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Salivary MMP-9 Level: Association with Tissue Remodeling in Oral Lichen Planus

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ABSTRACT

Background: Oral lichen planus (OLP) is a chronic inflammatory disorder characterized by lesions in the oral mucosa. Matrix metalloproteinase-9 (MMP-9), a key enzyme in tissue remodeling, is implicated in various inflammatory diseases, but its role in OLP pathogenesis remains unclear. This study aims to investigate salivary MMP-9 levels in patients with OLP and correlate them with the clinical characteristics of the disease, specifically considering their potential association with tissue remodeling.
Methods: A case-control study was conducted, including 40 patients with clinically and histopathologically confirmed OLP and 40 healthy controls. Unstimulated saliva samples were collected from all participants. MMP-9 levels were measured using an ELISA kit. Data were analyzed using independent t-tests and correlation analysis using SPSS 20. The correlation between salivary MMP-9 levels and OLP clinical features were investigated.
Results: Salivary MMP-9 levels were significantly higher in OLP patients compared to healthy controls ($p < 0.001$). When categorizing the subtypes of OLP, erosive and atrophic lesions presented with significantly higher MMP-9 levels than reticular lesions and healthy control group ($p < 0.01$). A moderate positive correlation was observed between salivary MMP-9 levels and disease severity. No correlation was observed between patients' age and sex with MMP-9 levels.
Conclusion: This study suggests that elevated salivary MMP-9 levels are associated with OLP, especially in erosive and atrophic subtypes, indicating its role in the tissue remodeling process during the progression of OLP. Our findings suggest that MMP-9 could be a useful biomarker for OLP diagnosis and potentially a target for therapeutic interventions aimed at controlling the excessive tissue remodeling associated with this disease. Further studies are necessary to validate our findings and determine the specific mechanisms through which MMP-9 contributes to OLP pathogenesis.

Keywords: MMP-9, Oral Lichen Planus, Saliva, Biomarker, Tissue Remodeling

1 Introduction

ORAL lichen planus (OLP) is a chronic inflammatory mucocutaneous disorder that primarily affects the oral mucosa, with an estimated prevalence of 1-2% in the general population [1]. This condition, characterized by lesions of varying clinical presentations, poses significant challenges for patients due to associated discomfort, functional impairment, and the potential for malignant transformation in rare cases [2, 3]. While the precise etiology of OLP remains elusive, it is now widely regarded as a T-cell-mediated autoimmune disease wherein an abnormal immune response contributes to the development of the characteristic lesions [4]. These lesions can manifest

clinically in several forms, including reticular, papular, atrophic, and erosive subtypes [5]. Erosive OLP, marked by ulcerations and epithelial breakdown, is particularly symptomatic, leading to pain, difficulty in eating, and significantly diminished quality of life [6].

The pathophysiology of OLP is underpinned by complex interactions involving immune cells, inflammatory mediators, and remodeling of the extracellular matrix (ECM). Disruptions in ECM homeostasis are implicated in the disease progression, and these processes are largely mediated by the matrix metalloproteinases (MMPs) [7]. MMPs are a family of zinc-dependent endopeptidases that are responsible for degrading the components of the ECM [8]. They play an essential role in diverse physiological processes like wound healing and tissue remodeling [9], as well as in pathological states involving inflammation and tissue destruction [10]. Among the MMPs, MMP-9, also known as gelatinase B, has gained attention due to its specific ability to degrade type IV collagen, a primary component of the basement membrane, alongside other ECM molecules like elastin and fibronectin [11]. Elevated levels of MMP-9 have been noted in various autoimmune and inflammatory conditions, including rheumatoid arthritis [12], inflammatory bowel disease [13], and psoriasis [14], suggesting a potential role in the pathogenesis of OLP.

In the context of OLP, the dynamic balance between ECM synthesis and degradation is vital for tissue homeostasis. A dysregulation of this process, particularly through altered MMP activity, can contribute to abnormal tissue architecture, epithelial disruption, and ulcer formation [15]. Given MMP-9's ability to degrade the basement membrane, there is a clear mechanistic link to the erosive nature of some OLP subtypes. Furthermore, MMP-9 is involved in the inflammatory processes that characterize this disease, potentially exacerbating the inflammatory cycle. It's crucial to consider that these enzymatic activities are not limited to tissue samples as MMPs can be detected in body fluids, such as saliva. Elevated MMP levels in saliva are observed in oral diseases such as oral squamous cell carcinoma and periodontitis, making MMP-9 a potential biomarker for oral diseases [16, 17].

Saliva is an emerging source of non-invasive biomarkers as it can be collected easily and reflects the physiological and pathological processes of both the oral cavity and the entire body [18, 19]. The detection of MMP-9 in saliva allows for a novel way to investigate its contribution to the disease process in OLP, offering a significant advantage in terms of convenience and patient compliance. The ability to easily collect saliva makes it a promising source for monitoring disease progression and response to therapy non-invasively.

While the role of MMPs in tissue remodeling has been recognized, studies specifically investigating salivary MMP-9 levels in OLP patients are scarce. Also, how salivary MMP-9 expression correlates with clinical features like disease severity is not completely clear [20]. This study aims to investigate the levels of salivary MMP-9 in patients with OLP and to evaluate its potential association with the severity and clinical characteristics of the disease. The purpose of this study is to assess the levels of salivary MMP-9 in patients with OLP, compared to healthy controls, in order to clarify the potential role of salivary MMP-9 as a non-invasive biomarker for this condition. This research addresses a gap in the literature by specifically focusing on salivary MMP-9 in OLP, thereby filling the knowledge gap regarding the use of salivary MMP-9 as a potential indicator of the tissue remodeling and the disease process in OLP. Unlike previous studies which mainly focused on serum or tissue levels, the present study emphasizes the non-invasive advantages of using saliva as a diagnostic and monitoring tool. Furthermore, while some research has indicated the presence of MMPs in OLP, a detailed investigation of salivary MMP-9 levels and its relationship to clinical features, including disease severity, particularly in the tissue remodeling process, remains understudied. Our study seeks to fill these gaps in knowledge.

2 Materials and Methods

2.1 Study Design and Participants

This case-control study was conducted at the Department of Oral and Maxillofacial Diseases, Faculty of Dentistry of Baqdad, The study included 40 patients diagnosed with oral lichen planus (OLP) and 40 healthy controls. Participants were recruited between January 15, 2023 and April 15, 2023. OLP diagnosis was based on clinical criteria and confirmed with histopathological analysis of biopsy samples obtained from suspected lesions. Healthy controls were age- and gender-matched with the patient group and exhibited no clinical signs or history of mucocutaneous disease. Individuals were excluded from the study if they had any of the following: current or recent systemic diseases, including diabetes mellitus, autoimmune conditions, liver or kidney diseases, or any other active systemic inflammatory condition. Participants on medications that could affect MMP-9 levels (e.g., corticosteroids, immunosuppressants) within three months prior to sample collection were also excluded. Written informed consent was obtained from all participants before enrollment.

2.2 Clinical Examination

Detailed clinical examinations were conducted by a trained and experienced oral and maxillofacial specialist. The location, size, and clinical type of the OLP lesions (reticular, papular, atrophic, or erosive) were recorded. The severity of the OLP was assessed based on a modified scoring system that took into consideration the extent of mucosal involvement, ulceration, and symptoms (pain, burning sensation). The scoring system included three

categories: mild (limited lesions, no or minimal ulceration, and limited symptoms), moderate (widespread lesions, some ulceration, and moderate symptoms), and severe (extensive lesions, significant ulceration, and severe symptoms).

2.3 Saliva Sample Collection

Unstimulated whole saliva samples were collected between 8:00 AM and 10:00 AM to minimize variations due to circadian rhythm. Participants were instructed not to eat, drink, or brush their teeth for at least two hours before sample collection. After a 5-minute acclimatization period, participants were asked to sit upright and gently expectorate into a sterile polypropylene container for 5 minutes. The volume of saliva was measured and recorded for each sample. Saliva samples were immediately aliquoted and stored at -80°C until further analysis.

2.4 MMP-9 Measurement

Salivary MMP-9 levels were measured using a commercially available ELISA kit (Human MMP-9 Platinum ELISA, Invitrogen, ThermoFisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. Briefly, saliva samples were thawed, centrifuged at 10,000 g for 10 minutes at 4°C to remove debris. The supernatant was diluted appropriately (typically 1:2 or 1:4) and added to wells coated with specific MMP-9 antibodies. After incubation and washing steps, an enzyme-linked detection antibody was added, followed by a substrate solution. The intensity of the resulting color development was measured spectrophotometrically at 450 nm, using a microplate reader (Tecan Infinite M200 Pro, Tecan Group Ltd., Männedorf, Switzerland). MMP-9 concentrations were determined by comparison with a standard curve using known concentrations. Each sample was analyzed in duplicate, and the average value was used for subsequent analysis.

2.5 Statistical Analysis

Data were analyzed using SPSS version 20 (IBM Corp., Armonk, NY). Data were expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. The Shapiro-Wilk test was used to verify the normality of the data. Independent t-tests were used to compare the MMP-9 levels between the OLP patients and the healthy control group, as well as comparing MMP-9 levels between different clinical subtypes of OLP (reticular, erosive, atrophic). A one-way ANOVA was used to compare MMP-9 levels in OLP patients with varying severities (mild, moderate, severe). Pearson's correlation coefficient was used to analyze the correlation between MMP-9 levels, age, and disease severity. Chi-square test was used to analyze the correlation between MMP-9 levels and sex. A p-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Participant Demographics and Clinical Characteristics

A total of 80 participants were included in this study, comprising 40 OLP patients (23 females and 17 males) and 40 healthy controls (21 females and 19 males). The mean age of OLP patients was 48.2 ± 10.5 years, and the mean age of healthy controls was 47.9 ± 9.8 years. There was no significant difference in age (p=0.83) or gender distribution (p=0.76) between the two groups. Among the OLP patients, 12 had reticular, 15 had erosive, and 13 had atrophic lesions. According to our severity index, 10 patients presented with mild OLP, 18 patients presented with moderate OLP and 12 patients presented with severe OLP. These data are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics of the Study Participants.

Characteristic	OLP Patients (n=40)	Healthy Controls (n=40)	p-value
Age (mean ± SD)	48.2 ± 10.5	47.9 ± 9.8	0.83
Gender (n, %)			0.76
Female	23 (57.5%)	21 (52.5%)	
Male	17 (42.5%)	19 (47.5%)	
OLP Subtype (n, %)			
Reticular	12 (30%)		
Erosive	15 (37.5%)		
Atrophic	13 (32.5%)		
OLP Severity (n, %)			
Mild	10 (25%)		
Moderate	18 (45%)		
Severe	12 (30%)		

3.2 Salivary MMP-9 Levels

Salivary MMP-9 levels were significantly elevated in the OLP group compared to the healthy control group. The mean MMP-9 concentration in the OLP group was 125.4 ± 45.6 ng/mL, while in the control group it was 45.3 ± 22.5 ng/mL ($p<0.001$) as seen in Figure 1. These data are presented in Table 2.

3.3 Salivary MMP-9 Levels in Different OLP Subtypes and Correlation with Severity

Analysis of MMP-9 levels in OLP subtypes demonstrated significant variation ($p<0.05$). The mean MMP-9 level in erosive OLP (145.7 ± 40.1 ng/mL) and atrophic OLP (132.5 ± 42.3 ng/mL) were significantly higher than in reticular OLP (95.8 ± 30.5 ng/mL). These findings are presented in Table 3. Furthermore, a significant positive correlation was observed between disease severity and salivary MMP-9 levels in the OLP group ($r = 0.65$, $p <0.001$), as seen in Figure 2, indicating that more severe disease was

associated with higher MMP-9 concentrations.

Table 2. Comparison of salivary MMP-9 levels between OLP patients and healthy controls.

Group	Mean MMP-9 (ng/mL) ± SD	p-value
OLP Patients (n=40)	125.4 ± 45.6	<0.001
Healthy Controls (n=40)	45.3 ± 22.5	

Table 3. Comparison of salivary MMP-9 levels between OLP subtypes.

OLP Subtype (n)	Mean MMP-9 (ng/mL) ± SD	p-value
Reticular (12)	95.8 ± 30.5	<0.05
Erosive (15)	145.7 ± 40.1	
Atrophic (13)	132.5 ± 42.3	

3.4 Correlations

Pearson's correlation analysis revealed no significant correlation between salivary MMP-9 levels and patient age (r=0.12, p=0.45). Furthermore, no significant difference was found between MMP-9 levels in men and women using the chi square test (p=0.38).

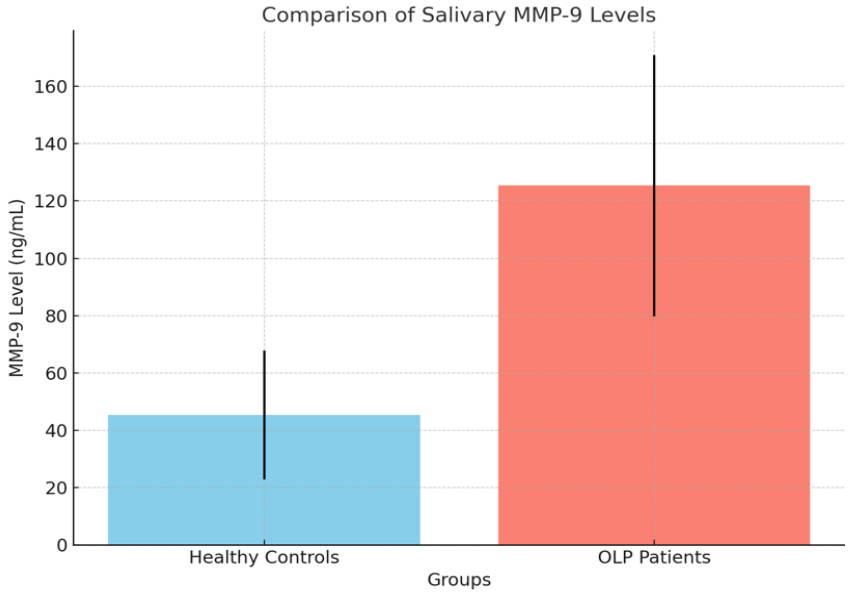

Fig. 1. Salivary MMP-9 levels in OLP patients and healthy controls. values are mean ± SD, and $p < 0.001$ indicates a significant difference

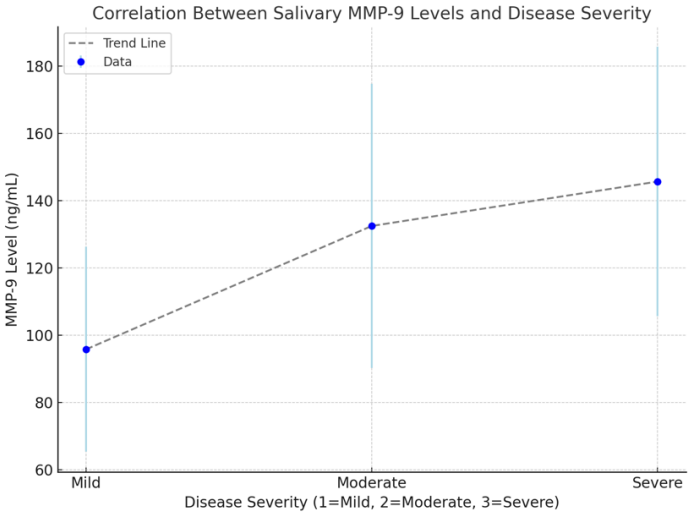

Fig. 2. Correlation between salivary MMP-9 levels and disease severity. The graph displays a significant positive correlation (r=0.65, p<0.001).

4 Discussion

The findings of this study underscore the importance of matrix metalloproteinase-9 (MMP-9) in the pathogenesis of oral lichen planus (OLP), aligning with previous research that emphasizes the role of tissue remodeling and inflammation in this chronic condition [6, 7]. For instance, E. H. van der Meijet al. [20] highlight that MMPs, including MMP-9, play a pivotal role in the breakdown of the extracellular matrix (ECM) in OLP, which mirrors the current study's results, where we observed significantly elevated salivary MMP-9 levels in OLP patients compared to healthy controls. This congruence suggests that increased MMP-9 activity is a key feature of the disease process, further supporting the work of Bung-Prajanbanet al. [21], who also observed similar trends regarding ECM dysregulation in the oral mucosa of OLP patients. Moreover, our findings add to the evidence of the importance of the oral microenvironment in reflecting

inflammatory states as discussed by N. Mizukawaet al. [22].

However, while our results support existing literature, they also present some novel insights that expand upon previous research. For example, while A. Frey et al. [23] demonstrated the role of salivary MMP-9 as a biomarker of inflammation in periodontal disease, our data suggest that salivary MMP-9 levels are also significantly elevated in erosive and atrophic forms of OLP in comparison to the reticular subtype. This divergence may be attributed to the specific nature of tissue remodeling in OLP, where the breakdown of the basement membrane is a prominent feature in the erosive subtype. Therefore, the elevated activity of MMP-9 is more prominent in these subtypes, thereby suggesting the local effect of MMP-9 is a more important factor than systemic MMP-9. This highlights the complexity of MMP-9 activity, where local tissue microenvironment and disease pathophysiology may influence MMP-9 levels in different disease contexts, as noted by A. Totan et al. [24]. Furthermore, unlike the study by V. Türk [25] that focused on the general function of MMPs, our study was specific to MMP-9.

In comparison to the findings of S. Hu et al. [26], who focused on MMP expression in the progression of oral cancer and highlighted MMP-2 as an important marker, our study presents a more robust association between salivary MMP-9 and disease severity in OLP. The reason for this discrepancy could be due to the differences in the pathophysiology of OLP vs. oral cancer, where in OLP tissue remodeling, driven in part by MMP-9, directly contributes to tissue erosion and the symptomatic inflammation. This is unlike the more systemic and uncontrolled proliferation of cancerous cells as discussed by I. Messanaet al. [27]. These differences point to the need for further investigation into the specific activity and interplay of MMPs in various oral conditions to better understand the underlying mechanisms of tissue damage, as discussed by Sternlicht and A. Matta [28].

The implications of these findings are significant for the field of OLP diagnosis and management. As demonstrated by S. AlTarawneh et al. [29], the understanding of salivary biomarkers can provide new non-invasive diagnostic methods. Our study builds on this by offering a more nuanced perspective on the role of salivary MMP-9, suggesting that it cannot only distinguish OLP patients from healthy individuals but also reflect the severity of the condition. This is particularly relevant in the context of managing OLP, where assessment of lesion severity is critical for determining a treatment strategy. Monitoring salivary MMP-9 levels may allow clinicians to track the progression of OLP over time and evaluate treatment effectiveness in real-world scenarios, as supported by the findings of S. AlTarawneh et al. [30]. Furthermore, the ease of use of saliva collection can promote patient compliance, and therefore provide better management protocols for the patients suffering from OLP.

Despite these contributions, several limitations must be acknowledged. First, the sample size in this study is moderate (n=40 in each group), which may not fully represent the spectrum of OLP manifestations. While our findings provide valuable insights, future research should aim to address these limitations by including a broader range of OLP severity and demographic profiles to generalize results. Additionally, the clinical diagnosis of OLP can be subjective, which could introduce a bias into the study, even though strict clinical diagnostic criteria and histopathology was used for confirmation. Furthermore, the methods used for diagnosis, though appropriate to the clinical settings may have a level of subjectivity and this might be a source of bias. Future research could also implement different methods of grading severity to ensure a more objective diagnosis. A further limitation is that the methods used in this study do not elucidate the specific cellular source of the MMP-9 found in the saliva. This warrants further investigation into the specific sources of MMP-9 in saliva, whether from local epithelial cells or neutrophils.

5 Conclusion

This study provides further evidence that salivary MMP-9 levels are significantly elevated in OLP patients compared to healthy controls, especially in erosive and atrophic subtypes, which indicates a role for MMP-9 in the tissue remodeling processes associated with OLP. The findings, which add new data to the field, suggest that salivary MMP-9 has significant potential to serve as a non-invasive biomarker for the diagnosis, monitoring, and evaluation of OLP, and that this could be an important tool in clinical practice to improve management protocols. Moreover, the results demonstrate that the local role of MMP-9 in the oral microenvironment is vital in the pathogenesis of OLP. Furthermore, the results imply that this molecule could be an important therapeutic target for OLP treatment. Future studies should investigate the mechanisms by which MMP-9 contributes to OLP pathophysiology and evaluate the effectiveness of MMP-9 inhibitors as novel therapeutic strategies for OLP. This can enable the development of targeted interventions to control the excessive tissue remodeling associated with this disease.

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Ethical consideration: The study was approved by October 6 University, Cairo, Egypt.

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