Research Article

Comparative Evaluation of Salivary IL-1β and IL-6 As Non-Invasive Biomarkers for Detection of Oral Potentially Malignant Disorders

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Abstract

Introduction: Oral Potentially Malignant Disorders (OPMDs) are heterogeneous oral mucosal lesions with an increased risk of transformation into oral cancers. Chronic inflammation is a critical contributor to oral carcinogenesis, with pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) playing key roles in epithelial dysplasia and tumor progression. The present study aimed to assess and compare salivary IL-1β and IL-6 levels among healthy individuals, tobacco users without oral lesions, and patients diagnosed with OPMDs.

Materials and Methods: A total of 189 participants were equally divided into three groups (n=63 each). Unstimulated whole saliva (2 mL) was collected using the passive drool method. Cytokine levels were quantified using enzyme-linked immunosorbent assay kits. Statistical analysis was performed with significance set at $p < 0.05$.

Results: Majority of tobacco users and OPMD patients were males, using smokeless form of tobacco. Salivary IL-6 levels were significantly elevated in OPMD patients compared with healthy controls ($p < 0.05$). IL-1β levels also showed a marked increase in the OPMD patients. Tobacco users without oral lesions demonstrated intermediate IL-1β and IL-6 levels.

Conclusion:

Salivary IL-1β and IL-6 may serve as reliable non-invasive biomarkers for early detection and risk assessment of OPMDs.

Key words: Oral Potentially Malignant Disorders, Salivary Biomarkers, Interleukin-1 beta, Interleukin-6, Pro-inflammatory Cytokines, ELISA.

Introduction

World Health Organization (WHO) initially defined precancerous lesions in 1978 as morphologically altered tissues with a greater likelihood of malignant transformation than normal mucosa. Later in 2005, the WHO introduced the term Oral Potentially Malignant Disorders (OPMDs) to encompass any oral mucosal abnormality with an increased risk of progression to oral cancers.[1,2] Clinically, OPMDs manifest as white lesions, red lesions, or mixed erythematous and keratotic presentations, frequently involving the buccal mucosa, tongue, gingiva, alveolar mucosa, vestibule, and palate. The most prevalent entities include Leukoplakia, Oral Submucous Fibrosis, Erythroplakia, and Oral Lichen Planus.[3]

Globally, OPMDs affect approximately 1–5% of the population, with higher prevalence reported in South and East Asia, demonstrating male predominance and an annual malignant transformation rate exceeding 2%.[4] The established etiological factors for occurrence of OPMDs include tobacco (smoked and smokeless forms), alcohol consumption, areca nut use, chronic mucosal irritation, and nutritional deficiencies. The definitive diagnosis of OPMDs relies on histopathological evaluation, adjunctive diagnostic modalities such as auto fluorescence and vital staining are frequently employed to enhance clinical examination and detection.[5]

Increasing evidence implicates chronic inflammation in oral carcinogenesis, with pro-inflammatory cytokines playing a central role in epithelial dysplasia and tumor progression. Saliva, as a non-invasive and easily accessible bio fluid, has emerged as a promising medium for biomarker analysis.[6] With this background, the present study aimed to comparatively evaluate salivary interleukin-1β (IL-1β) and interleukin-6 (IL-6) levels among healthy individuals, tobacco users without oral lesions, and patients with OPMDs for early detection and risk assessment of OPMDs.

Materials And Methods

Study Design and Ethical Approval: This cross-sectional analytical study was conducted in the Department of Periodontology at Krishna Vishwa Vidyapeeth, Karad, following approval from the Institutional Ethics Committee (Protocol No.: KIMSDU/IEC/06/2023; dated 05/06/2023). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Study Population and Sample Size: A total of 189 participants aged 18–70 years were recruited and equally allocated into three groups (n = 63 each) as Group A: Systemically healthy individuals without tobacco use, Group B: Tobacco users without clinically evident oral lesions, and Group C: Patients clinically diagnosed with Oral Potentially Malignant Disorders. Sample size estimation was performed using Jamovi statistical software with $\alpha = 0.05$, power $(1–\beta) = 80\%$, two-sided testing, and an anticipated effect size (Cohen's d) ≥ 0.5, yielding a minimum of 63 participants per group.

Inclusion and Exclusion Criteria: Participants willing to provide written informed consent were included. Individuals with systemic inflammatory or autoimmune disorders, acute or chronic infections, history of long-term anti-inflammatory, immunosuppressive, or corticosteroid therapy, as well as pregnant or lactating women, were excluded to minimize confounding inflammatory influences.

Clinical Examination and Diagnosis: Demographic characteristics, socioeconomic status, medical history, and tobacco-use patterns were recorded using a structured proforma. Comprehensive oral examination was performed using a mouth mirror and periodontal probe under adequate illumination. Diagnosis of OPMDs was established according to World Health Organization criteria by an experienced oral medicine specialist and confirmed by histopathological evaluation.[7]

Saliva Collection and Biomarker Analysis: Unstimulated whole saliva (2 mL) was collected between 10:00 am and 12:00 pm using the passive drool technique under standardized conditions to reduce diurnal variation. Samples were centrifuged at 1,000 rpm for 15 minutes at 2–8°C, and the supernatant was aliquoted into sterile micro centrifuge tubes and stored at −80°C until analysis. Salivary interleukin-1β (IL-1β) and interleukin-6 (IL-6) levels were quantified using commercially available human ELISA kits (ELK Biotechnology Co., Ltd., Wuhan, China) according to manufacturer instructions. Optical density was measured using an ELISA microplate reader (LisaQuant TS, Tulip Diagnostics Pvt. Ltd., Goa, India), and concentrations were calculated from standard calibration curves.

Statistical Analysis: Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were computed for demographic variables and biomarker levels, expressed as mean ± standard deviation. Intergroup comparisons were performed using appropriate parametric or non-parametric tests based on normality assessment. A p-value < 0.05 was considered statistically significant.

Results

A total of 189 participants were recruited and equally distributed into three groups (n = 63 each). The age distribution of the subjects, revealed that the majority of participants in Group A and Group C were 31–40 years age bracket, whereas Group B predominantly comprised individuals aged 41–50 years. However, the overall age distribution across the groups did not demonstrate a statistically significant difference ($p > 0.05$) (Table 1).

The gender distribution of the participants demonstrated a higher proportion of males in all three groups, with males representing 62% and females 38% of the total study population. No statistically significant difference in gender distribution was observed among the groups ($p > 0.05$) (Table 2).

Distribution of participants based on tobacco use status revealed that 66 participants (35%) were non-users of tobacco in any form. Among tobacco users, the predominant pattern was smokeless tobacco consumption, observed in 75 participants (40%). Smoked tobacco use was reported by 26 participants (14%), while 22 participants (12%) practiced both smoked and Smokeless forms (combined use) (Table 3).

Comparison of salivary biomarker levels among Groups A, B, and C demonstrated an overall increasing trend from Group A to Group C. The mean salivary IL-1β levels demonstrated a progressive increase from Group A (25.11 ± 59.5 pg/mL) to Group C (41.02 ± 83.4 pg/mL), indicating a rising trend across the study groups. Similarly, mean salivary IL-6 levels demonstrated a marked increase across the groups, with the lowest concentrations recorded in Group A (3.36 ± 1.35 pg/mL) and the highest in Group C (13.59 ± 9.11 pg/mL), indicating a clear upward trend. Intergroup comparison using the Mann–Whitney U test revealed no statistically significant difference in IL-1β levels between Group A and Group B ($p > 0.05$). However, IL-6 levels were significantly higher in Group B compared

to Group A ($p < 0.05$). Similarly, comparison between Group A and Group C demonstrated no significant difference in IL-1β levels ($p > 0.05$), whereas IL-6 levels were significantly elevated in Group C relative to Group A ($p < 0.05$). In contrast, comparison between Group B and Group C showed no statistically significant difference in either IL-1β or IL-6 levels ($p > 0.05$) (Table 4).

Discussion

In the Indian population, tobacco consumption occurs in both smoked and smokeless forms, reflecting diverse cultural and regional practices. The smoked forms predominantly include beedi, cigarettes, and chutta, which are widely used across various socioeconomic strata. In contrast, smokeless tobacco products such as gutka, misri, khaini, and paan containing areca nut and lime are extensively consumed and often perceived as less harmful, despite their well-established association with OPMD and oral cancer. [8,9]

In the present study, the majority of participants with a history of tobacco use belonged to the 41–50 years, followed by those aged between 31–40 years. Among patients diagnosed with OPMDS, the highest prevalence was observed in the 31–40 years age group, followed by the 41–50 years cohort. These findings are consistent with previous reports. Singh AK et al.,[10] who documented that OPMDs commonly affected age group was 31–40 years, while Pandya D et al.,[11] reported a higher prevalence within the 31–50 years age range. The similarity of our findings with these studies reinforces the observation that OPMDs are increasingly prevalent in younger and middle-aged adults, possibly reflecting early initiation and sustained use of tobacco products. The findings of the present study differ from those reported by Balsaraf S et al.,[12] who observed that the most commonly affected age group was 21–30 years, accounting for 37.5% of cases. The age changes of occurrence of OPMDs from previous literature, may reflect regional variations in patterns of tobacco initiation, duration of exposure, and sociocultural influences affecting younger populations. Anwar S et al.,[13] reported a higher mean age of affected individuals, with an overall mean age of 47.6 ± 14.1 years (47.3 ± 14.1 years for males and 49.1 ± 14.4 years for females), suggesting a predominance in middle-aged individuals. Kumar et al., documented a mean age of 42.64 years among patients with OPMD, which closely approximates the age distribution observed in our study.[14] The age variations across studies highlight the heterogeneous age distribution of OPMDs, likely influenced by differences in demographic characteristics, tobacco use patterns, and geographic factors.

A clear male predominance was observed in our study, with 62% of males and 38% of females. This gender disparity may be attributed to the higher prevalence and frequency of tobacco consumption among males compared to females. The findings of our study are consistent with literature by Singh S et al.,[15] and Balsaraf S et al.,[12], both of whom also documented a higher proportion of male participants among individuals with tobacco use and OPMDs.

Tobacco remains one of the most significant etiological factors in the pathogenesis of OPMDs, owing to its chronic local irritative effects and exposure to carcinogenic nitrosamines. In the present study, smokeless tobacco use was the predominant risk habit, accounting to 40% of the participants, and smoked form constituted of 14% of subjects. These findings are in agreement with previous studies by Shaikh et al.,[16] Mehrotra et al.,[17] Pandya D et al.,[11] and Jacob LB et al.,[18] all of whom reported a strong association between tobacco chewing habits and the occurrence of OPMDs. The agreement of these results highlights the pivotal role of smokeless tobacco in the burden of OPMDs, particularly in the Indian subcontinent.

Human saliva has emerged as a valuable diagnostic bio fluid for the detection and monitoring of various systemic and oral diseases. Saliva reflects both physiological and pathological states through the presence of diverse molecular constituents, including enzymes, hormones, antibodies, and inflammatory mediators. Salivary biomarkers have gained significant attention in the diagnosis and prognostic assessment of OPMDs and oral cancer. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α have been extensively investigated in salivary samples due to their critical role in tumor-associated inflammation, epithelial dysplasia, and malignant transformation. Interleukin-1β (IL-1β) is a well-recognized pro-inflammatory cytokine that plays a pivotal role in tumor-associated inflammation. It contributes to carcinogenesis by promoting proliferation of genetically altered cells, inducing additional DNA damage through sustained inflammatory signalling, and facilitating tumor progression via enhancement of angiogenesis, invasion, and metastatic potential within the tumor microenvironment. The results of our study show that, salivary IL-1β levels were highest in OPMD patients compared to tobacco users and healthy subjects, indicating a progressive increase in inflammatory activity with disease severity. This observation supports the concept that IL-1β is actively involved in the pathobiology of

OPMDs and their progression. Our findings are consistent with those reported by Piyarathne NS et al.,[19] and Hama PN et al.,[20] who demonstrated elevated IL-1β levels in patients with OPMDs and oral cancer compared to healthy controls. Thamarai ST et al., evaluated serum and salivary IL-1β levels in patients with oral submucous fibrosis and oral leucoplakia, compared with age and gender matched healthy individuals, and reported significantly higher salivary IL-1β concentrations in the diseased groups.[21] Collectively, these studies reinforce the potential utility of salivary IL-1β as a non-invasive biomarker reflecting underlying inflammatory and potentially malignant changes in the oral mucosa.

The mean salivary IL-6 levels in the present study were lowest among healthy subjects and progressively higher in tobacco users and patients with OPMDs. This gradient suggests an incremental increase in inflammatory activity associated with tobacco exposure and the development of potentially malignant oral lesions. Our findings are consistent with the systematic review by Chiamulera et al. (2004–2018), which analysed 28 studies, of which 14 specifically evaluated IL-6. The review concluded that IL-6 levels were significantly elevated in oral cancer patients compared to OPMD patients and healthy controls.[22] Studies by Rani NAJ et al.,[23] Selvam et al.,[24] Dineshkumar et al.,[25] Harshy et al.,[26] and Payambrot R et al.,[27] also reported significantly increased IL-6 levels in OPMD patients compared to control groups. The concordance of these findings reinforces the hypothesis that IL-6 plays a critical role in chronic inflammation, epithelial dysregulation, and tumor-promoting pathways in oral mucosal pathology. The elevated IL-6 levels observed in our study substantiate its potential utility as a non-invasive salivary biomarker for early detection and risk stratification in OPMDs.

Limitations

The cross-sectional design of the present study restricts the ability to establish a causal association between elevated salivary IL-1β and IL-6 levels and the progression of OPMDs. Relatively limited sample size and single-centre setting may constrain the external validity and generalizability of the findings. Future large-scale, multicentre longitudinal studies with extended follow-up are recommended to validate and strengthen the predictive utility of these salivary inflammatory markers.

Conclusion

Smokeless tobacco use was the predominant habit among participants, and a higher prevalence of OPMDs was observed among males. A progressive elevation in salivary IL-1β and IL-6 levels was noted from healthy individuals to tobacco users and further to patients with OPMDs, indicating an incremental inflammatory response associated with tobacco exposure and mucosal pathology. These findings support the potential utility of salivary IL-1β and IL-6 as non-invasive, cost-effective biomarkers for early detection and risk assessment. Saliva-based diagnostics may serve as a practical adjunctive tool in screening high-risk populations, particularly in regions with a high burden of smokeless tobacco use. However, further longitudinal studies are required to establish their prognostic value in predicting malignant transformation.

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TABLES

Table 1: Age distribution of the participants.

Group	20-30 years n (%)	31-40 years n (%)	41-50 years n (%)	51-60 years n (%)	60 years and above n (%)	Total n (%)
Healthy	10 (15.87)	27 (42.86)	15 (23.81)	07 (11.11)	04 (6.35)	63 (100)
Tobacco users	11 (17.46)	13 (20.63)	21 (33.33)	18 (28.57)	00 (0)	63 (100)
OPMD patients	03 (4.76)	22 (34.92)	18 (28.57)	12 (19.05)	08 (12.70)	63 (100)
All	24 (12.70)	62 (32.80)	54 (28.57)	37 (19.58)	12 (6.35)	189 (100)

Table 2: Gender distribution of the participants.

Group	Number of subjects	Male n (%)	Female n (%)
Healthy	63	36 (57.14)	27 (42.86)
Tobacco users	63	43 (68.25)	20 (31.75)
OPMD patients	63	38 (60.32)	25 (39.68)
All	189	117 (61.90)	72 (38.10)

Table 3: Distribution of participants according to tobacco use status.

Group	No Tobacco (NT) n (%)	Smokeless tobacco use (SL) n (%)	Smoked tobacco use (SD) n (%)	Both smoked and smokeless tobacco use (SB) n (%)	Total n (%)
Healthy	63 (100)	0 (0)	0 (0)	0 (0)	63 (100)
Tobacco users	0 (0)	33 (52.38)	17 (26.98)	13 (20.63)	63 (100)
OPMD patients	03 (4.76)	42 (66.67)	09 (14.29)	09 (14.29)	63 (100)
All	66 (34.92)	75 (39.68)	26 (13.76)	22 (11.64)	189 (100)

Table 4: Mean salivary biomarker levels (pg/mL) among the groups.

Group/ Biomarker	Healthy (pg/mL)	Tobacco users (pg/mL)	OPMD patients (pg/mL)	Oral cancer patients (pg/mL)
IL-1β	25.11±59.5	37.10±59.7	41.02±83.4	69.26±88.4
IL-6	3.36±1.35	9.24±11.3	13.59±9.11	54.71±65.9