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Nutritional Therapy in the Treatment of Recurrent Aphthous Stomatitis: A Literature Review

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is one of the most common oral diseases, with an estimated prevalence of 25% of oral ulcerations. Factors that involves in its progressions, such as genetic predisposition, immunological abnormalities, viral and bacterial infections, psychological stress, hormonal state, and nutritional deficiencies. Since the etiology and pathogenesis of RAS remain unclear, there is currently no consensus regarding a definitive curative therapy. However, nutritional improvement is thought to be able to support RAS healing optimally. This literature review aims to examine a few of the nutritional therapies which are usually given to support the treatment of RAS. The results obtained indicate that the nutritional therapy of RAS should be based on the detailed clinical history and possible underlying systemic causes along with complementary procedures such as laboratory tests, where required. The vitamins that are used most in the RAS are vitamin B12, folic acid, vitamin D, and zinc. There is little evidence regarding the effectiveness of the use of nutritional therapy in the treatment of RAS because most of the previous studies showed the comparison between the value of reduced vitamin levels in RAS patients and healthy individuals. Studies using nutritional/vitamin therapy as sole therapy in RAS patients are needed to be explored.

Keywords: *recurrent aphthous stomatitis, vitamin B12, folic acid, vitamin D, zinc*

1. INTRODUCTION

Recurrent aphthous stomatitis (RAS) is characterized by solitary painful ulceration that is generally present in 25% of the general population. The recurrence within three months can occur up to 50% [1, 2]. Recurrent aphthous stomatitis is an idiopathic condition that can occur in any individual. Previous studies have shown that RAS is caused by malfunction of the immune system that destroys epithelial cells resulting in T-cell-mediated local response [3].

The inflammatory cytokine; tumor necrosis factor (TNF)-α that was produced by macrophages and mast cells might have an important role in the pathogenesis of RAS. However, the etiology of RAS' onset is still unknown and involved many complex predisposition factors [4]. Several factors are thought to be involved in the development of RAS, including genetic factors, trauma, infections, gastrointestinal disease, hematological deficiencies (vitamin B12, iron, and folic acid), hormonal factors, nonsmoking state, stress, and mineral deficiency (zinc) [5].

Recurrent aphthous stomatitis is lesions that are characterized by solitary or sometimes multiple small, medium, and large size ulcers. The shape of the lesions is ovoid or round shape surrounded with erythematous circumscribed margins and whitish or yellowish base. The severe, major, and sometimes multiple forms of RAS ulcers can impact the quality of life of individual activities such as eating, speaking, and swallowing [6]. Since the etiology and pathogenesis of RAS remain unclear, there is currently no determination regarding a definitive preventive and curative of RAS therapy. The therapy that is highly recommended for RAS is topical corticosteroids, but the healing of RAS lesions is also dependent on the patient's systemic condition. In patients who have a low immune system, RAS healing will be delayed [7]. This supports that in addition to topical therapy, supportive therapy is also needed to accelerate the healing of the lesions. Currently, nutritional therapy

is an option because the onset of RAS is also caused by several vitamin and mineral deficiencies. This literature review will describe several nutrients that can help accelerate the healing process of RAS ulcers.

2. NUTRITIONAL THERAPY

Nutritional therapy or nutritional medicine is an effort to improve health through nutritional intake and support for healthy living [8]. It is also a healing system that believes natural foods can provide ingredients that can maintain or improve health. Nutritional therapy aims to nourish the body without using drugs that contain chemicals to prevent or treat disease. Nutritional therapy has been used to treat several diseases such as obesity, diabetes mellitus, cardiovascular disease, arthritis, and depression [8].

2.1. Vitamin B12 (Cyanocobalamin)

2.1.1. Food Sources and Recommended Amount

Vitamin B12 is found in animal products, such as meat, eggs, ham, pork, poultry, lamb, fish especially haddock and tuna, dairy products, such as milk, cheese, and yogurt, soya milk, and cereals fortified with vitamin B12. The National Institutes of Health (NIH) recommended that the maximum dose limit that can be consumed by adults over 14 years old is 2.4 micrograms (mcg), pregnant women to 2.6 mcg, and lactating women to 2.8 mcg. Individuals who consume excess vitamin B12 usually do not show toxic side effects. Some drugs that can interfere with the absorption of vitamin B12 are proton pump inhibitors, metformin, and H2 receptor agonists. Classes of antibiotics that can interfere with the absorption of vitamin B12 are chloramphenicol or chloromycetin, so they can detain the production of red blood cells.

2.1.2. Mechanism of Action

Vitamin B12 is a water-soluble vitamin. This vitamin plays important role in metabolic reactions in the body's system especially hematopoietic disorders and spinal cord-related neuropathies [9]. Vitamin B12 contains a chemical substance namely cobalt, thus vitamin B12 is known as cobalamin. Vitamin B12 helps the formation of blood cells and prevent anemia, increases the bone remodeling process, induces the formation of serotonin; a chemical that stabilizes emotions and gives a feeling of happiness. This vitamin also reduces the amount of homocysteine. Homocysteine is an important amino acid. However, in large amounts, these substances can increase the risk of heart disease and stroke. In addition, the intake of this vitamin is believed to control the buildup of plaque in the blood vessels so it can control cholesterol and high blood pressure. It also can reduce the risk of macular degeneration or visual impairment associated with aging, prevents the risk of dementia occurrence due to nerve cell death, and increase the risk of birth defects, such as neural tube defects. Vitamin B12 deficiency may lead to premature birth or miscarriage.

2.1.3. Vitamin B12 and RAS

Vitamin B12 and Hb deficiency were shown to be the etiology of RAS [10]. Apparently, The low Hb is not only owned by RAS patients but also in healthy individuals, although in a smaller percentage [10]. The anemia condition in RAS patients can cause a decrease in the ability of red blood cells to transport oxygen to the surface of the oral mucosa so that it can cause mucosal atrophy [11]. Iron in Hb, vitamin B12, and folic acid play important roles in epithelial cell functions especially in deoxyribonucleic acid (DNA) synthesis and cell division [12]. Oral epithelial cells have a high turnover rate, so if the patient has a vitamin B12 deficiency, the condition of oral epithelial atrophy due to a lack of this vitamin will cause a thin layer and easy ulceration [12]. This may explain why patients with hematinic deficiencies are prone to having RAS.

Vitamin B12 is one of the coenzymes in the metabolism of proteins, carbohydrates, and fatty acids. The deficiency of vitamins B12, B6, and folic acid can increase high blood homocysteine levels so that it can increase the frequency of thrombosis of arterioles in oral tissues. This condition will cause a lack of supply of nutrients and oxygen to the oral epithelial cells, resulting in a breakdown of the oral epithelium or a decrease in the oral epithelial barrier and facilitating ulcerations. Homocysteine is a by-product of methionine metabolism. Elevated homocysteine levels cause coronary artery disease and premature atherosclerosis [13].

Volkov *et al.* showed that daily consumption of vitamin B12 over some time can reduce RAS symptoms, but this study was not accompanied by the proof of increased serum vitamin B12 levels [2]. Hematinic deficiency is one of the important factors in the etiopathogenesis of RAS, but daily intake of vitamin B12 is not recommended because of the lack of evidence of the efficacy of vitamin B12 in serum in reducing the incidence of RAS [1]. The most appropriate strategy in the treatment of RAS is routine hematological screening and supplementation when there are indications of hematinic deficiencies. If RAS occurs without haematinic deficiency, the most appropriate therapy is a local or topical treatment, such as mouthwashes and topical corticosteroids. Systemic supplementation is not the main recommendation in this RAS therapy [14].

Koybasi *et al.* showed that the most common predisposing factors for RAS were vitamin B12 deficiency, positive family history (genetic), and nonsmoking status [15]. Recurrent aphthous stomatitis mostly affects the nonkeratinized mucosal layer than the

keratinized mucosa. In smokers, the thickened keratin layer can block the entry of antigens from cigarettes so that ulceration rarely occurs [15]. Nicotine in burning tobacco can decrease pro-inflammatory cytokines such as TNF-a, IL1, and IL6, and increase anti-inflammatory cytokine IL-10 [4]. Systemic administration of vitamin B12 by injection has better effectiveness than oral administration, does not require large costs, and has a smaller risk of side effects.

2.2. Vitamin B9 (Folic Acid)

2.2.1. Food Source and Recommended Amounts

Folic acid is found in dark green vegetables such as broccoli, spinach, asparagus, and lettuce; peanuts, sunflower seeds, fresh fruits, seafood, meat, liver, egg, and milk. Although a large number of natural sources contain folate, the supplemental form of folate was usually added to food because it is more easily absorbed. The Recommended Dietary Allowance (RDA) for adults 19 years and older can consume 400 mcg dietary folate equivalents (DFE). The recommended intake of folate in pregnant and lactating women is 600 mcg DFE and 500 mcg DFE, respectively. The same amount or at least 600 mcg of DFE is recommended for people who regularly drink alcohol because alcohol can interfere with the absorption of folate in the blood.

2.2.2. Mechanism of Action

Vitamin B9 is a water-soluble vitamin that plays an important role in DNA biosynthesis. The synthetic form of vitamin B9 is folic acid. Folate will be converted into tetrahydrofolic acid (THF), which functions in the synthesis of nitrogenous bases in DNA and ribonucleic acid (RNA) and the maturation of red blood cells (RBCs). Folate reserves are stored in the liver and kidneys. Folic acid deficiency will cause macrocytic megaloblastic anemia. Anemia can also occur due to malabsorption disorders, chronic alcoholism, pregnancy, and hemolytic anemia. Other functions of folic acid in the body are as a protector against neoplasia, ulcerative colitis, cervical dysplasia, vitiligo, maintaining the balance of hematopoiesis in macrocytic anemia, and increasing the resistance of the gums to local irritants [16]. Treatment using a combination of vitamins B12 and B9 is better at improving cognitive performance than vitamin B9 or B12 administration alone.

2.2.3. Folic Acid and RAS

A previous study showed that RAS patients had vitamin B12 and folate deficiencies including hematological abnormalities [17]. Systemic therapy with these vitamins in RAS patients results in improvement of their severity of lesions [18]. Folic acid plays a role in the formation of coenzymes to help protein synthesis and erythropoiesis. Recurrent aphthous stomatitis patients have lower folic acid levels than healthy people [19]. Decreased levels of vitamin B12 and folic acid are generally caused by impaired absorption or lack of intake of foods containing these vitamins [18].

Ghafoor *et al.* reported that patients with recurrent aphthous stomatitis showed that hemoglobin levels in red blood cells were normal in these patients [20]. However, there is a significant fall in RBC folate levels seen in another population of RAS patients that could be due to anemia, which indicates that RAS has a relationship with deficiency of folic acid. These findings prove that the role of folic acid in RAS lesions is still controversial in some populations.

2.3. Vitamin D

2.3.1. Food Source and Recommended Amounts

Vitamin D is a steroid hormone that has a crucial role in immunity and calcium metabolism. Vitamin D receptors are found on the surface of immune cells such as dendritic cells and macrophages, and lymphocytes T [21]. vitamin D's role in the immune system is increasingly being researched and developed. Vitamin D is the only nutrient that is produced when exposed to sunlight. However, up to 50% of the world's population may have vitamin D deficiency. Two types of vitamin D are most found, namely: vitamin D_2 dan D_3. Vitamin D_2 (ergocalciferol) is produced by ultraviolet B (UVB) radiation from the sun and then reacts with ergosterol in plants and fungi (mushrooms) sterol ergosterol. Oily fishes, such as herring, salmon, sardines, and mackerel; liver, red meat, egg yolks, fortified foods, such as fat spreads and cereals are the food sources of vitamin D_2.

The production of vitamin D_3 (cholecalciferol) is synthesized by the reaction of 7-dehydrocholesterol (7-DHC) in the lower layer of the skin epidermis with ultraviolet B radiation. Vitamin D_3 is produced through a two-step process in which the B ring is broken by UV light (spectrum 280–320 UVB) radiation from the sunlight, forming vitamin pre-D3 that isomerizes to vitamin D_3 in a thermo-sensitive but a noncatalytic process. The UVB intensity and skin pigmentation level have contributed to the rate of vitamin D_3 formation in the body. The amount of melanin in the skin can block UVB from reaching 7-DHC, thus limiting vitamin D_3 production, as do dark color clothing and sun protector factor (SPF) levels in sunscreen lotion. The intensity of UVB radiation varies according to latitude and season. People who live in a place further from the equator have less time of the year to get sunlight exposure to produce vitamin D_3. The recommended daily amount of vitamin D is 400 IU for children up to age 12 months, 600 IU for

people ages 1 to 70 years, and 800 IU for people over 70 years.

2.3.2. Mechanism of Action

Vitamin D is a fat-soluble secosteroid and has an important role in the regulation of the calcium and phosphorus balance. Previous studies showed that decreasing vitamin D levels and vitamin D receptor polymorphism have roles not only in cardiovascular and skeletal diseases, but also in cancers, infections, autoimmune diseases, central nervous system, and dermatological disorders [22]. Vitamin D also arranges the bony tissue metabolism, acts as a potent anti-inflammatory and immunomodulatory agent, and affects the oral cavity homeostasis.

2.3.3. Vitamin D and RAS

The role of vitamin D in the treatment of RAS is controversial and shows conflicting results. Krawiecka *et al.* showed that the replacement vitamin D therapy to patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome was able to decrease the frequency and duration of the ulcers [23]. However, another study reported that Vitamin D is not included in one of the triggering factors for RAS [24]. Although several studies on the administration of vitamin D_2 as a therapy for RAS have been conducted and the results are quite valid, however, treatment RAS with vitamin D_3 derived from sunlight has never been done, even though the effect of this type is assumed to be rapidly metabolized by the body.

2.4. Zinc

2.4.1. Food Sources and Recommended Amounts

Food sources that contain large amounts of zinc include whole grains, milk products, cereals fortified with zinc, seafood such as oysters (74.1 mg/300 g) and crabs (8-11 mg/100g), red meat (5-9 mg/100 g), pork, poultry, baked beans, chickpeas, and nuts (cashews and almonds) contains 1-2 mg/100 g, and vegetables (1 mg/100 g). The recommended daily amount of zinc for women is 8 mg and 11 mg for men.

2.4.2. Mechanism of Action

Zinc is a micronutrient that functions in the body's metabolic reactions of lipids, proteins, and carbohydrates. Zinc is one of the building blocks of cell material and structure and helps stabilize cell membranes and DNA so that it can be an excellent antioxidant for the body. This cell-forming function also helps iron to form hemoglobin. In the body, zinc works as a co-enzymatic and activator of human enzymes. Zinc modifies the development and turnover process of epithelium, regulates DNA and RNA biosynthesis, and helps to maintain the vitamin A concentration in serum [25]. Zinc has been shown to modify the immune response in facing the disease. Zn deficiency is proved to decrease the IL-2 secretion and lymphocytes. Zinc deficiency is characterized by a broad spectrum of clinical symptoms that include: impaired cells maturation, loss of appetite and decrease body weight, cause skin lesions (eczema and stretch mark), the impaired healing process, vision disturbances, acceleration of premature aging, psychiatric and neurosensory disturbances, reduced resistance to infections, and elevated risk of diabetes mellitus due to increased glucose tolerance [25]. Zinc has antioxidant activity by inhibiting the oxidation of unsaturated fatty acids so it can interfere the bacterial conjugation.

2.4.3. Zinc and RAS

Aphthous ulcerations develop from an immunologic reaction to oral antigen, a depletion of the oral mucosa barrier, or immune dysregulation against the antigen [26]. The disturbance of initiated cascade of cytokines followed by the activation of abnormal immune processes leads to local oral tissue damage and induces inflammation. Zinc plays a role in overcoming the immunologic reactions that occur on the oral mucosal surface. Zinc deficiency can lead to RAS. This is evidenced in studies showing zinc deficiency in RAS patients [27]. However, the role of zinc in the etiopathogenesis of RAS is still controversial. Slebioda *et al*. reported that there was no significant difference in serum zinc levels between the RAS group and healthy controls, but zinc deficiency was observed in a minority of RAS patients [28]. Therefore, it can be concluded that although zinc can influence the onset of RAS, zinc does not appear to be the main modifying factor in the development of RAS.

3. CONCLUSION

There is little evidence regarding the effectiveness of the use of nutritional therapy in the treatment of RAS because most previous studies showed the comparison between the value of reduced vitamin levels in RAS patients and healthy individuals. Studies using nutritional/vitamin therapy as sole therapy in RAS patients are needed to be explored. Literacy in the form of a systematic review with a good design method is required for further exploration.

AUTHORS' CONTRIBUTIONS

L.M.S. conceived of the presented idea, contributed to the design and to the writing of the manuscript.

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