

## ASSESSMENT OF OXIDATIVE STRESS AND INFLAMMATORY MARKERS OF MEDICAL IMPORTANCE IN ORAL SQUAMOUS CELL CARCINOMA

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**Abstract:** There is an increased prevalence of oral squamous cell carcinoma (OSCC) globally but especially in Asian countries, and it is a well-known human malignant cancer. Oxidative stress markers might be helpful in diagnosis and to assess the progression of malignancy. The current analysis aimed to determine the altered levels of oxidative stress and inflammatory markers in oral squamous cell carcinoma. This research was conducted by the general pathology department of Institute of dentistry, CMH Lahore, from September 17, 2021, to January 17, 2022. Total of sixty age and sex matched participants were included in the study and further divided into two groups. In study group thirty confirmed cases of oral squamous cell carcinoma on histopathology were recruited. Oxidative stress markers were measured and statistically analyses done by using SPSS software version 25. The results showed increase levels of malondialdehyde, 8-hydroxy-2-deoxyguanosine, isoprostanes, interleukin-6 and tumor necrosis factor alpha as compared to the control group ( $p= 0.023, 0.001, 0.041, 0.000$  and  $0.033$  respectively). Elevated levels of oxidative stress markers were found in patients of OSCC. That may lead to swift progression of disease and may increase mortality rate.

**Keywords:** Oxidative Stress Marker, Oral Squamous Cell Carcinoma, Dentistry, Oral Pathology, Malignancy

### Introduction

Oral cancer is the cause of 2-4% of all cancers in the world. The incidence of oral cancer is higher in certain countries, with 10% of all cancers in Pakistan, and around 45% in India (Saraswat et al., 2021). In oral cancer, there is a group of neoplasms affecting different sections of the oral cavity, salivary glands and pharyngeal regions. Oral squamous cell carcinoma (OSCC) estimated to be the most common oral neoplasms and more than 90% of all oral neoplasms is considered to be OSCC (del Carmen Migueláñez-Medrán et al., 2019). It is a main reason behind oral sickness and death in Southeast Asian

countries. Addictions of tobacco, alcohol and caffeine, chewing habits of betel quid leaves and Areca nut are the most common in this region. Their use is very famous in India, Taiwan, Pakistan and parts of Southern China. It is estimated that about 85% of a person's are found to be habitual of Areca nut chewing live in Southern Asian countries. It's an addiction contributes to the high prevalence of oral cancer (Gunjal et al., 2020).

The large number of products containing Areca nut such as gutka, pan and pan masala are available in these countries. These products contain higher carcinogenic and genotoxic capability. It has been

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observed that by increasing consumption of these products equally increases the risk of OSCC. During the last 30 years, there is very slow improvement in the morbidity and mortality rates of OSCC in spite of the advancements in therapeutic approaches. OSCC is generally diagnosed in later stages (Ketabat et al., 2019). The WHO Global Oral Health Program has expected approximately 90% of oral cancers are caused by smoking and alcohol. Glyco-conjugates are the main reason for the malignancy of cells through aberrant glycosylation (Luo et al., 2021).

Through increased rates of secretion or shedding glycoproteins and glycolipids are released into the blood stream and are important diagnostic and prognostic tools. Among tobacco smokers and chewers, the progression of mouth cancer is associated with increased production of reactive oxygen species (ROS) (Islam et al., 2019). Tobacco is teratogenic, genotoxic and carcinogen because of excessive DNA damage that can lead to cancer. It causes increased production of ROS and free radical which play a role in the development of tumor, and they do it by harming the DNA that causes the degeneration of cellular content. Free radicals are produced during the various stages of carcinogens which can cause DNA damage, increased expression of proto-oncogenes and damage to tumor suppressor genes (Unsal et al., 2020).

A critical role is played by glutathione, which is a key intracellular antioxidant in defending against diseases by detoxifying harmful hydrogen peroxide and neutralizing oxidative stress caused by increased production of free radicals. It provide protection against development of oral cell carcinoma (Soldati et al., 2018; Zahra et al., 2021). Hence, in order to assess the amount of oxidative stress of an individual, ranks of MDA and GSH can be calculated which are supposed to be consistent stress markers. Even with the advancements in radiotherapy, chemotherapy and surgery, the death rate of oral cancer is 50% per 5-year all over the world and it has not been improved in recent 50 years. The reason for this may be due to lack of diagnostic tool for pre assessment of oral cell carcinoma in individuals at high risk. The present study was designed to assess modified levels of oxidative stress markers and inflammatory markers in OSCC.

#### Material and methods

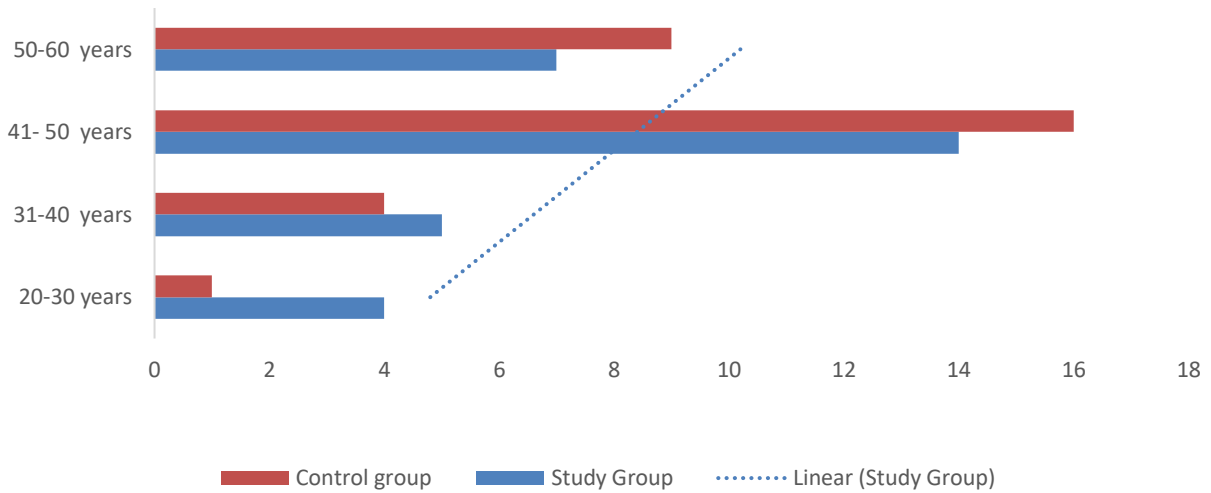
The present case and control study was carried out at the general pathology department of Institute of dentistry, CMH Lahore, from September 17, 2021, to

January 17, 2022, after the approval of ethical research committee of hospital. Total of sixty participants (n=60) were recruited. Both genders age ranging from 20 to 60 years were recruited after taken the informed written consent. The carcinoma was confirmed on pathological examination of specimen taken from the oral cavity. Participants having congenital diseases, HIV, HCV, uncontrol diabetes and other inflammatory diseases such inflammatory bowel disease (IBS) were excluded from the study. In the control group thirty age and sex matched healthy participant were included. For the biochemical assays 5ml of venous blood was obtained in the vials and serum was separated and stored at -80 degree Celsius.

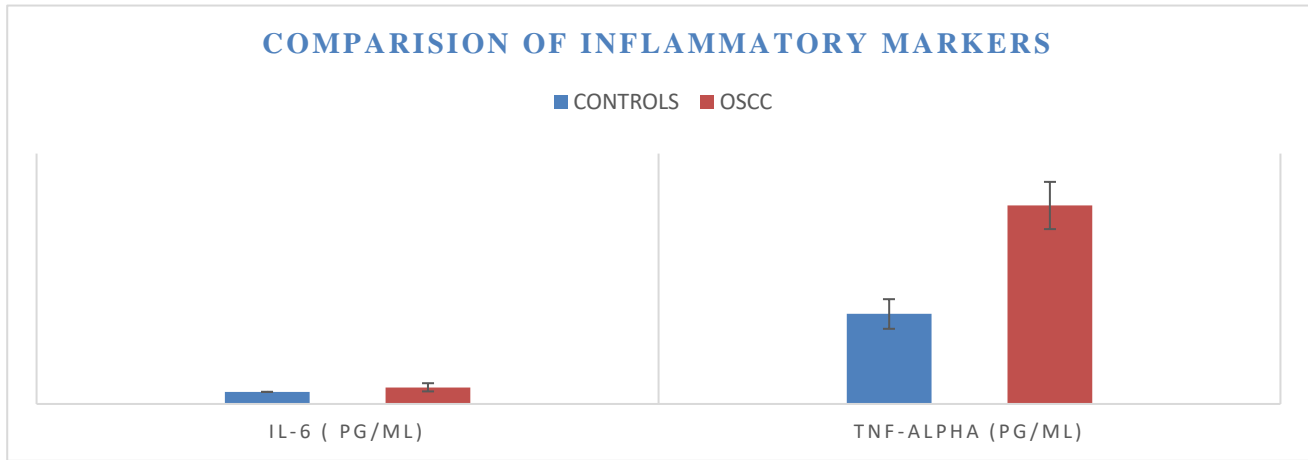
Malondialdehyde (MDA) or lipid peroxidation were evaluated through calorimetrically by the estimation of Thiobarbituric acid reactive substances (TBARS). The levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), and Isoprostanes levels were estimated with the help of commercially available ELISA kits by (ENZO-Pharma and Cayman Chemical respectively). Similarly, measurement of interleukin-6 and tumor necrosis factor alpha was done by using commercially available ELISA kits (Abcam and DIACLONE respectively). Statistical analysis was done with the help of software SPSS version 25 and *p* value less than 0.05 was considered statistically significant.

#### Results

The male to female ratio in study group was 19:11 and 17:13 in control group. The age group wise prevalence is shown in graph 1. Trendline of the study group showed the risk of oral squamous cell carcinoma increases with age, but due to limited sample size more study and extensive data needed to justify this finding. Results presented in table 01 showed that levels of MDA were increased significantly ( $p=0.023$ ) in serum of the OSCC patients ( $3.95\pm 0.74$  nmol/ml) as compared to healthy controls ( $0.89\pm 0.003$  nmol/ml). Levels of Isoprostanes-F2 $\alpha$  were amplified significantly in serum of the OSCC patients ( $37.26\pm 3.29$  pg/ml) as compared to healthy controls ( $0.98\pm 0.0027$  pg/ml). Similarly elevated levels of 8-OHdG ( $1.08\pm 0.009$  pg/m) as compared to the control group. IL-6 and TNF- $\alpha$  in serum of the OSCC patients ( $13.99\pm 0.98$  pg/ml, and  $47.56\pm 5.66$  pg/ml respectively) were measured higher as compared to the healthy individuals ( $0.03\pm 0.0019$  pg/ml,  $2.89\pm 0.008$  pg/ml and  $21.56\pm 3.55$  pg/ml respectively) (Graph 2).



Graph-1 shows the age group wise distribution of OSCC patients



Graph-2 Comparison of inflammatory markers in OSCC

TABLE- 01: LEVELS OF DIFFERENT OXIDATIVE STRESS MARKERS IN OSCC

VARIABLES	CONTROL (n=30)	SUBJECTS (n=30)	P- VALUE
MDA (nmol/ml)	0.89±0.003	3.95±0.74	0.023
IsoP- F2α (pg/ml)	0.98±0.0027	37.26±3.29	0.041
8-OHdG (pg/ml)	0.03±0.0019	1.08±0.009	0.001
IL-6 (pg/ml)	2.89±0.008	3.99±0.98	0.000
TNF-α (pg/ml)	21.56±3.55	47.56±5.66	0.033

**Discussion**

Early detection of oral squamous cell carcinoma is critical for reducing mortality and morbidity. Currently, detection of OSCC is done in a clinical and histopathological study of suspect areas, but in hidden areas, it may be undetectable. Therefore, sensitive and accurate biomarkers from the OSCC could be useful in screening high-risk patients. For

early detection of cancer, biomarkers should have the following features: Changes can be accurately measured. The alteration should occur in high-risk tissues rather than normal tissues; it should be assessed in small samples; there should be alterations in the initial phases of cancer development. OSCC, compared to other cancers, can be easily examined, samples can be easily taken for analysis, and can be

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easily treated. Specimen collection is important in obtaining patterns of genomic or proteomic expression of a disease (Zhong et al., 2018). Species that investigate the cancer-related cell changes, including proteins, DNA and RNA, are found in bodily fluids such as saliva or blood and tumor tissue. Body fluids have gained much more attention in identifying biomarkers than tissue biopsies. Up till now, many researchers found altered levels of biomarkers in OSCC body fluids. Saliva and blood are the most important bodily fluids, which may include consistent biomarkers for OSCC identification (Khurshid et al., 2018). When there is a partial decrease of oxygen, free radicals' production takes place and it causes a severe harm to tissues and important organs, mainly connective tissues, nucleic acids and membrane lipids of cells. These free radicals and ROS destroy proteins and leads to DNA-strand breaking and damage cellular membrane integrity through interaction with DNA, lipids and proteins (Juan et al., 2021). Various destructive aldehydes are produced by a lipid peroxidation reaction which continually provides free radicals which lead to further peroxidation. The aldehyde formation is mainly malondialdehyde (MDA), IsoP-F-2 $\alpha$  and 8-OHdG.

MDA is a major metabolite of arachidonic acid and a coherent marker of lipid peroxidation and tissue damage. It occurs in various biochemical responses containing covalent binding to DNA, RNA and protein. Under oxidative stress, endogenous formation of MDA takes place, and it reacts with biologically significant macromolecules which lead to the formation of MDA-DNA adducts an appropriate biomarker of endogenous DNA degradation. In an oxidative stress ROS are produced by various internal or external factors which eventually lead to DNA damage and then to carcinogenesis. The main factors of OSCC are smoking and chewing tobacco that act by producing ROS (Lee and Tseng, 2020). But the degree of DNA damage is not only caused by ROS production, it also depends on the body's defense system against ROS involving different cellular antioxidants (Xian et al., 2019). The disturbance of the oxidant-antioxidant balance in favor of oxidants is known as oxidative stress, which plays an etiological role in carcinogenesis (Osredkar et al., 2019).

In OSCC, oxidative stress and inflammation work together where they have a potential to trigger one another and initiate OSCC. Lipid peroxidation is a reaction in which ROS are produced continuously for the initiation of further peroxidation. In this reaction different damaging aldehydes are produced, and

MDA is one of them (Yalcinkaya et al., 2019). An increase serum malondialdehyde levels were observed in oral cancer as compared to normal. Hence, serves as a potential biomarker of an oxidative stress or a disease condition (Mohideen et al., 2021). Another oxidative stress biomarker in OSCC is Isoprostane-F2 $\alpha$  that is produced by the peroxidation of arachidonic acid, catalyzed by free radicals. It is an important marker for the discovery of an oxidative injury (Meera et al., 2020). Levels of Iso-F2 $\alpha$  were examined in plasma, levels of Iso-F2 $\alpha$  esterified to plasma lipids and in urine of diseased and normal individuals. So, this causes the oxidative modifications of important biological molecules in the body and leads to the diseased condition (Singh et al., 2019). Like MDA and Isoprostanes another stress markers known as 8-hydroxy-2-deoxyguanosine is also used to assess the oxidative stress. In our study all of the oxidative stress markers were significantly elevated as compared to healthy individual. Similarly, results were noted by K Babiuch et al and many other researchers (Babiuch et al., 2019; Bozan et al., 2018; Cherian et al., 2019; Contant et al., 2021).

Interlukin-6 is a multifunctional cytokine having a wide range of immunological activities, and it is also a potential mediator in the cancer development. It is known to promote proliferation of OSCC cell lines and on the other hand stabilizes the antibody inhibited growth in vivo (Minabe et al., 2019). OSCC patients were examined to determine the expression of IL-6 and IL-6 receptor. There were ultimately over expressions of IL-6 and IL-R as compared to normal. So, it suggests that it is associated with tumor development independently (Chang et al., 2018). Tumor necrosis factor- $\alpha$  is another inflammatory cytokine which is very important for the immune response to a wide variety of immune-inflammatory and infectious diseases. It is also useful in host defense system, but its excessive and uncontrollable production could lead to a disease (Jing et al., 2019). In OSCC patients' alterations of immune function have been identified. According to a huge amount of study, the therapeutic antitumor effects of TNF- $\alpha$  have been verified and there is some increasing evidence that it may promote the cancer development. To observe TNF- $\alpha$  expression, some OSCC patients were genotyped by using polymerase chain reaction-double restriction fragment length polymorphism, as compared to controls. It was higher in OSCC patients and lower in the normal control group. Hence, it is somehow associated with the risk for developing OSCC (Ahmad et al., 2021). Similar results were noted in our study.

## Conclusion

Based on our study, it was concluded that in OSCC patients, oxidative stress markers are increased because of increased oxidants. With a low antioxidant defense system and elevated levels of ROS, cells become more sensitive to the genotoxic effects of reactive oxygen species. Reactive oxygen species results in DNA damage which leads to carcinogenesis. Similarly inflammatory markers were also found to be elevated in OSCC patients.

**Limitation:** Sample size was small. We need large sample size to justify the role of oxidative and stress markers as a potential diagnostic and prognostic tools.

**Conflict of interest:** Authors declared no conflict of interest

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