

The Etiology, Pathophysiology, and Treatment of Oral Ulcers: A Review Article

Safa Hasan Radhi¹, Shatha Hameed Ali Al-Hajjar², Shymaa A.G. Al-hussainy³, Ali A. Al-fahham⁴

¹ Biology Department, College of Science, Al-Qasim Green University, Babylon 51013, Iraq

² Department of Oral Diagnosis, Faculty of Dentistry, Kufa University, Najaf, Iraq

³ Department of community Health Techniques, Technical Institute of Babylon, Al-Furat Al-Awsat Technical University (ATU), Babylon, Iraq

⁴ Corresponding Author, Faculty of nursing, University of Kufa, Iraq

ABSTRACT: Oral ulcers are painful lesions that can considerably penetrate the quality of life of a human being and arise from many etiological factors. The present review of the literature aimed to update recent findings on oral ulcer etiology, concentrating more on Oral Lichen Planus, Behçet's disease, recurrent aphthous stomatitis, inflammatory bowel diseases, and chemotherapy as a systemic treatment. Oral ulcers are a very common clinical condition that can greatly affect a patient's quality of life. The pathophysiology of oral ulcers has great complexity and multiple factors: many underlying mechanisms depend on the specific type of ulcer and associated systemic conditions. Oral ulcers are very common but painful conditions that can assess about any quality of life. They can arise from various etiological factors such as medication side effects, systemic diseases, nutritional deficiencies, and cancer treatments. From looking at the many sides of these issues, this review shows how complicated oral ulcers are and points out where more research is needed. It also wants to bring together what new studies found about the causes of oral ulcers, shining a light on key discoveries and gaps in our knowledge that need more study.

INTRODUCTION

Oral ulcers are lesions that can be very painful and may considerably compromise the quality of life of an individual, thus being associated with a multitude of etiological factors. The present literature review aims to combine the newest findings regarding the etiology of oral ulcers, concentrating particularly on Oral Lichen Planus (OLP), Behçet's disease (BD), recurrent aphthous stomatitis (RAS), inflammatory bowel diseases (IBD), and the influence of systemic therapies including chemotherapy. From the diverse nature of these conditions, complexity in oral ulceration can be drawn with a basis for future research through revealed knowledge gaps. Oral ulcers represent one major category stemming from chronic inflammatory diseases Lichen Planus (LP) and Inflammatory Bowel Disease (IBD). In LP, a persistent inflammatory condition that involves the mucous membrane of the mouth, the involved pathophysiology is T-cell mediated immune responses that can finally lead to erosive lesions (Gorouhi et al., 2014). The clinical subtypes of LP in fact, erosive oral LP are crucial for comprehending oral ulcers since they represent the immunopathogenesis, which continues to be not well understood (Gorouhi et al., 2014).

Chronic recurrent oral aphthous ulcers are the most common oral ulcerative condition and therefore warrant appropriate treatment. Topical antiseptic agents, corticosteroids, and anesthetics may be used (source). Most important, however, in the prevention of flare-ups of oral ulcers is the withdrawal irritant foods, hard and acidic. Optimal treatment requires individualized management according to the severity and frequency of the ulcers. This underscores the need for a thorough understanding of the clinical picture and its accompanying factors to steer appropriate therapeutic decision-making. In addition, oral aphthous ulcers are among the most typical manifestations in patients with IBD; hence, it represents a systemic disease that can express itself through oral symptoms severing intestinal manifestations (Rogler et al., 2021).

The pathophysiology above may be exacerbated by active states of disease, thus underlining the interplay between local and systemic factors. Oral ulcers, in this regard, deserve to be considered as adequate predictors of systemic disease, hence guiding treatment approaches. Recent studies have addressed the effectiveness of natural oral mucoadhesive gels, containing aloe vera and myrrh, in treating minor recurrent aphthous stomatitis. These gels were able to reduce ulcer dimensions, pain, and other associated symptoms. From this standpoint, the capacity of natural products to offer symptomatic relief and hasten healing underscores the idea that alternative and complementary therapies may be integrated into treatment plans for oral ulcers to improve therapeutic outcomes. This area of research longs for more in-depth studies as patients seeking natural therapies would greatly benefit from these approaches.

The Etiology, Pathophysiology, and Treatment of Oral Ulcers: A Review Article

PATHOPHYSIOLOGY OF ORAL ULCERS

Oral Potentially Malignant Disorders (OPMD) also remain a great threat due to their high potential for malignant transformation. The pathophysiology of OPMD is associated with the dysregulation of some microRNAs at the cellular level, which are mainly involved in oral carcinogenesis. On a clinical basis, a timely diagnosis of malignancy in OPMD is significant because it relates to ulcers, which might be precancerous. The salivary microRNA changed in expression and observed as a potential biomarker will open up everything to a new horizon for research and practice (Tan et al., 2023).

Oral Submucous Fibrosis is a disease of oral ulcers involving aberrant remodeling and fibrosis of the tissues. The pathophysiology of this OSF highlights the molecular mechanisms to be imparted because ulceration and restricted mouth opening have severe impacts on oral health and quality of life. Malignant potential in OSF further emphasizes the need for prevention and/or treatment measures. The role of microbial interactions in the pathogenesis of oral ulcers is considered with chronic inflammatory diseases and malignant conditions as well. The dysbiosis, or imbalance, in the systemic relationship of oral microbes can be a trigger mechanism for opportunistic infections that may eventually lead to ulcer formation (Maheswari et al., 2018). Pathogen-pathogen interactions, such as those of *Candida albicans* with streptococci, need to be discussed to have a comprehensive picture of infection mechanisms on the oral mucosa and their potentiality in ulcers of the same. Such microbial interactions should be explored in future studies to guide preventive and therapeutic strategies (Abati et al., 2020).

Despite the insights obtained from recent studies, there are still some gaps in knowledge regarding the pathophysiology of oral ulcers. For example, though immune dysregulation plays a key role in conditions like LP and Behçet's disease, the exact triggering factors for the development of ulcers are yet to be fully understood. Another point is that the relationship between dietary factors and the recurrence of oral ulcers is rather unexplored and should be looked into further for chronic diseases such as recurrent aphthous ulcers. And while there have been great strides in the discovery of biomarkers for early malignancy in OPMD, wider studies are needed that take those findings into action within clinics. Future research in that direction should seek therapeutic targets from the molecular mechanisms involved with OSF and OPMD to have an intervention that can actually work on oral ulcers (Choudhari et al., 2014).

CAUSATIVE FACTORS IN ORAL ULCERS

Oral Lichen Planus (OLP)

OLP is a long-term inflammatory condition, marked by different mouth sores, like ulcers. The cause of OLP is mostly unknown, but it seems to involve both specific and general body defenses. The buildup of T cells and keratinocyte apoptosis are important in the development of mouth sores in those with OLP. This complexity requires a full plan for treatment that may be used for other types of oral sores (Roopashree et al., 2010).

Behçet's Disease (BD)

Behçet's disease is recurrent and sometimes very severe oral ulcers, which may dramatically influence the patient's prognosis. Since immunomodulatory and immunosuppressive agents developed to treat BD can affect oral ulcers, a well-controlled BD reduces both the frequency and intensity of oral ulcers which significantly improves the quality of life of the patients. An in-depth knowledge of BD pathophysiology, including genetic and immune factors, is therefore important for developing more specific therapies. Thus, systemic and local therapy based on an interdisciplinary approach is warranted, to effectively manage oral ulcers in the context of Behçet's disease; it is a well-defined condition based on the special relationship with the recurrent form of oral ulceration, often preceding other systemic evidence. The exact etiology of BD involves genetic factors and dysregulation of the immune system, understanding how BD develops immunologically is essential for developing targeted therapies and recognizing mucocutaneous lesions is of paramount importance for early diagnosis (Alpsoy, 2016; Zeidan et al., 2016). This draws attention to the association between persistent inflammation in BD and how important the development of effective management strategies for these sores bears (Altenburg et al., 2014).

Recurrent Aphthous Stomatitis (RAS)

RAS has been defined as painful oral ulcers in otherwise healthy individuals. The controversy over its etiopathogenesis mirrors the complexity of oral ulceration. The association of RAS with systemic diseases, such as celiac disease, suggests that oral ulcers may have their origin in genetic, immunological, and environmental factors. On the other hand, ongoing drug trials aimed at reducing pain and ulcer frequency in RAS patients highlight a significant need for more understanding regarding the underlying causes of this condition (Bugshan & Farooq, 2020).

Inflammatory Bowel Diseases (IBD)

The relationship between IBD and oral ulcers emphasizes the role of systemic diseases in oral ulceration. Oral ulcers, among IBD patients, probably become ameliorated due to intestinal inflammation treatment, thereby implying a relationship between the management of the systemic disease and concomitant oral health. Hence, this association calls for a more comprehensive view of the etiology of oral ulcers, integrating local and systemic aspects (Rogler et al., 2021).

The Etiology, Pathophysiology, and Treatment of Oral Ulcers: A Review Article

ORAL CANCER

Oral cancer matters because some precancerous lesions can show up as ulcers. The many causes of oral cancer include risk factors like tobacco use, alcohol consumption, and betel quid chewing; all these add to long-term irritation and ulcerative lesions that could turn into cancer. Finding it early and taking action is key for handling oral lesions and stopping cancer from getting worse (Kumar et al., 2016).

ORAL MUCOSITIS

One of the most painful and potentially debilitating sides of anticancer therapies is oral mucositis. The consequences of mucositis can be very serious: it may lead to dentition interruption of cancer treatments, negatively affecting patient prognosis. Nutritional intervention is considered one of the major treatments for oral mucositis; high-energy oral nutritional supplements reduce ulcer severity. In addition, cryotherapy as a preventive measure has also been effective in reducing the incidence of oral mucositis. Hence, a careful preventive and managing approach would improve patient care regarding this particular cohort. Oral mucositis is a usually outcomable complication in patients undergoing cancer therapy, ulcerative lesions induced by chemotherapy and radiotherapy. The etiology of oral mucositis involves systemic therapies that compromise mucosal integrity necessitating preventive measures and effective management strategies that can enhance patient outcomes. Research into treatments like oral cryotherapy proves the point that there is still a need for more research in interventions that could actually help. (Ashraf & Ostrosky-Zeichner, 2012; Cho et al., 2011).

MEDICATION-INDUCED ORAL ULCERS

Oral ulcers can appear as an adverse reaction to drugs, which complicates treatment of the lesions. Drug-induced mucosal reactions should be in the knowledge base of oral health care providers so that they can intervene appropriately with specific managements directed towards the underlying causes of oral ulcers. Particularly those patients who are treated with targeted therapies and biologic agents may need a dual approach: relief of symptoms and modification of the causative medication. This awareness underlines the necessity of knowing oral mucosal reactions to steer effective treatment strategies (Lingen, 2017).

CONCLUSION

In conclusion, oral ulcers are therefore a very challenging clinical entity with diverse etiological factors. Oral Lichen Planus (OLP), Behçet's Disease (BD), Recurrent Aphthous Stomatitis (RAS), Inflammatory Bowel Diseases (IBD), and even oral cancer are just a few examples of how complicated ulceration may present in the oral cavity. These are viewed as relationships advancing the management approach and patient outcomes. The majority of future studies should probably be directed at yet unexplored issues in view of identifying the etiology of oral ulcers to reach their effective treatment. The pathophysiology of oral ulcers may serve as an indicative marker for a large spectrum of different chronic inflammatory pathological conditions, neoplasms, infectious agents, and systemic diseases. Therefore, further study is required to fill the major gaps that impede the advance of treatment of this common condition. The management of oral ulceration is both symptomatic and directed toward the underlying etiology. Literature review will concentrate mostly on drug-induced ulcers since the condition is systemic concerning Behçet's and the role of supportive management in cancer patients and natural therapies. Further studies are warranted to address the shortcomings of current knowledge and to upgrade strategies in treatments aimed at bettering the fates of emptor sufferers with oral ulcers.

REFERENCES

- 1) Abati, S., Bramati, C., Bondi, S., Lissoni, A., & Trimarchi, M. (2020). Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. *International Journal of Environmental Research and Public Health*, 17. <http://doi.org/10.3390/ijerph17249160>
- 2) Alpsoy, E. (2016). Behçet's disease: A comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. *The Journal of Dermatology*, 43. <http://doi.org/10.1111/1346-8138.13381>
- 3) Altenburg, A., El-Haj, N., Micheli, C., Puttkammer, M., Abdel-Naser, M. B., & Zouboulis, C. (2014). The treatment of chronic recurrent oral aphthous ulcers. *Deutsches Arzteblatt international*, 111 40, 665-73. <http://doi.org/10.3238/arztebl.2014.0665>
- 4) Armstrong, D., Tan, Tze-Woei., Boulton, A., & Bus, S. (2023). Diabetic Foot Ulcers: A Review. *JAMA*, 330 1, 62-75. <http://doi.org/10.1001/jama.2023.10578>
- 5) Ashraf, M., & Ostrosky-Zeichner, L. (2012). Ventilator-Associated Pneumonia: A Review. *Hospital Practice*, 40, 105 - 93. <http://doi.org/10.3810/hp.2012.02.950>
- 6) Ashraf, M., & Ostrosky-Zeichner, L. (2012). Ventilator-Associated Pneumonia: A Review. *Hospital Practice*, 40, 105 - 93. <http://doi.org/10.3810/hp.2012.02.950>

The Etiology, Pathophysiology, and Treatment of Oral Ulcers: A Review Article

- 7) Baccaglini, Lorena., Lalla, Rajesh V., Bruce, Alison J., Sartori-Valinotti, J., Latortue, MC., Carrozzo, M., & Rogers, Roy S.. (2011). Urban legends: recurrent aphthous stomatitis.. *Oral diseases* , 17 8 , 755-70 . <http://doi.org/10.1111/j.1601-0825.2011.01840.x>
- 8) Bjordal, J., Bensadoun, R., Tunér, J., Frigo, L., Gjerde, K., & Lopes-Martins, R.. (2011). A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Supportive Care in Cancer* , 19 , 1069-1077 . <http://doi.org/10.1007/s00520-011-1202-0>
- 9) Bugshan, Amr S., & Farooq, I.. (2020). Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. *F1000Research* , 9. <http://doi.org/10.12688/f1000research.22941.1>
- 10) Chamoli, Ambika., Gosavi, Abhishek S., Shirwadkar, Urjita P., Wangdale, Khushal V., Behera, S., Kurrey, N., Kalia, K., & Mandoli, A.. (2021). Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics.. *Oral oncology* , 121 , 105451 . <http://doi.org/10.1016/j.oraloncology.2021.105451>
- 11) Cho, Sung Bin., Cho, Suhyun., & Bang, D.. (2011). New Insights in the Clinical Understanding of Behçet's Disease. *Yonsei Medical Journal* , 53 , 35 - 42 . <http://doi.org/10.3349/ymj.2012.53.1.35>
- 12) Choudhari, Sheetal., Chaudhary, M., Gadbail, A., Sharma, Aparna., & Tekade, S.. (2014). Oxidative and antioxidative mechanisms in oral cancer and precancer: a review.. *Oral oncology* , 50 1 , 10-8. <http://doi.org/10.1016/j.oraloncology.2013.09.011>
- 13) Gorouhi, F., Davari, P., & Fazel, N.. (2014). Cutaneous and Mucosal Lichen Planus: A Comprehensive Review of Clinical Subtypes, Risk Factors, Diagnosis, and Prognosis. *The Scientific World Journal* , 2014. <http://doi.org/10.1155/2014/742826>
- 14) Kheder, A., & Nair, K.. (2012). Spasticity: pathophysiology, evaluation and management. *Practical Neurology* , 12 , 289 - 298 . <http://doi.org/10.1136/practneurol-2011-000155>
- 15) Kheder, A., & Nair, K.. (2012). Spasticity: pathophysiology, evaluation and management. *Practical Neurology* , 12 , 289 - 298 . <http://doi.org/10.1136/practneurol-2011-000155>
- 16) Kumar, Malay., Nanavati, Ronak S., Modi, Tapan G., & Dobariya, C.. (2016). Oral cancer: Etiology and risk factors: A review.. *Journal of cancer research and therapeutics* , 12 2 , 458-63 . <http://doi.org/10.4103/0973-1482.186696>
- 17) Lingen, M. W. (2017). Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*
- 18) Maheswari, TN Uma., Venugopal, Archana., Sureshbabu, Nivedhita Malli., & Ramani, Prathiba. (2018). Salivary micro RNA as a potential biomarker in oral potentially malignant disorders: A systematic review. *Tzu-Chi Medical Journal* , 30 , 55 - 60 . http://doi.org/10.4103/tcmj.tcmj_114_17
- 19) McDermott, K., Fang, Michael., Boulton, A., Selvin, E., & Hicks, C.. (2022). Etiology, Epidemiology, and Disparities in the Burden of Diabetic Foot Ulcers.. *Diabetes care* , 46 1 , 209-221 . <http://doi.org/10.2337/dci22-0043>
- 20) Peng, X., Cheng, Lei., You, Yong., Tang, Chengwei., Ren, B., Li, Yuqing., Xu, Xin., & Zhou, Xuedong. (2022). Oral microbiota in human systematic diseases. *International Journal of Oral Science*, 14. <http://doi.org/10.1038/s41368-022-00163-7>
- 21) Prajna, Venkatesh N., Krishnan, Tiruvengada., Rajaraman, Revathi., Sushila, Patel, Srinivasan, M., Das, M., Ray, Kathryn J., Kieran, S., O'Brien., Oldenburg, C., McLeod, S., Michael, E., Zegans, ., Porco, T., Acharya, N., Lietman, T., & Rose-Nussbaumer, Jennifer. (2016). Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): A Randomized Clinical Trial. *JAMA ophthalmology*, 134 12, 1365-1372 <http://doi.org/10.1001/jamaophthalmol.2016.4096>
- 22) Rogler, G., Singh, A., Kavanaugh, A., & Rubin, D... (2021). Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology*. <http://doi.org/10.1053/j.gastro.2021.07.042>
- 23) Rogler, G., Singh, A., Kavanaugh, A., & Rubin, D. (2021). Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology*. <http://doi.org/10.1053/j.gastro.2021.07.042>
- 24) Roopashree, M., Gondhalekar, R., Shashikanth, M., George, J., Thippeswamy, S., & Shukla, Abhilash. (2010). Pathogenesis of oral lichen planus--a review... *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 39 10, 729-34 <http://doi.org/10.1111/j.1600-0714.2010.00946.x>
- 25) Shih, Yin-Hwa., Wang, Tong-Hong., Shieh, Tzong-Ming., & Tseng, Yu-Hsin. (2019). Oral Submucous Fibrosis: A Review on Etiopathogenesis, Diagnosis, and Therapy. *International Journal of Molecular Sciences*, 20 <http://doi.org/10.3390/ijms20122940>

The Etiology, Pathophysiology, and Treatment of Oral Ulcers: A Review Article

- 26) Tan, Yunhan., Wang, Zhihan., Xu, Mengtong., Li, Bowen., Huang, Zhao., Qin, Siyuan., Nice, Edouard C., Tang, Jing., & Huang, Canhua. (2023). Oral squamous cell carcinomas: state of the field and emerging directions. *International Journal of Oral Science*, 15. <http://doi.org/10.1038/s41368-023-00249-w>
- 27) Xu, Hao., Zhong, L., Deng, Jia-Qi., Peng, J., Dan, H., Zeng, X., Li, Taiwen., & Chen, Qianming. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, 12. <http://doi.org/10.1038/s41368-020-0074-x>
- 28) Yoneda, T., Hagino, H., Sugimoto, T., Ohta, H., Takahashi, S., Soen, S., Taguchi, A., Nagata, T., Urade, M., Shibahara, T., Toyosawa, S., & Jaw, Japanese Allied Committee on Osteonecrosis of the. (2016). Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. *Journal of Bone and Mineral Metabolism*, 35, 6-19. <http://doi.org/10.1007/s00774-016-0810-7>
- 29) Yoneda, T., Hagino, H., Sugimoto, T., Ohta, H., Takahashi, S., Soen, S., Taguchi, A., Nagata, T., Urade, M., Shibahara, T., Toyosawa, S., & Jaw, Japanese Allied Committee on Osteonecrosis of the. (2016). Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. *Journal of Bone and Mineral Metabolism*, 35, 6-19. <http://doi.org/10.1007/s00774-016-0810-7>
- 30) Zecha, Judith A E M., Raber-Durlacher, J., Nair, R., Epstein, J., Sonis, S., Elad, S., Hamblin, Michael R., Barasch, A., Migliorati, C., Milstein, D. M., Genot, M., Lansaat, L., Brink, R., Arnabat-Domínguez, J., Molen, L., Jacobi, I., Diessen, J., Lange, J., Smeele, L., Schubert, M., & Bensadoun, R.. (2016). Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. *Supportive Care in Cancer*, 24, 2781-2792. <http://doi.org/10.1007/s00520-016-3152-z>
- 31) Zeidan, M., Saadoun, D., Garrido, M., Klatzmann, D., Six, A., & Cacoub, P.. (2016). Behçet's disease physiopathology: a contemporary review. *Auto-Immunity HHighlights*, 7. <http://doi.org/10.1007/s13317-016-0074-1>