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Original Article

The diagnostic and prognostic utility of insulin growth factor of squamous cell carcinoma in oral cavity

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Abstract

Objective: The present study was conducted to find the utility of insulin growth factors (IGFs) as diagnostic and prognostic biochemical parameters in patients suffering from squamous cell carcinoma of oral cavity. **Materials and Methods:** A total of 360 male and female patients diagnosed with precancerous conditions (PCC) and oral squamous cell carcinoma (OSCC) of Stage I to IV were selected for the present study. Patients were interviewed using a structured questionnaire to ascertain their demographic and medical history. After completing the history and physical examination, patients were subjected to routine blood investigations along with determining insulin growth factor (IGF-1, IGFBP-3) levels. The data obtained were then subjected to statistical analysis using SPSS 20.0 version. **Results:** The mean values of IGF-1, insulin-like growth factor-binding protein-3 (IGFBP-3), and ratio of IGF-1 and IGFBP-3 were obtained. The intergroup comparison was done between PCC and all the stages of OSCC for all the IGFs. The result obtained was found to be statistically significant ($P < 0.05$). **Conclusion:** The present study concluded that a positive correlation was observed for various insulin growth factors (IGF-1, IGFBP-3; and ratio of IGF-1 and IGFBP-3) between OSCC and PCC such as erythroplakia and oral submucous fibrosis. Thus, the study highlighted the use of IGFs as diagnostic and prognostic parameters in patients suffering from cancerous conditions.

Keywords: *Insulin growth factor, Oral squamous cell carcinoma, Precancerous conditions, Tumo–node–metastasis staging*

Introduction

Oral cancer is the sixth most common cancer worldwide, with a report of 75,000–80,000 new cases in India annually. Nearly 94% of all the oral cancer cases are of oral squamous cell carcinomas (OSCCs) [1], which are mostly attributed to various exogenous factors such as tobacco smoking and heavy alcohol consumption [2]. Other factors include genetics, human papilloma virus infection, and inflammation [3,4]. Intraoral and oropharyngeal tumors are more common in men, with male:female ratio being over 2:1. However, the disparity in the male:female ratio has become less pronounced over the past half century, probably because women have been equally exposing themselves to known oral carcinogens such as tobacco and alcohol [5]. OSCCs have a propensity to early and extensive lymph node metastases that is probably because of delay in early detection of OSCC. Despite advancements in surgical procedures, radiation therapy, and chemotherapy, the five-year survival rate for oral cancer has not improved significantly over the past several decades [6]. The 5-year survival rate of early and late-stage OC is found to be 82% and 20%, respectively [7].

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More than 90%–95% of oral cancers are SCC or one of its variants. SCC typically presents as a persistent mass, nodule, or indurate ulcer. The three most common sites of involvement are tongue, lip, and floor of the mouth. They can develop from precancerous lesions, such as leukoplakia and erythroplakia, or apparently normal epithelium. Normal cells transform into preneoplastic cells and then to cancer after a series of clinical and histopathological stages involving genetic and molecular changes. These stages are clinically represented by manifestations on oral mucosa, such as leukoplakia, erythroplakia, or leukoerythroplakia, and they all represent a predictive factor of malignant transformation [8]. Another premalignant form such as oral submucous fibrosis (OSMF) is a condition characterized by a fibrous aspect, a significant morbidity with pain and reduced mouth opening, which

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may affect any site of the oral cavity [9]. Most OSCCs develop within the fields of precancerized epithelium which contain keratinocytes at different stages of transformation. The persistence of such precancerized fields on the areas, where there has previously been OSCC, is the reason for the high-rate of occurrence of new tumors [10].

The degree of differentiation of tumor may vary from one part to another. Tumor stages are classified according to tumo–node–metastasis (TNM) classification. However, it has been found that the histological grading of tumors poorly correlates with patient outcome and thus it has a limited value for prognostication. Tumor size and nodal status are the most significant prognostic factors. At the time of diagnosis, the majority of patients with squamous cell carcinoma present with advanced stage of disease (Stage III-IV), and approximately one-third of them shows lymph node metastasis. Increased levels of insulin-like growth factor-1 (IGF-1) and decreased levels of insulin-like growth factor-binding protein-3 (IGFBP-3) or an increase in the ratio of IGF-1 to IGFBP-3 has been reported to be related to hyperproliferation of tumor cells, development, and progression of several common cancers including breast, prostate, lung, colon, and esophagus cancers [11].

Therefore, the present study was conducted to find the utility of various diagnostic and prognostic biomarkers such as IGF-1 and IGFBP-3 and their association with squamous cell carcinoma of oral cavity.

Materials and methods

The study was conducted in SMS Medical College and Attached Hospital, Jaipur, Rajasthan. The study was a descriptive observational study conducted from the time period from May 2018 to April 2020. Ethical approval for this study (Ethical Committee No. IRB/406/MC/EC/2019) was provided by the Ethical Committee IRB of SMS Medical College and Attached Hospital, Jaipur, on 22 July 2019. Written informed consent was obtained from all patients prior to their enrollment in this study.

The sample size for the present study (n = 338) was calculated at 5% level of significance with an allowable error of 15%. After adding the nonresponse error of 10%, an additional 32 patients were added, making it to 360 patients in total. The patients diagnosed with precancerous conditions (PCC) and OSCC from stage I to IV were selected based on the inclusion and exclusion criteria. The inclusion criteria included both male and females, diagnosed with OSCC and PCC such as erythroplakia and OSMF based on TNM staging [12]. The exclusion criteria included carcinoma patients who have received either chemo or radiotherapy or undergone surgery; patients with severe cardiovascular, cerebrovascular, hepatic, or renal diseases; and patients suffering hypertension, diabetes, endocrinal diseases, tuberculosis, and polycystic ovarian syndrome.

After obtaining informed consent from each patient, they were then interviewed using a structured questionnaire to ascertain demographic characteristics, personal, family, drug, and medical history. A thorough physical examination was done, followed by complete blood investigations. After an overnight fasting, 5 mL of venous blood sample was drawn from antecubital vein using aseptic technique and 1 ml of blood was placed in vials with EDTA. Routine blood investigations were performed, i.e., hemoglobin, renal function tests, liver function tests, random blood sugar, and lipid profile using commercially available kits. Special investigations were also performed that included the evaluation of IGF-1 and IGFBP-3.

The values of routine and special laboratory investigations were recorded. The data obtained were then subjected to statistical analysis using the IBM SPSS Statistics 20.0 Data Editor software (Microsoft Corporation Inc., Chicago, IL, USA).

Results

The values of various laboratory investigations were derived and the data obtained were subjected to statistical analysis for all the four stages of OSCC and PCC such as erythroplakia and oral submucous fibrosis.

The mean values of IGF-1 were recorded for all the patients. It was found to be maximum in erythroplakia and stage I of OSCC and minimum for stage IV of OSCC and OSMF. One-way ANOVA statistical analysis was done for intergroup comparison between all stages of OSSC and PCC for IGF-1. It was found that the level of significance was highly significant (P = 1.1102e-16). *Post hoc* Tukey's test revealed that all individual intergroup comparisons were also found to be significant ($P < 0.05$), except comparison between OSMF and erythroplakia ($P = 0.899$) [Table 1].

The mean value of IGFBP-3 was found to be maximum in erythroplakia and stage I, whereas it was minimum for stage III of OSCC and OSMF. One-way ANOVA statistical analysis revealed a statistically significant (P = 1.1001e-16) correlation. *Post hoc* Tukey's test was done for intergroup comparisons and it was found that all intergroup comparisons were significant ($P < 0.05$), except comparison between stage I versus II, II versus IV, III versus IV, and OSMF versus erythroplakia [Table 2].

The mean value of IGF-1 and IGFBP-3 ratio was determined and found to be maximum in Stage III (64.72 ± 35.44) and minimum in Stage IV of OSCC (42.72 ± 23.52). One-way ANOVA test showed a statistically significant (P = 0.0124) correlation. *Post hoc* Tukey's test found that all intergroup comparisons were significant, except comparison between stage II versus III, III versus IV, and III versus erythroplakia [Table 3].

Discussion

Oral cancer most commonly occurs in middle-aged and older individuals, although a disturbing number of these malignancies is also being documented in younger adults in recent years [13]. According to the surveillance by epidemiology and end results program, the overall 5-year relative survival rate is 62.2% [14].

Table 1: Mean values and intergroup comparison between all stages of OSCC and precancerous conditions for insulin growth factor-1

IGF-1	Stage I	Stage II	Stage III	Stage IV	OSMF	Erythroplakia
Mean	101.5500	83.8500	71.4500	60.3000	131.1000	132.4500
SD	9.81124	7.52732	7.97678	10.35222	5.81197	6.09119

One-way ANOVA for intergroup comparison between all stages of OSCC and PCC for IGF-1

Source	SS	Degrees of freedom (vv)	MS	*F* statistic	*P*
Treatment	92,250.9667	5	18,450.1933	280.5402	1.1102e-16*
Error	7,497.4000	114	65.7667		
Total	99,748.3667	119			

*P<0.05 is significant. SS: Sum of squares, MS: Mean square, SD: Standard deviation, PCC: Precancerous conditions, IGF: Insulin growth factor, OSMF: Oral submucous fibrosis, OSCC: Oral squamous cell carcinoma

Table 2: Mean values and intergroup comparison between all stages of OSCC and precancerous conditions for insulin-like growth factor-binding protein-3

IGFBP-3	Stage I	Stage II	Stage III	Stage IV	OSMF	Erythroplakia
Mean	2.3150	1.9700	1.3750	1.70	2.905	3.055
SD	0.827	0.448	0.599	0.667	0.395	0.380

One-way ANOVA for intergroup comparison between all stages of OSCC and PCC for IGFBP-3

Source	SS	Degrees of freedom (vv)	MS	*F* statistic	*P*
Treatment	44.4480	5	8.8896	26.7646	1.1102e-16*
Error	37.8640	114	0.3321		
Total	82.3120	119			

*P<0.05 is significant. SS: Sum of squares, MS: Mean square, SD: Standard deviation, PCC: Precancerous conditions, IGF: Insulin growth factor, OSMF: Oral submucous fibrosis, IGFBP: Insulin-like growth factor-binding protein, OSCC: Oral squamous cell carcinoma

Table 3: Mean values and intergroup comparison between all stages of OSCC and precancerous conditions for ratio of insulin growth factor -1 and insulin-like growth factor-binding protein-3

Ratio of IGF-1 and IGFBP-3	Stage I	Stage II	Stage III	Stage IV	OSMF	Erythroplakia
Mean	51.47	45.03	64.72	42.72	45.99	44.001
SD	24.73	13.200	35.44	23.52	7.17	5.86

One-way ANOVA for intergroup comparison between all stages of OSCC and precancerous conditions for ratio of IGF-1 and IGFBP-3

Source	SS	Degrees of freedom	MS	*F* statistic	*P*
Treatment	6847.5271	5	1369.5054	3.0644	0.0124*
Error	50,947.3261	114	446.9064		
Total	57,794.8532	119			

*P<0.05 is significant. SS: Sum of squares, MS: Mean square, SD: Standard deviation, PCC: Precancerous conditions, IGF: Insulin growth factor, OSMF: Oral submucous fibrosis, IGFBP: Insulin-like growth factor-binding protein, OSCC: Oral squamous cell carcinoma

Staging of oral cancer is important for establishing proper treatment and determining prognosis. Tumors are staged using the TNM system, where T represents size of the primary tumor, N indicates status of the regional lymph nodes, and M indicates the presence or absence of distant metastases. Various authors have advocated the development of databases summarizing the genetic events associated with OSCCs [12-14].

Invasive OSCC is often preceded by the presence of clinically identifiable premalignant changes of the oral mucosa. These lesions often present as either white or red patches, known as leukoplakia and erythroplakia [15]. A study by Neville [16] reviewed the clinical features of oral cancer and premalignant oral lesions, with an emphasis on early detection of cancers. They revealed that PCCs are associated with appearance of oral cancers. Thus, in the present study, we compared the most common premalignant lesions, OSMF, and erythroplakia with all the four stages of OSCC.

Normal cells transform into preneoplastic and then to neoplastic cells after a series genetic and molecular changes, representing a predictive factor of malignant transformation [17]. The advances in molecular analysis of cell alterations, causing malignant transformation, have revealed the mechanisms leading to the occurrence and progression of malignancies. Cell alterations can be detected in various body fluids such as blood, serum, or saliva either by immunochemistry or biochemical methods. The products synthesized by tumor cells or by the body in such abnormal situation are known as "tumor markers." These tumor markers can be used for early screening and detection of cancer [18].

Recent studies have implicated the role of IGFs, specifically IGF-1, and its IGFBP-3 in cancer development. IGF-1 is essential in regulating cell proliferation and differentiation. The functions of IGF-1 are partly regulated by IGFBP-3, as more than 90% of circulating IGF-1 is complexed with IGFBP-3. IGFBP-3 normally inhibits the mitogenic action of IGF-1 by preventing it from binding to its receptor. Recent prospective and retrospective studies have demonstrated that elevated serum IGF-1 levels are

associated with increased risk of a variety of epithelial cancers. A study by Baxter RC[19] revealed that elevated serum levels of IGFBP-3 are associated with either increased or decreased cancer risk, whereas other studies do not detect any association between serum levels of IGFBP-3 and cancer risk. This inconsistency might be because of the dual role of IGFBP-3 [19]. Hence, we conducted a study to shed light on the IGF-1 and IGFBP-3 expression in OSCC patients and potential clinical consequences and interactions.

In the present study, the levels of IGF factors (IGF-1 and IGFBP-3) were found to be maximum in stages with better prognosis, i.e., OSCC Stage I and PCC like erythroplakia. Whereas, the levels of IGF factors decrease in conditions having worst prognosis like OSMF, and OSCC stages like Stage III and IV. The mean values of IGF-1 were found to be maximum in erythroplakia and minimum for stage IV of OSCC. The result of our study was in contrast to a study by Chong *et al*. [20], who found that high serum IGF-1 levels were associated with increased cancer mortality. The results of our study were similar as observed by Wu *et al*. [21] in 2004 who found the potential role of elevated serum levels of IGF-1 and deregulated (high or low) IGFBP-3 levels as predictors of the risk to develop primary tumors in the patients with head and neck SCC. Therefore, the association between low serum IGF-1 and increased cancer mortality could be confounded by the fact that patients with early undiagnosed tumors have a poor general health, resulting in low serum IGF-1 concentrations. It is less likely that the association between low serum IGF-1 and increased mortality from malignant diseases was confounded by patients with low serum IGF-1 values due to undiagnosed cancers. Future studies should be conducted to determine whether different types of cancer underlie the associations between low and high IGF-1, respectively, and cancer death.

IGFBP-3 is the main carrier of somatomedin C (also called IGF-1) in the body. The mean values of IGFBP-3 were found to be maximum in erythroplakia (3.055 ± 0.380), whereas minimum for stage III of OSCC. Similar results were found in various other studies [22,23]. Evidence from various studies has indicated that IGFBP-3 levels vary in the incidence of various cancers, including colon cancer, breast cancer, and malignant melanoma. Similar results to our study were obtained by Liu *et al*. [22] and Kaklamani *et al*. [23] who revealed that immune histochemistry assays indicated that brown signal representing IGFBP3 protein was markedly stronger in the cells of SCC tissue than that in the cells of normal skin tissue. The mean value of IGF-1 and IGFBP-3 ratio was found to be maximum in Stage III of OSCC and minimum in stage IV.

Thus, the present study revealed an association of insulin growth factors (IGFs) with precancerous lesions and oral cancers. IGFs are proved to be an important investigation parameter and it should be considered as a routine investigation procedure in cancer patients. The early diagnosis of precancerous or cancerous conditions can be made based of change in levels of IGF. Hence, this is helpful in early diagnosis and management of cancer patients.

Limitations of the study

The results of the present study are based on findings obtained from a smaller sample size. Thus, there is the need to obtain the data from investigations to be done on larger population. Further research should be conducted evaluating the association of age and gender with these special investigations. More elaborated studies are required to study the role of other biomarkers in OSCC.

Hence, health-care workers must be encouraged to perform oral cancer examinations as part of their patient's health-care regime, and they should be knowledgeable about early signs of oral carcinoma. Thus, understanding of oral cancers and their associations with various biomarkers can be furthered carried out by retrograde analysis of existing databases and prospective studies in future.

Conclusion

The programs for cancer control are based on the idea of early detection, so that better outcomes in terms of increased survival and reduced mortality can be achieved. The present study concluded that a positive correlation was observed for various (IGF-1, IGFBP-3; and ratio of IGF-1 and IGFBP-3) between OSCC and PCC such as erythroplakia and oral submucous fibrosis. Variations in the values of IGF-1 and IGFBP-3 in carcinogenic conditions revealed that we can use IGF as diagnostic and prognostic parameter. During routine examination of the patient, if IGF levels vary, it can indicate the existence of precancerous or cancerous conditions. And, if levels of IGF are found to be elevated, this can indicate a precancerous or cancerous condition with bad prognosis. Thus, the study indicates the use of IGFs as diagnostic and prognostic parameters in patients suffering from precancerous or cancerous conditions.

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Conflicts of interest

There are no conflicts of interest.

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