Original Article

# Quantitative Assessment of Receptors of Advanced Glycation End Products Expression in Tissue Samples from Patients with oral Submucous Fibrosis, Leukoplakia, and Oral Squamous Cell Carcinoma

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## Abstract

**Background and Aim:** Oxidative stress markers have been firmly established as elevated in oral squamous cell carcinomas (OSCCs). These markers play a crucial role in the pathogenic mechanism underlying the accumulation of advanced glycation end products (AGEs) and their respective receptors. The primary objective of this study is to discern and compare the levels of receptors of AGEs (RAGEs) within tissue samples from patients diagnosed with oral submucous fibrosis (OSMF) at varying stages, oral leukoplakia at various stages, and OSCC. **Materials and Methods:** A cross-sectional investigation was conducted, enrolling a total of 49 patients, distributed across three distinct groups. Tissue samples were meticulously collected from the aforementioned patient groups. Subsequently, these samples underwent a process of homogenization and centrifugation. The supernatant obtained was subjected to enzyme-linked immunosorbent assay analysis to precisely determine the concentration of RAGE. **Results:** The concentration of RAGEs was found to be significantly higher at various stages of OSMF when compared to the reference group of OSCC ($P < 0.05$). This difference was statistically significant, indicating a substantial association. In contrast, the levels of RAGE in patients with hyperkeratosis accompanied by epithelial dysplasia at various stages were observed to be lower than those in the OSCC group, with the difference in concentration being statistically insignificant ($P > 0.05$). **Conclusion:** This comprehensive study has provided compelling evidence demonstrating the heightened levels of RAGE in OSMF when compared to OSCC. These findings collectively suggest the potential utility of anti-RAGE interventions as a promising avenue for novel therapeutic strategies in potentially malignant disorders such as OSMF.

**Keywords:** *Hyperkeratosis, leukoplakia, oral submucous fibrosis, receptors of advanced glycation end products*

## Introduction

Noncommunicable diseases (NCDs) have emerged as the predominant global cause of mortality in the 21st century. Among these NCDs, cancer is poised to become the leading contributor to worldwide mortality, presenting a formidable obstacle to increasing life expectancy worldwide.[1] The escalating incidence and mortality rates of cancer are complex phenomena influenced by numerous factors. These factors include demographic shifts driven by aging and population growth, along with dynamic changes in the prevalence and distribution of major cancer risk factors, many of which are intricately linked to socioeconomic development.[1-3]

The GLOBOCAN database, meticulously maintained by the International Agency for Research on Cancer, highlights the global impact of cancer and has identified the Asian region as the epicenter of cancer-related deaths, constituting a staggering 57.3% of the global burden. Within this regional context, India, with its rapidly expanding population, plays a significant role, accounting for approximately 7.8% of global cancer incidence.[4] In India, oral cancer occupies a prominent position, representing nearly 30% of all cancer types. This high incidence is coupled with an alarmingly elevated mortality rate, making India the global epicenter for oral cancer.[2,5] Oral cancer poses a substantial challenge to the development and well-being of the Indian population, emphasizing the urgent need for early detection and intervention.[6]



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Oral cancers often arise as a consequence of precursor lesions, now reclassified as potentially premalignant oral epithelial lesions (PPOEL), formerly known as oral potentially malignant disorders.[7] While statistical evidence supports the notion that PPOELs exhibit an increased propensity for malignant transformation, it is crucial to acknowledge that not all lesions inevitably progress to cancer. Clinical parameters may aid in risk assessment, but the gold standard diagnostic procedure remains a biopsy and histologic examination.[8] Notably, Silverman *et al*. reported that 36% of dysplastic lesions progressed to carcinoma, while 16% of leukoplakic lesions lacking dysplasia exhibited cancer progression.[9] Given the intricate nature of oral carcinogenesis, there is an urgent need for clinical or histologic biomarkers capable of reliably distinguishing lesions with malignant potential from those that remain benign.[10]

Carcinogenesis is a multifaceted process influenced by various factors. Chronic inflammation which is recognized as a hallmark of cancer, encompasses within this context, oxidative stress, denoting an imbalance between free radical production and anti-oxidative defenses, plays a pivotal role in the pathogenesis of inflammatory diseases and cancer. Glycation, a spontaneous nonenzymatic reaction involving free reducing sugars and free amino groups in proteins, DNA, and lipids, leads to the formation of Amadori products and advanced glycation end products (AGEs). The receptor for AGEs (RAGE), a multiligand receptor, interacts with various ligands, including high mobility Group B-1/amphoterin, AGEs, β-amyloids, and S100 proteins. As a member of the immunoglobulin superfamily, RAGE orchestrates intracellular signaling pathways governing inflammation, apoptosis, proliferation, and autophagy.[11,12] These receptors are known to be elevated in numerous pathological conditions, including various cancers.[13]

Furthermore, experimental evidence has showcased that the blockade of RAGE signaling holds promise in diminishing tumor growth and metastasis by regulating tumor proliferation, invasion, and the expression of matrix metalloproteinases in animal models.[14] In light of this multifaceted landscape, this study is designed to evaluate the prevalence of RAGE among patients with oral squamous cell carcinoma (OSCC), oral submucous fibrosis (OSMF) at various histological grades, and various clinical stages of leukoplakia.

## Materials and Methods

### Study design

This *in vivo* cross-sectional study aimed to investigate the expression of RAGEs in tissue samples representing various grades of OSMF, hyperkeratosis, and well-differentiated OSCC.

### Ethical clearance

Prior to the commencement of the study, ethical clearance was obtained from the Scientific Review Board (Approval ID: SRB/SDMDS16OMP/04).

### Subject selection criteria

#### *Inclusion criteria*

- Patients with histologically confirmed moderately advanced and advanced OSMF
- Patients with histologically confirmed well-differentiated OSCC
- Patients with clinically confirmed leukoplakia displaying hyperkeratosis with various grades of dysplasia (moderate and severe).

#### *Exclusion criteria*

- Patients with systemic comorbidities
- Terminally ill patients.

### Sample collection

A total of 49 tissue samples were collected, 16 tissue samples were collected from patients who had histopathologically confirmed OSMF, 16 samples from patients with histopathologically confirmed hyperparakeratosis, and 17 samples from patients with OSCC.

Tissue samples were procured by performing biopsies of the lesional regions. These samples were then immediately transferred to round-bottom microfuge tubes and snap-frozen in liquid nitrogen. Subsequently, the frozen samples were stored at −80°C for future analysis.

### Sample preparation

Upon thawing, the tissue samples were homogenized using a tissue homogenizer. The resulting homogenates were then centrifuged at 5000 × g for 5 min to obtain the supernatant. This supernatant was carefully pipetted into microfuge tubes and used for subsequent analysis.

### Enzyme-linked immunosorbent assay

The enzyme-linked immunosorbent assay (ELISA) analysis was performed using the RAY BIOTECH ELISA kit. Optical density readings were obtained at a wavelength of 450 nm.

### Data analysis

Statistical analysis was carried out using IBM SPSS Statistics software (Version 23.0, IBM Corporation, Armonk, NY, USA, 2015). The Newman–Keuls Multiple comparison test was employed to compare the different groups. A significance level of $P < 0.05$ was considered statistically significant, while $P > 0.05$ indicated no significant difference between groups.

## Results

### Demographic data

The study encompassed a total of $n$ = 49 participants, categorized into three distinct groups. Group I comprised patients with well-differentiated squamous cell carcinoma ($n$ = 17), Group II encompassed patients with OSMF (moderate and advanced) ($n$ = 16), and Group III consisted of individuals with oral leukoplakia at moderate and severe clinical stages ($n$ = 16). These were confirmed histopathologically [Figure 1].

The mean age among the carcinoma group was 51.06 years, 42.75 years among the OSMF group, and 48.69 years among the leukoplakia group. Male participants dominated in all three groups, constituting 89.8% of the patients enrolled and 10.2% were females. The distribution of age and sex is visually represented in a graphical format as Figure 2.

### Receptor for advanced glycation end products in control samples – Oral squamous cell carcinoma

Among the 17 control samples subjected to analysis, all 17 exhibited the presence of RAGE in the tissue samples. The prevalence of RAGE within the control group stood at 100%, with a minimum value of 12.20498 pg/ml of tissue lysate and a maximum value of 19.12721 pg/ml.

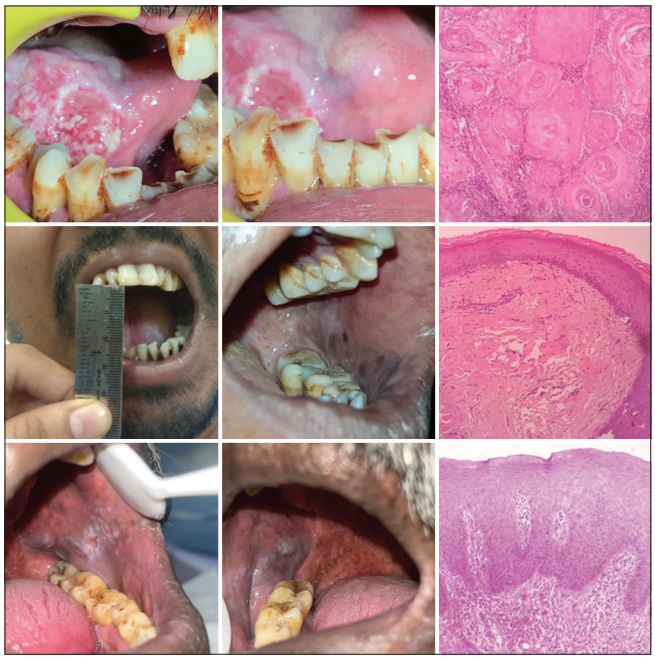

**Figure 1: A comprehensive collage of clinical and histopathological images (10x magnification), organized into three distinct rows, each focusing on a different oral lesion: well differentiated squamous cell carcinoma in the first row, oral submucous fibrosis in the second row, and leukoplakia in the third row**

### Receptor for advanced glycation end products in moderately advanced and advanced oral submucous fibrosis

In the case of the 16 tissue samples from patients with moderately advanced and advanced OSMF, all 16 samples demonstrated the presence of RAGE. The prevalence of RAGE in this group was 100%, with a minimum value of 16.21259 pg/ml of tissue lysate and a maximum value of 35.15764 pg/ml.

### Receptor for advanced glycation end products in moderately severe and severe hyperkeratosis with epithelial dysplasia

Among the 16 tissue samples analyzed from individuals with moderately severe and severe hyperkeratosis presenting with epithelial dysplasia (leukoplakia), all 16 samples exhibited the presence of RAGE. The prevalence of RAGE in this group also stood at 100%, with a minimum value of 9.290361 pg/ml of tissue lysate and a maximum value of 16.21259 pg/ml.

### Comparison of prevalence of receptor for advanced glycation end products

Comparison of prevalence of RAGE among tissue samples [Figure 3] of moderately advanced and advanced OSMF and OSCC patients:

- When comparing the prevalence of RAGE between the groups, statistical significance was observed, with a notably higher prevalence of the RAGE receptor among OSMF patients in comparison to OSCC patients. Table 1 for the prevalence of RAGE among tissue samples of moderately advanced and advanced OSMF and OSCC patients. The levels of RAGE were significantly higher in moderately advanced and advanced OSMF than in OSCC patients (Newman–Keuls multiple comparison test, $P < 0.05$ – statistically significant).

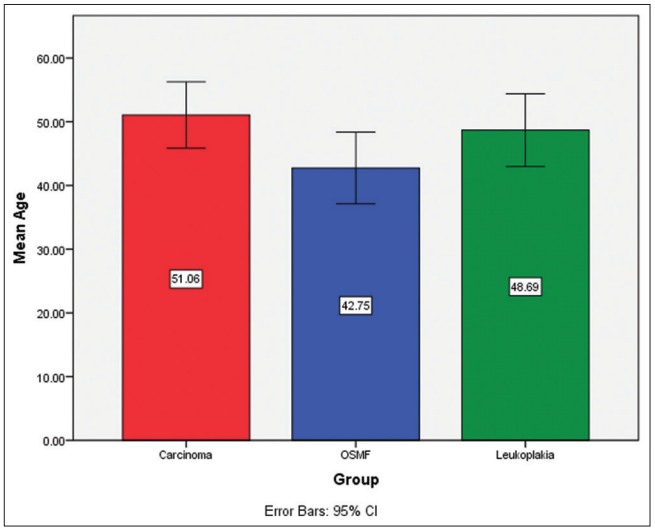


**Figure 2: The mean age of the participants in each group. CI: Confidence interval, OSMF: Oral submucous fibrosis**

**Table 1: Prevalence of receptors of advanced glycation end product among tissue samples of moderately advanced and advanced oral submucous fibrosis and oral squamous cell carcinoma patients**

| Groups | Mean difference | *Q* | *P* |
|---|---|---|---|
| OSCC versus OSMF (pg/mL) | −6.6 | 8.5 | <0.05 |

OSMF: Oral submucous fibrosis; OSCC: Oral squamous cell carcinomas

**Table 2: Prevalence of receptors of advanced glycation end product among tissue samples of moderately severe and severe hyperkeratosis and oral squamous cell carcinoma patients**

| Groups | Mean difference | *Q* | *P* |
|---|---|---|---|
| OSCC versus leukoplakia (pg/mL) | −2.2 | 2.9 | >0.05 |

The comparison of the means and Standard deviations (SD)

Comparison of prevalence of RAGE among tissue samples of moderately severe and severe hyperkeratosis with epithelial dysplasia and OSCC patients:

- In contrast, although a comparison between the groups did not yield statistical significance, a lower prevalence of RAGE was identified among various stages of hyperkeratosis with moderately severe and severe epithelial dysplasia (leukoplakia) when compared to OSCC patients. Table 2 for a detailed representation of the prevalence of RAGE among tissue samples of moderately severe and severe hyperkeratosis and OSCC patients. The results indicated that the levels of RAGE were lower in moderately severe and severe hyperkeratosis compared to OSCC patients, although this difference was statistically insignificant (Newman–Keuls multiple comparison test, $P > 0.05$ – not statistically significant).

## Discussion

Oral cancers, predominantly represented by OSCC, have historically been managed through surgical procedures, radiation therapy, and chemotherapy. However, the quest for targetable biomarkers has intensified in recent years, aimed at enhancing patient survival and personalized treatment strategies. Biomarkers serve various roles in oncology, including prediction, diagnosis confirmation, treatment efficacy assessment, and prognosis. Early detection remains pivotal in cancer prevention and overall patient survival.[1]

OSCC accounts for a substantial majority (90%) of malignancies in the oral cavity and is a multifactorial disease with numerous associated risk factors. Globally, tobacco and areca nut consumption contribute to approximately 25% of all oral cancer cases.[10] In addition, arecoline, a compound found in areca nut, plays a significant role in the pathogenesis of OSMF, a potentially malignant disorder with a malignant transformation rate

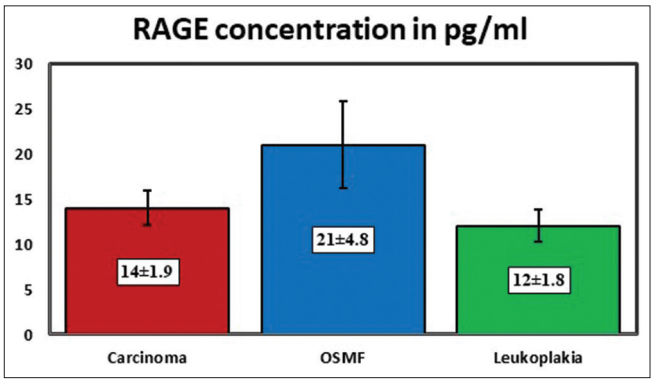


**Figure 3: The receptors of advanced glycation end products (RAGE) using enzyme-linked immunosorbent assay. The bar chart showing the concentration of RAGE in oral squamous cell carcinomas tissue samples is 14 ± 1.9 pg/ml (blue), 21 ± 4.8 pg/ml in oral submucous fibrosis (red), and 12 ± 1.8 pg/ml in hyperkeratosis with epithelial dysplasia (green) in a scale of 0–25 (Y axis = Concentration of RAGEs in pg/ml). The asterisk suggests the statistical significance of the comparison between the groups. RAGE: Receptors of advanced glycation end products, OSMF: Oral submucous fibrosis**

ranging from 7% to 13%.[15] Oral leukoplakia, characterized by predominantly white lesions or plaques with uncertain behavior, exhibits a malignant transformation rate of up to 43%.[16]

RAGE have been implicated in invasion, migration, and angiogenesis in oral malignancies, although the precise mechanisms governing interactions with various ligand families remain incomplete. Notably, the diagnostic potential of RAGE markers in oral potentially malignant disorders has not been thoroughly explored. The present study aims to shed light on the presence of these receptors at various stages of OSMF and hyperkeratosis with epithelial dysplasia.

Our study observed a male predominance, with 89.8% of participants being males, reflecting the prevalence of deleterious habits such as tobacco use and smoking among the male population. The effects of these products are more discernible in males compared to females. Among females, tobacco product consumption and chronic irritation were identified as significant etiological factors.

Furthermore, our findings revealed a higher incidence of these lesions in the older age group, with 30.6% ($n$ = 15) of participants falling within the 51–60 years age group, followed by 26.5% ($n$ = 13) in the 41–50 years age group. This suggests that these lesions are more common among older individuals, potentially linked to long-term habits. The duration, type, frequency, and length of tobacco and areca nut product use were identified as important factors influencing lesion development. As individuals age, mucosal thickness decreases, rendering them more susceptible to these changes.

Our study participants included 34.6% ($n$ = 17) with well-differentiated squamous cell carcinoma, 22.4% ($n$ = 11) with hyperkeratosis and moderate

epithelial dysplasia, and 10.2% ($n$ = 5) with hyperkeratosis and severe epithelial dysplasia. In addition, 18.3% ($n$ = 9) had advanced OSMF, and 14.2% ($n$ = 7) had moderately advanced OSMF, while early or milder forms of potentially malignant disorders were not included due to ethical concerns and patient compliance issues. This study, therefore, represents the first attempt to assess RAGE concentration in oral potentially malignant disorders at various histological stages, offering promising avenues for innovative treatments and improved patient outcomes.

Our results indicated that RAGE concentration in tissue samples from well-differentiated squamous cell carcinoma was 14 ± 1.9 pg/ml, which was lower than the previously reported 57 ± 1.9 pg/ml. This discrepancy may be attributed to the cancer stage. Sasahira *et al*. suggested that RAGE concentration decreases as cancer progresses, possibly due to the utilization of these molecules during cancer development, alongside other factors that become prominent in later cancer stages.[16] Thus, RAGE concentration may be depleted in advanced cancer stages.

In contrast, tissue samples from hyperkeratosis with epithelial dysplasia exhibited RAGE concentrations of 12 ± 1.8, which were statistically insignificant compared to RAGE levels in well-differentiated squamous cell carcinoma. This suggests that RAGE levels are lower in such lesions. Our study aligns with Metgud and Bajaj who reported lower levels of reactive oxygen species (ROS) in oral leukoplakia cases compared to OSCC. Reduced ROS and other RAGE-associated factors may contribute to the lower RAGE levels in hyperkeratosis with epithelial dysplasia.[17]

Remarkably, RAGE levels significantly increased in OSMF by 7 pg/ml, reaching 21 ± 4.8 pg/ml when compared to OSCC, with $P < 0.05$. The pathogenesis of OSMF is complex, involving various factors such as chili consumption, nutritional deficiency, areca nut chewing, genetic susceptibility, altered salivary constituents, autoimmunity, and collagen disorders. Chewing tobacco, including pan masalas, exerts cytotoxic effects through ROS production, leading to lipid peroxidation and cell membrane structural modifications.[18]

Consistently, tissue levels of malondialdehyde (MDA) and ROS were higher in Grade 1 and Grade 2 OSMF compared to controls. However, tissue levels of MDA and ROS decreased in Grade 3 OSMF when compared to controls. This phenomenon could be attributed to the utilization of ROS and MDA in collagen crosslinking. Extensive fibrosis reduces vascularity, leading to hypoxia in fibroblasts and surface epithelium, causing epithelial atrophy and ulceration through apoptosis. Hypoxia-induced factor-1α overexpression is also observed in OSMF, influencing cell proliferation, maturation, and metabolic adaptation, thereby increasing the likelihood of malignant transformation.[19]

Given the abundance of these factors in OSMF, the increased RAGE levels align with the multiligand property of RAGE. Notably, our study found that RAGE levels were higher in OSMF than in OSCC. This suggests that RAGE, known as a multiligand receptor, plays a role in multiple pathways that contribute to carcinogenesis, enhancing the potential for malignant transformation in these lesions and promoting carcinogenesis.

Several studies have demonstrated the effectiveness of antisense-RAGE oligonucleotides in reducing receptor activity and its associated ligands, emphasizing RAGE as a promising therapeutic target. Further investigations are warranted to validate the use of anti-RAGE therapy for potentially malignant disorders, offering tailored treatment options that target RAGE as the central molecule.[20]

Our study highlights the presence of RAGE receptors in both OSMF and hyperkeratosis with epithelial dysplasia, with significantly higher RAGE levels in OSMF compared to OSCC. This pioneering study elucidates the role of these multiligand receptors in potentially malignant disorders, underscoring their involvement in pathways leading to carcinogenesis. Future research is needed to explore the potential of anti-RAGE therapy for these conditions, paving the way for personalized treatment approaches and ultimately improving patients' disease-free lives, which is the ultimate goal of any treatment.

## Conclusion

While existing literature has shed light on the role of RAGE in OSCC, this study is a pioneering endeavor that explores the presence and concentration of RAGEs in potentially malignant disorders. Specifically, we examined patients with OSMF and hyperkeratosis with epithelial dysplasia (leukoplakia) at various stages and compared their RAGE levels to a reference group of patients with well-differentiated OSCC.

### Key findings

- RAGE prevalence: We observed a 100% prevalence of RAGE in all groups, indicating that these receptors are present in all studied conditions
- Higher RAGE levels in OSMF: Significantly higher RAGE concentrations were found in tissue samples from patients with OSMF compared to the reference OSCC group ($P < 0.05$). This suggests a substantial association between elevated RAGE levels and OSMF
- Similar RAGE levels in hyperkeratosis with dysplasia: RAGE levels in patients with hyperkeratosis and epithelial dysplasia at various stages were found to be lower than those in the OSCC group, but this difference was statistically insignificant ($P > 0.05$). This suggests that RAGE levels in this group are similar to those in OSCC patients.

These findings collectively imply that RAGEs play a potentially critical role in the pathogenesis of OSMF, making them a promising target for further investigation and potential therapeutic interventions in potentially malignant disorders. While the study provides valuable insights, further research is needed to validate these findings and explore the utility of anti-RAGE interventions as a novel therapeutic strategy in OSMF and potentially malignant disorders. Such targeted therapies may offer a more effective and personalized approach to managing these conditions, ultimately improving patient outcomes.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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