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RESEARCH ARTICLE

EVALUATION OF SALIVARY VITAMIN D3 LEVELS AND ITS ROLE IN THE PATHOGENESIS OF ORAL SUBMUCOUS FIBROSIS- A CASE CONTROL STUDY

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ABSTRACT

Background: Oral Submucous Fibrosis (OSMF) is a chronic, progressive disorder characterized by fibrosis of the oral mucosa, leading to restricted mouth opening and significant functional impairment. It is strongly associated with areca nut consumption and is classified as a potentially malignant disorder. Vitamin D, known for its pleiotropic effects, has been implicated in modulating fibrosis, inflammation, and oxidative stress, which are key factors in OSMF pathogenesis.

Objective: The aim of the study was to evaluate the salivary levels of 25(OH)D3 in patients with OSMF and explore a potential correlation between vitamin D3 deficiency and the progression of OSMF.

Methods: A comparative analysis was conducted to assess salivary Vitamin D levels in OSMF patients and healthy controls. The potential mechanisms by which Vitamin D influences collagen metabolism, immune responses, and oxidative stress were reviewed in the context of existing literature.

Results: The study revealed significantly lower salivary Vitamin D levels in OSMF patients (mean: 36.39 ng/ml) compared to healthy controls (mean: 54.01 ng/ml), with a statistically significant difference (p-value = 0.010). Vitamin D deficiency was associated with increased fibrosis due to dysregulated fibroblast activity, impaired matrix metalloproteinase (MMP) expression, and upregulated transforming growth factor-beta (TGF-β). Additionally, low Vitamin D levels correlated with enhanced inflammation, oxidative stress, and a higher potential for malignant transformation.

Conclusion: The findings highlighted a strong association between Vitamin D deficiency and OSMF pathogenesis. Given its antifibrotic, anti-inflammatory, and antioxidant properties, Vitamin D supplementation may serve as a potential adjunctive therapy for OSMF management. Future research should explore the therapeutic benefits of Vitamin D in preventing disease progression and reducing the risk of malignant transformation.

Keywords: Vitamin D, OSMF, fibrosis, collagen

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially debilitating disorder that predominantly affects the oral cavity and, in advanced stages, may involve the pharynx and upper esophagus. It is widely recognized as a potentially malignant condition and a collagen metabolic disorder, marked by excessive deposition of collagen fibers, which leads to mucosal rigidity, blanching, burning sensation, and restricted mouth opening.[1]

Over time, the affected tissues lose elasticity and resilience, resulting in functional impairment of the oral structures. Severe cases may present with additional complications such as tongue and soft palate hypomobility, xerostomia, gustatory deficits, pharyngeal and esophageal fibrosis, hearing disturbances, sunken cheeks, muscular atrophy, hoarseness of voice, and nasal speech, significantly impairing the patient's quality of life.[1]

The pathogenesis of OSMF is multifactorial and involves a disruption in collagen homeostasis, characterized by upregulated collagen synthesis and downregulated degradation.[2]

Several risk factors have been identified, among which the most prominent are the use of areca nut, tobacco products, and betel quid—substances widely consumed across South and Southeast Asia. Epidemiological studies conducted in India report that individuals with mixed habits (such as chewing areca nut, gutkha, smoking, and consuming tobacco in various forms) are at a particularly high risk of developing OSMF.[3] The condition affects individuals across a broad age spectrum (11–60 years), with a higher prevalence observed in males (0.2–2.3%) compared to females (1.2–4.6%).[3 4]

The ready availability and cultural acceptance of commercial smokeless tobacco products, such as gutkha, have been closely linked to the rising incidence of OSMF.[4 5] India currently bears the highest global burden of oral cancer, with an estimated 75,000–80,000 new cases reported annually.[5]

Gutkha, in particular, has emerged as a major contributing factor not only in the onset of OSMF but also in its malignant transformation.[6]

It contains several cytotoxic substances, including free radicals like hydroxyl radicals (OH), which are capable of causing DNA damage and initiating carcinogenesis.[7]

These reactive species disrupt the normal cellular environment and promote the transition of OSMF to oral squamous cell carcinoma (OSCC). This highlights the need for vigilant screening and early diagnosis of OSMF to intercept malignant progression.

The carcinogenic progression of OSMF follows a multistep model, transitioning from chronic inflammation and fibrosis to epithelial dysplasia and ultimately invasive carcinoma.[4 5] This model underscores the urgent need to identify early biomarkers capable of detecting premalignant changes before the onset of overt malignancy. Translational oncology is increasingly focusing on molecular approaches to aid early diagnosis and improve therapeutic outcomes.[6 7]

A critical mechanism implicated in carcinogenesis is the evasion of apoptosis—a process essential for maintaining tissue homeostasis. Resistance to apoptosis is often associated with therapy resistance and tumor recurrence in OSCC.[8] Consequently, agents that can restore apoptotic pathways or modulate the tumor microenvironment have become the focus of ongoing research.

Recent studies have pointed to the pleiotropic role of Vitamin D in regulating fibrosis, inflammation, immunity, and cellular proliferation.[9] Beyond its classical role in calcium homeostasis, Vitamin D—particularly its active form, 1,25-dihydroxyvitamin D3—has shown potential in modulating extracellular matrix remodeling, inhibiting fibrogenic pathways, and regulating immune responses.[9] It has been found to downregulate pro-fibrotic cytokines such as transforming growth factor-beta (TGF-β), enhance the expression of matrix metalloproteinases (MMPs), and suppress fibroblast activation—all of which may be beneficial in halting or reversing the fibrotic changes characteristic of OSMF.[9] Additionally, Vitamin D exerts anticancer effects by inhibiting cell proliferation, angiogenesis, and metastasis while promoting differentiation and apoptosis in various cell types, including oral keratinocytes.

Despite these promising biological roles, there is a significant knowledge gap regarding the relevance of Vitamin D status—particularly Vitamin D3 levels—in patients with OSMF. While serum Vitamin D assessments are common in systemic

diseases, the use of saliva as a diagnostic fluid has gained traction due to its non-invasive, cost-effective, and convenient nature. Salivary diagnostics offer a viable alternative for early disease detection, especially in conditions localized to the oral cavity. However, studies investigating salivary Vitamin D3 levels in OSMF patients are less, and its potential as a biomarker for disease presence, severity, or progression remains underexplored.

Given the complex interplay between fibrosis, oxidative stress, and carcinogenesis in OSMF, and the multifaceted role of Vitamin D in modulating these pathways, this study seeks to bridge the existing research gap. The primary aim is to evaluate and compare the salivary Vitamin D3 levels in individuals diagnosed with OSMF and healthy controls, to investigate whether a significant correlation exists between Vitamin D3 status and OSMF pathogenesis. Furthermore, by identifying any potential deficiency or alteration in salivary Vitamin D3 levels, this study aims to assess the feasibility of using it as a non-invasive diagnostic biomarker and explore its therapeutic implications in the management and prevention of malignant transformation in OSMF.

MATERIALS AND METHODS

A prospective cohort study was conducted at Saveetha Dental College and Hospitals, Chennai, Tamil Nadu, India, involving 40 participants. The study protocol received approval from the Scientific Review Board (IHEC/SDC/UG-2294/24/PHARM/095). Participants were aged between 25 and 70 years.

The study included two groups: the case group comprised 20 patients histopathologically diagnosed with Oral Submucous Fibrosis (OSMF), while the control group consisted of 20 healthy individuals without systemic disorders. Exclusion criteria included individuals taking Vitamin D supplements, those undergoing chemotherapy, radiotherapy, or any surgical procedures (except biopsy), and patients with systemic conditions known to influence salivary Vitamin D levels, such as parathyroid disorders, rickets, osteomalacia, and sarcoidosis. Additionally, individuals with active infections (e.g., hepatitis, HIV, tuberculosis), chronic kidney or liver disease, malnutrition, or metastasis were excluded.

Medical histories were recorded, clinical examinations were performed, and informed consent was obtained from all participants. Unstimulated saliva samples (2 ml) were collected between January and July 2024 from each subject between 8:00 a.m. and 9:00 a.m. Participants were instructed to follow their routine South Indian diet the night before and on the morning of sample collection. Samples were centrifuged at 5000 rpm for 10 minutes and stored at 4°C for further analysis.

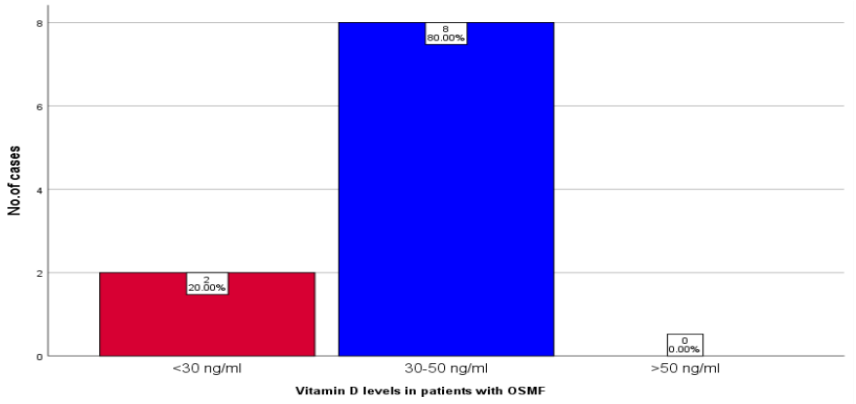
Vitamin D levels (total 25-hydroxy vitamin D) were measured using the Vitamin D Quanti Microlisa kit, which employs a delayed competitive ELISA method. Salivary and serum Vitamin D levels were compared between the case and control groups. To eliminate dietary influences, a diet history was documented, and individuals consuming Vitamin D-fortified foods or supplements were excluded.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.). A paired t-test was used to assess correlations between variables, with a p-value of ≤ 0.05 considered statistically significant.

RESULTS

Expression of salivary 1-25dihydroxycholecalciferol levels in patients with Oral Submucous Fibrosis

Salivary1,25dihydroxycholecalciferol levels in patients undergoing orthodontic treatment was evaluated using delayed competitive ELISA. There was a mean salivary1-25dihydroxycholecalciferol level of **36.39 ng/ml** in patients with Oral Submucous Fibrosis. (Fig. 1)



Figur.1 Graph showing the mean salivary 1-25 dihydroxycholecalciferol levels in patients with OSMF

Expression of salivary 1-25dihydroxycholecalciferol levels in healthy subjects

Salivary1,25dihydroxycholecalciferol levels in patients undergoing orthodontic treatment was evaluated using delayed competitive ELISA. There was a mean salivary1-25dihydroxycholecalciferol level of **54.01 ng/ml** in healthy subjects (Figure 2).

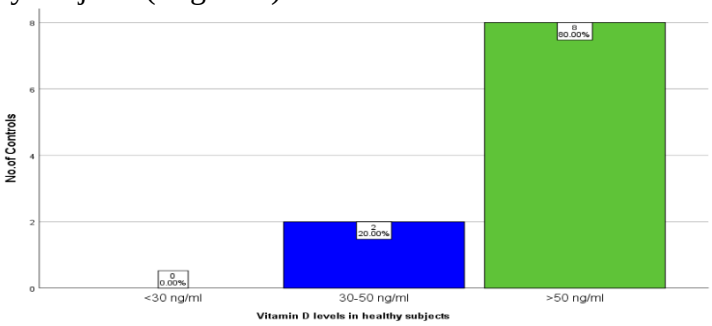


Fig.2 Graph showing the mean salivary 1-25 dihydroxycholecalciferol levels in normal healthy subjects

Comparison of salivary 1-25dihydroxycholecalciferol levels in patients with Oral Submucous Fibrosis and in healthy subjects

In order to compare salivary levels of vitamin D in two groups, paired t-test was used. The results showed that there was a significant difference between the levels of salivary vitamin D in healthy subjects (mean 54.01ng/dl) and salivary vitamin D levels in people with oral submucous fibrosis (mean 36.39 ng/dl) (p-value = 0.010). The results clearly indicate that the level of salivary vitamin D in patients with OSCC was less than that of healthy subjects.(Table).

Table 1. Table showing the comparison of salivary vitamin D3 levels between the two groups done using paired- t-test.

Paired t test		
STUDY GROUP	**Mean**	**Significance (2 Tailed)**
CASE (Patients with OSMF)	36.39 ng/dl	
CONTROL (Healthy subjects)	54.01 ng/dl	0.010

DISCUSSION

Oral Submucous Fibrosis (OSMF) is a progressive, chronic condition that primarily affects the oral cavity and, in some cases, extends into the oropharynx and esophagus. This disease manifests insidiously, characterized by a gradual loss of oral mucosal elasticity, increasing stiffness, and limited mouth opening, often resulting in impaired speech, difficulty chewing, and swallowing challenges. As fibrosis progresses, it deeply compromises a patient's quality of life. The fundamental pathological process driving OSMF is excessive collagen deposition—resulting from both overproduction and inadequate degradation of extracellular matrix components, particularly collagen. This disruption in collagen homeostasis underscores the irreversible nature of the disease in many advanced cases, despite ongoing research into potential therapeutic targets and interventions.[1]

Among the various etiological agents implicated, areca nut chewing remains the primary contributor, frequently compounded by the use of betel quid and gutkha. These habits are particularly widespread in South and Southeast Asia. The compounds present in areca nut—such as alkaloids (arecoline), tannins, and reactive oxygen species (ROS)—stimulate fibroblasts and enhance collagen synthesis while suppressing the enzymatic systems responsible for its degradation. Over time, the cumulative exposure to these irritants induces a sustained inflammatory response and promotes fibrosis. Alarmingly, OSMF is classified as a potentially malignant disorder, with studies suggesting a 7% to 13% risk of transformation into oral squamous cell carcinoma (OSCC).[10 11]

This malignant potential, coupled with the irreversible fibrotic changes in advanced cases, calls for a more refined understanding of its pathogenesis and alternative therapeutic strategies. One such promising area of exploration lies in Vitamin D, a fat-soluble secosteroid traditionally known for its role in calcium homeostasis and bone metabolism. More recently, however, its pleiotropic effects—including anti-inflammatory, antifibrotic, antioxidant, and anticancer properties—have attracted attention across multiple fields of research. Vitamin D exists in two primary forms: D_2 (ergocalciferol) and D_3 (cholecalciferol), the latter of which is synthesized in the skin upon exposure to ultraviolet B (UVB) light and can also be obtained through dietary sources. In the body, it undergoes hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D], the major circulating form, and is further activated in the kidneys to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], which binds to the Vitamin D receptor (VDR) expressed in a variety of tissues—including the oral mucosa.

The activation of VDRs initiates a cascade of gene transcription events that regulate several physiological processes. In the context of OSMF, the most relevant mechanisms include modulation of fibroblast behavior, regulation of matrix metalloproteinases (MMPs), inhibition of pro-fibrotic signaling, and attenuation of chronic inflammation. The pathological hallmark of OSMF—excessive collagen accumulation—is influenced by fibroblast hyperactivity. Interestingly, $1,25(OH)_2D$ has been shown to reduce fibroblast proliferation and downregulate collagen gene expression, thus curbing the primary pathological mechanism of the disease. Moreover, Vitamin D plays a key role in balancing the enzymes that remodel the extracellular matrix. It enhances the expression of MMPs, particularly MMP-1 and MMP-9, while simultaneously suppressing tissue inhibitors of metalloproteinases (TIMPs), which are known to inhibit collagen breakdown. This dual action facilitates the degradation of excess collagen and could potentially slow down or reverse the fibrotic changes seen in early-stage OSMF. The Transforming Growth Factor-Beta (TGF-β) pathway, a well-established mediator of fibrosis, is also a significant target of Vitamin D action. TGF-β promotes fibroblast activation and encourages cross-linking of collagen fibers, which results in the stiff, inelastic mucosa characteristic of OSMF. Vitamin D has been reported to suppress this pathway, thereby impeding the perpetuation of fibrosis.[12–15]

These mechanisms are not unique to the oral cavity. In fact, similar antifibrotic effects of Vitamin D have been documented in other chronic fibrotic conditions, including hepatic fibrosis and idiopathic pulmonary fibrosis. It seems likely that these shared pathways of fibrogenesis could be therapeutically modulated across various tissues through Vitamin D-based interventions.

Another critical factor in OSMF is persistent inflammation, which acts both as a trigger and a driver of disease progression. The habitual use of areca nut and tobacco contributes to sustained mucosal irritation and generates a pro-inflammatory environment marked by elevated levels of cytokines such as IL-6, TNF-α, and IFN-γ. These molecules not only amplify local inflammation but also promote fibroblast activation. Here too, Vitamin D exerts a protective role. By downregulating pro-inflammatory cytokines and enhancing anti-inflammatory mediators like IL-10, Vitamin D helps re-establish immune equilibrium. Inhibiting the nuclear factor-kappa B (NF-κB) signaling pathway—another key driver of chronic inflammation and fibrosis—further strengthens this immunomodulatory profile. These anti-inflammatory effects have been supported by findings from researchers like Kongsbak et al. (2013) and Prietl et al. (2013), who have illustrated the broad-spectrum immune-regulatory capabilities of Vitamin D.[17] [18]

Yet, inflammation is not the only pathological factor exacerbated by lifestyle habits associated with OSMF. Oxidative stress, largely fueled by the ingestion of free radicals in areca nut and tobacco, contributes significantly to tissue damage. Reactive oxygen species (ROS) initiate lipid peroxidation, damage DNA, and denature proteins, setting the stage for fibrosis and potentially malignancy. Vitamin D, as it turns out, possesses potent antioxidant properties. It promotes the expression of endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), which collectively neutralize ROS and protect against cellular injury. Furthermore, by reducing lipid peroxidation, Vitamin D decreases the formation of harmful metabolites that perpetuate tissue damage and inflammatory responses.

The malignant transformation potential of OSMF further highlights the necessity of interventions that can act at multiple levels of disease progression. Remarkably, Vitamin D also demonstrates anticancer properties. It inhibits angiogenesis—disrupting the vascular supply essential for tumor growth—and promotes apoptosis in neoplastic cells. By regulating keratinocyte proliferation and reducing epithelial-to-mesenchymal transition (EMT), Vitamin D supports cellular differentiation and reduces the | risk of dysplasia and invasive transformation.

Garland et al. (2006) emphasized the protective role of Vitamin D against a variety of cancers, lending further weight to its potential relevance in managing premalignant oral disorders like OSMF.[18–20]

In the present study, we observed that OSMF patients exhibited significantly lower salivary Vitamin D3 levels compared to healthy individuals. The average level in affected subjects was 36.39 ng/ml, notably lower than the 54.01 ng/ml recorded in controls. This difference was statistically significant ($p = 0.010$), suggesting a meaningful association between Vitamin D deficiency and the pathogenesis of OSMF. While causation cannot be definitively established from a cross-sectional study, the data support the hypothesis that insufficient Vitamin D may worsen fibrosis, impair mucosal healing, and weaken immune surveillance. In a condition known for its resistance to treatment and potential for malignancy, such findings should not be taken lightly.

Nonetheless, this study is not without limitations. Salivary Vitamin D levels may be influenced by various factors including hydration status, salivary flow rate, and individual metabolic variations. Future studies with larger sample sizes and serum Vitamin D evaluations could help corroborate these results and clarify the pathophysiological links further.

The implications of this study are promising. Ensuring adequate Vitamin D levels through supplementation or lifestyle changes may offer a low-cost, low-risk adjunctive strategy for managing OSMF. Therapeutic possibilities include: (i) Vitamin D Supplementation—either oral or injectable forms to address deficiency and potentially reverse early fibrotic changes; (ii) Dietary Interventions—incorporating foods rich in Vitamin D such as oily fish, fortified dairy products, and egg yolks; (iii) Sunlight Exposure—sensible UVB exposure can significantly enhance endogenous Vitamin D synthesis; (iv) Behavioral Modifications—cessation of areca nut and tobacco use remains critical and may work synergistically with Vitamin D-based interventions; and (v) Adjunctive Therapy—integrating Vitamin D with current modalities such as antioxidants, intralesional corticosteroids, and enzymes like hyaluronidase to improve

therapeutic response.[21 22]

While OSMF remains a complex disorder with multifactorial etiology, Vitamin D appears to intersect with several key aspects of its pathogenesis—fibrosis, inflammation, oxidative stress, and malignant transformation. It is not a cure, nor a standalone solution, but it does represent a biologically plausible and clinically feasible component of a broader management plan. Future longitudinal and interventional studies are warranted to validate these findings and optimize treatment protocols.

CONCLUSION

There was a significant association between reduced Vitamin D levels and OSMF, reinforcing its role in fibrosis, inflammation, and oxidative stress. The study also showed a decrease in salivary Vitamin D levels of OSMF patients, highlighting the potential of Vitamin D supplementation as an adjunctive strategy to mitigate disease progression and reduce the risk of malignant transformation.

DECLARATIONS

Conflict of interest: No conflict of interest is declared by all the authors.

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Data availability: All data and materials of the study are available and can be provided on request. The corresponding author can be contacted anytime to get the data of the study.

Ethics approval and consent to participate: Ethical Committee Clearance Number: (IHEC/SDC/UG-2294/24/PHARM/095). "The study was approved by the institutional human ethical committee board of Saveetha Dental College and Hospitals. (IHEC/SDC/UG-2294/24/PHARM/095). The protocol of the study was approved by the Scientific Review Board (IHEC/SDC/UG-2294/24/PHARM/095) and it conforms to the provisions of the declaration of Helsinki. Informed consent was obtained from all the patients and their legal guardians by informing and clearly explaining the details of the study. All the methods in the study were performed in accordance with the relevant regulations and guidelines.

Consent to participate: Informed consent was obtained from all the patients and their legal guardians by informing and clearly explaining the details of the study.

Consent for publication: Informed consent was obtained from all the patients and their legal guardians by informing and clearly explaining the details of the study.

Author contributions: KK and SS wrote the manuscript. PR and GJ reviewed the manuscript.

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