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EXPRESSION OF SALIVARY LEVELS OF S100A7 AND ITS DIAGNOSTIC POTENTIAL IN ORAL SUBMUCOUS FIBROSIS AND ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) and oral submucous fibrosis (OSMF) are epithelial disorders with malignant transformation potential, and the recognition of non- invasive salivary biomarkers may enhance the early detection and risk assessment.

Aim and Objective: To evaluate and compare salivary S100A7 levels in OSMF and OSCC with those of healthy controls in order to assess diagnostic value.

Setting and Design: Cross-sectional analytical study was conducted in a tertiary dental institution.

Materials and Methods: 135 participants were included in the study and were divided into three groups: healthy controls, OSMF, and OSCC, with 45 subjects in each group. Clinical diagnoses were confirmed histopathologically. Unstimulated whole saliva was collected under standardised conditions and centrifuged prior to analysis. Salivary S100A7 concentration was measured using enzyme-linked immunosorbent assay in duplicate.

Statistical Analysis Used: Data were analysed using Chi-square test, one-way analysis of variance with Tukey HSD post hoc testing, independent samples t-test, and Karl Pearson correlation. A p value less than 0.05 was considered statistically significant.

Results and Conclusion: Gender distribution differed significantly among groups ($p = 0.001$), and mean age showed significant variation ($p < 0.001$). Mean salivary S100A7 levels differed significantly among groups ($p < 0.001$), with the highest mean observed in oral submucous fibrosis (39.91 ± 10.66), followed by oral squamous cell carcinoma (29.78 ± 14.12) and controls (21.70 ± 6.79). Pairwise comparisons confirmed significant differences between all groups. A moderate negative correlation between age and S100A7 was observed ($r = -0.318$, $p < 0.001$). Lesion site and habit pattern were not significantly associated with S100A7 levels. Salivary S100A7 estimation may assist in differentiation of potentially malignant and malignant oral conditions.

KEYWORDS: Carcinogenesis, Enzyme-Linked Immunosorbent Assay, Liquid Biopsy, Malignant Transformation, Oral Potentially Malignant Disorders, Salivary Biomarkers, S100A7 Protein.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common malignant tumors of the oral cavity and forms a major proportion of head and neck cancers worldwide. The incidence is high in South-East Asia, where tobacco use, areca nut chewing, and alcohol consumption are common risk exposures.[1] The 5-year survival rate has improved in the recent years because many patients report at an advanced stage, thus necessitating the recognition at an early stage.[2] Oral potentially malignant disorders (OPMDs), particularly oral submucous fibrosis (OSMF), are recognized precursors of OSCC and demonstrate defined rates of malignant transformation.[3] The prevalence of OSMF is high in populations with habitual areca nut consumption.[4]

Histopathological biopsy is the standard for confirmation of epithelial dysplasia and carcinoma. The procedure is invasive and may be influenced by sampling variation. The development of non-invasive approaches has therefore focused on liquid biopsy strategies that use oral fluids.[5] Saliva contains proteins, nucleic acids, cytokines, and other molecular constituents that represent biological activity within the oral cavity.[6,7] Numerous salivary biomarkers have been investigated in oral cancer and potentially malignant disorders; however, only a limited number demonstrate sufficient diagnostic performance for clinical use.[2]

S100 calcium-binding protein family regulates epithelial cell proliferation, differentiation, and inflammatory signaling.[8] The S100A7 protein, also termed psoriasin, shows increased expression in oral epithelial dysplasia and OSCC.[9,10]

Increased S100A7 expression has been identified as a predictor of malignant transformation and poor clinical outcome in head and neck cancer.[11,12] Experimental studies show that S100A7 activates the p38/MAPK and RAB2A signaling pathways, promoting tumor progression and resistance to anoikis,[13,14] Clinical investigations have detected elevated salivary S100A7 levels in OSMF and leukoplakia, indicating its potential as a salivary biomarker.[3,4,15] The expression pattern varies with lesion severity and transformation risk.[16,17] Standardized protocols for salivary collection and validated diagnostic cut-off values for S100A7 have not been established.[18] Most available studies examine tissue expression, and direct comparison of salivary S100A7 levels
in OSMF and OSCC is limited, while its association with malignant transformation risk requires clearer definition.[19,20] The present study evaluated salivary S100A7 levels in patients with OSMF and OSCC and compared them with healthy controls to determine its diagnostic value as a non-invasive biomarker for early detection and risk assessment in oral epithelial disease.

METHODOLOGY

Study Design and Participants

135 subjects aged 18 years and above were included in a cross-sectional analytical study conducted in the Department of Oral Medicine, Diagnosis and Radiology, Meenakshi Ammal Dental College. Participants were allocated into three groups of 45 each: healthy controls without oral lesions, patients with clinically and histopathologically confirmed OSMF, and patients with newly diagnosed, untreated OSCC. Subjects with previous malignancy, immunodeficiency, autoimmune disease, hepatitis, or human immunodeficiency virus infection were excluded.

Clinical Assessment

Clinical examination was performed for each participant, and habit history was recorded. Histopathological evaluation confirmed the diagnosis in OSMF and OSCC groups. Periodontal status was assessed using the modified gingival index to reduce the influence of gingival inflammation on salivary S100A7 levels.

Saliva Collection and Processing

Participants were instructed not to eat, drink, smoke, or perform oral hygiene procedures for at least one hour before sample collection. Unstimulated whole saliva was collected by the drooling method in sterile containers, with approximately 5 mL obtained from each participant. Samples were centrifuged at 3500 rpm for 15 minutes at 4°C, and the supernatant was separated and stored until analysis.

Estimation of Salivary S100A7

Salivary S100A7 concentration was measured using a commercially available enzyme-linked immunosorbent assay kit. All samples were analyzed in duplicate. Optical density was measured using a spectrophotometer. Concentrations were calculated from a standard calibration curve derived from known standards.

Statistical Analysis

The data were analyzed using SPSS software. The Chi-square test assessed differences in gender distribution among groups. One-way analysis of variance evaluated differences in mean age and mean salivary S100A7 levels across groups, followed by Tukey HSD post hoc testing for pairwise comparisons. Independent samples t-test compared mean S100A7 levels between two groups and between genders. Karl Pearson correlation tested the association between age and S100A7 levels. A p value <0.05 was considered statistically significant.

RESULTS

Table 1A shows a statistically significant difference in gender distribution among groups (Chi- square test, $p = 0.001$), with male proportions of 91.1% in OSMF and 88.9% in OSCC. Table 1B shows a significant difference in mean age among groups (one-way ANOVA, $p < 0.001$). Mean age was 36.00 ± 0.00 years in OSMF and 52.38 ± 11.21 years in OSCC. Tukey HSD analysis in Table 1C confirmed a significant pairwise difference between OSMF and OSCC ($p < 0.001$).

Table 2A shows a statistically significant difference in mean salivary S100A7 levels among groups (one-way ANOVA, $p < 0.001$). Mean values were 39.91 ± 10.66 in OSMF and 29.78 ± 14.12 in OSCC. Table 2B demonstrates a significant pairwise difference between OSMF and OSCC (mean difference 10.13, $p < 0.001$). Table 2C confirms this finding, with the independent samples t-test showing significantly higher S100A7 levels in OSMF compared with OSCC ($p < 0.001$)

Table 3A presents the overall comparison of mean salivary S100A7 levels by gender. Males ($n = 109$) showed a significantly higher mean value (31.68 ± 13.59) than females ($n = 26$; 25.38 ± 10.00), with the independent samples t-test indicating statistical significance ($p = 0.028$). Table 3B presents the within-group comparisons. In controls, mean S100A7 levels were 22.36 ± 6.70 in males and 20.61 ± 7.00 in females ($p = 0.408$). In OSMF, males showed 40.02 ± 11.14 and females 38.82 ± 2.75 ($p = 0.834$). In OSCC, males showed 29.65 ± 14.61 and females 30.82 ± 10.45 ($p = 0.864$). No within-group difference was statistically significant

Table 4A summarizes mean salivary S100A7 levels according to lesion site in the overall lesion group ($n = 90$). The overall mean value was 34.85 ± 13.44, and one-way ANOVA showed no statistically significant difference among sites ($p = 0.258$). Table 4B presents the site-based
analysis within the OSCC group ($n = 45$), where the overall mean was 29.78 ± 14.12. No statistically significant difference was observed among lesion sites in OSCC ($p = 0.288$).

Table 5A summarizes mean salivary S100A7 levels according to habit pattern in the overall lesion group ($n = 90$). The overall mean was 34.85 ± 13.44, and one-way ANOVA showed no statistically significant difference among habit categories ($p = 0.152$). Table 5B presents the analysis within the OSMF group ($n = 45$), where the overall mean was 39.91 ± 10.65. No statistically significant difference was observed among habit patterns in OSMF ($p = 0.654$).

Table 6A presents the Karl Pearson correlation analysis between age and salivary S100A7 levels in the overall sample (n = 135), which showed a statistically significant moderate negative correlation ($r = -0.318$, $p < 0.001$). Table 6B shows the group-wise analysis. In the control group (n = 45), a negative correlation was observed that was not statistically significant ($r = -0.280$, $p = 0.063$). In the OSCC group (n = 45), a very weak negative correlation was noted ($r = -0.061$, $p = 0.690$). Correlation was not computed in OSMF because age was constant.

Table 1. Baseline Characteristics of Study Groups

A. Gender Distribution (Chi-Square Test)

Gender	Control n (%)	OSMF n (%)	OSCC n (%)	Total n (%)	p-value*
Male	28 (62.2)	41 (91.1)	40 (88.9)	109 (80.7)	0.001
Female	17 (37.8)	4 (8.9)	5 (11.1)	26 (19.3)	
Total	45 (100.0)	45 (100.0)	45 (100.0)	135 (100.0)	

B. Age Comparison (One-way ANOVA with Tukey HSD Post Hoc)

Group	N	Mean Age (years)	Std. Dev.	p-value†
Control	45	46.96	8.82	<0.001
OSMF	45	36.00	0.00	
OSCC	45	52.38	11.21	
Total	135	45.11	10.65	

C. Tukey HSD Post Hoc Pairwise Comparisons

Comparison	Mean Difference	p-value
Control vs OSMF	10.96	<0.001
Control vs OSCC	-5.42	0.006
OSMF vs OSCC	-16.38	<0.001

Table 2. Comparison of Mean Salivary S100A7 Levels Among Groups

A. One-way ANOVA

Group	N	Mean	Std. Dev.	p-value‡
Control	45	21.70	6.79	<0.001
OSMF	45	39.91	10.66	
OSCC	45	29.78	14.12	
Total	135	30.46	13.18	

B.Tukey HSD Post Hoc Pairwise Comparisons

Comparison	Mean Difference	p-value
Control vs OSMF	-18.21	<0.001
Control vs OSCC	-8.09	0.002
OSMF vs OSCC	10.13	<0.001

C.Independent Samples t-Test (OSMF vs OSCC)

Group	N	Mean	Std. Dev.	p-value§
OSMF	45	39.91	10.66	<0.001
OSCC	45	29.78	14.12	

Table 3. Comparison of Mean Salivary S100A7 Levels by Gender

A. Overall Comparison

Gender	N	Mean	Std. Dev.	p-value§
Male	109	31.68	13.59	0.028
Female	26	25.38	10.00	

B. Within-Group Comparison

Group	Gender	N	Mean	Std. Dev.	p-value§
Control	Male	28	22.36	6.70	0.408
	Female	17	20.61	7.00	
OSMF	Male	41	40.02	11.14	0.834
	Female	4	38.82	2.75	
OSCC	Male	40	29.65	14.61	0.864

	Female	5	30.82	10.45	

Table 4. Comparison of Mean Salivary S100A7 Levels by Lesion Site

A. Overall (n = 90)

Site	N	Mean	Std. Dev.	p-value‡
BM	76	35.24	12.43	0.258
AM – Maxilla	3	31.74	10.02	
AM – Mandible	1	14.63	.	
Tongue ventral surface	5	42.43	25.05	
Buccal vestibule – left	1	15.47	.	
Labial mucosa	1	46.34	.	
Retromolar region	1	30.59	.	
Tongue – lateral	2	21.63	12.66	
Total	90	34.85	13.44	

B. OSCC Group (n = 45)

Site	N	Mean	Std. Dev.	p-value‡
BM	31	28.47	11.82	0.288
AM – Maxilla	3	31.74	10.02	
AM – Mandible	1	14.63	.	
Tongue ventral surface	5	42.43	25.05	
Buccal vestibule – left	1	15.47	.	
Labial mucosa	1	46.34	.	
Retromolar region	1	30.59	.	
Tongue – lateral	2	21.63	12.66	
Total	45	29.78	14.12	

Table 5. Comparison of Mean Salivary S100A7 Levels by Habit Pattern

A. Overall (n = 90)

Habit	N	Mean	Std. Dev.	p-value‡
Chewing	66	33.09	14.15	0.152
Smoking	5	39.34	8.11	
Chewing & Smoking	9	36.44	13.57	
Chewing & Alcohol	10	42.75	6.40	
Total	90	34.85	13.44	

B. SMF Group (n = 45)

Habit	N	Mean	Std. Dev.	p-value‡
Chewing	21	40.18	11.61	0.654
Smoking	5	39.34	8.11	
Chewing & Smoking	9	36.44	13.57	
Chewing & Alcohol	10	42.75	6.40	
Total	45	39.91	10.65	

Table 6. Correlation Between Age and Salivary S100A7 Levels (Karl Pearson Correlation)

A. Overall

Variable	Correlation (r)	p-value	N
S100A7 value vs Age	-0.318	<0.001	135

B. Group-wise

Group	Correlation (r)	p-value	N
Control	-0.280	0.063	45
OSMF	.	.	45
OSCC	-0.061	0.690	45

DISCUSSION

The present study assessed salivary S100A7 expression in OSMF and OSCC and compared the values with healthy controls. A statistically significant elevation in salivary S100A7 was observed in both OSMF and OSCC groups when compared with controls (Table 2). The highest mean concentration was recorded in OSMF (39.91 ± 10.66), followed by OSCC (29.78 ± 14.12), whereas controls showed the lowest levels (21.70 ± 6.79). Intergroup differences were significant on one-way ANOVA with Tukey HSD pairwise testing. These findings indicate that salivary S100A7 corresponds with epithelial pathological alteration. Saliva contains proteins and molecular mediators which are derived from oral epithelial cells and the surrounding tissue environment. The changes in salivary protein composition have been documented in oral cancer and OPMDs.[2,6,7] The present results show that salivary S100A7 levels vary significantly between healthy individuals and patients with oral epithelial disease.

S100 calcium-binding protein family regulates epithelial proliferation, differentiation, and inflammatory activity.[8,21] The S100A7 protein, also known as psoriasin, has been examined in several epithelial malignancies. Increased tissue expression of S100A7 has been demonstrated in oral epithelial dysplasia and OSCC.[9-12] Kaur *et al*.[11] and Tripathi *et al*.[12] documented that increased S100A7 expression was associated with transformation risk and adverse prognosis in head and neck carcinoma. The salivary findings in the present study correspond with these tissue data, indicating that elevated intracellular expression is accompanied by increased salivary concentration. Elevated salivary S100A7 levels have been documented in OSMF and leukoplakia.[3,4,15] Proteomic profiling has identified S100A7 among proteins with altered expression in dysplastic lesions and OSCC.[22,23] The present study compared OSMF and OSCC within the same analytical design and demonstrated significant intergroup differences (Table 2C). The higher mean level in OSMF may relate to chronic inflammation and fibrosis, which can promote sustained epithelial stress and increased S100A7 secretion. The inflammatory profile of OSMF may explain the elevated salivary S100A7 levels observed in this study. S100 proteins regulate inflammatory signalling and immune responses within epithelial tissues.[8] Continuous exposure to areca nut components in OSMF leads to epithelial injury, oxidative stress, and cytokine activation, thus leading to a chronic inflammatory environment. These conditions can increase S100A7 expression and secretion. Raffat *et al.*[3,4] have reported elevated levels of salivary S100A7 in patients with OSMF thus indicating that the increase may occur before progression to OSCC. S100A7 protein also participates in signalling pathways associated with cellular proliferation and survival in OSCC.[13,14,17,21] Increased nuclear expression has been associated with adverse clinical outcomes in OSCC.[12] These molecular interactions provide a biological basis for elevated salivary S100A7 levels in OSMF and OSCC and their association with epithelial dysplasia and malignant transformation.

The present study evaluated demographic variables in relation to salivary S100A7 levels. A significant male predominance was observed in OSMF and OSCC groups (Table 1A). Higher oral cancer incidence in males has been attributed to greater exposure to tobacco, alcohol, and areca nut habits.[1] However, within-group comparison did not demonstrate statistically significant gender-based differences in S100A7 levels (Table 3B) therefore indicating that biomarker elevation is associated more closely with disease status than with sex. Age differed significantly among groups, with OSCC patients being older than OSMF and control participants (Table 1B). A moderate negative correlation was identified between age and salivary S100A7 levels in the overall sample (Table 6A). The higher mean concentration observed in the younger OSMF group may have influenced this association. Sood *et al*.[9] observed that that the expression of S100A7 in OSCC is present in different age groups, which indicated that its biological role is not confined to a particular age category.

The lesion site analysis did not demonstrate statistically significant variation in salivary S100A7 levels among different anatomical locations (Table 4). The buccal mucosa was the most frequent site of involvement; however, S100A7 concentrations did not differ significantly between sites. The whole saliva contains secretions from multiple regions of the oral mucosa, and measured protein levels therefore represent cumulative epithelial release rather than secretion confined to a single lesion. Veronese *et al*.[5] discussed that liquid biopsy using whole saliva represents a composite sample derived from multiple oral surfaces, which may reduce site-specific variability in biomarker concentration. Riccardi *et al*.[7] reported that salivary protein profiling in OSCC reflects integrated secretion from different mucosal regions rather than isolated lesion sites. The habit-based analysis did not demonstrate statistically significant
differences in salivary S100A7 levels among participants with chewing, smoking, or combined habits (Table 5). These exposures are recognised risk factors for OSMF and OSCC, and measured biomarker concentrations were comparable between habit categories. Protein expression related to epithelial transformation may persist once pathological alteration has developed, irrespective of exposure pattern.[20,24]

The variability in S100A7 expression described in squamous cell carcinoma should be considered when interpreting salivary findings. Differences in cellular differentiation and local microenvironmental influences can influence expression levels.[17] Such biological variation may account for the larger standard deviation observed in the OSCC group when compared with controls in the present study (Table 2). Probstmeier *et al.*[24] emphasised that molecular variability in S100 protein expression should be taken into account when defining diagnostic thresholds for clinical application. They noted that reliable cut-off values require validation in larger study populations. Pellegrini *et al*.[19] emphasised that diagnostic discrimination and prognostic evaluation serve different clinical purposes in salivary biomarker research in OSCC. Increased tissue expression has been linked to malignant transformation and reduced survival in head and neck

carcinoma.[11,12] Salivary biomarker research in OSCC has highlighted the importance of separating disease detection from outcome prediction.[19] The present study demonstrates diagnostic differentiation among controls, OSMF, and OSCC; however, longitudinal transformation was not evaluated. Elevated levels in OSMF may indicate increased transformation risk which was in accordance with the immunohistochemical observations in dysplastic lesions.[10,16,25]

The comparison of salivary S100A7 with other reported biomarkers provides important clinical context for its interpretation. Interleukins and inflammatory mediators have been described as candidate salivary markers in OSCC.[2] These cytokines mainly indicate inflammatory activity, whereas S100A7 participates directly in epithelial differentiation and oncogenic signalling pathways.[8,13] S100A7 participates in epithelial transformation and may help distinguish dysplastic lesions from inflammatory conditions. Periodontal evaluation limited the effect of gingival inflammation on salivary measurements. S100 proteins in OSCC have highlighted the need for larger populations to define diagnostic thresholds.[18] Studies have indicated that S100A7 participates in epithelial transformation and is detectable in saliva during pathological states,[9,11-13,17] with elevated levels also documented in OSMF and leukoplakia.[3,4,15]

Strengths and limitations: The study included three well-defined groups of equal size with histopathological confirmation of OSMF and OSCC. Unstimulated whole saliva was collected using a uniform protocol, which reduced procedural variation. Statistical analysis applied appropriate comparative tests with pairwise evaluation, allowing clear group differentiation. Demographic factors, habit patterns, lesion sites, and age correlation were also examined to provide clinical context for S100A7 levels. The cross-sectional design did not allow assessment of malignant transformation over time. The single-centre setting and moderate sample size limit generalizability. Diagnostic accuracy measures such as sensitivity, specificity, and threshold estimation were not determined.

CONCLUSION

The study identified significantly higher salivary S100A7 concentrations in OSMF and OSCC compared with healthy individuals, with peak levels recorded in OSMF. The findings show clear separation between healthy mucosa, potentially malignant change, and carcinoma based on salivary S100A7 values. This difference indicates that salivary S100A7 measurement can aid in distinguishing pathological epithelial conditions from health through a non-invasive approach. Further investigations with larger and diverse populations are required to establish reliable diagnostic thresholds and determine performance characteristics such as sensitivity and specificity. Prospective monitoring of OSMF cases would clarify its value in identifying lesions at increased risk of malignant transformation.

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