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Periodontal Disease and Subgingival Microbiota as Contributors for RA Pathogenesis: Modifiable Risk Factors?

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Abstract

Purpose of review—Since the early 1900s, the role of periodontal disease in the pathogenesis of rheumatoid arthritis has been a matter of intense research. The last decade has witnessed many advances supporting a link between periodontitis, the presence of specific bacterial species (i.e., *Porphyromonas gingivalis*) and their effects in immune response. This review will examine available evidence on the subject.

Recent findings—Epidemiological studies have stressed the commonalities shared by periodontal disease and rheumatoid arthritis. Many groups have focused their attention towards understanding the periodontal microbiota and its alterations in states of health and disease. The presence of circulating antibodies against periodontopathic bacteria and associated inflammatory response has been found in both RA patients and subjects at-risk for disease development. Most recently, the periodontal microbiota of smokers and patients with RA has been elucidated, revealing profound changes in the bacterial communities compared to that of healthy controls. This has led to several small clinical trials of PD treatment as adjuvant for disease-modifying therapy in RA.

Summary—Smoking and periodontal disease are emerging risk factors for the development of RA. Epidemiological, clinical and basic research has further strengthened this association, pointing towards changes in the oral microbiota as possible contributors to systemic inflammation and arthritis.

Keywords

Periodontal; Microbiota; *Porphyromonas*; Rheumatoid; Smoking; TNF

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Conflict of Interest:

The authors declare no conflicts of interest.

Introduction

Rheumatoid arthritis (RA) describes a relatively novel term defining one of the most common inflammatory arthropathies. It affects roughly 1% of the Caucasian population and its incidence peaks in middle-age women[1]. Some ethnic groups, particularly those belonging to various Native American tribes, have a strikingly high prevalence of the disease, leading to the speculation that RA is rather a disease of the New World that has been ‘transmitted’ to other populations after the Conquest [2,3]. Genes have been implicated, but the current discoveries by gene-wide association studies (GWAS) can only explain about a quarter of the disease variance[4]. Further, studies in monozygotic twins revealed a concordance rate of up to 15%, suggesting that environmental and/or epigenetic factors are required for clinically evident RA[5–7].

Anti-citrullinated peptide antibodies (ACPAs) are immunoglobulins highly specific for the diagnosis of RA and are markers for worse prognosis and disease progression[8]. Intriguingly, they are detectable in circulation many years prior to the development of clinically classifiable RA (i.e., pre-clinical phase of disease)[9]. During this phase, curiously, the synovial architecture shows no signs of inflammation or immune cell activation[10]. This, coupled with the fact that ACPA and cytokine titers only rise just a few months prior to clinical arthritis[11], has led to many investigators to propose that there must be a ‘second hit’ beyond the mere presence of humoral autoimmunity in order to trigger the synovitis phase of RA.

Many environmental factors have been contemplated in RA pathogenesis over time[12]. Chief among those is tobacco smoking[13]. Recent epidemiological data supports this association, particularly in the context of genetic predisposition and seropositivity[14]. The mechanistic reasons behind this connection are likely multifactorial, but a plausible explanation may relate to the deleterious effects of tobacco and other substances in mucosal sites, particularly in the periodontium and distal airways. In this review we will cover the most current knowledge on smoking as a risk factor for both PD and RA, periodontal disease pathogenesis (and its microbiota changes) and rheumatoid arthritis development.

The Healthy Periodontal Microbiome

The oral cavity harbors billions of bacteria and ranks second in total microbial load when compared to the human gut and other body sites. Over 1000 species or phylotypes have been detected in the oral cavity by our group and others[15,16].

Early observations employing 16S rRNA gene-sequencing evaluated the oral microbiome of clinically healthy individuals[17]. Biofilm samples from subgingival sites with no signs of disease or inflammation (gingival sulci) were obtained. Whereas several species of *Streptococcus* and *Gemella* were often found, species associated with periodontal disease, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, could not be detected. Other studies have identified these putative periodontal pathogens in healthy gingival tissues, although at low levels[18,19].

Interestingly, the microbiome diversity of the healthy oral cavity is dependent on geographic localization. Examination of healthy gingival sulci has unraveled a distinct predilection of *Streptococci* at high levels for the vestibular gingival sulci and of *Fusobacterium* for the lingual gingival sulci[20]. These differences are related to the oxygen conditions, which are lower for the lingual sites, leading to selection for anaerobic species such as *Fusobacterium*. Conversely, oxygen levels in the vestibular sites are higher, providing a biologically stable environment for aerobes or facultative anaerobes such as *Streptococci*. This fact underscores the need to sample multiple sites when studying the subgingival microbiome.

Other studies using 454-pyrosequencing suggested that the relative abundance of Actinomyces, was higher in health when compared to PD patients[21].

Lastly, a study employing a small number of periodontally healthy subjects confirmed previous studies showing that gram-positive genera such as *Streptococcus*, *Actinomyces*, and *Granulicatella* were significantly enriched in healthy periodontal samples[22]. Moreover, this study looked at the functional potential of the healthy periodontal microbiome. A limited number of pathways were significantly enriched in the periodontally healthy microbiome including pathways for fatty acid biosynthesis, purine metabolism, and glycerol-3-phosphate metabolism. Fatty acids in particular have been shown to have a protective role in periodontal health, suggesting that some of these metabolites are synthesized by the healthy microbiota in an effort to protect against periodontopathic taxa.

Smoking and Periodontal Diseases

Tobacco smoking is an established and modifiable risk factor for periodontal inflammation and destruction[23]. Similarly, smoking has a negative impact on several inflammatory diseases, including rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease[24].

The epidemiology of the effects of tobacco smoking on periodontal health and possible associated mechanisms has been extensively reviewed [25,26] and is beyond the scope of this manuscript. Evidence for the association between smoking and destructive periodontitis is apparent in several cross-sectional studies. The strength of these associations derives from one of the largest studies involving over 1300 subjects[27]. Participants who smoked were at greater risk for experiencing severe bone loss compared to never-smokers. Light and heavy smokers exhibited odds ratios for PD of 3.35 and 7.8, respectively. A more recent study based on 12,239 participants in NHANES III database corroborated earlier findings and showed that current smokers were 4 times more likely to be diagnosed with destructive periodontitis than non-smokers and that a dose-response could be demonstrated[28].

Longitudinal studies have also provided evidence of the relationship of smoking and PD in young and older adults alike[29–32], demonstrating that tooth loss, bone loss and attachment loss significantly increased overtime in smokers when compared to non-smokers. Interestingly, the periodontal health condition in former smokers is similar to that of non-smokers and remains stable over time, suggesting that smoking cessation can reverse at least partially periodontal homeostasis.

Observations of the Effects of Smoking on the Selection of Periodontal Pathogens

Periodontal diseases are chronic polymicrobial infections that lead to local inflammatory reactions mediated by antigenic challenges. Evaluation of how microbes activate the immune system in the periodontal tissues is possible through sampling of subgingival periodontal biofilms. Available data related to the effects of smoking on the selection of periodontal pathogens suggests that smokers may harbor a putative periodontal pathogenic flora. Early observations using culture-dependent methods showed that *Porphyromonas gingivalis*, *Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans* were more prevalent in smokers than in no-smokers[33]. Others have studied the effects of smoking on selected periodontal pathogens in periodontal patients[34]. Using logistic regression analysis, one group revealed that smoking and specific measures for PD (i.e., increased periodontal probing depth) significantly correlated with the detection of *A. actinomycetemcomitans*, *Prevotella intermedia*, and *Eikenella corrodens*. Employing real time PCR, Teixeira et al. have also demonstrated a positive dose-response relationship between smoking and levels of putative periodontal pathogens, most notably *P. gingivalis*[35,36].

These findings have been somehow controversial, as others have reported no differences between smokers and non-smokers with respect to the detection of periodontal pathogens [37,38] in terms of prevalence [39] and microbial load [34] in the subgingival domain.

A more recent study looked at the subgingival microbiota of current and never-smokers with PD using 16S sequencing [40]. The microbial profile of smoking-associated PD was distinct from that of non-smokers, with significant differences in the prevalence and abundance of multiple organisms, including increases in pro-periodontopathic taxa such as *Parvimonas*, *Fusobacterium*, and *Treponema*. Taken together, these studies suggest that smoking can be associated with a specific microbial signature independent of PD status.

Smoking and Rheumatoid Arthritis

Tobacco smoking is perhaps the best-established environmental risk factor for RA development[41–43].

A recent meta-analysis has corroborated this relationship, particularly in those patients that are seropositive and heavy smokers[44].

Population-based case–control studies[43] have shown that smokers have twice the risk of developing seropositive RA when compared with never smokers. This association appears to be dose-dependent on lifetime exposure to smoking.[45,46]

As discussed, compelling evidence has also shown strong gene–environment interactions between smoking and human leukocyte antigen (HLA)-containing shared epitope alleles (HLA-DR SE)[47]. This gene–smoking interaction appears to markedly influence the development of anticitrulline antibody (ACPA)–positive RA[48]. This interaction, however, cannot be demonstrated in patients with ACPA–negative RA. Notably, antibodies against

citrullinated peptides are found in sera from patients with aggressive PD without arthritis[49], although a gene-environment interaction between HLA-DR SE genes and chronic PD has not been reported.

Little is known about the effects of smoking cessation on future risk of RA. A recent study in women[50] showed that the risk of RA decreases over time after smoking cessation. However, when former smokers were compared to never smokers, the risk was still statistically significantly higher. Interestingly, investigators have also been able to show effects of smoking cessation on the gut microbiome[51]. Marked shifts in the microbial composition after smoking cessation could be demonstrated with an increase of Firmicutes and Actinobacteria and lower proportions of Bacteroidetes and Proteobacteria. In addition, an increase in microbial diversity could be observed after smoking cessation. This could explain, at least partially, why smoking exacerbates Crohn's disease. Whether these shifts in the gut microbiome after smoking cessation translates into decreased risk for RA remains to be established.

The Microbiome in Periodontal Disease

A classical study in the field of periodontology looked at bacterial complexes involved in PD, based on microbial analyses of 185 subjects in over 13,000 subgingival plaque samples[52]. The results showed unequivocally that higher levels of *P. gingivalis*, *T. forsythia* and *T. denticola* in dental plaque are strongly associated with periodontal disease. Since then, this group of microorganisms has been termed the 'red complex bacteria' and numerous studies have replicated these findings.

The subgingival microbiome of diseased and healthy sites were also evaluated by 16S rRNA sequencing in PD and controls[15]. The relative abundance of 51 of 170 genera and 200 of 746 species were found to be significantly different between healthy and diseased sites. Within the deep sites, several species implicated in the original PD studies exhibited significant increases. This was particularly true for *P. gingivalis*, *Porphyromonas endodontalis*, *Fusobacterium nucleatum*, *Prevotella nigrescens*, *Treponema denticola*, *Treponema medium* and *Tannerella forsythia*.

Periodontal Disease, Subgingival Microbiota, *P. gingivalis* and Rheumatoid Arthritis

The concept that PD is implicated in RA pathogenesis is not original. In the early days of the 20th century, the 'oral sepsis' hypothesis was proposed to involve apical infections of the teeth in the etiology of RA[53]. This led to the use of dental extraction as a therapeutic option, which went on for at least four decades until it was eventually deemed not clinically beneficial. A more refined and complex hypothesis was suggested a decade ago by Rosenstein and Weissman[54], who proposed that it was actually the humoral immune response to *P. gingivalis* what provided a stimulus for the development of RA. Multiple recent lines of investigation have supported this relationship between PD, *P. gingivalis*, ACPA and RA[55]. First, several studies have shown an increased prevalence of PD in RA patients, even at the onset of disease[56–59], arguing for either a causal relationship and/or a

common etiopathogenic pathway. Second, it has been postulated that ACPA generation is the result of citrullination of arginine residues in human tissues by the enzyme Peptidyl Arginine Deiminase (PAD). This is of particular importance because *P. gingivalis* is reportedly the only bacterial species that carries PAD as part of its enzymatic machinery. Notably, *P. gingivalis*-derived PAD is able to citrullinate human peptides[60], while human citrullinated peptides (such as alpha-enolase) are sufficient for triggering inflammatory arthritis in animal models[61]. Moreover, the presence of antibodies to *P. gingivalis* has also been correlated with autoimmunity (i.e., circulating ACPA) and clinical RA. This is not only true for patients with established RA[62–64], but also in subjects at-risk for disease development (i.e., first-degree relatives)[65]. However, the demonstrated prevalence of such humoral response has been variable, mostly due to the heterogeneity of the assays employed in the different studies[66].

Finally, only a handful of reports looked at the presence of *P. gingivalis* (or other microorganisms) in subgingival biofilms of patients with RA. With the use of high-throughput, bacterial DNA sequencing, we have shown that about 55% of new-onset, untreated RA patients carried *P. gingivalis*, twice as many as healthy controls[57]. This difference did not reach statistical significance and was mostly due to the high prevalence of the advanced forms of PD in the RA groups, rather than secondary to arthritis phenotype. These findings suggest that while both PD and the presence of *P. gingivalis* may promote autoantibody formation in RA, only PD demonstrate an independent relationship with established seropositive RA (both in the new-onset and the chronic phases of the disease). Utilizing low-throughput PCR technology, Mikuls et al. have recently validated these observations in a large case-control study[67]. A smaller study by Wolff B. et al., reported similar clinical associations in early RA patients and a trend towards *P. gingivalis* increase[68].

Interestingly, we and others have identified additional bacterial species that correlate with either RA-related autoantibodies (*Anaeroglobus geminatus*) or early RA (i.e., *Prevotella*, *Leptotrichia* and *Tannerella* species). This reinforces the notion that RA may require other antigenic triggers in the context of PD, as recently demonstrated by Abdollahi et. al., using a murine model of PD and RA in which both *P. gingivalis* and *Prevotella nigrescens* were able to promote subgingival and synovial inflammation, albeit through different immune mechanisms[69].

Periodontal Disease Treatment as Adjuvant for Disease-Modifying Antirheumatic Drugs (DMARDs)

Scaling and root planning remains the mainstay of therapy for PD. It consists of a non-surgical process aimed at eliminating the etiologic agents of PD, namely dental plaque, its products, and calculus formation. If in fact PD is at least partially responsible for the systemic inflammatory process found in RA, then it follows that scaling and root planning should help ameliorate synovitis and disease outcomes. To date, only a few relatively small studies have looked at this hypothesis. One of the first such trials evaluated disease outcomes in 20 subjects with RA on background DMARDs and 20 receiving DMARDs plus anti-TNF treatment[70]. Each of the groups was randomized to either scaling/root planning

or no PD treatment. Patients that received PD treatment showed a significant decrease in DAS28, ESR and serum TNF- α levels compared to those without PD therapy. Curiously, anti-TNF therapy also resulted in a significant improvement in clinical PD parameters. These findings have also been corroborated independently in different geographic regions[71–73]. In a recent prospective study on RA patients about to undergo anti-TNF treatment, it was shown that the presence of persistent PD hampered the clinical response to TNF-blockade since only those patients without established periodontitis achieved good RA outcomes[74].

Taken together, these studies support the notion that PD may affect treatment efficacy in patients with RA and that a dual, combination approach may be warranted to potentially increase the clinical response of various immunosuppressive drugs.

Conclusion

The role of tobacco smoking in PD has been established many decades ago. Emerging epidemiologic and mechanistic work is now revealing that smoking is also a risk factor for the development of RA, particularly in the ACPA-positive, SE-positive subset. An association between tobacco, PD, presence of *P. gingivalis* and RA has been strengthened by multiple lines of research, particularly with the advent of novel bacterial DNA sequencing technologies that bypass the need for classic microbiologic culture methods. Because smoking and PD are readily modifiable contributing factors to RA pathogenesis, it is plausible that a multidisciplinary approach to treatment may hold the key for achieving better outcomes in more patients with RA. Small-scale data supports the potential utility for such approach. A large, randomized, clinical trial will be therefore required to address this highly relevant question. Incorporating periodontal microbiota analyses and RA/PD outcomes will also be necessary in order to better understand the biologic connection between these two seemingly interdependent disease processes.

Abbreviations

RA	Rheumatoid Arthritis
PD	periodontal disease
DMARD	disease-modifying anti-rheumatic

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011; 365:2205–2219. [PubMed: 22150039]
2. Rothschild BM, Woods RJ, Rothschild C, Sebes JI. Geographic distribution of rheumatoid arthritis in ancient North America: implications for pathogenesis. *Semin Arthritis Rheum*. 1992; 22:181–187. [PubMed: 1295091]
3. Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. *Nat Rev Rheumatol*. 2011
4. Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, Kraft P, Chen R, Kallberg HJ, Kurreeman FA, et al. Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis. *Nat Genet*. 2012; 44:483–489. [PubMed: 22446960] •• one of the latest analyses of genetic contribution in RA, including the rare variants implicated in disease variance.

5. Aho K, Koskenvuo M, Tuominen J, Kaprio J. Occurrence of rheumatoid arthritis in a nationwide series of twins. *J Rheumatol.* 1986; 13:899–902. [PubMed: 3820198]
6. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, Ollier WE. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. *Br J Rheumatol.* 1993; 32:903–907. [PubMed: 8402000]
7. Svendsen AJ, Holm NV, Kyvik K, Petersen PH, Junker P. Relative importance of genetic effects in rheumatoid arthritis: historical cohort study of Danish nationwide twin population. *BMJ.* 2002; 324:264–266. [PubMed: 11823356]
8. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, van Venrooij WJ. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* 2000; 43:155–163. [PubMed: 10643712]
9. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, Habibuw MR, Vandenbroucke JP, Dijkmans BA. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum.* 2004; 50:380–386. [PubMed: 14872479]
10. van de Sande MG, de Hair MJ, Schuller Y, van de Sande GP, Wijbrandts CA, Dinant HJ, Gerlag DM, Tak PP. The features of the synovium in early rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria. *PLoS One.* 2012; 7:e36668. [PubMed: 22574210] •very important study that underscores the presence of circulating autoantibodies in subjects with normal synovial histology.
11. Sokolove J, Bromberg R, Deane KD, Lahey LJ, Derber LA, Chandra PE, Edison JD, Gilliland WR, Tibshirani RJ, Norris JM, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. *PLoS One.* 2012; 7:e35296. [PubMed: 22662108] •this is a comprehensive study of ACPA epitope recognition spreading and cytokine production months before the clinically evident phase of RA.
12. Arend WP, Firestein GS. Pre-rheumatoid arthritis: predisposition and transition to clinical synovitis. *Nat Rev Rheumatol.* 2012; 8:573–586. [PubMed: 22907289]
13. Silman AJ. Smoking and the risk of rheumatoid arthritis. *J Rheumatol.* 1993; 20:1815–1816. [PubMed: 8308762]
14. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren AK, Rantapaa-Dahlqvist S, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006; 54:38–46. [PubMed: 16385494]
15. Ge X, Rodriguez R, Trinh M, Gunsolley J, Xu P. Oral microbiome of deep and shallow dental pockets in chronic periodontitis. *PLoS One.* 2013; 8:e65520. [PubMed: 23762384]
16. Peterson SN, Snesrud E, Liu J, Ong AC, Kilian M, Schork NJ, Bretz W. The dental plaque microbiome in health and disease. *PLoS One.* 2013; 8:e58487. [PubMed: 23520516] •this study delineates the bacterial composition of dental plaque and serves as a guidance for studies in the field.
17. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol.* 2005; 43:5721–5732. [PubMed: 16272510]
18. Bik EM, Long CD, Armitage GC, Loomer P, Emerson J, Mongodin EF, Nelson KE, Gill SR, Fraser-Liggett CM, Relman DA. Bacterial diversity in the oral cavity of 10 healthy individuals. *ISME J.* 2010; 4:962–974. [PubMed: 20336157]
19. Ximenez-Fyvie LA, Haffajee AD, Socransky SS. Comparison of the microbiota of supra- and subgingival plaque in health and periodontitis. *J Clin Periodontol.* 2000; 27:648–657. [PubMed: 10983598]
20. Simon-Soro A, Tomas I, Cabrera-Rubio R, Catalan MD, Nyvad B, Mira A. Microbial geography of the oral cavity. *J Dent Res.* 2013; 92:616–621. [PubMed: 23674263]
21. Abusleme L, Dupuy AK, Dutzan N, Silva N, Burleson JA, Strausbaugh LD, Gamonal J, Diaz PI. The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation. *ISME J.* 2013; 7:1016–1025. [PubMed: 23303375]

22. Liu B, Faller LL, Klitgord N, Mazumdar V, Ghodsi M, Sommer DD, Gibbons TR, Treangen TJ, Chang YC, Li S, et al. Deep sequencing of the oral microbiome reveals signatures of periodontal disease. *PLoS One*. 2012; 7:e37919. [PubMed: 22675498]
23. Kinane DF, Chestnutt IG. Smoking and periodontal disease. *Crit Rev Oral Biol Med*. 2000; 11:356–365. [PubMed: 11021635]
24. Johannsen A, Susin C, Gustafsson A. Smoking and inflammation: evidence for a synergistic role in chronic disease. *Periodontol* 2000. 2014; 64:111–126. [PubMed: 24320959]
25. Ryder MI. The influence of smoking on host responses in periodontal infections. *Periodontol* 2000. 2007; 43:267–277. [PubMed: 17214844]
26. Palmer RM, Wilson RF, Hasan AS, Scott DA. Mechanisms of action of environmental factors--tobacco smoking. *J Clin Periodontol*. 2005; (32 Suppl 6):180–195. [PubMed: 16128837]
27. Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, Zambon JJ, Hausmann E. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol*. 1995; 66:23–29. [PubMed: 7891246]
28. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. *J Periodontol*. 2000; 71:743–751. [PubMed: 10872955]
29. Baljoon M, Natto S, Bergstrom J. Long-term effect of smoking on vertical periodontal bone loss. *J Clin Periodontol*. 2005; 32:789–797. [PubMed: 15966888]
30. Machtei EE, Dunford R, Hausmann E, Grossi SG, Powell J, Cummins D, Zambon JJ, Genco RJ. Longitudinal study of prognostic factors in established periodontitis patients. *J Clin Periodontol*. 1997; 24:102–109. [PubMed: 9062856]
31. Beck JD, Sharp T, Koch GG, Offenbacher S. A 5-year study of attachment loss and tooth loss in community-dwelling older adults. *J Periodontol Res*. 1997; 32:516–523. [PubMed: 9379319]
32. Holm G. Smoking as an additional risk for tooth loss. *J Periodontol*. 1994; 65:996–1001. [PubMed: 7853136]
33. Zambon JJ, Grossi SG, Machtei EE, Ho AW, Dunford R, Genco RJ. Cigarette smoking increases the risk for subgingival infection with periodontal pathogens. *J Periodontol*. 1996; 67:1050–1054. [PubMed: 8910822]
34. Stoltenberg JL, Osborn JB, Pihlstrom BL, Herzberg MC, Aeppli DM, Wolff LF, Fischer GE. Association between cigarette smoking, bacterial pathogens, and periodontal status. *J Periodontol*. 1993; 64:1225–1230. [PubMed: 8106950]
35. Teixeira SR, Mattarazo F, Feres M, Figueiredo LC, de Faveri M, Simionato MR, Mayer MP. Quantification of *Porphyromonas gingivalis* and *fimA* genotypes in smoker chronic periodontitis. *J Clin Periodontol*. 2009; 36:482–487. [PubMed: 19508247]
36. Gomes SC, Piccinin FB, Oppermann RV, Susin C, Nonnenmacher CI, Mutters R, Marcantonio RA. Periodontal status in smokers and never-smokers: clinical findings and real-time polymerase chain reaction quantification of putative periodontal pathogens. *J Periodontol*. 2006; 77:1483–1490. [PubMed: 16945023]
37. Salvi GE, Ramseier CA, Kandylaki M, Sigrist L, Awedowa E, Lang NP. Experimental gingivitis in cigarette smokers: a clinical and microbiological study. *J Clin Periodontol*. 2005; 32:441–447. [PubMed: 15842257]
38. Apatzidou DA, Riggio MP, Kinane DF. Impact of smoking on the clinical, microbiological and immunological parameters of adult patients with periodontitis. *J Clin Periodontol*. 2005; 32:973–983. [PubMed: 16104962]
39. Darby IB, Hodge PJ, Riggio MP, Kinane DF. Microbial comparison of smoker and non-smoker adult and early-onset periodontitis patients by polymerase chain reaction. *J Clin Periodontol*. 2000; 27:417–424. [PubMed: 10883871]
40. Shchipkova AY, Nagaraja HN, Kumar PS. Subgingival microbial profiles of smokers with periodontitis. *J Dent Res*. 2010; 89:1247–1253. [PubMed: 20739702]
41. Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. *J Rheumatol*. 1993; 20:1830–1835. [PubMed: 8308766]

42. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. *Arthritis Rheum.* 1996; 39:732–735. [PubMed: 8639169]
43. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, Alfredsson L, group Es. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis.* 2003; 62:835–841. [PubMed: 12922955]
44. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis.* 2010; 69:70–81. [PubMed: 19174392]
45. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther.* 2014; 16:R61. [PubMed: 24594022] •a complete meta-analysis confirming the risk of RA development in cigarette smokers, even when longlife exposure is low.
46. Hutchinson D, Moots R. Cigarette smoking and severity of rheumatoid arthritis. *Rheumatology (Oxford).* 2001; 40:1426–1427. [PubMed: 11752525]
47. Karlson EW, Chang SC, Cui J, Chibnik LB, Fraser PA, De Vivo I, Costenbader KH. Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. *Ann Rheum Dis.* 2010; 69:54–60. [PubMed: 19151010]
48. Klareskog L, Padyukov L, Ronnelid J, Alfredsson L. Genes, environment and immunity in the development of rheumatoid arthritis. *Curr Opin Immunol.* 2006; 18:650–655. [PubMed: 17010589]
49. Hendler A, Mulli TK, Hughes FJ, Perrett D, Bombardieri M, Hourri-Haddad Y, Weiss EI, Nissim A. Involvement of autoimmunity in the pathogenesis of aggressive periodontitis. *J Dent Res.* 2010; 89:1389–1394. [PubMed: 20940360]
50. Di Giuseppe D, Orsini N, Alfredsson L, Askling J, Wolk A. Cigarette smoking and smoking cessation in relation to risk of rheumatoid arthritis in women. *Arthritis Res Ther.* 2013; 15:R56. [PubMed: 23607815]
51. Biedermann L, Zeitz J, Mwinyi J, Sutter-Minder E, Rehman A, Ott SJ, Steurer-Stey C, Frei A, Frei P, Scharl M, et al. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One.* 2013; 8:e59260. [PubMed: 23516617]
52. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol.* 1998; 25:134–144. [PubMed: 9495612]
53. Hunter W. Oral Sepsis as a Cause of Disease. *Br Med J.* 1900; 2:215–216. [PubMed: 20759127]
54. Rosenstein ED, Greenwald RA, Kushner LJ, Weissmann G. Hypothesis: the humoral immune response to oral bacteria provides a stimulus for the development of rheumatoid arthritis. *Inflammation.* 2004; 28:311–318. [PubMed: 16245073]
55. Scher JU, Abramson SB. Periodontal disease, *Porphyromonas gingivalis*, and rheumatoid arthritis: what triggers autoimmunity and clinical disease? *Arthritis Res Ther.* 2013; 15:122. [PubMed: 24229458]
56. de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol.* 2008; 35:70–76. [PubMed: 18050377]
57. Scher JU, Ubeda C, Equinda M, Khanin R, Buischi Y, Viale A, Lipuma L, Attur M, Pillinger MH, Weissmann G, et al. Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis. *Arthritis Rheum.* 2012; 64:3083–3094. [PubMed: 22576262] ••our study is the first to utilize high-throughput pyrosequencing to investigate the oral microbiota in early RA patients. PD was present in more than 75% of all RA patients, including those with new-onset disease. *P. gingivalis* was twice as prevalent in RA vs healthy subjects. Other species not previously associated with arthritis were unique to the oral microbiota of new-onset RA patients.
58. Dissick A, Redman RS, Jones M, Rangan BV, Reimold A, Griffiths GR, Mikuls TR, Amdur RL, Richards JS, Kerr GS. Association of periodontitis with rheumatoid arthritis: a pilot study. *J Periodontol.* 2010; 81:223–230. [PubMed: 20151800]
59. Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. *J Periodontol.* 2001; 72:779–787. [PubMed: 11453241]

60. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, Kinloch A, Culshaw S, Potempa J, Venables PJ. Peptidylarginine deiminase from *Porphyromonas gingivalis* citrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis. *Arthritis Rheum.* 2010; 62:2662–2672. [PubMed: 20506214]
61. Kinloch AJ, Alzabin S, Brintnell W, Wilson E, Barra L, Wegner N, Bell DA, Cairns E, Venables PJ. Immunization with *Porphyromonas gingivalis* enolase induces autoimmunity to mammalian alpha-enolase and arthritis in DR4-IE-transgenic mice. *Arthritis Rheum.* 2011; 63:3818–3823. [PubMed: 21953289]
62. Arvikar SL, Collier DS, Fisher MC, Unizony S, Cohen GL, McHugh G, Kawai T, Strle K, Steere AC. Clinical correlations with *Porphyromonas gingivalis* antibody responses in patients with early rheumatoid arthritis. *Arthritis Res Ther.* 2013; 15:R109. [PubMed: 24017968]
63. Smit MD, Westra J, Vissink A, Doornbos-van der Meer B, Brouwer E, van Winkelhoff AJ. Periodontitis in established rheumatoid arthritis patients: a cross-sectional clinical, microbiological and serological study. *Arthritis Res Ther.* 2012; 14:R222. [PubMed: 23075462]
64. Mikuls TR, Payne JB, Reinhardt RA, Thiele GM, Maziarz E, Cannella AC, Holers VM, Kuhn KA, O'Dell JR. Antibody responses to *Porphyromonas gingivalis* (*P. gingivalis*) in subjects with rheumatoid arthritis and periodontitis. *Int Immunopharmacol.* 2009; 9:38–42. [PubMed: 18848647]
65. Hitchon CA, Chandad F, Ferucci ED, Willemze A, Ioan-Facsinay A, van der Woude D, Markland J, Robinson D, Elias B, Newkirk M, et al. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. *J Rheumatol.* 2010; 37:1105–1112. [PubMed: 20436074]
66. Brusca SB, Abramson SB, Scher JU. Microbiome and mucosal inflammation as extra-articular triggers for rheumatoid arthritis and autoimmunity. *Curr Opin Rheumatol.* 2014; 26:101–107. [PubMed: 24247114]
67. Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, Markt J, McGowan D, Kerr GS, Redman RS, et al. Periodontitis and *Porphyromonas gingivalis* in Patients with Rheumatoid Arthritis. *Arthritis Rheum.* 2014••one of the latest and largest studies looking at clinical periodontitis and presence of *P.gingivalis* in subgingival plaque. The authors find that while both PD and *P.gingivalis* correlate with the presence of autoantibodies, only PD is an independent risk factor for RA.
68. Wolff B, Berger T, Frese C, Max R, Blank N, Lorenz HM, Wolff D. Oral status in patients with early rheumatoid arthritis: a prospective, case-control study. *Rheumatology (Oxford).* 2014; 53:526–531. [PubMed: 24273047]
69. Sabrina G. de Aquino SA-R, Marije I. Koenders, Fons A. J. van de Loo, Ger J. M. Puijn, Renoud J. Marijnissen, Birgitte Walgreen, Monique M. Helsen, Liduine A. van den Bersselaar, Rafael S. de Molon, Mario J. Avila Campos, Fernando Q. Cunha, Joni A Cirelli, Wim B. van den Berg. van den Berg: Periodontal Pathogens Directly Promote Autoimmune Experimental Arthritis by Inducing a TLR2-and IL-1–Driven Th17 Response. *Journal of Immunology.* 2014 **ePub ahead of print March 28, 2014.**
70. Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, Askari A. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol.* 2009; 80:535–540. [PubMed: 19335072]
71. Erciyas K, Sezer U, Ustun K, Pehlivan Y, Kisacik B, Senyurt SZ, Tarakcioglu M, Onat AM. Effects of periodontal therapy on disease activity and systemic inflammation in rheumatoid arthritis patients. *Oral Dis.* 2013; 19:394–400. [PubMed: 22998534]
72. Ribeiro J, Leao A, Novaes AB. Periodontal infection as a possible severity factor for rheumatoid arthritis. *J Clin Periodontol.* 2005; 32:412–416. [PubMed: 15811060]
73. Al-Katma MK, Bissada NF, Bordeaux JM, Sue J, Askari AD. Control of periodontal infection reduces the severity of active rheumatoid arthritis. *J Clin Rheumatol.* 2007; 13:134–137. [PubMed: 17551378]
74. Savioli C, Ribeiro AC, Fabri GM, Calich AL, Carvalho J, Silva CA, Viana VS, Bonfa E, Siqueira JT. Persistent periodontal disease hampers anti-tumor necrosis factor treatment response in rheumatoid arthritis. *J Clin Rheumatol.* 2012; 18:180–184. [PubMed: 22647860] ••in a small but

intriguing study, the presence of baseline PD diminishes the efficacy of anti-TNF therapy in patients with RA.

Key points

- Genetic risk alleles in rheumatoid arthritis have been extensively studied, although they can only explain a fraction of the total disease variance.
- Environmental factors implicated in RA include smoking and chronic infections.
- Periodontal diseases and the microbes harboured in the dental plaque, particularly *porphyromonas ginigivalis* and the elicited humoral immune response, appear to have a pathogenic role.
- The oral microbiota and its local and systemic effects in health and disease are being elucidated.
- A combination therapeutic approach using DMARDs and non-surgical PD treatment may improve RA outcomes.