

Identifying and treating periodontitis in patients with rheumatoid arthritis

Rheumatoid arthritis (RA) and periodontitis (PD) are chronic, inflammatory diseases causing tissue destruction with an epidemiologic link. PD may be directly involved in RA pathogenesis by facilitating peptide citrullination. *Porphyromonas gingivalis*, an oral pathogen in PD, expresses peptidylarginine deiminase that catalyzes protein citrullination. Small, single-center studies have shown improvements in RA measures with PD treatment, but this needs confirming by larger, well-designed investigations. Self-report surveys have recently been developed as an initial screening tool before subjecting patients to a resource-intensive full-mouth periodontal examination. In this report, we review the epidemiologic data linking PD with RA risk and progression, studies suggesting that PD may serve as a target for RA treatment, and briefly summarize methods that might be used for PD case finding.

Keywords: autoimmunity • *P. gingivalis* • periodontitis • rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting synovial tissues, resulting in progressive joint destruction, substantial physical impairment, decreased quality of life and premature mortality [1]. Periodontitis (PD) is a chronic, destructive, inflammatory disease of hard and soft supporting structures of the teeth that can result in tooth loss [2]. Given similarities in disease features, substantial research has been conducted into a possible linkage of these chronic inflammatory conditions. In this article, we summarize our current understanding of the relationship between RA and PD, the influence of PD treatment on RA outcomes, and tools that might aid in the identification of comorbid PD in this population.

Epidemiologic links between rheumatoid arthritis & periodontitis

Several epidemiologic studies have demonstrated an increased prevalence and severity of PD in individuals with RA. Cross-sectional and case-control studies have consistently demonstrated a 1.5- to 8-fold increased

prevalence of PD in RA patients even after adjusting for confounders such as oral hygiene and smoking history [3–9]. Individuals seropositive for rheumatoid factor (RF) or anticyclic citrullinated peptide (anti-CCP) antibody are disproportionately impacted by more severe PD [3,9,10]. Notably, the increased prevalence and severity of PD in RA is even seen in early, treatment-naïve RA [8,11,12]. Scher and colleagues found that moderate-to-severe PD was present in 78% of new-onset/treatment-naïve RA patients compared with just 39% of healthy controls [11].

A limitation of many of these prior case-control studies includes the comparison of RA patients to healthy population-based controls. To address this potential source of bias, our group examined the prevalence of PD by comparing RA patients (n = 287) to osteoarthritis (OA) patients (n = 330), a comparator group sharing many characteristics with RA patients including age, health behaviors, sex distribution, and frequent comorbidity [9]. These factors have the potential to confound the relationship between PD and RA. We found the odds of PD were 1.5-times higher

Bryant R England^{1,2}, Brian W Coburn¹, Jeffrey B Payne^{1,3}, Geoffrey M Thiele^{1,2} & Ted R Mikuls^{*,1,2}

¹Division of Rheumatology, Department of Internal Medicine, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

²Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE, USA

³University of Nebraska Medical Center, Division of Periodontics, Department of Surgical Specialties, College of Dentistry, Lincoln, NE, USA

*Author for correspondence: tmikuls@unmc.edu

in RA than OA, a risk that was greatest in anti-CCP antibody positive patients and that was independent of multiple confounding factors including oral hygiene status and smoking, among others.

There is also an increased prevalence of RA in those with PD [5]. In a large Taiwanese, population-based, case-control study using administrative data, PD was associated with increased odds of RA (odds ratio 1.16) after adjusting for multiple confounders [13]. In the prospective Nurses Health Study, however, women who reported prior periodontal surgery or tooth loss were not at an increased risk of developing RA [14]. Though the total sample size was large ($n = 81,132$) in this study, the relatively small number of incident RA cases ($n = 292$) limited study power. Furthermore, PD was determined via self-report of either prior surgery or tooth loss, a method suffering from poor sensitivity.

RA severity also appears to be adversely influenced by PD. In a cross-sectional study, RA patients with severe PD had higher Disease Activity Scores (DAS) and CRP values than those without severe PD [4]. An association between radiographic wrist damage and PD, but not between PD and other markers of disease severity such as DAS28 and erythrocyte sedimentation rate (ESR), has also been reported [15]. Results from at least one small study suggest that the association of PD with heightened RA disease severity could relate to its effects on treatment responsiveness [16]. This study demonstrated that patients with comorbid PD were less likely than patients without PD to respond to anti-TNF therapy.

Periodontitis in the pathogenesis of rheumatoid arthritis

Given strong epidemiologic links between PD and RA, it has been hypothesized that PD is directly involved in RA pathogenesis. Both PD and RA share common risk factors, with the most important risk factor being a history of cigarette smoking [17,18]. These conditions may also share genetic risk factors. *HLA-DRB1* shared epitope containing alleles represent the strongest known genetic risk factor in RA and are also associated with periodontal bone destruction [15]. However, there appears to be more linking PD and RA than simply shared risk factors.

There are several studies of PD that have used animal models to explore this relationship. In these studies, PD due to oral infection with *Porphyromonas gingivalis* resulted in earlier and more severe arthritis [19–22]. The increased severity of arthritis may have resulted from the induction of proinflammatory Th17 responses [20,21]. *P. gingivalis* PPAD expression appears to play a key mechanistic role in these findings as PPAD knockout mice were protected from these effects [22].

Human studies have similarly implicated citrullination as a possible pathway linking PD with RA. Nesse and colleagues have shown that the periodontium of PD patients contains citrullinated proteins in a pattern that is strikingly similar to that observed in RA synovial tissues [23]. Moreover, higher titers of anticitrullinated protein antibodies (ACPAs), particularly those recognizing citrullinated forms of vimentin and histone, have been independently associated with increased alveolar bone loss [24].

But what triggers citrullination to occur? One hypothesis centers on the contributions of the prokaryote *P. gingivalis* (Figure 1) [25]. Our group previously observed elevated titers of antibodies to *P. gingivalis* outer membrane antigen (OMA) in RA patients compared with healthy controls and an association of these titers with both anti-CCP antibody and CRP [26]. Elevated anti-*P. gingivalis* antibodies were similarly found in those with severe PD and RA compared with those with severe PD alone as well as in those with early RA [4,27]. The presence of periodontal bacteria (including *P. gingivalis*) DNA within the serum and synovium of patients with refractory RA has been reported [28]. Recently, we observed modest (but highly significant) correlations between anti-*P. gingivalis* antibodies and anti-CCP antibody titer in RA patients with PD as well as an overexpression of ACPAs against citrullinated filaggrin and histone, independent of smoking status [9]. Following PD treatment, titers of anti-*P. gingivalis* decreased in those with and without RA [29,30]. Those with RA had a reduction in serum citrulline, but no change in anti-CCP antibody, while those without RA had decreased anti-CCP antibody titers.

Associations between *P. gingivalis* and RA have not been consistently observed. In a large study of more than 600 early RA patients, there were no case-control differences in antibody titers to *P. gingivalis* lipopolysaccharide (LPS) [31]. Among RA cases, there were also no associations of anti-*P. gingivalis* antibody with ACPA status. Another study by our group failed to demonstrate a difference in antibody titers to *P. gingivalis* OMA and LPS in RA compared with those with OA [9].

Mechanistically, *P. gingivalis* generates citrullinated host peptides by protein cleavage with arginine gingipains followed by citrullination through PPAD (Figure 1) [32]. ‘Auto-citrullination’ of PPAD occurs *in vitro* and elevated citrulline-specific antibody responses to PPAD in RA compared with PD and controls has been observed, suggesting that PPAD itself may induce RA-associated autoimmunity and promote tolerance loss [33]. Again, these are not universal findings. A separate study found no elevation of anti-PPAD or anticitrullinated PPAD antibodies in RA and no correlation of anti-PPAD antibodies with anti-CCP levels or RA

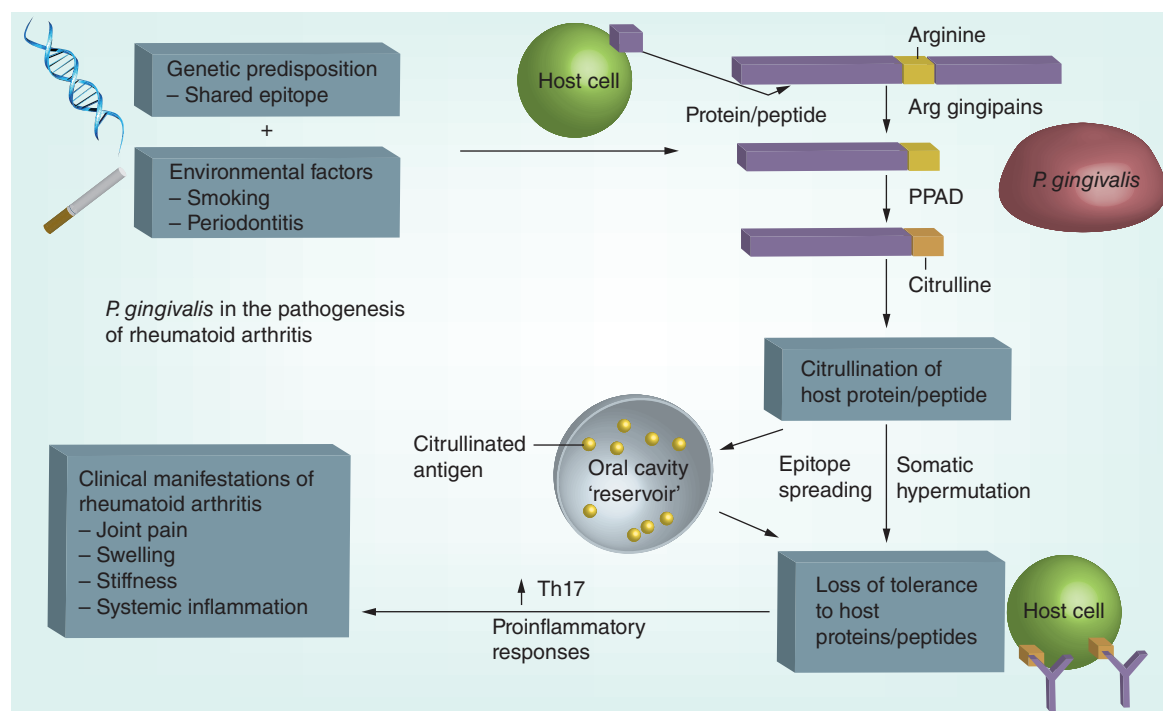


Figure 1. Schema is demonstrating the hypothesized role of *P. gingivalis* infection in rheumatoid arthritis pathogenesis. Individuals with a genetic predisposition are exposed to environmental factors such as smoking and periodontitis (PD). Host cells encounter *P. gingivalis* in the setting of PD. *P. gingivalis* arginine gingipains cleave proteins to expose an arginine residue that subsequently undergoes citrullination by PPAD. The oral cavity serves as a reservoir for these citrullinated antigens. Loss of tolerance occurs through epitope spreading and somatic hypermutation. Once tolerance is lost, upregulation of inflammatory responses, particularly through Th17, lead to the development of the clinical manifestations of RA. PPAD: *P. gingivalis* peptidylarginine deiminase.

disease activity [34]. The authors of this last report suggested the N-terminal processing of PPAD in *P. gingivalis* may protect the enzyme from autocitrullination, and previous results may have been due to the autocitrullination occurring in full-length PPAD expression in *E. coli*. Conversely, differences in antibody reactivity may relate to differences in the PPAD substrates tested.

Individuals with preclinical RA represent an extremely informative population to study to understand disease pathogenesis. In autoantibody positive individuals at higher risk for future RA, our group found increased anti-*P. gingivalis* OMA antibodies, but no increases in antibodies to other oral pathogens [35]. The presence of PD, but not the presence of subgingival *P. gingivalis*, predicted progression from arthralgias to methotrexate prescription for the diagnosis of RA [36]. A separate investigation similarly showed no association between anti-*P. gingivalis* antibodies and the risk of future classifiable RA in patients with arthralgias and RF or ACPA positivity [37].

Treatment of periodontitis in rheumatoid arthritis

The American Academy of Periodontology recommends oral hygiene instructions, smoking cessation (among

other risk factor modifications), removal of supra- and subgingival plaque and calculus through scaling and root planing (SRP), chemotherapeutic agents targeted at oral microbial pathogens or the host response, and various resective, soft tissue, osseous and/or regenerative procedures as the comprehensive therapy for PD [38]. Despite the numerous studies investigating PD and RA, few studies have been conducted examining the effects of PD treatment on RA outcomes.

Ribeiro *et al.* examined the impact of PD treatment on RA in 2005 [39]. Forty-two patients with established RA and PD, defined by ≥ 2 teeth with ≥ 2 sites of probing pocket depth ≥ 5 mm and clinical attachment loss (CAL) ≥ 6 mm, were studied. The treatment group received full-mouth SRP at baseline and 1 month later, if necessary, while the control group received oral hygiene instruction and supragingival teeth cleaning. After 3 months of follow-up with no changes to RA medications, the treatment group had improved ESR and nonstatistically significant trends towards improvement in Health Assessment Questionnaire (HAQ) scores and RF titers.

In a subsequent study of 38 RA patients with mild-to-moderate generalized chronic PD for at least 3 years,

patients were randomized to a PD intervention (oral hygiene instruction and SRP) or no intervention [40]. Patients were excluded if RA medications were altered during the study period. After 8 weeks of follow-up, an improvement in DAS28 and ESR occurred in the treatment group that correlated with improvements in PD measures. A high dropout rate and not reporting RA disease duration limited this study.

Pinho *et al.* conducted a study of 30 patients with RA and PD (≥ 2 teeth with CAL ≥ 6 mm and ≥ 1 tooth with probing depth ≥ 5 mm), 15 edentulous RA patients, 15 patients with PD alone, and 15 healthy controls [41]. Half of the patients with RA and PD were randomized to full-mouth SRP treatment while the others received no treatment. After 6 months of follow-up and no RA medication changes, PD measures, but not inflammatory markers, improved in the treatment group.

Ortiz *et al.* examined 40 RA patients on disease-modifying antirheumatic drug (DMARD) therapy and generalized severe PD [42]. Half of the patients were randomized to PD treatment consisting of oral hygiene instruction and full-mouth SRP with the remaining patients assigned no intervention. After 6 weeks, the periodontal treatment group had statistically significant improvements in DAS28, ESR and serum TNF- α . Furthermore, there was a significant between-group difference in DAS28 at study completion favoring those receiving PD treatment.

Okada *et al.* examined 55 patients with RA and PD, the latter defined as having at least one site with CAL ≥ 4 mm [29]. Twenty-six patients were randomized to receive PD treatment consisting of oral hygiene instruction and supragingival scaling while 29 patients were randomized to a control group in which PD therapy was deferred until after study completion. Those receiving PD therapy had significant reductions in DAS28-CRP, IgG anti-*P. gingivalis* antibodies and citrulline over 8 weeks of follow-up. Swollen and tender joint counts, CRP, IL-6, TNF- α , RF and anti-CCP antibody did not differ from baseline to reassessment.

Erciyas *et al.* compared 30 RA patients with DAS28 ≥ 3.2 and chronic PD (≥ 4 teeth with probing depth ≥ 5 mm and ≥ 2 mm CAL) to 30 patients with DAS < 3.2 and chronic PD [43]. All patients received SRP and oral hygiene instructions. Both groups had a significant reduction in PD parameters, ESR, CRP, DAS28, and TNF- α , though the degree of reduction was greater in the DAS28 ≥ 3.2 group (except for TNF- α). The absence of a control group that did not receive PD treatment was a limitation to this study.

Given the small sample size of these studies, short follow-up periods, varying classification criteria for PD, and heterogeneous findings, a recent systematic review and meta-analysis was completed, pooling results from

available reports examining the impact of PD interventions on disease activity in established RA [44]. In their analysis, the authors found a statistically significant reduction in ESR following PD treatment and a trend toward reductions in DAS28 and circulating TNF- α concentration. Still, these results are inconclusive, as the aggregation of these studies was hampered by the varied outcomes measured, underlying methodological heterogeneity, and highly variable follow-up periods.

The aforementioned studies enrolled patients with established RA; however, the timing of PD therapy may influence results. Salemi *et al.* reported an intriguing case of ACPA positive, erosive, early RA which resolved following only PD therapy that was composed of SRP, debridement of periodontal pockets and endodontic treatment (root canal) [45]. RA resolution persisted throughout the entire 17 months of follow-up. These preliminary treatment studies consistently suggest that PD therapy itself improves RA outcomes among those with comorbid PD. However, these studies were universally single-center studies with small sample sizes, examining different outcomes and employing varying classification criteria for both RA and PD. Additionally, current and former smoking were exclusion criteria in many of these studies, limiting the generalizability of these findings to 'real-world' RA populations. Given these limitations, it is difficult to make definitive conclusions from these studies and future studies with larger patient populations employing rigorous methodology are needed.

To address this knowledge gap, a multicenter, open-label randomized controlled study is currently underway [46]. In this study, 40 participants with RA and DAS28 values between 3.2 and 5.1 (reflecting 'moderate' disease activity) as well as PD defined by ≥ 1 site of probing depth ≥ 4 mm and CAL ≥ 3 mm on ≥ 4 teeth will be randomized and followed for 3 months. The intervention group will receive biofilm staining, full-mouth disinfection, SRP, systemic antibiotics (amoxicillin for 7 days), and oral hygiene instructions, while the control group will receive the same intervention after the 3-month follow-up period. The primary outcome is changes in DAS28 at 3 months. In addition to multicenter enrollment, strengths of this study include the incorporation of a comprehensive PD treatment strategy, the collection of longitudinal RA disease activity measures, and the use of intention-to-treat analysis. Limitations include the small sample size (though powered to detect a 0.6 change in DAS28), relatively brief follow-up period and the use of amoxicillin for antibiotic therapy. While the use of doxycycline or minocycline (frequently used in PD treatment) may complicate interpretation given their dual action as a DMARD [47], it has been hypothesized that the

use of these antibiotics might result in a more favorable response as part of PD therapy [48].

Identification of periodontitis in patients with rheumatoid arthritis

With treatment of PD showing promise for improving RA disease activity measures, it becomes increasingly important for healthcare providers and researchers alike to identify PD in RA patients. PD is currently classified using a full-mouth periodontal evaluation including the systematic measurement of probing depths and CAL [49]. In addition to the time and resource intensive nature of full mouth examination, PD classification poses a challenge based simply on the number of different case definitions available for PD. A systematic review revealed the heterogeneity of techniques and values of probing depths and CAL used to define PD in epidemiologic studies [50]. A minimum diagnostic threshold of CAL of 2 mm and probing depth of 3 mm at a given site was universal among studies reviewed.

Since a full-mouth periodontal evaluation is not always feasible, considerable effort has been made in population-based studies to develop self-report surveys for PD identification. In a review of 16 studies of self-reported PD, including 13 studies using self-report questionnaires, 13 self-report questions were identified with validity for PD, but only 5 of those were valid for multiple clinical measures [51]. The three best questions identified were: 'Have you had periodontal disease with bone loss?', 'Do you have periodontal disease with bone loss?' and 'Has any dentist/hygienist told you that you have deep pockets?' While the specificity of these items was >90%, these measures suffered from a lack of sensitivity (range 39–55%) suggesting many cases of PD were not identified. This review was limited by the heterogeneity of the 'gold standard,' both in

terms of methods (PD exam vs radiography) and values of clinical measurements.

Given the need for less resource intensive identification of PD, the Centers for Disease Control commenced a PD surveillance initiative in collaboration with the American Academy of Periodontology and developed eight closed-ended self-report measures for PD. Eke *et al.* tested the validity of these measures compared with a full-mouth exam in a study of 3743 individuals [52]. Individual questions were predictive of PD and independent of responses to the other questions. More importantly, by combining the response to multiple questions, they were able to optimize the sensitivity for identifying PD. Lastly, by adding risk factors for PD (age, gender, race, smoking status, among others) to their multivariable model the C-statistic (equivalent to the area under the receiver operator curve) improved dramatically from 0.68 to 0.81. The C-statistic remained unchanged when the authors reduced their model to the five best questions.

None of the previous studies examining the use of self-reported measures of PD was completed in RA patients. Our group recently studied the performance of self-reported measures for PD in RA [53]. Individuals with RA (n = 287) underwent full-mouth PD exam and completed a 6-item questionnaire. We found individual questions to have high specificity but limited sensitivity for moderate-to-severe PD. While combining responses to multiple questions did not dramatically improve the sensitivity or specificity of the instrument, the addition of PD risk factors greatly enhanced model performance yielding a C-statistic approaching 0.8 (a threshold typically defined as showing 'strong' predictive capacity) (Table 1). These results suggest that a combination of self-report questions, coupled with PD risk factors (primarily smoking status, gender and age) could be used to rapidly evaluate RA patients

Table 1. Associations of self-report questionnaire responses in rheumatoid arthritis with comorbid moderate-to-severe periodontitis detected by full-mouth periodontal examination.

Question response	Odds ratio (95% CI)	Sensitivity	Specificity	Final model ^a
Gums bleed	1.42 (0.63–3.21)	20.9	84.3	–
Bone loss/deep pocket	4.35 (1.51–12.58)	27.0	92.2	–
Periodontal treatment	3.82 (1.46–10.03)	29.4	90.2	3.39 (1.12 – 10.30)
See periodontist	0.78 (0.40–1.54)	26.3	68.8	–
Loose teeth	1.74 (0.50–6.02)	9.8	94.1	–
Periodontal surgery	1.22 (0.48–3.10)	14.6	87.8	–
C-statistic	–	–	–	0.80

^aAdditional statistically significant variables in the final logistic regression model were: age (in years) odds ratio 1.05 (95% CI: 1.01–1.08), male gender 2.51 (1.17–5.35), and high school education 0.79 (0.65–0.95); odds ratios only shown in the final model for those with p-value < 0.05.

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for PD risk. With further refinements, such an instrument could be deployed clinically or in the research arena as an initial case-finding tool with those screened as being high-risk subsequently referred for full-mouth examination by a periodontist or other appropriately trained health care provider.

Conclusion

Epidemiologic studies have demonstrated an increased prevalence and severity of PD in those with RA, and conversely, an increased risk of RA in those with PD. Though far from conclusive, current evidence suggests that this epidemiologic link may be attributable in part to infection with specific oral pathogens. *P. gingivalis*, the only prokaryote known to express PPAD as a virulence factor, has been subject to the most intense investigation to date. A prevailing hypothesis is that *P. gingivalis* infection leads to local peptide citrullination and neoantigen formation leading to eventual loss of tolerance and the development of RA-related autoimmune responses. Small, single-center trials have further demonstrated that PD treatment improves the signs and symptoms of RA. Larger, multicenter trials are needed and will require rapid and efficient means of identifying patients with PD. Recent reports suggest that self-reported signs and symptoms of PD, coupled with select risk factor assessment, may allow for a rapid and efficient means of case-finding for future studies in the context of RA.

Future perspective

Both the quantity and quality of research examining the links between RA and PD have grown exponentially in recent years. Naturally, with an improved understanding of this relationship, come additional questions. What are the precise mechanisms linking PD or infection with *P. gingivalis* to RA development? Important questions remain regarding the timing of PD therapy, the optimal PD treatment strategy to be used, and the expected duration of benefits in terms of RA treatment response. Specifically, can treatment in the pre-clinical period prevent or even delay RA onset? What role does PD treatment play in established RA? Can treatment in early RA yield disease remission or retard RA disease progression? In addition to these and other questions, research will be needed to further explore more efficient means of identifying patients with PD. Combining PD risk factors with self-report questionnaires shows promise for fulfilling this need, although biomarker discovery could greatly enhance case-finding strategies moving forward.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Periodontitis (PD) is associated with an increased prevalence and severity of rheumatoid arthritis (RA).
- *P. gingivalis*, an oral pathogen implicated in RA risk, has the capacity to citrullinate proteins that are targeted by RA-specific autoantibodies and has, therefore, been speculated to play a role in RA pathogenesis.
- Although limited in size and scope, several small trials have shown that the treatment of PD leads to improved outcomes in patients with RA.
- Early efforts suggest that self-reported signs and symptoms of PD, coupled with risk factor assessment, may provide an efficient approach for identifying patients that would benefit from the referral for full-mouth examination and possible PD treatment.

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