oral Fe, and if intolerant of this or target Hb levels are not reached within three months, IV Fe therapy should be implemented. For those receiving HD, IV Fe therapy should be offered; (II) in adult anemic CKD patients receiving ESA therapy and children receiving HD, IV Fe therapy should be provided, while for children who are not receiving HD, oral Fe should be considered. If the child is intolerant of oral Fe or target HD levels are not reached within three months, IV Fe therapy should be offered (44,51). The European Renal Best Practice position statement states that in adult ND-CKD patients or PD patients, absolute iron deficiency is indicated when TSAT <20% and serum ferritin <100 ng/mL, or TSAT <25% and ferritin <200 ng/mL in ND-CKD patients, or TSAT <25% and ferritin <300 ng/mL in dialysis patients, and iron therapy should be considered. Because high-dose baseline Fe therapy is associated with poor outcome in HD patients, the limit of TSAT for both ND-CKD and dialysis patients should not exceed 30%, and the limit of serum ferritin should not exceed 500 ng/mL (53,54). If the gastrointestinal is tolerated, oral Fe should be used as first-line therapy for at least 3 months to protect the arm veins needed for dialysis. If anemia is severe or oral Fe is ineffective, IV Fe is preferred (44).

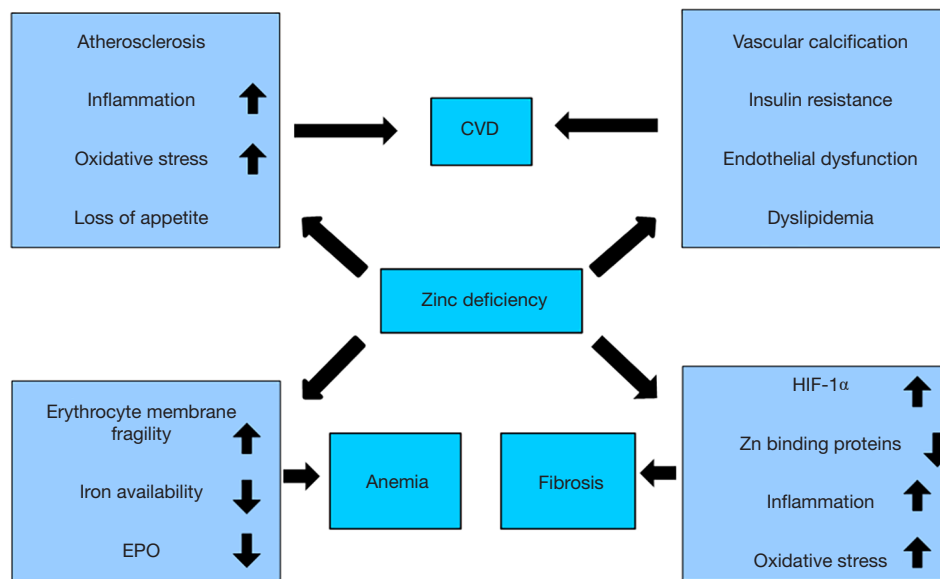


Figure 2 Association of zinc deficiency with anemia, fibrosis, and cardiovascular disease in CKD. ↑: promotion; ↓: inhibition. CVD, cardiovascular disease; EPO, erythropoietin; HIF-1 α , Hypoxia-inducible factors-1 α ; Zn, Zinc; CKD, chronic kidney disease.

Zn

Zn is the second most abundant divalent cation in the human body (2–3 g) (55). It is involved in various cellular and subcellular levels of regulation and has antioxidant and anti-inflammatory effects (56,57). Zn mainly comes from dietary sources including dairy products, seafood, meat, and poultry, and is absorbed by the intestine and excreted in the stool (58). More than 90% of absorbed Zn is stored in muscles and bones, with only 0.1% in plasma. Adjustments in urinary Zn excretion are minor in comparison with gastrointestinal adjustments (59), and 64% of individuals suffering from CKD have low serum or plasma Zn levels (60). A 2022 study showed the serum Zn level of CKD and HD patients was significantly lower than that of healthy controls, and the serum Zn level after HD was higher than that before HD (61). Patients with CKD have lower circulating Zn levels, but higher 24h urinary Zn excretion compared with non CKD individuals, which is possibly because of defective tubular reabsorption (62). Tokuyama divided 312 patients with CKD into two groups with a serum Zn concentration of 60 $\mu\text{g}/\text{dL}$ as the threshold, and survival analysis showed Zn deficiency was a risk factor for ESKD or death (63). The possible causes of decreased plasma Zn levels in patients with CKD are as follows: Decreased absorption of Zn from the gastrointestinal tract; limited Zn intake; higher urinary Zn excretion; and redistribution of Zn in the body (64). Zn is

associated with anemia, cardiovascular disease, and repair of kidney damage in patients with CKD (Figure 2).

Zn and anemia

Zn deficiency causes increased brittleness of the erythrocyte membrane. It is suspected that when levels of sulphhydryl in Na-K-ATPase and Ca-ATPase in the erythrocyte membrane drop, the membrane's resistance becomes weak, making the red blood cells fragile (65). The mechanical stimulation of HD then causes the rupture of red blood cells, leading to hemolysis.

Appropriate Zn supplementation can improve anemia in patients with CKD and is recognized as enhancing production ability and increasing Fe levels (66). Fukushima showed that daily supplementation of 34 mg Zn is effective in improving anemia in maintenance HD patients with plasma Zn levels <80 mg/dL, and possible Zn deficiency anemia should be considered in the treatment of refractory anemia that does not respond to erythropoietin. It was concluded that the improvement in anemia after Zn treatment did not affect the ability of blood cells to metabolize hemoglobin but increased their ability to produce hemoglobin (67). In patients with CKD, the kidneys do not produce enough erythropoietin to stimulate erythropoiesis. Feng studied 5/6-nephrectomized rats that became uremic and anemic at 25 days post-surgery, and found Zn stimulated EPO production in the medium,

and that the level of EPO produced depended on the concentration of Zn supplementation. Production of erythropoietin through Zn supplementation involves the process of erythropoiesis (68).

Zn and cardiovascular disease (CVD)

Cardiovascular complications from atherosclerotic disease are a major cause of morbidity and mortality in patients with CKD. All stages of CKD are associated with increased risks of cardiovascular morbidity, premature mortality, and/or decreased quality of life as patients have multiple atherosclerosis risk factors, such as insulin resistance, wasting, inflammation, oxidative stress, and endothelial dysfunction (69). The antioxidant and anti-inflammatory mechanisms of Zn include: (I) inducing the expression of metallothionein to remove reactive oxygen species (ROS) and delay the oxidation process; (II) increasing the activation of antioxidant proteins and enzymes, such as glutathione and catalase; and (III) a Fenton reaction against redox-active transition metals (56,70). Zn deficiency is associated with CVD events in CKD patients (71). A meta-analysis showed Zn supplementation benefited the nutritional status of HD patients providing anti-inflammatory and antioxidant effects and showed a time-dependent effect (72).

Vascular calcification occurs in vascular smooth muscle cell (VSMC) layers and eventually causes the blood vessel wall to lose flexibility and become stiff. Vascular calcification is a life-threatening clinical condition in CKD and is associated with reduced Zn serum levels. One of the primary mechanisms for VSMC calcification is VSMC apoptosis (73), and Zn deficiency leads to cell death by activating the pro-apoptotic enzyme caspase-3. Apoptosis in the VSMC layer of the aorta was significantly increased in Zn-deficient rats and was induced via dephosphorylation (apoptotic activation) of the pro-apoptotic protein Bcl-2 associated death promoter protein (74). Zn is also effective in preventing cell death in cases of atherosclerosis where calcification of vascular smooth muscle has progressed (75). Annamária found Zn inhibited phosphate-induced mineralization of VSMC in a dose-dependent manner and attenuated the procalcification effect of prolyl hydroxylase inhibitors in phosphate-induced mineralization (76). Jakob proposed Zn supplementation ameliorated phosphate-induced osteo-/chondrogenic transdifferentiation of VSMC and vascular calcification through an active cellular mechanism resulting from the GPR39-dependent induction of TNFAIP3 and subsequent suppression of the NF- κ B pathway (77). Zn supplementation may be a simple treatment

to reduce the burden of vascular calcification in CKD.

Dyslipidemia can lead to CVD, and Zn homeostasis disorders negatively affect the lipid profile and cytokine secretion. Mice fed a Zn-deficient diet had significantly increased concentrations of cholesterol and triglycerides in the very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) fractions (78). Zn protected the liver, reduced triglycerides, C reactive protein, and IL-6, and raised HDL-C in lipid disturbance rabbits (79). According to a meta-analysis summarizing data from 32 studies, Zn supplementation significantly reduced total cholesterol, LDL cholesterol, and triglycerides, and may have the potential to reduce the incidence of atherosclerosis related morbidity and mortality (80). However, a meta-analysis of 15 randomized controlled trials showed the effects and trends of Zn supplementation on lipids in maintenance HD patients may be inconsistent or even contradictory, which may have been due to differences in the medical history and diet of included patients (72).

Zn α 2-glycoprotein (ZAG) is a major histocompatibility complex I molecule and lipid-mobilizing factor which has been shown to promote lipid metabolism and glucose utilization and regulate insulin sensitivity (81) by binding to Zn and fatty-acids. It has been reported that ZAG has two strong and 15 weak binding sites for Zn, and Zn binding to these sites influences that of ZAG to fatty-acids and β -adrenergic receptors (82). Plasma ZAG levels in HD patients were seen to be significantly higher than in healthy subjects and there was a negative correlation between plasma ZAG level and obesity parameters (83). One study observed an inverse correlation between ZAG and inflammatory proatherogenic markers such as TNF- α , VCAM-1, and anti-LDL(-) antibodies in HD patients (84). Pelletier found increased plasma concentrations of ZAG in CKD may have been due to increased production and secretion rather than reduced renal clearance (85). Therefore, elevation of ZAG compounds the effects of lipoprotein lipase and VLDL receptor deficiencies in CKD by promoting lipolysis and inhibiting fatty acid synthesis. Further, Bouchara's investigation of adult HD patients showed ZAG was a strong predictive factor of cardiovascular events (86).

Zn and renal fibrosis

Fibrosis is the final pathological process of maladaptive repair, defined by the formation of local mesenchymal cells and accumulation of extracellular matrix. Fibrosis in CKD is a progressive process that worsens not only the kidneys but also the heart, leading to severe myocardial dysfunction,

regardless of cause (87). In addition to kidney disease, as their disease progresses, patients with CKD have increased CVD, myocardial cell hypertrophy, and apoptosis leading to myocardial fibrosis (88). The fibrotic mechanism of CKD involves inflammation, the renin-angiotensin system, the parathyroid hormone, FGF23/klotho, microRNAs, and the vitamin D hormonal system (87).

Zn has an anti-fibrotic effect in the liver and lungs (89-91) and may reduce the risk of fibrosis in patients with CKD. Cao fed mice with diets of different Zn levels and found cardiomyocytes died extensively in the Zn deficiency group, and that Zn deficiency enhanced the oxidative stress response of myocardial tissue and eventually triggered myocardial fibrosis (92). Xu showed Zn deficiency caused necrosis of kidney cells and exacerbated fibrosis by increasing kidney inflammation in mice fed with different concentrations of Zn (93). In a DN rat model, a Zn deficient diet resulted in significant levels of apoptosis, extensive thickening of basement membrane, collagen deposition, and increased interstitial fibrosis in renal tissue. The histological morphology improved after Zn supplementation, which may be related to the antioxidant and anti-inflammatory effect of Zn, suggesting it has a potential protective effect on kidney injury caused by diabetes (94). In another DN model, Zn had an important anti-fibrosis role, and a novel mechanism was identified that contributed to Zn protection on renal tubular epithelial cells from high glucose/hypoxia-induced epithelial-to-mesenchymal transition through activation of the PI3K/Akt/GSK-3 β signaling pathway, which subsequently leads to the downregulation of the expression of HIF-1 α (95). A recent study observed the combination of Zn and Se reduced the cytotoxicity and fibrosis of Ochratoxin A-induced human renal proximal tubule epithelial cells (96), while many Zn binding proteins (such as matrix metalloproteinases, snail family Zn finger 1, and ZAG) play an anti-fibrosis role in CKD (97-99).

Zn excess

Although Zn deficiency is common in CKD, animal studies have shown excessive intake can lead to decreased intestinal Cu absorption and subsequent deficiency. Hence, many of the toxic effects of Zn excess are due to Cu deficiency. This correlation seems to be caused by the competitive absorption relationship of Zn and Cu within enterocytes, mediated by metallothionein (100). Zn intake is also associated with an increase in basal blood pressure and a decrease in kidney function (101). Stephanie reported a case of erythropoietin-resistant anemia secondary to Zn-induced

hypocupremia acid in an HD patient and the symptoms improved after Zn treatment was discontinued. To minimize the risk of Zn-induced Cu deficiency, Nishime suggested a safe upper Zn limit of 78.3 $\mu\text{g}/\text{dL}$ for HD patients (102).

Excess Zn can also affect blood pressure. Carpenter reported higher serum Zn levels and lower serum Cu levels in patients with hypertension compared with those with normal blood pressure (103), while a cohort study of an Iranian population showed a significant increase in systolic blood pressure with increased serum Zn (104). Excessive Zn use or prolonged parenteral nutrition can present as anemia, leukopenia, neutropenia, or myeloneuropathy (105).

Se

Se intake varies widely worldwide, from about 7 to 4,990 μg per day (106). In the UK, the recommended intake is 75 $\mu\text{g}/\text{day}$ for males and 60 $\mu\text{g}/\text{day}$ for females (107), while the European guidelines set the tolerable upper intake at 300 $\mu\text{g}/\text{day}$ for adults. For children, the tolerable upper intake is 60 $\mu\text{g}/\text{day}$ to 250 $\mu\text{g}/\text{day}$ (108). The concentration of Se in serum of healthy people is 0.5 to 2.5 $\mu\text{mol}/\text{L}$. In one study, Se was distributed as selenoprotein P (57%), glutathione peroxidases (GSH-Px) (20%), and albumin (23%) in plasma irrespective of concentration (21–162 ng/mL) (109). Foods rich in Se include grains, vegetables, seafood, meat, dairy products, and nuts, and it is transported to the duodenum and caecum for absorption and excreted through the kidneys (108). The main component of Se metabolism is glutathione, which is involved in many reduction reactions, and the nutritional functions of Se are achieved by 25 selenoproteins that have selenocysteine at their active center. Se plays an important role in the human body, such as antioxidant stress, thyroid hormone formation, nucleotide synthesis, growth and development, and reproduction (110), and its homeostasis is achieved through the storage of selenomionine in the kidney and liver.

Of all human organs, the kidney and thyroid have the highest Se content (111). CKD patients are prone to Se deficiency due to low dietary intake, impaired intestinal absorption, decreased Se-binding protein, and increased urinary and dialysis losses (112-114). However, some researchers found no significant loss or gain of Zn or Se from the PD itself in ESKD patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (115). A study of Se status and CKD in 5,381 middle-aged and older Chinese people suggested adequate Se intake might have a positive effect on CKD (116), and a Taiwanese study found it modified GFR in environmental toxic-induced CKD (117).

Results of a prospective randomized double-blind placebo-controlled trial showed an association between low Se status and impaired renal function, and that Se supplementation and coenzyme Q10 significantly improved renal function (118). In HD patients, reduced serum Se levels may lead to immune dysfunction and are inversely associated with the risk of death, especially from infectious disease (119). Some studies have shown Se levels begin to decrease in the early stage of the disease, until the whole blood and plasma Se of ESKD are significantly reduced, suggesting Se reduction is proportional to the progression of CKD (120). There are several mechanisms by which Se affects CKD.

Se and Oxidative stress

Most ROS are by-products of cellular redox processes, and in excess may be harmful (121). While many studies have shown increased oxidative stress in patients with CKD (122), Se itself has no antioxidant activity, and most of the 25 selenoproteins synthesized by it have a redox enzyme function, among which are well-known redox-active selenoenzymes such as five GSH-Pxs, three thioredoxin reductases, and methionine sulfoxide reductase 2, which contain Se at their active site (123).

GSH-Px is an intracellular antioxidant enzyme that protects organisms from oxidative stress by catalyzing the reduction of hydrogen peroxide, lipid hydroperoxides, and organic hydroperoxides to water or corresponding alcohols (110). In healthy individuals, plasma GSH-Px is produced by the cells of the renal proximal tubule, and Se is the co-factor of this enzyme. After HD, glutathione in blood decreases, and the activities of GSH-Px and superoxide dismutase in red blood cells decrease before and after dialysis, while the activity of catalase increases (124,125). In addition, contact between blood and the artificial dialysis membrane can cause respiratory eruption of neutrophils and release many ROS including oxygen free radicals (126). Earlier study suggested a lack of GSH-Px in HD patients was not associated with Se deficiency, as Se supplementation of the enzyme did not change, and it is possible that damaged kidneys in HD patients cannot synthesize GSH-Px even after Se supplementation (127). Recent animal experiment had shown Se deficiency can cause kidney damage in mice, and elevated oxidative stress caused by Se deficiency may lead to mitochondrial damage and disruption of the energy supply. Renal tubules and podocytes are rich in mitochondria, which can lead to renal insufficiency (128). Study demonstrated Se supplementation can induce mitochondrial biogenesis by elevating the levels of

the nuclear mitochondrial biogenesis regulators PGC-1 α and NRF1 (129), and a randomized clinical trial showed significant increases in plasma Se concentration and erythrocyte GSH-Px activity in patients with CKD at different stages when supplemented with 200 mg Se daily for three months (130). Se supplementation in type 2 diabetes has also been found to increase GSH-Px-3 activity, improve renal perfusion, and increase glomerular filtration by enhancing host antioxidant defense (131).

Se and inflammation

Inflammation is closely related to oxidative stress, and oxidation can induce inflammation by activating multiple pathways. Se deficiency induces oxidative stress, which also regulates kidney inflammation (132). In animal experiment, Se deficiency caused renal injury, as evidenced by an increased kidney index the appearance of inflammatory lesions, increased numbers of lymphocytes and neutrophils, and atrophied renal tubules, possibly by activating the nuclear factor kappa B (NF- κ B) and HIF-1 α pathway (133). Se may inhibit the activation of NF- κ B by modulating the expression of genes. Moreover, Se supplementation in chronic inflammation restores depleted hepatic and serum levels by increasing selenoprotein biosynthesis, leading to suppressed C-reactive protein production and attenuating the inflammatory process (134). The toxic effects of aluminum in patients with advanced CKD are expressed by severe encephalopathy and bone disease (135), and experiment on mice found Se-rich yeast (SeY) prevented renal toxicity caused by aluminum via regulation of inflammatory responses, ATPase activities, and transcription of their subunits (136). DNA damage in white blood cells is higher in CKD patients on HD than in healthy controls, and Se supplementation prevents the damage to DNA (137).

In addition, Se helps fight inflammation in CKD by boosting the immune system through enhancing T cell proliferation, natural killer cell activity, and lymphocyte function (138). Se levels can also affect T cell and macrophage differentiation, B cell numbers and antibody production, and regulate dendritic cell differentiation and immune function in mice (139).

Se and fibrosis

The progression of CKD is characterized by the loss of renal cells and their replacement by extracellular matrix, leading to fibrosis (140). Se supplementation has a protective effect on liver fibrosis and pulmonary fibrosis, while deficiency may aggravate the progression

of renal fibrosis. Animal model has shown Se deficiency leads to accumulation of extracellular matrix and changes in matrix metalloproteinases expression, promoting the occurrence of fibrosis. Research shows that wnt/ β -catenin may be involved in the process of renal fibrosis caused by Se deficiency (141), although the mechanism is unclear. In addition, peritoneal fibrosis caused by long-term PD is always the main reason for its withdrawal (142). Se inhibits epithelial-to-mesenchymal transition by modulating ROS generation and ROS/MMP-9 signaling pathways in peritoneal mesothelial cells. Moreover, it may decrease the epithelial-mesenchymal transition events of peritoneal mesothelial cells via inhibition of PI3k/AKT pathways (143). Se supplementation reduces the risk of peritoneal fibrosis in PD patients.

Se toxicity

Studies have shown a daily supplement of 200 μ g Se (SeY) is safe and effective in patients with CKD treated with HD (137,144,145). Daily supplementation of 200 μ g organic SeY tablets can also improve renal function in elderly people with Se deficiency (118). The maximum recommended allowance dose for Se is 400–450 μ g/day (144), although toxicity can occur with acute or chronic ingestion. Human doses of 10 mg/kg and above are associated with a risk of mortality, and blood levels of 1,000 μ g/L and above are associated with high mortality. The main cause of toxicity is that when high concentrations of Se enter the human body, there is competition between it and sulfur. Se can easily replace sulfur in sulfur-containing amino acids and interfere with protein expression, obstructing biochemical reactions and causing damage to tissues and organs (146). The toxicity of organic Se is low, and poisoning mainly occurs in cases of excessive intake of inorganic Se (147). Symptoms of Se toxicity may include diarrhea, fatigue, hair loss, joint pain, discoloured/brittle nails, nausea, headache, tingling, vomiting, fever, and ataxia. Discolored, brittle, or peeling nails were most reported, and both nail clippings and dissolved fragments accurately quantified Se exposure (148). Therefore, regular monitoring of Se concentration is necessary for patients with CKD.

Cu

Following Zn and Fe, Cu is the third most abundant trace element in the body and is an important catalyst for heme synthesis and Fe absorption. The average daily intake of Cu in the US is about 1 mg Cu with the primary source being dietary (149). Cu is found in natural mineral water, and

water pipes can also release some Cu into drinking water, while seafood, organ meat, cocoa products, nuts (particularly cashew), and seeds are also important sources (150). Cu is absorbed in the intestine and secreted into the portal vein circulation, where it binds to albumin, transporters, low molecular weight Cu histidine complexes, or combinations of them as Cu^{2+} and is excreted into the gastrointestinal tract, either via the bile or in a non-absorbed form (151). The recommended dietary allowance for Cu increases throughout later childhood and adolescence, and is 900 μ g/day in adults (152).

As CKD progresses, GFR decreases, leading to an imbalance of certain trace elements, and higher CKD stages are associated with increased levels of Cu and decreased levels of Zn (153). This suggests the Cu/Zn ratio could be used as a marker for early and late detection of renal failure (154). Elevated circulating Cu levels may be a causal risk factor for CKD (155), although there are varying reports of Cu concentrations in patients on HD, such as moderate Cu deficiency, high Cu levels, or Cu toxicity (156). Higher levels of blood Cu and lower levels of blood Zn and Se were independently associated with higher nutritional risk in HD patients (157). In addition, researchers identified intracellular Cu accumulation as playing a unique role in kidney fibrosis by activating lysyl oxidase mediated collagen and elastin crosslinking, and inhibition of intracellular Cu overload may be a potential approach to alleviate kidney fibrosis (158).

Cu and anemia

Plasma Zn concentration decreases in HD patients, and supplementation can increase hemoglobin levels and improve anemia. However, improper Zn supplementation can lead to Cu deficiency. Zn antagonizes the uptake of divalent cations, including Fe and Cu, in erythrocyte precursors. Cu is required for Fe transfer from cells to blood, ensuring dietary Fe absorption and systemic Fe distribution (159). Cu also binds to a variety of Cu-dependent enzymes in the blood, and deficiency prevents these enzymes from working properly, leading to hematological or neurological symptoms (160). In addition, activity of Cu/Zn superoxide dismutase (Cu/Zn-SOD), an antioxidant enzyme, is decreased to 20% of the normal erythrocyte Cu/Zn-SOD in Cu-deficient subjects, which may accelerate oxidation reaction and shorten the life span of erythrocytes. Cu deficiency anemia is characterized by fewer red and/or white blood cells, or even pancytopenia, and can be present as microcytic, normocytic, or macrocytic (161). One

study also found a higher blood Cu/Zn ratio was independently associated with lower hemoglobin levels and anemia in HD patients (162). Cu deficiency may be a new mechanism of erythropoietin resistant anemia in patients with CKD, and correction of its deficiency can improve erythropoietin non-response in patients with HD anemia (163).

If Cu deficiency is observed, it should be treated with oral or IV Cu replacement in the form of Cu gluconate, Cu sulfate, or Cu chloride, while dietary supplements containing Cu are also an option (161). Cu deficiency anemia can be diagnosed by measuring serum Cu, serum ceruloplasmin, or a 24-hour urine Cu sample, and serum Zn and Cu measurements should be taken every 2–3 months during Zn supplementation to prevent Cu deficiency.

Cu and oxidative stress

Studies have found elevated levels of serum Cu trigger oxidative stress and activate inflammation. The release of Cu during inflammatory tissue injury also increases plasma Cu levels. As free radicals produced in redox reactions can lead to oxidation degradation of biological macromolecules, excessive Cu can be toxic to living organisms (164). Cu can induce oxidative stress via two mechanisms. First, it can directly catalyze the formation of ROS via a Fenton-like reaction. Second, exposure to elevated levels of Cu significantly decreases glutathione levels (165). Zebrafish inflammatory models showed the use of Cu sulfate as a stressor produced a robust acute inflammatory response that stimulated leukocyte infiltration within 20 minutes of Cu exposure, while activities of the oxidative stress markers catalase, glutathione, SOD, and nitric oxide increased. Pro-inflammatory cytokine-related genes IL-1 β , TNF, and COX-2 were upregulated, and levels of PGE2 and myeloperoxidase increased (166).

Oxidative stress of Cu has also been studied in the kidney. Cu induces mitochondria-mediated apoptosis in the kidney, while long-term exposure significantly increases renal tissue and mitochondrial damage in rats, and higher levels significantly increase expression of the Keap1/Nrf2 signaling pathway and redox state related genes (167). Excessive Cu can also induce oxidative stress and autophagy in the renal tubular epithelial cells of ducks by activating the ROS/Ho-1/NQO1 pathway (168). The toxic effects of Cu can lead to the granular and vacuolar degeneration of renal tubular epithelial cells, and eventually cause chronic or acute renal failure. When renal podocytes were treated with Cu nanoparticles *in vitro*, their cell viability and apoptosis decreased significantly. Cu nanoparticles

affected the oxidation-antioxidant balance, and were cytotoxic to podocytes, resulting in increased production of ROS and malondialdehyde (169). Similarly, Cu oxide nanoparticles can induce cytotoxicity and oxidative stress in human embryonic kidney cells (170). Oxidative stress increases in CKD patients undergoing long-term dialysis, and disruption of Cu and Zn homeostasis increases the risk of adverse outcomes. Significant negative associations between the Cu/Zn ratio and peripheral T-lymphocyte subsets (CD3 and CD4) and B-lymphocytes CD19 exist in CAPD patients, suggesting variations in the Cu/Zn ratio can indicate oxidative stress and inflammation status in CAPD patients (171). Zn supplementation significantly increases plasma Zn concentration, decreases Cu concentration and Cu/Zn ratio, and decreases C-reactive protein and pro-inflammatory cytokines concentrations in HD patients (172). Cu concentration in the kidney decreases significantly after transplantation, possibly due to inflammation and immune system changes caused by immunosuppressive drugs used by the graft recipient (173).

Diabetes is a group of metabolic diseases characterized by hyperglycemia, which is one of the leading causes of ESKD. In a series of studies involving animals or diabetic patients, diabetes was linked to oxidative stress. Cu is a cofactor of Cu, Zn-superoxide dismutase, in which Zn²⁺ plays a structural role and enhances stability, whereas Cu²⁺ is directly involved in the catalytic cycle and can decrease oxidative damage to cells (174). The alteration in antioxidant systems (SOD) is correlated only with Cu, and CKD patients are at risk of Cu deficiency, leading to a decrease in the activity of this enzyme (175). Many studies have shown the importance and further significance of Cu, Zn-SOD activity in diabetes mellitus (176). Animal model showed Cu, Zn-SOD dismutase alleviated the decreased activity of SOD1 and SOD3 in DN (177), while research by the same team demonstrated a deficiency of SOD1, but not SOD3, increased renal superoxide in the setting of diabetes and caused overt renal injury in nephropathy-resistant diabetic mice (178).

Moreover, obesity and hyperlipidemia are the most prevalent independent risk factors for CKD, suggesting lipid accumulation in the renal parenchyma is detrimental to renal function. Excess free fatty acids can damage renal tissue through various mechanisms, and particularly by promoting the production of ROS and lipid peroxidation, mitochondrial damage, and tissue inflammation (179). Cu is also a protector in the process of atherosclerosis, and its shortage is likely to accelerate this via several mechanisms.

The effect of Cu deficiency on lipid metabolism, including an elevation of lipids in the serum, has been well established, and one study has found an inverse relationship between Cu and peripheral lipid levels (180).

Cu toxicity

In addition to the damage caused by oxidative stress, Cu overload can cause other adverse effects. Large doses of acute excess Cu can be fatal, whereas small doses of acute Cu excess present early with gastrointestinal reactions, such as nausea and vomiting, possibly due to stimulation of the vagus nerve (151). Other symptoms include abdominal pain, gastrointestinal hemorrhage, melena, jaundice, anorexia, severe thirst, diarrhea, and liver and kidney failure (181).

Wilson's disease is a classic model of chronic Cu poisoning, characterized by a large accumulation of Cu in the liver leading to the death of hepatocytes, and the released Cu accumulates in the central nervous system, resulting in neurological abnormalities. Therefore, Wilson's disease can present as a disease of the liver or nervous system. In addition, Cu deposits in the cornea, kidneys, and bones can cause symptoms (182). In fish model, Cu at different concentrations caused blood cells DNA strand breaks and altered liver gene expression and metabolite concentrations in a concentration-dependent manner (183). Similar to a mouse model of Wilson's disease, genes related to cholesterol biosynthesis were overexpressed and consistently downregulated. (183). Another study identified that the accumulation of Cu could cause mitochondrial dysfunction, induce mitochondria-mediated apoptosis, and activate the AMPK-mTOR pathway in the hypothalamus (184).

Iodine

Iodine is an essential trace element for thyroid hormones synthesis, and diets lacking in it may promote a deficiency that affects thyroid function. The main natural sources of iodine are marine fish, seafood, seaweed, and dairy products, although in most countries, the main dietary source is fortified salt (185). Iodine is absorbed in the small intestine, and inorganic iodine is cleared from plasma by the thyroid gland and stored in the lumen of follicular cells as iodine compound. Approximately 90% of iodine is eliminated in urine (186). The World Health Organization (WHO)/UNICEF/International Council for the Control of IDD recommends a daily intake for adults of 150 µg/d, increasing to 250 µg/d for pregnant women (187).

Iodine and the thyroid

The induction of hypothyroidism by iodine was first described in 1948 and is known as the Wolff-Chaikoff effect. This sees iodopeptides temporarily inhibit thyroid peroxidase mRNA and protein synthesis and, subsequently, thyroglobulin iodinations, around 48 hours after the onset of exposure to iodine (188). Povidone-iodine 10% in the PD cap may be the source of the high plasma iodine levels, as the iodine levels in PD fluid are higher than in the plasma, and overnight continuous-cycle PD-infants develop hypothyroidism due to iodine exposure through the Wolff-Chaikoff effect (189). Elevated serum iodine levels have been demonstrated in patients with advanced renal insufficiency, and as CKD progresses, decreased excretion of urinary iodine increases the serum inorganic iodine level and iodine content of the thyroid, which consequently enlarges the gland. Some dialysis patients in areas with high iodine intake have goiters with high levels of iodine, and studies have shown hypothyroidism is reversible in such patients by limiting iodine intake (190). The frequency of goiter increases as the duration of dialysis increases, which is attributable to the increased cutaneous absorption of povidone-iodine (191).

Several indicators are used to assess the iodine status of a population, including thyroid volume, urinary iodine concentration (UIC), and the blood constituents thyrotropin and thyroglobulin. A major indicator corresponding to iodine nutrition and reflecting recent changes in iodine intake in period of days is the concentration of iodine in urine. According to the WHO, urinary iodine below 20 µg/L denotes severe iodine deficiency, 20–49 µg/L is moderate, and 50–99 µg/L is mild iodine deficiency. A UIC of 100–199 µg/L reflects adequate iodine intake, whereas 200–299 µg/L is more than adequate, and more than 300 µg/L is excessive (187). Consequences of iodine deficiency include goiter, intellectual impairments, growth retardation, neonatal hypothyroidism, and increased pregnancy loss and infant mortality (192).

Iodinated contrast media and CKD

The use of iodinated contrast media for imaging diagnosis is a common clinical method. However, this may cause contrast-induced nephropathy (CIN) in patients with CKD and the risk of developing CIN increases as kidney function decreases. CIN is diagnosed when serum creatinine levels increase by ≥ 0.5 mg/dL or $\geq 25\%$ from baseline within

72 h after contrast radiography using iodinated contrast media (193). CIN is a form of AKI that develops after exposure to iodinated contrast media which is diagnosed based on decreased renal function after angiography and after excluding other causes (193). However, the American College of Radiology suggests the presumed risks of IV iodine contrast in patients with decreased renal function are overstated and are due to the combination of contrast-associated AKI and contrast-induced AKI. Although the real risk of contrast-induced AKI is still unknown, IV saline prophylaxis is indicated for patients with AKI or with a GFR of less than 30 mL/min/1.73 m² who are not concomitant with vascular dialysis. In individual high-risk cases, preventive measures at the discretion of the clinician may be considered in patients with GFR of 30–44 mL/min/1.73 m² (194).

The pathophysiology of CIN is complex and involves many different mechanisms, and both a reduction in renal perfusion and toxic effects on tubular cells are recognized as pivotal factors. Altered renal microcirculation and enhanced oxygen consumption within a region with low partial oxygen tension induce medullary ischemia and appear to play a key role in the development of CIN (195). CKD patients may develop contrast-induced medulla injury due to endothelial dysfunction, and those with CIN have a poor prognosis, for which the primary risk factor is GFR (196).

The risk of CIN in CKD seems to depend on the route of contrast administration and the pathophysiology of the patient. While diabetes with CKD has been reported to be a risk factor for CIN, diabetes and CKD alone are not (197). Other risk factors include nephrotoxic drugs and exposures, hypoperfusion, proteinuria, and renal ischemia (198). Contrast-induced AKI increases with the progression of CKD, but the actual risk remains uncertain in patients with severe kidney disease. A meta-analysis of pooled data from 2,727 patients indicated the use of the isosmolar contrast medium iodixanol was associated with smaller rises in Cr and lower rates of CIN than low-osmolar contrast media, especially in patients with CKD or CKD + diabetes (199). However, a recent meta-analysis suggested that in patients with CKD stage 3 and above undergoing coronary angiography, the use of isosmolar contrast medium iodixanol showed an overall non-significant difference in incidence of CIN compared to low-osmolar contrast media (200). In addition, IV contrast media is much safer than intra-arterial injection, which is carried out during endovascular intervention (201).

Residual renal function is strongly associated with survival in HD and PD patients. A meta-analysis of seven

studies reported no change in residual renal function after iodine contrast medium in dialysis patients (202). Although the effect of IV iodinated contrast media on residual renal function remain unclear, loss of residual renal function may have adverse effects, and if the loss is clinically important, specialists should consider and weigh the pros and cons.

Mn

While Mn is a toxin, it is essential to the normal operation of various metabolic enzymes and cofactors. It is also an essential trace element which maintains normal bodily function. Mn is a cofactor of many enzymes and is essential for substance and energy metabolism, immune function, and blood glucose regulation, and has antioxidant effects (203). The Institute of Medicine's dietary reference intake for Mn is 2 mg/d as an adequate intake for adults and 1.2–1.5 mg/d for children (204). Mn mainly comes from plants, such as whole grains, seeds, nuts, and vegetables, but is also found in natural mineral water, dietary supplements, and vitamins. The level of Mn in fresh water typically ranges from 1 to 200 µg/L (205). Mn is absorbed by diffusion in the mucosal cells of the small intestine, and approximately 32% of absorbed Mn is excreted in the feces through bile secretion, whereas only 0.1–3% is excreted in the urine (206). Fe and Mn are inversely related because of shared transporters in the gut, so Mn absorption is greater if the Fe content is low (207).

There are few reports on Mn in CKD, and the results are conflicting. While it has been reported that the blood Mn level in healthy subjects, HD, and PD patients is similar (208), there are also reports of elevated blood Mn, with one study finding CKD in predialysis patients was associated with increases in the circulating levels (209). However, other study has shown significant reductions in Mn concentration in CKD patients (210), and with the prolongation of HD, the plasma concentration of Mn gradually decreased (211). These differing results may be related to the diet of the patients, degree of malnutrition, or the method of measurement. Imaging findings showed Mn deposition in the basal ganglia was present only in HD patients, suggesting it could be caused by the HD method itself rather than uremia and renal failure, which were positively correlated with dialysis duration (208). The increase in circulating Mn level may be due to the gradual aggravation of chronic renal failure with time. In addition, CKD patients often have different degrees of Fe deficiency, which affects the transport of Mn and increases its intestinal absorption, leading to an increase in Mn levels in various tissues. Fe deficiency is associated with increased accumulation of Mn in the brain in

a region-specific manner (207).

Mn and oxidative stress

Mn, as a cofactor of Mn superoxide dismutase (MnSOD), catalyzes the generation of hydrogen peroxide (H_2O_2) from superoxide through the Mn^{2+}/Mn^{3+} cycle, which detoxifies free radicals in mitochondria to prevent oxidative stress (212). MnSOD is located in the inner mitochondrial membrane and is highly active in the human kidney. MnSOD dysfunction is associated with glomerular and tubular interstitial fibrosis, inflammation, excessive apoptosis of renal cells, and tubular cell injury.

MnSOD dysfunction and related mitochondrial oxidative stress were found to be involved in infection-induced AKI (213,214). Hyperglycaemia increases the production of ROS and causes oxidative stress, which influences multiple pathways implicated in DN (215). High glucose first induces superoxide generation and hyperpolarization in the mitochondria, followed by a decline in ATP levels, partial Complex III inactivation, and loss of cell viability. These high-glucose-induced changes are completely prevented by overexpression of MnSOD in renal proximal tubular cells (216). It was found that enhanced oxidative stress in kidney mitochondria of diabetic db/db mice could be achieved by decreasing MnSOD activity and increasing tyrosine nitrification modification. Resveratrol improves oxidative stress and protects against DN through normalization of MnSOD dysfunction in the AMPK/SIRT1-independent pathway (217). The expression of general control of amino acid synthesis 5-Like 1 was significantly increased in human and mouse diabetic kidney disease renal tissues and hyperglycemic renal tubular epithelial cells. Amino acid synthesis 5-Like 1 deletion could reduce the acetylation of lysine 68 by MnSOD and activate its activity, removing excessive ROS and alleviating oxidative stress-induced nephritis and fibrosis (218). A rat model of type 2 diabetes induced by low-dose streptozotocin suggested liraglutide may exert a renoprotective effect via a FoxO1-mediated upregulation of renal MnSOD expression in early diabetic kidney disease (219). Oxidative stress is the main factor leading to renal damage in hypertensive patients, and in animal experiments, hypermethylation of antioxidant enzymes in the aged kidney during hypertension worsened redox imbalance leading to kidney damage (220). TLR4 deficiency can reduce oxidative stress and increase the antioxidant capacity of MnSOD, and macrophage activation can decrease TGF- β -induced extracellular matrix protein deposition in the kidney in angiotensin-II induced

hypertension (221).

Mn toxicity

Mn toxicity is concentrated in the central nervous system, and typical symptoms include neurobehavioral disorders and extrapyramidal damage associated with damage to the basal ganglia, similar to Parkinson's disease. Although the mechanism is still unknown, neuronal damage in Mn toxicity may be related to oxidative stress and disturbance to mitochondrial function and the inflammatory pathway, with typical gliosis suggesting astrocytes play a key role (222). In an *in vitro* study, the toxicity of $MnCl_2$ to five types of cells was compared, and the result showed 1 mM $MnCl_2$ significantly decreased the cell viability of glial and neuronal cells, while liver and kidney were less affected, indicating the central nervous system is the most sensitive target of Mn poisoning (223). The data also showed that, despite a high capability to accumulate Mn, the kidney was relatively resistant to its toxic effect (224).

Mn exposure produces cardiotoxicity, and clinical evidence has shown workers exposed to it are at increased risk of creatine kinase and creatine kinase isoenzyme elevation (225). Animal studies have shown Mn can accumulate rapidly in heart tissue, leading to acute or subacute CVDs such as acute cardiac depression and hypotension (225-227). The possible mechanisms of cardiovascular toxicity induced by Mn include changes in autonomic nerve function, Ca^{2+} channel obstruction, myocardial mitochondrial damage, reduction of dopamine and 5-hydroxytryptophane, interference with cholinesterase synthesis, and reduction of superoxide dismutase activity (228). In addition, there were positive associations between diastolic blood pressure and plasma Mn over 24 hours and during daytime and between systolic blood pressure and urinary Mn at night (229).

Mn can also damage the liver, which absorbs and excretes it. Chronic Mn exposure leads to hepatocyte denatured nuclear karyopyknosis, increased inflammatory factors, and increased hepatic transporters (230). Animal experiments showed exposure to $MnCl_2$ caused liver injury in rats, and the degree of injury was positively correlated with exposure time. $MnCl_2$ plays a stronger role in mitochondria than in the membrane or nucleus, and most of the changes in these biomarkers were reversed when Mn exposure was stopped (231). Long-term low-dose Mn exposure causes slight pathological changes in liver structure, but high-dose exposure affects liver structure and function, which may be related to the inhibition of nuclear factor E2-related factor-2 expression, the inhibition of transcription

of its potential antioxidant genes, and down-regulation of corresponding proteins (232). The accumulation of Mn in the liver may also lead to cirrhosis and fibrosis.

In conclusion, the human body is a huge balance system. Essential trace element homeostasis involves the processes of absorption, storage, and excretion. Water and food are the primary sources for trace elements. Most of the trace elements are absorbed from the gastrointestinal tract and flow out in the portal circulation by binding to the plasma proteins. These trace elements are used by tissues or organs and excreted through the urine, but also through bile, sweat, and even breath. Consequences of trace elements imbalance may include anemia, infection, atherosclerosis, oxidative stress, muscle spasms, bone diseases, encephalopathy, mental disorders, and risk of death. The imbalance of essential trace elements is one of the main risk factors for CKD, especially the imbalance of iron, zinc, selenium and copper.

Summary

Essential trace elements differ in patients with CKD, and in particular those with ESKD requiring dialysis maintenance. Existing evidence shows essential trace element homeostasis plays an indispensable role in maintaining the normal operation of the body, fighting inflammation, regulating oxidative stress, improving anemia, and preventing fibrosis. However, there are many adverse reactions to excessive trace elements, and their timely supplementation and adjustment are of great significance in the treatment and recovery of CKD patients. In addition, there are few studies on trace element levels in children with CKD. Therefore, more prospective studies are required to evaluate the effects of essential micronutrients, and regular monitoring of their concentrations in CKD patients is necessary in clinical work.

Conclusions

Imbalance of essential trace elements is a common complication of CKD and a risk factor for progression of CKD, cardiovascular events and death. Paying attention to the essential trace elements in patients with CKD throughout the treatment process of CKD is a great significance for improving the diagnosis and treatment of CKD, delaying the progression of the disease, improving the prognosis of patients and reducing medical costs.

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Footnote

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