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SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

Association Between Rheumatoid Arthritis and Periodontitis: Recent Progress

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Abstract

Purpose of Review While a number of reviews have been published in recent years covering all aspects of the relationship between rheumatoid arthritis and periodontitis, this review considers only the very most recent advances in the field by reporting on studies published from January 2018 to August 2019.

Recent Findings The number of published studies that have investigated this relationship has increased dramatically in recent years. These studies have established a number of important biochemical, cellular, genetic and microbiological processes that link these two conditions at the clinical level.

Summary There is now very good evidence to support a relationship between RA and periodontitis. It is clear that very good progress is being made but there is need for continuing investigations to better identify the defining mechanism(s) that drive this intriguing relationship.

Keywords Rheumatoid arthritis · Periodontitis · Association

Introduction

The concept of an association between rheumatoid arthritis (RA) and periodontitis (PD) has been discussed for over two centuries. In the 1949 Proceedings of the Royal Society of Medicine, it was suggested that dental infections may play a role in various rheumatic syndromes [1]. Following this statement, there has been a steady growth of evidence linking rheumatic disorders with periodontal inflammation and infection. Among the rheumatic diseases, RA has gained most attention due to the similarities in the pathological features between RA and PD such as being chronic inflammatory in nature and it involves dysregulation of the immune system as well as destruction of soft and hard tissues [2].

Thus far, proposed explanations for the relationship include the direct action of PD-associated bacteria, autoantigen production during the course of PD and the shared inflammatory pathway exacerbating both diseases [3–6]. However, in 2013, the European Federation of Periodontology and American Association of Periodontology workshop on PD and systemic diseases conveyed their concern on the limited sound epidemiological evidence to support the role of PD as a risk factor for RA and vice versa [7]. In response to this statement, extensive work has been carried out to further explore the plausible biological link between RA and PD. A recent review by Bartold and Lopez-Olivia in *Periodontology 2000* thoroughly reviewed the available evidence published until 2017 and concluded that there was remarkable progress in evaluating the link between RA and PD and most of the studies showed a trend of supporting the association [8].

From January 2018 to August 2019, an additional 55 studies concerning RA and PD have been published (Table 1). Thirteen of these publications are review articles including two systematic reviews analysing the cohort studies and microbiological evidence. Similar to publications from the year

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Table 1 Publications concerning link between RA and PD in 2018–2019

Theme of studies	Number of publications
Narractive reviews	10
Epidemiology and genetic studies	13
Role of microorganism in the association	13
Production of autoantigens independent to periopathogens	4
Molecular mechanism underlying the association and environmental studies	8
Intervention studies	7

2012 till 2017, recent evidence of RA and PD over the past 2 years has resulted from 10 publications on population-based cohort studies and also cross-sectional studies examining the specific microbiological or molecular aspects of the association. However, there has been a shift in the trend of experimental studies conducted, moving from animal studies to human studies especially in the form of clinical trials to assess the effect of periodontal treatment on RA or the affect anti-rheumatic drugs in RA patients with PD. Therefore, following the comprehensive review by Bartold and Lopez-Olivia (2020), this article aims to summarize the most recent scientific evidence and further appraise the association between RA and PD. The studies covered in this review are summarized in Table 2 which excludes narrative reviews.

Epidemiologic Evidence on Association Between RA and PD

From the 11 published cohort studies, 4 publications were cross-sectional studies, 3 were case-control studies and 1 systematic review. Fifty percent of these studies were carried out in the Asia Pacific region. Among the cross-sectional studies, 4 out of 6 studies reported an association between RA and PD [9–12]. The two studies that did not find any association between the two diseases was a cross-sectional study carried out in Malaysia which only found 2 out of 44 RA patients recruited who presented with pocket depths deeper than 3 mm [13] and a study carried out in South Korea of 20,297 subjects which reported that RA was only associated with tooth loss in younger adults [14]. All case-control studies demonstrated a positive association between RA and PD [15–17].

Interestingly, in three studies where the sample size of RA patients was less than 100 and recruited from a single rheumatology centre, the prevalence of those suffering PD was either very low [13] or very high [9, 11, 18]. However, in a larger population using data from the Korea National Health and Nutrition Examination Survey, the prevalence was only approximately 28% [12] to 32% [14] compared with 60 to 70% in the former studies [9, 11].

Jung and colleagues found 1.5% of their subjects had RA, which was in agreement with previous prevalence studies [19, 20]. Using a univariate analysis, the risk for periodontal disease was shown to be 1.64 times higher in subjects with RA than those without RA, and 1.97 times higher when adjusted for sex and age, which was statistically significant [12]. This was also in agreement with another prevalence study carried out in the USA [21] and Taiwan [22]. A recent systematic review suggested an association between RA and PD by the common pro-inflammatory profiles. A further meta-analysis also showed a higher RA prevalence for subjects with PD (OR 1.97; CI 1.68–2.31; $p < 0.00001$) although considerable heterogeneity among studies was significant [23].

Genetic Basis of Relationship Between RA and PD

Previous studies carried out prior to 2018 have mostly reported on the genetic association between RA, PD and the highly polymorphic human leucocyte antigen (HLA) class II molecules, in particular the HLA-DRB1 phenotype [8]. In addition to this, the possible role of other RA-related genetic polymorphisms has also been investigated to analyse the association with the destruction of the periodontium as well. Previous studies have concluded that interleukin-1 (IL-1) and interleukin-10 (IL-10) gene polymorphisms may have some correlations between PD and RA [8].

In a recent case-control study by Kobayashi and colleagues, their multiple logistic regression analysis showed that the single nucleotide polymorphisms (SNP) rs2237892 of KCNQ1 gene also resulted in a significant association with the coexistence of RA and chronic PD, which suggests that individuals carrying the T allele may likely have both diseases [24]. Another case-control study by Schulz and colleagues further emphasized the association of genetic variation in TNFα and IFNγ, as well as cytokine receptor IL4R-α with RA and PD. However, their multivariate analysis showed that only the A allele of IFN-gamma appeared to be a significant marker of RA and PD comorbidities [25]. Genetic studies in relation to the association between RA and PD still warrant further investigations as most studies to date have been carried out in a relatively small sample sizes.

Plausible Mechanisms Linking RA and PD

Role of PD-Associated Bacteria

Since 2018, a further 4 animal studies have been reported investigating PD-associated bacteria in the link between PD and RA. The human studies looking at this association have however progressed from hypothesis-driven studies such as

Table 2 Study design and findings from studies concerning link between RA and PD in 2018–2019

1. Population-based studies between 2018 and 2019 investigating the association between RA and PD

a. Cross-sectional studies

Study	Location	Study sample	Association found	Conclusion
Mobini et al. [9]	Iran	74 RA patients	Yes	Prevalence of PD in RA patients was 60%
Kim et al. [14]	South Korea	20,297 (RA: 157, non-RA: 20,140)	No	Prevalence of PD in RA subjects was only 32%. RA was not associated with PD but was associated with tooth loss in younger adults
Wan-Mohamad et al. [13]	Malaysia	44 RA patients	No	Only 2 subjects presented with sites of PPD > 3 mm
Jung et al. [12]	South Korea	14, 264	Yes	Prevalence of PD in RA patients was higher (28.4%) as to PD in non-RA patients (27.9%). Prevalence of RA in PD patients was higher (1.6%) as to PD in non-RA subjects (1.5%). There is a significant relationship between RA and periodontal disease regardless of age or sex
Nik-Azis et al. [11]	Malaysia	63 RA patients	Yes	Prevalence of PD in RA patients was 70%. There is increased severity of PD in RA patients. Duration of RA affects the severity of PD
Furuya et al. [10]	Japan	5600 RA patients	Yes	Among 5600 RA subjects, 31.0% reported gingival bleeding during toothbrushing, 18.3% was recently diagnosed with PD, 20.4% reported had history of PD

b. Case-control studies

Kim et al. [15]	South Korea	260 RA patients 86 healthy controls	Yes	The presence of RA was associated with high values of periodontal indices and PD severity
Antal et al. [16]	Hungary	73 RA patients 77 healthy controls	Yes	Presence of PD in all RA subjects
Rodriguez-Lozano et al. [17]	Spain	187 RA patients 157 healthy controls	Yes	Odd ratio for PD in RA subjects was 20.67. PD severity was associated with RA disease activity. The association was more evident in patients with pronounced PD and higher RA disease activity
Zhao et al [18]	China	128 RA patients 109 healthy controls	Yes	Higher odds of PD in Chinese RA patients with increased prevalence if gingivitis and periodontitis in RA patients

c. Systematic review

de Oliveira-Fereira el al [23]	–	9 articles for qualitative assessment 3 articles for meta-analysis	Yes, for qualitative analysis	Higher RA prevalence for persons with PD compared to controls

2. Studies between 2018 and 2019 investigating genetic basis of relationship between RA and PD

Study	Aims of study	Conclusion
Kobayashi et al. [24]	To assess the distributions of genotypes and minor alleles for IL-1, IL-6, TNFα, STAT3, PADI4, PTPN22 and KCNQ1 SNPs in patients with RA	The KCNQ1 rs2237892 was significantly associated with comorbidity of RA and PD after adjustment for age, gender and smoking status; and associated with higher DAS28-CRP score

Table 2 (continued)

	and PD, in patients with type II diabetes mellitus and PD, in patients with PD only, and in systemically and periodontally healthy controls in a cohort of Japanese adults			
Schulz et al. [25]	To assess allele, genotype and haplotype frequencies of these genes in RA patients suffering from PD of different severities and systemically healthy controls without RA and severe PD		SNP rs2430561 of the proinflammatory cytokine IFNγ may constitute a shared genetic risk factor for PD and RA. An allele of IFNγ SNP rs240561 is associated with both RA and PD	
3. Microbiological studies between 2018 and 2019 investigating the role of PD-associated bacteria in the association between RA and PD				
a. Animal studies				
Study	Aims of study	Population	Conclusion	Role for *P. gingivalis*
Jeong et al. [26]	To examine the pathogenic and therapeutic correlation between *Pg*-induced PD and RA in a mouse model of arthritis	30 mice	Pg-induced PD increases the incidence and severity of RA in an experimental mouse model involving dendritic cells, macrophages and neutrophils. However, these effects are ameliorated when Pg is pre-treated with Fimbriae A antibodies\	Yes
Courbon et al. [27]	To investigate the priming role of oral *Pg* in PD and subsequent RA and assess biomarkers of bone resorption and arthritis development in rats	30 rats	PD induced by oral exposure to *Pg* triggered seropositive arthritis, with systemic inflammation and bone erosions	Yes
Sakaguchi et al. [28]	To examine whether ACPA could be detected in saliva and associated with periodontal disease	5 groups of mice (number of mice in each group was not reported)	*Pg*-infected arthritis-induced mice exhibited inflammation and bone resorption at foot. Serum level of ACPA in *Pg*/RA mice was significantly higher and positively correlated with saliva concentration of ACPA	Yes
Lubcke et al. [29]	To demonstrate therapeutic eradication *Pg* may ameliorate RA	8 groups of mice (number of mice in each group was not reported)	Treatment with chlorhexidine mouthwash before collagen-induced arthritis decreased the incidence of arthritis in mice	Yes
b. Human studies				
Beyer et al. [46]	To describe the bacterial component of the subgingival microbiome in RA patients with different degrees of periodontal disease and to relate this to RA disease activity and periodontal status	78 established RA patients	Microbiomes from individuals with active RA had higher proportion of *Corynebacterium matruchotii* (OTU2), *Actinomyces* (OTU22), *Veillonella* (OTU5) and *Streptococcus* (OTU628) than individuals with RA disease in remission. *Pg* was present in 21.8% of the patients	No
Lopez-Olivia et al. [47]	To investigate the role of RA in modulating the periodontal microbiome by comparing periodontally healthy individuals with RA to those without RA	RA: 22 Non-RA: 19 (all periodontally healthy)	Oral microbiome in RA is enriched for inflammophilic and citrulline-producing organisms, e.g. higher anaerobes except *Pg* and *Aa*	No
Ayala-Herera et al. [40]	To determine and compare the distribution of *Pg fimbriae A* genotypes in patients affected by RA and PD.	PD + RA: 128 RA: 104 PD: 73 Controls: 89	*Pg* is most frequent in patients with RA than PD/RA, but the genotype *fimbriae A II* was more frequently detected in PD/RA (76.7%)	Yes
Correa et al. [43]	To characterize the subgingival microbiome of RA patients and its association with periodontal status,	RA: 42 Controls: 48	RA patients had a higher bacterial load, a more diverse microbiota, an increase in bacterial species associated	No

Table 2 (continued)

	inflammatory markers and RA scores to establish links between these parameters		with periodontal disease, more clinical attachment loss and increased production of inflammatory mediators including IL-17, IL-2, TNF and IFNγ. Furthermore, changes in the oral microbiota were linked to worse RA conditions	
Bender et al. [41]	To determine the expression of human glutaminyl cyclases and *Pg*-derived glutaminyl cyclase in patients with chronic PD and RA	Healthy: 10 RA: 10 CP: 10	mRNA expression of QC was significantly increased in the peripheral blood from RA patients vs. healthy subjects and PD patients. In GCF of RA patients, QC mRNA was detected more frequently than in healthy controls. PgQC is expressed in *Pg* strains	Yes
Herrera et al. [45]	To determine and compare the frequency of both bacteria in patients with PD, RA, and PD and RA simultaneously	Healthy: 60 PD: 60 RA: 60 PD + RA: 60	These bacteria are more frequent in patients with PD than PD with RA, but in RA patients could influence some clinical periodontal parameters, contributing to the initiation and progression of PD	No
Eriksson et al. [44]	To investigate the periodontal health of patients with established RA in relation to oral microbiota, systemic and oral inflammatory mediators, and RA disease activity	40 RA patients	Patients with ACPA-positive RA have more severe forms of PD, irrespective of DMARD therapy or the presence of subgingival *Pg*. The subgingival microbial profile differed significantly between patients with moderate/severe and no/mild PD	No
Mankia et al. [42]	To examine periodontal disease and periodontopathic bacteria in ACPA-positive at-risk individuals without arthritis	ACPA positive, no arthritis: 38 Early RA: 26 Healthy controls: 32	Higher prevalence of PD in early RA and ACPA positive as to healthy controls. More abundant *Pg* in both healthy and diseased sites in early RA and ACPA positive as to controls	Yes
c. Systematic review				
Kriauciunas et al. [39]	To review and analyse the literature on the influence of the enzyme PPAD produced by the bacteria *Pg* causing inflammation in the joints	10 articles	*Pg* bacterium have a significant influence on the pathogenesis of RA. The DNA of bacteria *Pg* is found not only in the serum, but also in the synovial fluid, which supports its influence on the pathogenesis of RA	Yes
4. Studies in 2018–2019 investigating the role of post-translational modifications of proteins in the association between RA and PD				
a. Citrulllination				
Study	Aims of study	Conclusions		Role for inflammation or bacteria
Lopez-Olivia et al., Mankia et al. [42, 47]	(as described under microbiological studies)			Bacteria
Eriksson et al. [44]	(as described under microbiological studies)			Inflammation
Loutan et al. [57]	To evaluate periodontal status in first-degree relatives of patients with RA (FDR-RA) and detect correlation with presence of ACPA	High prevalence and severity of PD in FDR-RA was associated with seropositivity to ACPAs		Inflammation
Reichert et al. [32]	To investigate ACPA-derived from filaggrin and citrullinated α-enolase (anti-CEP-1) among patients with RA as a function of periodontal findings	*Aa* were associated with ACPA-positive. HLA-DRB1*04 was associated with increased adjusted odds ratio for both autoantibodies positivity		Bacteria
b. Carbamylation				
Study	Aims of study	Conclusion		
Bright et al. [63]	To identify the presence of all three post-translational protein modifications in inflamed human periodontal tissues and confirm the periodontium as a source of	The presence of citrullinated, carbamylated and MAA adduct modified proteins in inflamed periodontal tissues showed inflamed periodontium as potential extracapsular source post-translational modified proteins in RA		

Table 2 (continued)

	extra-synovial citrullination, carbamylation and MAA adduct formation	
Kaneko et al. [64]	To compare the circulating levels of CarP and NETs among patients with RA and PD, patients with PD only, and systemically and periodontally healthy controls.	The circulating levels of CarP and NETs are associated with PD severity and influenced by periodontal treatment in patients with RA
5. Studies in 2018–2019 investigating the possible molecular mechanism involved in the association between RA and PD		
Study	Aims of study	Conclusion
Thilagar et al. [71]	To assess and compare the cytokine level (TNFα) in the serum of chronic PD, RA, RA with PD and healthy volunteers	Serum TNFα concentration was highest in RA with PD, no association between serum TNFα and periodontal parameters
Panezai et al. [75]	To investigate the serum markers OPN, TNFR1 and TNFR2, RANKL and RANKL/OPG ratio and compare them in PD and RA groups	RA with PD patients had highest serum levels of RANKL, OPG, TNFR1 which negatively correlated with BoP and PPD < 5 mm
Ayravainen et al. [73••]	To investigate the concentrations of MMP8, TIMP-1 and IL-6 in serum and saliva in RA patients and control participants and to correlate the levels with the periodontal status; and the impact of disease activity of RA and treatment of RA on these biomarkers	Serum concentrations of MMP-8 and IL-6 and the MMP-8/TIMP-1 ratio were higher in patients with chronic active RA compared to patients with early RA Disease activity and inflammation in the RA patients was reflected in serum MMP-8 and IL-6 concentrations. There was significant correlation between salivary MMP-8 levels and the MMP8/TIMP-1 ratio and periodontal parameters
Kindstedt et al. [76]	To investigate whether PD, characterized by marginal jawbone loss, precedes the onset of symptoms of RA, and to analyse plasma levels of RANKL (a cytokine that is crucial for bone resorption) and ACPAs in pre-symptomatic individuals compared with matched referent controls	In subjects who subsequently developed RA, more pronounced marginal jawbone loss was associated with pre-existing PD. Marginal jawbone loss and the plasma RANKL level were related in ACPA-positive pre-symptomatic subjects
Schmalz et al. [74]	To investigate of associations between different RA-related blood parameters and periodontal condition as well as selected periodontal pathogenic bacteria in RA patients under MTX immunosuppression	Periodontal inflammation was associated with MMP-8 and TIMP-1 in the blood though GCF concentration of MMP-8 and TIMP-1 did not correlate with blood concentration
6. Environmental studies in 2018–2019 investigating factors influencing parameters in the association between RA and PD		
Study	Aims of study	Conclusion
Beyer et al. [77]	To relate marine fatty acids and Vitamin D status to RA disease status and periodontal conditions	An omega-3 index > 8 was associated with better RA disease outcome
Hashimoto et al. [84]	To examine whether the severity of RA is associated with the oral hygiene and periodontal status of RA patients who do not find performing routine oral hygiene difficult	There was no significant association of RA with deep PD when the plaque index was added as an independent variable to the multivariate analyses
Ziebolz et al. [78••]	To investigate clinical periodontal findings as well as prevalence of selected potentially periodontal pathogenic bacteria in patients with RA treated with different immunosuppressive rheumatic medications	RA medication is associated with periodontal inflammation, without differences in periodontal disease severity.
7. Interventional studies in 2018–2019 investigating the effect of treatment on RA and PD		
a. Effect of periodontal therapy on RA disease activity		
Study	Aims of study	Effect on RA disease activity
Zhao et al. [80]	To evaluate their correlation and investigate the effects of NSPT on RA	No significant effect
Cosgarea et al. [72••]	To compare the effect of NSPT on clinical and inflammatory parameters in patients with moderate to severe PD and RA (RA-PD) with that in PD patients without RA	No significant effect
Monsarrat et al. [82]	To assess the effect of periodontal treatment on clinical and biochemical parameters of RA and quality of life (QoL) in patients with moderately active RA who were diagnosed with PD	No significant effect
Kaushal et al. [81]	To examine the effects of NSPT on disease activity of RA	Improvement in RA disease activity
Marriatte et al. [83]	To investigate if a good oral hygiene could improve activity of RA	No significant effect
b. Effect of DMARDs in RA patients with PD		

Table 2 (continued)

Study	Aims of study	Effect on PD parameters or markers
Jung et al. [94]	To evaluate the effect of treatment with DMARDs on the response to NSPT in patients with RA	After NSPT, PPD reduction was greatest in group taking combination of 3 DMARDs
Rinaudo-Gaujous et al. [95]	To correlate marker of PD severity (MMP-3, anti-P. gingivalis and anti-*P. intermedia* antibodies) and to assess effect of infliximab therapy on PD severe biomarkers in RA patients	Reduction in serum levels of MMP-3 after infliximab therapy

PCR studies looking mainly at the presence of *Porphyromonas gingivalis* to hypothesis-free studies performing sequencing.

Animal Studies

Of the four latest animal studies investigating the association between periodontal disease and RA, all have confirmed the contributing role of *P. gingivalis* in this association [26–29]. Inoculation of mice with *P. gingivalis* has been shown to increased serum levels of anti-citrullinated protein autoantibodies (ACPA) and an increasing trend is also seen in the saliva [28]. In the aetio-pathogenesis of periodontal disease, *P. gingivalis* fimbriae are the major extracellular components that adhere to the host cell surfaces. Using a mouse model of arthritis, Jeong et al. (2018) demonstrated that inhibiting *P. gingivalis* adhesion using a FimA antibody (Ab) prevented RA progression. They also showed that orally inoculated *P. gingivalis* may utilize dendritic cells, macrophages and neutrophils to migrate to the joints of collagen-induced arthritis mice which will then result in synovial inflammation [26]. Similarly, eradication of bacteria by using chlorhexidine prior to collagen-induced arthritis was shown to reduce the incidence of experimental arthritis in mice [29].

Human Studies

The development of a subgingival bacterial biofilm has been recognized as one of the essential factors in the initiation and progression of periodontitis. Numerous bacteria have been implicated as contributory agents in the aetio-pathogenesis of RA [3, 30]. This assumption arises following the detection of bacterial DNA and high levels of oral anaerobic bacterial antibodies of *P. gingivalis* within the synovial fluid of inflamed joints in RA subjects [3, 30]. There is an assumption that genetic material is carried from the periodontium to joints in free form of DNA via bloodstream [31–33].

P. gingivalis has been one of the most widely studied bacteria in relation to the association between PD with RA. It is the only known microorganism with the ability to produce a peptidylarginine deiminase enzyme (PPAD) that catalyses citrullination of arginine in both host and bacterial proteins [34]. This citrullinated peptide antigen has been reported to be present in the inflamed periodontium of PD subjects and thus further activates the adaptive immune response that is selective to RA [35]. Therefore, it has been proposed to play an active role in RA development [36, 37]. Since PPAD is not calcium dependent, it can also be autocitrullinated but this finding has not been proven to occur in-vivo [8].

Aggregatibacter actinomycetemcomitans (*Aa*) has also been widely studied as it has been shown to be able to

dysregulate peptidylarginine deiminases (PAD) in neutrophils, leading to the extracellular release of autoantigens following neutrophil apoptosis via *Aa*-induced hypercitrullination. This process is mediated by its major virulence factor, leukotoxin A (LtxA), which forms pores on the cell membrane of neutrophils, allowing PAD activation and citrullination of a broad range of peptides [38]. This process provides an additional biologically plausible oral microbiological link (other than *P. gingivalis*) between a bacteria and the promotion of autoimmunity directed against citrullinated proteins.

Prior to 2018, other oral bacteria that have been studied widely and found to be present in the synovium of RA subjects, or these subjects having reported to have increased antibody levels against these bacteria, are *Prevotella intermedia*, *Tannarella forsythia*, *Prevotella melaninogenica*, *Filifactor alocis*, *Prevotella* spp. and *Leptotrichia* spp. [8]. However, next generation sequencing studies which have been done to look for associations between the two diseases have however found no evidence for this association [8].

Since 2018, nine studies have investigated the role of oral bacteria in the association between PD and RA. One systematic review confirmed a significant influence of *P. gingivalis* on the pathogenesis of RA as higher frequency of *P. ginigivalis* DNA was found in the serum and synovial fluid of RA patients and thus supports its role in the pathogenesis of RA [39]. The presence of *P. gingivalis* fimA genotype II has also been reported to be more frequently detected in RA subjects with PD [40]. In a pilot study, Bender et al. (2019) also reported a potential link between glutaminyl cyclase synthesized by *P. gingivalis* in patients with RA based on its similarity to human glutaminyl cyclases (QC and isoQC) which play an important role in maintaining inflammatory conditions [41]. However, of the 9 studies reported between 2018 and 2019, only 3 studies found a higher prevalence for *P. gingivalis* in RA with PD subjects [40–42]. Thus the actual role of *P. gingivalis* in the aetio-pathogenesis of RA still needs further validation.

RA subjects have been reported to have a higher bacterial load, a more diverse microbiota and an increase in bacterial species associated with periodontal disease [43]. Among the species reported are *Capnocytophaga* sp., *Tannerella forsythia*, *Desulfobulbus* sp., *Prevotella* sp., *NA* sp., *Bulleidia* sp., *Filifactor alocis* and *Dialister pneumosintes* [44, 45]. However, the subgingival microbiome in RA subjects with active disease on anti-inflammatory therapy was also reported to be healthier and comprised of *Corynebacterium matruchotii*, *Actinomyces*, *Veillonella* and *Streptococcus* as compared to RA subjects in remission especially those who were smokers [46]. They have suggested that the potential role of microbial community types in patient stratification and personalized therapy should be further assessed in longitudinal studies. In periodontally healthy individuals, it has been reported that RA is able to enrich the oral microbiome for inflammophilic and citrulline-producing organisms such as *Cryptobacterium curtum*, another organism capable of producing large amounts of citrulline [47].

Despite all the studies that have reported the presence of bacteria and the role of PPAD or dysbiosis in the association between PD and RA, these associations have yet to be biologically and clinically proven. The looming question still remains as to whether the association is truly related to PPAD causing a change in the immune tolerance or whether it is due to PPAD causing an increase in virulence of *P. gingivalis* and subsequently an increase in the severity of the periodontal inflammation which ultimately leads to increase in RA severity [8]. Similarly, the presence of other bacteria may indeed cause the dysbiosis that ultimately leads to an increase in the periodontal inflammation present and the subsequent increase in RA severity (Fig. 1).

PD and Autoantigen Production

Citrullination

Citrullination is a conversion process of positively charged arginine residues to neutral citrulline residues by a family of enzymes called PAD. This process takes place in the presence of calcium as part of the normal physiological process and functioning of the immune system [48]. Apart from the involvement in physiological processes, citrullination also takes part in pathological inflammatory conditions as part of the innate response to bacterial infection and cell death mechanism. For example, PAD-4-induced citrullination is known to play an important role in altering chemokines' function and has been actively participating in neutrophils extracellular traps (NETs) formation as part of the antibacterial mechanism. It has often been linked to chronic inflammatory disorders such as multiple sclerosis, Alzheimer's disease, psoriasis, and RA [48, 49].

The enzymatic deimination of arginine residues to citrulline by PAD (post-translational modification) alters the tertiary structure, antigenicity, and function of proteins [50, 51]. Subsequently, this may expose the previously hidden immune epitopes and induce an autoimmune response as citrulline is not a standard amino acid of proteins [52]. In a susceptible patient, these citrullinated peptides will act as an antigenic determinant that could break the immunological tolerance and evoke an autoimmune response by binding onto the antigen presenting cells. As a result, pathogenic T and B cells will be activated, leading to the RA-specific ACPA formation [50]. These ACPA will then form immune complexes with citrullinated peptides, resulting in the production of inflammatory mediators and ultimately causing joint destruction in RA [36, 53]. ACPA has emerged as a specific serological marker

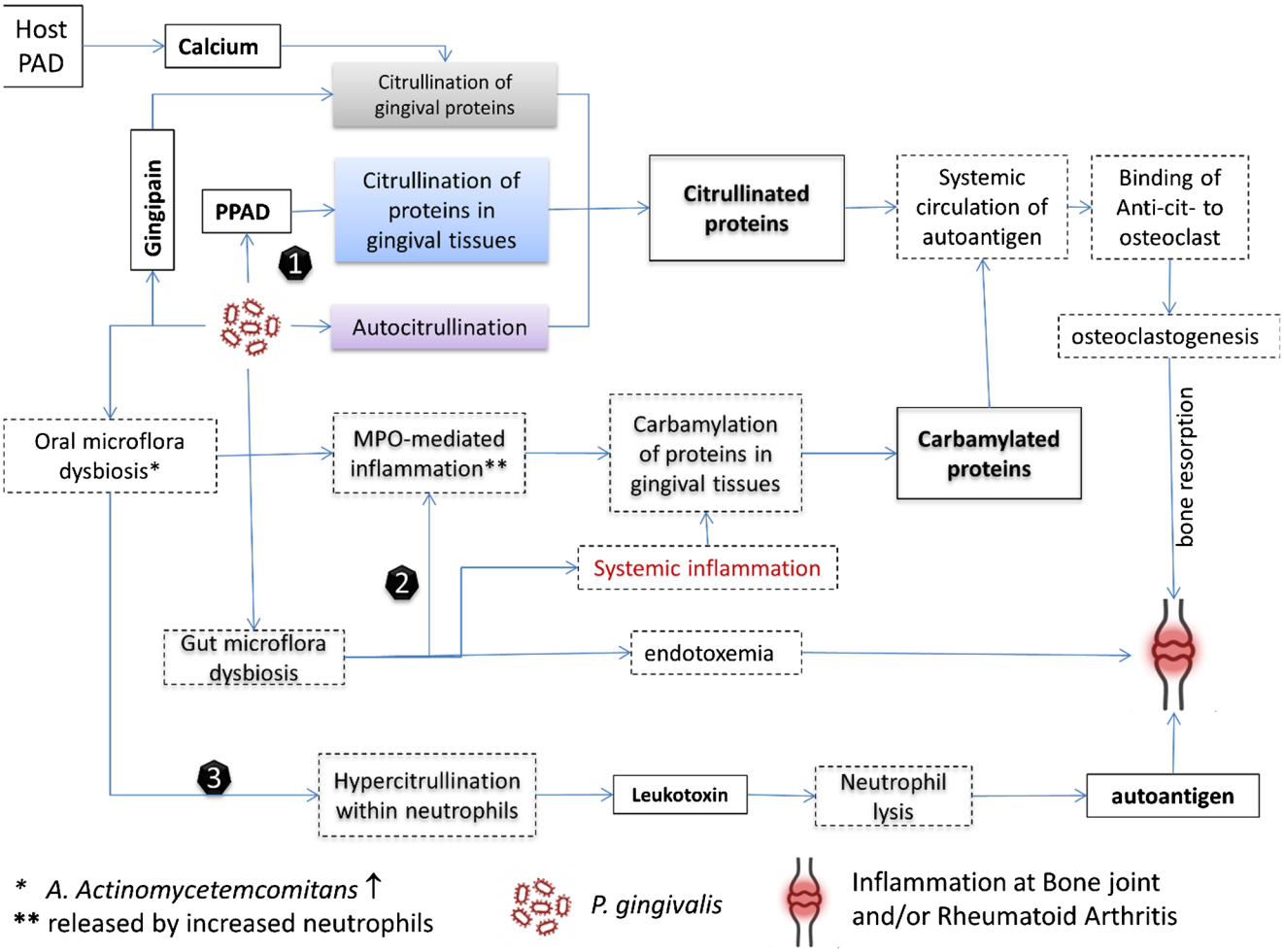

Fig. 1 Possible mechanisms on how PD aggravates RA (taken from Lee et al. (2019) [97]). The role of *P. gingivalis* in contributing to the formation of autoantigens either directly through protein citrullination or indirectly through inflammation-mediated carbamylation (*1*). *P. gingivalis* as a keystone pathogen in causing alterations to the gut microflora and potentially leading to endotoxemia and the persistence of low-grade systemic inflammation which may exacerbate the inflammatory response within the joint (*2*). Extracellular release of autoantigens following neutrophil apoptosis as a result of *A. actinomycetemcomitans*-induced hypercitrullination (*3*)

for RA due to its high specificity and predictive value for RA [54].

Apart from inflamed synovial joints in RA, citrullinated proteins have also been detected in inflamed periodontal tissues of patients with PD. The presence of citrullinated proteins in periodontal tissues was first revealed by Nesse et al. [55]. Citrullinated proteins, as well as PAD-2 and PAD-4 (both these PADs are associated with citrullination in RA) were also found in inflamed periodontal tissues in PD patients without any signs of RA [56]. Based on these findings, it was postulated that PD could provide a conducive environment for citrullination and initiation of anti-CitP targeting citrullinated peptides in joints. Prior to 2018, studies looking at citrullination and ACPA in RA and PD have focused on either periodontal inflammation as the driving force for citrullination or periodontal pathogens (as explained in the previous section) as the primary driver of citrullination [8].

Since 2018, there have been 5 studies looking at citrullination and ACPA in the link between PD and RA. Microbes such as *P. gingivalis*, *Aa*, and citrulline-producing microorganisms have been reported to be drivers of citrullination in 3 studies [32, 42, 47]. Two studies reported that inflammation was the primary driver for ACPA formation [44, 57]. In their study on first-degree relatives of RA subjects, Louton et al. (2019) have demonstrated that severe PD was associated with ACPA+ve subjects as compared to mild PD which was associated more with ACPA−ve subjects [57]. Further studies need to be done in the search for the primary driving force in associating citrullination in the link between PD and RA.

Carbamylation

Carbamylation is a non-enzymatic myeloperoxidase (MPO)-dependent post-translational modification of free amino acid

lysine into homocitrulline [58]. Bright et al. proposed inflamed periodontal tissues as a source of carbamylated proteins due to high production of MPO by neutrophils during the release of NETs [59]. The formation of carbamylated proteins in addition to citrullinated proteins in PD may break the immune tolerance leading to production of autoantibodies [59–61].

Previously, an animal study demonstrated the presence of anti-carbamylated proteins antibodies precedes signs of joint damage [62]. Since 2018, studies on RA patients with PD-verified production of carbamylated proteins in PD and the circulating level of carbamylated proteins and NETs are associated with severity of PD in RA patients that can be significantly improved with non-surgical periodontal treatment (NSPT) [63, 64]. Therefore, inflammatory-driven carbamylation of proteins may explain the plausible link between RA and PD.

Molecular Mechanisms Uniting PD and RA

The underlying molecular mechanism in the relationship between PD and RA resides in the concept that both conditions involve overproduction of pro-inflammatory mediators and dysregulation of cytokine networks [65, 66]. The two-hit model, proposed to explain the association between RA and PD, describes local inflammatory lesions in periodontal tissues triggered by subgingival microflora (1st hit) and the release of pro-inflammatory cytokines from joints (2nd hit), escalating the systemic inflammatory cascades that further amplify local inflammatory or osteoclastogenic mediators such as prostaglandins, receptor activator of nuclear factor κ-B ligand (RANKL), and matrix metalloproteinases (MMPs) in synovium or periodontal tissues [5]. The connection between RA and PD may also lie in mutual underlying inflammatory pathways that are either driven by, or results in, production of common mediators [6].

Before 2018, two systematic reviews had been published which analysed the cytokine profile in serum and gingival crevicular fluid of RA patients with PD [67, 68]. A number of inflammatory mediators or enzymes such as TNFα, interleukins (IL), RANKL, and MMPs in RA patients with PD have been studied with regard to possible molecular mechanisms linking between two diseases [68]. Subsequent to these two systematic reviews, further works including genetic studies have been conducted to explore the role of TNFα, IL-1 and IL-6 but the results are still unclear to understand the common pathological pathway between these two diseases [8].

Since 2018, 5 studies have scrutinized the molecular aspects of the association between PD and RA and specific attention has been given to the role of proteolytic enzymes and osteoclastogenic mediators such as MMPs and RANKL. TNFα and IL-1β are still the major cytokines under investigation since both have been shown to be elevated in RA and PD patients and both cytokines have pro-inflammatory effect that promotes connective tissue turnover and bone resorption [69, 70]. A recent study assessing serum TNFα level in RA patients with PD who were not on TNFα inhibitors substantiated that the presence of PD in these subjects was associated with overproduction of TNFα [71]. However, the correlation between pro-inflammatory cytokines and parameters of PD and RA is still unclear. On the other hand, the serum level of anti-inflammatory cytokine, IL-10 in RA patients with PD was described as very low. However after periodontal therapy, the level of IL-10 in systemically healthy PD patients increased as compared to RA-PD subjects [72••].

MMP-8 is a collagenase that is involved in connective tissue degradation and is frequently found in the synovial fluid of RA patients and GCF in PD patients [69, 70]. In line with previous evidence, latest investigations revealed raised levels of MMP-8 in the serum and GCF of RA patients with PD compared to systemically and periodontally healthy subjects [73••, 74]. The serum level of MMP-8 is associated with periodontal inflammation and clinical attachment loss [74]. However, in contrast to early RA patients, established RA patients with high disease activity have persistent elevated levels of MMP-8 regardless of additional biologic therapy to conventional disease modifying anti-rheumatoid drugs (DMARDs) [73••].

Recent studies have also shown that individuals with either RA or PD or both have increased serum levels of RANKL [75, 76]. This suggests that dysregulation of inflammatory cascades in patients with RA and PD leads to sustained overproduction of osteoclastogenic mediators and enzymes such as RANKL and MMPs.

An environmental study on the effect of diet on the inflammatory response in RA patients experiencing PD reported an association between increase in serum omega-3 levels due to diet or supplements and favourable outcome of RA [77]. However, it is premature to conclude that the anti-inflammatory effect of omega-3 improves disease activity of RA and PD, but it may suggest that diet could influence the inflammatory pathway in these patients. In addition, DMARDs, such as combination of methotrexate and TNF-inhibitors, have shown to affect the biochemical markers as well as periodontal inflammation [78••]. Therefore, further work to evaluate and confirm the biomarkers' profile of RA patients with PD is needed to control confounders including the effect of diet and DMARDs.

Periodontal Therapy in RA Patients with PD

Over the past decade, numerous studies have been conducted to assess the effect of periodontal treatment on RA. Most of the studies tested NSPT in RA patients with PD and observed a clinical change in RA disease activity. NSPT has been established to be successful in reducing periodontal pocket

depths and improving periodontal inflammatory status in PD patients [79]. Similar findings can be found when NSPT was performed on PD patients who concurrently suffer from RA demonstrating that RA status does not hamper the periodontal outcomes of NSPT [67, 80, 72••].

Prior to 2018, systematic reviews and interventional studies suggested that NSPT may have beneficial effects on periodontal and RA disease activities, but more thorough and larger controlled trials are needed to convincingly substantiate the effect of NSPT on improvement of RA disease activity [8]. Over the last 2 years, no systematic review has been published concerning NSPT on RA patients. There have been five interventional studies published evaluating the effect of periodontal therapy on rheumatologic disease activity parameters, but all the studies involved very low number of subjects [80–82, 72••] except one multicentre randomized trial nested in a cohort study in France which involved 472 subjects [83]. However, this French study only looked at oral hygiene instructions in their test group while the control group did not receive any therapy. The findings in this study indicated no significant improvement in RA disease activity. It was also noted that the oral hygiene of all subjects was good at baseline [83] in contrary to an observational study by Hashimoto et al. (2019) that suggested poor oral hygiene could explain the severity of PD in RA patients [84].

With reference to the role of NSPT in improving RA disease activity, currently available studies have produced conflicting results. This may be due to a number of factors including the issue of small sample size, discrepancies in evaluation periods, and case definitions of PD which were adopted by the studies. Only one study incorporated bleeding on probing (BOP) at sites with attachment loss as one of the criteria to define a PD case [81]. BOP is an established quantitative tool to assess gingival inflammation which can discriminate periodontal health and disease [85]. There is a marked discrepancy in mean BOP scores at baseline among the intervention studies which ranged from 12 to 97% [82, 86]. The magnitude of changes in BOP following NSPT is associated with significant improvement in DAS28 scores [87]. Hence, the difference in extent of periodontal inflammation at baseline among the studies might explain the heterogeneous RA-related outcomes of NSPT. The inflammatory burden in the periodontal tissues may reflect or affect the disease activity of RA considering inflammation plays a key role in orchestrating the pathomechanism link between RA and PD [8]. Therefore, to observe greater magnitude of periodontal therapy impact on RA disease activity, future studies need to assess the effect of periodontal therapy in active RA patients with extensive periodontal inflammation, and aim for subjects attaining periodontal health and not delivery of periodontal treatment per se.

Effect of DMARDs in RA Patients With PD.

In view of the association between RA and PD, the effect of RA treatment on periodontal status can be reasonably anticipated. Host modulation drugs such as DMARDs have been used extensively in the management of RA and as a result these drugs have stimulated research interest in their use as adjuncts in periodontal therapy [88, 89].

RA patients tend to have higher levels of TNFα in oral fluids [68]. Consequently, previous studies have assessed the effect of TNFα inhibitor in RA patients with PD. The interventional studies have demonstrated that the potential benefit of TNFα inhibitor drugs on periodontal inflammatory status and clinical attachment levels was not independent of periodontal therapy [90, 91]. Studies on other conventional or biologic DMARDs such as IL-6 inhibitor and anti-B lymphocytes demonstrated similar effects on periodontal clinical parameters [92, 93]. DMARDs may be advantageous as an adjunct to NSPT in improving periodontal parameters in RA patients with PD [8]. Since 2018, two studies have reported findings supporting the beneficial effect of DMARDs on periodontal status. A clinical trial on RA patients revealed that a cocktail of DMARDs was an assistance in reduction of periodontal pocket depth in conjunction to NSPT as compared to DMARDs used as monotherapy [94].

Similarly, a longitudinal study examining the impact of infliximab therapy on PD-related biochemical markers in RA patients found significant improvements in serum levels of MMP-3 after therapy [95]. This improvement was seen even in subjects with the presence of concurrent PD which contradicts a previous study by Savioli et al. [96]. Nevertheless, with scant evidence and inconsistent findings, the impact of periodontal inflammation on RA treatment outcome is still equivocal. A larger controlled trial is required to verify this potential issue.

Concluding Comments

In this review we have highlighted the most recent progress in the last 20 months (January 2018 to August 2019) in the field studying the relationship between PD and RA. This field continues to be a very vibrant of investigation at the population, biochemical, cellular, genetic, microbiological and clinical levels. There is now unequivocal evidence to indicate that this relationship is very strong. However, studies to date have not been able to identify any unifying link between these two chronic inflammatory conditions. The evidence assessed in this review indicates that while there is strong evidence to support a role for underlying dysregulation of inflammatory processes and autoimmune responses in the relationship between PD and RA, the precise processes that link them remain elusive. It is clear that while the association can be bi-

directional there is no evidence to suggest that either condition is causative of the other. It seems most likely that there will be subsets of individuals who suffer specifically from both conditions and it is these individuals for whom our attention should now focus.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kersley GD. Dental sepsis and chronic rheumatism. Proc R Soc Med. 1949;42(3):151–3.
2. Snyderman R, McCarty GA. Analogous mechanisms of tissue destruction in rheumatoid arthritis and periodontal disease. In: Genco RJ, Mergenhagen SE, editors. Host-parasite interaction in periodontal diseases. Washington, DC: American Society of Microbiology; 1982. p. 354–62.
3. Moen K, Brun J, Valen M, Skartveit L, Eribe E, Olsen I, et al. Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin Exp Rheumatol. 2006;24(6):656–63.
4. 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(6):311–8.
5. Golub L, Payne J, Reinhardt R, Nieman G. Can systemic diseases co-induce (not just exacerbate) periodontitis? A hypothetical "two-hit" model. J Dent Res. 2006;85(2):102–5.
6. Bartold PM, Marshall R, Haynes D. Periodontitis and rheumatoid arthritis: a review. J Periodontol. 2005;76:2066–74.
7. Linden GJ, Herzberg MC. Workshop periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol. 2013;40:S20–S3.
8. Bartold PM, Lopez-Oliva I. Rheumatoid arthritis and periodontitis: an update 2012-2017. Periodontol 2000. In Press 2020.
9. Mobini M, Maboudi A, Mohammadpour RA. Periodontitis in rheumatoid arthritis patients, abundance and association with disease activity. Med J Islam Repub Iran. 2017;31:44.
10. Furuya T, Inoue E, Tanaka E, Maeda S, Ikari K, Taniguchi A, et al. Age and female gender associated with periodontal disease in Japanese patients with rheumatoid arthritis: results from self-reported questionnaires from the IORRA cohort study. Mod Rheumatol. 2019;7:1–6. https://doi.org/10.1080/14397595.2019.1621461.
11. Nik-Azis N-M, Mohd-fadzilah F, Mohd-Shahrir M-S, Baharin B, Mohd N. Impact of rheumatoid arthritis functional status on oral and periodontal health in a multi-ethnic population. Sains Malays. 2019;48(3):645–52.
12. Jung ES, Choi YY, Lee KH. Relationship between rheumatoid arthritis and periodontal disease in Korean adults: data from the Sixth Korea National Health and Nutrition Examination Survey, 2013 to 2015. J Periodontol. 2019;90(4):350–7.
13. Wan-Mohamad WM, Jia SK, Ghazali WSW, Taib H. Anti-cyclic citrullinated peptide antibody and periodontal status in rheumatoid arthritis patients. Pak J Med Sci. 2018;34(4):907.
14. Kim J-W, Park J-B, Yim HW, Lee J, Kwok S-K, Ju JH, et al. Rheumatoid arthritis is associated with early tooth loss: results from Korea National Health and Nutrition Examination Survey V to VI. Korean J Intern Med. 2018;34(6):1381.
15. Kim J-H, Choi IA, Lee JY, Kim K-H, Kim S, Koo K-T, et al. Periodontal pathogens and the association between periodontitis and rheumatoid arthritis in Korean adults. J Periodontal Implant Sci. 2018;48(6):347–59.
16. Antal M, Battancs E, Bocskai M, Braunitzer G, Kovács L. An observation on the severity of periodontal disease in past cigarette smokers suffering from rheumatoid arthritis- evidence for a long-term effect of cigarette smoke exposure? BMC Oral Health. 2018;18(1):82.
17. Rodríguez-Lozano B, González-Febles J, Garnier-Rodríguez JL, Dadlani S, Bustabad-Reyes S, Sanz M, et al. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: a case–control study. Arthritis Res Ther. 2019;21(1):27.
18. Zhao R, Gu C, Zhang Q, Zhou W, Feng G, Feng X, et al. Periodontal disease in Chinese patients with rheumatoid arthritis: a case control study. Oral Dis. 2019;00:1–7.
19. Sacks JJ, Luo YH, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001–2005. Arthritis Care Res (Hoboken). 2010;62(4):460–4.
20. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376:1094–108.
21. 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(1):70–6.
22. Chen H-H, Huang N, Chen Y-M, Chen T-J, Chou P, Lee Y-L, et al. Association between a history of periodontitis and the risk of rheumatoid arthritis: a nationwide, population-based, case–control study. Ann Rheum Dis. 2013;72(7):1206–11.
23. de Oliveira FR, de Brito SR, Magno MB, Carvalho Almeida APCPS, Fagundes NCF, Maia LC, et al. Does periodontitis represent a risk factor for rheumatoid arthritis? A systematic review and meta-analysis. Ther Adv Musculoskelet Dis. 2019;11:1–16.
24. Kobayashi T, Kido J-I, Ishihara Y, Omori K, Ito S, Matsuura T, et al. The KCNQ1 gene polymorphism as a shared genetic risk for rheumatoid arthritis and chronic periodontitis in Japanese adults: a pilot case-control study. J Periodontol. 2018;89(3):315–24.
25. Schulz S, Pütz N, Jurianz E, Schaller H-G, Reichert S. Are there any common genetic risk markers for rheumatoid arthritis and periodontal diseases? A case-control study. Mediat Inflamm. 2019;2019:2907062. https://doi.org/10.1155/2019/2907062.
26. Jeong SH, Nam Y, Jung H, Kim J, Rim YA, Park N, et al. Interrupting oral infection of *Porphyromonas gingivalis* with anti-FimA antibody attenuates bacterial dissemination to the arthritic joint and improves experimental arthritis. Exp Mol Med. 2018;50:e460.
27. Courbon G, Rinaudo-Gaujous M, Blasco-Baque V, Auger I, Caire R, Mijola L, et al. *Porphyromonas gingivalis* experimentally

induces periodontitis and an anti-CCP2-associated arthritis in the rat. Ann Rheum Dis. 2019;78(5):594–9.
28. Sakaguchi W, Toy M, Yamamoto Y, Inaba K, Yakeishi M, Saruta J, et al. Detection of anti-citrullinated protein antibody (ACPA) in saliva for rheumatoid arthritis using DBA mice infected with *Porphyromonas gingivalis*. Arch Oral Biol. 2019;108:104510. https://doi.org/10.1016/j.archoralbio.2019.104510.
29. Lübcke PM, Ebbers MN, Volzke J, Bull J, Kneitz S, Engelmann R, et al. Periodontal treatment prevents arthritis in mice and methotrexate ameliorates periodontal bone loss. Sci Rep. 2019;9(1):8128.
30. Ogrendik M. Rheumatoid arthritis is linked to oral bacteria: etiological association. Mod Rheumatol. 2009;19(5):453–6.
31. Martinez-Martinez RE, Abud-Mendoza C, Patiño-Marin N, Rizo-Rodríguez JC, Little JW, Loyola-Rodríguez JP. Detection of periodontal bacterial DNA in serum and synovial fluid in refractory rheumatoid arthritis patients. J Clin Periodontol. 2009;36(12):1004–10.
32. Reichert S, Haffner M, Keyßer G, Schäfer C, Stein JM, Schaller HG, et al. Detection of oral bacterial DNA in synovial fluid. J Clin Periodontol. 2013;40(6):591–8.
33. Totaro MC, Cattani P, Ria F, Tolusso B, Gremese E, Fedele AL, et al. *Porphyromonas gingivalis* and the pathogenesis of rheumatoid arthritis: analysis of various compartments including the synovial tissue. Arthritis Res Ther. 2013;15(3):R66.
34. McGraw WT, Potempa J, Farley D, Travis J. Purification, characterization, and sequence analysis of a potential virulence factor from *Porphyromonas gingivalis*, peptidylarginine deiminase. Infect Immun. 1999;67(7):3248–56.
35. Mikuls TR, Thiele GM, Deane KD, Payne JB, O'Dell JR, Yu F, et al. *Porphyromonas gingivalis* and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis. Arthritis Rheum. 2012;64(11):3522–30.
36. Liao F, Li Z, Wang Y, Shi B, Gong Z, Cheng X. *Porphyromonas gingivalis* may play an important role in the pathogenesis of periodontitis-associated rheumatoid arthritis. Med Hypotheses. 2009;72(6):732–5.
37. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nat Rev Rheumatol. 2017;13(10):606–20.
38. Konig MF, Abusleme L, Reinholdt J, Palmer RJ, Teles RP, Sampson K, et al. *Aggregatibacter actinomycetemcomitans*-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med. 2016;8(369):369ra176.
39. Kriauciunas A, Gleiznys A, Gleiznys D, Janužis G. The influence of *Porphyromonas gingivalis* bacterium causing periodontal disease on the pathogenesis of rheumatoid arthritis: systematic review of literature. Cureus. 2019;11(5).
40. Ayala-Herrera JL, Abud-Mendoza C, Gonzalez-Amaro RF, Espinosa-Cristobal LF, Martínez-Martínez RE. Distribution of *Porphyromonas gingivalis* fimA genotypes in patients affected by rheumatoid arthritis and periodontitis. Acta Odontol Scand. 2018;76(7):520–4.
41. Bender P, Egger A, Westermann M, Taudte N, Sculean A, Potempa J, et al. Expression of human and *Porphyromonas gingivalis* glutaminyl cyclases in periodontitis and rheumatoid arthritis—a pilot study. Arch Oral Biol. 2019;97:223–30.
42. Mankia K, Cheng Z, Do N, Hunt L, Meade J, Kang J, et al. An increased prevalence of periodontal disease and Porphyromonas gingivalis in anti-CCP positive individuals at-risk of rheumatoid arthritis: a target for prevention? JAMA Netw Open. In Press 2019.
43. Corrêa JD, Fernandes GR, Calderaro DC, Mendonça SMS, Silva JM, Albiero ML, et al. Oral microbial dysbiosis linked to worsened periodontal condition in rheumatoid arthritis patients. Sci Rep. 2019;9(1):8379.
44. Eriksson K, Fei G, Lundmark A, Benchimol D, Lee L, Hu YOO, et al. Periodontal health and oral microbiota in patients with rheumatoid arthritis. J Clin Med. 2019;8(5):630.
45. Herrera JLA, Patrón LA, Martínez REM, Pérez RAD, Mendoza CA, Castro BH. *Filifactor alocis* and *Dialister pneumosintes* in a Mexican population affected by periodontitis and rheumatoid arthritis: an exploratory study. Microbiol Immunol. 2019;63:392–5.
46. Beyer K, Zaura E, Brandt BW, Buijs MJ, Brun JG, Crielaard W, et al. Subgingival microbiome of rheumatoid arthritis patients in relation to their disease status and periodontal health. PLoS One. 2018;13(9):e0202278.
47. Lopez-Oliva I, Paropkari AD, Saraswat S, Serban S, Yonel Z, Sharma P, et al. Dysbiotic subgingival microbial communities in periodontally healthy patients with rheumatoid arthritis. Arthritis Rheumatol. 2018;70(7):1008–13.
48. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev. 2010;233(1):34–54.
49. van Gaalen FA, Visser H, Huizinga TW. A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. Ann Rheum Dis. 2005;64(10):1510–2.
50. Schellekens GA, De Jong B, Van den Hoogen F, Van de Putte L, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1998;101(1):273–81.
51. Schellekens GA, Visser H, De Jong BA, Van Den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155–63.
52. György B, Tóth E, Tarcsa E, Falus A, Buzás EI. Citrullination: a posttranslational modification in health and disease. Int J Biochem Cell Biol. 2006;38(10):1662–77.
53. Koziel J, Mydel P, Potempa J. The link between periodontal disease and rheumatoid arthritis: an updated review. Curr Rheumatol Rep. 2014;16(3):408.
54. Mangat P, Wegner N, Venables PJ, Potempa J. Bacterial and human peptidylarginine deiminases: targets for inhibiting the autoimmune response in rheumatoid arthritis? Arthritis Res Ther. 2010;12(3):209.
55. Nesse W, Westra J, van der Wal JE, Abbas F, Nicholas AP, Vissink A, et al. The periodontium of periodontitis patients contains citrullinated proteins which may play a role in ACPA (anti-citrullinated protein antibody) formation. J Clin Periodontol. 2012;39(7):599–607.
56. Harvey G, Fitzsimmons T, Dhamarpatni A, Marchant C, Haynes D, Bartold P. Expression of peptidylarginine deiminase-2 and-4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva. J Periodontal Res. 2013;48(2):252–61.
57. Loutan L, Alpizar-Rodriguez D, Courvoisier DS, Finckh A, Mombelli A, Giannopoulou C. Periodontal status correlates with anti-citrullinated protein antibodies in first-degree relatives of individuals with rheumatoid arthritis. J Clin Periodontol. 2019;46(7):690–8.
58. Shi J, van Veelen PA, Mahler M, Janssen GM, Drijfhout JW, Huizinga TW, et al. Carbamylation and antibodies against carbamylated proteins in autoimmunity and other pathologies. Autoimmun Rev. 2014;13(3):225–30.
59. Bright R, Proudman S, Rosenstein E, Bartold P. Is there a link between carbamylation and citrullination in periodontal disease and rheumatoid arthritis? Med Hypotheses. 2015;84(6):570–6.
60. Mydel P, Wang Z, Brisslert M, Hellvard A, Dahlberg LE, Hazen SL, et al. Carbamylation-dependent activation of T cells: a novel mechanism in the pathogenesis of autoimmune arthritis. J Immunol. 2010;184(12):6882–90.

61. Steinbrecher UP, Fisher M, Witztum JL, Curtiss LK. Immunogenicity of homologous low density lipoprotein after methylation, ethylation, acetylation, or carbamylation: generation of antibodies specific for derivatized lysine. J Lipid Res. 1984;25(10):1109–16.
62. Verheul MK, Vierboom MP, Bert A, Toes RE, Trouw LA. Anti-carbamylated protein antibodies precede disease onset in monkeys with collagen-induced arthritis. Arthritis Res Ther. 2017;19(1):246.
63. Bright R, Thiele GM, Manavis J, Mikuls TR, Payne JB, Bartold P. Gingival tissue, an extrasynovial source of malondialdehyde-acetaldehyde adducts, citrullinated and carbamylated proteins. J Periodontal Res. 2018;53(1):139–43.
64. Kaneko C, Kobayashi T, Ito S, Sugita N, Murasawa A, Nakazono K, et al. Circulating levels of carbamylated protein and neutrophil extracellular traps are associated with periodontitis severity in patients with rheumatoid arthritis: a pilot case-control study. PLoS One. 2018;13(2):e0192365.
65. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. New Engl J Med. 2011;365(23):2205–19.
66. Kinane DF, Preshaw PM, Loos BG, Periodontology. Host-response: understanding the cellular and molecular mechanisms of host-microbial interactions—Consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol. 2011;38:44–8.
67. Kaur S, White S, Bartold P. Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res. 2013;92(5):399–408.
68. Javed F, Ahmed HB, Mikami T, Almas K, Romanos GE, Al-Hezaimi K. Cytokine profile in the gingival crevicular fluid of rheumatoid arthritis patients with chronic periodontitis. J Investig Clin Dent. 2014;5(1):1–8.
69. Preshaw PM, Taylor JJ. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? J Clin Periodontol. 2011;38:60–84.
70. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. New Engl J Med. 2001;344(12):907–16.
71. Thilagar S, Theyagarajan R, Sudhakar U, Suresh S, Saketharaman P, Ahamed N. Comparison of serum tumor necrosis factor-α levels in rheumatoid arthritis individuals with and without chronic periodontitis: a biochemical study. J Indian Soc Periodontol. 2018;22(2):116.
72.•• Cosgarea R, Tristiu R, Dumitru RB, Arweiler NB, Rednic S, Sirbu CI, et al. Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis. Clin Oral Investig. 2019;23(1):141–51. **In patients with RA and CP, non-surgical periodontal therapy is a relevant modality not only to improve the periodontal condition but also to decrease RA activity.**
73.•• Äyräväinen L, Heikkinen AM, Kuuliala A, Ahola K, Koivuniemi R, Laasonen L, et al. Inflammatory biomarkers in saliva and serum of patients with rheumatoid arthritis with respect to periodontal status. Ann Med. 2018;50(4):333–44. **Concentrations of inflammatory biomarkers in serum and saliva are different between patients with RA and healthy controls. Concentrations of MMP-8 and of IL-6 in serum were elevated in patients with chronic RA reflecting joint inflammation and the burden of established RA. Concentrations of MMP-8 in saliva were elevated already at early stage RA. Level of salivary MMP-8 was associated with poor periodontal health both in patients with early and chronic RA.**
74. Schmalz G, Davarpanah I, Jager J, Mausberg RF, Krohn-Grimberghe B, Schmidt J, et al. MMP-8 and TIMP-1 are associated to periodontal inflammation in patients with rheumatoid arthritis under methotrexate immunosuppression—first results of a cross-sectional study. J Microbiol Immunol Infect. 2019;52(3):386–94.
75. Panezai J, Ghaffar A, Altamash M, Engström P-E, Larsson A. Periodontal disease influences osteoclastogenic bone markers in subjects with and without rheumatoid arthritis. PLoS One. 2018;13(6):e0197235.
76. Kindstedt E, Johansson L, Palmqvist P, Koskinen Holm C, Kokkonen H, Johansson I, et al. Association between marginal jawbone loss and onset of rheumatoid arthritis and relationship to plasma levels of RANKL. Arthritis Rheumatol. 2018;70(4):508–15.
77. Beyer K, Lie SA, Kjellevold M, Dahl L, Brun JG, Bolstad AI. Marine ω-3, vitamin D levels, disease outcome and periodontal status in rheumatoid arthritis outpatients. Nutrition. 2018;55:116–24.
78.•• Ziebolz D, Rupprecht A, Schmickler J, Bothmann L, Krämer J, Patschan D, et al. Association of different immunosuppressive medications with periodontal condition in patients with rheumatoid arthritis: results from a cross-sectional study. J Periodontol. 2018;89(11):1310–7. **RA medication is associated with periodontal inflammation, without differences in periodontal disease severity. Thereby, combination of MTX + TNF-α shows an increased potential to periodontal inflammation. Additionally, several differences in prevalence of selected bacteria were detected.**
79. Cobb CM. Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing. J Clin Periodontol. 2002;29:22–32.
80. Zhao X, Liu Z, Shu D, Xiong Y, He M, Xu S, et al. Association of periodontitis with rheumatoid arthritis and the effect of non-surgical periodontal treatment on disease activity in patients with rheumatoid arthritis. Med Sci Monit. 2018;24:5802.
81. Kaushal S, Singh AK, Lal N, Das SK, Mahdi AA. Effect of periodontal therapy on disease activity in patients of rheumatoid arthritis with chronic periodontitis. J Oral Biol Craniofac Res. 2019;9(2):128–32.
82. Monsarrat P, Fernandez de Grado G, Constantin A, Willmann C, Nabet C, Sixou M, et al. The effect of periodontal treatment on patients with rheumatoid arthritis: ESPERA randomised controlled trial. Joint Bone Spine. 2019;86(5):600–9.
83. Mariette X, Perrodeau E, Verner C, Struillou X, Picard N, Schaeverbeke T, et al. Role of good oral hygiene on clinical evolution of rheumatoid arthritis: a randomized study nested in the ESPOIR cohort. Rheumatology. 2019. https://doi.org/10.1093/rheumatology/kez368.
84. Hashimoto H, Hashimoto S, Muto A, Dewake N, Shimazaki Y. Influence of plaque control on the relationship between rheumatoid arthritis and periodontal health status among Japanese rheumatoid arthritis patients. J Periodontol. 2018;89(9):1033–42.
85. Chapple IL, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89:S74–84.
86. Khare N, Vanza B, Sagar D, Saurav K, Chauhan R, Mishra S. Nonsurgical periodontal therapy decreases the severity of rheumatoid arthritis: a case-control study. J Contemp Dent Pract. 2016;17(6):484–8.
87. 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(3):134–7.
88. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
89. Preshaw PM. Host response modulation in periodontics. Periodontol 2000. 2008;48(1):92–110.

90. Han JY, Reynolds MA. Effect of anti-rheumatic agents on periodontal parameters and biomarkers of inflammation: a systematic review and meta-analysis. J Periodontal Implant Sci. 2012;42(1):3–12.
91. Kadkhoda Z, Amirzargar A, Esmaili Z, Vojdanian M, Akbari S. Effect of TNF-α blockade in gingival crevicular fluid on periodontal condition of patients with rheumatoid arthritis. Iran J Immunol. 2016;13(3):197–203.
92. Kobayashi T, Yoshie H. Host responses in the link between periodontitis and rheumatoid arthritis. Curr Oral Health Rep. 2015;2(1):1–8.
93. Coat J, Demoersman J, Beuzit S, Cornec D, Devauchelle-Pensec V, Saraux A, et al. Anti-B lymphocyte immunotherapy is associated with improvement of periodontal status in subjects with rheumatoid arthritis. J Clin Periodontol. 2015;42(9):817–23.
94. Jung G-U, Han J-Y, Hwang K-G, Park C-J, Stathopoulou PG, Fiorellini JP. Effects of conventional synthetic disease-modifying antirheumatic drugs on response to periodontal treatment in patients with rheumatoid arthritis. Biomed Res Int. 2018;2018:1465402. https://doi.org/10.1155/2018/1465402.
95. Rinaudo-Gaujous M, Blasco-Baque V, Miossec P, Gaudin P, Farge P, Roblin X, et al. Infliximab induced a dissociated response of severe periodontal biomarkers in rheumatoid arthritis patients. J Clin Med. 2019;8(5):751.
96. Savioli C, Ribeiro ACM, Fabri GMC, Calich AL, Carvalho J, Silva CA, et al. Persistent periodontal disease hampers anti-tumor necrosis factor treatment response in rheumatoid arthritis. J Clin Rheumatol. 2012;18(4):180–4.
97. Lee YH, Lew PH, Cheah CW, Rahman MT, Baharuddin NA, Vaithilingam RD. Potential mechanisms linking periodontitis to rheumatoid arthritis. J Int Acad Periodontol. 2019;21(3):99–110.

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