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RESEARCH STATUS OF VITAMIN D IN RECURRENT APHTHOUS ULCER

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ABSTRACT

Recurrent aphthous ulcer is the most common oral mucosal disease, of which pathogenesis is still unclear. In the process of treatment of recurrent aphthous ulcer, relapses often occur to patients. Existing research points out that vitamin D deficiency may be associated with the pathogenesis of recurrent aphthous ulcer. The immunomodulatory function of vitamin D may be beneficial to cure recurrent aphthous ulcer. Based on the two arguments above, this article reviews and analyzes the relevant articles on the research status of vitamin D in recurrent aphthous ulcer.

Keywords: Recurrent aphthous ulcer; vitamin D; T lymphocyte; immunoregulation

1 INTRODUCTION

Recurrent aphthous ulcer (RAU) is the most common oral mucosal disease, of which incidence in the general population is about 5% to 25%[1].It is more prevalent among young and middle-aged individuals and occurs more frequently in women than in men. The prevailing view is that the onset of RAU is influenced by genetic, immune, and environmental factors. Immune response triggered by these factors above leads to the local destruction of oral epithelium under specific conditions[2].According to the characteristics of clinical manifestations, RAU can be classified into three types: minor RAU, major RAU, and herpetiform RAU[3]. Clinically, RAU presents as a depressed yellow pseudomembrane surrounded by a red halo, accompanied by significant pain. It has variable onset periods and is generally self-limited[4]. Patients with RAU often suffer from a burning sensation, which interferes with physiological functions such as language, eating, and swallowing.

Vitamin D is an essential nutrient comprising over ten different compounds with varying molecular structures. Among these, ergosterol (vitamin D2) and cholecalciferol (vitamin D3) are particularly important for human health[5]. When ingested, vitamin D is processed in the body: first, it is converted into 25-hydroxyvitamin D [25(OH)D] by the enzymes CYP2R1 and CYP27A1 in the liver. Subsequently, it is transformed into the active form, 1α,25-dihydroxyvitamin D3 [$1\alpha,25(OH)_2D_3$], through the action of the enzyme CYP27B1 in the kidneys[6]. This active form is also known as calcitriol.$1\alpha,25\ (OH)_2D_3$ can bind to the vitamin D receptor[7] to enhance calcium absorption and support bone health[8]. However, recent research has discovered that vitamin D also provides several non-classical benefits beyond its role in bone health, including anti-inflammatory effects and regulation of the immune system[9].

Existing studies have pointed out that RAU is associated with an abnormal immune response mediated by Tlymphocytes[10], and vitamin D has been found to have an immunomodulatory effect, which could regulate the T lymphocyte-mediated immune response[11]. This article aims to explore the correlation between the deficiency of vitamin D and RAU, as well as investigate whether vitamin D has therapeutic effects on RAU by reviewing and analyzing the relevant literature.

2 Immunological pathogenesis of RAU

Patients with RAU experience disorders in cellular immune function, including the imbalance of T lymphocyte subsets[12]. In these patients, the mucosal epithelial cells become the target cells of the immune system, which would be destroyed due to the over expression of immune cells and the release of inflammatory factors[13]. The severity of RAU is closely linked to the ratio and quantity of $CD4^+$and $CD8^+$ T lymphocytes[14].Immunohistochemicalstudies of biopsy samples from ulcer tissues showed that $CD4^+$T lymphocytes are predominant during the pre-ulcer and healing stages, while $CD8^+$T lymphocytes are predominant during the ulcer stage. In addition, the occurrence and progression of RAU are significantly associated with helper T cell 1(Th1) cytokines, such as interleukin 2 (IL-2), interferon γ(IFN-γ), and tumor necrosis factor α (TNF-α). In the lesion tissue of RAU, the expression of Th1-relatedgenes is heightened, and there is a marked increase in the number and activity of Th1 cells, along with elevated secretion of related cytokines[15].

3 Immunomodulatory effects of vitamin D

Vitamin D plays a crucial role in regulating both innate and adaptive immunity. Its effects on innate immunity primarily enhance the body's antibacterial activity, while in adaptive immunity, it mainly reduces the expression of antigen and the activity of T andBlymphocytes[16].The immune cells regulated by vitamin D include mononuclear phagocytes, dendritic cells (DCs), and T/B lymphocytes. In particular, vitamin D can inhibit the differentiation of T lymphocytes and decrease the secretion of cytokines such as IL-12, TNF-α, IL-2, and IFN-γ. At the same time, it promotes the production of cytokines like lL-4,IL-5, and IL-10,which leads to the inhibition of Th1 activation and encourages $CD4^+$T lymphocytes to transform into Th2[17]. Then, the production of $CD4^+/CD25^+$ regulatory T cells will be induced, ultimately enhancing the function of regulatory T lymphocytes[18].

4 Studies of vitamin D in RAU

Khabazi et al. (2020) first elucidated the association between vitamin D and RAU by comparing 25 (OH) D serum levels in patients with RAU to those in healthy individuals matched by age and sex[19].They reported a significant difference in serum 25(OH)D levels between the two groups. Bahramian et al.(2018)[20], Al-Amad et al.(2020)[21], and Zakeri et al.(2021)[22] have conducted similar experiments and supported this point. In addition, Al-Maweri et al. (2020) performed a comprehensive search and meta-analysis of existing articles on the link between vitamin D deficiency and RAU in the databases of PubMed, Scopus, and Web of Science. Their result shows that all but one study indicated that there are significantly lower vitamin D levels in patients with RAU compared to healthy individuals. When pooling data from five studies, they found that vitamin D levels were significantly reduced in RAU patients, highlighting a potential association between low vitamin D levels and RAU[23].Zichuan et al. (2017) critiqued the study by Khabazi et al. (2020), which only compared serum 25(OH)D levels between RAU patients and healthy individuals without examining levels during different stages of RAU. To address this gap, they measured serum 25(OH)D levels in RAU patients during both the onset and asymptomatic phases, as well as in healthy individuals. Their findings indicated that serum 25(OH)D levels were lowest during the onset of RAU[24].

5 Conclusions

In recent years, vitamin D has gained attention among medical scholars due to its non-classical effects. Vitamin D drugs are being utilized across various medical fields, aside from their well-known use in treating osteoporosis. Due to its high absorption efficiency, relative safety, and good patient acceptance, ongoing studies are exploring the application of vitamin D in stomatology. For instance, some researchers suggest that $1\alpha,25(OH)_2D_3$ plays a role in regulating tooth growth. Additionally, $1\alpha,25(OH)_2D_3$ may help treat periodontitis by influencing specific cytokines. It also can regulate bone metabolism to remodel alveolar bone during orthodontic treatment[25]. In oral mucosal disease, researchers have been investigating the immunomodulatory effects of vitamin D.

In conclusion, vitamin D deficiency may be associated with the pathogenesis of RAU. The pathogenesis of RAU is closely linked to a T cell-mediated immune response. Vitamin D has been shown to regulate various immune cells, including the reduction of T cell-mediated responses, indicating its potential therapeutic benefits for RAU. Supplementing with vitamin D could have a therapeutic effect on RAU by modulating the immune system, particularly by regulating T cell-mediated immune responses. This may help relieve the pain of patients and shorten the healing time of lesions[25].

Declarations of interest: None.

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