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Research Article

Correlation of Serum Vitamin D Levels with Severity of Oral Submucous Fibrosis; A Cross-Sectional Study Evaluating Clinical Staging and Grading

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ABSTRACT

Introduction: Oral Submucous Fibrosis (OSMF) is a progressive chronic and possibly malignant disorder that is on the rise among the South Asian populations. Vitamin D, which has been said to have immunomodulatory and anti-fibrotic effects, could be involved in the pathogenesis and progression of OSMF. This paper set out to assess the relationship between Vitamin D concentration in the serum and the severity of OSMF.

Methodology: The analytical study was cross-sectional with 90 patients diagnosed with OSMF. Clinical staging was founded on mouth opening with histopathological grading being based on biopsy. Serum ELISA was used to measure the levels of vitamin D. The analysis of data was done with SPSS version 25. Descriptive statistics, independent t-test, ANOVA and post hoc Tukey test, Chi-square, MannWhitney U test, Multivariate linear regression, correlation analysis and multivariate linear regression were used. A p-value ≤ 0.05 was considered statistically significant

Results: The average serum Vitamin D was 18.6 ± 6.4 ng/mL, and most of the patients were deficient. A major reduction in Vitamin D level was found with advancing clinical stages and histopathological grades ($p < 0.001$). ANOVA and post hoc were used to verify that there was significant intergroup. differences. Chi-square test demonstrated that Vitamin D status was significantly correlated with an occurrence of disease. severity ($p = 0.001$). There was a significant negative correlation between Vitamin D levels and both. clinical staging ($r = -0.61$) and histological grading ($r = -0.58$). The multivariate analysis revealed Vitamin D as. a disease severity predictor.

Conclusion: Deficiency of Vitamin D in serum is considerably related to the severity of OSMF and can be taken as a service. a helpful biomarker of disease development.

Keywords: Oral Submucous Fibrosis, Vitamin D, Clinical Staging, Histopathological Grading, Fibrosis, Biomarker, Areca Nut

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a progressive, chronic and possibly malignant disease of the oral. area of the mucosa of the mouth complicated with fibrosis, which causes stiffness, limitation of the mouth opening and a persistent burning sensation [1]. It is quite common among the South Asian populations especially in Pakistan. and India, because of the universal use of areca nut, betel quid, and gutka [2]. The OSMF pathogenesis. is the chronic irritation of the oral mucosa, which leads to an increase in the production of collagen, a decrease in. collagen loss, and over growth of fibrous tissue in the subepithelial layers. These pathological alterations ultimately result in epithelial atrophy and greatly raise the chances of malignant. mutation to oral squamous cell carcinoma [3].

Vitamin D is a fat soluble vitamin, which is crucial in calcium homeostasis and bone assembly. Besides its classical actions, Vitamin D

is a valuable immunomodulatory, anti-inflammatory and anti-fibrotic agent [4]. It controls cellular growth and differentiation by interacting with Vitamin D receptors (VDR) found in several tissues, such as oral mucosa. There is some emerging evidence of a role of Vitamin D deficiency in the pathogenesis of chronic inflammatory and fibrotic diseases [5].

The deficiency of vitamin D is quite common among South Asian populations since there are several factors which contribute to the deficiency including exposure to sun, insufficient food intake, skin pigmentation, and some socio-cultural practices [6]. This lack can possibly contribute to the change in immune responses and the predisposition to chronic illnesses, such as oral potentially malignant conditions such as OSMF. Moreover, Vitamin D was demonstrated to prevent the synthesis of collagen and stimulate its degradation, which are directly applicable to the pathophysiology of OSMF [7].

The severity and progression of OSMF is usually measured using clinical staging and histopathological grades. Clinical staging is mainly founded on functional parameters like mouth opening and histological grading assesses epithelial alterations and degree of fibrosis [8]. Nevertheless, such approaches might not be able to fully address the biochemical and molecular factors of disease development. Hence, the necessity to find the credible biomarkers able to correlate with the severity of the disease and offer some prognostic information is increasing [9].

Research Gap

Although the role of Vitamin D in chronic inflammatory and fibrotic diseases has become a topic of growing interest, little and contradictory evidence exists as to its particular association with Oral Submucous Fibrosis. The bulk of the existing literature has been concerned with the incidence of Vitamin D deficiency or its overall association with oral diseases, but has not determined a clear relationship with the severity of OSMF. Also, there are very few studies that measured the correlation between the levels of serum Vitamin D and clinical staging and histopathological grading of OSMF concurrently. The absence of such a complete data demonstrates the important gap in the knowledge on whether Vitamin D can serve as a disease progression biomarker in OSMF.

Objective of study

This research paper aims to determine the relationship between serum Vitamin D levels and severity of Oral Submucous Fibrosis by determining clinical staging and histopathological grading. It is proposed that lower levels of Vitamin D correlate with higher severity of diseases and that it can be used as a prognostic marker in patients with OSMF.

METHODOLOGY

Study Design and Setting

This cross-sectional analytical research was done in the Department of Pathology in a Tertiary Care dental hospital. The experiment was conducted within a six month time span. All the subjects were provided with informed consent that was in written form, prior to being included in the study.

Study Population

The sample used was the group of patients who were clinically diagnosed with Oral Submucous Fibrosis (OSMF), and who attended the outpatient department over the course of the study. The inclusion criteria were patients of either sex, aged 18-60 years. Only individuals with a confirmed clinical diagnosis of OSMF and who were willing to have blood investigations and biopsy were recruited. The study excluded patients with systemic diseases that impact Vitamin D metabolism, Vitamin D supplements, pregnant or lactating women, and those with other oral potentially malignant disorders or malignancies.

Sample Size Calculation

The sample size was calculated using the formula for correlation studies:

n=(Zα+Zβ)2(1−r2)r2n = \frac{(Z_{\alpha} + Z_{\beta})^2 (1 - r^2)}{r^2}n=r2(Zα+Zβ)2(1−r2)

Where *n* represents the sample size, *Zα* is the standard normal deviate at a 95% confidence interval (1.96), *Zβ* corresponds to 80% power (0.84), and *r* is the expected correlation coefficient. Based on previous literature, a moderate correlation coefficient (r = 0.30) between serum Vitamin D levels and severity of OSMF was assumed.

Substituting the values:

n=(1.96+0.84)2(1−0.09)0.09≈79n = \frac{(1.96 + 0.84)^2 (1 - 0.09)}{0.09} \approx 79n=0.09(1.96+0.84)2(1−0.09)≈79

The final sample size was adjusted to 90 participants after considering a potential non-response or drop-out rate of 10 percent in order to have sufficient statistical power.

Sampling Technique

A non-probability consecutive sampling method was used in which all the eligible patients that came during the study period were sampled until the desired sample size was obtained.

Data Collection Procedure

A structured proforma was used to collect data. Demographic information including age, gender, and other habit history including use of areca nut and tobacco were captured. The oral cavity was

examined clinically in detail under normal conditions.

Clinical staging of OSMF was conducted according to that of mouth opening according to interincisal distance using vernier caliper. The established criteria were used to classify the patients into various clinical stages. In the case of histopathological grading, an incisional biopsy was taken on the mucosa that was affected under aseptic conditions. The biopsy specimens were treated in formalin, processed and viewed under a microscope with a qualified oral pathologist to ascertain the grade of fibrosis and epithelial alterations.

Each participant had his/her venous blood collected under aseptic conditions. The serum was divided and the Vitamin D concentration was determined through enzyme-linked immunosorbent assay (ELISA). Standard reference values were used to classify vitamin D levels as deficient, insufficient or sufficient.

Study Variables

Serum Vitamin D level was the independent variable in the study and clinical staging and histopathological grading of OSMF were the dependent variables. Other variables including age, gender and length of habits were taken as potential confounders.

Statistical Analysis

Statistical Package of Social Sciences (SPSS) version 25.0 was used to enter and analyze the data. All variables were computed using descriptive statistics (mean and standard deviation in continuous variables and frequencies and percentages in categorical variables).

The test used to determine the normality of data distribution was the Shapiro-Wilk test. To compare the mean Vitamin D levels in various clinical stages and histopathological grades, one-way Analysis of Variance (ANOVA) was used when data are normally distributed and post hoc Tukey test was used to compare multiple data. Kruskal-Wallis test was employed in situations where data were not normally distributed.

The Chi-square test was used to analyze the association between categorical variables (Vitamin D status categories and OSMF stages). Pearson correlation coefficient was used to test the parametric data and Spearmann rank correlation was used to test the non-parametric data to determine the correlation between serum Vitamin D levels and the severity of OSMF (both clinical staging and histological grade).

The independent sample t-test or Mann-Whitney U test was used respectively as the appropriate tests to compare two groups. Linear regression was used to conduct multivariate analysis to adjust the possible confounders and to determine the independent effect of Vitamin D level on the severity of the disease.The p-value of 0.05 was taken to be statistically significant.

RESULTS

A total of 90 patients diagnosed with Oral Submucous Fibrosis (OSMF) were included in the study. The data were compared to determine the association of serum Vitamin D levels and the severity of OSMF in regards to clinical staging and histopathological grading.

Demographic Characteristics and Habit Profile

The participants had a mean age of 34.7 ± 9.2 years with most of the patients in the age group of 21-40 years. There was a male predominance, with 62 (68.9%) males and 28 (31.1%) females. The majority of the respondents indicated that they had used areca nuts or gutka with a mean of 6.8 years of consumption. Table 1 shows the demographic characteristics of the population and the habit profile of the study population.

Table 1: Demographic and Habit Characteristics (n = 90)

Variable	Category	Frequency (n)	Percentage (%)
Age Group	18–20	8	8.9
	21–40	54	60.0
	41–60	28	31.1
Gender	Male	62	68.9
	Female	28	31.1
Habit Type	Areca nut	38	42.2
	Gutka	32	35.6
	Betel quid	20	22.2
Duration of Habit	<5 years	30	33.3
	5–10 years	42	46.7
	>10 years	18	20.0

Distribution of Clinical Staging and Histopathological Grading

Mouth opening and functional limitation were used to classify patients into various clinical stages. Most of the patients were in Stage II (40.0%), then Stage III (33.3%). The distribution of clinical staging and histopathological grading is summarized in Table 2 which showed Grade II fibrosis (37.8) as the most prevalent.

Table 2: Distribution of Clinical Stages and Histopathological Grades

Parameter	Category	Frequency (n)	Percentage (%)
Clinical Stage	Stage I	16	17.8
	Stage II	36	40.0
	Stage III	30	33.3
	Stage IV	8	8.9
Histological Grade	Grade I	14	15.6
	Grade II	34	37.8
	Grade III	28	31.1
	Grade IV	14	15.6

Serum Vitamin D Levels (Descriptive Statistics)

The average serum Vitamin D level of the study population was 18.6 + 6.4 ng/mL, which reflects a general deficient state. A significant percentage of patients (63.3) was Vitamin D deficient. Table 3 shows the descriptive statistics and categorical distribution of Vitamin D levels.

Table 3: Serum Vitamin D Levels (Descriptive and Categorical Distribution)

Variable	Value
Mean ± SD (ng/mL)	18.6 ± 6.4
Minimum	8.2
Maximum	34.5

Comparison of Vitamin D Levels Across Clinical Stages (ANOVA Test)

The average Vitamin D levels were found to decrease as clinical stages were more severe. Stage I patients recorded the highest mean Vitamin D level (25.4 ± 4.8 ng/mL) with Stage IV patients recording the lowest levels (11.2 ± 3.6 ng/mL).

ANOVA test showed that there was a statistically significant difference in Vitamin D levels among the clinical stages ($F = 18.72$, $p < 0.001$). Post hoc Tukey test showed significant differences between Stage I vs III, Stage I vs IV and Stage II vs IV. The detailed comparison is in Table 4.

Table 4: Comparison of Mean Vitamin D Levels Across Clinical Stages (ANOVA)

Clinical Stage	Mean ± SD (ng/mL)
Stage I	25.4 ± 4.8
Stage II	20.3 ± 5.2
Stage III	15.6 ± 4.7
Stage IV	11.2 ± 3.6
Test	**Value**
ANOVA (F-value)	18.72
p-value	<0.001
Post Hoc (Tukey)	Significant (I vs III, I vs IV, II vs IV)

Association Between Vitamin D Status and Clinical Stage (Chi-square Test)

There was a strong correlation between Vitamin D status groups and clinical stages of OSMF. The majority of Stage III and IV patients were Vitamin D deficient.

The **Chi-square test** showed a statistically significant association ($\chi^2 = 22.45$, $p = 0.001$). Table 5 presents the cross-tabulation.

Table 5: Association Between Vitamin D Status and Clinical Stage (Chi-square Test)

Clinical Stage	Deficient	Insufficient	Sufficient
Stage I	6	6	4
Stage II	20	12	4
Stage III	23	6	1
Stage IV	8	0	0

Test	Value
Chi-square (χ^2)	22.45
p-value	0.001

Correlation Between Vitamin D Levels and Disease Severity

A strong negative correlation was observed between serum Vitamin D levels and severity of OSMF.

Pearson's correlation analysis showed a significant inverse correlation between Vitamin D levels and clinical staging (**r = -0.61, p < 0.001**) as well as histopathological grading (**r = -0.58, p < 0.001**).

It means that the disease severity was correlated with the lower level of Vitamin D.

Comparison of Vitamin D Levels Across Histopathological Grades (ANOVA Test)

There was a significant decrease in the mean Vitamin D levels with increasing histological grades. ANOVA showed that there was a statistically significant difference (F = 16.35, p < 0.00

Table 6: Comparison of Mean Vitamin D Levels Across Histopathological Grades

Histological Grade	Mean ± SD (ng/mL)
Grade I	24.8 ± 5.1
Grade II	19.7 ± 4.6
Grade III	14.9 ± 4.2
Grade IV	10.8 ± 3.5
Test	**Value**
ANOVA (F-value)	16.35
p-value	<0.001

Multivariate Analysis (Linear Regression)

Multivariate linear regression analysis was conducted to examine the independent effect of Vitamin D levels on severity of the disease controlling the age, gender and duration of the habit. Serum Vitamin D level continued to be a major independent predictor of the severity of OSMF (= -0.52, p < 0.001).

Summary of Findings

Overall, the results demonstrated that lower serum Vitamin D levels were significantly associated with increased severity of OSMF, both clinically and histopathologically. The results also showed consistency in the various statistical tests such as ANOVA, Chi-square, correlation, and regression analysis, and thus made the findings more valid.

DISCUSSION

The current paper showed that there is a strong negative correlation between the levels of serum Vitamin D and the severity of Oral Submucous Fibrosis (OSMF). The Vitamin D levels in patients at the advanced clinical stages and patients with higher histopathological grades were significantly less than those in patients at earlier stages [10,11]. The results were congruently obtained in various statistical tests such as ANOVA, Chi-square, Mann-Whitney U test and correlation test indicating a strong relationship between Vitamin D deficiency and disease progression [12,13].

Vitamin D depletion with the progression of clinical severity indicates that it may be involved in the pathogenesis of OSMF [14,15]. This can be attributed to the anti-inflammatory and anti-fibrotic effects of Vitamin D that controls the growth of fibroblasts and collagen breakdown. Lower Vitamin D concentrations can cause excessive collagen deposition and decreased degradation, which in turn causes fibrosis and limitation of mouth opening seen in severe cases of OSMF [16,17]. Also, the fact that Vitamin D levels have a significant negative correlation with the clinical staging and histological grading is further evidence of its role in the severity of the disease [18,19].

The difference in the levels of Vitamin D between males and females with males having lower levels can be explained by increased exposure to risk behaviors like using areca nuts and gutka. On the same note, the length of period

of harmful habits was observed to correlate with more severity of the disease which is in line with the already known etiological determinants of OSMF [20,21].

In comparison to the literature, the results of the present study correspond to that of the previously conducted studies which reported a high level of the Vitamin D deficiency in patients with OSMF [22,23]. Similar trends of decreasing Vitamin D levels with increasing severity of oral potentially malignant disorders have also been reported. The observed significant association between Vitamin D deficiency and advanced stages of fibrosis is consistent with studies highlighting the role of Vitamin D in modulating fibrotic pathways and immune responses. However, some studies have reported weaker or non-significant correlations, which may be due to differences in sample size, study design, population characteristics, and methods of Vitamin D assessment. Unlike many previous studies, the present study provides a more comprehensive evaluation by correlating Vitamin D levels with both clinical staging and histopathological grading, thereby strengthening the evidence for its role as a potential biomarker [24,25].

Limitations

This study had certain limitations that should be considered while interpreting the results. The cross-sectional design limits the ability to establish a causal relationship between Vitamin D deficiency and the progression of OSMF. The study was conducted in a single center with a relatively limited sample size, which may affect the generalizability of the findings. Also, other determinants of Vitamin D. Other factors like nutritional intake, sun rays, and seasonal change were not examined. The singletime measure of Vitamin D use might not be a long-term measure.

Future Suggestions

The longitudinal designs should be used in future research to develop causal relationship between lack of Vitamin D and the development of OSMF. It is advisable that larger multi-centre studies that include more varied populations to maximize the generalizability of findings. The impact of Vitamin D supplementation on the disease progression and symptom improvement in OSMF patients is also recommended to be evaluated. Moreover, the incorporation of other biochemical and molecular indicators can give more information on the pathophysiology of the disease, as well as assist in creating specific treatment approaches.

CONCLUSION

The current article showed a significant negative relationship between serum Vitamin D and the extent of Oral Submucous Fibrosis. Reduced Vitamin D levels were always related to advanced clinical stages and elevated histopathological grades which shows that it can be used as a biomarker to indicate the severity and progression of the disease.

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