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Research Article

The Association of Trace Elements and Vitamins with Lichen Planus: Review Article

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Abstract

Lichen planus is a continual mucocutaneous inflammatory disorder of multifactor nature with numerous clinical symptoms. Numerous researchers attribute a key role in disease development to disruptions in the immune system. Appropriate doses of micronutrients are essential for the immune system to perform effectively. Micronutrient deficiency suppresses immunity by influencing the innate immune system, responses to T-cell mediated and adaptive antibody, resulting in disruption of the balanced host response. Since these trace elements and vitamins have an important role in the immune system and oral lichen planus has a significant relationship with the disturbances in the immune system, the importance of these elements should be considered for each patient. Just several articles examined the hematological anomalies and nutritional imbalances in OLP patients. In this study, all required information about trace elements and vitamins in OLP patients is obtained.

Keywords: Oral Lichen Planus; Trace Elements; Vitamins; Immune System

Introduction

Lichen planus

Lichen planus is a continual mucocutaneous inflammatory disorder of multifactor nature with numerous clinical symptoms, involving skin, nails, hair, and mucous membranes. Despite various articles done by researchers, the disease etiology is still a hot topic. Numerous researchers attribute a key role in disease development to disruptions in the immune system [1-4]. Besides, patients with Oral Lichen Planus (OLP) have hematological anomalies [5].

Earlier research suggested the presence of both nonspecific and antigen-specific mechanisms in OLP. Nonspecific systems contain activation of the matrix metalloproteinase and degranulation of the mast cell in OLP lesions. Antigen-specific systems contain antigen presentation by basal keratinocytes and antigen-specific keratinocyte removed by CD8+ cytotoxic T-lymphocytes [6]. Mast cells release chemokines, cytokines, and matrix metalloproteinases which stimulate activation, migration, proliferation, and differentiation of T-cell by T-cell and mast cell interactions in OLP lesions [7].

OLP is histologically defined by liquefaction degeneration of basal epithelial cells and subepithelial and intraepithelial infiltrate of mononuclear cells, which are primarily CD8+. CD4+ cells can be commonly observed in the deep lamina propria [8].

Micronutrient

Appropriate doses of micronutrients are essential for the immune system to perform effectively. Micronutrient deficiency suppresses immunity by influencing the innate immune system, responses to T-cell mediated and adaptive antibody, resulting in disruption of the balanced host response. Micronutrients help the body's natural protection by improving physical barriers (skin/mucosa), cellular immunity and generating antibody. Vitamins A, C, E and zinc can help to strengthen the skin barrier function. The vitamins A, B6, B12, C, D, E and folic acid, zinc, iron, selenium and copper collaboratively act to improve the defensive activities of the immune cells. Lastly, all these micronutrients, except for vitamin C and iron, are crucial to the development of an antibody [9].

Trace elements

Trace elements are necessary chemicals in small quantities, generally as part of a crucial element [10]. Trace elements, i.e. copper and zinc, are closely involved in metabolic processes which are critical for cell replication and differentiation. Level changes of trace elements are generally regarded as a part of defense strategies of organisms, playing an important role in the stability of the cell

membrane, host metabolism, apoptosis and enzyme activity [11]. Based on WHO classification, 19 trace elements are categorized into three major classes: Essential elements, Probably essential elements, Potentially toxic elements [12].

Essential trace elements consist of zinc, copper, selenium, cobalt, chromium, manganese, iodine and molybdenum. Although these elements constitute just 0.02% of the total body weight, they still play a pivotal role. Since every trace element is associated with several enzymes, the insufficiency of one trace element is not related to any particular clinical presentation, but instead behaves like a combination [12].

Biological significance of trace elements

Enzymes related to trace elements are an integral part of chemical and biological reactions. They function in conjunction with proteins and often other coenzymes. They absorb substrate molecules and facilitate their transformation to an end-product. Some trace elements are involved in oxidation-reduction reactions, e.g. burning of food items. Some trace elements have structural functions by providing three-dimensional structures and stability to crucial biological molecules [12].

Essential nutritional elements

There are a wide range of criteria to decide whether a micronutrient is essential or not as follows: the nutrient existence in a healthy living tissue, if there is a micronutrient in the fetus and neonates and whether the body is able to maintain the control balance over intake and excretion in the hematopoietic flow or tissue [13].

Essential micronutrients are as follows [12]: Zinc, copper, selenium, fluorine, chromium, molybdenum, iron, iodine, manganese, and cobalt.

While trace elements are needed in limited quantities, their existence in the optimum amount is necessary for the standard physiological functioning of the body. They play a significant role in the maintenance of body biodynamic. Whether a surplus or shortage of trace elements causes initiation, promotion, and progression to numerous disease processes [14].

Since OLP was considered as a T-lymphocyte-mediated immunological disease, just several articles examined the hematological anomalies and nutritional imbalances in OLP patients [15]. In this study, all required information about trace elements and vitamins in OLP patients is obtained.

Method and Materials

PubMed, Medline, Ovid, Science Direct and Google Scholar were searched from 1988 to 2020. The search terms used for medical subject heading were 'oral lichen planus', 'trace elements' and 'vitamins'.

Results and Discussion

Vitamin B12

Vitamin B12 is a crucial component for an accurate and consistent human immune function [16]. A human study in patients having the lack of vitamin B12 examined the alterations of immunological measures following the manipulation of vitamin B12. A substantial decrease was observed in these patients based on the number of CD8+ cells and lymphocytes as well as the proportion of CD4+ cells. Furthermore, results indicated an extremely high CD4+/CD8+ ratio and inhibited Natural Killer (NK) cell activity. Such impacts have been reversed by supplementation with vitamin B12 suggesting that it can function as a modulatory factor for cellular immunity, particularly regarding CD8+ and NK cells [17].

In 2010, Sahebjamee., *et al.* evaluated 48 individuals including 32 cases of histopathologically confirmed OLP and 16 healthy cases. While there was no significant difference in the deficiency of vitamin B12 between OLP patients and healthy individuals, it was roughly twice as much as the control group. Vitamin B12 can be proposed as being efficient in OLP pathogenesis [18].

In 1973, Jolly., *et al.* examined the lack of vitamins B1 and B6 in 48 lichen planus patients and there was no significant difference in terms of the prevalence of such lack between patients and the control group. The prescription of the supplementary drug caused partial recovery of patients' clinical signs, but the disease was not fully recovered [19].

In 2013, Nosratzehi., *et al.* performed a study on 32 patients with OLP and 32 persons as the control group. This study showed that there is no statistically significant difference in terms of the serum level of vitamin B12 ($P = 0.93$) [20].

In 2001, Thongprasom., *et al*. conducted a study on 41 patients with lichen planus and they found no statistically significant difference in terms of the serum level of vitamin B12 between healthy individuals and oral lichen planus patients [21].

In 2014, Chen., *et al.* examined 352 OLP patients and found that there is a significant association between deficiency of vitamin B12 and OLP [15].

Folic acid

Folate plays a vital role in the synthesis of nucleic acid and protein and consequently, insufficient amount of folate drastically changes the immune response. Deficiency of folate modifies immune competence, susceptibility to infections and also cell-mediated immunity by lowering the circulating T-lymphocytes proportion and proliferation with regards to mitogen activation [22]. Thus, this dietary supplement improved innate immunity and protected elderly people against infections [23].

Folic acid is a key element for the accurate function of the human immune system. OLP, besides, has long been recognized as an immune-mediated disease [16].

In 2010, Sahebjamee., *et al*. evaluated 48 people including 32 cases of histopathologically confirmed OLP and 16 healthy cases. Each person's serum folic acid was evaluated, and t-test was applied to analyze the results. Deficiency of folic acid is not a significant risk factor for OLP [18].

In 2014, Chen., *et al.* examined 352 OLP patients and concluded that there is a significant association between deficiency of folic acid and OLP [15].

In 2013, Nosratzehi., *et al.* performed a study on 32 patients with OLP as the case group and 32 persons as the control group. This study showed that there is a statistically significant difference in terms of the serum level of folic acid (P = 0.03) [20].

Additionally, studies of Thongprasom [21], Challacombe [5] and Kleier [24] showed that the serum level of folic acid in healthy individuals is largely higher than that in lichen planus patients which is controversial with results found by Sahebjamee., *et al* [18]. This difference could be due to the differences in dietary habits of groups studied.

Vitamin B12 and folic acid

Vitamin B12 and folic acid are the micronutrients required for immune system function. Deficiency of these two factors disrupts immune function and apoptosis of progenitor cells in bone marrow. Lack of vitamin B12 can disrupt folate metabolism and finally deficiency of folic acid; therefore, it is recommended to measure folic acid in patients having vitamin B12 deficiency [20].

Vitamin D

Active vitamin D, also known as 1,25-dihydroxycholecalciferol, plays an important role in phosphorus and calcium metabolism. Numerous articles discussed the importance of vitamin D in regulating immune responses. The proliferation of helper T-cells is blocked, regulatory T-cells are stimulated, B-lymphocyte differentiation is reduced, and vitamin D prevents immunoglobulin secretion. Vitamin D also limits the presentation of antigen by macrophages and regulates the maturation of dendritic cells [25].

OLP is an autoimmune mucocutaneous disease in which cell mediated immunity is important and it may also be associated with levels of serum vitamin D [26].

In 2018, Zhao., *et al.* indicated that Lipopolysaccharide (LPS) reduces vitamin D receptor (VDR) expression in oral mucosal epithelia depending on TNFα-miR346 signaling, and vitamin D/VDR can inhibit LPS-induced keratinocytes apoptosis by adjusting NF-κB stream. Therefore, vitamin D/VDR is protective in the oral mucosal barrier integrity to address the bacterial challenges, preventing or slowing the growth of OLP. Considering the inadequate levels of VDR observed in OLP patients, targeting VDR expression in oral epithelial cells can be a useful method for OLP management [27].

In 2016, Zhang., *et al.* suggested that 1,25(OH)2-vitamin D3 is anti-inflammatory in OLP by facilitating the NF-κB signaling pathway, but not the AP-1 signaling pathway with a VDR-dependent manner. Thus, vitamin D supplement could be a promising technique for OLP management [28].

In 2017, Gupta., *et al.* [26] examined 102 clinically diagnosed OLP patients and concluded that patients with OLP have significantly lower serum vitamin D levels than healthy individuals. Although there was more vitamin D deficiency in OLP cases, insufficiency was more common in the control group, suggesting that serum vitamin D was typically deficient in the North Indian population. Vitamin D administration in patients with OLP can likely help to prevent the adverse reactions of the immune system activity.

Vitamin A

Vitamin A, operating by all-trans retinoic acid, 9-cis retinoic acid, or other metabolites and nuclear retinoic acid receptors, is pivotal in controlling the innate and cell-mediated immunity and humoral antibody response [29,30]. The integrity of mucosal epithelium is affected in the case of vitamin A deficiency [31]. Vitamin A deficiency is linked to decrease phagocytic and oxidative burst activation of inflammation-activated macrophages [32] and a reduced number and activity of NK cells [33].

From 1995 to 1998, Nagao., *et al.* [34] found that the mean serum retinol level (2.820 ± 0.849 μmol/l) was significantly higher than that of the control group (2.562 ± 0.735 μmol/l) among 9536

cases. The findings of this article show that the low level of serum retinol is not a risk factor for lichen planus incidence.

In 2007, Piattellia., *et al.* [35] showed that the retinoid may have established a partial or full regression of the clinical OLP lesions through the restoration of cell proliferation and apoptosis blockage in the squamous epithelium. This research verified that the topical use of 13-cis-retinoic acid can be effective for OLP patients.

Zn

Zinc plays several essential roles in the growth and reproduction of a cell, standard immune, collagen synthesis, functions, and wound healing. Zinc deficiency is associated with many physiological anomalies. It is also possible that the deficiency of zinc may be directly involved in the pathogenesis of certain oral mucous disorders [36].

Over the last few years, the immune-related roles of zinc have been studied. Zinc is important for highly proliferating cells, particularly in the immune function and impacts both innate and acquired immune systems. Zinc is useful for cytosolic protection against oxidative stress. It is also a critical cofactor for thymulin modifying cytokine release and stimulates proliferation. Appropriate absorption of zinc promotes the Th1 response and helps preserve the skin and mucosal membrane integrity [9].

A slight shortage of zinc may lead to reduce the thymulin function and the secretion of interleukin2 (IL-2) [37]. Moreover, zinc deficiency can lead to the T-helper (TH) lymphocytes imbalance and the lower number of TH1 lymphocytes contributes to an increase in TH2 as the reimbursement phase. The TH2 function rise is associated with the lichen planus generation, increasing cytotoxicity and pathogenesis of lichen planus [38].

Arora., *et al*. emphasized the role of zinc deficiency in psoriasis, acne vulgaris and leprosy [39]. Khademi., *et al*. [40] showed a lower level of serum zinc in patients with recurrent aphthous stomatitis. OLP, recurrent aphthous stomatitis (RAS), atrophic glossitis (AG), burning mouth syndrome (BMS), and xerostomia are among the most frequent oral mucosal diseases and they usually need several visits to the specialist outpatient services. The etiology and pathogenesis of these disorders are still widely debated [36].

In 2016, Chuykin., *et al.* [41] studied 191 people with different types of OLP and found that increasing the severity of the clinical signs leads to a significant reduction of zinc level, mostly in the oral fluid, which may worsen the severity of OLP.

In 2014, Gholizadeh., *et al*. [42] examined 88 individuals as follows: 22 patients with erosive OLP, 22 patients with nonerosive OLP and 44 healthy persons as the control group. They showed that Zinc is an essential element for the epithelium growth and the lack of zinc causes the cytotoxic activity of T-helper2 cells, which is correlated with lichen planus. In patients with erosive OLP, the levels of serum zinc were declined. This result can show the significant role of zinc in the development of OLP.

Bao., *et al.* [36] studied a total of 368 individuals including OLP, RAS, BMS, AG and xerostomia patients, and healthy control group. They found that there are statistically significant differences in terms of zinc level between patients with the oral mucosal disease (e.g. OLP) and control group. Hence, the lack of zinc and lower levels of serum zinc contribute to the pathogenesis of oral mucosal diseases and a reduction of serum zinc level may be a risk factor for the development of an OMD.

Ca

Calcium is one of the factors that in case of interacting with cadherin molecules can strengthen the process of cell junction as an external stimulation and adjust the performance of the immune system as an intracellular mediator. This element is also important in distinguishing immune cells, DNA transcription and strengthening immune system activities. Recently, in researches looking for causes of oral ulcers such as aphthous, serum calcium changes have been described as one of the potential causes. Aphthous and lichen planus are under oral ulcers group for which autoimmune pathogenesis is presented and considering the above-mentioned role of calcium in maintaining the integration of epithelium and hence preventing from the incidence of erosive autoimmune diseases, the association between lichen planus and the serum calcium level is not impossible [43].

In 2014, Mehdipour., *et al.* examined 36 patients with erosive lichen planus and 72 individuals in the control group concluded that the amount of total calcium and ionized calcium in the case group was lower than in the control group [43].

Se

Selenium plays a vital role in the response of optimum immune and impacts the innate and acquired immune functions. It is essential for the regulation of oxidation-reduction and antioxidant function by glutathione peroxidases removing excessive possibly harmful radicals generated during oxidative stress. Therefore, selenium is essential for balancing the oxidation-reduction state and helps the host to protect from oxidative stress induced by the macrophage microbicide effects and during inflammatory reactions. The deficiency of selenium reduces immunoglobulin titers and cell-mediated immunity aspects. Supplementation with selenium can reduce these effects [9].

In 2015, Belal., *et al*. [44] studied 30 patients with a clinical and histopathologic OLP diagnosis and found that in case of using selenium combined with Vitamins A, C and E (SE-ACE) as well as topical corticosteroids plus antifungal, this approach may be beneficial in controlling ulcerative lesions of OLP; however, further studies with greater sample size and a longer examination period are required.

In 2020, Qataya., *et al*. [45] demonstrated that selenium (both topical formulation and systemic administration) could be efficient in treating OLP erosive lesions considering reasonable results to topical corticosteroids (based on clinical assessment).

Fe

The deficiency of iron is followed by a thin layer formation of the epithelium, which is responsive to environmental factors [46]. Ions of iron are also heavily engaged in the vascular bed formation, and iron deficiency leads to higher vascular permeability and lower vascularization of tissues [46,47].

Since 2001, numerous studies have reviewed the immune-related roles of iron. Iron is important for electron transfer processes, oxygen binding and transport, gene regulation, and regulation of cell differentiation and cell growth. Iron is also a vital element of peroxide and nitrous oxide producing enzymes. This element is involved in controlling the cytokine production and action mechanism and activating the protein kinase C, which is necessary for the phosphorylation of factors manipulating the cell proliferation [9].

When dealing with the shortage of iron, the clinical results indicate inflammatory and atrophic changes in mucous membranes, and immunodeficiency states [48].

In 2017, Chuykin., *et al.* [48] studied 191 persons with different types of lichen planus of the oral mucosa (LP OM) and 30 patients without LP OM as the control group. In the case group, an iron imbalance in oral fluid of the pathological nature and blood serum has been identified, which is helpful in the disease pathogenesis.

In 2014, Chen., *et al.* examined 352 OLP patients and concluded that there is a significant relationship between iron deficiency and OLP [15].

Laboratory tests showed low serum folate and high serum ferritin in a 48-years-old man. High levels of serum ferritin related to OLP have not been identified. OLP lesion in this patient may correlate with high levels of ferritin because he was healthy and did not use any medicines [49].

Cu

Copper is the third most common mineral in the body, as well as being essential for many other enzymes. Copper plays an important role in immune system development and maintenance. Many experimental reviews showed that the copper level affects several facets of monocytes, neutrophils, and superoxide dismutase. Copper deficiency and high absorptions over longer periods can modify some aspects of the immune response [9].

In 2016, Chuykin., *et al.* [50] studied 191 people with different types of OLP and 30 patients without OLP and concluded that increasing the severity of the clinical signs leads to a significant reduction of copper level, mostly in the oral fluid, which may worsen the severity of OLP.

Mg

Magnesium is essential for the body trace element such that it can stabilize cell membranes and nerve conduction [50]. Manganese constitutes just 0.00016% of the human body and can perform as an activator and also a component of several enzymes in the body [14].

In 2016, Chuykin., *et al*. [41] studied 191 people with different types of OLP and 30 patients without OLP and concluded that increasing the severity of the clinical signs leads to a significant increase in the copper level, mostly in the oral fluid, which may worsen the severity of OLP.

Conclusion

Since these trace elements and vitamins have an important role in the immune system and oral lichen planus has a significant relationship with the disturbances in the immune system, the importance of these elements should be considered for each patient. Additionally, further studies should be conducted in the future to identify an accurate association between some trace elements and vitamins and OLP when there are contradictions among the results of studies.

Conflict of Interest

There is no conflict of interest.

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