REVIEW

Periodontitis in oral pemphigus and pemphigoid: A systematic review of published studies

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Periodontitis and autoimmune bullous diseases, including pemphigus vulgaris and mucous membrane pemphigoid, are immunoinflammatory disorders leading to microbial plaque- and autoantibody-elicited tissue injury of the oral cavity, respectively. Evidence indicates that these autoimmune conditions may represent a risk factor for periodontitis, but no systematic evaluation exists to corroborate this assumption. A systematic literature review of periodontal status in pemphigus and pemphigoid was conducted. Electronic searches using PubMed from inception to July 2016 identified 10 studies meeting predetermined inclusion and exclusion criteria. Most reported some correlation between poor periodontal health and both oral pemphigus vulgaris and mucous membrane pemphigoid. Some demonstrated beneficial effects of oral hygiene procedures on periodontal parameters and clinical disease severity of the established blistering diseases. Inconsistent results were found between studies and within analyzed patient cohorts, likely because of methodological shortcomings. This review preliminarily suggests that patients with oral pemphigus vulgaris and mucous membrane pemphigoid appear somewhat more susceptible to periodontitis, which in turn may potentially trigger the bullous disorders. These patients should be encouraged by dermatologists to pursue collaborative professional periodontal follow-up with dentists. The true relationship and mutual interaction between both diseases needs to be more comprehensively addressed in well-designed prospective studies. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.10.028.)

Key words: autoimmune disease; mucous membrane; pemphigoid; pemphigus; periodontal status; periodontitis.

Pemphigus and pemphigoid diseases are rare and potentially fatal autoimmune disorders characterized by antidesmosomal and antihemidesmosomal autoantibody-induced intraepithelial and subepithelial split formation, respectively. Clinically, these diseases manifest as blisters and erosions on the skin and close-to-surface mucous membranes.[1,2]

Pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) represent the major subtypes of autoimmune bullous diseases that most commonly and predominantly affect the oral mucosa; both usually require long-term immunosuppressive treatment.[1,2] Although any area in the oral cavity can be involved, gingival sloughing with erythema and erosive and/or vesiculobullous lesions is, especially in MMP, a common finding. This is referred to as desquamative gingivitis.[3] In PV, mucosal lesions are classically caused by autoantibodies to desmoglein 3. In MMP, the autoantibody response can be directed against different autoantigens of the basement membrane zone, of which type XVII and VII collagen along with laminin 332 are best characterized.[1,2]

Abbreviations used:

IL:	interleukin
MMP:	mucous membrane pemphigoid
PV:	pemphigus vulgaris

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Periodontitis is a chronic inflammatory disease that affects the tooth supporting structures. It can lead to progressive injury of the soft tissue, ligaments, and alveolar bone, resulting in potential loss of affected teeth. Periodontitis is multifactorial in nature being influenced by genetic and environmental risk factors, such as smoking, and associated with accumulation of microbial plaque.[4,5]

It has been discussed that oral lesions such as desquamative gingivitis could play a role in increasing the risk for periodontal tissue breakdown in patients with oral autoimmune bullous diseases.[6-15] This potential influence may possibly be indirectly based on plaque accumulation as a result of pain-related compromised oral hygiene practices and less frequent dentist visits for checkups and cleanings. Immunosuppressive treatment-associated reduced immune response to periodontal pathogens could represent another possibility. Direct effects related to possible shared pathogenic mechanisms between autoantibody-induced and bacterial-elicited inflammatory tissue damage may also be plausible.[2,5]

Because the potential link between autoimmune blistering disorders affecting the oral mucosa and periodontitis is not fully understood, a systematic review of published studies that addressed the periodontal status in these diseases has been conducted.

CAPSULE SUMMARY

- Co-occurrence of immunoinflammatory periodontitis and oral pemphigus/pemphigoid has been documented.
- Most studies have demonstrated a correlation between compromised periodontal status and pemphigus vulgaris or mucous membrane pemphigoid.
- Follow-up with dentists should be suggested for these patients.

METHODS

The literature for this review from inception to July 2016 was comprehensively searched using the US National Library of Medicine National Institutes of Health PubMed by 2 independent researchers and checked by a third researcher separately. The key words used in this search consisted of "*pemphigus*" or "*pemphigoid*" combined with "*periodontitis*" or "*periodontal*." The inclusion criteria were peer-reviewed full-length original articles related to the search terms and indexed in the above-mentioned database. Reviews, single case reports, and articles not related to both pemphigus/pemphigoid and periodontitis were excluded.

RESULTS

A total of 44 different citation hits related to the terms used in the electronic literature search were retrieved. After critical screening of titles, abstracts, and full text, 10 original articles were suitable in this review. These comprised case-control and pilot studies on periodontal disease, of which 4 were related to patients with PV (n = 94) and 6 to patients with MMP (n = 65).[6-15] These studies are summarized in Supplemental Table I (available at http://www.jaad.org).

Diagnosis of PV and MMP was based on characteristic clinical disease features confirmed by histopathologic and/or direct immunofluorescence microscopic analysis without performing immunoserologic tests in all but 1 study,[7-15] in which diagnostic criteria were not reported.[6] In the majority of articles (70%), the analyzed cohorts were mainly composed of women, which was particularly marked among MMP but not patients with PV (female:male ratio 4:1 and 0.88:1, respectively). The mean age ranges for patients with PV and MMP were 35 to 60 years and 54 to 76 years, respectively. In all, 3 articles reported subjects with a smoking history, 3 reported subjects without a smoking history,[8,10-13,15] and 4 did not mention smoking status.[6,7,9,14] Some studies established diabetes mellitus, cardiovascular disease, infectious disease, and/or any systemic disease other than the autoimmune bullous disorder as exclusion criteria,[8-11,13,14] whereas the others did not specifically address comorbidities.[6,7,12,15] PV and MMP lesions were reported to affect the oral/gingival mucosa in all but 1 study,[7-15] in which the precise location of PV lesions was not described.[6] Except for 1 study reporting an exclusive gingival localization of MMP,[13] information on the clinical status of other mucosal sites or concomitant cutaneous disease manifestation was generally lacking. In most articles (80%),[6,8-12,14,15] the duration of disease symptoms was not reported or specified. Considering the medication of patients, 4 articles reported no pharmacologic treatment,[12-15] and 1 study did not specify the drug therapy.[8] In the remainder of the studies, treatment included systemic/topical corticosteroids, azathioprine, and dapsone.[6,7,9-11]

Seven studies more or less broached the relationship of patients with oral PV along with MMP and periodontitis. These investigations indicated that worse periodontal disease parameters exist compared with control populations or unaffected gingival sites.[7,8,10-13,15] Inconsistent results were

found between studies and within the study cohorts.[6-8,10-12,15] Beneficial effects of oral hygiene procedures on periodontal clinical parameters and clinical disease activity of PV and MMP were shown by 3 studies.[9,13,14] One study was related to microbiological aspects in patients with MMP.[15]

DISCUSSION

The literature search identified a limited number of case-control and pilot studies related to periodontitis in autoimmune bullous diseases with oral involvement that were restricted to PV and MMP.[6-15] This is likely a result of the rarity of these blistering disorders with an estimated incidence of 0.75 to 5 and 1.3 to 2 per million per year, respectively.[1,2] Similarly to what was recently described in patients with rheumatoid arthritis,[16] it was observed in the identified studies that patients with PV and MMP showed an increase in the incidence of periodontitis as compared with healthy individuals. These patients had worse periodontal parameters such as bleeding on probing, clinical attachment level of the periodontal ligament, probing depth, plaque index, and/or gingival index/recession.[7,8,10,11,13] In 1 study, results have been obtained by the community periodontal index of treatment needs.[7] The only partial periodontal data recording on which this index is based on may not reflect the true state of periodontal health or disease and is not adequately correlated with attachment loss.[12,17-19] Moreover, the increase in gingival index observed in patients with MMP, which describes the degree of clinical gingival inflammation, erythema, and edema, should be regarded with caution because this measure may have been biased by the MMP morphology.[10,11]

This latter finding raises the possibility not only of a clinical overlap but also of a pathophysiologic similarity or interference between MMP and periodontitis. Periodontitis is a chronic inflammatory disease where leukocyte infiltration and their persistent activation in response to chronic presence of local plaque bacteria including *Porphyromonas gingivalis* results in destruction of structural components of the periodontium. The mechanisms of tissue injury comprise the release of proinflammatory cytokines (eg, interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor-α) and matrix metalloproteinases (eg, gelatinase B).[5] Similar inflammatory processes are also involved in the pathogenesis of pemphigoid diseases. These include antihemidesmosomal autoantibody-induced cytokine production (eg, IL-6 and IL-8) and complement-mediated recruitment of matrix metalloproteinase− (eg, gelatinase B) and reactive oxygen species−releasing leukocytes that ultimately degrade basal membrane zone components resulting in dermoepidermal splitting.[2] In accordance, increased clinical attachment level, gingival recession, plaque accumulation, and certain trend of deeper probing depths were found in desquamative gingivitis−positive compared with nonaffected sites in patients with MMP. However, there was no difference regarding the relative percentage of periodontitis-associated microbial species on the total bacterial load.[12,15] The pathophysiologic mechanisms of MMP are different from in PV, in which autoantibodies exert a direct blister-provoking effect just by binding to epithelial cell surface antigens.[1] Erosive gingival PV lesions may equally act as a potential reservoir for plaque accumulation and thus promote periodontitis. It is also conceivable that the locally generated inflammatory process associated with periodontitis could trigger and perpetuate the autoimmune response (eg, by enhanced presentation of antigenic epitopes in the damaged periodontium). Hypotheses have been proposed to explain a relationship between periodontitis and systemic disorders, such as atherosclerosis and rheumatoid arthritis. Periodontitis-induced elevations of inflammatory mediators and acute-phase proteins may play a role in the development of these diseases.[20]

The possible relationship between periodontitis and oral PV/MMP is challenged by conflicting results that were observed between the studies and within the patient cohorts. These comprised the lack of a correlation between the existence or severity of oral PV/MMP lesions and periodontal parameters.[7,8,12,15] In addition, patients with MMP who had a higher level of gingival and periodontal inflammation than matched control subjects did not show a greater risk in having an increased progression of the periodontal disease over a 5-year observation period.[11]

Controversial data also exist with regard to immunosuppressive treatment. It represents the mainstay of therapy for PV and MMP,[1,2] but may alter the host immune defense response to the biofilm. This in turn can negatively affect periodontal health as has been recently demonstrated in a large group of patients undergoing long-term corticosteroid therapy.[21] Two studies revealed no effects of immunosuppressive treatment, including systemic corticosteroids, on periodontitis parameters in patients with PV, although in 1 of these trials the drug therapy was not specified.[7,8] In contrast, another study with patients with PV showed a decrease in bleeding index and increase in gingival recession in a corticosteroid dose-related fashion.[6] In addition, patients with MMP under topical corticosteroid

treatment were reported to have a significantly higher plaque index compared with those in remission.[10] These observations do not allow drawing any robust conclusion regarding a possible impact of immunosuppressive therapy on the periodontal status of patients with orally manifesting autoimmune bullous diseases.

There is evidence for effects of a conservative treatment in these patients. Nonsurgical periodontal therapy, including dental scaling, and detailed oral hygiene instructions improved both periodontal clinical parameters and the severity of PV and MMP lesions or symptoms.[9,14] The observation that higher levels of gingival and periodontal inflammation in patient with MMP compared with healthy control subjects were associated with probably pain-related worse scores in domiciliary oral hygiene routines[13] argues for the need of education of these patients about treatments aiming at reduction of foci of infection in the oral cavity. Whether professional hygiene treatment alone is sufficient enough to control localized oral disease in PV or MMP is yet rather questionable. Nevertheless, it may be concluded from these studies that mechanical friction associated with this local treatment does not seem to aggravate the course of bullous-erosive lesions in patients with autoantibody-mediated desquamative gingivitis.

It has to be stressed that several limitations, including potential confounding factors partly already discussed above, exist in the summarized studies, which could have affected the study outcomes. These comprise overall small study population sizes; scant or missing characterization of patients concerning their clinical and molecular status (ie, sites of involvement and autoantibody specificity, respectively); unknown disease duration; lack of uniform, standardized severity score indices for both the autoimmune and periodontal disease; and incomplete information on smoking habits, comorbidities, and administered drugs.

In conclusion, this systematic review of the available literature preliminarily suggests that patients with oral PV and MMP appear somewhat more susceptible to periodontitis, which in turn may potentially trigger the bullous disorders. These patients should be encouraged by dermatologists to pursue collaborative professional periodontal follow-up with dentists. The true relationship and mutual interaction between both diseases needs to be more comprehensively addressed in well-designed prospective studies.

REFERENCES

1. Bystryn JC, Rudolph JL. Pemphigus. *Lancet*. 2005;366:61-73.
2. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;381:320-332.
3. Gagari E, Damoulis PD. Desquamative gingivitis as a manifestation of chronic mucocutaneous disease. *J Dtsch Dermatol Ges*. 2011;9:184-188.
4. Stabholz A, Soskolne WA, Shapira L. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. *Periodontol 2000*. 2010;53:138-153.
5. Yucel-Lindberg T, Båge T. Inflammatory mediators in the pathogenesis of periodontitis. *Expert Rev Mol Med*. 2013;15:e7.
6. Markitziu A, Zafiropoulos G, Flores de Jacoby L, et al. Periodontal alterations in patients with pemphigus vulgaris taking steroids. A biannual assessment. *J Clin Periodontol*. 1990;17:228-232.
7. Akman A, Kacaroglu H, Yilmaz E, et al. Periodontal status in patients with pemphigus vulgaris. *Oral Dis*. 2008;14:640-643.
8. Thorat MS, Raju A, Pradeep AR. Pemphigus vulgaris: effects on periodontal health. *J Oral Sci*. 2010;52:449-454.
9. Gambino A, Carbone M, Arduino PG, et al. Conservative approach in patients with pemphigus gingival vulgaris: a pilot study of five cases. *Int J Dent*. 2014;2014:747506.
10. Tricamo MB, Rees TD, Hallmon WW, et al. Periodontal status in patients with gingival mucous membrane pemphigoid. *J Periodontol*. 2006;77:398-405.
11. Schellinck AE, Rees TD, Plemons JM, et al. A comparison of the periodontal status in patients with mucous membrane pemphigoid: a 5-year follow-up. *J Periodontol*. 2009;80:1765-1773.
12. Lo Russo L, Guiglia R, Pizzo G, et al. Effect of desquamative gingivitis on periodontal status: a pilot study. *Oral Dis*. 2010;16:102-107.
13. Arduino PG, Farci V, D'Aiuto F, et al. Periodontal status in oral mucous membrane pemphigoid: initial results of a case-control study. *Oral Dis*. 2011;17:90-94.
14. Arduino PG, Lopetuso E, Carcieri P, et al. Professional oral hygiene treatment and detailed oral hygiene instructions in patients affected by mucous membrane pemphigoid with specific gingival localization: a pilot study in 12 patients. *Int J Dent Hyg*. 2012;10:138-141.
15. Lo Russo L, Gallo C, Pellegrino G, et al. Periodontal clinical and microbiological data in desquamative gingivitis patients. *Clin Oral Investig*. 2014;18:917-925.
16. Araújo VM, Melo IM, Lima V. Relationship between periodontitis and rheumatoid arthritis: review of the literature. *Mediators Inflamm*. 2015;2015:259074.
17. Baelum V, Fejerskov O, Manji F, et al. Influence of CPITN partial recordings on estimates of prevalence and severity of various periodontal conditions in adults. *Community Dent Oral Epidemiol*. 1993;21:354-359.
18. Baelum V, Manji F, Fejerskov O, et al. Validity of CPITN's assumptions of hierarchical occurrence of periodontal conditions in a Kenyan population aged 15-65 years. *Community Dent Oral Epidemiol*. 1993;21:347-353.
19. Baelum V, Manji F, Wanzala P, et al. Relationship between CPITN and periodontal attachment loss findings in an adult population. *J Clin Periodontol*. 1995;22:146-152.
20. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol*. 2015;15:30-44.
21. Beeraka SS, Natarajan K, Patil R, et al. Clinical and radiological assessment of effects of long-term corticosteroid therapy on oral health. *Dent Res J (Isfahan)*. 2013;10:666-673.

Supplemental Table I. Summary of published studies relating to periodontitis and pemphigus/pemphigoid

Authors	Study population	Demographic characteristics	Exclusion criteria	Periodontal disease assessment	Treatment of patients	Main outcomes
Markitziu et al,[6] 1990	19 Patients with PV, 7 corticosteroid nonpretreated and 12 corticosteroid pretreated	7 Female and 12 male; 18-54 (mean 36) y; disease duration not informed, but systemic corticosteroid pretreatment from 3-13 y; smoking status not informed	Patients receiving additional medication (eg, azathioprine, antibiotics) during the study	ABH, BI, calculus, GR, PI, and PD	Systemic corticosteroids, dental scaling and root planing, and oral hygiene instructions	Significant decrease in BI and increase in GR in a corticosteroid dose-related manner in nonpretreated and premedicated subjects during follow-up
Akman et al,[7] 2008	20 Patients with PV; 22 healthy individuals	PV: 9 female and 11 male; 42.9 $\pm$ 9.8 y; disease duration 12.9 $\pm$ 11.6 y; smoking status not informed; healthy control subjects: 8 female, 14 male; smoking status not informed	Not informed	CPITN, carious teeth	Systemic corticosteroids, azathioprine	Significantly higher CPITN values and number of carious teeth in patients with PV compared with healthy control subjects; no significant difference in CPITN values between patients with PV when related to disease duration, immunosuppressive treatment, or severity of oral PV lesions
Thorat et al,[8] 2010	50 Patients with PV; 50 healthy subjects	PV: 24 female and 26 male; 35.2 $\pm$ 7.8 y; disease duration not informed, but treatment for $\geq$2 y; all nonsmokers; healthy control subjects: 24 female and 26 male; 37.0 $\pm$ 8.4 y; all nonsmokers	Periodontal therapy within 6 mo, systemic disease other than PV, and smokers	ABL, BI, CAL, PD, and PI	Immunosuppressive treatment (not specified)	Significantly higher CAL, PD, and PI in patients with PV compared with healthy control subjects; no significant difference in CAL and PD between patients with PV when related to immunosuppressive treatment or severity of oral PV lesions

Continued

Supplemental Table I. Cont'd

Authors	Study population	Demographic characteristics	Exclusion criteria	Periodontal disease assessment	Treatment of patients	Main outcomes
Gambino et al,[9] 2014	5 Patients with PV	4 Female and 1 male; mean 59.5 y; disease duration not informed, but mean systemic corticosteroid pretreatment time 102 mo; smoking status not informed	Pregnancy, topical treatment for DG lesions and previous periodontal therapy, <18 teeth, and diabetes mellitus	BOP, PD, and PI	Nonsurgical periodontal therapy including dental scaling and oral hygiene instructions	Significant reduction in BOP and oral PV lesions during follow-up
Tricamo et al,[10] 2006	20 Patients with MMP; 20 control subjects	MMP: 12 female and 8 male; 70.5 ± 2.58 y; disease duration not informed, but mean time since diagnosis 8.35 y; smoking status not specified; control subjects: 70.5 ± 2.58 y; smoking status not specified, but smoking history matched	Pregnancy, diabetes mellitus, uncontrolled cardiovascular disease, and active infectious disease (AIDS, tuberculosis, and hepatitis)	BOP, CAL, dental mobility, furcation, GI, GR, missing teeth, PD, and PI	Topical corticosteroids	Significantly higher GI in patients with MMP compared with control subjects; significantly higher PI in treated patients with MMP compared with those in remission; significantly greater class I furcation and GR in MMP groups with >5 y compared with <5 y since diagnosis
Schellinck et al,[11] 2009	10 Patients with MMP; 10 control subjects (study participants represent part of the cohort from Tricamo et al,[10] 2006)	MMP: 6 female and 4 male; mean 76 y; disease duration not informed, but mean time since diagnosis 12.1 y; smoking status not specified; control subjects: 6 female and 4 male; mean 75 y; smoking status not specified, but smoking history matched	Pregnancy, diabetes mellitus, uncontrolled cardiovascular disease, active infectious disease (AIDS, tuberculosis, and hepatitis), and control subjects who developed gingival MMP or other conditions causing DG during follow-up	BOP, CAL, dental mobility, furcation, GI, GR, missing teeth, PD, and PI	Systemic and topical corticosteroids, dapsone, and dental cleaning (latter also performed in control subjects)	Significantly higher GI and GR in patients with MMP at baseline and follow-up compared with control subjects; significant increase in CAL and GR during follow-up in both groups, but no significant difference in change between groups

Lo Russo et al,[12] 2010	4 Patients with MMP	3 Female and 1 male; 57.7 ± 13.5 y; disease duration not specified; no current smokers	Pregnancy, treatment for DG lesions or periodontal disease, and participation in oral hygiene maintenance programs	BOP, CAL, missing teeth, PD, and PI	None	No significant difference in BOP, CAL, PD, or PI between DG affected and unaffected sites; significant negative and positive association between DG lesions and PD <4 mm and PD 4-6 mm, respectively
Arduino et al,[13] 2011	29 Patients with MMP; 30 healthy subjects	MMP: 25 female and 4 male; 54.2 ± 2.7 y; mean disease duration 24.5 wk; 3 current smokers; healthy control subjects: 20 female and 10 male; 51.7 ± 2.4 y; 5 current smokers	Pregnancy, treatment for DG lesions or periodontal disease, <18 teeth, diabetes mellitus, and uncontrolled cardiovascular diseases	BOP, CAL, dental mobility, furcation, GR, missing teeth, PD, and PI	None	Significantly increased BOP, CAL, PD, PI, and tooth loss in patients with MMP compared with control subjects because of significant differences in oral hygiene routines
Arduino et al,[14] 2012	12 Patients with MMP	12 Female; mean 59.5 ± 14.52 y; disease duration and smoking status not informed	Pregnancy, treatment for DG lesions and previous periodontal therapy, <18 teeth, and diabetes mellitus	BOP and PI	Nonsurgical periodontal therapy including dental scaling and oral hygiene instructions	Significant reduction in BOP, PI, and gingival-related pain at follow-up
Lo Russo et al,[15] 2014	4 Patients with MMP (study participants represent the cohort from Lo Russo et al,[12] 2010)	3 Female and 1 male; 57.7 ± 13.5 y; disease duration not informed; no current smokers	Pregnancy, treatment for DG lesions or periodontal disease, and participation in oral hygiene maintenance programs	BOP, CAL, GR, PD, and PI	None	Significantly higher CAL, GR, and PI in DG-positive compared with DG-negative sites; no significant difference between DG-positive and DG-negative sites regarding relative percentage of periodontitis-associated microbial species on the total bacterial load

ABH, Alveolar bone height; *ABL*, alveolar bone loss; *BI*, bleeding index; *BOP*, bleeding on probing; *CAL*, clinical attachment level; *CPITN*, community periodontal index of treatment needs; *DG*, desquamative gingivitis; *GI*, gingival index; *GR*, gingival recession; *MMP*, mucous membrane pemphigoid; *PD*, probing depth; *PI*, plaque index; *PV*, pemphigus vulgaris.