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Beyond calcium homeostasis: Vitamin D signaling in salivary gland biology and disease: Current evidence and emerging perspectives

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ABSTRACT

Background: Vitamin D is a pleiotropic secosteroid hormone that regulates numerous biological processes beyond calcium and phosphate homeostasis, including epithelial differentiation, immune function, oxidative stress responses, and tissue repair. These effects are mediated primarily through the vitamin D receptor (VDR), which is expressed across multiple cellular compartments of the salivary gland. Although researchers have extensively studied vitamin D in skeletal biology and mineralized oral tissues, its role in salivary gland physiology and pathology has received comparatively little attention.

Highlight: VDR signaling has been implicated in salivary gland homeostasis through effects on epithelial differentiation, antimicrobial defense, immune regulation, and secretory-cell integrity. Experimental studies further link VDR signaling to redox regulation and ferroptosis, and recent salivary gland-specific evidence indicates that its effects on cell survival and glandular function are context-dependent rather than uniformly protective. The vitamin D-VDR axis also regulates the salivary gland immune microenvironment by modulating antimicrobial peptide production and innate and adaptive immune responses. Current data implicate altered vitamin D signaling in several salivary gland disorders, including Sjögren syndrome, salivary gland tumors, and sialolithiasis, although most evidence comes from experimental studies and observational clinical investigations. In

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addition, vitamin D-related biomarkers, particularly vitamin D-binding protein, show potential for non-invasive assessment of oral and salivary gland health.
Conclusion: Collectively, these findings support a broader role for vitamin D signaling in salivary gland biology than previously recognized. Future studies that integrate systemic vitamin D status, local VDR activity, salivary biomarkers, and functional outcomes are needed to clarify the diagnostic, prognostic, and therapeutic relevance of this pathway in salivary gland disease.

List of abbreviations

DBP	Vitamin D-binding protein
RXR	retinoid X receptor
SGs	salivary glands
SS	Sjögren syndrome
VDR	vitamin D receptor
VDREs	vitamin D response elements (binding sites for the VDR-RXR complex)

1. Introduction

Vitamin D is a pleiotropic secosteroid hormone whose biological functions extend far beyond calcium and phosphate homeostasis in bone metabolism. Its effects are mediated through the vitamin D receptor (VDR), a ligand-activated transcription factor, and local enzymatic machinery that enables tissue-specific activation and degradation of vitamin D metabolites [1,2].

Beyond bone mineral metabolism, vitamin D regulates epithelial differentiation, oxidative stress, tissue repair, and immune homeostasis. Functional VDR expression has been demonstrated across a wide range of epithelial and secretory tissues. In these tissues, vitamin D helps maintain barrier function and cellular turnover across multiple organs [3]. Furthermore, vitamin D regulates both innate and adaptive immune responses by promoting antimicrobial peptide production and limiting excessive inflammatory signaling, thereby preserving tissue homeostasis [4,5].

Within the oral cavity, research on vitamin D has largely focused on mineralized tissues, including tooth development, alveolar bone remodeling, and periodontal health. In contrast, researchers have paid far less attention to the salivary glands (SGs), despite their essential role in maintaining oral homeostasis through saliva secretion, antimicrobial defense, mucosal protection, and local immune regulation [6]. SG dysfunction is a common feature of autoimmune diseases, aging, radiation-induced injury, and metabolic disorders. It contributes to xerostomia, oral infections, dental caries, mucosal lesions, and reduced quality of life. Components of the vitamin D pathway have been identified in SGs [7]. Current evidence remains fragmented and largely disease-oriented, and the physiological role of vitamin D signaling in SG biology has not been comprehensively synthesized.

Therefore, this review synthesizes current evidence on vitamin D signaling in SGs, focusing on epithelial homeostasis and immune regulation, glandular pathology, and emerging translational perspectives.

2. Discussion

2.1. Vitamin D metabolism and VDR signaling

Vitamin D_3 (cholecalciferol) is synthesized in the skin after ultraviolet B exposure and can also be obtained from dietary sources. It undergoes hepatic 25-hydroxylation, predominantly by CYP2R1, with contributions from CYP27A1 and other cytochrome P450 enzymes, generating 25-hydroxyvitamin D_3 [25(OH)D_3, calcidiol], the major circulating vitamin D metabolite [8].

In circulation, most 25(OH)D_3 is bound to vitamin D-binding protein (DBP), which stabilizes vitamin D metabolites and influences their bioavailability and delivery to target tissues [9]. Subsequent 1α-hydroxylation by CYP27B1 produces biologically active 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$, calcitriol], whereas CYP24A1 mediates the metabolic inactivation of vitamin D metabolites [10].

Although the kidney is the principal source of circulating 1,25$(OH)_2D_3$, CYP27B1 is expressed in numerous extrarenal tissues, including SG, enabling local intracrine and paracrine calcitriol generation and thereby allowing tissue-specific regulation of vitamin D responses [11,12]. Calcitriol exerts its canonical genomic effects through VDR, a ligand-activated nuclear receptor (Fig. 1) [2]. Ligand-activated VDR functions primarily as a heterodimer with retinoid X receptor (RXR) binding to vitamin D response elements (VDREs), where it recruits transcriptional coregulators to produce cell- and gene-specific changes in transcription [13]. Vitamin D may also elicit rapid, non-genomic responses via membrane-associated signaling, including the activation of intracellular signaling molecules, such as PKC, PI3K/Akt, MAP kinases, CaMKII and PLA2 [14].

Thus, tissue-specific vitamin D signaling depends not only on the availability of circulating 25(OH)D_3 as substrate but also on its local conversion to active 1,25$(OH)_2D_3$ by CYP27B1, its catabolism by CYP24A1, VDR expression, and the cell-specific transcriptional context.

2.2. VDR distribution and vitamin D signaling in normal SGs

SGs are highly specialized exocrine organs that secrete saliva and maintain oral homeostasis through lubrication, digestion, antimicrobial defense, mucosal protection, and local immune surveillance [15]. Acinar cells produce the primary salivary fluid and secrete proteins and mucins, whereas ductal cells modify its electrolyte composition as it moves toward the oral cavity. Myoepithelial cells surround acini and proximal ducts, contributing to secretory mechanics and structural support [16]. This compartmental organization is particularly relevant to vitamin D signaling because VDR distribution within SGs is not uniform across cell populations.

Vitamin D-related molecules are also detectable in saliva. Salivary vitamin D concentrations are considerably lower than circulating concentrations and may occasionally fall below detection limits [17]. DBP is likewise present in saliva. Its salivary output increases after SG stimulation and is predominantly secreted by mucous glands rather than the parotid gland [18]. Importantly, salivary DBP concentrations do not reliably reflect systemic vitamin D status [18]. These observations suggest that the salivary vitamin D-related milieu is shaped not simply by passive transfer from plasma but by gland-specific secretory processes.

Preclinical studies showed that vitamin D deficiency reduces salivation [19]. In chronically vitamin-D-deficient rats, pilocarpine-stimulated parotid flow fell by over 65% while total amylase output was unchanged, indicating that fluid and electrolyte secretion, but not transepithelial calcium transport or protein secretion, is vitamin D-dependent, likely via a vitamin D-dependent protein required for the use of extracellular calcium in secretion [20]. A clinical study broadly supports these findings, suggesting that vitamin D status influences salivary flow, although the underlying mechanism remains unclear [21].

Direct evidence of vitamin D responsiveness in SG tissue primarily derives from VDR localization studies. Autoradiographic analyses identified nuclear targeting of vitamin D metabolites in epithelial and

myoepithelial cells, with prominent labeling in ductal compartments [22,23]. Subsequent comparative studies identified epithelial and myoepithelial cells as major vitamin D-responsive populations across mammalian SGs [22]. Cultured SG epithelial cells exhibited ligand-responsive VDR signaling after exposure to $1,25(OH)_2D_3$ [24]. More recent immunohistochemical analyses confirmed VDR expression in both murine and human SGs, with particularly strong localization in ductal epithelial cells [24]. In murine submandibular salivary glands, VDR expression exhibited sexual dimorphism, with higher levels in females, a pattern not observed in other VDR-rich organs such as the kidneys [25].

Collectively, these findings link vitamin D deficiency to reduced salivation. However, they do not demonstrate that direct VDR activation enhances physiological salivary secretion. The localization of VDR to defined epithelial compartments provides an anatomical basis for cell-specific vitamin D responses, but its direct contribution to fluid and protein secretion remains unresolved.

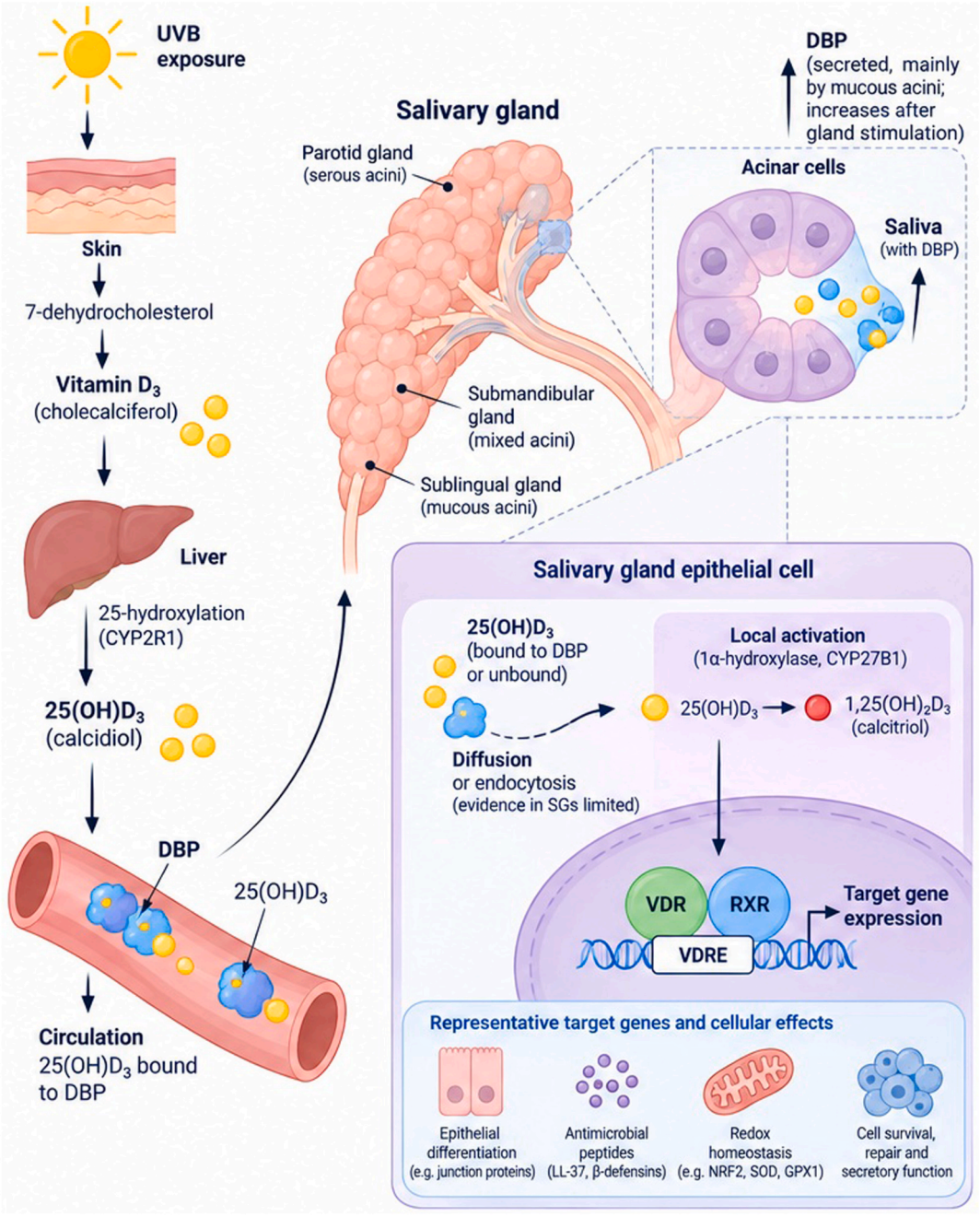


Fig. 1. Vitamin D metabolism and VDR signaling in the salivary gland. Circulating 25-hydroxyvitamin D_3 [$25(OH)D_3$, calcidiol], predominantly transported by vitamin D-binding protein (DBP), serves as a substrate for local CYP27B1-mediated formation of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$, calcitriol] in salivary gland cells. The mechanism by which circulating vitamin D metabolites enter salivary gland epithelial cells remains incompletely defined, and salivary gland-specific evidence for megalin/cubilin-mediated uptake is currently lacking. Calcitriol activates the vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor (RXR) and regulates transcription through vitamin D response elements (VDREs). VDR-responsive pathways have been implicated in epithelial differentiation, antimicrobial defense, redox homeostasis, immune regulation, and cellular integrity; however, these effects should not be interpreted as evidence that VDR activation directly stimulates physiological saliva secretion. DBP is also present in saliva, with its output increasing after gland stimulation and occurring predominantly from mucous rather than parotid glands.

2.3. Epithelial identity and differentiation

Maintaining SG function requires preserving an organized epithelial architecture, in which acinar, ductal, and myoepithelial cells maintain distinct identities through tightly regulated programs governing differentiation, proliferation, polarity, and cell fate [26]. In murine SGs, ΔNp63-positive myoepithelial cells support both the myoepithelial compartment and distinct ductal lineages, underscoring the persistence of lineage plasticity within the adult gland [27].

Direct evidence that vitamin D–VDR signaling contributes to this balance in salivary epithelium remains limited but is increasingly informative. In cultured murine submandibular gland cells, 1,25 $(OH)_2D_3$ increased expression of the differentiated ductal marker keratin 7, whereas the basal/progenitor-associated marker keratin 5 showed a downward trend [24]. VDR activation also reduced total cell number and the proportion of proliferating cells, including the keratin 5-positive fraction, and decreased the proportion of cycling cells in S, G_2, and M phases [24]. These findings support a shift toward a more differentiated epithelial state after VDR activation, accompanied by restraint of proliferative activity rather than a nonspecific cytostatic effect.

VDR activation also markedly suppressed periostin (*Postn)* expression in the same model [24]. Periostin is a matricellular protein involved in extracellular-matrix organization and cell–matrix signaling, processes that contribute to epithelial differentiation. Recent experiments have shown that alterations in basement-membrane heparan sulfate composition can disrupt myoepithelial maintenance, acinar polarity, and salivary function, underscoring the importance of extracellular-matrix cues in preserving epithelial identity [28]. However, the precise role of periostin in normal SG differentiation remains unclear; accordingly, its suppression by $1,25(OH)_2D_3$ should be interpreted as evidence that VDR signaling may influence an extracellular-matrix-associated epithelial program rather than as proof of a defined periostin-dependent mechanism.

Importantly, the cellular effects observed *in vitro* were not accompanied by major structural changes *in vivo*. Chronic dietary vitamin D restriction reduced circulating 25(OH)D but did not disrupt overall glandular architecture [24]. These findings suggest that vitamin D–VDR signaling may fine-tune epithelial differentiation and proliferative competence without being strictly required to maintain gross adult gland morphology under basal conditions. Its contribution may become more relevant during development, regeneration, or cellular stress, when epithelial plasticity and remodeling increase substantially (Fig. 2).

2.4. Oxidative stress and redox balance

Vitamin D-VDR signaling has been implicated in regulating oxidative stress responses in SG cells. The interplay between iNOS-derived •NO (nitric oxide) and reactive oxygen species determines whether the cellular environment leans toward physiological signaling or oxidative stress. iNOS converts L-arginine into L-citrulline and nitric oxide during inflammation. In bovine submandibular fibroblasts, vitamin D enhanced nitric oxide synthase 2 (NOS2) expression and potentiated inducible nitric oxide synthase (iNOS) responses following LPS stimulation [29]. In human sublingual epithelial cells, vitamin D altered the expression of multiple genes involved in inflammatory signaling and cellular homeostasis, including CYP24A1, NR3C1, PTGES, SEMA4D, and KCNK10 [30].

SG epithelium is particularly sensitive to oxidative injury because secretory cells have high metabolic demands and depend on intact mitochondrial function, membrane integrity, and tightly regulated redox signaling. Experimental models link excessive reactive oxygen species to impaired acinar function, loss of secretory markers, and reduced salivary output. In human submandibular gland cells, oxidative stress reduced AQP5 and amylase expression, whereas attenuating oxidative injury restored both epithelial markers and secretory function [31]. Similar relationships among oxidative damage, impaired antioxidant capacity, histopathological injury, and reduced salivary secretion have been observed in experimental models of gland dysfunction [32].

Ferroptosis provides a compelling link between oxidative stress and loss of SG function. This regulated form of cell death is driven by iron-dependent lipid peroxidation and failure of antioxidant systems, especially the glutathione–GPX4 axis. Recent studies have directly implicated this pathway in SG epithelial dysfunction. Reduced GPX4 expression promotes lipid reactive oxygen species accumulation and suppresses AQP5 through a pSTAT4-dependent mechanism, linking ferroptotic stress directly to impaired secretory capacity [33].

Recent SG-specific evidence identifies VDR as a context-dependent regulator of ferroptosis under oxidative stress. In A253 salivary gland cells, oxidative stress increased VDR expression and promoted its accumulation at the cell membrane. VDR overexpression altered ferroptosis-associated gene expression, including SLC3A2, SLC7A11, and TFRC [25]. In female Sod1-deficient mice, increased VDR and TFRC expression was accompanied by enhanced ferroptosis and reduced salivary secretion [25]. Together, these findings link VDR signaling to iron-dependent oxidative injury and suggest that, under excessive oxidative stress, increased VDR activity may contribute to ferroptotic susceptibility and secretory dysfunction rather than exerting a uniformly cytoprotective effect (Fig. 2).

The KEAP1–NRF2 (Kelch-like ECH-associated protein 1- nuclear factor erythroid 2–related factor 2) pathway is a central regulator of a primary cellular feedback loop that manages oxidative stress and maintains redox homeostasis in tissues. Under basal conditions, KEAP1 promotes NRF2 degradation, whereas oxidative stress stabilizes NRF2, enabling its nuclear accumulation and the activation of antioxidant-response-element-dependent genes involved in glutathione metabolism, detoxification, and protection against electrophilic and oxidative damage. Importantly, this pathway's relevance has been demonstrated directly in SGs. Genetic reduction of Keap1 in aged mice enhanced NRF2 activity and attenuated oxidative damage, DNA injury, collagen and iron accumulation, inflammatory-cell infiltration, and apoptosis in submandibular glands, supporting NRF2 as an endogenous determinant of glandular resistance to age-associated oxidative stress [34].

2.5. Potential antioxidant functions of vitamin D in SGs: insights from other epithelial tissues

Vitamin D has been linked to antioxidant regulation across multiple biological levels. A clinical trial meta-analysis indicates that vitamin D supplementation can influence systemic oxidative-stress markers [35], while experimental studies support VDR-dependent regulation of antioxidant pathways, including NRF2-associated responses [36,37]. However, these observations largely derive from non-salivary tissues, and direct evidence that vitamin D or VDR activates NRF2 specifically in SG epithelium remains limited. This distinction is important because the presence of an NRF2-dependent antioxidant program in SGs does not by itself, establish that vitamin D is its physiological upstream regulator.

More recent epithelial studies nevertheless strengthen the plausibility of VDR–NRF2 crosstalk. In human bronchial epithelial cells, calcitriol increased VDR expression, enhanced NRF2 activity, and promoted transcription of NRF2-regulated cytoprotective genes such as *HMOX1* and *NQO1* under oxidant exposure [38]. Although this mechanism has not yet been demonstrated in SG epithelium, it provides a biologically relevant framework for investigating whether local VDR signaling modulates antioxidant capacity in salivary epithelial cells.

Current evidence suggests that vitamin D-VDR signaling contributes to SG redox homeostasis by modulating oxidative stress and ferroptosis-related pathways, although the molecular interaction between VDR and canonical antioxidant systems such as NRF2 remains incompletely defined (Fig. 2).

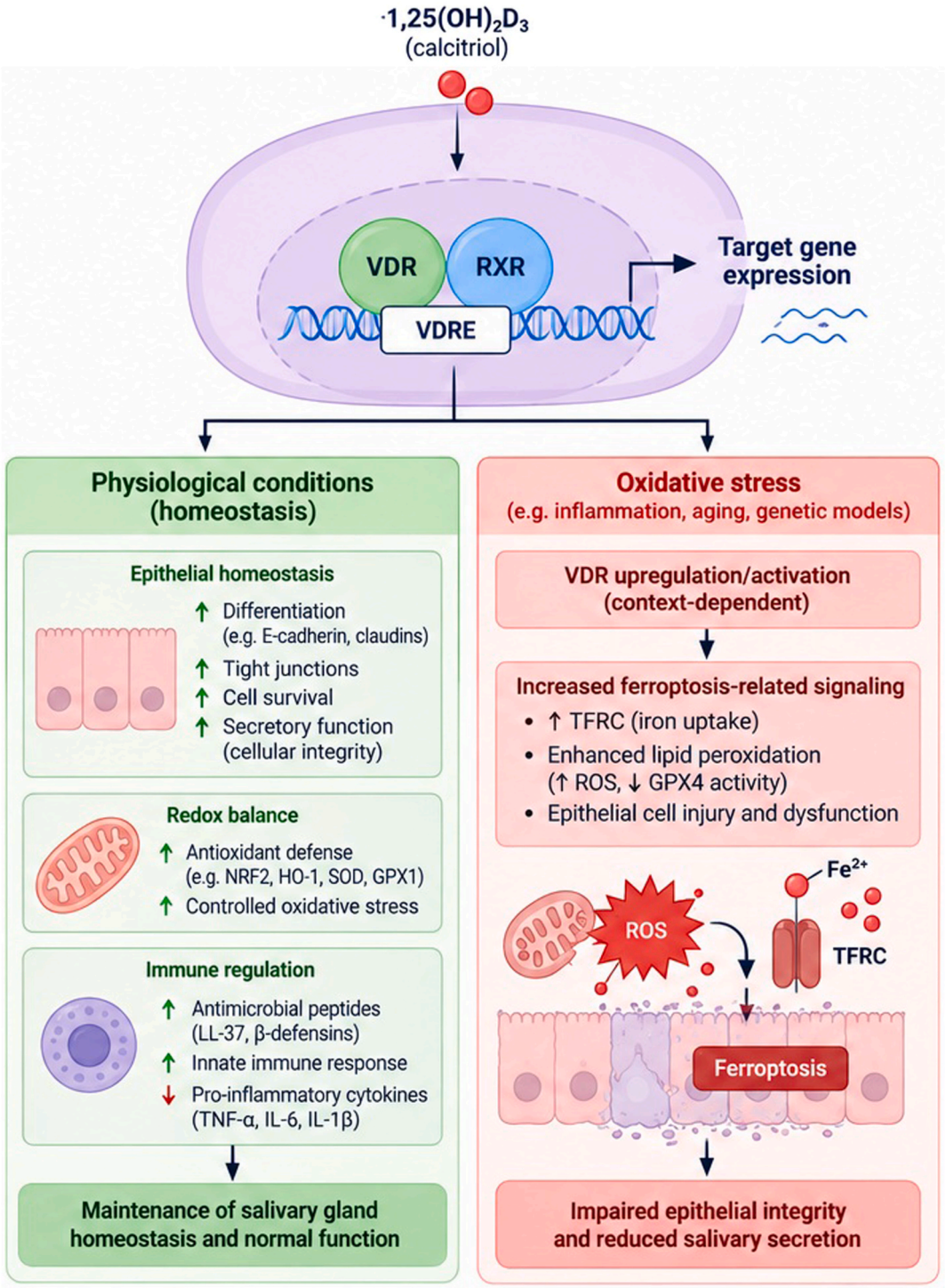


Fig. 2. Context-dependent effects of Vitamin D–VDR signaling on salivary gland homeostasis, oxidative stress, and ferroptosis. Under physiological conditions, vitamin D–VDR signaling has been linked to epithelial differentiation and integrity, immune regulation, antimicrobial defense, and redox homeostasis, though many of these relationships remain incompletely characterized in salivary gland tissue. Under oxidative stress, VDR signaling may have different effects: experimental salivary gland models indicate that increased VDR expression or activity can promote ferroptosis-related signaling, including increased transferrin receptor 1 (TFRC)-dependent iron uptake and lipid peroxidation, which contribute to epithelial injury and reduced salivary secretion. Conversely, antioxidant pathways such as Nuclear factor erythroid 2-related factor 2 (NRF2)-dependent signaling protect salivary gland tissue from oxidative damage, but direct VDR-mediated activation of NRF2 in salivary gland epithelium remains unestablished. Thus, the effects of VDR signaling on redox balance and cell survival appear to be context-dependent rather than uniformly cytoprotective, and preservation of epithelial integrity should be distinguished from direct stimulation of physiological saliva secretion (ROS, Reactive Oxygen Species).

2.6. Vitamin D and the SG immune microenvironment

SGs are immunologically active exocrine organs in which epithelial and immune cells form an integrated regulatory network. Acinar and ductal epithelial cells participate in microbial sensing, cytokine and chemokine production, antigen presentation, and communication with resident and recruited immune populations [39,40]. Recent SG-specific studies further indicate that macrophage populations occupy distinct epithelial, vascular, and neural niches and contribute to epithelial regeneration after injury [41]. Thus, local immunity is functionally coupled to the maintenance of glandular integrity rather than being relevant only during overt inflammation.

Vitamin D signaling can intersect with this network at both epithelial and immune-cell levels. VDR is expressed in epithelial cells, macrophages, dendritic cells, T cells, and B cells, while several immune populations also express CYP27B1 and can convert 25(OH)D_3 to 1,25 $(OH)_2D_3$ locally [42]. This creates the potential for intracrine and paracrine signaling in which immune activation alters local calcitriol availability and subsequent VDR-dependent transcription. Direct evidence of such metabolic coupling in normal SG tissue remains limited.

Vitamin D signaling enhances innate immunity by inducing cathelicidin, an antimicrobial protein that helps eliminate intracellular pathogens and modulates inflammatory responses [43]. In innate immune and oral epithelial cells, pattern-recognition signaling can induce CYP27B1 and VDR-dependent antimicrobial programs, while ligand-activated VDR/RXR complexes bind vitamin Dresponse elements within the *CAMP* regulatory region and increase cathelicidin expression [44,45]. The resulting peptide LL-37 contributes not only to membrane-disruptive antimicrobial activity but also to chemotaxis and modulation of epithelial inflammatory responses. In the salivary compartment, vitamin D and LL-37 concentrations show positive associations, with a stronger relationship in saliva than in serum [17]. Clinical studies have consistently reported that vitamin D supplementation increases salivary sIgA and LL-37 [21,46]. Although these data do not prove direct glandular synthesis or causation, they provide one of the most compelling links between vitamin D availability and local mucosal defense.

Vitamin D also influences inflammatory transcriptional programs in antigen-presenting and lymphoid cells. VDR signaling can restrain dendritic-cell maturation, alter cytokine production, and modify T- and B-cell activation [42,47]. Experimental vitamin D_3 supplementation has been associated with normalization of T-cell proliferative responses, changes in the CD4+/CD8+ distribution, reduced NF-κB p65 activation, and shifts in humoral responses during immune dysregulation [48]. These findings are not SG-specific, but they illustrate molecular pathways through which VDR signaling may limit persistent inflammatory activation.

This is particularly relevant because SG epithelial cells can adopt an immune-active phenotype. Under inflammatory conditions, they increase antigen presentation and co-stimulatory capacity, and produce chemokines, interferon-responsive mediators, and B-cell-supporting factors [39,40,49,50]. Such signaling can reinforce lymphocyte recruitment and sustain epithelial–immune feedback. In Sjögren syndrome (SS), this network is associated with persistent interferon pathway activation and chronic lymphocytic infiltration [49,50]. SS is a chronic autoimmune disease affecting the salivary and lacrimal glands.

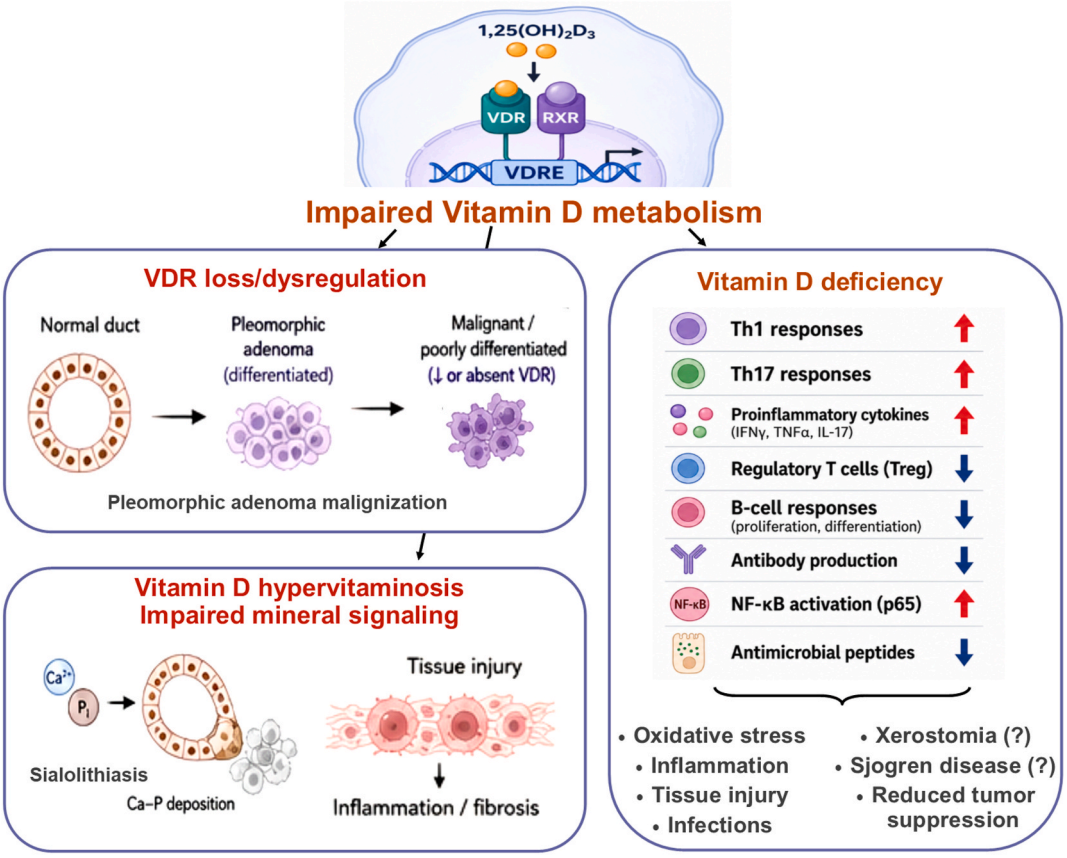


Fig. 3. Potential consequences of impaired vitamin D metabolism in SG disorders.
Altered vitamin D signaling may affect immune responses, epithelial differentiation, and mineral homeostasis, potentially contributing to salivary gland inflammation, xerostomia, tumor progression, and pathological calcification. Impaired immune responses and loss of VDR expression in benign tumors are linked to their malignant transformation and metastasis. Both vitamin D deficiency and excessive vitamin D signaling may produce tissue-specific effects, highlighting vitamin D's context-dependent role in salivary gland homeostasis.

Vitamin D is of interest in SS because of its immunomodulatory effects on lymphocyte responses and glandular inflammation. A meta-analysis found lower circulating vitamin D levels in patients with SS than in healthy controls [51]. Low systemic vitamin D levels have also been linked to specific clinical manifestations in patients with SS, including peripheral neuropathy and lymphoma [52,53]. However, these observational associations do not establish vitamin D deficiency as a cause or consequence of SS, and current evidence does not support a causal relationship between serum vitamin D levels and SS risk [54] (Fig. 3).

Sialolithiasis is the most common non-neoplastic disorder of the major SGs and is characterized by the formation of calcified structures within the ductal system. It arises from complex interactions among salivary composition, ductal factors, and inflammation. Salivary stones contain substantial amounts of calcium phosphate, although systemic disturbances in calcium–phosphate metabolism have not been established as a primary cause of their formation [55]. Given vitamin D's central role in mineral metabolism, its involvement in salivary calcification is biologically plausible; however, direct clinical evidence linking vitamin D deficiency or circulating vitamin D concentrations to human sialolithiasis remains limited. Short-term $1,25(OH)_2D_3$ treatment (4 μg kg^{-1} BW i.p., once daily for two consecutive days) did not alter mRNA expression of inorganic phosphate and Ca^{2+} transporter genes (Slc34a2, Slc20a1, Slc20a2, Xpr1, Trpv6, Atp2b1) in SGs; chronic treatment remains to be investigated [56] (Fig. 3). Excessive vitamin D exposure in rats induced SG ductal degeneration, inflammatory infiltration, and calcification within the submandibular gland [7]. These findings demonstrate that excessive vitamin D exposure can promote pathological SG calcification in an experimental setting, but they should not be interpreted as a model of human sialolithiasis. Spontaneous ductal stone formation comparable to human disease has not been reported, and a causal role of vitamin D status in human sialolithiasis remains unestablished. Reduced serum vitamin D concentrations have been observed in patients with calculous sialadenitis [57]. Additionally, postoperative calcium and vitamin D supplementation has been reported to enhance tissue recovery following sialolith removal, reducing postoperative edema, hyperemia, and scar contracture formation [57].

Overall, vitamin D-VDR signaling is best viewed as a potential modifier of the SG immune microenvironment rather than a dominant upstream regulator (Fig. 2). Its most clearly defined molecular links include local calcitriol generation, VDR-dependent transcription of antimicrobial genes, and modulation of inflammatory transcriptional programs. However, direct evidence for these processes within intact human SG tissue remains limited.

2.7. Vitamin D signaling in SG diseases: insights from clinical studies

Experimental studies have shown that vitamin D primarily affects cellular phenotype and functional integrity rather than gross SG morphology [24]. Accordingly, vitamin D supplementation has protective effects against experimentally induced SG injury, including fatty degeneration associated with calcium-deficient diets [58,59]. Conversely, excessive vitamin D exposure can induce ductal degeneration, inflammatory infiltration, and pathological calcification, underscoring that both deficient and excessive signaling may disrupt glandular physiology [7]. However, clinical evidence remains considerably more limited than experimental data.

In minor SG biopsies, low vitamin D correlates with focal lymphocytic sialadenitis but not with more advanced histological stages [60]. Genetic evidence is similarly inconclusive: common VDR polymorphisms, including *Taq*I, *Bsm*I, *Apa*I, and *Fok*I, have not shown significant associations with primary SS susceptibility [61].

Immunohistochemical evidence indicates substantial alterations in VDR expression during neoplastic transformation. VDR expression is absent in neoplastic epithelial components and in malignant SG tumors, including adenoid cystic, squamous cell, and mucoepidermoid carcinomas, compared with normal SG tissue or SG benign tumors [24]. Evidence from mammary tumor models indicates that VDR loss can impair epithelial lineage fidelity and promote epidermal/squamous transdifferentiation [62]. Although this mechanism has not been established in SG tumors, it provides a comparative framework for investigating whether altered VDR signaling contributes to epithelial plasticity during SG tumor progression (Fig. 3). *In vitro* and *in vivo*, vitamin D reduces tumor size, cell proliferation, cisplatin resistance, and cell motility in salivary adenoid cystic carcinoma by inhibiting NF-κB activation and subsequently downregulating GPX1 and uPA [63] (Fig. 3). Given the central role of the uPA-plasmin system in extracellular proteolysis, tissue remodeling, and inflammatory processes within the oral environment [15], these findings provide a biologically plausible link between vitamin D signaling, redox regulation, and tumor-invasive behavior. Moreover, patients with head and neck cancer frequently have inadequate vitamin D intake at baseline, after treatment, and during follow-up [64].

These tissue and experimental findings are not mirrored by circulating vitamin D concentrations. A clinical study comparing patients with benign and malignant SG tumors to healthy controls found no significant differences in serum vitamin D status [65]. Thus, local VDR activity and tumor-specific signaling may be more informative than systemic vitamin D levels, although their prognostic or therapeutic significance remains to be established.

Vitamin D signaling in tissues is typically assessed by immunohistochemical staining or by gene expression analysis of VDR and the vitamin D-metabolizing enzymes CYP27B1 and CYP24A1, which regulate vitamin D activation and degradation, respectively [66,67]. To date, most research has focused on breast cancer, a glandular malignancy that shares notable similarities with SG tumors.

Overall, current evidence suggests that vitamin D-VDR signaling may influence SG disease by modulating immune regulation, tumor progression, and mineralization, and that vitamin D status is associated with selected manifestations of SS and early glandular inflammation. However, the predominantly observational and heterogeneous nature of existing studies precludes causal inference and underscores the need to distinguish systemic vitamin D status from local VDR-mediated mechanisms (Fig. 3).

2.8. Vitamin D-related biomarkers: translational perspectives in SG health and disease

DBP, the principal carrier of vitamin D metabolites, is present in saliva and appears to be actively secreted by SGs, making it a potential biomarker of local vitamin D signaling [18,68]. Although evidence in this area remains limited, several clinical studies have examined DBP and other biomarkers of vitamin D metabolism as potential predictors of susceptibility to oral disease, disease progression, and treatment outcomes. Table 1 summarizes these studies.

These findings indicate that circulating vitamin D levels, salivary DBP, and VDR-related genetic variants provide complementary, not interchangeable, information about vitamin D signaling in oral tissues. Fig. 4 illustrates the potential clinical applications of vitamin D-related biomarkers. However, the translational potential of this axis for SG therapy remains largely unexplored. The accessibility of saliva, combined with evidence that SGs actively secrete DBP, makes simultaneous assessment of salivary DBP, vitamin D metabolites, and potentially VDR-related molecular signatures an attractive strategy for non-invasive phenotyping [75]. Rather than relying on a single marker, future studies should assess whether integrated biomarker profiles can distinguish systemic vitamin D deficiency from local alterations in glandular vitamin D signaling. Standardized sampling, longitudinal designs, and correlations with salivary flow, glandular imaging, and tissue-level VDR expression will be essential before these markers can be translated into diagnostic, prognostic, or treatment-monitoring tools [75].

Table 1
Potential biomarkers of vitamin D signaling in oral diseases: summary of clinical studies.

	Biomarker	Clinical significance	Source
1	Salivary DBP	Elevated salivary DBP levels reported in patients with generalized aggressive periodontitis and gingivitis, suggesting its potential utility as a biomarker of periodontal inflammation.	[69, 70]
2	Salivary DBP	Salivary DBP concentrations vary across pubertal developmental stages, supporting its potential use as an adjunctive biomarker of skeletal maturation.	[71]
3	Salivary DBP	Both low and high salivary DBP concentrations are associated with reduced orthodontic tooth movement, whereas intermediate concentrations are associated with greater tooth movement, indicating a possible role in bone remodeling dynamics.	[72]
4	Circulating vitamin D	Reduced circulating vitamin D levels observed in patients with chronic periodontitis, suggesting a potential association between vitamin D deficiency and periodontal disease.	[73]
5	VDR *Apa*I SNP C/T polymorphism (rs731236)	The VDR *Apa*I SNP C/T polymorphism (rs731236) associated with susceptibility to chronic periodontitis in a Libyan population.	[74]

2.9. Future perspectives

Vitamin D–VDR signaling in SG has largely completed its descriptive phase. Receptor and enzyme expression have been documented, mechanisms have been inferred from related glandular tissues, and clinical associations continue to accumulate. The task now is to convert this into a causal, SG tissue-specific understanding.

Future work should treat SG tissue vitamin D, rather than vitamin D in the circulation, as the unit of analysis when determining its effects on SG tissues. Tissue-specific vitamin D signaling depends not only on the availability of circulating 25(OH)D_3 as substrate but also on its local conversion to active 1,25(OH)$_2D_3$ by CYP27B1, its catabolism by CYP24A1, VDR expression, and the cell-specific transcriptional context. Any of these can uncouple systemic status from local response, so serum concentration alone is an inadequate exposure measure; the intraglandular system should be quantified directly, with receptor target genes used as functional readouts of pathway activity.

The enrichment of VDR in ductal and myoepithelial populations provides an anatomical basis for cell-specific vitamin D effects and warrants further investigation into how VDR activation influences epithelial differentiation, cellular stress responses, and secretory competence. Single-cell and spatial profiling, compartment-restricted receptor deletion, and organoid systems that preserve lineage hierarchy would assign effects currently attributed to the whole gland to defined populations. Most studies have assessed vitamin D–VDR signaling, either at the transcript or protein level, in a single SG type, usually the parotid or submandibular gland, whereas data on the sublingual and minor SGs are largely lacking.

Despite a growing literature linking vitamin D to oral and glandular health, no study has demonstrated that VDR activation improves salivation. This is the single most consequential gap in the field, because clinical interest in vitamin D for SG disease rests almost entirely on an assumption of secretory benefit.

Secretion is the endpoint on which clinical interest ultimately rests, yet it has been inferred rather than measured and should be adopted as a prespecified outcome in clinical and preclinical studies. A related question is regenerative: interventions that promote epithelial differentiation may either restore secretory competence or deplete the progenitor reserve on which recovery depends. Distinguishing these outcomes requires lineage-based approaches in injury models, not marker expression alone.

Vitamin D signaling has been described as both protective and destructive in epithelial tissue. Resolving this requires systematically defining conditions such as concentration, iron availability, redox status, age, and the presence of injury or transformation under which the pathway supports survival rather than promoting regulated cell death. It also requires positioning VDR relative to the gland's canonical antioxidant machinery, rather than treating the two as separate systems.

Because the receptor and the activating enzyme are present in epithelial and immune compartments alike, SGs can plausibly generate and respond to locally produced calcitriol. This coupling should be tested directly in resting and inflamed tissue rather than inferred from systemic supplementation outcomes, with clinical endpoints paired with gland-level molecular readouts from accessible biopsy tissue.

Understanding the mechanisms of vitamin D–VDR signaling in preclinical and *in vitro* studies will provide the foundation for clinical implementation. These studies identify which cells respond to the signal and therefore indicate whether its use is justified in a given disease, since a treatment is rational only if responsive target cells are present in the tissue and retain the capacity to respond. The most informative clinical settings are those in which glandular reserve is already compromised: patients with autoimmune sialadenitis, radiation injury, inflammatory diseases of SG, xerostomia, polypharmacy and age-related SG dysfunction [76–78]. In neoplasia, analytical frameworks developed for better-studied SG malignancies can be adapted, provided the distinct molecular drivers of SG tumors are respected. Progress depends on validated reagents, physiologically attainable concentrations, standardized saliva collection, and endpoints defined in advance.

Vitamin D–VDR signaling is therefore best positioned as a candidate modifier of glandular epithelial homeostasis, redox balance, and mucosal immunity. Whether it also influences secretion will determine

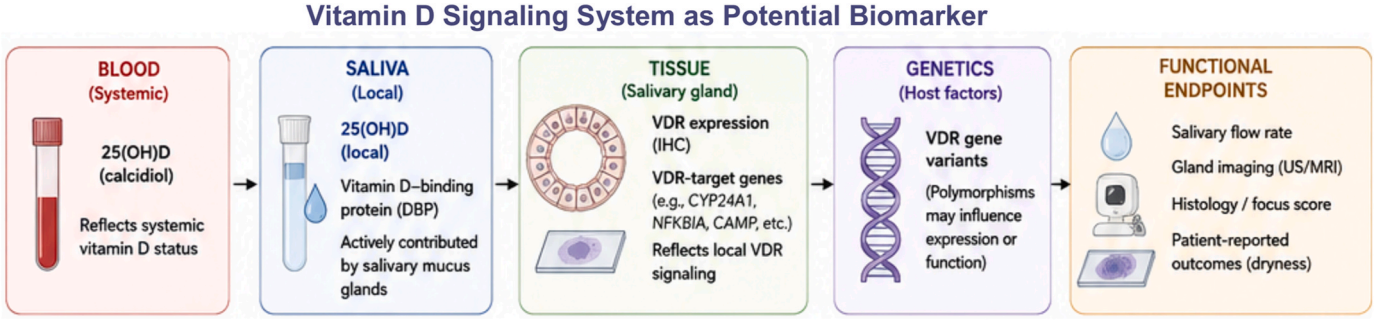


Fig. 4. Vitamin D signaling molecules as a potential biomarker framework for SG diseases.
An integrated assessment of systemic 25(OH)D, salivary 25(OH)D and DBP, tissue VDR signaling, VDR genetic variants, and functional glandular parameters may provide complementary insights into vitamin D status and local signaling.

whether it is a therapeutic target or remains a biological correlate.

3. Conclusion

Vitamin D–VDR signaling has been implicated in multiple aspects of SG biology, including epithelial differentiation, redox homeostasis, and immune regulation, but its direct role in physiological salivary secretion remains incompletely defined. SG-specific evidence linking VDR signaling to ferroptosis and salivary hyposecretion further indicates that its effects on glandular function are context-dependent and cannot be predicted by circulating vitamin D levels alone. Although associations with SG disorders are biologically plausible, clinical evidence remains largely observational and insufficient to establish causation. Future studies integrating systemic, salivary, and tissue-level biomarkers are needed to clarify the diagnostic, prognostic, and therapeutic relevance of vitamin D signaling in SG and oral diseases.

Ethical statement

The present study is a narrative review. Hence, ethical approval is not applicable.

Author contribution

Maksym Skrypnyk: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing, project administration, funding acquisition.

Dmytro Labudzynskyi: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing, visualization.

Tetiana Yatsenko: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing, visualization.

Roman Skrypnyk: Investigation, writing—review and editing.

Margarita Skikevych: Investigation, writing—review and editing, project administration.

Igor Skrypnyk: Investigation, writing—review and editing, project administration.

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Taro Osada: Writing—review and editing, funding acquisition.

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Beate Heissig: Conceptualization, writing—original draft preparation, writing—review and editing, supervision, project administration, funding acquisition.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used AI-assisted tools to design part of the illustrations. After using these tools, the authors carefully reviewed and edited the content as needed and assume full responsibility for the publication's content.

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Competing of interest

The authors declare no conflict of interest.

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