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The Role of Zinc in Chronic Kidney Disease Patients on Hemodialysis: A Systematic Review

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Abstract

Objective: Zinc has been studied for its antioxidant and anti-inflammatory properties and also for its immune function in end stage renal disease patients. The aim of this review is to clarify whether there is a relationship between zinc levels and ESRD patients in hemodialysis. Methodology: A search through LILACS and MEDLINE database using the keywords "zinc", "chronic kidney disease" and "hemodialysis" was performed. Articles in English and Portuguese performed in humans with the previous words were selected. Studies with subjects younger than 18 years of age were excluded. Moreover, exclusion criteria included patients with absence of diagnosis of end stage renal disease and not in hemodialysis; patients treated with peritoneal dialysis, absence of abstract available, absence of clear association between zinc deficiency and worse prognosis. Results: The search found a total of 214 articles. A total of 44 publications were selected after appliance of exclusion criteria. Conclusion: Zinc deficiency is highly prevalent, and it not only showed influence on inflammatory and immunological processes, but also interfered with metabolism and other systems. Zinc supplementation was considered positive. In summary, lower zinc levels are related to end stage renal disease patients in hemodialysis and supplementation seems to be a promising approach in such cases.

Keywords

Zinc, Chronic Kidney Disease, Hemodialysis

1. Introduction

Chronic kidney disease (CKD) is a condition highly prevalent worldwide. Although there is no reliable statistical

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information in Brazil, it is estimated that over 8 million people were suffering from CKD in the United States in the year 2000 [1] and over 400 thousand of them were undergoing hemodialysis (HD) in the year 2009 [2].

Zinc has multiple roles in the body. It is not only directly involved in the metabolism of proteins, complex carbohydrates and lipids, but also in the synthesis of nucleic acids, the gastrointestinal absorption of other elements, the bone metabolism and oxygen transportation [1] [3]-[12]. Moreover, besides being a component of neurotransmitters [3], zinc plays an essential role in the proper functioning of the immune response, both humoral and cellular.

It is a fact that 40% to 78% of individuals who suffer from CKD present low serum levels of zinc [13]. This finding may be basically explained by three different reasons: changes in this element reservoirs in the body; its decreased absorption by the gastrointestinal tract; a decrease in zinc intake, owing to the fact that dietary restrictions for these patients limit the consumption of foods richer in zinc [3] [5] [9] [14] [15]. A fourth reason for zinc deficiency in hemodialysis patients is the dialysate composition which, given the osmolarity difference, allows an abundant zinc excretion during the filtration process [12].

The main zinc reservoirs are present in tissues especially in the liver where zinc metalloenzymes are synthesized. Regarding serum zinc, it is known that 66% of it is linked to albumin whereas 8% of its total is associated with alpha-2 macroglobulin [6].

Food restrictions and the low zinc absorption by the GUT are other reasons for the resultant low levels of zinc in CKD patients [3] [4]. Only 20% - 40% of the oligo element is absorbed once the disease is established [5].

Since zinc serum levels are not routinely measured in Brazilian dialysis units, it is important to show the multiple relations between zinc deficiency, CKD and the effects of its supplementation.

The aim of this review is to find out the role of zinc serum levels in patients with CKD and in hemodialysis.

2. Methods

The current study is a review of the literature through the articles providedby the databases LILACS and MEDLINE from the beginning of their historical series to present days. The descriptors “zinc and chronic kidney disease” and “zinc and hemodialysis” were used. Inclusion criteria were limited to human studies in English and Portuguese with adult patients. Articles were excluded when: they had no abstract available; patients did not have diagnosis of CKD and were not treated with HD; patients in peritoneal dialysis. The search was carried out by two independent researchers and evaluated by a third party investigator.

Figure 1 shows the articles inclusion and exclusion flowchart according to the criteria previously established.

2.1. Role of Zinc in the Function of Body System and Its Relationship with CKD and HD

2.1.1. Chronic Kidney Disease

Chronic kidney disease patients have higher BUN levels, a condition that favors the production of reactive oxygen species (ROS) as well as inflammation [7] [8] [14] [16]-[21]. HD itself intensifies these two highly damaging processes due to the contact between the blood and the dialytic membrane, which results in an increased morbidity [7] [8] [17].

Zinc exerts a great influence on the oxidative stress in such cases. The process occurs from the formation of ROS with unpaired electrons, which may damage macromolecules in particular by interfering in the cellular membrane fluidity and in the cellular function [7] [16] [17] [22]. ROS formation occurs continuously in every organism. However, in healthy individuals these species are neutralized by endogen antioxidants.

McGrath *et al.* show that CKD patients have a decrease in glutathione levels and glutathione reductase and peroxidase activities. HD can cause an increase in ROS production and aggravate the deficit of these enzymes [7] [16]. Moreover, the superoxide dismutase (SOD) enzyme depends on the amount of ROS release to trigger its activity. Therefore, there is a higher demand for this enzyme during the treatment, and low zinc concentrations compromise the full activity of the enzyme.

Pawlak *et al.* [8] reported that the enzyme Cu/Zn-SOD is the main antioxidant mechanism in the body once it can transform the superoxide anion into hydrogen peroxide. This complex is produced by a great number of cells, including macrophages and activated monocytes, thus linking oxidative stress to the inflammatory response once again [8]. This study corroborates McGraff’s findings, which show that SOD action is reduced with zinc depletion thus increasing oxidation [7] [8]. As a result, many studies reveal that Cu/Zn-SOD gradient is an effective marker of oxidative stress for the evaluation of kidney disease progression in the long run [7] [8] [19].

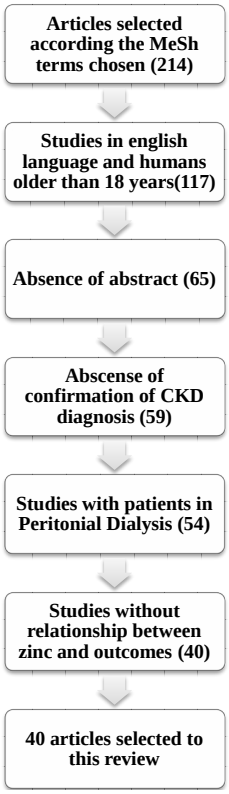

Figure 1. Inclusion/exclusion criteria flowchart.

Besides, the possibility of using synthetic analogs of Cu/Zn-SOD in the treatment of inflammatory diseases like rheumatoid arthritis is being studied, a fact that supports the importance of zinc in this kind of response [8].

Some evidences show that the increase of zinc concentrations in CKD patients on hemodialysis can reduce inflammatory markers. The reduction of pro-inflammatory cytokines, like interleukin-6 (IL-6), and the return of high levels of C-reactive protein to normal in these patients have been described in the literature [17] [20].

2.1.2. Immune System

Zinc deficiency clearly damages the immune system function with resultant abnormalities. This oligo element is connected to cellular division, especially to the lymphocyte growth and differentiation [12] [18]. The depletion of serum zinc concentrations can not only delay this process but also damage the function of all types of lymphocytes, particularly NK lymphocytes [12] [18] [22]-[25]. Other effects on immunity include thymus atrophy and inhibition of neutrophil and monocyte chemotaxis. There are evidences showing that zinc yields an improvement in the humoral response; nevertheless, further studies need to be conducted in this area [18] [22] [23].

As zinc deficiency is a known fact among CKD patients on HD, the constant evaluation of its levels is of paramount importance. Free zinc is immunologically active or, in other words, the kind that is not either bound to carriers like albumin and alpha 2-macroglobulin or found in tissue reservoirs [18]. In a study on the response to diphtheria vaccination, it was observed that non-responsive patients had an almost two-fold increase in levels of alpha 2-macroglobulin-bound zinc [18]. This molecule is capable of not only reducing the amount of free zinc, but also neutralizing cytokines, two facts that explain the obtained results.

According to Sagheb *et al.* [24], the difficulty to boost tetanus and diphtheria immune response in CKD patients on HD is a challenge once the protection rate in such individuals is much lower when compared with the general population. In addition to that, vaccine protection time is shorter in such cases [18] [23] [24]. Once again, zinc supplementation has proven to be quite promising as a mean to increase the response rate among these patients.

As to lymphocyte behavior, there are clear evidences of a decrease in lymphocyte levels related to zinc depletion. A sharp reduction in CD3 and CD4 percentage in hypozincemic patients on HD could be observed when

compared with patients on peritoneal dialysis under the same conditions [26]. The study that investigated this difference raises the hypothesis that it may be difficult to restore lymphocyte count in patients on HD, reinforcing the importance of understanding the use of the oligo element in the CKD therapeutic management. The same study shows the influence of low zinc concentration on the down-regulation of Th1 cytokine receptors, a fact that also contributes to a decreased immunological response [22].

The higher susceptibility to infections in hemodialysis patients has also been investigated. In their article, Cristopoulos *et al.* described how hard it is to diagnose tuberculosis in these patients given their immunological alterations. This difficulty can partially be explained by the fact that due to decreased zinc concentration, CKD patients are usually unresponsive to the classic tuberculin skin testing [23]. Another study with skin testing reactions reveals that zinc supplementation, when orally administered and normal blood levels are reached, can change this scenario by making these patients become more responsive to this sort of test [18]. Tuberculosis in CKD patients on HD is silent with non-specific symptoms, characteristics that are also related to immune system alterations [22].

Another interesting fact that relates zinc levels to the immune system is the itchy sensation caused by zinc deficiency, a very common complaint among patients on HD. Although the mechanism through which this sensation is triggered is not fully understood yet, it is believed that the histamine release mediated by this oligo element holds the key to this question. As stated in a study by Najafabadi *et al.*, hypozincemia can increase the number of itching complaints, and oral replacement significantly reduces the discomfort [25].

In an observational prospective study which followed up patients over a two-year period, it was revealed that whenever there was a decrease of 1 mg/dL of zinc in serum, there was a 2% increase in the infection hospitalization rate and a 2.8% increase in the mortality rate during this period of time [30]. Therefore, whether owing to the difficulties met in vaccination responses, in the commitment of the immune response against an antigen or in the establishment of an early diagnosis, there is a clear relation between low zinc concentrations and the immune inefficacy in these patients [26].

2.2. Role of Zinc in Metabolism

Some important metabolic alterations occur in chronic kidney disease patients. Just like in the other systems mentioned before, hemodialysis and low zinc concentrations help intensify such changes. It is, however, difficult to associate specific metabolic parameters with the deficiency of oligo elements in this group of patients [27].

The results obtained in a great part of the conducted studies are directly compromised by the alterations inherent to the disease and the treatment and by the fact that these patients rely on multiple drugs [5] [11] [16] [17] [27]-[29]. Nevertheless, a serious investigation on some tissues that suffer more functional alterations can be conducted.

Fat tissue has an acknowledged endocrine function [4] [11] [28] [29]. Adipocytes influence on glucose homeostasis, energy expenditure, insulin action and lipid consumption through the production of bioactive peptides, also known as adipokines [11]. Therefore, alterations in the adipose tissue and insulin resistance are closely related. In their study, Sörensen-Zender *et al.* describe the role of zinc-alpha-2-glycoprotein (ZAG, a protein encoded by the AZGP-1 gene), which is secreted by adipocytes and other cells in CKD patients. The researchers show that AZGP-1, an enzyme excreted by the kidneys, is associated not only with the protection to insulin resistance but also with the increase in BMI and triglycerides. With renal failure, a concentration increase of AZGP-1 was observed, which may significantly influence on mortality rates among CKD patients with cardiovascular problems related to metabolic syndrome and diabetes mellitus.

Following the same research line, another article reveals that an increase in the ZAG activity can be explained by both the low clearance of this enzyme due to renal failure and protein degradation [29]. Also, despite conflicts in the literature, there are evidences that the increase in ZAG expression is related to rapid insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and leptin levels [11].

It is important to consider the fact that there is an overlap of contributing factors that lead to anorexia and muscular mass loss in CKD patients on HD. The process may be explained by the relation between zinc and serum concentrations of leptin. In patients on hemodialysis there is an increase in leptin concentrations due to its decreased renal excretion. Moreover, protein-calorie malnutrition is a common complication in HD patients and debilitation is a common effect these individuals, who often have negative nitrogen balance and decreased mus-

cular mass, with a resultant increase in the mortality rate associated with the management of the disease [4] [5].

2.3. Relationship between Zinc and Other Diseases

2.3.1. Hematopoietic System

In HD patients there is a reduction in the iron absorption capacity, limiting the action of EPO to the available iron reservoirs in the body, and thus resulting in the anemic condition observed [9] [30] [31]. Another factor that explains the presence of anemia is the difficulty in the synthesis of some apolipoproteins due to zinc deficiency in this population. According to Chevalier *et al.*, hypozincemia hinders the synthesis of intestinal apolipoprotein B-48, triggering an anemia condition and the development of neurologic degeneration [9]. In this scenario, patients constantly complain about fatigue and dyspnea among other adverse effects caused by the condition. They also present depression symptoms and behavioral alterations due to the harm induced in the central nervous system.

In order to manage the condition, some strategies like the administration of recombinant erythropoietin have been proposed. However, the response obtained from endogenous EPO or from the administration of recombinant EPO depends on iron bioavailability, which involves the adequate synthesis of iron carrier protein [30].

Hosokawa *et al.* described the great beneficial effects of this substance administration over a period of two years. As related by the authors, the effects of recombinant EPO, with its action all over the body, surpasses the effects of erythropoiesis. An increase in serum protein levels was observed, suggesting an anabolic effect. In addition to that, the treatment was also effective in restoring serum zinc levels close to normal [32]. Another article shows the benefits of the zinc administration in parallel with recombinant EPO therapy. It reveals that zinc could significantly improve hemoglobin production with an undesirable decrease in reticulocytes [31]. Surprisingly, such decrease can simply be reverted with the administration of iron sulphate. Zinc is, therefore, an economic choice to reduce the use of recombinant EPO in CKD patients on hemodialysis.

A delicate matter regarding this system involves zinc supplementation. Although the reviewed studies conclude that zinc may bring beneficial effects, this oligo element can also induce anemia when administered in excess [8] [9] [15] [30]-[32]. This can be explained by the relation between the absorption of copper and zinc once they are both absorbed in the stomach and proximal duodenum and they compete with each other for the binding to metallo-thionein. As a result, the excess of zinc can upregulatemetallothionein, increasing the copper-binding to this molecule and reducing its absorption in the gastrointestinal tract. Therefore, hypocupemia represents a series of impacting conditions for patients, such as myelopathies, polyneuropathies, demyelination and anemia [15].

2.3.2. Alzheimer and CKD

The physiopathology of Alzheimer's disease, a very prevalent neurological condition that culminates in severe memory and cognition deficits, is characterized by the deposition of β/Aβ amyloid complexes along with increased levels of Ab peptides in the brain. One of the goals in the management of the disease is to reduce Ab peptide levels in order to prevent further deposition and the resultant disease aggravation.

In their study, Rubio *et al.* hypothesized that hemodialysis might help in this peptide clearance, thus justifying the low incidence of Alzheimer's dementia among CKD patients on HD. The researchers also tested the relation between Aβ peptides and the oligo elements Zn and Cu, which might alter their deposition capacity. Results showed that Zn and Cu levels were not apparently altered, and thus it is not possible to assert that there is a direct association with the depositions. However, the hemodialysis procedure itself proved to decrease the peptide plasma levels in up to 30%, probably reflecting on its levels in the brain and therefore justifying the lower rates of Alzheimer's in this population [33].

2.3.3. Erectile Disfunction

Jalaliet alstudied the role played by zinc in sexual impotence reported by male patients, particularly concerning the relation between this element and hormone production. Zinc is related to prostate, epididymal and testicular functions, and it affects the production of testosterone and luteinizing hormone. Nevertheless, an increase in follicle-stimulating hormone and prolactin levels could not be observed as zinc levels increased [34].

2.3.4. Cardiovascular Disease

Despite the fact that dyslipidemia is present in these patients, the increase in inflammatory reactions and oxidative

stress facilitate atherogenesis, including these individuals in the risk group for cardiovascular diseases [13] [14] [35]. It is important to point out that classic indicators like gender, age and smoking are less important in these individuals, and they make way for parathyroid malfunction, hyperhomocysteinemia, dialytic inadequacy, malnutrition and altered homeostasis of calcium and phosphates [35]. Therefore, many enzymes have been studied along with their behavior in the event of zinc deficiency in chronic kidney disease cases.

Rahumi-Ardabiliet al investigated the action of a calcium-dependant esterase (serum paraoxonase-PON) with zinc. PON is synthesized in the liver and, besides hydrolyzing specific lipids, it prevents the inflammatory response of arterial cells. Moreover, PON increases cholesterol efflux capacity of macrophages by means of HDL. The conclusion is that an increase in PON activity has gradually been associated with a decrease in the incidence of cardiovascular diseases.

The study results revealed that CKD patients on HD had lower levels of PON than patients from the control group. Another important finding is that in CKD there is a genetic polymorphism related to the enzyme. The association between uremia and dysmetabolic conditions contributes to the decrease in the action of PON, which, as mentioned before, has lower concentration levels. Zinc supplementation proved to stimulate PON activity in patients with renal failure, although this event does not seem to be related to metalloenzymes [14].

Ari *et al.* confirmed that copper and zinc levels are directly related to the thickness of the medial and intimal layers of the artery, a fact that once again shows the importance of this oligo element in the morbimortality control associated with CKD [35].

2.3.5. Zinc Supplementation

Zinc supplementation has been proposed as a viable alternative not only to reduce a series of complications in the etiology of CKD but also in the management of HD adverse effects. Few harmful effects of zinc replacement have been reported, even when its levels are above normal [1]. The major risk is posed by the decrease in copper concentration, a contributor to the onset of anemia among other repercussions. Zinc offers a decrease in the oxidative stress and the inflammatory response [7] [8] [14] [16] [19]-[22], the intensification of the immune response, especially with regard to vaccine immunization [18] [22]-[24], a metabolic improvement [4] [5] [11] [16] [27]-[29], a decrease in cardiovascular diseases [6] [13] [14] [35] and an increase in sexual hormones and paratormone [31]-[34]. Zinc can still interfere with erythropoiesis and the neurologic function [8] [9] [15] [30]-[33].

Regarding posology, the recommended dose ranges from 1.5 to 7.7 mmol a day or 1 mg/kg/day. Absorption is decreased in oral intake going from the dietary 40% - 90% to the supplementary 8% - 38% [1]. Nevertheless, this route of administration is still preferred to the intravenous form or through the dialysate fluid. Intravenous supplementation is limited due to the fact it can cause hyperproteinemia with a series of clinical manifestations [5].

On the other hand, the difficulty to establish a uniform mathematical model that indicates a satisfactory zinc status that allows for its osmotic passage through the dialysate makes this route rather empiric and confirms the oral supplementation as the route of choice [12].

2.3.6. Impact on the Quality of Life

As described by Raimundo *et al.*, around 47% of individuals who suffer from hypozincemia reported an overall compromised health status. The same study also revealed a reduction of 35% in the quality of life of patients who had lower serum levels of zinc, iron and vitamin B [36].

A countless number of benefits attributed to oral zinc supplementation were mentioned throughout this study, and the improvement brought to dialytic patients by this approach is quite clear. After all, reducing side effects like itching and sexual dysfunction positively affects these patients in their daily activities.

Besides, other indirect benefits like cardiovascular risk decrease, reduction in systemic inflammation and improvement in the immune profile also represent enhancement in quality of life in the long run since they help decrease mortality rates among these patients [37]-[40].

Depression is a condition that affects patients on HD and some studies correlate it to zinc deficiency [37]-[40]. Factors like the continuous period on hemodialysis and unemployment due to CKD are among the major causes that trigger depression in this population [39].

This study has some limitations. As a review it does not address any data about the issue; however it enlightens an important issue in the routine of dialysis patients. Many of the studies chosen for this review are not randomized and have small samples but this did not represent an exclusion criterion because the majority of the

data regarding zinc levels are observational.

3. Conclusion

In conclusion, the current review showed the role of zinc throughout the body systems and its relationship with CKD and HD. Its importance in these patients opens an extensive field of research to be explored owing to its beneficial effects in the control of comorbidities frequently related to these individuals as anemia, oxidative stress, immune modulation and inflammation related comorbidities in CKD individuals.

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