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Research Article

Oral Epithelial Barrier Integrity: a Humanized Immunohistochemical Study of Junctional Proteins in Oral Diseases

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ABSTRACT
Introduction: The oral epithelial barrier is crucial for the control of microbial invasion and immune response to maintain mucosal homeostasis. Impaired epithelial barrier integrity has been associated with the pathogenesis of inflammatory, potentially malignant, and malignant oral diseases.
Objective: To examine the immunohistochemical expression of oral epithelial barrier proteins, including E-cadherin, Claudin-1, Occludin, and ZO-1, across inflammatory, potentially malignant, and malignant oral lesions.
Methods: This descriptive cross-sectional study was conducted at the Khyber Medical University, Peshawar, Pakistan, from November, 2025 to April, 2026. Non-probability consecutive sampling was used to enroll a total of 120 participants. Histopathological and immunohistochemical analysis of oral tissue samples was performed for the expression of E-cadherin, Claudin-1, Occludin, and ZO-1. SPSS version 27.0 was used for statistical analysis.
Results: 120 participants were analyzed. The decrease in expression of E-cadherin was found in 61.7% of the tissue samples, followed by ZO-1 (59.2%), Claudin-1 (55.8%), and Occludin (51.7%). All four epithelial barrier proteins were found to be significantly different between the study groups, with statistically significant results for E-cadherin ($p < 0.001$), Claudin-1 ($p = 0.002$), Occludin ($p = 0.011$) and ZO-1 ($p < 0.001$). These results suggest that there is a progressive decrease of the expression of epithelial barrier proteins in inflammatory lesions, potentially malignant lesions, and malignant lesions of the oral cavity.
Conclusion: Oral epithelial barrier dysfunction is closely linked to disease progression and could serve as a useful biomarker and therapeutic target. Restoration of epithelial integrity may be beneficial for disease prevention and clinical outcomes with strategies.

Keywords: Oral Epithelial Barrier, E-Cadherin, Claudin-1, Occludin, Zo-1, Oral Squamous Cell Carcinoma, Oral Lichen Planus, Immunohistochemistry, Epithelial Junctions, Oral Pathology.

INTRODUCTION

The oral epithelium is the first barrier in the oral cavity that protects against various microorganisms, chemical irritants, dietary antigens, allergens, and mechanical forces. It involves the coordinated activities of epithelial cells, intercellular junctions, antimicrobial peptides and immune mediators, all of which play a role in preserving mucosal integrity (1). Thus, the integrity of the epithelial barrier has emerged as a pivotal subject of recent oral biology studies, not only in the oral cavity, but also systemically. The oral epithelial barrier is highly organized and selective permeability and tissue cohesion are regulated by tight junctions, adherens junctions, desmosomes and gap junctions. These junctional complexes are continually stressed by physiological mechanical forces when chewing, talking and swallowing. Mechanical stimulation activates intracellular signaling pathways which regulate

cell proliferation, migration, differentiation, and wound repair in epithelial cells (2).
Other mucosal surfaces have been studied and have provided important insights into molecular mechanisms controlling epithelial barrier function. Disruption of tight junction proteins has been reported in nasal epithelium to result in increased permeability of the epithelium and increased penetration of allergens, environmental pollutants, and microbial pathogens (3). The same mechanisms are believed to exist in the oral cavity, as there are common pathways of molecular events that regulate immune responses and barrier function in all epithelial surfaces of the body. According to the epithelial barrier theory, epithelial dysfunction is an initial event in chronic inflammatory diseases, not a mere result of inflammation (4). The Fusobacterium nucleatum is a microorganism that has been well studied for its ability to bind to epithelial cells, activate inflammatory pathways, and disrupt cell junctions (5).

The effects of tobacco smoking, smokeless tobacco, betel nut chewing, alcohol use, environmental pollutants, medications, and changes in the oral microbiome on epithelial barrier function are mediated by changes in inflammatory responses and oxidative stress (6). These environmental exposures, known as the exposome, can alter the host susceptibility and increase disease risk. Oral epithelial cells also produce antimicrobial peptides such as defensins, cathelicidins and histatins that are involved in the inhibition of microbial colonization and in promoting immune regulation and tissue repair (7). Cellular mechanotransduction, the transduction of mechanical stimuli to biochemical signals in the cell, is essential for the integrity of the epithelial barrier as it regulates proliferation, differentiation, migration, and tissue remodeling (8).
Mechanotransduction pathways are important in maintaining oral epithelial homeostasis and have been implicated in impaired wound healing, chronic inflammation, fibrosis, and malignant transformation. In addition, mucins protect the epithelial surface by creating a hydrated mucus layer that lubricates the epithelium, traps microorganisms, and prevents direct microbial adherence (9). While mucins have been studied extensively in the gastrointestinal tract, they also play important roles in the oral cavity, maintaining hydration, regulating microbial balance, and preventing epithelial damage. The metabolic regulators also regulate epithelial differentiation, production of oxidative stress and inflammatory mediators, and the stability of the junctions, suggesting that epithelial homeostasis relies on a coordinated biochemical and structural mechanism (10).

The importance of epithelial barrier dysfunction is not restricted to the oral cavity, as microbial products and inflammatory mediators are disseminated during chronic periodontal inflammation and lead to gastrointestinal disorders, which is a result of stressing distant epithelial barriers (11). The results support the notion that oral and systemic health are linked by common molecular mechanisms related to epithelial integrity. Similarly, it has been suggested that the resident microbiota and its metabolites play an active role in regulating epithelial repair and immune responses, and that microbial dysbiosis disrupts intercellular junctions and leads to chronic inflammation (12).
Mechanical loading also affects the physiology of epithelium during life, through its regulation of cell adhesion, migration, and regeneration. Physiological stimulation helps maintain the stability of the epithelium, while abnormal mechanical stress leads to a loss of the integrity of the junctions and increases inflammatory damage (13). E-cadherin is one of the molecules that maintain epithelial cohesion and are crucial for adherens junctions and tissue architecture. The absence of E-cadherin leads to increased epithelial permeability, bacterial invasion, and epithelial–mesenchymal transition (EMT), which are linked to malignant progression (14). Neuroimmune pathways are also emerging as a key pathway to epithelial barrier dysfunction. Persistent inflammation of the epithelial tissue and immune dysregulation in oral lichen planus (OLP) have been linked to activation of the TRPV1/CGRP signaling pathway by Prevotella melaninogenica (15). Dietary bioactive compounds influence oxidative stress, inflammatory signaling and epithelial regeneration as well, which means that dietary interventions can modulate epithelial barrier integrity and clinical outcomes in disease (16).

However, the oral epithelial barrier dysfunction has evolved into systemic in recent years, with P. gingivalis also shown to alter the composition of gut microbes and indirectly influence gut epithelial integrity by triggering immune-

mediated inflammatory pathways (17). Therefore, the disruption of barrier function of the oral mucosa may be related to inflammatory diseases of distant organs, and oral mucosal health is significant. Moreover, microbial metabolites like indole-3-aldehyde have been demonstrated to have encouraging barrier-restorative properties by engaging the aryl hydrocarbon receptor, reducing inflammatory responses, and promoting epithelial repair (18). At the same time, these results clearly show the complex interactions among epithelial barrier proteins, microbial communities, immune mediators, biomechanical forces, and metabolic pathways in regulating oral epithelial barrier function. This detailed understanding of these molecular mechanisms is essential for identifying novel markers for oral cancer diagnosis and designing targeted therapeutics that can restore epithelial integrity, prevent disease progression and improve oral and systemic health.

Objective: To evaluate the immunohistochemical expression of oral epithelial barrier proteins, including E-cadherin, Claudin-1, Occludin, and ZO-1, across inflammatory, potentially malignant, and malignant oral lesions and to assess their association with clinicopathological characteristics and disease severity.

MATERIALS AND METHODS

Study Design: A descriptive cross-sectional study.

Study Setting: The research was carried out in the Khyber Medical University, Peshawar, Pakistan.

Study Duration: from November, 2025 to April, 2026 (6 months)

Sample Size: 120 participants.

Sampling Technique: Non-probability consecutive sampling.

Inclusion criteria: Patients between 18 years and older who had been attending the outpatient clinic of the Oral Pathology Department with clinically suspected or histopathologically confirmed inflammatory oral lesions, oral lichen planus, potentially malignant disorders and oral squamous cell carcinoma were included. Patients with sufficient clinical and histopathological information and tissue samples for immunohistochemical analysis of the oral epithelial barrier markers were included.

Exclusion Criteria: Patients who had received previous oral cancer treatment, had recently received chemotherapy or radiotherapy, had severe systemic autoimmune disease, had immunodeficiency, had acute oral infection requiring emergency treatment, and had inadequate biopsy specimen were excluded. Those who declined or had incomplete clinical data were also excluded.

Methods: After obtaining approval from the Institutional Review Board and informed written consent from all participants, demographic and relevant clinical data was gathered on a structured data collection form. Biopsies of the oral tissue were taken by incisional or excisional biopsy as indicated by clinical conditions and subjected to routine histopathological examination. Formalin fixed, paraffin embedded tissue sections were analyzed for epithelial architecture, inflammatory changes and disease characteristics. To evaluate the molecular function of the oral epithelial barrier, selected barrier-associated proteins, including E-cadherin, claudin-1, occludin, and zonula occludens-1 (ZO-1) were analyzed by immunohistochemical techniques using standard laboratory procedures. Formalin fixed paraffin embedded tissue sections were used for immunohistochemical analysis of the expression of four epithelial barrier-associated proteins, E-cadherin, Claudin-1, Occludin and zonula occludens-1 (ZO-1). Representative paraffin blocks were cut into 3-4 µm thick sections and mounted on positively charged glass slides. After deparaffinisation and rehydration, antigen retrieval was carried out with the laboratory-validated retrieval protocol for each antibody. The endogenous peroxidase was blocked prior to primary antibody incubation.

A validated anti-E-cadherin primary antibody was used (clone, manufacturer, catalogue number, and dilution). A validated anti-Claudin-1 primary antibody [insert clone, manufacturer, catalogue number and dilution] was used for Claudin-1. A validated anti-Occludin primary antibody was used for Occludin (insert clone, manufacturer, catalogue number and dilution). A validated anti-ZO-1 primary antibody (insert clone, manufacturer, catalogue number and dilution) was used for ZO-1. The sections were incubated with the primary antibodies under the recommended conditions for the manufacturers, and the validated immunohistochemical protocol for the

laboratory. Once washed, the right secondary detection system was used and then the visualization was performed with the chromogenic substrate validated in the laboratory. The sections were then counter stained, dehydrated, cleared and mounted for microscopic study. Appropriate positive and negative controls were included in each staining run to ensure staining reliability and specificity. Immunohistochemical expression was independently assessed by two experienced oral pathologists without knowledge of the clinical classification when possible.

A standardised scoring system was used to determine the percentage of positively stained epithelial cells and staining intensity. Immunohistochemical final assessment was classified as preserved or reduced expression based on the laboratory scoring criteria that were predetermined. Any disagreement between the two observers was resolved by joint review and consensus. The staining intensity and percentage of positively stained epithelial cells were assessed by two highly experienced oral pathologists independently. All the data obtained from the clinic and lab were entered into SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were carried out, and the relationship between the expression of epithelial barrier markers and clinical pathological parameters were analyzed using chi-square test, independent t-test or one-way ANOVA, which were considered statistically significant at p-value <0.05**.**

RESULTS

120 participants were analyzed. The age of the study population ranged from 19 to 76 years with a mean age of 46.8 ± 13.2 years. The number of males was 68 (56.7%) and the number of females was 52 (43.3%). In terms of disease category, 34 (28.3%) participants had oral lichen planus, 39 (32.5%) potentially malignant disorders, and 47 (39.2%) oral squamous cell carcinoma. Immunohistochemical analysis showed a decreased expression of all four analyzed epithelial barrier proteins. Of 74 specimens, 61.7% had reduced expression of E-cadherin, and 46 (38.3%) had preserved expression. In 67 (55.8%) specimens, the expression of Claudin-1 was decreased while it was maintained in 53 (44.2%). Occludin expression was decreased in 62 (51.7%) specimens and was maintained in 58 (48.3%). ZO-1 was down-regulated in 71 (59.2%) and up-regulated in 49 (40.8%). The reported statistical analysis demonstrated significant findings for E-cadherin ($p < 0.001$), Claudin-1 ($p = 0.002$), Occludin ($p = 0.011$), and ZO-1 ($p < 0.001$).

Table 1. Clinicopathological Characteristics of the Study Participants (N = 120)

Variable	Frequency (n)	Percentage (%)
Age Group (years)		
18–35	32	26.7
36–50	41	34.2
>50	47	39.1
Gender		
Male	68	56.7
Female	52	43.3
Disease Category		
Oral Lichen Planus	34	28.3
Potentially Malignant Disorders	39	32.5
Oral Squamous Cell Carcinoma	47	39.2

Demographic and clinicopathological data of the study population are summarized in Table 1. The majority of participants were older than 50 years (39.1%), followed by 36-50 years (34.2%). The number of male participants was slightly higher than that of females, as tobacco- and betel-related oral diseases are more common in males. Oral squamous cell carcinoma (SCC) was the most common disease category (39.2%), followed by oral potentially malignant disorder (OPMD) (32.5%) and oral lichen planus (28.3%). These results show that epithelial barrier function was assessed in a wide range of oral diseases of different inflammatory and malignant potential.

Table 2. Immunohistochemical Expression of Oral Epithelial Barrier Markers

Marker	Preserved Expression n (%)	Reduced Expression n (%)	p-value
E-cadherin	46 (38.3)	74 (61.7)	<0.001

Claudin-1	53 (44.2)	67 (55.8)	0.002
Occludin	58 (48.3)	62 (51.7)	0.011
ZO-1	49 (40.8)	71 (59.2)	<0.001

Table 2 shows significant changes in the expression of the epithelial barrier proteins evaluated. We found that reduced E-cadherin expression was observed in 61.7% of tissue specimens, reduced ZO-1 expression in 59.2% of tissue specimens, reduced Claudin-1 expression in 55.8% of tissue specimens and reduced Occludin expression in 51.7% of tissue specimens. All four markers showed statistical significance between the differences with p-values of <0.001 for E-cadherin, 0.002 for Claudin-1, 0.011 for Occludin and <0.001 for ZO-1. The results of this study suggest that oral lesions examined were frequently associated with changes in the expression of epithelial junctional proteins.

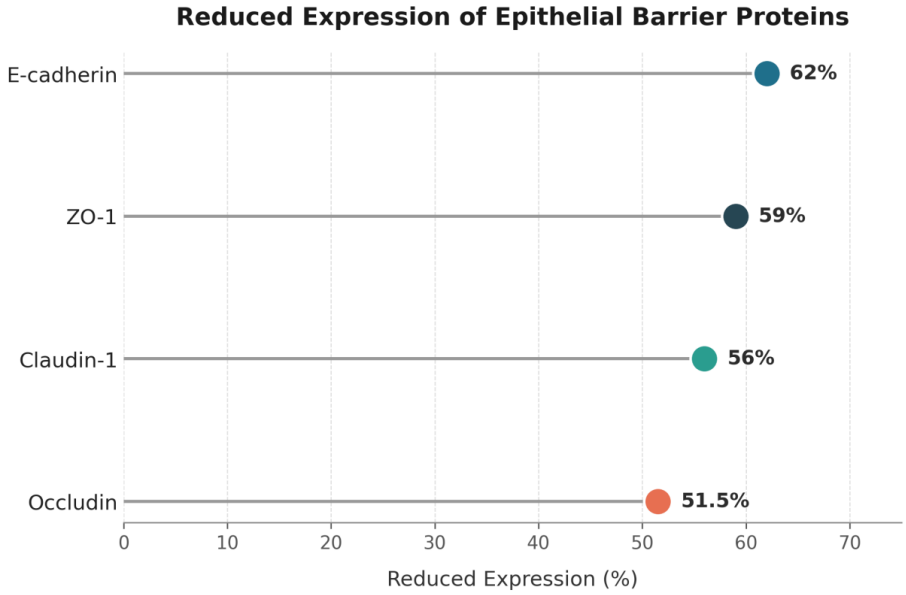

Figure 1. Reduced Expression of Epithelial Barrier Proteins

The percentage of tissue specimens with decreased expression of the four oral epithelial barrier proteins measured is shown in Figure 1. E-cadherin had the largest number of reduced expression (61.7%), followed by ZO-1 (59.2%), Claudin-1 (55.8%) and Occludin (51.7%). The results show that decreased expression of epithelial junctional proteins is a general phenomenon in the specimens studied and indicate that there is a lack of epithelial barrier integrity in the oral lesions examined.

DISCUSSION

The present study showed that the impairment of the integrity of the oral epithelial barrier is closely related to inflammatory and neoplastic oral diseases, because a significant number of patients expressed a decreased amount of E-cadherin, Claudin-1, Occludin, and ZO-1. The results confirm that epithelial barrier dysfunction is more than just a consequence of the disease process, but it is a basic pathogenic event that may result in chronic inflammation and tissue destruction (1). The epithelial barrier is a dynamic immunological interface that regulates host–microbial interactions, and disruption of this barrier allows for microbial penetration, continued immune activation, and epithelial injury (2). Therefore, our results further underscore the increasing awareness that maintaining epithelial integrity is critical for maintaining oral health and preventing disease. A key finding of the current study was the marked decrease in intercellular adhesion molecules in patients with advanced disease. Mechanotransduction pathways that maintain epithelial architecture during mastication, speech, and normal oral function are continuously activated by mechanical forces (3). Any disruption of these physiological processes compromises the barrier function of the epithelium and makes the tissue more susceptible to chronic inflammation and delayed wound healing of the oral mucosa. Mechanical regulation has also been shown to be critical to maintaining the integrity of the

oral epithelial barrier and tissue resiliency in response to physiological stress in previous experimental studies (4). The present results support the evidence from other mucosal systems showing that the disruption of the epithelial barrier is a common feature in different mucosal sites of the body. Studies of nasal epithelium have demonstrated that leakage of tight junctions allows allergens to penetrate, bacteria to enter the body, and chronic inflammatory responses to occur (5).

The oral cavity is not structurally similar to the respiratory tract, but both tissues are characterized by highly organized epithelial junctions that control the permeability and immune surveillance. Therefore, epithelial barrier disruption is a common mechanism involved in chronic mucosal inflammation, regardless of the site (6). Recent advances in epithelial biology further support the interpretation of our findings by highlighting the fact that epithelial dysfunction is a key early and ongoing event in chronic inflammatory disease. Barrier disruption leads to exposure of subepithelial immune cells to microbial antigens, leading to excessive production of cytokines and amplification of inflammatory signaling pathways. Chronic inflammation then leads to further damage of the epithelium and a vicious cycle of tissue destruction and poor healing. This mechanism could be responsible for the loss of barrier-associated proteins seen in the present study and suggests that restoration of epithelium is a therapeutic target (7).

Fusobacterium nucleatum is one of the microbial factors involved in epithelial injury that has been shown to directly change the integrity of the epithelial barrier (8). Experimental studies have shown that it is capable of binding to epithelial cells, inducing the production of inflammatory cytokines, weakening cellular junctions, and inducing apoptosis, which allows the bacteria to enter deeper tissues. Therefore, the abundance of reduced epithelial barrier markers in patients with oral inflammatory lesions and OSCC is consistent with the reported pathogenic role of F. nucleatum in altering oral epithelial homeostasis (9). Environmental exposures and microbial ecology are also important factors influencing epithelial function.

Tobacco products, betel nut, alcohol, food and drink, environmental pollution, and changes in the oral microbiome can all disrupt epithelial integrity by altering the host's immune response and junctional proteins (10). The exposome-resident microbiota interaction is gaining growing recognition as a significant factor in epithelial barrier health. Some of these mechanisms might account for the variability in epithelial marker expression seen within the participants in the present study (11). The decrease in epithelial barrier proteins found in this investigation might also be a sign of a dysfunction in innate immune defense mechanisms. Oral epithelial cells also produce antimicrobial peptides that have direct antimicrobial activity, but also modulate inflammation, promote wound healing, and maintain the integrity of the epithelium by interacting with immune cells and resident microorganisms (12). Changes or deficiencies of these peptides have been linked to an increased susceptibility to oral infections and chronic inflammatory diseases. Therefore, impaired antimicrobial peptide function could have contributed to barrier dysfunction in our study cohort (7).

The molecular changes found in this study could be another explanation for mechanotransduction signaling pathways. Integrins, focal adhesion complexes, ion channels, and cytoskeletal proteins are involved in cellular responses to mechanical stress, which regulate epithelial proliferation, migration, differentiation, and tissue repair. The dysregulation of these pathways may impair epithelial regeneration and promote chronic inflammatory responses, leading to progressive barrier dysfunction. The marked decrease in junctional protein expression observed in the present study is consistent with the emerging link between impaired mechanotransduction, epithelial injury, and disease progression (14). In addition to intercellular junctions, protective extracellular components, such as mucins, which provide a barrier to direct contact between microbes and epithelial cells, are required to maintain the epithelial barrier (15). Changes in the composition or production of mucin affect lubrication, microbial clearance, and susceptibility of the epithelium to inflammatory injury.

The biology of mucin has been mainly explored in the gastrointestinal tract, but the same protective mechanisms also exist in the oral cavity and play a significant role in maintaining epithelial homeostasis. In summary, the results of the present study further support the notion that oral epithelial barrier dysfunction is a multifactorial process involving structural,

immunological, microbial, and biochemical changes that all contribute to the initiation and progression of disease (16). Besides structural abnormalities, there is growing evidence of the association between epithelial barrier integrity and metabolic regulation and intracellular signaling pathways. Cellular metabolism can affect epithelial differentiation, responses to oxidative stress, production of inflammatory mediators, and tissue repair (17).

Dysfunctions in these metabolic pathways can affect the permeability of epithelial cells and disrupt the barrier function, leading to the development of chronic inflammatory diseases. The decreased expression of epithelial junctional proteins found in the present study may not only be due to local tissue damage but also to more systemic changes in molecular signaling pathways involved in epithelial homeostasis. The results are consistent with the emerging notion that metabolic modulation is a therapeutic target for maintaining epithelial integrity and disease progression (18). In recent years, there has been a growing awareness of the link between impaired epithelial barrier function and systemic disease. Chronic periodontitis has been demonstrated to play a role in gastrointestinal dysfunction by virtue of its persistent inflammation, systemic spread of microbes, and compromised oral cavity epithelial barriers. These mechanisms demonstrate the oral-systemic health connection and indicate that the epithelial barrier dysfunction of the oral mucosa could have implications for other organ systems.

CONCLUSION

The results of this study confirm that disruption of the oral epithelial barrier is an important molecular event in the development and progression of inflammatory, potentially malignant, and malignant oral diseases. This indicates a loss of critical barrier proteins such as E-cadherin, Claudin-1, Occludin, and ZO-1, and suggests that these proteins may be useful as markers for disease severity and progression. The study also highlights that the disruption of the epithelial barrier is a result of interactions between microbial pathogens, immune responses, mechanical stress, environmental exposures, and intracellular signaling pathways. These molecular mechanisms offer important insights into the pathogenesis of oral disease and possible therapeutic targets that would involve restoration of epithelial integrity. Preserving the epithelial barrier function, modulating host–microbiome interactions, and promoting tissue repair could lead to better disease prevention and clinical outcomes.

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