Periodontal disease in seropositive rheumatoid arthritis: scoping review of the epidemiological evidence

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Abstract

The link between periodontal disease (PD) and rheumatoid arthritis (RA) has been hypothesized to lie in the anti-cyclic citrullinated protein antibody (ACPA) molecules present in seropositive RA. This review aimed to discuss how RA and specifically ACPA-positive RA link to PD, and appraise the epidemiological evidence on the relationship between ACPA-positive RA and PD. Articles were searched following the PRISMA guideline across the MEDLINE, Web of Science, Scopus and Cochrane Library databases. A total of 21 articles met the inclusion criteria of reporting the epidemiological data on the different ACPA status of the subjects with RA and PD (or periodontitis) parameters. A discrepancy is noted in the epidemiological evidence on the difference in the prevalence and severity of PD between ACPA-positive and ACPA-negative RA patients. Although the link between RA and PD is mostly discussed in terms of ACPA, reports on the different manifestations of PD between the two RA subsets remains inconclusive.

Keywords **Anti-citrullinated protein antibodies, periodontal disease, periodontitis, rheumatoid arthritis, rheumatoid factor.**

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that typically affects the synovial joints, although extra-articular manifestations (e.g., of the skin, eyes, heart, lung, renal, nervous and gastrointestinal systems) also occur.[1] The main characteristic of RA is a persistent joint inflammation that results in joint damage and loss of function. Periodontal disease (PD) is an inflammatory condition triggered by the presence of pathogenic microorganisms of the dental plaque with biofilm formation. PD involves the soft and hard tissues of the tooth, namely, the gingivae, periodontal ligament, cementum and alveolar bone. This disease can broadly be divided into two categories, namely, gingivitis and periodontitis, depending on the degree of tissue involvement.

The prevalence of PD in patients with RA has been widely reported in the literature. The figure ranges from a low prevalence of 28.4%[2]-39%[3] when using national data, to a high prevalence of 98%[4]-100%[5] in observational studies. A recent systematic review has reported an association between RA and PD through the heredity, bacterial infection and the pro-

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inflammatory profile shared between both diseases.[6] A meta-analysis conducted has shown a high RA prevalence for subjects with PD (OR 1.97; 95%CI 1.68-2.31; p<0.00001), although considerable heterogeneity amongst the included studies was verified (I^2 = 96%, p <0.00001).[6]

The link between the two diseases has been hypothesized to lie in the anti-cyclic citrullinated protein antibody (ACPA) molecules present in seropositive RA. That is, PD is thought to trigger the autoimmune response in RA through the production of the ACPA molecules. The periodontal pathogen *Porphyromonas gingivalis* present in individuals with PD has been shown to be capable of citrullination and the creation of citrullinated peptides. These citrullinated peptides could lead to the antigen response characteristics in susceptible patients. However, most epidemiological evidence[3,7-11] and systematic reviews[12-14] did not differentiate between ACPA-positive and ACPA-negative RA. The current review aimed to discuss how RA and specifically ACPA-positive RA links to PD, and review the epidemiological evidence on the relationship between ACPA-positive RA and PD. The findings of this review can be used by researchers to further elucidate the biological relationship between RA and PD. Clinicians treating ACPA-positive patients may also choose to recommend ACPA-positive patients to undergo periodontal assessments based on the relationship between ACPA-positive RA and PD.

RA and PD

The similarities between RA and PD have been explored as early as the 1980s.[15] Several pathophysiological similarities between the two diseases include equivalent cell infiltrates, which are macrophages, T-lymphocytes, plasma cells and polymorphonuclear cells. They also have similar cytokines recruitment, including interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β). The tissue destruction enzymes involved in the two diseases, namely metalloproteinases, phospholipases and elastases, are also the same.[16,17] In terms of risk factors, HLA-DRB shared epitope alleles and smoking are risk factors common in the two diseases. However, PD is mostly caused by *P. gingivalis* infection.[18] Anti-*P. gingivalis* antibody has also been suggested as a biomarker of RA.[17]

The links between the two diseases have been broadly categorized by Farquharson et al.[19] into: (i) generation of autoantigens by bacteria, (ii) generation of autoantigens by local inflammation, (iii) direct bacterial insult, (iv) systemic inflammatory effects of PD.[19] Bacterial generation of autoantigens in (i) is explained by the role of the periodontal pathogen *P. gingivalis* in citrullinating its own and its host proteins. This is further explained in the subsequent sections.

Seropositivity in RA

Auto-antibodies to the Fc portion of the immunoglobulin are known as rheumatoid factor (RF), whilst antibodies that form against citrullinated proteins are called ACPA. ACPA is a comparatively new biomarker for RA and has been included in the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.[20] Seropositive status in RA is conferred when either or both RF and ACPA are positive.

Seroprevalence of ACPA has been found to be strongly associated with the presence of each of the RF isotypes, IgM and IgG. Additionally, seroprevalence of RF and ACPA has been reported to not increase or decrease with advancing age, age at onset and disease duration.[21] Some groups of RA patients are tested ACPA positive up to 10 years before the clinical development of the disease,[22] thereby resulting in the use of the term pre-clinical RA.

RF and ACPA have been associated with a significantly severe and erosive RA.[23] Given that the presence of ACPA indicates a more severe phenotype of RA with greater destruction potential, ACPA-positive RA has a worse prognosis with higher rates of erosive damage. ACPA-positive and ACPA-negative RA also have different risk factors. That is, ACPA-positive RA has a considerable genetic association and environmental risks, such as smoking and alcohol abstinence.

ACPA positivity and PD

Central to the shared pathogenesis between RA and PD is the presence of citrullinated antigens that are believed to drive adaptive immune responses. Citrullination is a post-translational modification of arginine residues, which is mediated by peptidylarginine deiminases (PAD). Citrullinated fibrin(ogen) and α-enolase are two of the physiological proteins that are targeted by ACPA in RA. These citrullinated antigens can be detected via the presence of ACPA in patients' serum. Citrullination of human proteins is associated with PAD. These enzymes are present physiologically in the human body and can cause post-translational changes to proteins at sites of tissues with inflammation injury.[24]

One of the explored theories on the link between PD and RA is the role of periodontal pathogens, namely, *P. gingivalis*, in the production of peptidylarginine deiminase (PPAD). PPAD could break immune tolerance and trigger a latent antibody response against citrullinated proteins prior to the onset of RA. *P. gingivalis* is the only known microorganism to produce the enzyme PAD, although the human PAD and bacterial PPAD differ in terms of their enzymatic activities.[25] Additionally, the enzyme PPAD produced by *P. gingivalis* is not calcium-dependent, and is capable of auto-citrullination to become a citrullinated bacterial protein by itself.[26] This result further supports the hypothesis that PPAD may break tolerance in RA and could be a target for RA therapy.

The relationship has been described as a 'two-hit' model of RA, in which tolerance breakdown to specific citrullinated peptides generated by periodontal pathogens (i.e., *P. gingivalis*) at the site of gingival inflammation precedes epitope-spreading in the inflamed joint to other host citrullinated proteins.[27] Periodontitis is considered the first hit, inducing inflammation that leads to RA as the second hit. Thereafter, this self-sustaining immune response would manifest through the chronic and destructive inflammation that characterizes RA. To further support this theory, Hitchon et al. reported that antibodies to *P. gingivalis* are associated with ACPA in patients with RA, as well as the relatives of these patients.[28]

Direct bacterial insult and local inflammation generating auto-antigens

P. gingivalis is a keystone pathogen capable of altering the microbial synergy, causing dysbiosis of the oral flora.[29] This pathogen is also capable of translocation to distant sites and has been detected in atherosclerotic plaques and the synovium of rheumatic joints.[30,31] A recent systematic review has proposed that inflammatory response against bacterial infection is another possible link between RA and PD.[6] The presence of periodontal bacteria DNA in the synovial joints of patients with RA and the formation of immune complexes in synovial joints involving *P. gingivalis*[31] and other periodontopathogens (e.g., *A. actinomycetecomitans*[32]) further supports this mechanism. The presence of oral pathogens can trigger the production of an inflammatory response at these distant sites, or exacerbate existing inflammation with the periodontal lesions in the mouth, thereby acting as a reservoir for these pathogens.

Search criteria

Before undertaking this review, an online search using PubMed determined that no reviews on this topic had been published. The current scoping review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis extensions for Scoping Reviews (PRISMA-ScR) guidelines.[33] The population, concept and context (PCC) strategy was used, in which observational studies on adults presenting with periodontitis and absence of periodontitis, the primary outcome of which was the diagnosis of ACPA-positive RA, were considered eligible. Article selection was based on the inclusion of epidemiological data on the different ACPA statuses of the RA subjects and PD (or periodontitis) parameters.

Studies were considered eligible if they: (i) were cross-sectional, case-control or cohort studies; (ii) reported on the ACPA status of RA subjects; (iii) reported on the prevalence and severity of PD according to ACPA status or (iv)

provided correlation coefficient between the ACPA and PD parameters. Only articles in English were considered, without any limits to the years considered and publication status. The articles were excluded if: (i) they were case reports or case studies, intervention studies and reviews; or if (ii) they had insufficient or overlapping data.

Two reviewers (i.e., NMNA and NM) independently searched for relevant articles the on Medline, Scopus, Web of Science and The Cochrane Library databases up to 30 March 2021. The grey literature was searched using Google Scholar. The keywords 'periodontitis', 'periodontal disease', 'anti-citrullinated protein antibodies', 'anti cyclic citrullinated protein antibodies' and 'rheumatoid arthritis' were chosen from the Medical Subjects Headings (MeSH) for the search. Other keywords used were 'adults' OR 'adult*', 'periodontal disease' OR 'periodontitis' OR 'periodontal disease.mp' OR 'periodontitis.mp' and 'rheumatoid arthritis' OR 'anti-citrullinated protein antibodies' OR 'anti-cyclic citrullinated protein antibodies' OR 'rheumatoid arthritis.mp'.

Titles and abstracts were first analysed according to the search criteria. Additional searches were conducted from the reference lists of the selected articles. A third reviewer (BB) was consulted in the case of disagreements. The full texts of all potentially eligible papers were independently reviewed by NMNA, NM and BB. The flow diagram of the database searches is shown in Figure 1.

Data extraction and analysis

Data extraction was done involving the following parameters: primary author, year of publication, location/country of study, type of study, sample size, diagnostic criteria of the two diseases, periodontitis/PD assessments, RA assessments, including seropositivity, correlation coefficients between the ACPA and PD parameters and conclusions. A predefined data extraction table was utilised and tested before use. Data were extracted independently by NMNA and NM. Any missing or unclear data were clarified with the authors of the selected studies.

A subjective assessment of the completed data extraction table was initially conducted. Significant difference was determined in the periodontal assessment and classification criteria, participant characteristics and study design of the included studies. The periodontal parameters reported also varied between the studies.

Review results

Study selection and characteristics

A total of 21 studies were found to report on epidemiological data on the different ACPA status of the RA subjects and PD (or periodontitis) parameters. Table 1 summarizes the details of the included studies.

In the included studies, the PD diagnostic criteria used varied widely with over 10 different classifications used.[34-41] For the RA diagnosis, the classifications were markedly consistent with the 1987[42] and 2010[20] American College of Rheumatology classifications being the standard reference. Studies reporting on ACPA in PD were mostly case control and cross-sectional studies, with one community-based prospective cohort study[43] and two population-based case-control studies.[44,45] For the case control studies, the population of choice was mostly healthy controls, although some studies had opted for osteoarthritis controls.

Prevalence, severity and associations between PD and ACPA seropositivity

Table 2 shows the data extraction of the relevant epidemiological evidence, specifically mentioning the difference between PD prevalence/severity in the two subsets of the ACPA serotype, as well as the association between the ACPA and PD parameters.

The ACPA and PD parameters were reported to be associated in 12 studies,[43,45,46-54] whilst 7 studies[44,55-60] reported no such associations. The PD parameters used to assess prevalence and severity of PD, as well as associations between PD and ACPA, varied widely. Some studies had measured mean periodontal pocket depth,[46] whilst others used parameters such as alveolar bone loss,[48] percentage of sites with probing depth >5 mm[47] and community periodontal index (CPI).[43]

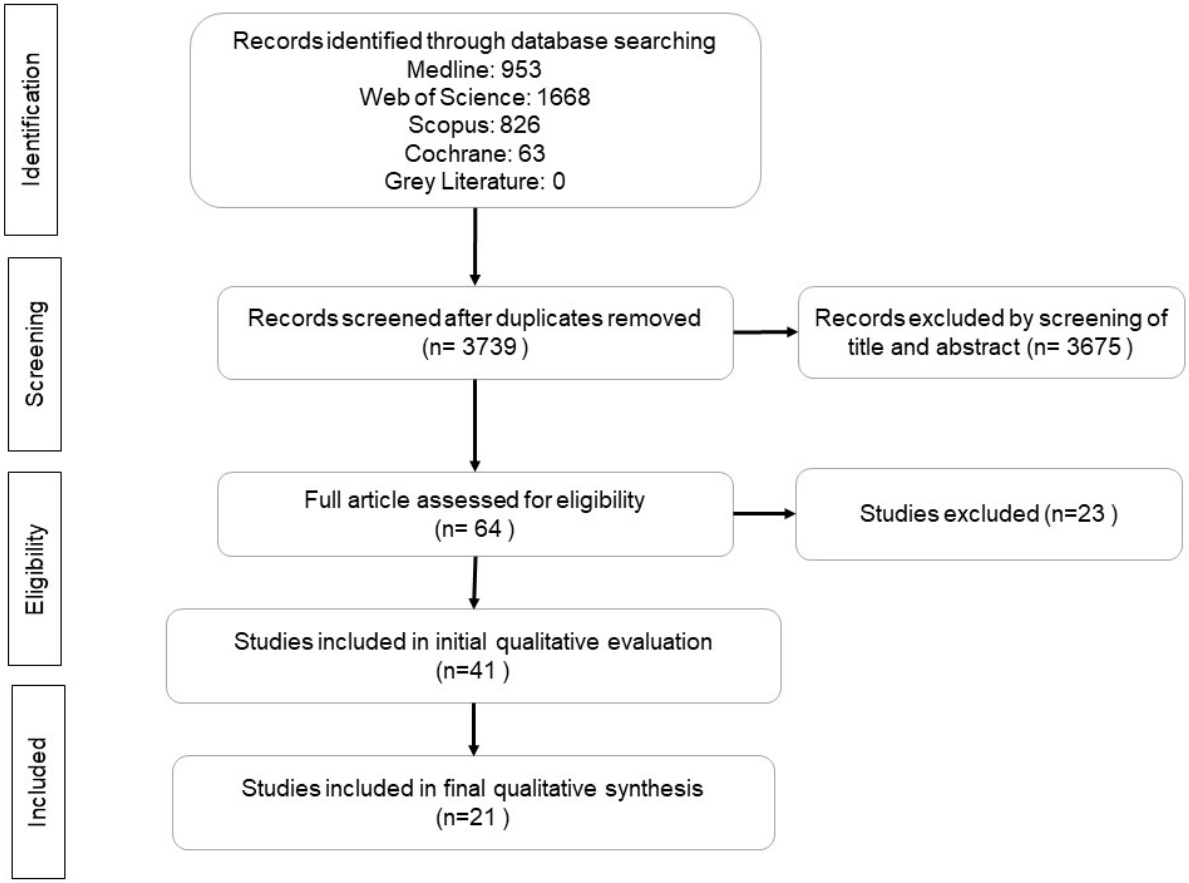

Figure 1. PRISMA flow diagram depicting the results of the search strategy

Table 1. Characteristics of the studies included in the review

Authors, year of publication	Setting/Location	Aims of the study	Sample numbers		Control Type	Type of study	PD diagnostic classification	RA diagnostic classification
			RA	Control				
Havemose-Poulsen, 2006[55]	Copenhagen, Denmark	To compare periodontal and hematological characteristics of patients with localized aggressive periodontitis (LAgP), generalized aggressive periodontitis (GAgP), juvenile idiopathic arthritis (JIA) or RA to those of control individuals.	LAgP=18, GAgP=27, JIA=10, RA=23	25	Healthy controls	Case control	AAP 1999 (Armitage et al, 1999)	ACR 1987; JIA Classification 1994 (Arnett et al, 1988; Petty et al, 1994)
Dissick, 2010[61]	United States veterans	To evaluate the prevalence and severity of periodontitis in a population of United States veterans with RA, making comparisons to a group of patients with non-inflammatory arthritis.	69	35	Osteoarthritis	Case control	AAP 2003 (Armitage et al, 2003)	ACR 1987 (Arnett et al, 1988)
de Smit, 2012[62]	Groningen, Netherlands	To further explore whether the association between periodontitis and RA is dependent on *P. gingivalis*, by comparing host immune responses in RA patients with and without periodontitis in relation to presence of cultivable *P gingivalis* in subgingival plaque	95	44, 36	Non-RA controls, healthy controls	Case control	DPSI (van der Velden, 2009)	ACR 1987 (Arnett et al, 1988)
Potikuri 2012[46]	Hyderabad, India	To find the strength of association between PD and RA in non-smoking, disease modifying antirheumatic drug-naive RA patients	91	93	Healthy controls	Case control	Mean pocket depth is ≥3 mm	ACR 1987 (Arnett et al, 1988)
Mikuls 2015[47]	United States veterans	To examine the degree to which shared risk factors explain the relationship of PD with RA and to examine associations of PD and *Porphyromonas gingivalis* with disease features.	287	330	Osteoarthritis	Case control	Machtei et al, 1992	ACR 1987 (Arnett et al, 1988)

Authors,	Setting/Location	Aims of the study	Sample numbers		Control Type	Type of	PD diagnostic	RA diagnostic
Gonzales, 2015[48]	United States veterans	1) To examine alveolar bone loss in (ACPA)-positive rheumatoid arthritis (RA) patients versus osteoarthritis controls and 2) To examine the association of alveolar bone loss with RA disease activity and ACPA concentrations, including multiple antigen-specific ACPA.	287	330	Osteoarthritis	Case control	Machtei et al, 1992	ACR 1987 (Arnett et al, 1988)
Terao, 2015[43]	Kyoto, Japan	To analyze the associations between PD status and RA-related autoantibodies especially ACPA	9575 subjects who did not have connective tissue diseases		NR	Community-based prospective cohort study	CPI (WHO)	NR
Choi, 2016[49]	Seoul, Korea	To investigate the association between severity of periodontitis and clinical manifestation of RA.	264	88	NR	Case control	AAP 2003 (Armitage et al, 2003)	ACR 1987 (Arnett et al, 1988)
Erikkson, 2016[44]	Sweden	To investigate the prevalence of periodontitis in the Swedish Epidemiological Investigation of RA (EIRA), a well-characterized population-based RA case-control cohort.	2,740	3,942	Healthy controls	Population-based case-control	AAP 1999 (Armitage et al, 1999)	ACR 1987 (Arnett et al, 1988)
Erikkson, 2018[50]	Sweden	To investigate the effects of smoking on the risk of periodontitis in seropositive and seronegative (ACPA/ RF) subsets of RA	2,327	NR	NR	Population-based case-control	AAP 1999 (Armitage et al, 1999)	ACR 1987 (Arnett et al, 1988)
Wan Mohamad, 2018[56]	Malaysia	To assess the presence of periodontal disease and whether the association with ACPA occurs among RA patients in local population.	44	NR	NR	Cross-sectional	The severity of periodontal status was defined as mild (1-2 mm CAL) or moderate to severe (≥3 mm CAL).	ACR 2010 (Aletaha et al, 2010)

Authors,	Setting/Location	Aims of the study	Sample numbers		Control Type	Type of	PD diagnostic	RA diagnostic
Erikkson, 2019[45]	Sweden	To investigate the severity of periodontitis in Swedish RA patients in relation to autoantibody status (ACPA and RF), inflammatory mediators, RA disease activity and medication as well as the microbiota in saliva and subgingival plaque.	40	NR	NR	Cross-sectional	CDC/AAP 2007 (Page et al, 2007)	ACR 2010 (Aletaha et al, 2010)
Rodríguez-Lozano, 2019[57]	Tenerife, Spain	To investigate the link between RA and periodontitis, to assess whether RA disease activity is associated with periodontitis severity and to determine the degree to which this association is affected by shared risk factors.	187	157	Osteoarthritis/ Soft tissue rheumatic disease	Case control	Tonetti et al, 2005	ACR 2010 (Aletaha et al, 2010)
Zhao, 2019[51]	Nantong, China	To assess the prevalence and severity of PD in Chinese RA patients and analyze to what extent confounders may affect the association potentially.	128	109	Healthy controls	Case control	No periodontitis; mild periodontitis ≤30% bone loss and minimal or no BOP; moderate periodontitis ≤50% bone loss, BOP, and tooth mobility <2; severe periodontitis ≥50% bone loss, marked BOP, and tooth mobility ≥2.	ACR 2010 (Aletaha et al, 2010)
González-Febles, 2020[52]	Spain	To investigate the link between periodontitis and its severity with the presence and levels of ACPA in RA patients, and the possible impact of shared risk factors as tobacco habit on the presence and levels of ACPA.	164	NR	NR	Cross-sectional	Tonetti et al, 2018	ACR 2010 (Aletaha et al, 2010)
Nguyen, 2020[53]	Ho Chi Minh City, Vietnam	To survey periodontal status of Vietnamese patients with RA and investigate the association between periodontitis and RA in these patients.	150	150	Osteoarthritis	Case control	CDC/AAP 2012 (Eke et al., 2012)	ACR 2010 (Aletaha et al, 2010)

Authors,	Setting/Location	Aims of the study	Sample numbers		Control Type	Type of	PD diagnostic	RA diagnostic
Rahajoe, 2020[60]	Yogyakarta, Indonesia	To assess RA associated autoantibodies, especially the IgA isotypes of ACPA and RF in the gingival crevicular fluid of RA patients and in healthy controls with or without PD.	72	151	Healthy controls	Case control	CDC/AAP 2012 (Eke et al., 2012)	ACR 2010 (Aletaha et al, 2010)
Reichert, 2020[54]	Martin-Luther University Halle-Wittenberg, Germany	to investigate a putative relationship between the periodontal status and/or the detection of five periodontal pathogenic bacteria in subgingival plaque with autoantibody levels against CEP-1 and/or CCP in patients with RA.	107	NR	NR	Cross-sectional	CDC/AAP 2012 (Eke et al., 2012	ACR 2010 (Aletaha et al, 2010)
Renvert, 2020[58]	Karlskrona, Sweden	To assess if a diagnosis of periodontitis is more common in individuals (≥61 years) with RA than among age-stratified individuals from the normal population without a diagnosis of RA.	126	249	Healthy controls	Case control	Gingivitis: BOP at ≥20% of sites. Periodontitis: BOP at >20% of sites, presence of >2 non-adjacent sites with (PPD) ≥5 mm, bone loss at ≥2 sites, furcation involvement.	ACR 1987 (Arnett et al, 1988) and ACR 2010 (Aletaha et al, 2010)
Stefanov, 2020[67]	Bulgaria	To investigate the relationship between serum ACPAs and the clinical parameters of periodontitis, as well as to define their predictive value for assessing severity and activity of the periodontal disease in patients with concomitant periodontitis and RA.	60	NR	NR	Cross-sectional	Tonetti et al, 2018	ACR 2010 (Aletaha et al, 2010)

Authors,	Setting/Location	Aims of the study	Sample numbers		Control Type	Type of	PD diagnostic	RA diagnostic
Svard, 2020[59]	Karlskrona, Sweden	To investigate the presence and levels of IgA ACPA in saliva and serum of elderly RA patients, in relation to clinically verified periodontitis and smoking.	132	NR	NR	Cross-sectional	Gingivitis: BOP at ≥20% of sites. Periodontitis: BOP at >20% of sites, presence of >2 non-adjacent sites with PPD ≥5 mm, bone loss at ≥2 sites, furcation involvement.	ACR 1987 (Arnett et al, 1988) and ACR 2010 (Aletaha et al, 2010)

AAP – American Association of Periodontology; **ACR** – American College of Rheumatology; **ACPA** – anti-citrullinated protein antibodies; **BOP** – bleeding on probing; **CAL** – clinical attachment loss; **CDC** – Centers for Disease Control and Prevention; **CPI** – community periodontal index; **DPSI** – Dutch periodontal screening index; **GAgP** – generalized aggressive periodontitis; **JIA** – juvenile idiopathic arthritis; **LAgP** – localized aggressive periodontitis; **NR** – not relevant; **PD** – periodontal disease; **PPD** – periodontal pocket depth; **RA** – rheumatoid arthritis; **RF** – rheumatoid factor.

Table 2. Prevalence and severity of periodontal disease according to RA serotype

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Havemose-Poulsen, 2006[55]	Plaque, BOP, PPD, CAL, ABL	Erythrocyte fraction, leukocytes and differential counts, ESR, CRP, RF, ACPA	NR	ACPA levels did not correlate with any of the PD variables	NR
Dissick, 2010[61]	BOP, erythema/edema, purulence, tooth mobility, ABL	Multidimensional health assessment questionnaire, CRP, RF, ACPA, DAS28, the presence of radiographic erosions on hand or foot films	Among patients who were ACPA seropositive, 56% had moderate to severe periodontitis, 31% had mild periodontitis, and 14% had no periodontitis. Patients who were ACPA negative had 22% (moderate to severe), 22% (mild), and 56% (none) periodontitis (p=0.01 for the difference).	NR	The presence of periodontitis in patients with RA was associated with ACPA seropositivity. Moderate to severe periodontitis was more frequently observed among RA patients who were seropositive for ACPA.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
de Smit, 2012[62]	Dutch periodontal screening index (DPSI) including BOP, PPD, CAL	DAS28, RA disease duration, subgingival plaque samples analysis for presence of *Porphyromonas gingivalis*	Between RA patients with no, moderate, or severe periodontitis, no differences were seen in ACPA levels	NR	NR
Potikuri 2012[46]	PPD, screening questionnaire for the presence of gingival swelling, gingival bleeding, tooth sensitivity, tooth mobility and past history of tooth loss due to PD	RA disease duration, early morning stiffness, TJC28, SJC28, joint deformities and patient global assessment of disease severity on a visual analogue scale, DAS 28-ESR	NR	1. Mean pocket depth was significantly higher in RA with ACPA positive patients compared with RA with ACPA negative (3.94 ± 1.13 mm vs 3.40 ± 1.25 mm; p=0.04). The mean pocket depth correlated positively with titers of ACPA (r=0.24; p=0.02). 2. ACPA titers were significantly higher in the PD group (753.05 ± 1088.27 vs 145.15 ± 613.16 IU/mL; p=0.001).	PD in RA is associated with high titers of ACPAs.
Mikuls 2015[47]	BOP, PPD, REC, supragingival plaque (serving as an indicator of oral hygiene, missing teeth, subgingival plaques specimen analysis	ACPA, RF, hs-CRP, HLA-DRB1 status analysis, TJC28, SJC28, VAS global well-being scores, DAS-28-CRP, posterior-anterior hand and wrist radiographs	PD was more common in ACPA positive RA (37%; OR^{unadj} 1.65; 95% CI 1.15, 2.36; p=0.006) compared to controls (26%).	1. After multivariable adjustment, including adjustments for smoking and HLA-DRB1 SE, PD remained significantly more frequent among ACPA positive RA cases (OR 1.59; 95%CI 1.01-2.49; p=0.043) than controls, an association that was attenuated and not significant when all RA cases including ACPA negative patients were evaluated (OR 1.36; 95%CI 0.89-2.06; p=0.153). 2. Relative to controls, ACPA positive cases (p=0.005) demonstrated a higher percentage of sites with probing depths ≥5 mm with a non-significant trend towards a higher proportion of sites with attachment loss ≥5 mm among ACPA positive cases (p=0.060).	PD demonstrated an independent relationship with established seropositive RA. Associations of PD with established seropositive RA were independent of all covariates examined including evidence of *Porphyromonas gingivalis* infection.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Gonzales, 2015[48]	BOP, PPD, REC, supragingival plaque (serving as an indicator of oral hygiene, missing teeth	ACPA, RF, hs-CRP, HLA-DRB1 status analysis, TJC28, SJC28, VAS global well-being scores, DAS-28-CRP, posterior-anterior hand and wrist radiographs	NR	1. ACPA-positive RA cases had a statistically significantly higher mean percentage of sites with alveolar bone loss greater than 20% compared to osteoarthritis controls (p=0.03). 2. Alveolar bone loss was associated with higher ACPA (p=0.007). 3. Following multivariate adjustment, high alveolar bone loss remained significantly associated with higher values of the continuous variables ACPA concentration (p=0.004).	There is an association between alveolar bone loss and ACPA concentrations and RA disease activity measures.
Terao, 2015[43]	Missing teeth, CPI, CAL	ACPA, RF	NR	1. Significant or suggestive positive associations between increasing positivity of ACPA and all of the PD parameters (missing teeth, CPI, CAL) conditioned with covariates (p=0.024, 0.0042 and 0.037). 2. CPI was shown to be associated with increasing ACPA positivity and levels when CPI was more than 2.	The significant associations between PD parameters and positivity and levels of ACPA in the healthy population support the fundamental involvement of PD with ACPA production.
Choi, 2016[49]	BOP, GI, PPD, CAL	ACPA, RF, TJC68, SJC68, disease duration, ESR, CRP	NR	1. BOP was correlated with ACPA (r=0.183, p=0.009). 2. GI was correlated with ACPA (r=0.203, p=0.004).	ACPA are more abundant in patients with more severe periodontal inflammation.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Erikkson, 2016[44]	Prevalence of periodontitis investigated using a self-administered questionnaire. Treatment codes for PD retrieved through the National Dental Health Registry.	Treatment codes for RA retrieved through linking the National Dental Health Registry	70% of ACPA +ve and 69% of ACPA -ve participants had PD	The prevalence of periodontal treatment codes did not differ between ACPA-positive and ACPA-negative RA ($p>0.05$).	No differences in PD parameters based on ACPA among RA subjects.
Erikkson, 2018[50]	Prevalence of periodontitis investigated using a self-administered questionnaire. Treatment codes for PD retrieved through the National Dental Health Registry.	Treatment codes for RA retrieved through linking the National Dental Health Registry	52.6% of ACPA +ve and 53.8% of ACPA -ve participants had PD	1. In ACPA-positive RA, smoking was associated with a significantly ($p<0.05$) higher prevalence of periodontitis, mainly in current smokers (OR=1.9, 95% CI 1.5-2.5). 2. The OR for periodontitis increased among patients double positive for ACPA and RF antibodies, with OR of 3.3 (95% CI 1.8-6.2) observed in current smoking men compared with never smokers.	The highest risk of periodontitis in patients with established RA was observed among seropositive current smokers, especially those that are double positive for ACPA and RF antibodies.
Wan Mohamad, 2018[56]	PS, GS, PPD, CAL	ACPA	33.3% of ACPA +ve and 55.7% of ACPA -ve participants had moderate to severe PD ($p=0.27$)	No significant association between ACPA levels and the severity of periodontal disease based on CAL.	The association with periodontal status was not evident in this study.
Erikkson, 2019[45]	BOP, PI, PPD, CAL, stimulated salivary flow, number of missing and mobile teeth, subgingival plaque sample	ACPA, RF, DAS-28, DAS28-CRP, CRP, VAS global well-being scores, HAQ	86% of ACPA +ve and 14% of ACPA -ve participants had PD	ACPA positivity was significantly ($p=0.032$) more frequent in patients with moderate/severe periodontitis (86%), compared to the group with no/mild disease (50%).	Patients with ACPA-positive RA have more severe forms of periodontitis, irrespective of DMARD therapy or the presence of subgingival *Porphyromonas gingivalis*.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Rodríguez-Lozano, 2019[57]	BOP, PI, PPD, CAL, REC, tooth loss	ACPA, RF, DAS28-CRP, CRP, clinical disease activity index, simplified disease activity index, VAS global well-being scores	NR	No association was observed between the immunological characteristics of RA (presence of ACPA) and the presence of periodontitis.	NR
Zhao, 2019[51]	BOP, PI, GI, PPD, CAL	ACPA, RF, DAS28-ESR, HAQ, CRP, ESR, radiographs	59 cases were ACPA positive in PD group and 8 cases were positive in non-PD group (67.82% vs 19.51%; p<0.001).	Multivariate logistic regression showed higher ACPA positivity were the variables related to periodontitis in RA patients (OR 8.963; 95% CI: 2.171-36.998, p<0.002).	PD is related to ACPA positivity.
González-Febles, 2020[52]	PI, BOP, PPD, CAL, number of missing and mobile teeth	ACPA, RF, DAS28-CRP, CRP, SDAI, VAS global well-being scores	100% of ACPA +ve and 98% of ACPA -ve participants had PD	1. ACPA positive patients showed significantly higher CAL (4.16 ± 1.43 vs 3.72 ± 0.85, p=0.015), higher numbers (16.93 ± 19.63 vs 11.64 ± 11.02, p=0.029) and percentages of pockets ≥5 mm (0.14 ± 0.16 vs 0.09 ± 0.09, p=0.014), and higher mean PI (31.0 ± 19.7 vs 22.4 ± 13.3, p<0.001), compared to their ACPA negative counterparts. 2. When ACPA were stratified by level, an ordinal logistic regression model showed a direct association between these levels and the mean CAL with an OR of 1.593 (95% CI 1.017-2.482, p=0.043) in patients with high ACPA titers versus non-ACPA patients. A significant association was also demonstrated for patients with high ACPA titers and the number of pockets ≥5mm and the mean PI with adjusted ORs of 1.031 (95%CI 1.003-1.062, p=0.031) and 1.060 (95% CI 1.027-1.093, p<0.001), respectively.	There is a link between ACPA titers and periodontitis, in which worsening periodontal conditions, in terms of mean CAL, mean PI, and number of pockets >5 mm, were statistically associated with both ACPA positivity and higher levels of ACPA titers.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Nguyen, 2020[53]	PI, GI, PPD, CAL, number of missing and mobile teeth	ACPA, RF, DAS28-CRP, CRP, VAS global well-being scores, TJC28, SJC28	74.7% of ACPA +ve and 54.2% of ACPA -ve participants had PD (p=0.16).	1. There was a positive correlation between ACPAs levels, ACPAs categories and severity of periodontitis (p<0.05). 2. There was a weak correlation between the level of periodontal status and serum ACPAs (Spearman's r 0.32, p<0.001).	Periodontal status was proportional to ACPAs positivity.
Rahajoe, 2020[60]	BOP, PPD, CAL, PISA, GCF sample	ACPA, RF, DAS28-ESR, ESR, disease duration	NR	ACPA levels in the RA patients' serum were not related to the presence of PD.	NR
Reichert, 2020[54]	BOP, PPD, CAL, PISA, PESA, subgingival plaque specimens	ACPA, anti-CEP-1 antibodies, human leukocyte antigen (HLA) typing	67.2% of ACPA +ve and 60% of ACPA -ve participants had moderate or severe PD (p=0.257).	Weak but significant association between periodontitis assessed as PESA and the prevalence of ACPA positivity (95% CI 1.000-1.005, p=0.040).	Periodontitis is if any only a minor risk factor for ACPA positivity.
Renvert, 2020[58]	BOP, PPD, CAL, ABL, number of missing, caries and mobile teeth	Disease duration, VAS pain score, ESR, CRP, DAS28-ESR, ACPA, RF	NR	No association between ACPA positivity and periodontitis was found (p=0.92).	NR
Stefanov, 2020[67]	Hygiene index, papilla bleeding index, BOP, PPD, CAL, REC, presence of furcation lesions, PISA	ACPA, DAS28-CRP, CRP	NR	No statistically significant difference in serum levels of ACPA depending on the severity of periodontal parameters. Serum ACPA levels showed a weak positive association only with the number of teeth lost (r=0.260, p=0.045).	Serum ACPA is not a biomarker that can well differentiate severe from mild periodontal lesions in patients with concomitant periodontitis and RA. The predictive value of ACPA for assessing the severity of periodontal disease in patients with RA is low.

Authors, year of publication	PD clinical parameters	RA clinical parameters	Prevalence/severity of PD and ACPA seropositivity	Association between ACPA and PD parameters	Author's conclusion regarding ACPA seropositivity and PD
Svard, 2020[59]	BOP, PS, PPD, CAL, ABL, number of missing, caries and mobile teeth	Disease duration, VAS pain score, ESR, CRP, DAS28-ESR, DAS28-CRP, ACPA, RF, SJC (28), TJC (28)	IgG ACPA in serum was found in 66% of RA patients with periodontitis, and in 69% of RA patients without periodontitis (p=0.849). IgA ACPA in serum was found in 35% of RA patients with periodontitis, and in 43% of RA patients without periodontitis (p=0.461).	No difference between levels of ACPA in RA patients with or without periodontitis.	No correlation was observed between periodontitis and saliva IgA ACPA or between periodontitis and IgA or IgG ACPA in serum. The findings do not support the hypothesis that periodontitis leads to increased formation of IgA ACPA in saliva or serum.

ABL – alveolar bone loss; **ACPA** – anti-citrullinated protein antibodies; **BOP** – bleeding on probing; **CAL** – clinical attachment level; **CPI** – community periodontal index; **CRP** – C-reactive protein; **DAS28** – disease activity-28; **ESR** – erythrocyte sedimentation rate; **GCF** – gingival crevicular fluid; **GI** – gingival index; **GS** – gingivitis score; **PESA** – periodontal epithelial surface area; **PISA** – periodontal inflamed surface area; **PS** – plaque score; **PPD** – probing pocket depth; **REC** – recession; **RF** – rheumatoid factor; **SJC** – swollen joint count; **TJC** – tender joint count; **VAS** – visual analogue score.

Generally, only a few studies reported the prevalence of PD in the different serotype groups. Only four studies reported a significantly high prevalence of PD in those who were ACPA positive.[45,47,51,61] Of the four studies, two research studies involved US veterans as participants.[47,61]

Discussion

The basis of the hypothesis that links RA and PD lies in the ACPA molecules triggering the autoimmune response in RA. This idea would manifest in a difference between prevalence and severity of PD amongst the population with different RA ACPA variants. The reason is that the PD-RA connections would not apply to patients who are seronegative. However, there is limited information on the ACPA status of subjects in case controlled or population-based studies because the majority of the studies did not differentiate between the two RA variants.

A discrepancy is noted in the epidemiological data between the two RA subsets in terms of PD prevalence and severity. In a large cohort of US veterans, the presence of periodontitis in patients with RA was associated with seropositivity of ACPA.[61] Mikuls et al. found that PD is markedly frequent amongst ACPA positive RA cases, but the association was no longer significant when including ACPA negative patients.[47] In a Korean study, the authors also found that periodontal inflammation is correlated with ACPA.[49] A Japanese study designed specifically to examine the associations between severity of PD parameters and levels of ACPA,[43] reported that CPI is shown to be associated with increasing ACPA positivity and levels when it is above 2.[43] Choi et al. found that ACPA was considerably abundant in patients with markedly severe periodontal inflammation.[49]

By contrast, a large Swedish population study – Epidemiological Investigation of Rheumatoid Arthritis (EIRA) – reported no difference on the basis of seropositivity amongst patients with RA in terms of their periodontal health.[44] Additionally, de Smit et al. reported no differences in ACPA levels between RA patients without periodontitis, with moderate periodontitis or with severe periodontitis.[62]

The fundamental involvement of PD with ACPA production is the basis of the relationship between RA and PD. However, epidemiological evidence supporting this relationship is currently equivocal. Conflicting evidence can be attributed to differences in study designs, in which some studies used healthy subjects as comparison, whereas others recruited patients with osteoarthritis as the control group.[47,48,61] The majority of the epidemiological studies investigating the RA-PD relationship[3,4,8,63-66] did not specify the difference between the two RA subsets, even though this aspect is the proposed foundation of the relationship between the two diseases.

Lack of standardized or specific classification criteria for PD, inadequate information on confounding factors and differences in the inclusion and exclusion criteria can also attribute to the contradictory evidence. Some studies, such as Terao et al.[43] and Eriksson et al.[44] used data from health registries, whilst others used population data as sampled from national health surveys.[43,44] The use of such data is advantageous in terms of the volume and breadth of samples but may lack specific details, including information on confounding factors.

The use of the clinical presentation of periodontitis or PD as a surrogate marker for the presence of *P. gingivalis* may not be accurate because not all PDs are characterized by the presence of *P. gingivalis*. Reports of the involvement of different periodontal pathogens (i.e., *A. actinomycetemcomitans*) also indicate the necessity of an improved study design, preferably one that accounts for the type of bacteria present in the subgingival microbiota. The use of an objective measurement of PD, such as quantifying the percentage of inflamed or ulcerated surface (e.g., those used by Rahajoe et al. and Stefanov et al.),[60,67] would overcome the lack of consensus on PD classification.

Although epidemiological data are necessary to gain an improved understanding of the PD-RA relationship, cross-sectional studies cannot determine whether PD or *P. gingivalis* infection precedes the development of ACPA and, consequently, RA. Hence, cause and effect

cannot be proven. This aspect must come from other study designs, including animal studies, clinical trials and longitudinal studies with well-defined subjects. Clinical trials studying the effects of the treatment of PD on RA will enable the evaluation of the 'effect' (i.e., RA) when the 'cause' (i.e., PD) is removed. Longitudinal studies investigating a susceptible cohort (e.g., those with family members suffering from RA) without RA and PD at recruitment will also lead to an improved understanding on which disease precedes the other.

Conclusions

Some epidemiological evidence supports a difference in the prevalence of PD between ACPA-positive and ACPA-negative RA patients. The qualitative analysis showed relative association between periodontal parameters and ACPA seropositivity but with a high degree of heterogeneity in the measures used for PD. Although the link between RA and PD is mostly discussed in terms of ACPA, reports on the different manifestations of PD between the two RA subsets remain inconclusive.

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References

1. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007;21:907-27. https://doi.org/10.1016/j.berh.2007.05.007
2. Jung GU, Han JY, Hwang KG, Park CJ, 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
3. Chen HH, Huang N, Chen YM, 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;72:1206-11. https://doi.org/10.1136/annrheumdis-2012-201593
4. Schmickler J, Rupprecht A, Patschan S, et al. Cross-sectional evaluation of periodontal status and microbiologic and rheumatoid parameters in a large cohort of patients with rheumatoid arthritis. J Periodontol. 2017;88:368-79. https://doi.org/10.1902/jop.2016.160355
5. Joseph R, Rajappan S, Nath SG, Paul BJ. Association between chronic periodontitis and rheumatoid arthritis: a hospital-based case-control study. Rheumatol Int. 2013;33:103-9. https://doi.org/10.1007/s00296-011-2284-1
6. de Oliveira Ferreira R, de Brito Silva R, Magno MB, et al. Does periodontitis represent a risk factor for rheumatoid arthritis? A systematic review and meta-analysis. Ther Adv Musculoskelet Dis. 2019;11:1759720X19858514. https://doi.org/10.1177/1759720X19858514
7. Suhaimi N, Kamaruzaman, Natasha Taib H, Wan Mohamad WM, Wan Ghazali WS. Assessment of Periodontal Status in patients with Rheumatoid Arthritis. J Int Dent Med Res. 2016;9:108-12.
8. Khantisopon N, Louthrenoo W, Kasitanon N, et al. Periodontal disease in Thai patients with rheumatoid arthritis. Int J Rheum Dis. 2014;17:511-8. https://doi.org/10.1111/1756-185X.12315
9. Monsarrat P, Vergnes JN, Blaizot A, et al. Oral health status in outpatients with rheumatoid arthritis: the OSARA study. Oral Health Dent Manag. 2014;13:113-9.
10. Pischon N, Pischon T, Kröger J, et al. Association among rheumatoid arthritis, oral hygiene, and periodontitis. J Periodontol. 2008;79:979-86. https://doi.org/10.1902/jop.2008.070501
11. 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;89:1033-42. https://doi.org/10.1002/JPER.17-0575
12. Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Front Immunol. 2016;7:80. https://doi.org/10.3389/fimmu.2016.00080
13. Kaur S, White S, Bartold PM. Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res. 2013;92:399-408. https://doi.org/10.1177/0022034513483142
14. Araújo VM, Melo IM, Lima V. Relationship between periodontitis and rheumatoid arthritis: review of the literature. Mediators Inflamm. 2015;2015:259074. https://doi.org/10.1155/2015/259074
15. Synderman R, McCarty GA. Host-parasite interactions in periodontal disease. Washington DC: American Society for Microbiology; 1982. pp. 354-362.
16. Abrão AL, Santana CM, Bezerra AC, et al. What rheumatologists should know about orofacial manifestations of autoimmune rheumatic diseases. Rev Bras Reumatol Engl Ed. 2016;56:441-50.

https://doi.org/10.1016/j.rbre.2016.02.006
17. Li R, Tian C, Postlethwaite A, et al. Rheumatoid arthritis and periodontal disease: what are the similarities and differences? Int J Rheum Dis. 2018;20:1887-901. https://doi.org/10.1111/1756-185X.13240
18. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ. Periodontitis in RA- the citrullinated enolase connection. Nat Rev Rheumatol. 2010;6:727-30. https://doi.org/10.1038/nrrheum.2010.139
19. Farquharson D, Butcher JP, Culshaw S. Periodontitis, *Porphyromonas*, and the pathogenesis of rheumatoid arthritis. Mucosal Immunol. 2012;5:112-20. https://doi.org/10.1038/mi.2011.66
20. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology / European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1892. https://doi.org/10.1136/ard.2010.138461
21. Gomez EL, Gun SC, Somnath SD, et al. The prevalence of rheumatoid factor isotypes and anti-cyclic citrullinated peptides in Malaysian rheumatoid arthritis patients. Int J Rheum Dis. 2011;14:12-7. https://doi.org/10.1111/j.1756-185X.2010.01573.x
22. Arkema EV, Goldstein BL, Robinson W, et al. Anti-citrullinated peptide autoantibodies, human leukocyte antigen shared epitope and risk of future rheumatoid arthritis: a nested case-control study. Arthritis Res Ther. 2013;15:R159. https://doi.org/10.1186/ar4342
23. Vander Cruyssen B, Peene I, Cantaert T, et al. Anti-citrullinated protein/peptide antibodies (ACPA) in rheumatoid arthritis: specificity and relation with rheumatoid factor. Autoimmun Rev. 2005;4:468-74. https://doi.org/10.1016/j.autrev.2005.04.018
24. Rosenstein ED, Kushner LJ, Kramer N. Rheumatoid arthritis and periodontal disease: a rheumatologist's perspective. Curr Oral Health Reports. 2015;2:9-19. https://doi.org/10.1007/s40496-014-0038-3
25. Koziel J, Mydel P, Potempa J. The link between periodontal disease and rheumatoid arthritis: an updated review. Curr Rheumatol Rep. 2014;16:408. https://doi.org/10.1007/s11926-014-0408-9
26. Quirke AM, Lugli EB, Wegner N, et al. Heightened immune response to autocitrullinated *Porphyromonas gingivalis* peptidylarginine deiminase: a potential mechanism for breaching immunologic tolerance in rheumatoid arthritis. Ann Rheum Dis. 2014;73:263-9. https://doi.org/10.1136/annrheumdis-2012-202726
27. Golub LM, Payne JB, Reinhardt RA, Nieman G. Can systemic diseases co-induce (not just exacerbate) periodontitis? A hypothetical "two-hit" model. J Dent Res. 2006;85:102-5. https://doi.org/10.1177/154405910608500201
28. Hitchon CA, Chandad F, Ferucci ED, et al. Antibodies to *Porphyromonas gingivalis* are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. J Rheumatol. 2010;37:1105-12. https://doi.org/10.3899/jrheum.091323
29. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012;10:717-25. https://doi.org/10.1038/nrmicro2873
30. Reichert S, Haffner M, Keyßer G, et al. Detection of oral bacterial DNA in synovial fluid. J Clin Periodontol. 2013;40:591-8. https://doi.org/10.1111/jcpe.12102
31. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nat Rev Rheumatol. 2017;13:606-20. https://doi.org/10.1038/nrrheum.2017.132
32. Konig MF, Abusleme L, Reinholdt J, et al. *Aggregatibacter actinomycetemcomitans*-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med. 2016;8:369ra176. https://doi.org/10.1126/scitranslmed.aaj1921
33. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169:467-73. https://doi.org/10.7326/M18-0850
34. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4:1-6. https://doi.org/10.1902/annals.1999.4.1.1
35. Armitage GC, Research, Science and Therapy Committee of the American Academy of Periodontology. Diagnosis of periodontal diseases. J Periodontol. 2003;74:1237-47. https://doi.org/10.1902/jop.2003.74.8.1237
36. Van der Velden U. The Dutch periodontal screening index validation and its application in The Netherlands. J Clin Periodontol. 2009;36:1018-24. https://doi.org/10.1111/j.1600-051X.2009.01495.x
37. Machtei EE, Christersson LA, Grossi SG, Dunford R, Zambon JJ, Genco RJ. Clinical criteria for the definition of "established periodontitis". J Periodontol. 1992;63:206-14. https://doi.org/10.1902/jop.1992.63.3.206
38. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78(Suppl 7):1387-99. https://doi.org/10.1902/jop.2007.060264
39. Tonetti MS, Claffey N, European Workshop in Periodontology group C. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. J Clin Periodontol. 2005;32 Suppl 6:210-3. https://doi.org/10.1111/j.1600-051X.2005.00822.x
40. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. J Periodontol. 2012;83:1449-54. https://doi.org/10.1902/jop.2012.110664
41. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Periodontol. 2018;89 Suppl 1:S159-72. https://doi.org/10.1002/JPER.18-0006

42. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24. https://doi.org/10.1002/art.1780310302
43. Terao C, Asai K, Hashimoto M, et al. Significant association of periodontal disease with anti-citrullinated peptide antibody in a Japanese healthy population - the Nagahama study. J Autoimmun. 2015;59:85-90. https://doi.org/10.1016/j.jaut.2015.03.002
44. Eriksson K, Nise L, Kats A, et al. Prevalence of periodontitis in patients with established rheumatoid arthritis: a swedish population based case-control study. PLoS One. 2016;11:e0155956. https://doi.org/10.1371/journal.pone.0155956
45. Eriksson K, Fei G, Lundmark A, et al. Periodontal health and oral microbiota in patients with rheumatoid arthritis. J Clin Med. 2019;8:630. https://doi.org/10.3390/jcm8050630
46. Potikuri D, Dannana KC, Kanchinadam S, et al. Periodontal disease is significantly higher in non-smoking treatment-naive rheumatoid arthritis patients: results from a case-control study. Ann Rheum Dis. 2012;71:1541-4. https://doi.org/10.1136/annrheumdis-2011-200380
47. Mikuls TR, Payne JB, Yu F, et al. Periodontitis and *Porphyromonas gingivalis* in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66:1090-100. https://doi.org/10.1002/art.38348
48. Gonzalez SM, Payne JB, Yu F, et al. Alveolar bone loss is associated with circulating anti-citrullinated protein antibody (ACPA) in patients with rheumatoid arthritis. J Periodontol. 2015;86:222-31. https://doi.org/10.1902/jop.2014.140425
49. Choi IA, Kim J, Kim YM, et al. Periodontitis is associated with rheumatoid arthritis: a study with longstanding rheumatoid arthritis patients in Korea. Korean J Intern Med. 2016;31:977-86. https://doi.org/10.3904/kjim.2015.202
50. Eriksson K, Nise L, Alfredsson L, et al. Seropositivity combined with smoking is associated with increased prevalence of periodontitis in patients with rheumatoid arthritis. Ann Rheum Dis. 2018;77:1236-8. https://doi.org/10.1136/annrheumdis-2017-212091
51. Zhao R, Gu C, Zhang Q, et al. Periodontal disease in Chinese patients with rheumatoid arthritis: A case-control study. Oral Dis. 2019;25:2003-9. https://doi.org/10.1111/odi.13176
52. González-Febles J, Rodríguez-Lozano B, Sánchez-Piedra C, et al. Association between periodontitis and anti-citrullinated protein antibodies in rheumatoid arthritis patients: a cross-sectional study. Arthritis Res Ther. 2020;22:27. https://doi.org/10.1186/s13075-020-2121-6
53. Nguyen VB, Nguyen TT, Huynh NC, Le TA, Hoang HT. Relationship between periodontitis and rheumatoid arthritis in Vietnamese patients. Acta Odontol Scand. 2020;78:522-8. https://doi.org/10.1080/00016357.2020.1747635
54. Reichert S, Schlumberger W, Dähnrich C, et al. Association of levels of antibodies against citrullinated cyclic peptides and citrullinated α-enolase in chronic and aggressive periodontitis as a risk factor of rheumatoid arthritis: a case control study. J Transl Med. 2015;13:283. https://doi.org/10.1186/s12967-015-0625-7
55. Havemose-Poulsen A, Westergaard J, Stoltze K, et al. Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol. 2006;77:280-8. https://doi.org/10.1902/jop.2006.050051
56. Mohamad WMW, Jia SK, Ghazali WSW, Taib H. Anti-cyclic citrullinated peptide antibody and periodontal status in rheumatoid arthritis patients. Pak J Med Sci. 2018;34:907-12. https://doi.org/10.12669/pjms.344.15007
57. Rodríguez-Lozano B, González-Febles J, Garnier-Rodríguez JL, et al. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: a case - control study. Arthritis Res Ther. 2019;21:2.7 https://doi.org/10.1186/s13075-019-1808-z
58. Renvert S, Berglund JS, Persson GR, Söderlin MK. The association between rheumatoid arthritis and periodontal disease in a population-based cross-sectional case-control study. BMC Rheumatol. 2020;20;4:31. https://doi.org/10.1186/s41927-020-00129-4
59. Svärd A, Renvert S, Sanmartin Berglund J, Persson RG, Söderlin M. Antibodies to citrullinated peptides in serum and saliva in patients with rheumatoid arthritis and their association to periodontitis. Clin Exp Rheumatol. 2020;38:699-704.
60. Rahajoe PS, de Smit M, Schuurmans G, et al. Increased IgA anti-citrullinated protein antibodies in the periodontal inflammatory exudate of healthy individuals compared to rheumatoid arthritis patients. J Clin Periodontol. 2020;47:552-60. https://doi.org/10.1111/jcpe.13277
61. Dissick A, Redman RS, Jones M, et al. Association of periodontitis with rheumatoid arthritis: a pilot study. J Periodontol. 2010;81:223-30. https://doi.org/10.1902/jop.2009.090309
62. de Smit M, 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. https://doi.org/10.1186/ar4061
63. Äyräväinen L, Leirisalo-Repo M, Kuuliala A, et al. Periodontitis in early and chronic rheumatoid arthritis: a prospective follow-up study in Finnish population. BMJ Open. 2017;7:e011916. https://doi.org/10.1136/bmjopen-2016-011916
64. Abdelsalam SK, Hashim NT, Elsalamabi EM, Gismalla BG. Periodontal status of rheumatoid arthritis patients in Khartoum State. BMC Res Notes. 2011;4:460. https://doi.org/10.1186/1756-0500-4-460

65. Kobayashi T, Murasawa A, Komatsu Y, et al. Serum cytokine and periodontal profiles in relation to disease activity of rheumatoid arthritis in Japanese adults. J Periodontol. 2010;81:650-7. https://doi.org/10.1902/jop.2010.090688
66. Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. J Periodontol. 2001;72:779-87. https://doi.org/10.1902/jop.2001.72.6.779
67. Stefanov L, Bolyarova-Konova T, Kolarov Z, Pavlova P, Ivanova M. Serum anti-CCP antibodies in periodontitis associated with rheumatoid arthritis - relative value for the severity of periodontitis. Rheumatol (Bulgaria). 2020;28:11-8. https://doi.org/10.35465/28.4.2020.pp3-18

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