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REVIEW PAPER

Revisiting copper and zinc in end-stage renal disease patients

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ABSTRACT

Numerous research projects have discovered how trace elements affect people with end-stage renal disease (ESRD). Thus, understanding the mechanism of action and the potential treatment options requires research into the chemical compounds that have an impact on the kidneys. Trace elements are components of metalloproteins and act as cofactors for numerous essential enzymes. Among the most important trace elements that affect renal function are zinc and copper. The newly published papers on changes in the effects of both trace element products in ESRD patients were studied, and the justifications gathered from earlier studies were compiled. This review's findings suggest that changes in trace element levels worsen ESRD patients' health condition by deepening kidney dysfunction, which has a negative impact on their health. The mechanism by which these effects occur is reviewed, and schemes were plotted in order to show a comprehensive view of the role of dysregulation of copper and zinc in ESRD patients.

KEY WORDS:

end stage renal diseases, trace elements, haemodialysis, copper, zinc.

END-STAGE RENAL DISEASE

The kidneys play a vital role in the elimination of blood wastes and excess fluid *via* the process of urine excretion. The body may experience the accumulation of fluid, electrolytes, and waste substances at toxic levels when the kidneys fail to filter these components [1]. When the gradual decline in renal function reaches an advanced stage, it reaches end-stage renal disease (ESRD), which is also known as end-stage kidney disease or kidney failure [1, 2]. National Kidney Foundation has categorised kidney disease into 5 distinct stages. Stage 5 specifically pertains to those with a glomerular filtration rate (GFR) of less than 15 ml *per* minute *per* 1.73 m^2 of body surface area or those who need dialysis irrespective of their GFR, including refractory oedema, uraemia, acidosis, hyperkalaemia, and/or unacceptable symptoms [3, 4]. Decreased or missing kidney function leads to a range of maladaptive alterations, such as extracellular volume excess, resulting in fluid retention, anaemia, disturbances in bone and mineral metabolism, dyslipidaemia, and protein energy deficit [5].

Patients with ESRD require either dialysis or a kidney transplant in order to survive. In order to effectively address symptoms and optimise the overall quality of life throughout the remaining period, it is essential to include conservative treatment measures [6]. Multiple studies have shown a reduction in zinc levels in the blood plasma of patients with chronic renal insufficiency who are undergoing conservative treatment or haemodialysis (HD) [7, 8]. Some authors have reported that zinc levels in erythrocytes are within the normal range in comparable patient groups, whereas others report higher levels [9, 10]. The primary contributors to the trace element

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decrease in HD patients are urine losses and losses to the dialysate [11, 12].

The influence of renal sickness on trace element concentration in uraemic patients is mostly determined by the severity of the condition [13]. Individuals diagnosed with ESRD often experience fluid retention, causing hypertension, heart ventricular failure, and subsequent cardiovascular incidents [14]. This fluid retention may cause the abnormal distribution of the metal ions between plasma and tissue reservoirs.

TRACE ELEMENTS

Trace elements are a set of metals that naturally occur in biological systems at low concentrations, such as zinc (Zn), iron (Fe), and copper (Cu) [15]. As a result of urbanisation and industrialisation, the amount of trace elements that individuals contribute to the environment is increasing overall [16], and because these elements do not biodegrade, they move through the environment in biogeochemical cycles. The concern around trace elements arises from their significant capacity to inflict damage upon organisms, even in small concentrations. Trace elements have a multitude of important functions inside the human body, including activating enzymatic reactions by enhancing the conversion of substrate molecules into certain end products [17]. The idea that the trace element status affects the probability of undesirable clinical outcomes seems worthy of inquiry because both trace element deficiencies and excesses may be treatable. To clarify the clinical significance and long-term implications of these trace element abnormalities, more research is required [18]. Among the important trace elements, we focused in the present review on the levels of serum copper and zinc in ESRD patients who underwent haemodialysis.

1- ZINC

Zinc is a vital trace metal that serves as a cofactor for more than 300 distinct enzymes involved in cell metabolism, growth, and development [19]. Zinc is involved in the metabolic processes of proteins, carbohydrates, lipids, and energy *via* its participation as a constituent of many enzymes [19]. It is essential for the synthesis of proteins and DNA, as well as for insulin action and the proper functioning of liver metabolism [20].

Patients undergoing HD appear to have lower zinc levels than the general population [21, 22]. Zinc deficiency is prevalent in undeveloped nations [23], and it is linked to immunological deficiencies that have defective T-cell function, poor phagocytosis, inappropriate cytokine production, and delayed wound healing [24], which causes an elevated risk of infection seen in HD patients. Anorexia in HD patients may also be brought on by or contributed to by zinc deficiency [25]. Anorexia and a diminished sense of taste and smell are just a few of the uremic symptoms that are allegedly associated with zinc deficiency in HD patients. Zinc shortage in individuals with uraemia may arise because of reduced food intake and intestinal absorption, with increased losses of zinc from the body [26]. Researchers believe that the hormone leptin might be used as a tool to investigate the physiological pathways that are responsible for zinc deficiency-induced anorexia [27]. The association between zinc and leptin has been widely found in HD patients [28]. The possible mechanisms of the alteration of zinc in kidney diseases are presented in Figure 1.

Many causes of zinc deficiency are presented in Figure 1, including diet restriction, albuminuria, loss by HD, malabsorption, and drug interactions [22, 29, 30]. To buffer the zinc deficiency, the zinc will be released from bone and tissues to supply the need for zinc to the erythrocyte formation. The role of dialysis treatment on zinc metabolism needs to be considered because of the presence of an inverse relationship between erythrocytes and zinc [31]. This negative association, as a measure of dialysis adequacy, could indicate a redistribution of zinc due to the loss of this element during the dialysis treatment [30]. However, studies have not shown a loss of zinc during haemodialysis, and a rise in plasma zinc was discovered during the dialysis procedure, which could be because of haem concentration [32], besides the leaked zinc from the haemolysed erythrocytes [33].

Zinc is the cofactor of many enzymes, including superoxide dismutase, which catalyses the elimination of intracellular free radicals, and metallothionein, which traps free radicals and prevents lipid peroxidation [34]. Numerous investigations have revealed that CKD patients who were receiving either conservative treatment or dialysis had a significant frequency of zinc deficiency [35]. In several illness situations, such as ESRD patients undergoing HD, the risk of zinc deficiency is extremely high [26]. The causes of zinc shortage that have been linked to previous studies include protein-energy malnutrition, inadequate dietary intake, abnormalities of absorption and transport, and increased excretion [29]. The plasma zinc concentration noticeably drops in ESRD patients who are receiving HD therapy. This decrease often leads to a genuine zinc deficiency, regardless of the specific type of HD being administered [36].

In one study, over half of the HD group had a major zinc deficit, and zinc levels were significantly lower in the HD group than in the control group [37]. The precise mechanism underlying the reduction of zinc concentration in patients with CKD remains uncertain. Patients on HD did not have low reported whole-body zinc levels, in contrast to low serum zinc levels [38]. Several factors have observed decreases in nutritional intake seem to be associated with a limitation on protein, while inadequate gastrointestinal absorption may be caused by a deficiency in vitamin D [39] or interactions between drugs, such as the use of phosphate binders [40]. An additional potential

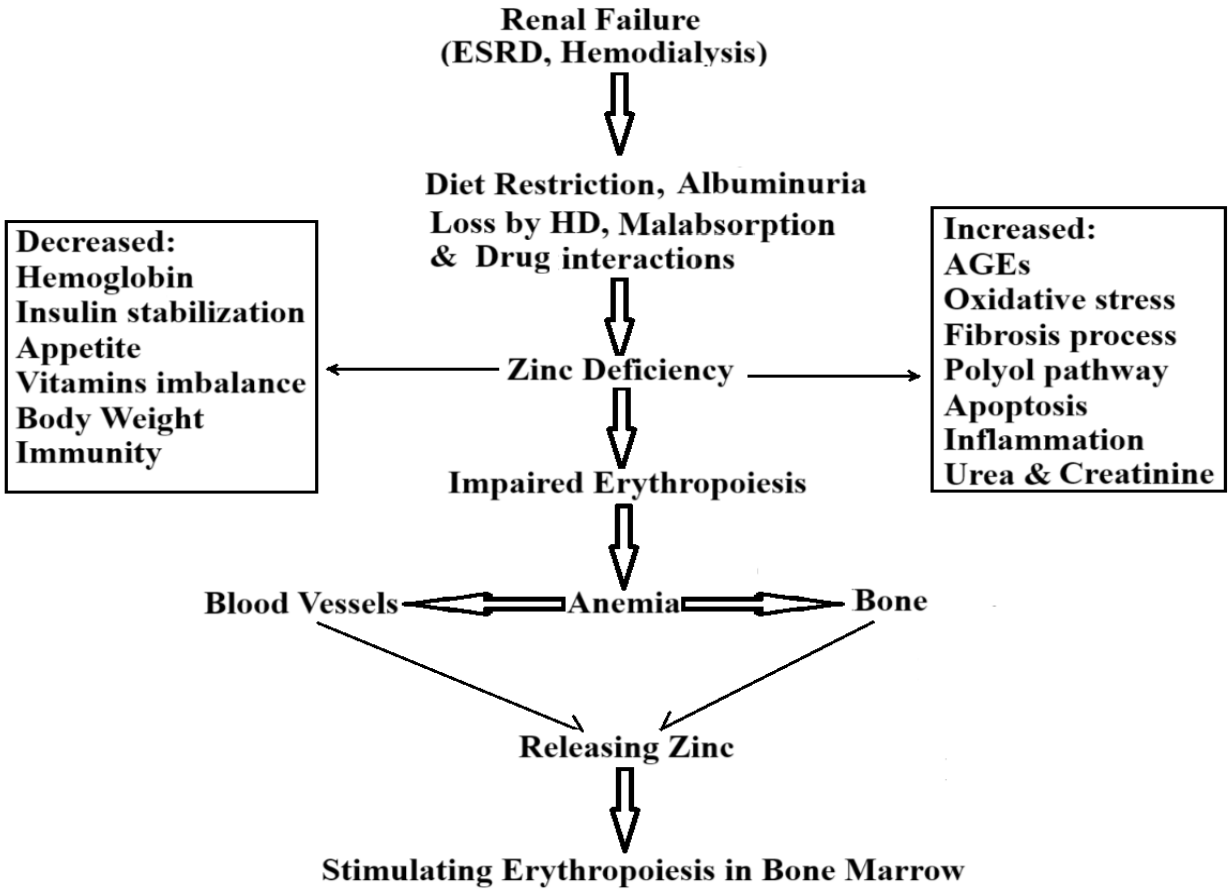

FIGURE 1. THE HARMFUL effect of hypozincaemia in end-stage renal disease patients

Anaemia causes the release of zinc from bone to compensate for zinc deficiency.
AGEs – advanced-glycated end-product, ESRD – end-stage renal disease, HD – haemodialysis

factor contributing to diminished zinc levels in patients with CKD is excessive urinary excretion of zinc. Patients with CKD had lower levels of zinc in their bloodstream due to the higher levels of excretion in their zinc compared to the control group [41]. Importantly, zinc and copper levels were inversely correlated, suggesting that taking zinc acetate orally may increase the risk of copper insufficiency. After the prescription of zinc acetate, it may be prudent to check both zinc and copper levels every month [42].

Zinc is transported by albumin [43]. Hypoalbuminaemia or a systemic inflammatory response both caused low plasma zinc concentration, suggesting that zinc insufficiency may have been misdiagnosed by interpreting low plasma zinc concentration as being caused by hypoalbuminaemia [44].

2-COPPER

In the intestines, copper is absorbed and then transferred to the liver bound with albumin. Copper is transported to various tissues in a second phase after being processed in the liver. The majority of the copper in the blood is carried by the protein ceruloplasmin, which is involved in copper transport in the liver [45]. Wheat, barley, fish, sunflower, and chicken are the finest dietary sources of copper for the human body [46]. Copper is an element that is essential to the functioning of several enzymes, including cytochrome oxidase, monoamine oxidase, and superoxide dismutase (SOD) [47].

Furthermore, because of its presence in many enzymes, copper is engaged in a wide range of metabolic reactions. The inclusion of copper in SOD, for example, aids in the conversion of superoxide to hydrogen peroxide and oxygen [48]. Copper is required for the haematopoietic and nervous systems as well as musculoskeletal. The gene expression during neural development and apoptosis, because it shows the molecular functions of copper and zinc [49], demonstrates that copper affects the protein structure of neurons to promote neurotransmission. Copper could alter the neuroproteostasis of CNS neurons, changing the excitability of those neurons [50]. It is required for bone growth and synthesis, aids in the incorporation of Fe into haemoglobin, aids in the absorption of Fe from the gastrointestinal tract, and facilitates the transport of Fe from tissues to plasma [46]. Copper deficiency is seldom seen in individuals who are in good health; however, it may manifest in children. The copper deficiency arises mostly as a result of impaired copper absorption [46]. A copper-rich diet can lead to the accumulation of this microelement in the kidney causing proximal tube necrosis caused by oxidative

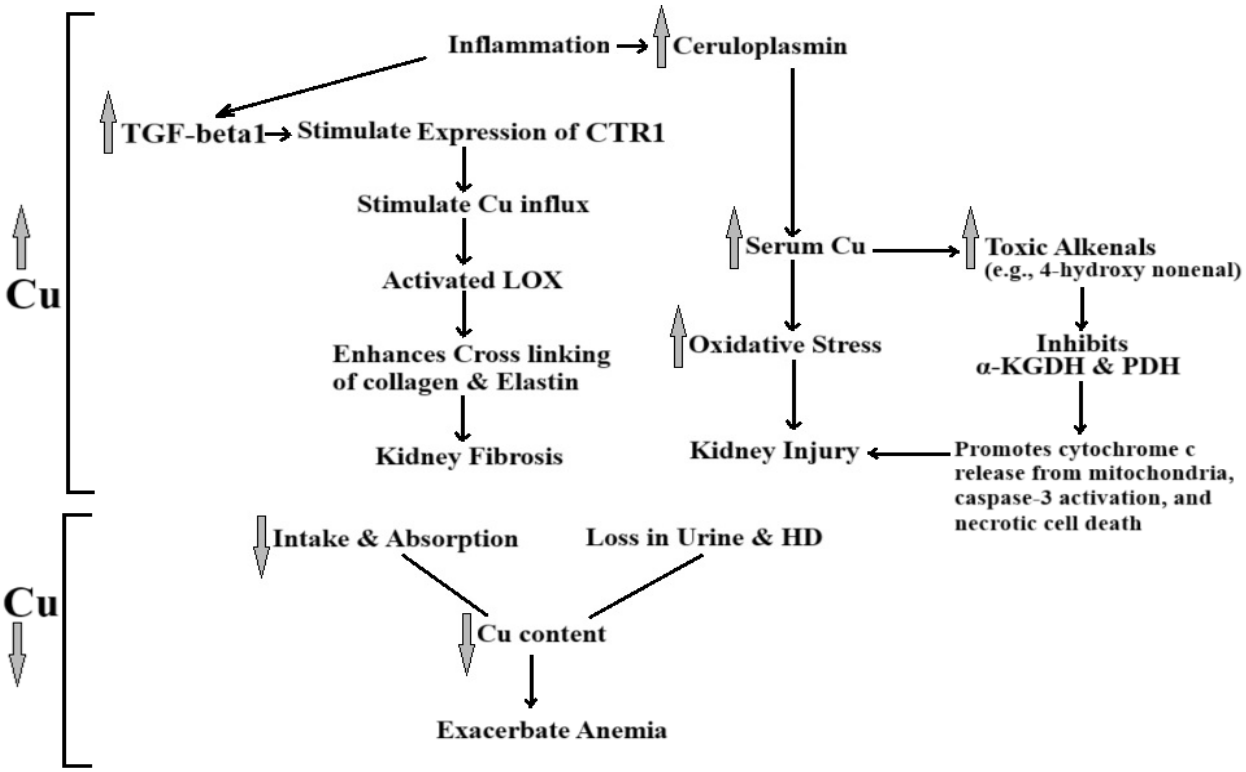

FIGURE 2. Hypercupraemia in end-stage renal disease patients and its effects on the kidney

The routes of copper loss are also illustrated.
AGEs – advanced-glycated end-product, α-KGDH – α-ketoglutarate CTR1 – copper transporter 1, HD – haemodialysis, LOX – lysyl oxidase, PDH – pyruvate dehydrogenase, TGF-β – transforming growth factor β

stress [51] and damage to cells, leading to a reduction in kidney function [52]. Figure 2 illustrates the harmful effects of hypercupraemia on the kidney in addition to the mechanisms of loss of Fe in HD patients.

The expression of copper transporter 1 (CTR1) in renal tissues was elevated in patients with renal fibrosis, causing anaemia. Transforming growth factor β (TGF-β)-treated renal tubular epithelial cells and fibroblasts demonstrated comparable outcomes [53, 54]. Mechanistically, TGF-β signalling upregulated CTR1 and induced increased intracellular copper influx. The activation of lysyl oxidase was seen as a result of elevated levels of intracellular copper ions, leading to an increase in the cross-linking of collagen and elastin [53, 54]. Furthermore, this phenomenon was shown to contribute to the development of renal fibrosis. The results of the alterations in serum copper and zinc levels are subject to conflicting interpretations. Some researchers found decreased blood levels of zinc and copper in ESRD patients [55]. Previous studies on uremic patients have shown inconsistent results about low levels of serum zinc and copper [56]. The first measure to decrease copper in ESRD patients is through treatment of inflammation to reduce the ceruloplasmin that acts as an acute phase reactant protein [57]. Conversely, people with ESRD have low zinc, but high serum copper [58, 59]. In patients on HD with low serum zinc concentrations, leukopaenia, which can be megaloblastic or sideroblastic, and copper deficiency may coexist [60]. However, compared to healthy controls, HD patients' average blood concentrations of physiologically significant trace elements like copper and zinc were significantly different [61]. Besides organelle malfunction and lipid peroxidation, the disruption of copper homeostasis results in the toxic alkenal formation, including the production of 4-hydroxynonenal that acts as an inhibitor of pyruvate dehydrogenase and α-keto-glutarate dehydrogenase (α-KGDH) [62, 63]. When the α-KGDH complex is inhibited, cytochrome c is released from mitochondria, caspase-3 is activated, and necrotic cells die [64]. The recommended daily allowance for copper is 900 μg *per* day. To prevent copper deficiency or toxicity, individuals need to consume an appropriate quantity of copper in their diet [65]. To maintain health, the body needs modest amounts of copper from meals to prevent anaemia associated with renal diseases [66]. However, in children treated with HD, copper supplements are used to adjust the haematological abnormalities [42]. Normally, the liver excretes excess copper by releasing it in bile, but a buildup of copper is dangerous and, if left untreated, can cause brain damage, liver failure, or even death [67].

CONCLUSIONS

In ESRD patients, abnormal zinc and copper homeostasis are widely recorded, which may lead to an increase in the probability of a poor prognosis due to the importance of these trace elements in many biological processes. Therefore, it is important to take therapeutic measures,

such as screening and treatment, to mitigate the adverse effects caused by abnormal levels.

DISCLOSURES

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