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Local vitamin D_3 bioactivation in oral tissue, from inactive to influential: A narrative review

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ABSTRACT

Objectives: Vitamin D_3 status profoundly affects oral health and disease. Over the last decade, evidence has emerged that vitamin D_3 activation can also occur in peripheral tissues. This narrative review was conducted to critically analyze the state of the art about the presence and activity of enzymes involved in the bioactivation of vitamin D_3 in the oral tissues.

Design: A comprehensive literature search was performed in PubMed and Google Scholar. The search included articles published in English without any time limit. Keywords included but not limited to the combinations of: "vitamin D_3", "$25(OH)D_3$", "$1,25(OH)_2D_3$", "oral tissues", "megalin", "CYP27B1", "extrarenal", and "antimicrobial peptides". Further studies were identified by screening the reference lists of the relevant publications.

Results: Various vitamin D_3 metabolites influence the inflammatory response and the production of antimicrobial peptides in various oral cells. The enzyme CYP27B1, which is responsible for the conversion of $25(OH)D_3$ into $1,25(OH)_2D_3$ and its bioactivation, is present in various oral tissues and cells. The existence and physiological significance of local vitamin D_3 activation in oral tissues remain unclear. Most of $25(OH)D_3$ is bound to the vitamin D-binding protein (DBP) and must be dissociated for activation. It is unclear whether and how this uncoupling occurs in oral tissue.

Conclusion: Currently, there is rather indirect evidence that vitamin D_3 could be bioactivated in oral tissues. Further studies on the local conversion of vitamin D_3 to $25(OH)D_3$ and, subsequently, to $1,25(OH)_2D_3$ in oral tissue, their regulation, and the role of free and bioavailable vitamin D_3 metabolites are required.

In this narrative review, we examine the local effects of various vitamin D_3 metabolites on oral tissue. In particular, we will summarize evidence on the local activation of vitamin D_3 in oral tissue, such as oral mucosa, gingiva, and periodontal ligament. Further, the effects of various vitamin D_3 metabolites on oral cells *in vitro* and *in vivo*, the potential role of free and bioavailable vitamin D_3, and the significance of local vitamin D_3 in saliva are discussed. The role of vitamin D_3 status in oral health and disease will be addressed only superficially, as it has already been described in numerous experimental studies and systematic reviews (Botelho et al., 2020; Liang et al., 2023; Lu, 2023; Machado et al., 2020). The review will focus exclusively on the conversion of vitamin D_3 to $25(OH)D_3$, and subsequently to $1,25(OH)_2D_3$, as well as other related metabolites. Alternative vitamin D_3 activation pathways associated with the formation of $20(OH)D_3$ in skin, mediated by CYP11A1 (Slominski et al., 2024), are out of the scope of the present review.

Abbreviations: BGLAP, bone gamma-carboxyglutamate protein; DBP, vitamin D binding protein; FBS, fetal bovine serum; FGF-23, fibroblasts growth factor 23; GCF, gingival crevicular fluid; IFN, interferon; IL, interleukin; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry; MSCs, mesenchymal stromal cells; OPG, osteoprotegerin; OTM, orthodontic tooth movement; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor κB; TGF, transforming growth factor; TNF, tumor necrosis factor; VDR, vitamin D receptor.

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1. Systemic vitamin D_3 production and metabolism

1.1. Vitamin D_3 production and metabolites

Vitamin D_3 is considered both a secosteroid hormone and a vitamin because, on the one hand, like hormones, it can be produced by the human body (Ellison & Moran, 2021; Wacker & Holick, 2013), and on the other hand, like other vitamins, its deficiency has detrimental effects on the body, and it should be obtained through the diet (Amrein et al., 2020; Vieth, 2004). Most commonly, vitamin D_3 (cholecalciferol) is produced from 7-dehydrocholesterol in the skin upon UV exposure (Wacker & Holick, 2013). In addition to endogenous production, vitamin D_3 can be obtained from foods such as oily fish, mushrooms, reindeer lichen, and fish liver oils, as well as from dietary supplements (Benedik, 2022). Upon formation or dietary uptake, vitamin D_3 is transported to the liver, where it is metabolized to 25-hydroxyvitamin D_3 (25(OH)D_3, calcifediol) (Jones, 2008). This process is mediated by CYP2R1, a major but not exclusive 25-hydroxylase (Bikle, 2014; Cheng et al., 2004). 25(OH)D_3 has a half-life of about 15 days and is commonly used as an indicator of vitamin D_3 status (Giustina et al., 2024). As the next step, 25(OH)D_3 is further transported to the kidney, where it is converted to 1,25-dihydroxyvitamin D_3 (1,25$(OH)_2D_3$, calcitriol) by CYP27B1, also known as 1α-hydroxylase (Hewison et al., 2000). 1,25$(OH)_2D_3$ is a biologically active vitamin D_3 metabolite. Activation of the vitamin D receptor (VDR) upregulates several genes (Haussler et al., 1998), including CYP24A1, which is the cytochrome P450 component of the 24-hydroxylase enzyme (Jones et al., 2012). This mitochondrial enzyme catalyzes the 24-hydroxylation of 1,25$(OH)_2D_3$, thereby inactivating it and forming 1,24,25-trihydroxyvitamin D_3 (1,24,25$(OH)_3D_3$) metabolites (Jones et al., 2012). Besides, CYP24A1 can also hydroxylate 25(OH)D_3, resulting in the formation of another vitamin D_3 metabolite, 24,25$(OH)_2D_3$ (Jones et al., 2012). For a long time, both 24,25$(OH)_2D_3$ and 1,24,25$(OH)_3D_3$ were considered as biologically inactive, but this assumption was denied by several recent studies(Boyan et al., 1988; Domzalski et al., 2025; Pedrozo et al., 1999). However, the exact role and significance of these vitamin D_3 metabolites has still to be investigated.

1.2. Vitamin D_3 status assessment and systemic levels of various vitamin D_3 metabolites

Vitamin D_3 status is usually evaluated based on the measurements of the total level of 25(OH)D_3 metabolite in serum (Giustina et al., 2024). Although the question of what is the optimal serum level of vitamin D_3 is still a matter of debate and is differently regarded by various regulatory agencies, it is broadly accepted that a serum level of total 25(OH)D_3 lower than 20 ng/mL (or 50 nmol/L) is an indicator of vitamin D deficiency (Amrein et al., 2020; Holick & Chen, 2008). There is no consensus on the optimal serum 25(OH)D_3 levels: they may vary by age, gender, race, and other factors (Fuleihan Gel et al., 2015; Giustina et al., 2024). Several reports suggest that optimal serum 25(OH)D_3 levels, or vitamin D_3 sufficiency, are achieved when levels exceed 30 ng/mL (75 nmol/L) (Alshahrani & Aljohani, 2013; Bischoff-Ferrari, 2014). Interestingly, the recently issued Endocrine Society guidelines no longer endorse specific 25(OH)D_3 levels to define vitamin D_3 sufficiency, insufficiency, and deficiency (Demay et al., 2024), and suggest that optimal 25(OH)D_3 levels be specific for the specific health state, age, and population.

Other vitamin D_3 metabolites, besides 25(OH)D_3, are also detectable in serum. The biologically active 1,25$(OH)_2D_3$ is not considered an ideal marker of vitamin D_3 status due to its relatively short half-life of 4–6 h and its regulation by parathyroid hormone (PTH) (Holick, 2009). Serum 1,25$(OH)_2D_3$ levels are about 1000 times lower than those of 25(OH)D_3 (Holick, 2009); the levels of about 20–30 pg/mL (48–72 pmol/L) were reported (Aksoy et al., 2000; Biancuzzo et al., 2013). Supplementation with vitamin D_3 has only a marginal or no effect on serum 1,25$(OH)_2D_3$ levels (Biancuzzo et al., 2013), which is due to the regulation of its production by PTH (Holick, 2009). The most abundant product of 25(OH)D_3 catabolism, 24,25$(OH)_2D_3$, has a half-life of about 7 days and is present in serum in nanomolar concentrations (Bosworth et al., 2012; Leeuwenkamp et al. 1993). One study measured serum 24,25$(OH)_2D_3$ levels in 1996 young healthy British Army recruits using the LC–MS/MS method and reported the reference interval of this metabolite of 1.1–13.5 nmol/L (Tang et al., 2017). A total 24,25$(OH)_2D_3$ level above 4.2 nmol/L was suggested to correspond to a 25(OH)D_3 level above 20 ng/mL (50 nmol/L) (Tang et al., 2017). An earlier study reported serum levels of 1,24,25$(OH)_3D_3$ of 3.9–7.8 pg/mL (9.3–18.5 pmol/L) as measured by radioimmunoassay (Clemens et al., 1982). Later studies using mass spectrometry have reported slightly higher values for this metabolite, with a mean of about 15 pg/mL (35 pmol/L), accounting for about 35–40% of 1,25$(OH)_2D_3$ (Turner et al., 2023, 2022).

1.3. Vitamin D binding protein and free hormone hypothesis

The majority of assays used in clinical and research settings estimate total vitamin D_3 metabolite levels and do not discriminate between free and protein-bound forms. In healthy individuals, only approximately 0.03% of the total 25(OH)D_3 is free, whereas about 85% of 25(OH)D_3 is bound to the vitamin D binding protein (DBP) and 15% to albumin (Bikle & Schwartz, 2019). The vitamin D-binding protein (DBP) is well conserved across vertebrates and specifically binds all known vitamin D_3 metabolites (Bouillon et al., 2019). DBP is highly polymorphic: different DBP variants exhibit distinct abilities to bind vitamin D_3 and are associated with various pathologies(Rozmus et al., 2020). It is assumed that 25(OH)D_3 bound to DBP is biologically unavailable until it is transported into the cells and uncoupled from DBP. This function is fulfilled by the complex megalin/cubulin, which is abundant in kidney proximal tubule epithelial cells (Nykjaer et al., 1999) and mediates the endocytosis of DBP−25(OH)D_3 complex and its uncoupling from DBP (Christensen & Birn, 2001). Although megalin is most abundantly expressed in the kidney proximal tubuli (Kukida et al. 2020), it was also detected in some extra-renal tissues and cells, particularly parathyroid glands, placenta, and macrophages (Khan et al., 2022; Lundgren et al., 1997; Pieper-Furst et al., 2011).

The binding of 25(OH)D_3 to albumin is weaker than to DBP, and therefore albumin-bound 25(OH)D_3 can be easily processed by cells (Bhan et al., 2012). The sum of free and albumin-bound 25(OH)D_3 is considered bioavailable 25(OH)D_3 and was postulated to be biologically active by the free hormone hypothesis (Bhan et al., 2012; Bikle & Schwartz, 2019; Chun et al., 2014). Measuring free vitamin D_3 metabolite levels in serum is technically challenging, and the rationale for doing so remains debated (Alexandridou et al., 2025; Bikle et al., 2017; Macova & Bicikova, 2021; Tsuprykov et al., 2018). Most studies use a formula to calculate free and bioavailable 25(OH)D_3 from its total level, and the levels of DBP and albumin (Bikle et al., 1986; Powe et al., 2011). It should be noted that vitamin D_3 supplementation also increases DBP (Glendenning et al., 2013). Furthermore, genetic polymorphisms in DBP can also affect vitamin D_3 status (Newton et al., 2019; Sinotte et al., 2009). Nevertheless, a study on 5060 patients investigated the relationship between total and free 25(OH)D_3 and found a near-linear association, with a correlation coefficient of about 0.84 (Zeng et al., 2021). This study suggests that a free 25(OH)D_3 level of 8.5 pg/mL corresponds to a total 25(OH)D_3 level of 30 ng/mL (Zeng et al., 2021).

2. Vitamin D_3 metabolism in oral tissues and its regulation

The classical role of the vitamin D_3 pathway includes regulating intestinal calcium absorption, renal calcium reabsorption, and calcium and phosphate mobilization from bone (Christakos et al., 2011; Khazai et al., 2008; Kumar et al., 2012). In addition to these classical effects, which are beyond the scope of the present review, vitamin D_3 exerts pleiotropic effects across various tissues (Bikle, 2009; Christakos et al., 2016). These effects are particularly associated with the regulation of

the innate and adaptive immune response, cancer metabolism, and the cardiovascular system (Christakos et al., 2016). Various vitamin D_3 metabolites have been shown to affect the activity and properties of various oral tissues and cells, including oral epithelial cells and mesenchymal stromal cells (MSCs) from different tissues (Andrukhov et al., 2020; Karaca et al., 2025; Menzel et al., 2019). The expression of CYP2R1 and CYP27B1, which are responsible for the conversion of vitamin D_3 to 25(OH)D_3 and further to 1,25$(OH)_2D_3$, respectively, was also described in various oral tissues and cells (Andrukhov et al., 2020; Liu et al., 2012a; Menzel et al., 2019; Sundaram et al., 2014). In this chapter, we will address the potential bioactivation of vitamin D_3 in oral tissues.

2.1. Expression and regulation of CYP27B1 in oral tissues

It is well recognized that CYP27B1, an enzyme responsible for the conversion of 25(OH)D_3 into biologically active 1,25$(OH)_2D_3$, is expressed in numerous extrarenal tissues, but its physiological significance remains unclear and is currently under investigation (Adams & Hewison, 2012; Bikle et al., 2018). However, it has already been shown that there are essential differences in the regulation of the renal and extrarenal forms of this enzyme. In the kidney, CYP27B1 expression is activated by PTH and suppressed by fibroblast growth factor 23 (FGF−23) and 1,25$(OH)_2D_3$ (Meyer & Pike, 2023). In contrast, extrarenal CYP27B1 is not regulated by these factors, but rather by inflammatory environments (Adams et al., 2014; Meyer et al., 2019; Zittermann, 2025). There are some indications that extrarenal CYP27B1 contributes to the 1,25$(OH)_2D_3$ production *in vivo* (Meyer et al., 2024).

The evidence on the expression and activity of CYP27B1 in oral tissue primarily comes from *in vitro* studies based on the ability of various cells to activate VDR-regulated proteins upon treatment with 25(OH)D_3 (Andrukhov et al., 2020). Thus, the ability to be activated by 25(OH)D_3 was shown for the mesenchymal stromal cells isolated from gingiva (Liu et al., 2012a), periodontal ligament (Andrukhov et al., 2014; Behm et al., 2023), dental pulp (Khanna-Jain et al., 2010), and dental follicle (Khanna-Jain et al., 2010; Meyer & Pike, 2023), as well as for different types of oral epithelial cells (Karaca et al., 2025; Menzel et al., 2019; Zhang et al., 2018). To date, only one histological study described the expression of CYP27B1 protein in both the gingival epithelium and connective tissue, and this expression was increased in the inflamed tissue of patients with periodontitis (Liu et al., 2021).

The regulation of CYP27B1 in oral tissues is generally understudied, and the data are partly contradictory. The expression of CYP27B1 in dental pulp- and dental follicle-derived MSCs is upregulated by 25(OH)D_3 but not by 1,25$(OH)_2D_3$ (Khanna-Jain et al., 2010). In MSCs derived from the gingiva and periodontal ligament, CYP27B1 expression was up-regulated by interleukin (IL)−1β and sodium butyrate, but not affected by *Porphyromonas gingivalis* LPS, PTH, calcium chloride, and 1,25$(OH)_2D_3$ (Liu et al., 2012b). In gingival epithelial cells, the expression of CYP27B1 is upregulated by 1,25$(OH)_2D_3$ (McMahon et al., 2011). Our data show that the expression of CYP27B1 in periodontal ligament-derived MSCs is regulated by pro- and anti-inflammatory cytokines, such as interleukin (IL)−1β, tumor necrosis factor α, interferon γ, and transforming growth factor β, and is only weakly influenced by PTH and FGF−23 (unpublished data). Despite the presence of CYP27B1 in various oral tissues, whether and how 25(OH)D_3 is activated in oral tissues *in vivo*, and the physiological significance of this activation, remain to be established. The major issue is that, as mentioned above, most of 25(OH)D_3 is bound to DBP and therefore is biologically unavailable. Activation of 25(OH)D_3 by CYP27B1 in the oral tissues and its conversion to biologically active 1,25$(OH)_2D_3$ would be possible only after the transport of 25(OH)D_3 inside the cells and its uncoupling from DBP and/or albumin. The possibility of this process is discussed in the next paragraph.

2.2. Can 25(OH)D_3 be transported into the cells in oral tissues to be activated locally?

To be activated in peripheral tissue and converted to 1,25$(OH)_2D_3$ by local CYP27B1, 25(OH)D_3 should be uncoupled from the DBP and transported into cells. In the kidney proximal tubuli, this function is fulfilled by the complex megalin/cubulin (Christensen, Birn, 2001). There is evidence that megalin is also expressed in extrarenal tissues, such as bone and parathyroid cells (Khan et al., 2022). However, the expression of these proteins in oral tissue is either not reported or rarely investigated. Megalin expression was detected in premalignant and malignant oral squamous epithelial lesions but not in healthy oral mucosa (Zulijani et al., 2021). We did not find any report of megalin expression in gingiva- or periodontal ligament-derived MSCs. Analysis of the dataset from our single-cell RNA-seq study (Behm, Milek, Schwarz, Kovar, et al., 2024), which includes data from gingiva- and periodontal-ligament-derived MSCs, did not reveal megalin expression in these cells (unpublished observation). Megalin expression in extrarenal tissues may be individual-dependent. Thus, one study of bone marrow MSCs found variable megalin expression across donors: some exhibited high constitutive megalin expression, whereas others showed low expression (Gao et al., 2019). Further, this study showed that 25(OH)D_3 stimulated osteogenic differentiation and the expression of VDR-regulated genes only in cells with high constitutive megalin expression; silencing megalin with siRNA abolished this effect (Gao et al., 2019).

The ability of 25(OH)D_3 to influence the cellular activity in the cells of oral tissues *in vitro* should be interpreted with caution. In our studies, we observed that stimulation of human periodontal ligament-derived MSCs with 25(OH)D_3 at concentrations of 10–100 nM in fetal bovine serum (FBS)- free media significantly upregulates the expression of VDR-regulated genes, such as bone gamma-carboxyglutamate protein (BGLAP, also known as osteocalcin) (Blufstein et al., 2020) and CYP24A1 (unpublished observation, manuscript in preparation). However, under these conditions, almost all 25(OH)D_3 is bioavailable, which does not reflect the natural situation. The ability of 25(OH)D_3 to increase BGLAP expression is strongly diminished when human periodontal ligament-derived MSCs were cultured in the osteogenic differentiation media containing 10% FBS (Blufstein et al., 2021). Similarly, a stimulatory effect of 25(OH)D_3 on CYP24A1 is abolished by FBS in a concentration-dependent manner (unpublished observation, manuscript in preparation). This could be explained by the presence of DBP in FBS, which binds 25(OH)D_3 and prevents its entrance into the cells (Kongsbak et al., 2014; Rowling et al., 2006). Interestingly, a small stimulating effect of 25(OH)D_3 on the expression of BGLAP was observed even in the presence of 10% FBS after 21 days of culturing. Other studies have also observed a stimulating effect of 25(OH)D_3 on osteogenic differentiation in MSCs from bone marrow, dental pulp, and dental follicle (Khanna-Jain et al., 2010; Lou et al., 2017), typically induced by culturing in osteogenic media containing 10% FBS. These observations suggest that 25(OH)D_3 may enter various MSCs even in the presence of FBS and DBP. However, this assumption needs to be approved by additional well-designed experiments. In summary, the interpretation of *in vitro* data on the effects of 25(OH)D_3 and its bioactivation in oral tissues should be approached with caution, given the binding of 25(OH)D_3 to DBP and/or other serum components.

The possibility of local activation of vitamin D_3 in oral tissues is indirectly supported by animal studies on the topical application of vitamin D_3 (Ayyad et al., 2025; Kirkwood et al., 2024; Menzel et al., 2019; Salomo-Coll et al., 2016). In particular, a topical application of vitamin D_3 reduced bone loss and improved bone-to-implant contact in dogs (Salomo-Coll et al., 2016), reduced the expression of inflammatory genes in mouse gingiva(Menzel et al., 2019), and reduced bone loss and inflammation in a ligature-induced periodontitis model in mice (Kirkwood et al., 2024). Local vitamin D_3 metabolism may mediate the effects observed after topical application of vitamin D_3, but the exact

mechanisms underlying this action remain to be established.

3. Implications of vitamin D_3 metabolism in oral health and disease

Vitamin D_3 status and vitamin D_3 deficiency affect various aspects of oral health (Botelho et al., 2020). In particular, there is a connection between various pathological states, including periodontitis (Liang et al., 2023; Machado et al., 2020), caries (Dura-Trave & Gallinas-Victoriano, 2024; Nireeksha et al., 2024), temporomandibular disorders (Tabrizi et al., 2025), marginal bone loss in dental implants (Miron et al., 2025), oral lichen planus (Saeed et al., 2022), and oral malignant disorders (Hung et al., 2023; Samanta et al., 2024), and vitamin D_3 deficiency. A recently published case series also suggests a potential role for vitamin D_3 in oral mucosal wound healing (Siregar & Hidayat, 2023). In this chapter, we will discuss whether and how local vitamin D_3 metabolism may be implicated in the effects of vitamin D_3 on oral health and disease.

3.1. Antimicrobial effects of vitamin D_3 and its implications in oral health

It is largely recognized that vitamin D_3 induces the production of antimicrobial peptides and enhances their antimicrobial activity in a variety of cell types, and this effect is intracrine, i.e., associated with the local conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ (Hewison, 2011; Youssef et al., 2011). *In vitro* studies showed that $25(OH)D_3$ and $1,25(OH)_2D_3$ enhance the expression of genes encoding various antimicrobial peptides, particularly cathelicidin (LL−37) and beta-defensins, as well as their release by oral epithelial cells, gingiva- and periodontal ligament-derived MSCs, and immune cells (Aidoukovitch et al., 2024; De Filippis et al., 2017; Figgins et al., 2024; Karaca et al., 2025; McMahon et al., 2011; Menzel et al., 2019; Tada et al., 2016; Zhang et al., 2023). Furthermore, treatment of oral epithelial cells with $25(OH)D_3$ or $1,25(OH)_2D_3$ enhances their antibacterial activity against various periodontitis-associated microorganisms, particularly *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Filifactor alocis*, and *Fusobacterium nucleatum* (De Filippis et al., 2017; Karaca et al., 2025; McMahon et al., 2011). The extent and clinical relevance of vitamin D_3-induced antimicrobial peptide production *in vivo* remain to be investigated. A study on 72 healthy adults showed that salivary cathelicidin levels exhibited a stronger correlation with the salivary $25(OH)D_3$ levels (Pearson's r 0.667) than with serum $25(OH)D_3$ levels (Pearson's r 0.328) (Davidopoulou et al., 2025). This observation underlines a potentially important role of local vitamin D_3 activation in the production of antimicrobial peptides. Furthermore, VDR polymorphism is associated with differences in bacterial load and in the detection of certain periodontitis-associated bacteria by PCR (Cafiero et al., 2022). Stimulation of antimicrobial peptides production by vitamin D_3 can hypothetically contribute to caries prevention (Grundmann et al., 2025). This assumption is reinforced by a recent systematic review showing that VDR polymorphism, in combination with ethnic background, might influence the caries experience (Chisini et al., 2025). Nevertheless, the exact role of vitamin D_3-induced production of antimicrobial peptides *in vivo*, and their clinical relevance, still needs to be established.

3.2. The presence of vitamin D_3 metabolites in saliva and their functional importance

Several studies measured $25(OH)D_3$ in the saliva of patients with different oral statuses (Bahramian et al., 2018; Costantini et al., 2020; Davidopoulou et al., 2025; Nireeksha et al., 2024; Samanta et al., 2024). Most of these studies used commercially available ELISAs to assess total $25(OH)D_3$ and reported that salivary levels of these metabolites are about 2–3 times lower compared to those measured in serum. One study reported similar salivary and serum $25(OH)D_3$ levels and a moderate correlation between them (Sari et al., 2021). It should be noted that the concentration of reported salivary $25(OH)D_3$ could be influenced by the saliva collection method. The significance and role of salivary $25(OH)D_3$ are rather unclear. However, individual studies have reported an association between low salivary $25(OH)D_3$ levels and periodontitis (Costantini et al., 2020), caries (Nireeksha et al., 2024), and oral malignant disorders (Samanta et al., 2024). The origin of $25(OH)D_3$ in saliva and its physiological importance are rather unclear. Saliva is a promising diagnostic fluid, but the levels of various substances in saliva depend substantially on the collection method (Giannobile et al., 2009; Haririan et al., 2021).

3.3. Vitamin D_3 metabolism and periodontitis

Vitamin D_3 deficiency is widely recognized as an important risk factor for periodontitis (Laky et al., 2017; Liang et al., 2023; Machado et al., 2020). The reasons for this association are diverse and not yet fully understood and could be explained by various mechanisms, particularly the antimicrobial, immunomodulatory, and anti-inflammatory effects of vitamin D_3 (Moszura et al., 2026).

The association between vitamin D_3 deficiency and periodontitis could be partially attributed to the local anti-inflammatory or antimicrobial effects of vitamin D_3. In particular, both $25(OH)D_3$ and $1,25(OH)_2D_3$ have been shown to attenuate the response of various dental MSCs or MSCs-like cells to TLR agonists or inflammatory cytokines (Andrukhov et al., 2014; De Filippis et al., 2017; Hosokawa et al., 2015; Nakashyan et al., 2017; Nastri et al., 2018; Nebel et al., 2015). Dental MSCs fulfill various functions and may contribute to the inflammatory response in periodontitis and antimicrobial activities (Andrukhov, 2021; Andrukhov et al., 2021). Besides, dental MSCs possess the immunomodulatory properties (Andrukhov et al., 2019), which can be either enhanced or suppressed by various vitamin D_3 metabolites depending on the inflammatory environment (Behm et al., 2020, 2019, 2023; Behm, Milek, Schwarz, Rausch-Fan, et al., 2024). Furthermore, $25(OH)D_3$ and $1,25(OH)_2D_3$ modulate the inflammatory response in epithelial cells and macrophages (Figgins et al., 2024; Karaca et al., 2025; Xu et al., 2016). However, the clinical relevance of these effects should be critically regarded. The anti-inflammatory effects of $1,25(OH)_2D_3$ are reported for concentrations (> 1 nmol/L) that are markedly higher than those reported for the serum levels of this metabolite (usually < 100 pmol/L). Regarding $25(OH)D_3$, as discussed above, its effects are affected by the presence of DBP. However, some cells, particularly M1 macrophages, express very high levels of CYP27B1 and are able to convert $25(OH)D_3$ into $1,25(OH)_2D_3$ even in the presence of DBP in physiologically relevant concentrations (Lopez et al., 2021).

The evidence regarding the contribution of the local vitamin D_3 levels to periodontitis *in vivo* is rather limited. One study reported a moderately negative correlation between salivary levels of $25(OH)D_3$ and those of IL−17, IL−35, and matrix metalloproteinase−9 in periodontitis patients (Costantini et al., 2020). As already mentioned, local application of vitamin D_3 reduces the bone loss and inflammation in the experimental periodontitis model in mice (Kirkwood et al., 2024). Two studies also showed that DBP levels in gingival crevicular fluid (GCF) are elevated in periodontitis-affected pockets (Chakravarthy et al., 2022; Zhang et al., 2014). Moreover, one of these studies reported a negative correlation between DBP levels in GCF and clinical parameters, including pocket depth and clinical attachment loss (Zhang et al., 2014). Alteration in local DBP levels might affect the bioavailability of local vitamin D_3 metabolites. Therefore, the association between local DBP levels and clinical parameters of periodontitis might also indicate the importance of the local vitamin D_3 effects.

3.4. Vitamin D_3 metabolism and orthodontic tooth movement

Orthodontic tooth movement (OTM) is a process characterized by aseptic inflammation and complex interactions between the skeletal and immune systems (Behm et al., 2022; Chaushu et al., 2022; Jiang et al.,

2015). As summarized in recent systematic reviews, local application of $1,25(OH)_2D_3$ usually accelerates the orthodontic tooth movement in animal studies and clinical trials (Ferrillo et al., 2024; Gratton et al., 2026; Tini et al., 2024). These effects of $1,25(OH)_2D_3$ are presumably attributed to the regulation of the OPG/RANKL system. However, since these studies used a biologically active $1,25(OH)_2D_3$, they do not provide insight into whether the local activation of vitamin D_3 is essential for OTM. Nevertheless, there is still some evidence supporting such involvement. Particularly, a genetic polymorphism of CYP27B1 had a significant effect on the extent of external apical root resorption (Tini et al., 2024). Furthermore, local DBP levels also seem to affect the OTM (Bayirli et al., 2025; Tashkandi et al., 2021). In particular, very low or very high DBP levels in the saliva were associated with reduced tooth movement (Tashkandi et al., 2021). The levels of DBP in saliva and GCF exhibited negative and positive correlations with collagen degradation and synthesis, respectively (Bayirli et al., 2025).

4. Free and bioavailable vitamin D_3, vitamin D_3 metabolite ratio and oral health

To date, the association between free and bioavailable vitamin D_3 and oral health and disease remains largely unexplored. To the best of our knowledge, only one study reports the levels of free and bioavailable $25(OH)D_3$ in periodontitis patients (Aydin et al., 2023). However, this study did not measure free $25(OH)D_3$, but calculated these levels from measurements of total $25(OH)D_3$ and serum levels of DBP and albumin using a specific formula (Aydin et al., 2023). Total $25(OH)D_3$ levels were about 1.7 times higher in the healthy group than in the periodontitis group, whereas free and bioavailable $25(OH)D_3$ were about 2.2 and 2.5 times, respectively (Aydin et al., 2023). Thus, it seems that free and bioavailable $25(OH)D_3$ levels provide slightly better discrimination between healthy and periodontitis groups. The importance of free and bioavailable vitamin D_3 in periodontitis is also underscored by studies on serum DBP levels. Particularly, a recent systematic review suggests a positive association between serum DBP levels and periodontitis (Dhaif et al., 2024). The rationale for this association is that higher serum DBP

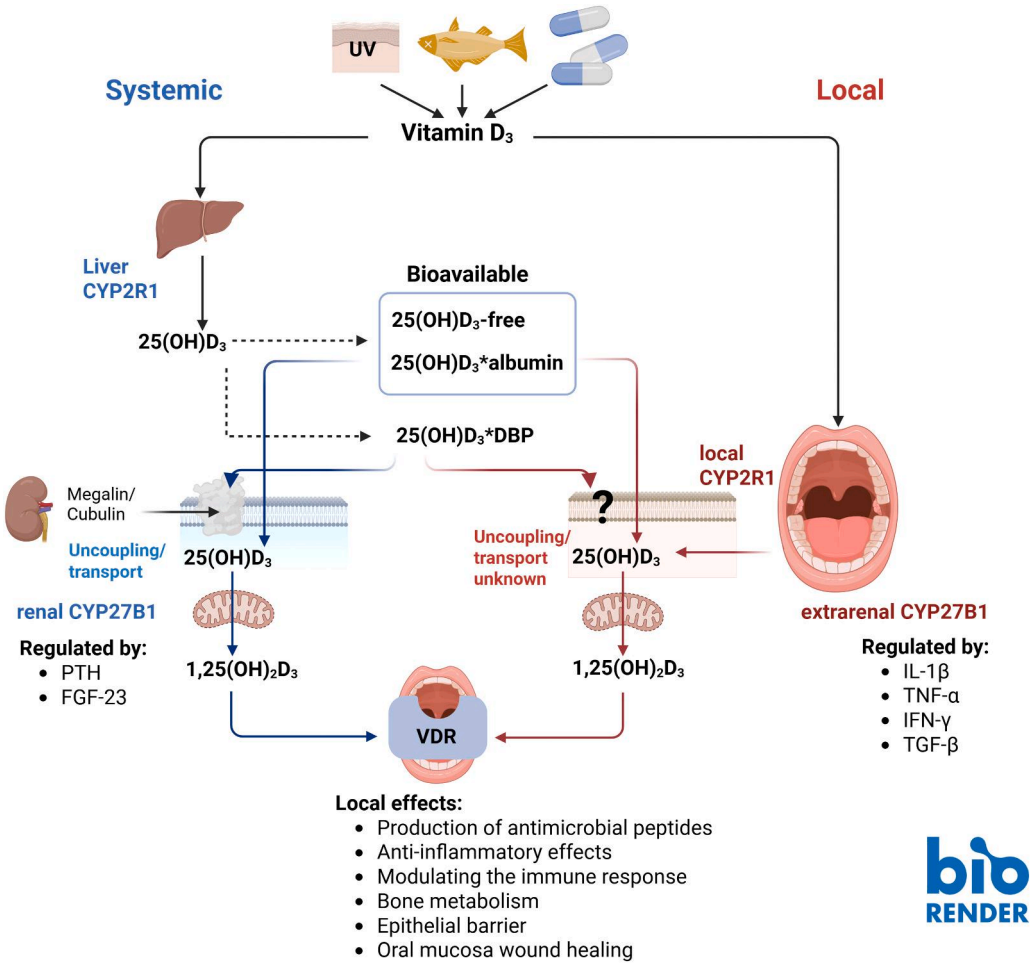

Fig. 1. *Systemic and local vitamin D_3 metabolism and its implications in oral tissues.* Vitamin D_3 is produced in the skin upon exposure to UV light or can be obtained from certain foods and supplements. The first step of systemic vitamin D_3 activation is its conversion to $25(OH)D_3$, which happens in the liver. In the blood, most of $25(OH)D_3$ is bound to vitamin D binding protein (DBP) and albumin, and only a small fraction is free. Albumin-bound and free $25(OH)D_3$ are considered bioavailable. A further step of systemic vitamin D_3 activation occurs in the kidney, where $25(OH)D_3$ is converted to the biologically active $1,25(OH)_2D_3$. This process is mediated by renal CYP27B1, which is regulated by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF−23). DBP-bounded $25(OH)D_3$ is uncoupled from DBP and transported into cells by megalin/cubulin complex, which is expressed in kidney proximal tubuli. The enzymes responsible for vitamin D_3 bioactivation are present in oral tissues. In contrast to the kidney, CYP27B1 in oral tissues is regulated by inflammatory cytokines, particularly interleukin−1β (IL−1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), as well as by transforming growth factor-β (TGF-β). Bioavailable $25(OH)D_3$ can be locally activated in oral tissues. It is unclear whether and how DBP-bounded $25(OH)D_3$ can be transported into oral cells. The local effects of locally or systemically produced $1,25(OH)_2D_3$ include the production of antimicrobial peptides and the regulation of inflammation, immune response, and bone metabolism. Created in BioRender. Andrukhov, O. (2026) https://BioRender.com/gv1pi3d.

levels are associated with lower free and bioavailable 25(OH)D_3. Furthermore, several studies reported an association between DBP polymorphism and the risk of periodontitis (Du et al., 2022; Nie et al., 2024). The local DBP levels also affect OTM. However, additional studies on the free and bioavailable levels of 25(OH)D_3, as well as on the levels of other vitamin D_3 metabolites in individuals with various oral conditions, would be essential.

5. Conclusion and future perspectives

Cells of oral tissue express enzymes involved in the activation of vitamin D_3 and its conversion to 25(OH)D_3 and the biologically active 1,25$(OH)_2D_3$, but it is not clear whether intracrine activation actually occurs *in vivo* (Fig. 1). To be activated, vitamin D_3 metabolites must first be dissociated from the vitamin D-binding protein (DBP). The proteins that fulfill this function in the kidney, megalin and cubulin, are rarely reported in oral tissues. Nevertheless, there are still some indications that vitamin D_3 might be locally activated. This assumption is supported by the effectiveness of topical vitamin D_3 application and the dependence of clinical parameters on local levels of 25(OH)D_3 and DBP. Furthermore, immune cells, particularly macrophages, can uncouple 25(OH)D_3 from DBP, transport it into the cell, and convert it to 1,25$(OH)_2D_3$. The major local effects of vitamin D_3 in oral tissues are thought to include regulation of the inflammatory response, stimulation of antimicrobial peptide production, regulation of epithelial barrier integrity, and wound healing. Future studies should focus on several questions, particularly the possibility of intracrine activation of 25(OH)D_3 in oral tissues *in vivo*, the role of free and bioavailable 25(OH)D_3 in various processes, and the possibility and effectiveness of local vitamin D_3 delivery.

CRediT authorship contribution statement

Marlies Holzmann: Writing – review & editing, Formal analysis. **Sandra Hilberath:** Writing – review & editing, Investigation, Formal analysis. **Christian Behm:** Writing – review & editing, Investigation, Formal analysis. **Markus Laky:** Writing – review & editing, Investigation, Formal analysis. **Oleh Andrukhov:** Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used the Grammarly tool to check grammar and spelling. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Oleh Andrukhov reports financial support was provided by Austrian Science Fund. Oleh Andrukhov is the co-Editor-in-Chief of the Archives of Oral Biology. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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References

Adams, J. S., & Hewison, M. (2012). Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Jul 1 *Archives of Biochemistry and Biophysics, 523*(1), 95–102. https://doi.org/10.1016/j.abb.2012.02.016.

Adams, J. S., Rafison, B., Witzel, S., Reyes, R. E., Shieh, A., Chun, R., Zavala, K., Hewison, M., & Liu, P. T. (2014). Regulation of the extrarenal CYP27B1-hydroxylase (Oct) *The Journal of Steroid Biochemistry and Molecular Biology, 144*(Pt A), 22–27. https://doi.org/10.1016/j.jsbmb.2013.12.009.

Aidoukovitch, A., Bankell, E., Svensson, D., & Nilsson, B. O. (2024). Vitamin D triggers hCAP18/LL-37 production: Implications for LL-37-induced human osteoblast cytotoxicity. Jun 18 *Biochemical and Biophysical Research Communications, 712-713*, Article 149962. https://doi.org/10.1016/j.bbrc.2024.149962.

Aksoy, H., Akcay, F., Kurtul, N., Baykal, O., & Avci, B. (2000). Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy (Feb) *Clinical Biochemistry, 33*(1), 47–51. https://doi.org/10.1016/s0009-9120(99)00085-5.

Alexandridou, A., Stokes, C. S., & Volmer, D. A. (2025). Measurement of serum free vitamin D concentrations: Importance, challenges, and the emerging role of mass spectrometry. Feb 3 *Clinical Chemistry, 71*(2), 254–265. https://doi.org/10.1093/clinchem/hvae202.

Alshahrani, F., & Aljohani, N. (2013). Vitamin D: Deficiency, sufficiency and toxicity. Sep 13 *Nutrients, 5*(9), 3605–3616. https://doi.org/10.3390/nu5093605.

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Kostenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020). Vitamin D deficiency 2.0: An update on the current status worldwide (Nov) *European Journal of Clinical Nutrition, 74*(11), 1498–1513. https://doi.org/10.1038/s41430-020-0558-y.

Andrukhov, O. (2021). Toll-like receptors and dental mesenchymal stromal cells. *Frontiers in Oral Health, 2*, Article 648901. https://doi.org/10.3389/froh.2021.648901

Andrukhov, O., Andrukhova, O., Hulan, U., Tang, Y., Bantleon, H. P., & Rausch-Fan, X. (2014). Both 25-hydroxyvitamin-D3 and 1,25-dihydroxyvitamin-D3 reduces inflammatory response in human periodontal ligament cells. *PLoS One, 9*(2), Article e90301. https://doi.org/10.1371/journal.pone.0090301

Andrukhov, O., Behm, C., Blufstein, A., & Rausch-Fan, X. (2019). Immunomodulatory properties of dental tissue-derived mesenchymal stem cells: Implication in disease and tissue regeneration. Sep 26 *World Journal of Stem Cells, 11*(9), 604–617. https://doi.org/10.4252/wjsc.v11.i9.604.

Andrukhov, O., Blufstein, A., & Behm, C. (2021). A review of antimicrobial activity of dental mesenchymal stromal cells: Is there any potential? *Frontiers Oral Health, 2*, Article 832976. https://doi.org/10.3389/froh.2021.832976

Andrukhov, O., Blufstein, A., Behm, C., Moritz, A., & Rausch-Fan, X. (2020). Vitamin D3 and dental mesenchymal stromal cells. *Applied Sciences, 10*(13), 4527. https://doi.org/10.3390/app10134527

Aydin, T., Dilsiz, A., Eminoglu, D. O., Sahin, A. B., Laloglu, E., & Bayrakdar, Y. E. (2023). Total, free, and bioavailable 25-hydroxyvitamin D levels in patients with periodontitis (stage III): A case-control study (Jan) *Clinical Oral Investigations, 27*(1), 421–430. https://doi.org/10.1007/s00784-022-04844-9.

Ayyad, B. M., Hamed, M. S., Elrody, A., Hanna, P. A., & Younis, A. A. (2025). Clinical and radiographic evaluation of topical vitamin D application on immediate dental implants: A randomized clinical trial. Jul 5 *BMC Oral Health, 25*(1), 1114. https://doi.org/10.1186/s12903-025-06465-6.

Bahramian, A., Falsafi, P., Abbasi, T., Ghanizadeh, M., Abedini, M., Kavoosi, F., Kouhsoltani, M., Noorbakhsh, F., Dabbaghi Tabriz, F., Rajaeih, S., & Rezaei, F. (2018). Comparing serum and salivary levels of vitamin D in patients with recurrent aphthous stomatitis and healthy individuals (Dec) *Journal of Dentistry, 19*(4), 295–300 ⟨https://www.ncbi.nlm.nih.gov/pubmed/30680302⟩ (Dec).

Bayirli, A. B., Yurdakurban, E., Uytun, M., Turkis, F. C., & Saruhan, E. (2025). Assessment of CTX, PINP, and vitamin D-binding protein in gingival crevicular fluid and saliva during fixed orthodontic treatment. Dec 22 *Diagnostics, 16*(1). https://doi.org/10.3390/diagnostics16010030.

Behm, C., Blufstein, A., Gahn, J., Kubin, B., Moritz, A., Rausch-Fan, X., & Andrukhov, O. (2020). Pleiotropic effects of vitamin D3 on CD4(+) T lymphocytes mediated by human periodontal ligament cells and inflammatory environment. Mar 11 *Journal of Clinical Periodontology*. https://doi.org/10.1111/jcpe.13283.

Behm, C., Blufstein, A., Gahn, J., Kubin, B., Nemec, M., Moritz, A., Rausch-Fan, X., & Andrukhov, O. (2019). 1,25(OH)2D3 differently affects immunomodulatory activities of mesenchymal stem cells depending on the presence of TNF-alpha, IL-1beta and IFN-gamma. Dec 14 *Journal of Clinical Medicine, 8*(12). https://doi.org/10.3390/jcm8122211.

Behm, C., Blufstein, A., Gahn, J., Moritz, A., Rausch-Fan, X., & Andrukhov, O. (2023). 25-hydroxyvitamin D(3) generates immunomodulatory plasticity in human periodontal ligament-derived mesenchymal stromal cells that is inflammatory context-dependent. *Frontiers in Immunology, 14*, Article 1100041. https://doi.org/10.3389/fimmu.2023.1100041

Behm, C., Milek, O., Schwarz, K., Kovar, A., Derdak, S., Rausch-Fan, X., Moritz, A., & Andrukhov, O. (2024). Heterogeneity in dental tissue-derived MSCs revealed by single-cell RNA-seq (Oct) *Journal of Dental Research, 103*(11), 1141–1152. https://doi.org/10.1177/00220345241271997.

Behm, C., Milek, O., Schwarz, K., Rausch-Fan, X., Moritz, A., & Andrukhov, O. (2024). 1,25-dihydroxyvitamin-D(3) distinctly impacts the paracrine and cell-to-cell contact interactions between hPDL-MSCs and CD4(+) T lymphocytes. *Frontiers in Immunology, 15*, Article 1448597. https://doi.org/10.3389/fimmu.2024.1448597

Behm, C., Zhao, Z., & Andrukhov, O. (2022). Immunomodulatory activities of periodontal ligament stem cells in orthodontic forces-induced inflammatory

processes: Current views and future perspectives. *Frontiers in Oral Health, 3*, Article 877348. https://doi.org/10.3389/froh.2022.877348
Benedik, E. (2022). Sources of vitamin D for humans (Mar) *International Journal for Vitamin and Nutrition Research, 92*(2), 118–125. https://doi.org/10.1024/0300-9831/a000733.
Bhan, I., Powe, C. E., Berg, A. H., Ankers, E., Wenger, J. B., Karumanchi, S. A., & Thadhani, R. I. (2012). Bioavailable vitamin D is more tightly linked to mineral metabolism than total vitamin D in incident hemodialysis patients (Jul) *Kidney International, 82*(1), 84–89. https://doi.org/10.1038/ki.2012.19.
Biancuzzo, R. M., Clarke, N., Reitz, R. E., Travison, T. G., & Holick, M. F. (2013). Serum concentrations of 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 in response to vitamin D2 and vitamin D3 supplementation (Mar) *The Journal of Clinical Endocrinology and Metabolism, 98*(3), 973–979. https://doi.org/10.1210/jc.2012-2114.
Bikle, D. (2009). Nonclassic actions of vitamin D (Jan) *The Journal of Clinical Endocrinology and Metabolism, 94*(1), 26–34. https://doi.org/10.1210/jc.2008-1454.
Bikle, D. D. (2014). Vitamin D metabolism, mechanism of action, and clinical applications. Mar 20 *Chemistry & Biology, 21*(3), 319–329. https://doi.org/10.1016/j.chembiol.2013.12.016.
Bikle, D. D., Gee, E., Halloran, B., Kowalski, M. A., Ryzen, E., & Haddad, J. G. (1986). Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein (Oct) *The Journal of Clinical Endocrinology and Metabolism, 63*(4), 954–959. https://doi.org/10.1210/jcem-63-4-954.
Bikle, D. D., Malmstroem, S., & Schwartz, J. (2017). Current controversies: Are free vitamin metabolite levels a more accurate assessment of vitamin D status than total levels? (Dec) *Endocrinology and Metabolism Clinics of North America, 46*(4), 901–918. https://doi.org/10.1016/j.ecl.2017.07.013.
Bikle, D. D., Patzek, S., & Wang, Y. (2018). Physiologic and pathophysiologic roles of extra renal CYP27b1: Case report and review (Jun) *Bone Reports, 8*, 255–267. https://doi.org/10.1016/j.bonr.2018.02.004.
Bikle, D. D., & Schwartz, J. (2019). Vitamin D binding protein, total and free vitamin D Levels in different physiological and pathophysiological conditions. *Frontiers in Endocrinology (Lausanne), 10*, 317. https://doi.org/10.3389/fendo.2019.00317
Bischoff-Ferrari, H. A. (2014). Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Advances in Experimental Medicine and Biology, 810*, 500–525. https://doi.org/10.1007/978-1-4939-0437-2_28
Blufstein, A., Behm, C., Kubin, B., Gahn, J., Moritz, A., Rausch-Fan, X., & Andrukhov, O. (2020). Transcriptional activity of vitamin D receptor in human periodontal ligament cells is diminished under inflammatory conditions. May 31 *Journal of Periodontology*. https://doi.org/10.1002/JPER.19-0541.
Blufstein, A., Behm, C., Kubin, B., Gahn, J., Rausch-Fan, X., Moritz, A., & Andrukhov, O. (2021). Effect of vitamin D3 on the osteogenic differentiation of human periodontal ligament stromal cells under inflammatory conditions (Jun) *Journal of Periodontal Research, 56*(3), 579–588. https://doi.org/10.1111/jre.12858.
Bosworth, C. R., Levin, G., Robinson-Cohen, C., Hoofnagle, A. N., Ruzinski, J., Young, B., Schwartz, S. M., Himmelfarb, J., Kestenbaum, B., & de Boer, I. H. (2012). The serum 24,25-dihydroxyvitamin D concentration, a marker of vitamin D catabolism, is reduced in chronic kidney disease (Sep) *Kidney International, 82*(6), 693–700. https://doi.org/10.1038/ki.2012.193.
Botelho, J., Machado, V., Proenca, L., Delgado, A. S., & Mendes, J. J. (2020). Vitamin D deficiency and oral health: A comprehensive review. May 19 *Nutrients, 12*(5). https://doi.org/10.3390/nu12051471.
Bouillon, R., Schuit, F., Antonio, L., & Rastinejad, F. (2019). Vitamin D binding protein: A historic overview. *Frontiers in Endocrinology(Lausanne), 10*, 910. https://doi.org/10.3389/fendo.2019.00910
Boyan, B. D., Schwartz, Z., Carnes, D. L., Jr., & Ramirez, V. (1988). The effects of vitamin D metabolites on the plasma and matrix vesicle membranes of growth and resting cartilage cells in vitro (Jun) *Endocrinology, 122*(6), 2851–2860. https://doi.org/10.1210/endo-122-6-2851.
Cafiero, C., Grippaudo, C., Dell'Aquila, M., Cimmino, P., D'Addona, A., De Angelis, P., Ottaiano, M. P., Costagliola, D., Benincasa, G., Micera, A., Santacroce, L., & Palmirotta, R. (2022). Association between Vitamin D Receptor Gene Polymorphisms and Periodontal Bacteria: A Clinical Pilot Study. Jun 15 *Biomolecules, 12*(6). https://doi.org/10.3390/biom12060833.
Chakravarthy, Y., Mishra, A., Krishnan, P., Pathakota, K. R., Vijaya, V., & Kamatham, S. N. (2022). Evaluation of serum and gingival crevicular fluid levels of Vitamin D binding protein in subjects with clinically healthy periodontium and chronic periodontitis: A clinico bio-chemical study (Jul-Sep) *Indian Journal of Dental Research, 33*(3), 301–306. https://doi.org/10.4103/ijdr.ijdr_646_21.
Chaushu, S., Klein, Y., Mandelboim, O., Barenholz, Y., & Fleissig, O. (2022). Immune Changes Induced by Orthodontic Forces: A Critical Review (Jan) *Journal of Dental Research, 101*(1), 11–20. https://doi.org/10.1177/00220345211016285.
Cheng, J. B., Levine, M. A., Bell, N. H., Mangelsdorf, D. J., & Russell, D. W. (2004). Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. May 18. *Proceedings of the National Academy of Sciences of the United States of America* (pp. 7711–7715). https://doi.org/10.1073/pnas.0402490101, 10120.
Chisini, L. A., Salvi, L. C., de Carvalho, R. V., Dos Santos Costa, F., Demarco, F. F., & Correa, M. B. (2025). Pathways of the vitamin D receptor gene and dental caries: A systematic review and meta-analysis (May) *Archives of Oral Biology, 173*, Article 106195. https://doi.org/10.1016/j.archoralbio.2025.106195.
Christakos, S., Dhawan, P., Porta, A., Mady, L. J., & Seth, T. (2011). Vitamin D and intestinal calcium absorption. Dec 5 *Molecular and Cellular Endocrinology, 347*(1-2), 25–29. https://doi.org/10.1016/j.mce.2011.05.038.
Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., & Carmeliet, G. (2016). Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects (Jan) *Physiological Reviews, 96*(1), 365–408. https://doi.org/10.1152/physrev.00014.2015.
Christensen, E. I., & Birn, H. (2001). Megalin and cubilin: synergistic endocytic receptors in renal proximal tubule (Apr) *American Journal of Physiology-Renal Physiology, 280*(4), F562–573. https://doi.org/10.1152/ajprenal.2001.280.4.F562.
Chun, R. F., Peercy, B. E., Orwoll, E. S., Nielson, C. M., Adams, J. S., & Hewison, M. (2014). Vitamin D and DBP: the free hormone hypothesis revisited (Oct) *Journal of Steroid Biochemistry and Molecular Biology, 144*(Pt A), 132–137. https://doi.org/10.1016/j.jsbmb.2013.09.012.
Clemens, T. L., Fraher, L. J., Sandler, L. M., & O'Riordan, J. L. (1982). Demonstration of circulating 1,24,25-trihydroxyvitamin D3 in man by radioimmunoassay (Apr) *Clinical Endocrinology, 16*(4), 337–343. https://doi.org/10.1111/j.1365-2265.1982.tb00725.x.
Costantini, E., Sinjari, B., Piscopo, F., Porreca, A., Reale, M., Caputi, S., & Murmura, G. (2020). Evaluation of Salivary Cytokines and Vitamin D Levels in Periodontopathic Patients. Apr 11 *International Journal of Molecular Sciences, 21*(8). https://doi.org/10.3390/ijms21082669.
Davidopoulou, S., Makedou, K., Kourti, A., Gkeka, I., Karakostas, P., Pikilidou, M., Tolidis, K., & Kalfas, S. (2025). Vitamin D and LL-37 in Serum and Saliva: Insights into Oral Immunity. *Current Issues in Molecular Biology, 47*(2). https://doi.org/10.3390/cimb47020102
De Filippis, A., Fiorentino, M., Guida, L., Annunziata, M., Nastri, L., & Rizzo, A. (2017). Vitamin D reduces the inflammatory response by Porphyromonas gingivalis infection by modulating human beta-defensin-3 in human gingival epithelium and periodontal ligament cells (Jun) *International Immunopharmacology, 47*, 106–117. https://doi.org/10.1016/j.intimp.2017.03.021.
Demay, M. B., Pittas, A. G., Bikle, D. D., Diab, D. L., Kiely, M. E., Lazaretti-Castro, M., Lips, P., Mitchell, D. M., Murad, M. H., Powers, S., Rao, S. D., Scragg, R., Tayek, J. A., Valent, A. M., Walsh, J. M. E., & McCartney, C. R. (2024). Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. Jul 12 *Journal of Clinical Endocrinology and Metabolism, 109*(8), 1907–1947. https://doi.org/10.1210/clinem/dgae290.
Dhaif, Y. G., Garcia-Sanchez, R., Albuquerque, R., & Lu, E. M. C. (2024). The association between vitamin D binding protein levels and periodontal status: A systematic review (Jun) *Journal of Periodontal Research, 59*(3), 421–430. https://doi.org/10.1111/jre.13232.
Domzalski, P., Nowak, J. I., Olszewska, A. M., Myszczynski, K., Tuckey, R. C., Piotrowska, A., & Zmijewski, M. A. (2025). 1,24,25(OH)(3)D(3) is a fully active catabolite of vitamin D in keratinocytes. Dec 11 *Scientific Reports, 16*(1), 2136. https://doi.org/10.1038/s41598-025-31780-x.
Du, F., Liu, Z., & Qing, S. (2022). Effect of vitamin D receptor gene polymorphisms on the risk of chronic and aggressive periodontitis: A systematic review and meta-analysis of the Chinese population (Dec) *Archives of Oral Bio, 144*, Article 105566. https://doi.org/10.1016/j.archoralbio.2022.105566.
Dura-Trave, T., & Gallinas-Victoriano, F. (2024). Dental caries in children and vitamin D deficiency: a narrative review (Feb) *European Journal of Pediatrics, 183*(2), 523–528. https://doi.org/10.1007/s00431-023-05331-3.
Ellison, D. L., & Moran, H. R. (2021). Vitamin D: Vitamin or Hormone? (Mar) *Nursing Clinics of North America, 56*(1), 47–57. https://doi.org/10.1016/j.cnur.2020.10.004.
Ferrillo, M., Calafiore, D., Lippi, L., Agostini, F., Migliario, M., Invernizzi, M., Giudice, A., & de Sire, A. (2024). Role of vitamin D for orthodontic tooth movement, external apical root resorption, and bone biomarker expression and remodeling: A systematic review. Jan 25 *Korean Journal of Orthodontics, 54*(1), 26–47. https://doi.org/10.4041/kjod23.064.
Figgins, E. L., Arora, P., Gao, D., Porcelli, E., Ahmed, R., Daep, C. A., Keele, G., Ryan, L. K., & Diamond, G. (2024). Enhancement of innate immunity in gingival epithelial cells by vitamin D and HDAC inhibitors. *Frontiers in Oral Health, 5*, Article 1378566. https://doi.org/10.3389/froh.2024.1378566
Fuleihan Gel, H., Bouillon, R., Clarke, B., Chakhtoura, M., Cooper, C., McClung, M., & Singh, R. J. (2015). Serum 25-Hydroxyvitamin D Levels: Variability, Knowledge Gaps, and the Concept of a Desirable Range (Jul) *Journal of Bone and Mineral Research, 30*(7), 1119–1133. https://doi.org/10.1002/jbmr.2536.
Gao, Y., Zhou, S., Luu, S., & Glowacki, J. (2019). Megalin mediates 25-hydroxyvitamin D (3) actions in human mesenchymal stem cells (Jun) *Faseb Journal, 33*(6), 7684–7693. https://doi.org/10.1096/fj.201802578R.
Giannobile, W. V., Beikler, T., Kinney, J. S., Ramseier, C. A., Morelli, T., & Wong, D. T. (2009). Saliva as a diagnostic tool for periodontal disease: current state and future directions. *Periodontol 2000, 50*, 52–64. https://doi.org/10.1111/j.1600-0757.2008.00288.x
Giustina, A., Bilezikian, J. P., Adler, R. A., Banfi, G., Bikle, D. D., Binkley, N. C., Bollerslev, J., Bouillon, R., Brandi, M. L., Casanueva, F. F., di Filippo, L., Donini, L. M., Ebeling, P. R., Fuleihan, G. E., Fassio, A., Frara, S., Jones, G., Marcocci, C., Martineau, A. R., Minisola, S., Napoli, N., Procopio, M., Rizzoli, R., Schafer, A. L., Sempos, C. T., Ulivieri, F. M., & Virtanen, J. K. (2024). Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows. Sep 12 *Endocrine Reviews, 45*(5), 625–654. https://doi.org/10.1210/endrev/bnae009.
Glendenning, P., Chew, G. T., Inderjeeth, C. A., Taranto, M., & Fraser, W. D. (2013). Calculated free and bioavailable vitamin D metabolite concentrations in vitamin D-deficient hip fracture patients after supplementation with cholecalciferol and ergocalciferol (Oct) *Bone, 56*(2), 271–275. https://doi.org/10.1016/j.bone.2013.06.012.
Gratton, M. P., Londono, I., Rompre, P., Moldovan, F., & Nishio, C. (2026). Vitamin D as an adjunctive therapy in orthodontics: Impact on alveolar bone and root resorption

in male rats. Mar 19 *Archives of Oral Biology, 187*, Article 106577. https://doi.org/10.1016/j.archoralbio.2026.106577.
Grundmann, J., Hertel, S., Hannig, C., & Woelber, J. P. (2025). Vitamin D - a forgotten preventive agent against caries? A narrative review. Dec 1 *Clinical Oral Investigations, 29*(12), 595. https://doi.org/10.1007/s00784-025-06605-w.
Haririan, H., Andrukhov, O., Laky, M., & Rausch-Fan, X. (2021). Saliva as a Source of Biomarkers for Periodontitis and Periimplantitis. *Frontiers in Dental Medicine, 2*. https://doi.org/10.3389/fdmed.2021.687638
Haussler, M. R., Whitfield, G. K., Haussler, C. A., Hsieh, J. C., Thompson, P. D., Selznick, S. H., Dominguez, C. E., & Jurutka, P. W. (1998). The nuclear vitamin D receptor: biological and molecular regulatory properties revealed (Mar) *J Bone Miner Res, 13*(3), 325–349. https://doi.org/10.1359/jbmr.1998.13.3.325.
Hewison, M. (2011). Antibacterial effects of vitamin D. *Nature Reviews Endocrinology, 7*(6), 337–345. https://doi.org/10.1038/nrendo.2010.226
Hewison, M., Zehnder, D., Bland, R., & Stewart, P. M. (2000). 1alpha-Hydroxylase and the action of vitamin D (Oct) *Journal of Molecular Endocrinology, 25*(2), 141–148. https://doi.org/10.1677/jme.0.0250141.
Holick, M. F. (2009). Vitamin D status: measurement, interpretation, and clinical application (Feb) *Annals of Epidemiology, 19*(2), 73–78. https://doi.org/10.1016/j.annepidem.2007.12.001.
Holick, M. F., & Chen, T. C. (2008). Vitamin D deficiency: a worldwide problem with health consequences (Apr) *American Journal of Clinical Nutrition, 87*(4), 1080S–1086S. https://doi.org/10.1093/ajcn/87.4.1080S.
Hosokawa, Y., Hosokawa, I., Shindo, S., Ozaki, K., & Matsuo, T. (2015). Calcitriol Suppressed Inflammatory Reactions in IL-1beta-Stimulated Human Periodontal Ligament Cells (Dec) *Inflammation, 38*(6), 2252–2258. https://doi.org/10.1007/s10753-015-0209-y.
Hung, M., Almpani, K., Thao, B., Sudweeks, K., & Lipsky, M. S. (2023). Vitamin D in the Prevention and Treatment of Oral Cancer: A Scoping Review. May 17 *Nutrients, 15*(10). https://doi.org/10.3390/nu15102346.
Jiang, C., Li, Z., Quan, H., Xiao, L., Zhao, J., Jiang, C., Wang, Y., Liu, J., Gou, Y., An, S., Huang, Y., Yu, W., Zhang, Y., He, W., Yi, Y., Chen, Y., & Wang, J. (2015). Osteoimmunology in orthodontic tooth movement (Sep) *Oral Diseases, 21*(6), 694–704. https://doi.org/10.1111/odi.12273.
Jones, G. (2008). Pharmacokinetics of vitamin D toxicity (Aug) *American Journal of Clinical Nutrition, 88*(2), 582S–586S. https://doi.org/88/2/582S [pii].
Jones, G., Prosser, D. E., & Kaufmann, M. (2012). 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Jul 1 *Archives of Biochemistry, 523*(1), 9–18. https://doi.org/10.1016/j.abb.2011.11.003.
Karaca, F., Bloch, S., Kendlbacher, F. L., Behm, C., Schaffer, C., & Andrukhov, O. (2025). Vitamin D(3) Modulates Inflammatory and Antimicrobial Responses in Oral Epithelial Cells Exposed to Periodontitis-Associated Bacteria. Jul 21 *International Journal of Molecular Sciences, 26*(14). https://doi.org/10.3390/ijms26147001.
Khan, S. S., Petkovich, M., Holden, R. M., & Adams, M. A. (2022). Megalin and Vitamin D Metabolism-Implications in Non-Renal Tissues and Kidney Disease. Sep 7 *Nutrients, 14*(18). https://doi.org/10.3390/nu14183690.
Khanna-Jain, R., Vuorinen, A., Sandor, G. K., Suuronen, R., & Miettinen, S. (2010). Vitamin D(3) metabolites induce osteogenic differentiation in human dental pulp and human dental follicle cells (Oct) *Journal of Steroid Biochemistry and Molecular Biology, 122*(4), 133–141. https://doi.org/10.1016/j.jsbmb.2010.08.001.
Khazai, N., Judd, S. E., & Tangpricha, V. (2008). Calcium and vitamin D: skeletal and extraskeletal health (Apr) *Current Rheumatology Reports, 10*(2), 110–117. https://doi.org/10.1007/s11926-008-0020-y.
Kirkwood, K. L., Van Dyke, T. E., Kirkwood, C. L., Zhang, L., Panezai, J., Duran-Pinedo, A. E., Figgins, E. L., Ryan, L. K., Frias-Lopez, J. J., & Diamond, G. (2024). Topical Vitamin D Prevents Bone Loss and Inflammation in a Mouse Model (Aug) *Journal of Dental Research, 103*(9), 908–915. https://doi.org/10.1177/00220345241259417.
Kongsbak, M., von Essen, M. R., Levring, T. B., Schjerling, P., Woetmann, A., Odum, N., Bonefeld, C. M., & Geisler, C. (2014). Vitamin D-binding protein controls T cell responses to vitamin D. Sep 18 *BMC Immunology, 15*, 35. https://doi.org/10.1186/s12865-014-0035-2.
Kukida, M., Sawada, H., Daugherty, A., & Lu, H. S. (2020). Megalin: A bridge connecting kidney, the renin-angiotensin system, and atherosclerosis (Jan) *Pharmacological Research, 151*, Article 104537. https://doi.org/10.1016/j.phrs.2019.104537.
Kumar, R., Tebben, P. J., & Thompson, J. R. (2012). Vitamin D and the kidney. Jul 1 *Archives of Biochemistry, 523*(1), 77–86. https://doi.org/10.1016/j.abb.2012.03.003.
Laky, M., Bertl, K., Haririan, H., Andrukhov, O., Seemann, R., Volf, I., Assinger, A., Gruber, R., Moritz, A., & Rausch-Fan, X. (2017). Serum levels of 25-hydroxyvitamin D are associated with periodontal disease (Jun) *Clin Oral Investigation, 21*(5), 1553–1558. https://doi.org/10.1007/s00784-016-1965-2.
Leeuwenkamp, O. R., van der Wiel, H. E., Lips, P., van der Vijgh, W. J., Barto, R., Greuter, H., & Netelenbos, J. C. (1993). Human pharmacokinetics of orally administered (24 R)-hydroxycalcidiol (Jul) *European Journal of Clinical Chemistry and Clinical Biochemistry, 31*(7), 419–426. https://doi.org/10.1515/cclm.1993.31.7.419.
Liang, F., Zhou, Y., Zhang, Z., Zhang, Z., & Shen, J. (2023). Association of vitamin D in individuals with periodontitis: an updated systematic review and meta-analysis. Jun 13 *BMC Oral Health, 23*(1), 387. https://doi.org/10.1186/s12903-023-03120-w.
Liu, K., Han, B., Hou, J., Zhang, J., Su, J., & Meng, H. (2021). Expression of vitamin D 1alpha-hydroxylase in human gingival fibroblasts in vivo. *PeerJ, 9*, Article e10279. https://doi.org/10.7717/peerj.10279
Liu, K., Meng, H., & Hou, J. (2012a). Activity of 25-hydroxylase in human gingival fibroblasts and periodontal ligament cells. *PLoS ONE, 7*(12), Article e52053. https://doi.org/10.1371/journal.pone.0052053PONE-D-12-28114 ([pii]).
Liu, K., Meng, H., & Hou, J. (2012b). Characterization of the autocrine/paracrine function of vitamin D in human gingival fibroblasts and periodontal ligament cells. *PLoS ONE, 7*(6), Article e39878. https://doi.org/10.1371/journal.pone.0039878
Lopez, D. V., Al-Jaberi, F. A. H., Woetmann, A., Odum, N., Bonefeld, C. M., Kongsbak-Wismann, M., & Geisler, C. (2021). Macrophages Control the Bioavailability of Vitamin D and Vitamin D-Regulated T Cell Responses. *Frontiers in Immunology, 12*, Article 722806. https://doi.org/10.3389/fimmu.2021.722806
Lou, Y. R., Toh, T. C., Tee, Y. H., & Yu, H. (2017). 25-Hydroxyvitamin D3 induces osteogenic differentiation of human mesenchymal stem cells. Feb 17 *Scientific Reports, 7*, Article 42816. https://doi.org/10.1038/srep42816.
Lu, E. M. (2023). The role of vitamin D in periodontal health and disease (Apr) *Journal of Periodontal Research, 58*(2), 213–224. https://doi.org/10.1111/jre.13083.
Lundgren, S., Carling, T., Hjalm, G., Juhlin, C., Rastad, J., Pihlgren, U., Rask, L., Akerstrom, G., & Hellman, P. (1997). Tissue distribution of human gp330/megalin, a putative Ca(2+)-sensing protein (Mar) *Journal of Histochemistry and Cytochemistry, 45*(3), 383–392. https://doi.org/10.1177/002215549704500306.
Machado, V., Lobo, S., Proenca, L., Mendes, J. J., & Botelho, J. (2020). Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. Jul 22 *Nutrients, 12*(8). https://doi.org/10.3390/nu12082177.
Macova, L., & Bicikova, M. (2021). Vitamin D: Current Challenges between the Laboratory and Clinical Practice. May 21 *Nutrients, 13*(6). https://doi.org/10.3390/nu13061758.
McMahon, L., Schwartz, K., Yilmaz, O., Brown, E., Ryan, L. K., & Diamond, G. (2011). Vitamin D-mediated induction of innate immunity in gingival epithelial cells (Jun) *Infection and Immunity, 79*(6), 2250–2256. https://doi.org/10.1128/IAI.00099-11.
Menzel, L. P., Ruddick, W., Chowdhury, M. H., Brice, D. C., Clance, R., Porcelli, E., Ryan, L. K., Lee, J., Yilmaz, O., Kirkwood, K. L., McMahon, L., Tran, A., & Diamond, G. (2019). Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss (Aug) *Journal of Periodontal Research, 54*(4), 444–452. https://doi.org/10.1111/jre.12646.
Meyer, M. B., Benkusky, N. A., Kaufmann, M., Lee, S. M., Redfield, R. R., Jones, G., & Pike, J. W. (2019). Targeted genomic deletions identify diverse enhancer functions and generate a kidney-specific, endocrine-deficient Cyp27b1 pseudo-null mouse. Jun 14 *Journal of Biological Chemistry, 294*(24), 9518–9535. https://doi.org/10.1074/jbc.RA119.008760.
Meyer, M. B., Lee, S. M., Cichanski, S. R., Cobice, D. F., & Pike, J. W. (2024). Spatial detection and consequences of nonrenal calcitriol production as assessed by targeted mass spectrometry imaging. Jun 25 *JCI Insight, 9*(15). https://doi.org/10.1172/jci.insight.181763.
Meyer, M. B., & Pike, J. W. (2023). Genomic mechanisms controlling renal vitamin D metabolism (Apr) *Journal of Steroid Biochemistry and Molecular Biology, 228*, Article 106252. https://doi.org/10.1016/j.jsbmb.2023.106252.
Miron, R. J., Estrin, N. E., Paz, A., Gruber, R., Farshidfar, N., Zhang, Y., Sculean, A., Wiedemann, T. G., & Ahmad, P. (2025). Relationship between vitamin D deficiency and early implant failure and osseointegration. *Periodontol 2000*. https://doi.org/10.1111/prd.70017
Moszura, J., Gawlak-Socka, S., Peksa, J., Bielecka-Kowalska, N., & Klosek, S. (2026). The Role of Vitamin D(3) in Periodontal Health: Implications for Bone Metabolism, Immune Modulation and Inflammation Control. Feb 10 *Nutrients, 18*(4). https://doi.org/10.3390/nu18040577.
Nakashyan, V., Tipton, D. A., Karydis, A., Livada, R., & Stein, S. H. (2017). Effect of 1,25(OH)(2) D(3) and 20(OH)D(3) on interleukin-1beta-stimulated interleukin-6 and -8 production by human gingival fibroblasts (Oct) *Journal of Periodontal Research, 52*(5), 832–841. https://doi.org/10.1111/jre.12452.
Nastri, L., Guida, L., Annunziata, M., Ruggiero, N., & Rizzo, A. (2018). Vitamin D modulatory effect on cytokines expression by human gingival fibroblasts and periodontal ligament cells (Jun) *Minerva Stomatol, 67*(3), 102–110. https://doi.org/10.23736/S0026-4970.18.04118-3.
Nebel, D., Svensson, D., Arosenius, K., Larsson, E., Jonsson, D., & Nilsson, B. O. (2015). 1alpha,25-dihydroxyvitamin D3 promotes osteogenic activity and downregulates proinflammatory cytokine expression in human periodontal ligament cells (Oct) *Journal of Periodontal Research, 50*(5), 666–673. https://doi.org/10.1111/jre.12249.
Newton, D. A., Baatz, J. E., Kindy, M. S., Gattoni-Celli, S., Shary, J. R., Hollis, B. W., & Wagner, C. L. (2019). Vitamin D binding protein polymorphisms significantly impact vitamin D status in children (Nov) *Pediatric Research, 86*(5), 662–669. https://doi.org/10.1038/s41390-019-0322-y.
Nie, Z., Hu, X., Hu, P., Li, P., Zhou, H., & Xie, X. (2024). Vitamin D binding protein and receptor prevalence in a large population with periodontitis: single nucleotide polymorphism and transcriptomic profiling. Dec 18 *BMC Oral Health, 24*(1), 1495. https://doi.org/10.1186/s12903-024-05227-0.
Nireeksha, Hegde, M. N., & Kumari, N. S. (2024). Potential role of salivary vitamin D antimicrobial peptide LL-37 and interleukins in severity of dental caries: an exvivo study. Jan 13 *BMC Oral Health, 24*(1), 79. https://doi.org/10.1186/s12903-023-03749-7.
Nykjaer, A., Dragun, D., Walther, D., Vorum, H., Jacobsen, C., Herz, J., Melsen, F., Christensen, E. I., & Willnow, T. E. (1999). An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. Feb 19 *Cell, 96*(4), 507–515. https://doi.org/10.1016/s0092-8674(00)80655-8.
Pedrozo, H. A., Schwartz, Z., Rimes, S., Sylvia, V. L., Nemere, I., Posner, G. H., Dean, D. D., & Boyan, B. D. (1999). Physiological importance of the 1,25(OH)2D3 membrane receptor and evidence for a membrane receptor specific for 24,25(OH)2D3 (Jun) *Journal of Bone and Mineral Research, 14*(6), 856–867. https://doi.org/10.1359/jbmr.1999.14.6.856.
Pieper-Furst, U., Hall, R., Huss, S., Hochrath, K., Fischer, H. P., Tacke, F., Weiskirchen, R., & Lammert, F. (2011). Expression of the megalin C-terminal

fragment by macrophages during liver fibrogenesis in mice (Dec) *Biochim Biophys Acta, 1812*(12), 1640–1648. https://doi.org/10.1016/j.bbadis.2011.09.003.

Powe, C. E., Ricciardi, C., Berg, A. H., Erdenesanaa, D., Collerone, G., Ankers, E., Wenger, J., Karumanchi, S. A., Thadhani, R., & Bhan, I. (2011). Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship (Jul) *Journal of Bone and Mineral Research, 26*(7), 1609–1616. https://doi.org/10.1002/jbmr.387.

Rowling, M. J., Kemmis, C. M., Taffany, D. A., & Welsh, J. (2006). Megalin-mediated endocytosis of vitamin D binding protein correlates with 25-hydroxycholecalciferol actions in human mammary cells (Nov) *Journal of Nutrition, 136*(11), 2754–2759. https://doi.org/10.1093/jn/136.11.2754.

Rozmus, D., Ciesielska, A., Plominski, J., Grzybowski, R., Fiedorowicz, E., Kordulewska, N., Savelkoul, H., Kostyra, E., & Cieslinska, A. (2020). Vitamin D Binding Protein (VDBP) and Its Gene Polymorphisms-The Risk of Malignant Tumors and Other Diseases. Oct 22 *International Journal of Molecular Sciences, 21*(21). https://doi.org/10.3390/ijms21217822.

Saeed, S., Choudhury, P., Ahmad, S. A., Alam, T., Panigrahi, R., Aziz, S., Kaleem, S. M., Priyadarshini, S. R., Sahoo, P. K., & Hasan, S. (2022). Vitamin D in the Treatment of Oral Lichen Planus: A Systematic Review. Nov 17 *Biomedicines, 10*(11). https://doi.org/10.3390/biomedicines10112964.

Salomo-Coll, O., Mate-Sanchez de Val, J. E., Ramirez-Fernandez, M. P., Hernandez-Alfaro, F., Gargallo-Albiol, J., & Calvo-Guirado, J. L. (2016). Topical applications of vitamin D on implant surface for bone-to-implant contact enhance: a pilot study in dogs part II (Jul) *Clinical Oral Implants Research, 27*(7), 896–903. https://doi.org/10.1111/clr.12707.

Samanta, I., Patil, D. J., & More, C. B. (2024). Assessment of vitamin D levels in patients with oral potentially malignant disorders and oral squamous cell carcinoma-A cross-sectional study (Jan-Feb) *Journal of Oral Biology and Craniofacial Research, 14*(1), 27–32. https://doi.org/10.1016/j.jobcr.2023.11.005.

Sari, D. K., Sari, L. M., Laksmi, L. I., & Farhat. (2021). The Moderate Correlation Between 25(OH)D Serum and Saliva in Healthy People with Low Vitamin D Intake. *International Journal of General Medicine, 14*, 841–850. https://doi.org/10.2147/IJGM.S302912

Sinotte, M., Diorio, C., Berube, S., Pollak, M., & Brisson, J. (2009). Genetic polymorphisms of the vitamin D binding protein and plasma concentrations of 25-hydroxyvitamin D in premenopausal women (Feb) *American Journal of Clinical Nutrition, 89*(2), 634–640. https://doi.org/10.3945/ajcn.2008.26445.

Siregar, F. D., & Hidayat, W. (2023). The Role of Vitamin D on the Wound Healing Process: A Case Series. *International Medical Case Reports Journal, 16*, 227–232. https://doi.org/10.2147/IMCRJ.S402005

Slominski, A. T., Kim, T. K., Janjetovic, Z., Slominski, R. M., Li, W., Jetten, A. M., Indra, A. K., Mason, R. S., & Tuckey, R. C. (2024). Biological Effects of CYP11A1-Derived Vitamin D and Lumisterol Metabolites in the Skin (Oct) *Journal of Investigative Dermatology, 144*(10), 2145–2161. https://doi.org/10.1016/j.jid.2024.04.022.

Sundaram, K., Sambandam, Y., Tsuruga, E., Wagner, C. L., & Reddy, S. V. (2014). 1alpha,25-dihydroxyvitamin D3 modulates CYP2R1 gene expression in human oral squamous cell carcinoma tumor cells (Apr) *Horm Cancer, 5*(2), 90–97. https://doi.org/10.1007/s12672-014-0170-5.

Tabrizi, R., Khanzadeh, H., Jamasbi, S. S. M., Rezaei, F., & Azadi, A. (2025). Vitamin D serum levels and temporomandibular disorders: A systematic review and meta-analysis (Jan) *Archives of Oral Biology, 169*, Article 106108. https://doi.org/10.1016/j.archoralbio.2024.106108.

Tada, H., Shimizu, T., Nagaoka, I., & Takada, H. (2016). Vitamin D3 analog maxacalcitol (OCT) induces hCAP-18/LL-37 production in human oral epithelial cells. *Biomedical Research, 37*(3), 199–205. https://doi.org/10.2220/biomedres.37.199

Tang, J. C. Y., Nicholls, H., Piec, I., Washbourne, C. J., Dutton, J. J., Jackson, S., Greeves, J., & Fraser, W. D. (2017). Reference intervals for serum 24,25-dihydroxyvitamin D and the ratio with 25-hydroxyvitamin D established using a newly developed LC-MS/MS method (Aug) *Journal of Nutritional Biochemistry, 46*, 21–29. https://doi.org/10.1016/j.jnutbio.2017.04.005.

Tashkandi, N., Zhao, Y., Mitchell-Lee, G., Stephens, D., Patel, M., Motro, M., Will, L. A., & Kantarci, A. (2021). Longitudinal assessment of salivary vitamin D binding protein during orthodontic tooth movement. Jul 5 *BMC Oral Health, 21*(1), 332. https://doi.org/10.1186/s12903-021-01689-8.

Tini, A., Kumar, S., Arasu, P., Munusamy, N., Balamurugan, B., & Antony, A. (2024). Influence of vitamin D in orthodontic tooth movement-a systematic review and meta-analysis of randomized controlled trials in humans. Oct 1 *European Journal of Orthodontics, 46*(5). https://doi.org/10.1093/ejo/cjae043.

Tsuprykov, O., Chen, X., Hocher, C. F., Skoblo, R., Lianghong, Y., & Hocher, B. (2018). Why should we measure free 25(OH) vitamin D? (Jun) *Journal of Steroid Biochemistry and Molecular Biology, 180*, 87–104. https://doi.org/10.1016/j.jsbmb.2017.11.014.

Turner, M. E., Rowsell, T. S., Kaufmann, M., Norman, P. A., Neville, K., Sarabia, S., White, C. A., Petkovich, M., Jones, G., Adams, M. A., & Holden, R. M. (2023). The 1,24,25(OH)(3)D(3) metabolite in clinical and experimental CKD: Impact of calcitriol treatment (Feb) *Journal of Steroid Biochemistry and Molecular Biology, 226*, Article 106207. https://doi.org/10.1016/j.jsbmb.2022.106207.

Turner, M. E., Rowsell, T. S., White, C. A., Kaufmann, M., Norman, P. A., Neville, K., Petkovich, M., Jones, G., Adams, M. A., & Holden, R. M. (2022). The metabolism of 1,25(OH)(2)D(3) in clinical and experimental kidney disease. Jun 28 *Scientific Reports, 12*(1), Article 10925. https://doi.org/10.1038/s41598-022-15033-9.

Vieth, R. (2004). Why "Vitamin D" is not a hormone, and not a synonym for 1,25-dihydroxy-vitamin D, its analogs or deltanoids (May) *Journal of Steroid Biochemistry and Molecular Biology, 89-90*(1-5), 571–573. https://doi.org/10.1016/j.jsbmb.2004.03.037.

Wacker, M., & Holick, M. F. (2013). Sunlight and Vitamin D: A global perspective for health. Jan 1 *Dermatoendocrinol, 5*(1), 51–108. https://doi.org/10.4161/derm.24494.

Xu, Q. A., Li, Z. F., Zhang, P., Cao, L. H., & Fan, M. W. (2016). Effects of 1,25-dihydroxyvitamin D(3) on Macrophage Cytokine Secretion Stimulated by Porphyromonas gingivalis. Nov 22 *Japanese Journal Of Infectious Diseases, 69*(6), 482–487. https://doi.org/10.7883/yoken.JJID.2015.396.

Youssef, D. A., Miller, C. W., El-Abbassi, A. M., Cutchins, D. C., Cutchins, C., Grant, W. B., & Peiris, A. N. (2011). Antimicrobial implications of vitamin D (Oct) *Dermatoendocrinol, 3*(4), 220–229. https://doi.org/10.4161/derm.3.4.15027.

Zeng, S., Chu, C., Doebis, C., von Baehr, V., & Hocher, B. (2021). Reference values for free 25-hydroxy-vitamin D based on established total 25-hydroxy-vitamin D reference values (Jun) *Journal of Steroid Biochemistry and Molecular Biology, 210*, Article 105877. https://doi.org/10.1016/j.jsbmb.2021.105877.

Zhang, C., Han, Y., Miao, L., Yue, Z., Xu, M., Liu, K., & Hou, J. (2023). Human beta-defensins are correlated with the immune infiltration and regulated by vitamin D(3) in periodontitis (Oct) *Journal of Periodontal Research, 58*(5), 986–996. https://doi.org/10.1111/jre.13159.

Zhang, P., Zhang, W., Zhang, D., Wang, M., Aprecio, R., Ji, N., Mohamed, O., Li, Y., Ding, Y., & Wang, Q. (2018). 25-Hydroxyvitamin D(3) -enhanced PTPN2 positively regulates periodontal inflammation through the JAK/STAT pathway in human oral keratinocytes and a mouse model of type 2 diabetes mellitus (Jun) *Journal of Periodontal Research, 53*(3), 467–477. https://doi.org/10.1111/jre.12535.

Zhang, X., Meng, H., Xu, L., Zhang, L., Shi, D., Feng, X., Lu, R., & Chen, Z. (2014). Vitamin d-binding protein levels in plasma and gingival crevicular fluid of patients with generalized aggressive periodontitis. *International Journal of Endocrinology, 2014*, Article 783575. https://doi.org/10.1155/2014/783575

Zittermann, A. (2025). Regulation of Renal and Extrarenal Calcitriol Synthesis and Its Clinical Implications. Jun 11 *International Journal of Molecular Sciences, 26*(12). https://doi.org/10.3390/ijms26125570.

Zulijani, A., Dekanic, A., Cabov, T., & Jakovac, H. (2021). Metallothioneins and Megalin Expression Profiling in Premalignant and Malignant Oral Squamous Epithelial Lesions. Sep 9 *Cancers, 13*(18). https://doi.org/10.3390/cancers13184530.