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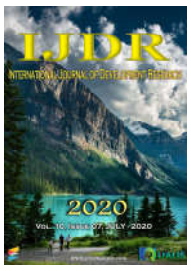

RESEARCH ARTICLE OPEN ACCESS

THE ROLE OF SELENIUM IN THE PROTECTION AGAINST OXIDATIVE STRESS IN PATIENTS WITH CHRONIC RENAL DISEASE

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ABSTRACT

Studies have shown the participation of minerals, such as selenium, involved in the antioxidant defense of patients with chronic kidney disease. Therefore, the purpose of this review is to provide data on nutrient participation in the control of the antioxidant defense system in individual's withchronic renal disease. A search of articles published in the PubMed and ScienceDirect database selected from March 2017 to February 2019 was performed using the keywords Selenium, Selenium supplementation, Oxidative stress, Antioxidant and Chronic Kidney Disease. Following the eligibility criteria, 39 articles were selected. The scientific evidence presented in this review shows the importance of selenium as an antioxidant for the reduction of oxidative stress in renal patients, thus, thesupplementation of this mineral can result in the reduction of oxidative stress, through your involvement in selenoprotein and GPx, inhibiting the production of reactive oxygen species; however, the efficacy of the intervention with selenium supplementation is still inconclusive.

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INTRODUÇÃO

Chronic kidney disease (CKD) is a multifactorial disease characterized by progressive and irreversible loss of renal function, which should be diagnosed and treated as early as possible in order to delay its progression, reduce mortality and metabolic disorders, such as cardiovascular diseases and diabetes mellitus(Chen, Yang, Hsiao, Huang and Huang, 2016; Rocha, Magalhães and Lima, 2010). According to the Brazilian Society of Nephrology (SBN, 2018), a total of 126,583 patients undergoing renal replacement therapy were counted until 2017, of which 90.1% underwent hemodialysis and 9.9% underwent peritoneal dialysis(Marinho, Penha, Silva and Galvão, 2017). It is worth mentioning that the disease induces modifications in the immunoglobulins and complement system, activating granulocytes and increasing the production of free radicals, with consequent depletion of antioxidants(Omrani, Golmohamadi, Pasdar, Jasemi and Almasi, 2016). In situations of imbalance between antioxidant defense and excess of free radicals, renal overload is established, which may contribute to the progression of CKD (Chen *et al.,* 2016). In this sense, it is opportune to mention the participation of nutrients with antioxidant action, such as vitamins and minerals that act in the prevention and deceleration of CKD. Selenium, in particular, is a mineral well studied for having antioxidant function, being cofactor of the enzyme glutathione peroxidase, and having anti-inflammatory activity. However, the status of selenium may be compromised in this disease due to: inefficient binding with its transport proteins; increased losses through urine and dialysis; low food intake and intestinal absorption (Stockler-Pinto *et al.,* 2014). Selenium at adequate concentrations helps in neutralizing ROS and preventing the development of inflammation in individuals

(Cominneti, Bortoli, Abdalla and Cozzolino, 2011; Kaushal, Hegde, Lumadue, Paulson and Prabhu, 2011). Selenium deficiency may contribute to increased oxidative damage by interfering with the synthesis of selenoproteins that have antioxidant action, such as glutathione peroxidase (GPx) and selenoprotein P (SepP). Therefore, considering the probable selenium deficiency in CKD, the performance of this mineral in the protection of the oxidative damage and the probable progression this isfrom the exhaustion of the antioxidant defense system, the objective of this review was to elucidate data on the participation of the nutrient in the control of the antioxidant defense system in individuals with CKD.

METHODOLOGY

This study is a narrative review based on a bibliographic survey of articles in the PubMed and ScienceDirect databases, with no limit to the year of publication, selected from March 2017 to February 2018. The keywords used for the research were Selenium, Selenium supplementation, Oxidative stress, Antioxidant and Chronic Kidney Disease. The descriptors were used alone or in combination using the AND and OR operators. This review included experimental studies, clinical trials, cross-sectional studies, case-control studies with relevant information about selenium and its relation with oxidative stress in renal patients, in the idioma English and Portuguese. The selection of articles was based on originality and relevance, preferring classic works and more recent articles. Dissertations, theses, articles not available in full and / or duplicates in different databases were excluded. Then, the articles included were analyzed by means of the reading of the titles, followed by summaries and, later, the complete text. At all stages, exclusion criteria were applied in consensus with the reviewers. At the end of the research, 39 articles were selected.

Chronic Renal Disease and Hemodialysis: The kidneys are responsible for the excretion of metabolic degradation products, produced by nitrogen metabolism (uric acid, urea, sulfates and phosphates), by the production, catabolism and regulation of hormones (Brasil, 2014). It is therefore emphasized that the main mechanisms used to maintain extracellular volume (sodium and water balance), ionic composition (calcium, phosphorus, sodium, chlorine, potassium, magnesium), acid-base balance (excretion of non-volatile acids and recovery of bicarbonate), long-term regulation of systemic blood pressure, maintenance and regulation of metabolic processes (gluconeogenesis, lipid metabolism), are performed through the control of chemical balance performed by the kidneys (Cuppari, Avesani, Mendonça, Martini and Monte, 2014). The progressive and irreversible loss of kidney function, which may occur after acute renal failure or as a complication of some other disease can lead to the emergence of Chronic Kidney Disease (CKD). This disease is not curable, but, if it discovered early, its progression can be delayed, avoiding complications, higher health costs, as well as increased cardiovascular morbidity(R. M. R. Bastos, Bastos, Ribeiro, Bastos and Teixeira, 2009; Piccolli, Nascimento and Riella, 2017; Riella and Martins, 2013). According to the National Kidney Foundation (NKF)(National Kidney Foundation, 2002), the definition of CKD is based on two independent criteria: (1) renal damage for more than three months, as determined by functional or structural abnormalities of the kidney, with or without a decrease in the Glomerular Filtration Rate , or (2) glomerular filtration rateless than 60mL/min/1.73m2 of body surface area for a period greater than or equal to three months. The DRC is divided into six functional stages and according to these, it is verified the severity of the signs and symptoms, which can indicate changes in the anatomy and renal physiology (M. G. Bastos and Kirsztajn, 2011). The incidence of CKD is increasing and today it is a major public health problem worldwide, with systemic arterial hypertension and diabetes mellitus as its main causes; therefore, it is urgent to control these diseases in order to delay progression to renal disease and prevent patients from developing into death or substitutive renal therapy (SBN, 2018). In the final stages of the disease, the symptoms are increasing and according to the glomerular filtration rate is indicated the substitutive renal therapy, which includes hemodialysis (HD), peritoneal dialysis (PD) and renal transplantation, aiming at the proper removal of the products of metabolic degradation. The indications for the initiation of substitutive renal therapymay be urgent or elective (Moura Neto *et al.,* 2014). The main factors that indicate their need are hyperphosphatemia, hyperkalaemia, azotemia, inappetence and weight loss, resistant to conservative treatment(National Kidney Foundation, 2002; O'Sullivan, Lawson, Chan and Kelly, 2002).The national estimate of the prevalence of chronic renal failure on dialysis was 610 patients per million people (pmp), and the incidence was 193 pmp. When sectorized by region, the prevalence of the Northeast region is close to the national average of 518 pmp (SBN, 2018). The prevalence rate of patients in renal replacement therapy is 1,750 pmp in the USA and 1,000 pmp in countries of Europe, Chile and Uruguay (Brasil, 2014). Since the 1960s, HD has become one of the most common TRS in Brazil. However, this procedure does not exclude the risks of morbidity and mortality, although it may help with the survival of the CKDpatient (Oliveira, Amorim and Felizardo, 2014). The procedure consists in the passage of blood through a semipermeable membrane of the artificial kidney, aiming at the diffusion of end products of metabolism and ultrafiltration of liquids (Terra *et al.,* 2010). The HD result in several nutritional changes, such as: loss of proteins in the SRT process, muscle loss, deficient intake of nutrients/foods such as selenium, inflammation, anorexia, oxidative stress, endocrine disorders and acid-base balance (Velludo *et al.,* 2007).

Oxidative Stress, Renal Disease and Selenium: Oxidative stress was defined by Sies(1993) as the imbalance between oxidants and antioxidants, favoring oxidants (free radicals). These molecules contain oxygen with an unpaired electron, being unstable and reactive, seeking to connect to other electrons that are in close structures, known as: acceptors (oxidants) or donors (reducers) of electrons (Halliwell and Gutteridge, 2015; Valko, Rhodes, Moncol, Izakovic and Mazur, 2006). The production of reactive oxygen species (ROS) occurs mainly through aerobic metabolism. In the healthy organism, the balance between ROS production and antioxidant defenses is maintained. Protection against these effects can be through prevention, interception and repair (Sies, 1993). According toHalliwell and Gutteridge (Halliwell and Gutteridge, 2015), antioxidant is "any substance that, when present in low concentrations compared to that of an oxidizable substrate, significantly delays or inhibits the oxidation of that substrate." The antioxidant defense system is responsible for reducing damage caused by EROs and reactive nitrogen species (ERNs), through enzymatic mechanisms, consisting of enzymes such as: glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), which are dependent on selenium, zinc/copper and iron, respectively

(Omrani *et al.,* 2016; Sies, 1993), and non-enzymatic, these being, enzymes (proteins) or nutrients (vitamins and minerals) (Kumar, Sharma and Vasudeva, 2017). Increased oxidative stress occurs due to high concentrations of ROS and ERNs, and depletion of the antioxidant defense system, resulting in the development of abnormalities of endothelial function and subclinical atherosclerosis, as well as pathophysiological dysfunctions in patients with CKD. It is common for cardiovascular outcomes, especially in the presence of disordered oxidative and glyco-oxidative chemotherapy and deleterious effects with alterations in the biological structures and/or function (Barbosa *et al.,* 2008; Ceballos-Picot *et al.,* 1996; Yildirim *et al.,* 2017).

Chronic kidney disease may be associated with oxidative stress, as evidenced by the decrease in antioxidant capacity, which is associated with a loss of renal function or an increase in the production of ROS, with elevation of the markers of this metabolic derangement (Cachofeiro *et al.,* 2008). The oxidative stress can be aggravated due to factors related to uremia, hemodialysis (Kao, Ang, Pall and Struthers, 2009; Kuo and Tarng, 2010) and to aging, such as: advanced age, presence of diabetes, and excessive parenteral iron administration. In addition, the antioxidant defense system is impaired by the reduction of vitamin C and E levels, glutathione system(Bossola & Tazza, 2015; Ceballos-Picot *et al*., 1996; Sárközy *et al.,* 2018; Tonelli *et al.,* 2009). The increase of oxidative stress and reduction of antioxidant defense in chronic renal patients is related to the decline of renal function(Johnson-Davis *et al*., 2011). Sedighi, Zargari, and Varshi(2014) point out an association between oxidative stress and the production of reactive oxygen species, leading to progression of CKD, through changes in the plasma concentrationsof some trace elements, such as selenium, copper and zinc. Selenium exerts beneficial effects on health, such as immune competence and improvement of reproductive capacity, as well as having cardio and neuroprotective properties and cancer prevention (Fairweather-Tait *et al.,* 2011). The antioxidant function of seleniumis related to selenoproteins, especially selenoprotein P and its GPx-dependent, they protect membrane lipids and other cellular and extracellular components against oxidative damage (Zoidis, Seremelis, Kontopoulos and Danezis, 2018).

The bioavailability of selenium depends on a number of factors, such as: amount of the micronutrientingested and its origin; ingestion of other nutrients; deficiency of their digestion; formation of absorbable compounds of mineral; intestinal transit time; presence of diseases of the gastrointestinal tract; and nutritional status relative to mineral. It is emphasized that the limiting period is the conversion of the nutrient to the biologically active form, not necessarily the absorption (Martens, Martens and Cozzolino, 2016). Studies have shown that, in renal patients, serum and erythrocyte concentrations of selenium are reduced, as there is a lower activity of GPx due to increased lipid peroxidation(Liakopoulos, Roumeliotis, Gorny, Dounousi and Mertens, 2017; Rucker, Thadhani and Tonelli, 2010). The synergistic effects of superoxide dismutase (SOD) and glutathione peroxidase (GPx), suppose that selenium deficiency interferes with SOD activity, implying the reduction of the dismutation of the superoxide radical (O^{2-}) in a less damaging form to the cells, (H^2O^2), then eliminated by catalases, GPx and peroxidases linked to thioredoxin (Barreiros, David and David, 2006; Silva and Marreiro, 2012). Reduced levels of selenium can also contribute to endothelial dysfunction, alter coronary flow and promote accelerated atherosclerosis(Atakan et al., 2013). The reduction of antioxidant defense in patients undergoing dialysis therapy seems to occur through the reduction of antioxidant enzymes, such as GPx, SOD and increased levels of MDA(Johnson-Davis *et al.,* 2011; Montazerifar, Hashemi, Karajubani, Sanadgol and Dikshit, 2012; Salehi *et al.,* 2012; B A Zachara, Gromadzinska, Wasowicz, Swiech and Zbrog, 2014; Bronislaw A Zachara *et al.,* 2004).

Plasma concentrations of GPx depend largely on renal function(Nishioka, Kanauchi and Dohi, 2001), since it of this enzyme is mainly synthesized in the kidney and in less quantity in the liver, lung, heart, breast, intestine, brain, skeletal muscle and placenta (Avissar *et al.,* 1994; Chu, Esworthy, Doroshow, Doan and Liu, 1992). Ceballos-Picot *et al.*(Ceballos-Picot *et al.,* 1996), Yoshimura *et al.* (Yoshimura *et al.,* 1996), and Zachara *et al.*(Bronisław A Zachara, Gromadzińska, Wasowicz and Zbróg, 2006) have shown that the plasma activity of GPx in chronic renal patients decreases with the progression of the disease. Studies involving selenium supplementation in chronic renal patients undergoing dialysis are scarce and controversial, since the forms and metabolism of mineral and the pathophysiological responses depend not only on the total intake of selenium, but also on the bioavailability of the nutrient and of the conditions associated with increased oxidative stress or inflammation(Stockler-Pinto, Mafra, Farage, Boaventura, & Cozzolino, 2010). The antioxidant and anti-inflammatory properties of selenium in hemodialysis patients present beneficial effects when associated with mineral supplementation on nutritional status, as an improvement in nutritional status, attributable to its effects on digestion and fat absorption, nutrient utilization for improve the synergy of protection and its effects on insulin (Salehi *et al.,* 2012). Stockler-Pinto *et al.*(2010)observed positive results with selenium supplementation improving their status and antioxidant activity of chronic renal patients. These authors recommend the consumption of one unit of Brazilian nuts per day in order to improve the nutritional status of selenium, since Brazilian nuts present a lower risk of toxicity compared to supplemented products, besides being naturally from Brazil and have a high Se content, being the richest known food source.

However, this study has limitations because the activity of GPx, the only enzyme evaluated as an antioxidant defense parameter, achieves a plateau effect when the selenium concentrations reach its recommendation, and it would still be convenient to analyze the selenium content present in the foods most commonly consumed in Brazil due to changes in soil mineral content. Impaired renal function could have its antioxidant effects increased with the administration of selenium, through diet or supplementation, aiming to increase plasma concentrations antioxidant enzymes (GPx, SOD), immunostimulatory properties and cardioprotection. Intervention studies with antioxidant supplementation continue to be pertinent in order to evaluate disease prevention or deceleration; they are still inconclusive due to the differences in nutrient metabolism between genders due to the endogenous antioxidant status and external factors that may exert influence in the results, such as: smoking, use of alcoholic beverages, supplementation (duration and doses), antioxidant cocktail or isolated use of antioxidants, dietary intake(Wang, Chun, & Song, 2013).

Final considerations

Increased serum, erythrocyte and lymphocyte concentrations levels of selenium in CKD patients can improve the activity of antioxidant enzymes and, consequently, reduce the effects of oxidative stress, enhancing the mechanisms of cardiovascular protection, immune system modulationand inflammatory. The beneficial effects of selenium on this population are unquestionable, so further research on representative samples is needed to elucidate the protective mechanisms exerted by of this mineralon the antioxidant status of these patients and to slow the progression of CKD.

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