



Periodontitis in First Degree-Relatives of Individuals With Rheumatoid Arthritis: A Short Narrative Review

Alkisti Zekeridou^{1*}, Benoit Gilbert², Axel Finckh² and Catherine Giannopoulou¹

¹ Division of Regenerative Dental Medicine and Periodontology, University Clinics of Dental Medicine, University of Geneva, Geneva, Switzerland, ² Division of Rheumatology, Geneva University Hospitals (HUG), Geneva, Switzerland

OPEN ACCESS

Edited by:

Anders Johansson,
Umeå University, Sweden

Reviewed by:

Giorgio Gabarrini,
Karolinska Institutet (KI), Sweden

*Correspondence:

Alkisti Zekeridou
alkistizek@gmail.com;
alkisti.zekeridou@unige.ch

Specialty section:

This article was submitted to
Oral Infections and Microbes,
a section of the journal
Frontiers in Oral Health

Received: 14 March 2022

Accepted: 13 April 2022

Published: 06 May 2022

Citation:

Zekeridou A, Gilbert B, Finckh A and
Giannopoulou C (2022) Periodontitis
in First Degree-Relatives of Individuals
With Rheumatoid Arthritis: A Short
Narrative Review.
Front. Oral. Health 3:895753.
doi: 10.3389/froh.2022.895753

Periodontal disease (PD) and rheumatoid arthritis (RA) are chronic inflammatory diseases with a bi-directional relationship. Both share common genetic and environmental risk factors and result in the progressive destruction of bone and connective tissue. First degree relatives of patients with RA (FDR-RA) are one of the at-risk populations for RA. The etiopathogenic mechanisms of their susceptibility are currently being explored, focusing mostly on the role of anti-cyclic citrullinated protein/peptide antibodies (ACPA) in triggering RA. Oral microbiota and their relation with oral health has been suggested as a factor influencing the risk of the FDR-RA developing RA. In particular, compromised periodontal status often correlates with ACPA seropositivity in FDR-RA. The presence of periodontal pathogens such as *Porphyromonas gingivalis*, in oral microbiota has been proposed to increase the risk of developing RA through its uniquely expressed peptidyl arginine deiminase (PPAD), capable of citrullinating both host and bacterial peptides. *Aggregatibacter actinomycetemcomitans* and its leukotoxin A (LtxA), also induces hypercitrullination in host neutrophils. Common risk factors of periodontitis and RA such as genetic predisposition, smoking, higher local and systemic inflammatory burden, are discussed in the literature. Based on those mechanisms periodontal disease seems to be presented as one of the factors triggering RA in FDR-RA. Larger studies evaluating all the potential mechanisms linking RA and periodontitis are needed in FDR-RA to confirm that periodontal disease should be considered in the screening of FDR-RA.

Keywords: first degree relatives, rheumatoid arthritis, periodontitis, ACPA, oral microbiota

INTRODUCTION

Before the clinical onset of rheumatoid arthritis (RA), a preclinical period exists during which genetic and environmental factors interact to initiate the autoimmune process. The ensuing autoimmune response is characterized by the production of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA). According to EULAR Standing Committee, this preclinical phase could be divided in three «at risk» stages: genetic and environmental risk, including first-degree relatives (FDR-RA) of patients with RA, systemic autoimmunity associated with RA and symptomatic preclinical phases [1].

This review focuses on FDR-RA, as defined by the EULAR terminology, who are good candidates for clinical and biomarker profiling, providing insight in the etiology of RA [2]. Our aim is to discuss the available evidence on mechanisms linking periodontitis and RA onset in this population.

RA and First-Degree Relatives

FDR- RA have a 3 to 5-fold increased risk of developing the disease [3]. While the shared epitope (SE) is the genetic factor which has been most associated with RA, genome wide association have revealed dozens of RA-associated single-nucleotide polymorphisms [4]. Based on twin studies, RA has been estimated to have an overall 30-60% heritability [5], predominantly for seropositive RA [6], with ~30-40% owing only to SE [7, 8]. Still, researchers have suggested that genetic predisposition might lead to RA only when encountering certain environmental conditions. Such gene-environment interaction has been demonstrated between the SE-positive human leukocyte antigen (HLA) alleles and inhaled pollutants, such as tobacco smoking, in seropositive RA patients [9-11]. The combination of smoking and double shared epitope increased the risk of RA up to 21-fold [95% CI (11-40)] [9]. It has to be underlined that SE positivity associates essentially with ACPA-positive RA and increases the risk of cardiovascular mortality [12]; suggesting subgroup-specific pathogenic mechanisms [13].

RA and Periodontal Disease

Mucosal exposure to exogenous antigens impacts the immune system [14]. Studies in healthy individuals demonstrated that IgA antibodies, such as ACPA and RF, can be secreted at mucosal sites in response to local inflammation [15, 16]. These auto-antibodies are frequently found in the sputum of RA patients, even when they are undetectable in the serum [17]. The latter suggests that the development of systemic auto-immunity could be a consequence of chronic mucosal barrier disruption, local immune activation, and subsequent systemic spread of auto-reactive cells. This theory is known as the “mucosal origins hypothesis” [15].

Chronic intestinal conditions [18], or chronic pulmonary disorders [19, 20], have been linked with RA. Similarly, periodontal disease (PD) [21-23] has been proposed as a trigger for RA. Periodontitis is mediated by an interplay between dysbiotic microbial communities and aberrant host immune-inflammatory responses within the gingival and periodontal tissues. The dysbiotic plaque biofilm contains high proportions of Gram-negative, anaerobic and facultative bacteria, and is microbially less diverse than a healthy biofilm. The term “keystone pathogen” is used to describe bacteria that support and stabilize a microbiota associated with disease and cause disruption of host-microbial homeostasis [24]. *Porphyromonas gingivalis* (*P. gingivalis*) is a keystone pathogen strongly associated with periodontitis by directly affecting the resident oral microbiota and indirectly modulating the native immune system. Individuals' susceptibility of developing periodontitis can also be affected by genetics, epigenetic factors and environmental lifestyle factors, such as suboptimal oral hygiene, stress, smoking, systemic conditions, medication, diet among many others [25].

A bi-directional relationship between PD and RA has been revealed in cross-sectional studies. A higher prevalence of periodontitis has been reported in patients with RA compared to healthy controls with odds-ratios (OR) ranging from 1.82 to 8.05 after adjusting for confounding factors such as plaque accumulation and gingival inflammation [26-28]. Conversely, an increased prevalence of RA has been found in patients with periodontitis, compared to periodontally healthy subjects (OR ranging from 1.16 to 4.28) [22, 23, 29]. Furthermore, the severity of periodontitis correlates with RA disease activity [30]. However, some studies failed to show significant differences in periodontitis prevalence between RA subjects and non-RA subjects [31]. The contradictory results may be attributed to different adjustments for confounding variables between studies (comorbidities, RA activity, medication) and differences in disease classification criteria for periodontitis.

LINK MECHANISMS BETWEEN RA AND PD

Periodontitis is included in the “two-hit” model for RA etiology, introduced by Golub et al. [32]. The first hit represents ACPA production due to chronic periodontitis followed by a second hit in the joint that induces RA. In other words, abnormal and bacterial citrullination by *P. gingivalis* within the periodontal tissue results first in a local autoimmune response to citrullinated proteins followed by the systemic production of ACPA in the joints that can induce RA [32].

ACPAs are the most specific antibodies associated with RA [33]. They are found in approximately 80% of the RA patients [34]. Their presence is highly associated with the HLA-shared epitope (SE), which is linked to the risk of developing RA and in particular for ACPA-positive RA. Interestingly, ACPA can appear years before the onset of RA, thus being a strong predictor of the disease [35].

Recent research has focused on the identification of external factors that could trigger such autoantibody production. The autoantibodies are produced following the excess formation of citrullinated proteins [36]. Citrullination refers to the post-translational process of the modification of the amino acid arginine into citrulline. The process is mediated by the peptidyle arginine deimase enzyme (PAD) of various immune cells such as the neutrophils, macrophages, monocytes and T and B lymphocytes. Five PAD enzymes have been identified in humans [37]; two isoforms of the PAD family, the PAD2 and PAD4 are expressed in inflamed periodontal tissues [38]. In addition to the human PADs, the periodontal pathogen *P. gingivalis*, has been shown to express a PAD enzyme (referred to as PPAD to distinguish from the human PAD) capable of citrullinating host and bacterial peptides. In particular, citrullinated fibrinogen and citrullinated alpha-enolase are targeted by anti-citrullinated protein antibodies. These autoantibodies are found, respectively, in up to 60% and 40-60% of patients with RA [39]. Thus, citrullination associated with the host-derived PAD is further increased by the bacterial-derived PADs, leading to an enhanced production of ACPA [40].

In addition to its ability to express PPAD, *P. gingivalis* can induce the production of various pro-inflammatory cytokines by the immune cells, stimulate a Th17 response and accelerate the development of RA. It has been established that Th17 cell-related cytokines are strong inducers of arthritis and that IL-17 plays important role in the osteoclast differentiation and bone erosions [41, 42].

A. actinomycetemcomitans, another important periodontal pathogen, has been also proposed as a potential trigger for the pathogenesis of RA. The bacteria possess a virulence factor, a pore-forming leukotoxin A (LtxA) which can dysregulate the activation of citrullinated enzymes and induce hypercitrullination in host neutrophils [43].

Aside from formation of ACPA due to citrullination, other molecular pathways have been also studied to link PD with RA. First, uncontrolled generation of neutrophil extracellular traps (NETs) has been found in several autoimmune diseases in response to periodontal pathogens. Accumulated NETs provide a source of autoantigens in both PD and RA [44]. A second mechanism, described as molecular mimicry, involves the capacity of *P. gingivalis* and some other bacteria in dental plaque to express antigens, that are structurally similar to host antigens, and can therefore cross-react with ACPAs. Bacterial enolase and bacterial heat shock protein 60 are the strongest and mostly studied candidates that trigger an immune response and generate antibodies [45]. Other potential mechanisms linking PD to RA focused on the capacity of *P. gingivalis*, as shown in an experimentally-induced periodontitis animal model, to modulate the gut microbiota composition [46] and to be hematogenously disseminated to synovial joints [47].

Genetic and environmental risk factors are common between PD and RA resulting in the progressive destruction of bone and connective tissue [48]. The shared epitope (SE) coding HLA-DRB alleles are potential genetic elements connecting RA and PD [49]; they have been associated with bone erosions in RA and alveolar bone destruction and PD progression [50]. Moreover, family transmission of putative periodontal pathogens between family members has been documented [51].

Finally, tobacco consumption is an established risk factor for periodontal destruction and RA. Case-control studies have shown that in smokers, the risk of developing seropositive RA was twice higher compared to non-smokers and the risk was dose-dependent on lifetime exposure to smoking [52]. Likewise, smoking affects in a dose dependent way all aspects of periodontal health such as prevalence of PD, severity of periodontal destruction and unfavorable results to periodontal treatment [53]. Exogenic risk factors such as nutrition, socioeconomic status, psychological factors (stress) and obesity are common between the two pathologies [44].

CLINICAL EVIDENCE OF THE RELATIONSHIP BETWEEN RA AND PD

As mentioned above, periodontopathic microorganisms may trigger, deteriorate and perpetuate RA [54]. Citrullinated proteins have been detected in periodontal tissues and in

inflammatory exudates [38, 55]. Thus, PD could act as an environmental stressor for ACPA-positivity. The hypothesis is that in genetically susceptible individuals, citrullination associated with periodontitis may cause a localized oral mucosal response, which can lead to a systemic ACPA production and the onset of RA.

The clinical evidence for the relation of PD and RA is large and variant. The Nagahama study included 9,575 subjects with no connective tissue disease and showed significant associations between periodontal parameters and ACPA seropositivity. In this population 27.9% were ACPA-positive, supporting the involvement of PD in ACPA production [56]. However, when serum levels were analyzed for ACPA quantification in subjects with or without RA, and with or without PD, no correlation was found between ACPA and the clinical parameters of PD [57].

Conflicting data and opinions have been reported regarding the relationship between periopathogenic bacteria and RA. In some studies, the subgingival presence of *P. gingivalis* and *A. actinomycetemcomitans* and the levels of serum anti-*Porphyromonas gingivalis* and anti-*Aggregatibacter actinomycetemcomitans* immunoglobulins were not associated with RA [58]. While other publications reported a weak but significant correlation between anti-*Porphyromonas gingivalis* outer membrane levels and ACPA titers [59]. The study of Schmickler et al. [60], revealed a higher number of *Fusobacterium nucleatum* and *P. gingivalis* in ACPA seropositive patients with RA. In cases of untreated new-onset RA, *P. gingivalis* was identified in 55% of the patients [60] whereas in the study of Bello-Gualtero et al. [61], *P. gingivalis* specific IgG was found to be associated with ACPA in early-RA, but not in pre-RA. This supports the hypothesis that *P. gingivalis* infection plays a role in the early loss of tolerance to potential self-antigens during the RA pathogenesis [61]. The study of Fisher et al. [62] agreed that *P. gingivalis* was not associated with pre-RA autoimmunity or risk of RA in an early phase before the disease onset.

THE FDR-RA AND PERIODONTITIS

All the above mechanisms linking PD and RA may potentially also apply to the susceptibility of FDR-RA of developing RA [2, 63]. However, only a limited number of studies evaluated the prevalence or indicators of periodontitis in FDR-RA [36, 64, 65]. These studies evaluated mainly the role of ACPA and oral microbiota, as main mechanisms.

Clinical Evidence of the FDR-RA and Periodontitis

Focusing on the FDR-RA population, the study of Barra et al. [66], including 88 RA patients, 50 unaffected FDR-RA and 20 healthy control subjects, investigated ACPA along with self-reported joint and PD symptoms. FDR-RA had four times higher prevalence of ACPA compared to controls. Joint and PD symptoms in the FDR-RA were significantly associated with smoking. However, in this study the periodontal status was similar in the three groups. The small sample size and the similar

hygiene attitudes between the groups may have overruled the potential differences [66].

On the other hand, Unriza-Puin et al. [67] found a difference in the periodontal status of FDR-RA compared to healthy participants. They investigated the body mass index (BMI), ACPA, the presence of periodontitis and the presence of IgG-1/IgG-2 antibodies against *P. gingivalis* in the two groups. Seventy-nine percent of the FDR-RA were diagnosed with periodontitis and 15% of them had a severe form of the disease, while only 56% of the controls presented periodontitis. Obesity, ACPA and periodontitis were correlated to FDR-RA status. It was concluded that these three factors are relevant conditions associated with the development of RA in FDR-RA [67].

Similarly, Loutan et al. [68] evaluated the periodontal and rheumatological status of FDR-RA. ACPA positive (ACPA+) and ACPA negative (ACPA-) FDR-RA participants were included, in order to elucidate the correlation between periodontitis and seropositivity. Interestingly all ACPA+ subjects had periodontitis, with either a moderate (44.1%) or a severe form (47.1%) of the disease, while ACPA- participants, presented mostly mild (30.8%) and moderate (27%) periodontitis. In multivariable analyses, ACPA status and age were significantly and independently associated with periodontal conditions. The findings that periodontitis in FDR-RA is associated with ACPA seropositivity, suggest that periodontal disease precedes the development of RA in this population and acts as a trigger for RA [63, 68].

When focusing more on the periodontal pathogens, one study included 24 FDR-RA and 124 healthy individuals matched for age and sex. The prevalence of periodontitis in the FDR-RA group was similar to that of the control group (60.5% vs. 59%, respectively). The presence of *P. gingivalis* was more frequent in the FDR-RA (62.1%) compared to the control (42.7%) group and was associated to gingival inflammation and compromised periodontal status. However, anti-*Porphyromonas gingivalis* IgG1 and IgG2 antibodies were more frequent in controls than in the FDR-RA group [69].

Immune responses to *P. gingivalis* and their correlation with ACPA were investigated in a group of patients with RA and their FDR-RA. The study was performed to a unique cohort of North American Native people from central Canada who has one of the highest prevalence of RA globally. This population is also characterized by familial clusters of RA cases, early age of RA onset and a high prevalence of ACPA and RF. In this population, both RA patients and their FDR-RA presented anti-*Porphyromonas gingivalis* antibodies which were strongly associated with ACPA positivity. Their results indicate that immune responses to *P. gingivalis* affects the immune tolerance to citrullinated antigens which may lead to an increased risk of developing RA [70].

In another cross-sectional study, early RA patients, FDR-RA and healthy participants were included. Adipokine levels, clinical, joint radiological statuses and periodontal variables were assessed in order to evaluate if *P. gingivalis* could be a link between periodontitis and RA by decreasing the patient's immunological response. FDR-RA showed deteriorated periodontal status, obesity and high prevalence of ACPA. The authors concluded

that obesity and periodontitis play a role in the development of RA in the FDR-RA group. Moreover, presence of *P. gingivalis* associates with the development of RA in this group [71].

Finally, Manoil et al. [72] examined the systemic responses against five periodontal pathogens in a cohort of four groups of FDR-RA divided according to the preclinical phases of RA. Serum IgG levels of the studied pathogens were not significantly different between the groups; they were associated neither with the preclinical phases of RA nor with ACPA seropositivity. However, significantly elevated serum levels of IgGs against the cluster of periodontopathogens and the red complex were found in all the ACPA-positive probands. These findings suggest that in individuals at risk of RA, periodontal bacteria as a complex, and not as single pathogens, contribute to the loss of immune tolerance to citrullinated antigens in terms of ACPA positivity.

DISCUSSION AND CONCLUSIONS

RA is a considerable health problem that affects all areas in the life of the diseased patients. Early diagnosis and preventive measures may decrease the prevalence and severity of RA, and improve the quality of life of patients. Because of the association between RA and PD, especially in the early phases of the disease, PD should be assessed in the baseline assessment of patients at high risk. Health care practitioners should be aware of the association and active screening of at-risk individuals should be considered [73].

FDR-RA are at higher risk for developing RA, but only limited data exist for the role of PD. ACPA status seems significantly associated with deteriorated periodontal conditions and higher risk of RA. Factors, such as smoking, increased age and high BMI are associated with ACPA seropositivity and with deteriorated periodontal conditions, thus increasing the risk of developing RA.

P. gingivalis and has been identified as a possible trigger for RA via the breakdown of tolerance against citrullinated proteins and the formation of ACPAs. However, in the literature, contrasting evidence for its role in the etiopathogenesis of RA is found. *A. actinomycetemcomitans* is another potential candidate.

Larger studies evaluating all the potential mechanisms linking RA and periodontitis are needed. In particular, longitudinal studies evaluating the effect of PD on the risk of developing RA in FDR-RA are required to confirm the role of PD as a trigger for RA development. And last but not least, the effect of periodontal treatment on the development of RA needs to be established before preventive oral health interventions can be definitely established in at-risk populations for RA.

AUTHOR CONTRIBUTIONS

CG and AZ performed the literature research. All authors contributed to the article and approved the submitted version.

FUNDING

AF's work is supported by research grant from the Swiss National Science Foundation (no. 310030E_205559/1; no. 320030_192471/1; no. 3200B0_120639).

REFERENCES

- Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. Eular Recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the study group for risk factors for rheumatoid arthritis. *Ann Rheum Dis*. (2012) 71:638–41. doi: 10.1136/annrheumdis-2011-200990
- Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. *Nat Rev Rheumatol*. (2016) 12:335–43. doi: 10.1038/nrrheum.2016.52
- Silman AJ, Hennessy E, Ollier B. Incidence of rheumatoid arthritis in a genetically predisposed population. *Br J Rheumatol*. (1992) 31:365–8. doi: 10.1093/rheumatology/31.6.365
- Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. *Nat Rev Rheumatol*. (2013) 9:141–53. doi: 10.1038/nrrheum.2012.237
- Terao C, Ikari K, Nakayamada S, Takahashi Y, Yamada R, Ohmura K, et al. A Twin study of rheumatoid arthritis in the Japanese population. *Mod Rheumatol*. (2016) 26:685–9. doi: 10.3109/14397595.2015.1135856
- Frisell T, Holmqvist M, Kallberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. *Arthritis Rheum*. (2013) 65:2773–82. doi: 10.1002/art.38097
- Deighton CM, Walker DJ, Griffiths ID, Roberts DF. The contribution of Hla to rheumatoid arthritis. *Clin Genet*. (1989) 36:178–82. doi: 10.1111/j.1399-0004.1989.tb03185.x
- Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, et al. Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis. *Nat Genet*. (2012) 44:483–9. doi: 10.1038/ng.2232
- Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger hla-dr (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum*. (2006) 54:38–46. doi: 10.1002/art.21575
- Criswell LA, Saag KG, Mikuls TR, Cerhan JR, Merlino LA, Lum RF, et al. Smoking interacts with genetic risk factors in the development of rheumatoid arthritis among older caucasian women. *Ann Rheum Dis*. (2006) 65:1163–7. doi: 10.1136/ard.2005.049676
- Karlson EW, Chibnik LB, Kraft P, Cui J, Keenan BT, Ding B, et al. Cumulative association of 22 genetic variants with seropositive rheumatoid arthritis risk. *Ann Rheum Dis*. (2010) 69:1077–85. doi: 10.1136/ard.2009.120170
- Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson V, Symmons D, et al. Association of the Hla-Drb1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. *Arthritis Rheum*. (2008) 58:359–69. doi: 10.1002/art.23149
- Huizinga TW, Amos CI, van der Helm-van Mil AH, Chen W, van Gaalen FA, Jawaheer D, et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the hla-drb1 shared epitope for antibodies to citrullinated proteins. *Arthritis Rheum*. (2005) 52:3433–8. doi: 10.1002/art.21385
- Longman RS, Littman DR. The functional impact of the intestinal microbiome on mucosal immunity and systemic autoimmunity. *Curr Opin Rheumatol*. (2015) 27:381–7. doi: 10.1097/BOR.0000000000000190
- Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y, et al. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. *Nat Rev Rheumatol*. (2018) 14:542–57. doi: 10.1038/s41584-018-0070-0
- Demoruelle MK, Harrall KK, Ho L, Purmalek MM, Seto NL, Rothfuss HM, et al. Anti-citrullinated protein antibodies are associated with neutrophil extracellular traps in the sputum in relatives of rheumatoid arthritis patients. *Arthritis Rheum*. (2017) 69:1165–75. doi: 10.1002/art.40066
- Willis VC, Demoruelle MK, Derber LA, Chartier-Logan CJ, Parish MC, Pedraza IF, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. *Arthritis Rheum*. (2013) 65:2545–54. doi: 10.1002/art.38066
- Nguyen Y, Mariette X, Salliot C, Gusto G, Boutron-Ruault MC, Seror R. Chronic diarrhoea and risk of rheumatoid arthritis: findings from the french E3n-epic cohort study. *Rheumatology (Oxford)*. (2020) 59:3767–75. doi: 10.1093/rheumatology/keaa133
- Quirke AM, Perry E, Cartwright A, Kelly C, De Soya A, Eggleton P, et al. Bronchiectasis is a model for chronic bacterial infection inducing autoimmunity in rheumatoid arthritis. *Arthritis Rheumatol*. (2015) 67:2335–42. doi: 10.1002/art.39226
- Janssen KM, de Smit MJ, Brouwer E, de Kok FA, Kraan J, Altenburg J, et al. Rheumatoid arthritis-associated autoantibodies in non-rheumatoid arthritis patients with mucosal inflammation: a case-control study. *Arthritis Res Ther*. (2015) 17:174. doi: 10.1186/s13075-015-0690-6
- Al-Katma MK, Bissada NF, Bordeaux JM, Sue J, Askari AD. Control of periodontal infection reduces the severity of active rheumatoid arthritis. *J Clin Rheumatol*. (2007) 13:134–7. doi: 10.1097/RHU.0b013e3180690616
- Chen HH, Huang N, Chen YM, Chen TJ, Chou P, Lee YL, 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. doi: 10.1136/annrheumdis-2012-201593
- Demmer RT, Molitor JA, Jacobs DR Jr, Michalowicz BS. Periodontal disease, tooth loss and incident rheumatoid arthritis: results from the first national health and nutrition examination survey and its epidemiological follow-up study. *J Clin Periodontol*. (2011) 38:998–1006. doi: 10.1111/j.1600-051X.2011.01776.x
- Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol*. (2012) 10:717–25. doi: 10.1038/nrmicro2873
- Heitz-Mayfield LJ. Disease progression: identification of high-risk groups and individuals for periodontitis. *J Clin Periodontol*. (2005) 32 Suppl 6:196–209. doi: 10.1111/j.1600-051X.2005.00803.x
- de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the us population. *J Rheumatol*. (2008) 35:70–6.
- Nilsson M, Kopp S. Gingivitis and periodontitis are related to repeated high levels of circulating tumor necrosis factor-alpha in patients with rheumatoid arthritis. *J Periodontol*. (2008) 79:1689–96. doi: 10.1902/jop.2008.070599
- Pischon N, Pischon T, Kroger J, Gulmez E, Kleber BM, Bernimoulin JP, et al. Association among rheumatoid arthritis, oral hygiene, and periodontitis. *J Periodontol*. (2008) 79:979–86. doi: 10.1902/jop.2008.070501
- Potikuri D, Dannana KC, Kanchinadam S, Agrawal S, Kancharla A, Rajasekhar L, 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. doi: 10.1136/annrheumdis-2011-200380
- Rodriguez-Lozano B, Gonzalez-Febles J, Garnier-Rodriguez 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) 21:27. doi: 10.1186/s13075-019-1808-z
- Eriksson K, Nise L, Kats A, Luttrupp E, Catrina AI, Askling J, et al. Prevalence of periodontitis in patients with established rheumatoid arthritis: a swedish population based case-control study. *PLoS ONE*. (2016) 11:e0155956. doi: 10.1371/journal.pone.0155956
- Golub LM, Payne JB, Reinhardt RA, Nieman G. Can systemic diseases co-occur (not just exacerbate) periodontitis? A Hypothetical “Two-Hit” Model. *J Dent Res*. (2006) 85:102–5. doi: 10.1177/154405910608500201
- Hensvold AH, Frisell T, Magnusson PK, Holmdahl R, Askling J, Catrina AI. How Well Do Acpa discriminate and predict ra in the general population: a study based on 12 590 population-representative swedish twins. *Ann Rheum Dis*. (2017) 76:119–25. doi: 10.1136/annrheumdis-2015-208980
- Nielsen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. (2004) 50:380–6. doi: 10.1002/art.20018
- Muller S, Radic M. Citrullinated autoantigens: from diagnostic markers to pathogenetic mechanisms. *Clin Rev Allergy Immunol*. (2015) 49:232–9. doi: 10.1007/s12016-014-8459-2
- de Molon RS, Rossa C, Thurlings RM, Cirelli JA, Koenders MI. Linkage of periodontitis and rheumatoid arthritis: current evidence and potential biological interactions. *Int J Mol Sci*. (2019) 20:4541. doi: 10.3390/ijms20184541

37. König MF, Giles JT, Nigrovic PA, Andrade F. Antibodies to native and citrullinated Ra33 (Hnrrp A2/B1) challenge citrullination as the inciting principle underlying loss of tolerance in rheumatoid arthritis. *Ann Rheum Dis.* (2016) 75:2022–8. doi: 10.1136/annrheumdis-2015-208529
38. Harvey GP, Fitzsimmons TR, Dhamarpatni AA, Marchant C, Haynes DR, Bartold PM. Expression of peptidylarginine deiminase-2 and-4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva. *J Periodontol Res.* (2013) 48:252–61. doi: 10.1111/jre.12002
39. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, et al. Peptidylarginine deiminase from porphyromonas gingivalis citrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis. *Arthritis Rheum.* (2010) 62:2662–72. doi: 10.1002/art.27552
40. Darrach E, Andrade F. Rheumatoid arthritis and citrullination. *Curr Opin Rheumatol.* (2018) 30:72–8. doi: 10.1097/BOR.0000000000000452
41. Moutsopoulos NM, Kling HM, Angelov N, Jin W, Palmer RJ, Nares S, et al. Porphyromonas gingivalis promotes th17 inducing pathways in chronic periodontitis. *J Autoimmun.* (2012) 39:294–303. doi: 10.1016/j.jaut.2012.03.003
42. de Aquino SG, Talbot J, Sonogo F, Turato WM, Grespan R, Avila-Campos MJ, et al. The aggravation of arthritis by periodontitis is dependent of IL-17 receptor a activation. *J Clin Periodontol.* (2017) 44:881–91. doi: 10.1111/jcpe.12743
43. König 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) 8:369ra176. doi: 10.1126/scitranslmed.aaj1921
44. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. *Nat Rev Rheumatol.* (2017) 13:606–20. doi: 10.1038/nrrheum.2017.132
45. Bright R, Proudman SM, Rosenstein ED, Bartold PM. Is there a link between carbamylation and citrullination in periodontal disease and rheumatoid arthritis? *Med Hypotheses.* (2015) 84:570–6. doi: 10.1016/j.mehy.2015.03.006
46. Sato K, Takahashi N, Kato T, Matsuda Y, Yokoji M, Yamada M, et al. Aggravation of collagen-induced arthritis by orally administered porphyromonas gingivalis through modulation of the gut microbiota and gut immune system. *Sci Rep.* (2017) 7:6955. doi: 10.1038/s41598-017-07196-7
47. Chukkappalli S, Rivera-Kweh M, Gehlot P, Velsko I, Bhattacharyya I, Calise SJ, et al. Periodontal bacterial colonization in synovial tissues exacerbates collagen-induced arthritis in B10Riii mice. *Arthritis Res Ther.* (2016) 18:161. doi: 10.1186/s13075-016-1056-4
48. Culshaw S, McInnes IB, Liew FY. What can the periodontal community learn from the pathophysiology of rheumatoid arthritis? *J Clin Periodontol.* (2011) 38:106–13. doi: 10.1111/j.1600-051X.2010.01669.x
49. Gehlot P, Volk SL, Rios HE, Jepsen KJ, Holoshitz J. Spontaneous destructive periodontitis and skeletal bone damage in transgenic mice carrying a human shared epitope-Coding Hla-Drb1 allele. *RMD Open.* (2016) 2:e000349. doi: 10.1136/rmdopen-2016-000349
50. Marotte H, Farge P, Gaudin P, Alexandre C, Mougou B, Miossec P. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the Hla-Dr shared epitope and severity of bone destruction. *Ann Rheum Dis.* (2006) 65:905–9. doi: 10.1136/ard.2005.036913
51. van Winkelhoff AJ, Boutaga K. Transmission of periodontal bacteria and models of infection. *J Clin Periodontol.* (2005) 32 Suppl 6:16–27. doi: 10.1111/j.1600-051X.2005.00805.x
52. Hutchinson D, Lynch MP, Moots RJ, Thompson RN, Williams E. The influence of current cigarette smoking on the age of onset of rheumatoid arthritis (Ra) in individuals with sporadic and familial Ra. *Rheumatology (Oxford).* (2001) 40:1068–70. doi: 10.1093/rheumatology/40.9.1068
53. Kinane DF. Causation and pathogenesis of periodontal disease. *Periodontol 2000.* (2001) 25:8–20. doi: 10.1034/j.1600-0757.2001.22250102.x
54. Leech MT, Bartold PM. The association between rheumatoid arthritis and periodontitis. *Best Pract Res Clin Rheumatol.* (2015) 29:189–201. doi: 10.1016/j.berh.2015.03.001
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) 39:599–607. doi: 10.1111/j.1600-051X.2012.01885.x
56. Terao C, Asai K, Hashimoto M, Yamazaki T, Ohmura K, Yamaguchi A, 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. doi: 10.1016/j.jaut.2015.03.002
57. Lew PH, Rahman MT, Safi SH, Baharuddin NA, Bartold PM, Sockalingam S, et al. Antibodies against citrullinated proteins in relation to periodontitis with or without rheumatoid arthritis: a cross-sectional study. *BMC Oral Health.* (2021) 21:360. doi: 10.1186/s12903-021-01712-y
58. Rahajoe PS, de Smit MJ, Raveling-Eelsing E, du Teil Espina M, Stobernack T, Lisotto P, et al. No obvious role for suspicious oral pathogens in arthritis development. *Int J Environ Res Public Health.* (2021) 18:9560. doi: 10.3390/ijerph18189560
59. Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, et al. Periodontitis and porphyromonas gingivalis in patients with rheumatoid arthritis. *Arthritis Rheumatol.* (2014) 66:1090–100. doi: 10.1002/art.38348
60. Schmickler J, Rupperecht A, Patschan S, Patschan D, Müller GA, Haak R, 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. doi: 10.1902/jop.2016.160355
61. Bello-Gualtero JM, Lafaurie GI, Hoyos LX, Castillo DM, De-Avila J, Munevar JC, et al. Periodontal disease in individuals with a genetic risk of developing arthritis and early rheumatoid arthritis: a cross-sectional study. *J Periodontol.* (2016) 87:346–56. doi: 10.1902/jop.2015.150455
62. Fisher BA, Cartwright AJ, Quirke AM, de Pablo P, Romaguera D, Panico S, et al. Smoking, porphyromonas gingivalis and the immune response to citrullinated autoantigens before the clinical onset of rheumatoid arthritis in a southern European nested case-control study. *BMC Musculoskelet Disord.* (2015) 16:331. doi: 10.1186/s12891-015-0792-y
63. Gilbert BTP, Lamacchia C, Mongin D, Lauper K, Trunk E, Studer O, et al. Cohort profile: screen-ra: design, methods and perspectives of a swiss cohort study of first-degree relatives of patients with rheumatoid arthritis. *BMJ Open.* (2021) 11:e048409. doi: 10.1136/bmjopen-2020-048409
64. Renvert S, Berglund JS, Persson GR, Soderlin MK. The association between rheumatoid arthritis and periodontal disease in a population-based cross-sectional case-control study. *BMC Rheumatol.* (2020) 4:31. doi: 10.1186/s41927-020-00129-4
65. de Smit MJ, Westra J, Brouwer E, Janssen KM, Vissink A, van Winkelhoff AJ. Periodontitis and rheumatoid arthritis: what do we know? *J Periodontol.* (2015) 86:1013–9. doi: 10.1902/jop.2015.150088
66. Barra L, Scinocca M, Saunders S, Bhayana R, Rohekar S, Racape M, et al. Anti-citrullinated protein antibodies in unaffected first-degree relatives of rheumatoid arthritis patients. *Arthritis Rheum.* (2013) 65:1439–47. doi: 10.1002/art.37911
67. Unriza-Puin S, Bautista-Molano W, Lafaurie GI, Valle-Onate R, Chalem P, Chila-Moreno L, et al. Are obesity, acpas and periodontitis conditions that influence the risk of developing rheumatoid arthritis in first-degree relatives? *Clin Rheumatol.* (2017) 36:799–806. doi: 10.1007/s10067-016-3519-z
68. Loutan L, Alpizar-Rodriguez D, Courvoisier DS, Finckh A, Mombelli A, Giannopoulos C. Periodontal status correlates with anti-citrullinated protein antibodies in first-degree relatives of individuals with rheumatoid arthritis. *J Clin Periodontol.* (2019) 46:690–8. doi: 10.1111/jcpe.13117
69. Chila-Moreno L, Rodriguez LS, Bautista-Molano W, Bello-Gualtero JM, Ramos-Casallas A, Romero-Sanchez C. Anti-carbamylated protein and peptide antibodies as potential inflammatory joint biomarkers in the relatives of rheumatoid arthritis patients. *Int J Rheum Dis.* (2020) 23:1698–706. doi: 10.1111/1756-185X.13977
70. Hitchon CA, Chandad F, Ferucci ED, Willemze A, Ioan-Facsinay A, van der Woude D, 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. doi: 10.3899/jrheum.091323
71. Chaparro-Sanabria JA, Bautista-Molano W, Bello-Gualtero JM, Chila-Moreno L, Castillo DM, Valle-Onate R, et al. Association of adipokines with rheumatic disease activity indexes and periodontal disease in patients with early rheumatoid arthritis and their first-degree relatives. *Int J Rheum Dis.* (2019) 22:1990–2000. doi: 10.1111/1756-185X.13724

72. Manoil D, Courvoisier DS, Gilbert B, Moller B, Walker UA, Muehlenen IV, et al. Associations between serum antibodies to periodontal pathogens and preclinical phases of rheumatoid arthritis. *Rheumatology (Oxford)*. (2021) 60:4755–64. doi: 10.1093/rheumatology/keab097
73. Mustufvi Z, Serban S, Chesterman J, Mankia K. Should we be screening for and treating periodontal disease in individuals who are at risk of rheumatoid arthritis? *Healthcare (Basel)*. (2021) 9:1326. doi: 10.3390/healthcare9101326

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zekeridou, Gilbert, Finckh and Giannopoulou. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.