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Evaluation of oxidative stress markers in patients with oral potentially malignant disorders

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Abstract:
Oral potentially malignant disorders are associated with an increased risk of malignant transformation, with oxidative stress playing an important role in their pathogenesis. This comparative observational study evaluated 120 participants, including 60 patients with clinically and histopathologically confirmed oral potentially malignant disorders and 60 age and sex matched healthy controls, by assessing malondialdehyde, superoxide dismutase, catalase, glutathione peroxidase and total antioxidant capacity in blood and saliva. Patients with oral potentially malignant disorders had significantly higher malondialdehyde (5.82±1.14 vs. 2.97±0.73 nmol/mL) and lower superoxide dismutase, catalase, glutathione peroxidase and total antioxidant capacity than controls (all $p<0.001$). The altered oxidative stress profile indicates increased lipid peroxidation and impaired antioxidant defence in patients with oral potentially malignant disorders. These findings advance knowledge by supporting oxidative stress biomarkers as promising adjunctive tools for early diagnosis, risk stratification and monitoring of oral potentially malignant disorders.

Keywords: Oral potentially malignant disorders (OPMDs), oxidative stress, malondialdehyde, superoxide dismutase, total antioxidant capacity, biomarkers

Background:
Oxidative stress is a pathological state caused by an imbalance between generation of reactive oxygen species (ROS) and body's antioxidant defence mechanisms. In the oral cavity, chronic exposure to environmental carcinogens like tobacco, areca nut, alcohol and microbial toxins increases ROS production, establishing an oral microenvironment that is conducive to cellular injury and malignant transformation **[1]**. There has been a lot of interest in the link between oxidative stress and oral diseases in recent years. Sardaro *et al.* have shown that oxidative stress is a major factor in the pathogenesis of oral mucosal diseases, which leads to chronic inflammation, epithelial injury and disturbance of normal cellular homeostasis, resulting in lipid peroxidation, DNA mutations and changes in intracellular signalling pathways that contribute to the initiation and progression of oral epithelial dysplasia **[2]**. These molecular events are especially important in oral potentially malignant disorders (OPMDs) where chronic oxidative stress may predispose to malignant transformation **[3]**. Oral potentially malignant disorders are a diverse group of lesions which have the potential to progress to oral squamous cell carcinoma (OSCC) **[4]**. Kumari *et al.* reviewed the etiological and molecular mechanisms underlying OPMDs and their transformation into oral cancer, emphasizing the importance of early detection and prevention of malignant progression **[5]**. Therefore, the search for reliable biochemical markers that can predict disease progression is an important research area in OPMDs, according to the World Health Organization (WHO) Collaborating Centre for Oral Cancer **[6]**. Saliva has gained attention as a non-invasive diagnostic medium for detecting oxidative-stress-related biomarkers in OPMDs and oral squamous cell carcinoma (OSCC). Sridharan described the potential utility of salivary oxidative-stress products for the early detection of oral cancer and its precursor lesions, while Ahmed *et al.* reported significant differences in oxidative-stress marker levels between patients with oral premalignant lesions or OSCC and healthy controls in their systematic review **[7, 8]**. In recent years, the evidence of the association between oxidative stress and oral carcinogenesis has been strengthened **[9]**. Oxidative stress enzymes like malondialdehyde, superoxide dismutase, catalase and glutathione peroxidase are significantly elevated in oral cancer patients compared to healthy controls in the systematic review and meta-analysis by Guo *et al.* and Chen *et al.* indicating their potential as valuable adjuncts for early diagnosis and prognosis of oral cancer **[10, 11].** Therefore, it is of interest to assess the levels of oxidative stress markers in patients with OPMDs and to compare them with healthy individuals.

Materials and Methods:
Study design:
The aim of the present study was to make a comparative observation study based on the hospital setting to assess the oxidative stress markers in patients with OPD and compare with the healthy individuals.

Study setting:

The study was carried out in the Department of oral medicine and radiology of a tertiary care dental teaching hospital in association with the Department of Biochemistry.

Study duration:
The study was conducted for 18 months after approval from the Institutional Ethics Committee.

Study population:
Patients who came to the outpatient department and were clinically suspected and histopathologically confirmed to have oral potentially malignant disorders were included in the study.

Sample size:
There were 120 enrolments. The total number of patients in group I (OPMD) was 60. Healthy Controls: 60 age and sex matched healthy volunteers (Group II).

Sampling technique:
Consecutive sampling was used to recruit eligible participants who met the inclusion criteria until the required number of participants was achieved.

Inclusion criteria:
Group I (OPMD)
[1] Patients 18 years or older.
[2] Clinically diagnosed and histopathologically confirmed cases of OPMDs.
[3] Newly diagnosed cases not being treated.
[4] Persons who are willing to give informed consent in writing.

Group II (controls)
[1] People who do not have oral mucosal lesions and are healthy.
[2] No family history of tobacco or areca nut use.
[3] No systemic inflammatory or malignant disease.
[4] Age- and sex-matched with the study group.

Exclusion criteria:
[1] Previously treated OPMDs.
[2] Oral squamous cell carcinoma confirmed by histopathology.
[3] Patients who have autoimmune diseases.
[4] Diabetes mellitus or chronic kidney disease.
[5] Liver disorders.
[6] Acute infections.
[7] Pregnancy and lactation.
[8] People using antioxidant pills, corticosteroid pills, or chemotherapy.
[9] Patients unwilling to participate.

Clinical examination:
A detailed clinical examination was carried out following WHO guidelines. Data on age, gender, occupation, socioeconomic status, tobacco use, alcohol use, length of habits, lesion characteristics and clinical diagnosis were obtained in a standardized case record form.

Histopathological confirmation:
Incisional biopsy was performed when indicated and tissue specimens were examined by experienced oral pathologists to make a diagnosis based on WHO classification.

Sample collection:
Blood Sample: Fasting venous blood was drawn under sterile conditions, 5 mL. The serum was obtained by centrifugation and kept at −80°C until biochemical analysis.
Saliva Sample: Unstimulated whole saliva was collected overnight fasted between 9:00 AM and 11:00 AM, approximately 5 mL. The samples were centrifuged and the supernatant was kept at -80°C.

Biochemical analysis:
The markers of oxidative stress were measured by using the commercially available standardized assay kits.
The following parameters were analysed:
[1] Malondialdehyde (MDA)
[2] Superoxide dismutase (SOD)
[3] Catalase (CAT)
[4] Glutathione peroxidase (GPx)
[5] Reduced glutathione (GSH)
[6] Total antioxidant capacity (TAC)
The biochemical analysis was carried out as per the protocol of the manufacturers in the same laboratory conditions.

Outcome measures:
Primary outcome:
Comparisons of oxidative stress markers in OPMD patients and healthy controls.

Secondary outcomes:
[1] Association of oxidative stress markers with various types of OPMD.
[2] Correlation of oxidative stress markers with severity of epithelial dysplasia.
[3] Relationship between oxidative stress markers and tobacco habit characteristics.

Data management:
Data from clinical and laboratory were entered into Microsoft Excel and checked for completeness and accuracy prior to statistical analysis.

Statistical analysis:
IBM SPSS Statistics version 27.0 was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented in frequencies and percentages. Two groups were compared using either Independent Student's t-test or Mann–Whitney U test. Multiple group comparisons were performed using one-way ANOVA and post hoc analysis. Categorical variables were analyzed using chi-square or Fisher's exact test. Association between oxidative stress markers and clinical variables were assessed using Pearson's or Spearman's correlation coefficient. A p-value of <0.05 was deemed as statistically significant.

Results:

A total of 120 participants were included in the study, comprising 60 patients diagnosed with Oral Potentially Malignant Disorders (OPMDs) (Group I) and 60 healthy controls (Group II). Demographic characteristics were comparable between the two groups (p>0.05). Biochemical analysis demonstrated significantly increased oxidative stress among OPMD patients, evidenced by elevated serum malondialdehyde (MDA) levels and reduced antioxidant enzyme activities. These findings indicate a disturbance in the oxidant-antioxidant balance in individuals with OPMDs. The mean age of participants was similar in both groups, indicating successful age matching. Males constituted 68.3% of the OPMD group and 65.0% of controls (p=0.704). Tobacco consumption was significantly higher among OPMD patients (80.0% vs. 20.0%; p<0.001), as was areca nut use (61.7% vs. 13.3%; p<0.001), supporting their established role as major etiological factors for oral potentially malignant disorders **(Table 1).** Patients with OPMDs exhibited significantly higher serum MDA levels (5.82 ± 1.14 nmol/mL) compared with controls (2.97 ± 0.73 nmol/mL, p<0.001), indicating enhanced lipid peroxidation. In contrast, antioxidant enzymes including SOD, CAT, GPx and TAC were significantly reduced in the OPMD group (all p<0.001), suggesting impairment of endogenous antioxidant defence mechanisms. These findings demonstrate increased oxidative stress in patients with oral potentially malignant disorders **(Table 2).** Among patients with OPMDs, 81.7% demonstrated elevated MDA levels, making it the most frequently altered oxidative stress marker. Reduced TAC was observed in 76.7%, followed by decreased SOD (73.3%), catalase (70.0%) and GPx (66.7%) of patients. All biochemical abnormalities were statistically significant (p<0.001), indicating that oxidative stress is consistently associated with oral potentially malignant disorders **(Table 3).**

Table 1: Demographic characteristics of the study population

Variable	OPMD (n=60)	Controls (n=60)	p-value
Mean Age (years)	44.9 ± 10.8	43.5 ± 11.1	0.482
Male	41 (68.3%)	39 (65.0%)	0.704
Female	19 (31.7%)	21 (35.0%)	
Tobacco Habit	48 (80.0%)	12 (20.0%)	<0.001
Areca Nut Habit	37 (61.7%)	8 (13.3%)	<0.001
Alcohol Consumption	21 (35.0%)	15 (25.0%)	0.236

Table 2: Comparison of oxidative stress markers between study groups

Oxidative Stress Marker	OPMD (Mean ± SD)	Controls (Mean ± SD)	p-value
Malondialdehyde (MDA) (nmol/mL)	5.82 ± 1.14	2.97 ± 0.73	<0.001
Superoxide Dismutase (SOD) (U/mL)	102.8 ± 18.6	146.3 ± 20.8	<0.001
Catalase (CAT) (kU/L)	41.6 ± 7.5	58.4 ± 8.3	<0.001
Glutathione Peroxidase (GPx) (U/L)	48.9 ± 9.8	70.6 ± 10.4	<0.001
Total Antioxidant Capacity (TAC) (mmol/L)	0.88 ± 0.19	1.46 ± 0.24	<0.001

Table 3: Distribution of oxidative stress marker status among OPMD patients

Parameter	Normal	Altered	Percentage Altered	p-value
Elevated MDA	11	49	81.7%	<0.001
Reduced SOD	16	44	73.3%	<0.001
Reduced CAT	18	42	70.0%	<0.001
Reduced GPx	20	40	66.7%	<0.001
Reduced TAC	14	46	76.7%	<0.001

Discussion:

In the present study, the levels of oxidative stress markers were assessed in patients with oral potentially malignant disorders (OPMDs) and it was found that the levels of oxidative stress markers were significantly elevated in patients with OPMDs than in healthy controls. Patients with OPMDs had significantly higher malondialdehyde (MDA) levels and significantly lower antioxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and total antioxidant capacity (TAC). These findings support the concept that disruption of oxidant-antioxidant homeostasis plays an important role in the initiation and progression of oral epithelial dysplasia and subsequent malignant transformation **[12-14].** In normal cell metabolism, reactive oxygen species (ROS) are produced continuously; when the production exceeds the capacity of the endogenous antioxidant system, oxidative injury of lipids, proteins and DNA occurs. The significantly higher serum MDA levels found in the present study thus suggest higher levels of lipid peroxidation in the membranes and higher levels of oxidative injury in the human tissues of patients with (OPMDs) **[15]**. Oxidative stress has been recognized as one of the major mechanisms involved in oral diseases. The significant increase in oxidative stress in the OPMD patients in the present study supports this biological mechanism and indicates that chronic exposure to tobacco, areca nut and other carcinogens may lead to continuous generation of ROS which may cause progressive changes in the epithelium **[16, 17].** The other major finding of the present study was the significant decrease in antioxidant enzymes in OPMD patients. Srivastava showed that patients with oral leukoplakia have significant decline in endogenous antioxidant reserve along with increased levels of oxidants during the course of the disease. The results of the present study further support this hypothesis, as similar decreases in SOD, CAT, GPx and TAC were found in the current study when oxidative stress is chronic. This diminished antioxidant activity could then lead to DNA instability and promote malignant transformation **[18]**. In a similar study, Senghore *et al.* found that there was a significant association of biomarkers of oxidative stress with the risk of potentially malignant oral disorders, indicating that elevated oxidative biomarkers could be useful markers to identify patients at higher risk for progression to OSCA. The current study showed a high percentage of patients with elevated MDA and decreased antioxidant enzyme activity, further supporting the clinical significance of these biomarkers **[19]**. Saliva and serum have been used for the assessment of oxidative stress and have attracted a lot of interest due to their easy and non-invasive collection. Therefore, biochemical markers in saliva could be used as practical adjunctive tools for screening and longitudinal monitoring of patients with OPMDs, as suggested by Javaid *et al.*, who pointed out that the oxidative stress markers in saliva closely reflect the local pathological changes **[12]**. The diagnostic potential of oxidative-stress biomarkers in oral premalignant

lesions and oral cancer has also been examined in recent literature. Ahmed *et al.*, in a systematic review, reported significant differences in oxidative-stress marker levels between cases and healthy controls, although they highlighted methodological limitations and geographic bias in the available evidence **[8]**. Recent molecular research has also provided more insight into the role of oxidative stress in oral carcinogenesis. Ma *et al.* reported that hyperactive ROS activate several signalling pathways such as NF-κB, MAPK and PI3K/Akt, which lead to an increase in cell proliferation, angiogenesis, immune evasion and apoptosis resistance **[13].** These molecular changes explain the biochemical changes observed in the present study. Moreover, in their systematic review and meta-analysis from 2026, Chen *et al.* found that oxidative stress markers were significantly higher and antioxidant levels lower in patients with oral leukoplakia, further highlighting the potential of oxidative biomarkers for diagnosis and prognosis in OPMDs **[11].** Sawczuk *et al.* observed higher levels of DNA/RNA damage and slightly higher levels of lipid peroxidation and protein oxidation products in patients treated surgically for head and neck cancer than in healthy controls. However, their study involved postoperative patients undergoing prosthetic rehabilitation and therefore provides related evidence on oxidative stress in cancer patients rather than direct evidence in OPMDs **[20]**. The present study showed statistically significant differences between the OPMD patients and healthy controls, but some limitations should be noted. The study was performed in a single center with a relatively small number of patients and follow-up for the occurrence of malignant transformation was not performed. Standardized reference values should be established in future multicenter prospective studies with larger patient numbers and serial monitoring of oxidative biomarkers to assess their predictive value for malignant transformation. The results of this study generally support the current evidence that oxidative stress is a key factor in the pathogenesis of OPDs. Increased lipid peroxidation and reduced antioxidant defences suggest a breakdown of cellular redox homeostasis and can play a major role in the progression of disease. The measurement of oxidative stress markers, such as MDA, SOD, CAT, GPx and TAC, may thus be used in addition to traditional clinical and histopathological evaluation, which may help in earlier diagnosis, better risk stratification and monitoring of patients with OPMDs.

Conclusion:

Patients with oral potentially malignant disorders exhibited significantly increased oxidative stress, characterized by elevated malondialdehyde levels and reduced antioxidant enzyme activities compared with healthy controls. Oxidative stress biomarkers may complement conventional clinical and histopathological assessment for early diagnosis, disease monitoring and risk stratification. Thus, data support the potential clinical utility of oxidative stress biomarkers in identifying patients at increased risk of disease progression and malignant transformation.

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