

Evaluation of Glucose Transporter 1 and Hypoxia Inducible Factor 1 α in Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma: An Immunohistochemical Cross- Sectional Study

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Abstract

Background and Purpose

Oral squamous cell carcinoma (OSCC) is frequently preceded by oral potentially malignant disorders exhibiting oral epithelial dysplasia (OED). Hypoxia and altered glucose metabolism are important features of tumor progression. Glucose transporter 1 (GLUT1) and hypoxia inducible factor 1 alpha (HIF-1 α) are associated with cellular adaptation to hypoxia and increased glycolytic activity. Hence purpose of this study is to evaluate the expression of GLUT1 and HIF-1 α in oral epithelial dysplasia and oral squamous cell carcinoma.

Materials and Methods

An in-vitro immunohistochemical cross-sectional study was carried out using paraffin embedded tissue sections diagnosed as normal oral mucosa, oral epithelial dysplasia and OSCC. Total of 64 samples were included and divided into Group I: normal oral mucosa (n = 10), Group II: oral epithelial dysplasia (n = 27), and Group III: OSCC (n = 27). Immunohistochemical evaluation of GLUT1 and HIF-1 α expression was performed quantitatively and qualitatively using staining intensity and distribution. Statistical analysis was performed using Kruskal Wallis test and Mann Whitney U test with $p < 0.05$ considered statistically significant.

Results

Both GLUT1 and HIF-1 α expression showed progressive increase from normal oral mucosa to OED and OSCC. Increased expression was noted with increasing histological grades of dysplasia and carcinoma. Significant intergroup differences were observed, suggesting a positive prognostic association between hypoxia-induced metabolic alteration and tumor progression.

Conclusion

The present study demonstrated that GLUT1 and HIF-1 α play a consistent role in tumor microenvironment alteration in both oral premalignant and malignant lesions. Their increased expression is associated with increased disease severity and malignant transformation. Co-expression of these proteins may serve as prognostic biomarkers in OED and OSCC.

Introduction

Oral cancer is a major global health burden and the sixth most common cancer worldwide,¹ with India accounting for nearly one-third of the global oral cancer burden due to the widespread use of tobacco and areca nut products.² Oral squamous cell carcinoma (OSCC) constitutes approximately 90% of all oral

malignancies.^{3,4} Despite advances in diagnosis and treatment, the five-year survival rate remains around 50% because of delayed diagnosis and aggressive tumor behavior.^{5,6} OSCC develops through a multistep process involving genetic, molecular and microenvironmental alterations. Oral potentially malignant disorders (OPMDs) often precede OSCC and exhibit varying grades of oral epithelial dysplasia (OED), which reflects the risk of malignant transformation.^{7, 8} The severity of dysplasia correlates with the likelihood of progression to invasive carcinoma, highlighting the need for reliable biomarkers for early detection.^{9,10}

Tumor progression is influenced by the tumor microenvironment, particularly hypoxia resulting from rapid cellular proliferation. Hypoxia induces metabolic adaptation, including increased glucose uptake and glycolysis despite adequate oxygen supply, known as the "Warburg effect."¹¹ Hypoxia-inducible factor-1 alpha (HIF-1α) is a major regulator of cellular adaptation to hypoxia. It activates genes involved in angiogenesis, glycolysis, and cell survival, while also regulating Glucose Transporter 1 (GLUT1) expression to promote glucose uptake and glycolytic metabolism in malignant cells.^{12,13} GLUT is a key glucose transporter and is then overexpressed in malignancies due to enhanced glycolysis, tumor aggressiveness, metastasis, and poor prognosis.^{14,15}

Although GLUT1 and HIF-1α have been studied individually in oral lesions, comparative studies evaluating their expression in both OED and OSCC are limited. Therefore, the present study was conducted to evaluate and compare expression of both these markers in various grades of OED and OSCC.

Materials and Methods

The present study was an in-vitro tissue-based immunohistochemical cross-sectional study conducted in the Department of Oral and Maxillofacial Pathology and Oral Microbiology after obtaining approval from the Institutional Ethical Committee. Paraffin embedded tissue blocks diagnosed histologically as normal oral mucosa, oral epithelial dysplasia and oral squamous cell carcinoma were retrieved from the archives of the department. Hematoxylin and eosin stained sections were re-evaluated to confirm the diagnosis before performing IHC. Sample size estimation was carried out using expected proportions derived from previous literature with a study power of 80%, alpha error of 5% and beta error of 20%. A total of 64 tissue samples were included in the study and categorized into three groups as Group I: Normal oral mucosa (n = 10), Group II: Oral epithelial dysplasia (n = 27) and Group III: Oral squamous cell carcinoma (n = 27). OED cases were further categorized into mild, moderate and severe dysplasia while OSCC cases were graded as well differentiated, moderately differentiated and poorly differentiated SCC. Histopathologically confirmed untreated cases of oral epithelial dysplasia and primary OSCC were included in this study. Age and site matched normal oral mucosa cases were considered for Group I. Patients with systemic illness or metabolic disorders, patients undergoing chemotherapy or radiotherapy, presence of second primary and histologically inconclusive cases were excluded from this study. Immunohistochemical staining was performed using monoclonal antibodies against GLUT1 and HIF-1α according to standard laboratory protocol.

For GLUT1, membranous and cytoplasmic staining pattern and for HIF-1 α , nuclear and cytoplasmic staining within epithelial cells and tumor islands were considered positive. Five representative high-power fields were selected for quantitative analysis.

IHC expression was evaluated using both quantitative and qualitative parameters according to the parent article. Quantitative assessment included counting the percentage of positive cells, while qualitative assessment was based on staining intensity and distribution of staining within the epithelium or tumor islands. The Immunoreactive Score (SI) was calculated of each specimen as - The percentage of positive cells (A) was rated as follows - 1: 0–25% of cells positive; 2: 26%–50% of cells positive; 3: 51–75% of cells positive; and 4: >75% of cells positive. The intensity of expression (B) was scored as - Negative (0) Mild (1) Moderate (2) Intense (3). Mean percentage of immunopositive cells (A) x Mean intensity score (B) = IRS This IRS was classified as: 1–3.0 = Low; 3.1–6 = Moderate; 6.1–12 = High. The distribution pattern was assessed according to the epithelial layers involved in dysplasia and the extent of staining in tumor islands in OSCC. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software. Kruskal Wallis test and Mann Whitney U test were used for intergroup comparisons. A p-value less than 0.05 was considered statistically significant.

Results

The present study evaluated the immunohistochemical expression of GLUT1 and HIF-1 α in normal oral mucosa, oral epithelial dysplasia and oral squamous cell carcinoma.

In normal oral mucosa, mild expression of GLUT1 was observed predominantly in the basal cell layer of the epithelium. HIF-1 α expression in normal mucosa was very minimal and restricted mainly to basal epithelial cells.

In oral epithelial dysplasia, progressive increase in expression of both GLUT1 and HIF-1 α was observed with increasing grades of dysplasia. Mild dysplasia demonstrated positivity primarily within basal and parabasal layers, whereas moderate and severe dysplasia showed extension of staining into suprabasal and superficial epithelial layers. GLUT1 expression in OED was predominantly membranous with focal cytoplasmic positivity. Increased staining intensity was noted in severe dysplasia compared to mild and moderate dysplasia. Similarly, HIF-1 α showed increased nuclear and cytoplasmic positivity with increasing severity of dysplasia and extension to superficial layers in severe dysplasia.

In OSCC, diffuse expression of GLUT1 and HIF-1 α was observed within tumor islands. GLUT1 positivity was more pronounced in peripheral tumor cells and areas surrounding keratin pearls. HIF-1 α expression was intense in regions adjacent to hypoxic and necrotic areas. Well differentiated OSCC demonstrated staining predominantly in peripheral tumor cells, whereas moderately and poorly differentiated OSCC exhibited diffuse and intense staining throughout tumor islands. Increased expression of both markers correlated with histological grade and tumor aggressiveness. Figure 1 Shows comparison of GLUT1 and HIF-1 α expression in normal oral mucosa, Fig. 2 shows comparison these markers in OED and Fig. 3 shows comparison of their expression in OSCC.

For GLUT1, the IRS was low in all 10 samples of Group I. In Group II, there were 13 (48.15%) low, 4 (14.81%) moderate and high 10 (37.07%) samples out of 27 samples. While in Group III, the IRS was low in 3 (11.11%), moderate in 9 (33.33%) and high in 15 (55.56%) samples out of 27 samples. For HIF-1 α the IRS was low in all 10 samples in Group I. In Group II, there were 12 (44.44%) low, 8 (29.63%) moderate and 7 (25.93%) high samples out of 27 samples. While in Group III, the IRS was low in 6 (22.22%), moderate in 9 (33.33%) and high in 12 (44.44%) samples out of 27 samples. Statistical analysis revealed significant intergroup differences in GLUT1 and HIF-1 α expression among normal oral mucosa, OED and OSCC groups. Significant differences were also observed among varying grades of dysplasia and carcinoma. Table 1 shows Inter group Pair wise comparison of Group I and II. Table 2 shows Inter group Pair wise comparison of Group I and III. Table 3 shows Inter group Pair wise comparison of Group II and III. Table 4 shows Inter group comparison of A X B for different grades of OED and OSCC. The results indicated that increased hypoxia-related molecular activity and enhanced glucose metabolism are associated with progression from dysplasia to invasive carcinoma.

Discussion

OSCC develops through progressive genetic, molecular, and metabolic alterations. A key metabolic adaptation is the Warburg effect, characterized by increased glucose uptake and glycolysis even under aerobic conditions.¹¹ GLUT1, a facilitative glucose transporter, is overexpressed in rapidly proliferating cells and reflects increased metabolic demand. In the present study, GLUT1 and HIF-1 α expression progressively increased from normal mucosa to oral OED and OSCC, supporting its role in oral carcinogenesis.

GLUT1 expression is usually focal and confined to the basal and occasionally parabasal cell layer. Staining is predominantly membranous, with little or no cytoplasmic staining. In a study done by Preethi Patlolla et al, mean percentage of GLUT-1-positive cells in normal oral mucosa was 31.35% and largely limited to basal cells.¹⁶ In our study, GLUT1 expression in normal mucosa was limited to weak membranous staining in the basal and suprabasal layers, with strong positivity in vascular endothelial cells, consistent with previous studies done by Angadi V. et al¹⁷, Reisser C. et al.¹⁸ Expression extends progressively upward in OED. This upward extension parallels increasing dysplasia severity.¹⁶ In our study, GLUT1 expression increased with dysplasia severity, extending from the basal layer in mild dysplasia to the superficial layers in moderate and severe dysplasia, likely reflecting enhanced glucose uptake during dysplastic progression. These findings were consistent with studies done by Ayala FR et al¹⁹, and Azad N et al²⁰. In OSCC, expression is seen normal mucosa mostly in peripheral cells of tumor islands and diffuse staining showing membraneous with or without cytoplasmic staining is seen in moderately and poorly differentiated tumors.²¹ In our Study also, GLUT1 expression increased with histological grades of OSCC. It was predominantly localized to the peripheral cells of tumor islands, whereas keratin pearls lacked expression, demonstrating the inverse relationship between glycogen accumulation and GLUT1 immunoreactivity.^{19,20,22,23} These findings were consistent with the previous report of study done by Rudlowski C. et al²² and Mendez LE et al²³

Under normal oxygen conditions, HIF-1 α protein is rapidly degraded by the proteasome. Therefore, normal mucosa generally shows absent or weak immunohistochemical staining, although a few basal epithelial cells may occasionally exhibit weak positivity because of physiological metabolic activity.²⁴ Weak expression may occur because HIF-1 α is involved in normal physiological processes such as cellular adaptation to transient hypoxia, angiogenesis, wound healing, basal epithelial metabolism.²⁵ Also, in our study, HIF-1 α expression was negligible in normal mucosa but increased significantly in OED and OSCC, showing diffuse cytoplasmic staining that correlated with histological grade. In OED, expression extended from the basal to superficial epithelial layers, while in OSCC, diffuse staining was observed throughout tumor islands, consistent with previous studies by Lin PY et al, Patel NR et al.^{26,27} HIF-1 α is stabilized under hypoxic conditions and regulates genes involved in angiogenesis, glucose metabolism, cell proliferation, pH regulation, and migration, thereby promoting GLUT1 leading to oral carcinogenesis.^{28–31} There is no specific range mentioned in the literature for percent increase in positive cells showing HIF-1 α and GLUT 1 expression when compared to normal cells. According to different studies conducted, OED demonstrates approximately 20–40% higher GLUT1 positive cells compared to normal oral mucosa with staining extending from the basal layer to suprabasal epithelial layers^{16,17,32} and compared to OED, OSCC demonstrates approximately 30–40% higher GLUT1-positive cells i.e. 50–90% more cells compared to normal mucosa, showing diffuse expression throughout tumour islands and particularly at the invasive front^{15,21,32} In case of HIF-1 α , OED demonstrates approximately 15–35% higher HIF-1 α -positive cells compared with normal oral mucosa, indicating activation of hypoxia-related pathways during dysplastic progression.^{26,27} Compared with OED, OSCC demonstrates approximately 20–40% higher HIF-1 α -positive cells i.e. 40–80% more positive cells compared to Normal mucosa with highest expression in poorly differentiated tumours and at the invasive front.^{24,25,33}

HIF-1 α lacks sufficient specificity and is expressed in many other malignancies. Therefore, it is not recommended as a routine standalone diagnostic marker for OED and OSCC.^{24,25} Also, GLUT-1 is not sufficiently specific or validated to serve as a standalone diagnostic marker. Hence, can be used as an adjunctive diagnostic marker, especially when histologic grading is difficult.³² Strong HIF-1 α and GLUT 1 expression has been associated with larger tumor size, advanced TNM stage, lymph node metastasis, increased risk of recurrence, shorter disease-free survival and poor overall survival^{25,34} Strong HIF-1 α expression increased the risk of tumor-related death by approximately 3.5 times, independent of TNM stage and histological grade.³³ A meta-analysis of 13 studies involving 1,301 patients found that high GLUT-1 expression was significantly associated with advanced stage, larger tumors, lymph node metastasis, and poorer overall survival, supporting its value as a prognostic biomarker.³⁵ Hence, such patients may require closer follow-up or may have a higher recurrence risk.^{21,35,36} Standard treatment decisions for OSCC are still based on TNM stage, Depth of invasion, Histological grade, Margins, Perineural invasion, Lymphovascular invasion, Nodal metastasis etc. Hence, HIF-1 α and GLUT1 are not included in current standard treatment guidelines for determining surgery, neck dissection, radiotherapy, or chemotherapy. Several HIF pathway inhibitors are under preclinical and early clinical investigation.

HIF-1 α is considered a promising therapeutic target but remains investigational.³⁶ Similarly, GLUT-1 is also being investigated as a potential therapeutic target, but this remains investigational.^{21,35}

The findings in this study, although significant, are preliminary because of low sample size. Also, statistical analysis may show variation because of less samples of severe dysplasia and poorly differentiated squamous cell carcinoma cases as compared to other grades of OED and OSCC. More such studies with larger sample size and equal number of subgroups of OED and OSCC should be considered to get more reliable results.

Conclusion

Co-expression of GLUT1 and HIF-1 α observed in the present study supports the close association between tumor hypoxia and glucose metabolism. IHC evaluation of GLUT1 and HIF-1 α may aid in identifying transformation from normal mucosa to OED followed OSCC. These biomarkers may also assist in predicting tumor behavior and planning targeted therapeutic strategies. Further studies with larger sample sizes and long-term follow-up are recommended to establish their prognostic utility and therapeutic implications.

Declarations

Conflicting Interest (If present, give more details): Nil

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Ethical Approval: For this type of study formal consent is not required.

Consent to Participate: For this type of study informed consent is not required.

Consent for Publication: For this type of study consent for publication is not required.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to institutional confidentiality and ethical restrictions.

Code Availability: No any software application or custom code has been used

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Tables

Table No. 1: Inter group Pair wise comparison of Group I and II using Mann-Whitney U test

		Mann-Whitney U value		p value of Mann-Whitney U test	
				Z value	
Avg AxB HIF 1α	45.000			-3.094	0.002**
Avg AxB GLUT 1	33.000			-3.501	0.000**

** - Highly significant

Table No. 2: Inter group Pair wise comparison of Group I and III using Mann-Whitney U test

	Mann-Whitney U value		p value of Mann-Whitney U test
		Z value	
Avg AxB HIF 1 α	0.000	-4.622	0.000**
Avg AxB GLUT 1	0.000	-4.622	0.000**

** - Highly significant

Table No.3: Inter group Pair wise comparison of Group II and III using Mann-Whitney U test

	Mann-Whitney U value		p value of Mann-Whitney U test
		Z value	
Avg AxB HIF 1 α	244.000	-2.087	0.037*
Avg AxB GLUT 1	253.500	-1.923	0.054#

* - Significant, # - Not significant

Table No. 4: Inter group comparison of A X B for different grades of OED and OSCC

Group	N	Mean	Std. Deviation	Median	Mean rank	Chi square value	p value of Kruskal- Wallis Test
Avg AxB 1	10	.30000	.216025		10.00	42.029	.000**
HIF 1α							
2	15	1.46667	1.988060		17.87		
3	7	6.42857	2.356349		44.79		
4	5	8.72000	1.360882		53.10		
5	13	4.63077	2.936944		37.08		
6	11	6.76364	3.246929		45.36		
7	3	8.33333	4.291076		50.67		
Avg AxB 1	10	.86000	.389301		8.80	47.117	.000**
GLUT 1							
2	15	2.01333	1.629139		17.87		
3	7	10.34286	1.934647		55.07		
4	5	7.32000	3.245304		43.00		
5	13	5.76923	2.907285		37.12		
6	11	6.98182	2.880909		42.36		
7	3	11.46667	.611010		58.33		

Group 1 – Normal, Group 2 – Mild dysplasia, Group 3 – Moderate dysplasia, Group 4 – Severe dysplasia, Group 5 – Well differentiated SCC, Group 6 – Moderately differentiated SCC, Group 7 – Poorly differentiated SCC.

** - Highly significant

Figures

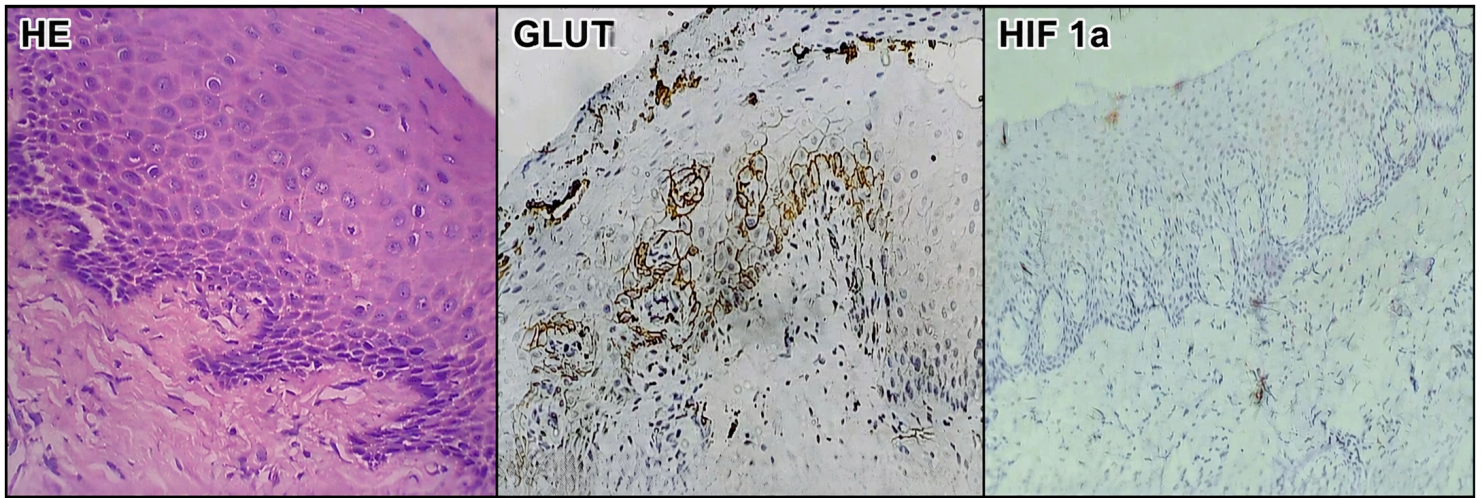


Figure 1

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Figure 2

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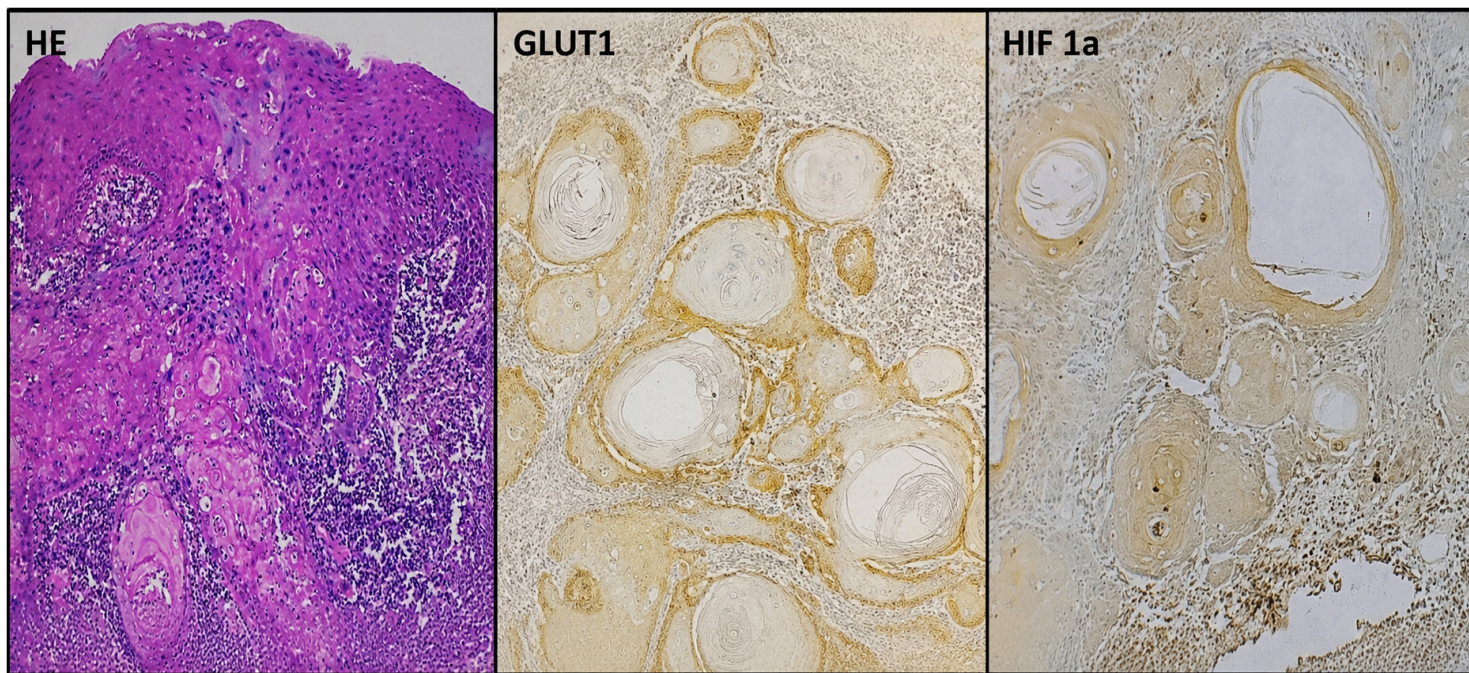


Figure 3

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