Silva et al. Int J Pathol Clin Res 2016, 2:029
Volume 2 | Issue 1
ISSN: 2469-5807

International Journal of
Pathology and Clinical Research

Mini Review: Open Access

Micronutrients Deficiencies in Rheumatoid Arthritis Patients

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves synovial joints and affects up to2% of adults worldwide. Poor nutrient status in RA patients has been reported and some drug therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed to alleviate RA symptoms, may increase the requirement for some nutrients and reduce their absorption. The importance of micronutrients in this disease is related to their cofactor role in immune system functions and in different metabolic processes in articular tissues. Dietary interventions can assist with the management of disease symptoms that accompany RA, such as pain, tender swollen joints, stiffness, and associated disability and disease progression. This paper reviews the scientific evidence for the role of diet and nutrient supplementation in the management of RA, by alleviating symptoms or decreasing progression of the disease.

Keywords

Micronutrients, Nutrition, Nutritional status, Rheumatoid arthritis, Selenium, Zinc, Calcium, Vitamin D

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology characterized by a symmetrical polyarticular inflammation of synovial membrane that affects most often the joints of the hands, wrists and feet. The localized and systemic inflammation can result in a progressive joint damage causing bone and cartilage degradation, until the loss of function. The RA occurs in all ethnicities, with slight variations and has a higher rate among women than men at a ratio of 3:1 [1-3]. The diagnosis is made based on the criteria established by the American College of Rheumatology (ACR) involving clinical, laboratory and radiographic assessments [4].

In relation to the nutritional status of these patients, observational studies have been reported a low energy intake from carbohydrates, high consumption of fat and a diet low in micronutrients [5]. The reduction of calorie intake in the case of patients with RA can also be associated with disease-related symptoms such as loss of motor function, fatigue, and pain, which in turn can interfere with the purchase, preparation and consumption of food. Furthermore, adverse reactions such as nausea, dyspepsia and change in taste caused by drug therapy, may also influence the decrease in calorie intake and, consequently, vitamins and minerals [6].

Studies addressing micronutrient deficiency in patients with RA are scarce. Thus, this short review has focused particularly on four important micronutrients in this disease: zinc, selenium, calcium and vitamin D.

Zinc

Although the pathophysiological basis of RA is not fully understood, studies show an important role of oxidative stress in this disease. Excessive production of reactive oxygen species (ROS) may be caused, for example, in response to an inflammatory stimulus, the presence of phagocytic leukocytes and inflammatory cytokines that stimulate the production of superoxide and hydroxyl radicals, highly reactive generated during phagocytosis by macrophages and neutrophils. Furthermore, the presence of ischemia and reperfusion during the performance of joint movement also contributes to the production of free radicals that act as mediators of tissue damage in RA [7-9]. The mineral zinc is important in human nutrition since it plays an important role as an antioxidant, by participating as a cofactor in the structure of superoxide dismutase (SOD), as well as in the inflammation, by inhibiting the activation pathway of NF-kB and reducing the production of pro-inflammatory cytokines [10,11]. In RA patients, in addition to these functions, some studies *in vitro* have been shown that this mineral can stimulate bone formation and inhibit osteoclastic activity [12]. The assessment of human nutritional status of zinc is made not only by evaluation of food consumption, but also through blood biomarkers.

Studies that have evaluated zinc intake in patients with RA are scarce in the literature, but they show that the dietary intake of this mineral is usually low [13,14]. The tools available for assessment of food consumption have flaws inherent to various factors that may hinder the collection of reliable data. However, the science of nutrition is improving more and more not only the question of the methodology of those instruments, but also encompassing the behavioral aspects, that is, considering the lifestyle of individuals and certain populations [15]. The lack of data on food consumption, especially of micronutrients, makes it difficult not only the investigation of the intake of these nutrients, but also the appropriate nutritional guidance to be made aiming the improvement of the nutritional status and the quality of life of these patients.

The zinc concentration in plasma is the biomarker indicated by the WHO/UNICEF/IAE/IZiNCG and the most widely used to assess the nutritional status of populations [16]. According to this parameter,

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Citation: Silva GB, Reis BZ, Cozzolino SMF (2016) Micronutrients Deficiencies in Rheumatoid Arthritis Patients. Int J Pathol Clin Res 2:029

Received: December 24, 2015: **Accepted:** February 26, 2016: **Published:** February 29, 2016

RA patients have low concentrations of plasma zinc [13,17-19]. These results can be explained by the fact that inflammatory cytokines involved in the pathogenesis of RA inhibit albumin synthesis in the liver, decreasing mineral binding capacity and its distribution to other tissues. Albumin is the main zinc binding protein (90%) in plasma [20]. Animal studies showed that during the inflammatory process there is a redistribution of zinc to the liver. This mechanism appears to be associated with a high mineral pool attached to metallothionein protein that acts in the metabolic regulation of metals. In obesity, for example, the production of inflammatory cytokines stimulates zinc carriers synthesis compromising the bioavailability of this element to the needs of the body of these individuals [21,22].

Other studies have assessed the zinc status using as a biomarker the serum, and these authors also found low concentrations of this mineral [18,23,24]. The pharmacological treatment can also influence in serum zinc concentrations. Önalet al. [25] observed significantly reduced serum zinc in 32 patients with RA compared to controls. Among the medications, the use of methotrexate increased serum zinc levels, but these patients were still deficient. The treatment with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and chloroquine did not affect serum concentrations of this mineral.

The concentration of zinc in erythrocytes is a biomarker that reflects the long-term changes in the nutritional status of this mineral since the half-life of erythrocytes is 120 days and it is not widely used in scientific studies. The studies using this biomarker are still controversial. Tuncer et al. [18] found significantly high levels ($p < 0.001$) of erythrocyte zinc in patients with RA compared with a control group, whereas Mierzek et al. [26] observed low concentrations, but with no significant difference between the groups.

In relation to the SOD activity, enzyme that depends on copper and zinc atoms so that it can perform its function as an antioxidant, there are a lot of data in the literature, but also with controversies. Karatas et al. [27] observed a significantly lower activity of SOD ($p < 0.005$) in patients diagnosed with RA than in control group. As described above, patients with RA have a low intake of zinc, decreasing the amount of substrate so that the enzyme cannot perform its normal activity. The decrease in SOD activity may indicate a process of enzyme degradation by ROS during the detoxification process [28]. Taysiet al. [29] observed a significantly higher activity ($p < 0.001$) of this enzyme. The exacerbated production of ROS in inflammatory processes makes the enzyme have a higher activity, acting as a compensatory mechanism to eliminate these compounds [18].

The effects of zinc supplementation in patients with RA need to be further studied, since data in the literature are still very scarce. It is also important to evaluate the effects of this supplementation on the bioavailability of other nutrients which may be consumed also as a supplement such as calcium. From the results of these studies will be possible to evaluate the most effective form of supplementation to these patients considering all aspects of the disease and the influence of drug therapy.

Selenium

Selenium is an essential micronutrient for the human health and exerts its biological functions as the amino acid selenocysteine (Sec) by means of selenoproteins. In mammalian, twenty five selenoproteins have been characterized, among which are the glutathione peroxidase (GPx), the thioredoxin reductases (TR), the iodothyronin deiodinases (IDI), the selenophosphate synthase2 (SPS2), selenoprotein P, (SePP), among others [30,31]. This mineral has several functions in human body, among them the anti-inflammatory and antioxidant. Selenium may act on the inflammatory response by inhibiting NF-kB cascade, reducing the production of inflammatory mediators, or even in immune cells, mainly in macrophages signal transduction pathways [32,33]. The antioxidant role of this micronutrient is assigned to its participation as an essential component of GPx enzyme [34].

The concentration of selenium in foods varies according to its content in soils and the plant's ability to absorb this element [35]. In consequence, the intake of this micronutrient by the population of different regions can vary widely. The scarcity of data regarding the assessment of dietary intake of selenium can be attributed to a lack of data on the concentration of this mineral in food. Because of the great variation in the concentration of this element in the soil of different regions of the world, the ideal would be that each country had its own food composition table, avoiding overestimating or underestimating the consumption of selenium by the population. The main food source of this mineral is the Brazil nut. The nutritional status of selenium can be assessed by measuring its concentration in the blood (plasma, serum and erythrocytes) or by evaluation of selenoproteins as GPx, SePP among others. Low selenium concentrations were observed in plasma, erythrocytes, leukocytes and synovial fluid of patients with RA [36-39]. Pemberton et al. [40] showed that these patients had low plasma selenium concentration when compared with the control group, and an increase of the lipid peroxidation marker (8-isoprostane), C-reactive protein (CRP), interleukin-6 (IL-6) and adhesion molecules(E-selectin and VCAM).

In case of selenium, the pharmacological treatment as the use of methotrexate, corticosteroids, NSAIDs and chloroquine do not seems to alter the concentration of this mineral [25]. Drug therapy is the main treatment of RA and with the development of new drugs, it is important that further studies be conducted to evaluate the drug-nutrient interaction. These data are essential to establish an appropriate nutritional therapy considering the bioavailability aspects of nutrients, particularly the micronutrients.

As an antioxidant mineral, the assessment of the GPx activity has been evaluated in several studies. Karatas et al. [24] observed that the GPx activity was significantly lower in patients with RA compared to controls. The same result were also found by other authors [8,28,29,41]. Staron et al. [42], in turn, did not observed significant difference in GPx activity between RA patients and the control group. Selenium regulates the activity of GPx *in vivo* and thus controls the intracellular levels of ROS. Increased expression of the GPx reduces ROS levels by inhibiting the phosphorylation of IκB-α, preventing the translocation of NF-kB to the nucleus. Furthermore, it was observed an increase in half-life of IkB, thereby preserving its degradation. Thus, the increasing of this micronutrient can prevent the transactivation of genes encoding inflammatory cytokines and inhibit the release of acute phase proteins [32,33,43].

The supplementation of selenium has been studied by some researchers, and present conflicting results. Some studies show that supplementation was effective in improving the nutritional status of selenium [36,44,45], while others found no change [46-48]. These differences may be explained by differences in studies design, the chemical form of the mineral that was used (selenomethionine, selenite, selenate), the time of supplementation, and pharmacological treatment. However, as in the case of zinc, more studies related to the effects of supplementation with selenium should be performed in order to evaluate the responses in different degrees of the disease, the type of supplement to be used and the interaction with the drug therapy.

Calcium

Calcium (alongside other nutrients such as vitamin D) is needed to develop and maintain healthy bones and teeth. Adequate calcium intake is important for the general population and especially for patients with RA which are vulnerable to steroid-induced and disease-associated osteoporosis. In RA, vertebral bone density has been found to be 5-15% less than aged matched controls [49]. In addition, corticosteroids, used in the treatment of RA, impair intestinal calcium absorption [50]. Doses a slow as 2.5 mg prednisone per day or equivalent for longer than 3 months increase the risk of vertebral fractures [51]. It appears that bone loss occurs rapidly within the first 6-12 months of corticosteroid therapy and then slows [52].

Glucocorticoids (GC) have indirect effects on bone by inhibiting gastrointestinal calcium absorption and decreasing renal tubular reabsorption of calcium, and direct effects on bone cells. GC decrease

bone remodeling and bone formation, leading to diminished bone quality and density with increased fracture risk [53-55].

Studies have examined the effect of calcium and vitamin D_3 supplementation on bone mineral density (BMD) among subjects taking corticosteroids in men and women who were predominantly post-menopausal [56-58]. Calcium prophylaxis alone appears to offer only minimal protection from corticosteroid-induced spinal bone loss [58]. A 2-year randomized control trial of calcium combined with vitamin D_3 in 65 RA patients taking corticosteroids demonstrated a reduction in BMD loss in both the spine and trochanter, but not the femoral neck [57].

No change in BMD with calcium and vitamin D_3 supplementation has been seen in RA patients not receiving corticosteroids [57] and therefore, considering the possible side-effect of hypercalcaemia [58] there is no evidence to support calcium and vitamin D supplementation in these patients, unless they have symptoms of hypocalcaemia or decreased blood biomarkers.

Vitamin D

Vitamin D is needed to regulate calcium absorption and homeostasis. It is important for healthy bones and teeth. Low vitamin D levels have been implicated in a number of chronic diseases (such as the metabolic syndrome and diabetes etc.) including RA [59].

It can be obtained from food sources, such as cod liver oil and from other fat-rich fish (salmon, tuna, mackerel), or from endogenous cutaneous synthesis, which represents the most important source of this vitamin for the majority of human beings [60]. In the skin, the precursor is the 7-dehydrocholesterol (7-DHC). During exposure to sunlight the ultraviolet B radiation converts 7-dehydrocholesterol to previtamin D3 which in turn rapidly isomerizes to vitamin D3. Once formed, vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 and in the kidneys to its active form 1,25- dihydroxyvitamin D3 ($1,25\text{-}(OH)_2D_3$) [61].

Vitamin D has been shown to alter the expressions of genes that affect cellular functions, such as, proliferation, differentiation, apoptosis, and angiogenesis [62]. Furthermore, vitamin D is involved in interleukin-2 inhibition, antibody production, and in lymphocyte proliferation, and, thus, is considered a regulator of the immune system [63] essential in the development and function of both T-regulatory cells [64,65] and dendritic cells [66,67].

Experimental evidence suggests that biologically active form of vitamin D ($1,25\text{-}(OH)_2D_3$) influences the process by which immune cells acquire signaling molecules that enable them to migrate to normal extra lymphoid tissue sites, as well as sites of inflammation [68]. In addition, it is known that $1,25\text{-}(OH)_2D_3$ inhibits IFN-γ secretion and negatively regulates IL-12 production by down regulating NF-κB [69].

The expression of vitamin D receptor (VDR) constitutively or after immune stimulation, on antigen presenting cells, dendritic cells, T and B cells, further suggests an immunoregulatory role of vitamin D [70-72].

Given the immunosuppressive effects of vitamin D and the potential link between vitamin D deficiency and autoimmune diseases, vitamin D has been studied as potential player in the pathogeneses of many autoimmune diseases. Epidemiologic data indicate low vitamin D concentrations in autoimmune diseases such as RA, inflammatory bowel disease and multiple sclerosis [73-76].

However, it is unclear whether low vitamin D intake is a risk factor of RA development, and the relation between low serum vitamin D levels and increased activity in RA patients remains controversial. Little data derived from systematic approaches to the relationship between vitamin D intake and development of RA or between serum vitamin D levels and RA activity are available [77].

A meta-analysis by Song et al. [77] examined the relation between serum vitamin D levels and RA activity from published observational studies. Three cohort and eight studies (six cross-sectional and two case-control studies) on the association between serum vitamin D levels and RA activity were included. After combining the data of the three cohort studies that assessed the effect of vitamin D intake on RA risk, a significant association was found between total vitamin D intake and RA incidence (relative risk (RR) of the highest vs. the lowest group = 0.758, 95% confidence interval 0.577-0.937 (p = 0.047). Individuals in the highest group for total vitamin D intake were found to have a 24.2% lower risk of developing RA than those in the lowest group. In the other eight studies, seven of them showed that vitamin D levels are inversely associated with RA activity, such as, DAS28.

However, these findings should be interpreted with care given the small number of studies incorporated in this meta-analysis and other limitations - the study did not combine data on vitamin D levels and RA activity because the individual study designs and clinical outcomes were too heterogeneous.

Further studies are necessary to elucidate the effect of vitamin D on the development and the activity of RA to test the hypothesis that vitamin D status directly contributes to the pathogenesis of RA and to determine whether vitamin D supplementation has a beneficial effect in RA.

Conclusion

Studies on the nutritional status of patients with RA, particularly on the intake of macronutrients and, even more about micronutrients are still scarce and inconclusive. The etiology of this disease has not been established, and treatment goals, which is mainly pharmacological, are to prevent and control joint damage, improve and maintain functional capacity, reduce pain and get the remission of the disease. Some nutrients have important functional properties that may help in health and quality of life of these patients. The zinc and selenium, for example, due to their antioxidant and anti-inflammatory properties may help attenuate the effects of chronic inflammation from disease. RA patients are more susceptible to osteoporosis frames and so the monitoring of adequate intake of calcium and vitamin D are important. Still, it emphasizes once again the importance of further studies on the evaluation of nutritional status of micronutrient in these patients. One must consider the importance of a good design of the study, and look for to the best assessment methods, the chemical forms of supplementation when there are indications of deficiency, and the interaction of the nutrient with the drugs used in the treatment. These data will contribute significantly to the establishment of appropriate prescribing of these nutrients for these patients.

Acknowledgement

We would like to thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for the financial support of our works with rheumatoid arthritis (processes numbers 2011/14801-0 and 2011/18025-4).

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