Zinc Supplementation on Nutritional Status in CKD

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Zinc is one of the most important and essential trace elements required by all living organisms for many physiologic functions, with three major biological roles catalytic, structural and regulatory ones. It is the second most abundant metal in mammalian tissues, after iron, with almost 90% of that found in muscle and bone. Likewise, the cellular Zn^{2+} concentrations are nearly as high as those of major metabolites like the ATP. Zinc is an essential cofactor that influences the expression and activity of numerous enzymes, transcription factors and regulatory proteins.

Keywords: serum zinc concentration ; hypozincemia ; chronic kidney disease ; serum albumin

1. Introduction

Over the last 10 years [1], chronic kidney disease (CKD) also known as chronic renal failure (CRF) is increasingly recognized as a global public health concern and an important contributor to morbidity and mortality [2]. While the burden of CKD is reasonably well defined in developed countries, increasing evidence indicates that the CKD burden may be even greater in developing countries [3]. Globally, the incidence and prevalence of CKD adults is increasing rapidly due to the rapid increase in the prevalence of risk factors such as diabetes, hypertension and obesity [2], which, in the future, will also produce a greater burden of CKD [1].

Even though it is more common in adults than in children, CKD is a chronic disease with severe long-term consequences. Moreover, although there are similarities between adult and pediatric populations with CKD, there are unique features and issues in childhood not evident in adults, such as the impact of the disease on growth [4]. The severe growth retardation is extremely common among CKD children and occurs in up to 35% of this population before the end-stage renal disease (ESRD) takes place [5]. Since the nutritional point of view, adequate nutrition and periodic evaluation are key components to prevent the development of protein-energy malnutrition (PEM) and meet the patient's vitamin and mineral needs [6].

The most important objective in CKD children is that they have a normal childhood. Nevertheless, this can be difficult because CKD creates a complex pathologic environment characterized by metabolic alterations that affect nutrient intake, metabolism and energy expenditure, predisposing patients to the development of malnutrition and an increased risk of morbidity and mortality [7]. The general decrease in nutritional intake, dietary restrictions, poor intestinal absorption, inflammatory state, metabolic acidosis and dialysate losses all put the CKD patient at risk of micronutrient deficiencies, which may contribute to comorbidities such as anemia, cardiovascular disease, and metabolic imbalances [8]. Furthermore, in CKD children malnutrition, metabolic acidosis, mineral and bone disorders, anemia and fluid and electrolyte abnormalities are risk factors that contribute to impaired growth [9].

Zinc is one of the most important [10] and essential trace elements required by all living organisms for many physiologic functions [11], with three major biological roles catalytic, structural and regulatory ones [10]. It is the second most abundant metal in mammalian tissues, after iron [12], with almost 90% of that found in muscle and bone [13]. Likewise, the cellular Zn^{2+} concentrations are nearly as high as those of major metabolites like the ATP are [14]. Zinc is an essential cofactor that influences the expression and activity of numerous enzymes, transcription factors and regulatory proteins [15]. It is indispensable for the structure and function of at least 3000 proteins [14] and cellular components and plays an important role in human physiology from its involvement in the proper function of the immune system to its role in cellular growth, cell proliferation, cell apoptosis, as well as in the activity of numerous zinc-binding proteins [10]. Additionally, zinc is an antioxidant with anti-inflammatory properties, and regulates innate and adaptive immune responses, which makes it crucial for resistance to infection [16].

The recent recognition of fundamental regulatory functions of Zn^{2+} ions released from cells or within cells; links this nutritionally essential metal ion to numerous human diseases. Zinc and its role in organ pathophysiology as well as in genetic, metabolic, chronic and infectious diseases are covered [14]. A high level of zinc has also been found in other

organs including the brain, heart, kidney, liver, prostate, pancreas, lung, skin and gastrointestinal (GI) tract. Maintaining a constant state of cellular zinc nutrition is essential for normal function. In the periphery, zinc homeostasis is a highly regulated and coordinated process that involves uptake through intestinal epithelial cells and reabsorption via the kidneys; changes in the absorption/excretion of zinc in the GI tract are the primary mechanisms for maintaining zinc homeostasis in the body [17][18].

Zinc is a multifunctional metal compatible with satisfactory growth, health and well-being [10]. It is known to regulate growth, neuronal development and immunity [19], and its deficit can affect the development of multiple organs, including the brain, lungs, skeleton, kidneys and heart [20]. This micronutrient plays a critical role in the microtubules function since microtubule formation involves tubulin polymerization, a process that is decreased by zinc deficiency (ZnD) [21]. ZnD is comorbid with CKD and worsens kidney complications. Besides, oxidative stress is implicated in the detrimental effects of ZnD [22]. NADPH oxidases (Nox) are the primary enzymes that contribute to renal reactive oxygen generation. Experimental findings show that ZnD exacerbates diabetic kidney damage by enhanced oxidative damage, fibrosis, and renal dysfunction [15].

2. Effects of Zinc Supplementation

CKD is a major health problem worldwide with increasing incidence and prevalence that is threatening to bring about the onset of a real ‘epidemic’ [23]. However, there are no reliable statistics about the prevalence of CKD in most of the developing world [3][24]. While data are available regarding vitamins in CKD, little is known about the trace elements, especially in children [25]. Even though dietary zinc deficiency affects 20%–25% of the world’s population [26] especially adolescents and postmenopausal women [27], zinc deficiency is rarely seen as a serious deficit [28]. However, data from the WHO [29] reported that zinc deficiency is the fifth largest health risk factor in developing countries and the eleventh in the world [30]. The main prevalence of ZnD is observed in developing countries in Africa, Asia and Central America as well as in Andean countries [31].

In Lima and Callao, the total number of children under 18-years-old in HD (58 cases) and CAPD (81 cases) was 139 patients. The prevalence of children under 18 years of age who were receiving renal replacement therapy (RRT) was 14 children per million populations (pmp). In 2015, the main aetiologies were primary glomerulopathies, chronic interstitial nephropathies and congenital aetiology [32]. Regardless of CKD aetiology, is accompanied by ZnD [33], which contributes to kidney damage [15][22]. In HD patients, zinc-deficient status is associated with immune system disturbances, poor nutritional status, atherosclerosis and high rates of hospitalization due to infections [16]. Conversely, improved zinc status is associated with alleviating oxidative stress, inflammation, dyslipidemia and malnutrition in dialysis patients [34].

In CKD children, since adequate nutritional status is important for normal growth and development, a careful monitoring of nutritional status is essential [6]. The Chronic Kidney Disease in Children study revealed that 7%–20% of pediatric CKD patients had protein-energy wasting (PEW) [35]. Depending on the clinical parameters used to define malnutrition, a prevalence of 20%–45% has been reported in children with CKD in various studies [36]. Malnutrition has been shown to increase the risk of morbidity and mortality in both adult and pediatric patients with CKD [37]. However, there was one single girl, who improved her obesity status (BMI from 3.5 to 2.5 SDS) after 30 mg/day for 3 months. The role of zinc dyshomeostasis in obesity was also confirmed by the results of supplementation trials. In particular, the administration of 30 mg/day zinc gluconate for 1 month resulted in a significant decrease in body weight and BMI values as well as serum triglycerides (TG) concentrations [38].

Additionally, there was another 10-year-old girl with chronic malnutrition and osteodystrophy, and CKD due to chronic interstitial nephritis, who at the beginning of the study could not walk alone and needed help to move around her house, hospital and other places. After 11 months of 30 mg/day of ZS, she improved her W/H, BMI and CRP. The most important improvement was that she could walk without help at the end of the study [39]. ZS may be the reason why this girl improved her health situation, because ZnD causes a marked reduction in circulating GH and IGF-I concentrations [40], and the administration of exogenous GH or IGF-I does not correct zinc deficiency-associated growth defects [41]. The zinc concentration is relatively high in bone, cartilage and teeth [42]. In addition to zinc’s active role in collagen formation in the epitheses, zinc ions are promoters of bone remodeling by osteoblast proliferation [43], and they contribute to extracellular matrix calcification through the synthesis of matrix proteins in osteoblasts [44].

Well-known complications of childhood CKD are a significant delay in growth and short stature [45]. Mean H/A Z-score below the lower limit of normal has been reported in most studies [46]. Even though, there was a slight decrease in cases with low H/A Z-score from 83.3% to 82.9% after ZS, this percentage continues to be high. Furthermore, 65.7% with H/A Z-score >2.5 SDS is important because short stature is associated with increased morbidity and mortality. This situation is

worrying because Wong et al. (2000) reported a 14% increase in death risk for each SDS decrease in height, in children with ESRD [47]. Moreover, poor growth has serious consequences, including hospitalization, mortality and poor quality of life [48]. Part of these issues may be due to an increased risk of infection in malnourished patients [45][46].

In spite of the nutritional status of this series, results show that the mean SZC before (75 ± 15.5 µg/dL, $p = 0.005$) and after ZS (73.5 ± 17.4 µg/dL, $p = 0.016$) were normal and differed significantly from the National Health and Nutrition Examination Survey (NHANES) 2011–2014 study (82.7 ± 0.6 µg/dL) performed in 4347 participants [49]. Nevertheless, after the 12-month supplementation with two doses of zinc, there were no significant changes in the mean SZC of the children. On the contrary, El-Shazly et al. (2015) studied this subject in 40 children between 5 and 18 years old on regular HD (mean age 13.8 ± 3.1 years), after 90 days of a daily ZS (50–100 mg zinc sulphate (equivalent to 11–22 mg elemental zinc)), according to age, sex and nutritional status of each child. They found that the mean SZC had significantly increased from 53.2 ± 8.15 µg/dL to 90.75 ± 12.2 µg/dL ($p = 0.001$) in comparison with the control group [50]. A recent randomized study by Tonelli et al. (2015) showed that low dose supplementation fails to correct low zinc status in the HD population [51].

Furthermore, Tonelli et al. demonstrated in 2009, that zinc levels were lower in the HD patient compared with controls in a meta-analysis of 128 studies [52]. Moreover, Esmaeili et al. (2019) in a group of 63 children with ESRD on regular HD (78.6 ± 21.6 µg/dL)), 45 on CAPD (74.2 ± 18.1 µg/dL) and 14 in CT (93.5 ± 16.2 µg/dL) highlighted that SZC in the group in HD was significantly lower than in the control group (91 ± 16.4 µg/dL) [53]. Youssef et al. (2012) also revealed that the SZC in children on regular HD was significantly lower than in healthy children or children with CKD in CT [54]. Similarly, Esfahani et al. (2006), pointed out that mean SZC was lower in the group of 40 patients on regular HD than in children on CT and healthy children ($p > 0.001$) [33].

This situation is also worrying because this specific dialyzed may be the reason why a zinc-deficient status is suffered by these children. Additionally, after ZS, the mean ZSC (73.5 ± 17.4 µg/dL) was normal and corresponded to 24 patients in HD, who were the only ones that completed more than 10 months of ZS. Even though the mean SZC after ZS was slightly lower than at the beginning of the study, there was not a significant difference in neither group A (from 78 to 71.9 µg/dL, $p = 0.310$) nor group B (from 77.9 to 75.4 µg/dL, $p = 0.505$). According to Thompson (1991), this decrease of SZC in both groups, despite ZS may be explained by increased avidity of depleted tissues for zinc, such as bone or muscle, or due to the disease itself [55].

In the NHANES 2011–2014 study, SZC were higher in males (84.9 ± 0.8 µg/dL) than in females (80.6 ± 0.6, $p < 0.0001$) [49]. In addition, in the NHANES 2011–2014 study there was no difference in SZC in those aged between 6 to 9-years-old (81.1 ± 1.1 µg/dL) compared with those aged ≥10-years-old (82.8 ± 0.6 µg/dL, $p = 0.59$) [49].

Henningar et al. (2019), regarding the NHANES 2011–2014 study carried out in the US, concerning the prevalence of low SZC indicated that around 4% and 8% of children and adults, respectively, have low SZC and may be at risk of ZnD [49]. Nonetheless, Roozbeh et al. (2011) pointed out CKD patients are at higher risk for ZnD, with up to 78% of HD patients being deficient [56].

According to Panel of Zinc Experts WHO/UNICEF/IAEA/IZiNCG (World Health Organization/United Nations International Children's Emergency Fund/International Atomic Energy Agency/International Zinc Nutrition Consultative Group), if more than 20% of the whole population (or population subgroup) has SZC below the cut-off point for age and sex. This population (or subgroup) should be considered at risk of zinc deficiency and a public health concern and an intervention to improve population zinc status is recommended [18][31][57]. Besides, serum zinc deficiency has been reported in CKD patients due to hypoproteinemia, tubular reabsorption impairment, proteinuria and calcitriol deficiency, which has a role in zinc intestinal absorption [58]. These facts support the idea that CKD children should receive ZS as a part of the treatment protocol.

Zinc is a micronutrient with anti-inflammatory properties [59] and ZnD is associated with a decline in the immune system [60], with increased susceptibility to infections, exaggerated inflammatory responses [59] and inflammation leading to chronicity [60]. Supplementation with zinc has reduced oxidative stress markers, inflammatory cytokines and infection incidence [59]. In a meta-analysis, Mousavi et al. (2018) displayed a significant reduction in circulating CRP levels ($p \leq 0.001$) after ZS. They concluded that SZ might have a beneficial effect on the serum CRP, especially at a dose of 50 mg/day, and in renal insufficiency adults patients compared with healthy subjects [61].

According to Expert Panel Reviews (2016), in patients with chronic malnutrition and/or acute illness in whom serum albumin is low, this should be considered as another confounding factor to interpret plasma zinc concentration (PZC), because albumin is the primary carrier protein for circulating zinc [18]. Hypoalbuminemia is common in CKD patients

associated with an increase in morbidity/mortality in both adults and children [6][62]. This situation is also worrying because Wong et al. (2002) draw attention to the fact that those patients under 18-years-old who start dialysis with hypoalbuminemia are at a higher risk of death. In 1723 children with ESRD identified through the United States Renal Data System, every 1 gr/dL fall of serum albumin at the start of dialysis was associated with a 54% higher risk of death [45][62].

Mean serum albumin was lower in ranges of hypoalbuminemia in patients in CAPD (2.9 ± 1.1 g/dL) than in HD (3.6 ± 0.6 g/dL) and in CT children (3.5 ± 0.8 g/dL; ANOVA, $p = 0.061$). Brem et al. (2002) pointed out that children maintained on CAPD were at greater risk of protein malnutrition compared with peers treated with HD. This may be due in part to losses in peritoneal dialysis fluid [63]. These results are in line with the NHANES 2011–2014 study, in which the SZC had a positive association with serum albumin ($p < 0.0001$) [49]. Moreover, hypozincemia has been reported in patients with CKD owing to hypoproteinemia, proteinuria and tubular reabsorption impairment [58][64][65]. Foote et al. (1984) drew attention to the fact that it was more likely to have SZC below the cutoff for albumin of 3.5 g/dL [66]. Furthermore, serum albumin concentrations responded to zinc supplementation in severely zinc-deficient individuals [67], although this has not been shown in marginally zinc-deficient individuals [68].

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