Vitamin D in Oral Diseases Development

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Vitamin D is a fat-soluble secosteroid that plays a significant role in the whole body, including the maxillofacial region. The discovery of its receptors in many cells and organs made it possible to reveal the participation of vitamin D not only in the regulation of calcium phosphate metabolism, but also in immune processes, in providing anti-inflammatory and antimicrobial effects, slowing down cell proliferation and stimulating differentiation. In this literature review, we demonstrate the association between low vitamin D levels and the development of recurrent aphthous stomatitis, the course and response to treatment of squamous cell carcinoma of the oral cavity, the severity of periodontal diseases, and the processes of osseointegration and bone remodeling during dental implantation and guided tissue regeneration.

Keywords: vitamin D imbalance ; osseointegration ; dental implantation ; maxillofacial region ; oral diseases

1. Introduction

Vitamin D belongs to the group of fat-soluble secosteroid biomolecules. It is obtained in the body in two ways: alimentary (with food products and food additives intake) and through endogenous synthesis in the skin under UV radiation.

Worldwide vitamin D deficiency has increased interest in this compound, and therefore further study is warranted of its effect on various human organs and systems [1][2].

The most studied and effectively proven effects of vitamin D and its derivatives are the regulation of calcium phosphate metabolism and bone remodeling by enhancing intestinal absorption of calcium, increasing its reabsorption in the kidneys, and decreasing urinary secretion.

In addition, the discovery of vitamin D receptors in many cells and organs, for example, macrophages, monocytes, dendritic cells, cells of the placenta, the parathyroid gland and prostate, osteoblasts, smooth muscle cells and epithelial cells of the gingival attachment, contributed to the discovery of its “extra-osseous” effects [3][4]. A significant role of vitamin D has been proven in the immune processes, providing anti-inflammatory and antimicrobial effects, inhibiting cell proliferation, and stimulating differentiation.

The question of the effects of vitamin D on the oral cavity in modern dentistry remains poorly understood and requires further examination.

2. Vitamin D Metabolism

There are two main native forms of vitamin D: vitamin D2 (ergocalciferol), which is contained in plants (yeast, mushrooms, crops) and enters the body only with food, and vitamin D_3 (cholecalciferol), which is mostly synthesized in the skin from provitamin D3 (7-dehydrocholesterol) under the effects of sunlight. Another source of vitamin D_3 is animals, such as wild salmon. Derivatives of vitamin D enter the extracellular matrix, and then bind to blood proteins in the bloodstream. Both forms are inactive and undergo further transformation in the body. Initially, hydroxylation occurs in the liver under the action of 25-hydroxylase transforming to 25(OH)D (calcidiol), which is the main circulating form of vitamin D. This indicator is used to quantify the serum level of vitamin D in clinical practice, since its half-life is up to 3 weeks [5]. According to the Russian Endocrine Society Clinical Practice Guideline, a level of vitamin D of 21–29 ng/mL (525–725 nmol/liter) is considered as insufficient, a 25(OH)D level below 20 ng/mL (50 nmol/liter) is defined as deficiency, and a blood level above 30 ng/mL is interpreted as optimal [2].

The subsequent stage of vitamin D metabolism, catalyzed by 1-hydroxylase, occurs mainly in the kidneys and, to a lesser extent, in bone tissue, lungs, liver, parothyroide glands and keratinocytes. The result of this process is the formation of the biologically active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol), which is responsible for all the effects [5][6][7].

3. Vitamin D Mechanism of Action

The mechanism of action of the active form of vitamin D is similar to that of other steroid hormones, and is realized by its binding to the nuclear receptor [8]. 1,25$(OH)_2$D is a high-affinity ligand for the vitamin D receptor (VDR), which is present not only in the intestines, bone tissue and kidneys—main organs responsible for calcium phosphate metabolism—but also in more than 38 different target organs [9]. Its binding leads to the formation of a hormone–receptor complex that modifies gene expression by linking its specific domain with the regulatory DNA sequence [10]. Thus, there is activation of the synthesis of some proteins (for example, calcium-binding protein, osteocalcin, osteopontin) and inhibition of others (proinflammatory cytokines: IL-6, IL-8) [11][12].

The gene encoding the VDR is located in the chromosome 12 in position 12q13.1. The gene allele variations of VDR are relatively common in the population, with some differences between people of diverse ethnic groups. The polymorphism of the VDR gene may play a key role in the course of tumor progress, decreasing bone density, and increasing susceptibility to infections and autoimmune diseases, since it can influence the action of vitamin D on a cellular level, including calcium metabolism, transcription, cellular divisions and the initiation of the immunologic response [6][13][14].

A large number of studies have shown the correlation between low vitamin D levels and a number of different systemic diseases, i.e., diabetes mellitus, cardiovascular diseases (including coronary artery disease, congestive heart failure, valvular calcifications, stroke, arterial hypertension), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Crohn's disease), chronic kidney disease, and many others [15].

Vitamin D's regulation of calcium phosphate metabolism and bone remodeling, as well as its anti-inflammatory and immunomodulatory effects (regulation cell proliferation and differentiation), can significantly affect the health of the oral cavity [6][16][17][18][19]. A number of studies and reviews have demonstrated the association between low vitamin D levels and the course and frequency of recurrent aphthous stomatitis (RAS), the course and response to treatment of squamous cell carcinoma in the oral cavity, the severity of periodontal disease, and the processes of osseointegration and bone remodeling during dental implantation and guided tissue regeneration [16][20][21][22][23][24][25][26][27][28][29][30].

4. Oral Mucosa

4.1. Recurrent Aphthous Stomatitis (RAS)

Recurrent aphthous stomatitis (RAS) is a chronic mucosal disorder of the oral cavity, manifested in the presence of single painful erosions or ulcers of round or oval shape, with necrosis in the center and a hyperemia along the periphery. The etiology of this disease is still unknown, but dysregulation of the immune response is consider to be a risk factor, along with genetic defects, local trauma, emotional stress, and vitamin deficiency [16][31][32].

The significant role of vitamin D in the innate and acquired immune system, its ability to influence the synthesis of proinflammatory cytokines, and the presence of VDR on macrophages, dendritic cells, T- and B-lymphocytes, can explain the potential association with RAS [17][20][21].

According to a few studies [16][20][21][33], in patients with recurrent aphthous stomatitis, the level of serum 25(OH)D is significantly lower than in healthy people of similar ages and genders. Thus, Ainure Oztekin and Joshkun Oztekin [16] recommend vitamin D supplementation as a supportive treatment in patients with recurrent aphthous stomatitis. In the randomized clinical trial of Bakr Islam [34], a beneficial effect of topical oral vitamin D was demonstrated in its lowering of oral mucositis. However, in another study carried out by Krawiecka et al. [32], there was no significant difference in serum vitamin D levels (**Table 1**).

4.2. Cancer Malignancy of the Oral Cavity

One of the most common malignancies of the head and neck area is oral squamous cell carcinoma, with more than 300,000 new cases worldwide [35].

Molecular and cellular changes are associated with the influence of exogenous and endogenous factors (tobacco use or alcohol consumption, viral infections such as human papillomavirus (HPV), Epstein–Barr virus, hepatitis C virus, HIV) [36]. These multi-step processes contribute to the emergence of resistance to apoptosis in cancer stem cells, which prolongs their lifespans [22][37]. The disturbance of programmed cell death is a key factor in the carcinogenesis of squamous cell carcinoma of the oral cavity, and it manifests itself in a low response to radio- and chemotherapy as well as resistance to most anticancer drugs [13][37].

In this regard, considerable interest has arisen in examining the chemopreventive and therapeutic potential of vitamin D and its derivatives [38].

The antitumor activity of 1,25-$(OH)_2D_3$ in a number of cells is provided by its ability to induce apoptosis, and to inhibit invasion, cell proliferation, and tumor angiogenesis [13][37][39][40].

In cancer cells, 1,25-$(OH)_2D_3$ activates inhibitors of cyclin-dependent kinases (p21, p27) and mitogenic growth factors (IGF-1, EGF), and promotes the activation of TGF-β, thus exhibiting antiproliferative properties [41].

According to Udeabor S.E. et al. (2020) [22], more than 74% of patients with squamous cell carcinoma of the oral cavity showed a decrease in serum vitamin D levels compared with a control group with no history of cancer. A positive association between the risk of squamous cell carcinoma and vitamin D deficiency, especially at levels below 25 ng/ml, increases the likelihood of developing a malignant neoplasm by 1.65-fold [22].

Anand et al. concluded that patients with oral squamous cell carcinoma, who received vitamin D_3 at a dose of 1000 International Units (IU) per day for 3 months, showed a reduction in the adverse effects associated with chemotherapy. There was a decrease in the severity of oral mucositis (a decrease in hyperemia, edema, ulceration, and pain), an improvement in swallowing function, and an increase in the quality of life compared with patients who did not receive vitamin D_3 [13]. The same conclusion was reached by Mostafa et al. based on the results of their research [42].

Table 1. Literature analysis of vitamin D level and oral mucosa diseases connection.

Author, Year	Pathology	Patients, Age	Vitamin D Level	Diagnostics of Vitamin D Imbalance	Treatment of Vitamin D Imbalance	Vitamin D Level	Positive Results—Main Pathology	Probability
RCT								
Bakr SI et al., 2020 [34]	The effectiveness of topical oral vitamin D gel in prevention of radiation induced oral mucositis	45, Absent	<20 ng/mL	Vitamin D serum evaluation	Topical vitamin D oral gel, every 1 g of the gel contains 4000 IU. It was given twice daily.	Absent	Topical oral vitamin D gel has a beneficial effect in lowering oral mucositis development and in reducing pain sensation during the radiation period, especially when combined with conventional therapeutic agents.	$p < 0.05$
Lalla RV et al., 2012 [43]	Recurrent aphthous stomatitis	160, >18	Absent	Absent	A generic multivitamin supplement containing only the U.S. reference daily intake (RDI) of the essential vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D and E.	Absent	Daily multivitamin supplementation, with the RDI of essential vitamins, did not result in a reduction in thenumber or duration of RAS episodes.	$p = 0.69$
Others								
Bahramian A et al., 2018 [20]	Recurrent aphthous stomatitis	52, 18–60	33.0.7 ± 12.41 ng/dL	The electrochemiluminescence technique	Absent	Absent	The serum levels of vitamin D in patients with RAS were significantly lower than those in healthy individuals.	$p < 0.001$

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Öztekin A et al., 2018 [16]	Recurrent aphthous stomatitis	110, >18	11.00 ± 7.03 ng/mL	The electrochemiluminescence binding method (COBAS reagent kit; COBAS e601 analyzer series, Roche Diagnostics, Basel, Switzerland)	Absent	Absent	Lower vitamin D levels in patients with recurrent aphthous stomatitis compared to healthy controls.	$p = 0.004$
Khabbazi A et al., 2015 [21]	Recurrent aphthous stomatitis	95, 33.4 ± 9.8	12.1 ± 7.7 ng/dL	The Enzyme-Linked Immunosorbent Assay (ELISA) method	Absent	30 < 25(OH) D < 100 ng/dL	Insufficiency and deficiency of 25(OH) D in the RAS groups were more common than in the control group.	$p = 0.0001$
Udeabor SE et al., 2020 [22]	Oral squamous cell carcinoma (OSCC)	51, 59.33 ± 12.54	20.42 ± 12.02	Absent	Absent	>35 ng/mL	A positive association between vitamin D deficiency and OSCC risk.	$p = 0.001$
Krawiecka E et al., 2017 [32]	Recurrent aphthous stomatitis	66, 34.15 ± 12.26	16.81 ng/mL	The electro-chemiluminescence binding assay (ECLIA)	Absent	30–50 ng/mL	Vitamin D does not seem to be a trigger factor for RAS occurrence and does not appear to influence the severity of the disease in the studied group.	$p = 0.2073$
Grimm M et al., 2015 [37]	Oral squamous cell carcinoma (OSCC)	42, Absent	12.2 ng/mL	The radioimmunoassay at Biovis laboratory (Limburg-Offheim, Germany)	Absent	>35 ng/mL	A significantly increased expression of VDR was observed in tumor cells of OSCC.	$p < 0.05$
Anand A et al., 2017 [13]	Oral neoplasms	110, 42.67 ± 10.83	−1.90 ± 0.43; range −3 to 0	The chemiluminescent immunoassay method	1000 IU BD per day for 3 months	30–100 ng/mL	Vitamin D scores were significantly lower in cases compared to healthy controls.	$p = 0.002$
Zakeri M et al., 2021 [33]	Recurrent aphthous stomatitis	86, 15–40	13.19 ± 8.19 ng/mL	The enzyme-linked immunosorbent assay (ELISA), using a laboratory kit (Cat. No. EUROIMMUN, EQ. 6411–9601; PerkinElmer, Lübeck, Germany)	Absent	30–50 ng/mL	The serum levels of vitamin D are lower in patients with RAS in comparison with healthy controls.	$p = 0.002$
Mostafa B El-D et al., 2015 [42]	Head and neck squamous cell cancer	80, 54.8 ± 11.7	The median level was 10.35 ng/mL	The enzyme-linked immunosorbent assay (ELISA) technique using CALBIOTECH ELISA kit for Human VD3 Immunoassay (catalog no: VD220B, Calbiotech, Spring Valley, California, USA)	Absent	>80 nmol/L	Vitamin D deficiency is prominent in patients with head and neck squamous cell carcinoma before treatment compared to controls.	$p < 0.001$

5. Periodontal Diseases

In modern dentistry practice, the problem of chronic generalized periodontitis is quite acute, stemming not only to the high prevalence of this pathology among the population—but also to the lack of the expected effect of treatment [44].

Quite often, dentists are faced with resistance to the treatment of chronic generalized periodontitis, a decrease in the duration of stable remission and an increase in the aggressive course of periodontitis. The presented problems demonstrate the need for a more thorough study of the components of the pathogenesis of chronic generalized periodontitis, and the search for means of complex treatment [44].

Periodontitis is characterized by damage to the tissues surrounding the tooth, caused by the host's immune inflammatory response to bacterial invasion. Since vitamin D plays an essential role in the metabolism of bone tissue and maintenance of the immune response, it is reasonable to suppose that its deficiency may affect the pathogenesis of the disease and the state of the periodontium [45][46].

The active metabolite of vitamin D—1,25$(OH)_2D_3$—is involved in specific immune defense and has an anti-inflammatory effect, acting on T- and B-lymphocytes, inhibiting the production of pro-inflammatory IL-6 and IL-8, which are involved in the development of acute inflammation [46][47][48][49].

The regulation of the nonspecific immune response occurs by stimulating the synthesis of antimicrobial peptides (defensins and cathelicidin) through vitamin D receptors (VDR), which have been found in monocytes, macrophages, neutrophils, and dendritic cells.

One of the defensins, beta-defensin 2, exhibits antimicrobial activity against oral pathogens, including bacteria associated with the development of periodontitis (Porphyromonas gingivalis, Fusobacterium nucleatum, and Aggregatibacter actinomycetemcomitans) [14][25].

The analysis of observations provided by Bashutski JD et al. [45] demonstrated that vitamin D deficiency leads to less effective outcomes after periodontal surgery (lower soft tissue attachment and changes in probing depth).

Pinto et al. [50] in their systematic review argued that the relation between periodontal disease and vitamin D deficiency may be justified, but most studies have significant limitations, which prevents the confirmation of the existence of this association.

Research by Isola et al. [26], as well as Anbarcioglu E et al. [25], showed that patients with periodontitis had lower serum vitamin D levels compared to healthy patients. Moreover, vitamin D deficiency negatively influenced the course of periodontal disease and increased the risk of aggressive periodontitis. Since this study confirms a relation between low serum vitamin D levels and the development of periodontitis, according to the authors, vitamin D assessment should be recommended at the beginning of periodontal therapy, as it may reduce the risk of developing this disease [26].

In addition to the above, the study by Garcia et al. demonstrates that calcium and vitamin D supplementation (1000 IU/day) had a moderate positive effect on periodontal health and improved clinical parameters [51]. The studies of Gao et al. and Meghil confirmed that supplementation with vitamin D significantly raised its serum level, improved such periodontal parameters as attachment loss and probing depth, and reduced systemic inflammation [52][53]. These results confirm the possibility of a positive effect of vitamin D on periodontal health (**Table 2**).

Table 2. Literature analysis of vitamin D level and periodontal diseases connection.

Author, Year	Pathology	Patients, Age	Vitamin D Level	Diagnostics of Vitamin D Imbalance	Treatment of Vitamin D Imbalance	Vitamin D Level	Positive Results—Main Pathology	Probability
RCT								
Gao W et al., 2020 [52]	Nonsurgical periodontal therapy	360, 30–70	Absent	Direct Elisa kit (Immunodiagnostic Systems Limited, IDS, East Boldon, Great Britain)	90 capsules of 2000 IU vitamin D3, 1000 IU vitamin D3 or placebo	Absent	Short-term supplementation of vitamin D significantly raised serum 25(OH)D levels and improved AL (attachment loss) and PD (probing depth) for moderate and deep pockets in patients with moderate to severe periodontitis	$p < 0.05$
Hiremath VP et al., 2013 [54]	Gingivitis	96, 18–64	20–65 ng/mL	Direct Elisa kit (Immunotek; Bensheim, Germany)	2000 IU/day, 1000 IU/day, 500 IU/day or placebo	Absent	Vitamin D has an anti-inflammatory effect in doses ranging from 500 to 2000 IU	$p < 0.001$
Others								

Author, Year	Pathology	Patients, Age	Vitamin D Level	Diagnostics of Vitamin D Imbalance	Treatment of Vitamin D Imbalance	Vitamin D Level	Positive Results—Main Pathology	Probability
Meghil MM et al., 2019 [53]	Generalized chronic moderate to severe periodontitis	23, 44.8 ± 9.4	Non-deficient	Enzyme immunoassay (Immunodiagnostic Systems, Fountain Hills, AZ, USA)	4000 IU/day oral Vitamin D supplementation for 16 weeks	Absent	An important role for vitamin D supplementation in inducing local and systemic anti-inflammatory response and enhancing the autophagic profile in PD patients after scaling and root planning	$p < 0.001$
Bashutski JD et al., 2011 [45]	Periodontal surgery and teriparatide administration in patients with severe chronic periodontitis	40, 30–65	28% of enrolled participants presenting with mild deficiency (16–19 ng/mL), participants with moderate to severe deficiency were excluded	Serum vitamin D level	Daily 1000 mg calcium and 800 IU vitamin D oral supplements was initiated 3 days prior to surgery and continued for 6 weeks	20–74 ng/mL	It is advisable to ensure adequate vitamin D levels well in advance of periodontal surgery, to attain the best possible results	$p < 0.01$
Emrah A et al., 2018 [25]	The association between vitamin D concentration and both aggressive and chronic periodontitis	129, 21–47	11.22 ± 4.8 ng/mL—aggressive periodontitis 16.13 ± 8.3 ng/mL—chronic periodontitis	Liquid chromatography–mass spectrometry (LC-MS/MS) (München, Germany).	Absent	>20 ng/mL	The study showed that lower 25(OH)D concentrations were associated with a higher risk of aggressive periodontitis	$p < 0.0002$
Isola G et al., 2019 [26]	The association between serum vitamin D levels and periodontitis in patients with chronic periodontitis (CP) and coronary heart disease (CHD)	179, ≥18	CP—17.4 ± 5.2 ng/mL CP + CHD—16.5 ± 5.6 ng/mL	Serum vitamin D level	Absent	≥20 ng/mL	Patients with CP and CP + CHD presented significantly lower serum levels of vitamin D compared to CHD and healthy controls	$p < 0.001$
Laky M et al., 2019 [46]	The association between vitamin D concentration and periodontal diseases	58, 35.41 ± 7.7	Absent	An enzyme-immunoassay, EIASON 25-OH-VitaminD® test kit, IASON GmbH, Graz, Austria	Absent	>30 ng/mL	25(OH)D deficiency is significantly associated with periodontal disease	$p < 0.05$

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Author, Year	Pathology	Patients Age	Vitamin D Level	Diagnostics of Vitamin D Imbalance	Treatment of Vitamin D Imbalance	Vitamin D Level	Positive Results—Main Pathology	Probability
Agrawal AA et al., 2019 [48]	The association between the levels of vitamin D and calcium in the serum of periodontally healthy, chronic gingivitis and chronic periodontitis patients with and without type-2 diabetes mellitus	100, 30–50	chronic gingivitis—49.05 ng/mL chronic periodontitis 26.94 ng/mL	ELISA kit	Absent	Absent	Vitamin D and calcium levels are inversely correlated with random blood sugar and glycosylated hemoglobin, and, also probing pocket depth and clinical attachment loss, thus may contribute to increases in the severity of periodontal disease activity	$p < 0.05$
Garcia MN et al., 2011 [51]	Vitamin D and calcium supplementation for better periodontal health: Proper or improper to patients not taking it	51, postmenopausal fem., males 50–80	Absent	Nutritional analysis	Vitamin D (400 IU/day) and calcium (1000 mg/day)	125 to 175 nmol/L	Calcium and vitamin D supplementation (1000 IU/day) had a modest positive effect on periodontal health	$p = 0.058$

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