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REVIEW ARTICLE

Periodontitis and rheumatoid arthritis—Global efforts to untangle two complex diseases

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Abstract

Understanding the impact of oral health on rheumatoid arthritis (RA) will inform how best to manage patients with both periodontitis and RA. This review seeks to provide an update on interventional and mechanistic investigations, including a brief summary of European Research programs investigating the link between periodontitis and RA. Recent clinical studies are described that evaluate how the treatment of one disease impacts on the other, as are studies in both humans and animal models that have sought to identify the potential mechanisms linking the two diseases.

KEYWORDS
arthritis, clinical trials, laboratory mice, periodontitis, rheumatoid

1 | INTRODUCTION

In the past decades, the association between periodontitis and rheumatoid arthritis (RA) has been widely investigated. A substantial body of work has sought to address the epidemiological and mechanistic association between periodontitis and RA. In 2012, a workshop held jointly by the European Federation of Periodontology and American Academy of Periodontology concluded that epidemiological data on this relationship were inconsistent.[1] Since then, several studies have confirmed the epidemiological association. The evidence up to 2017 was reviewed in this journal and the authors concluded that the evidence of epidemiological association should be moved from "minimal" to "substantial".[2] This conclusion is further strengthened by studies published since 2017, which continue to support a strong epidemiological relationship between these two chronic inflammatory conditions.[3]

While the epidemiological relationship is now clear, there are questions that have yet to be resolved; in particular, the effects of treating periodontitis or RA on the distant disease, and the biological mechanisms underpinning the epidemiological link. In this review, we discuss some of the latest evidence published since 2017 which attempts to further address these unresolved questions, asking (i) what is the clinical effect of periodontal therapy on RA; do (ii) human and (iii) pre-clinical animal data reveal potential mechanisms linking periodontitis and RA?

Isabel Lopez-Oliva and Jennifer Malcolm contributed equally.

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2 | CLINICAL EFFECT OF PERIODONTAL THERAPY ON RA

Randomized clinical trials (RCTs) have investigated the effect of periodontal therapy on RA, which have follow-up periods ranging between 6 weeks and 24 months, and 20–80 patients (Table 1). The studies use differing definitions of periodontitis and different parameters to measure RA status. A recent systematic review with meta-analysis included nine of these studies and concluded that non-surgical periodontal treatment could improve DAS28 (Disease activity score relating to 28 joints assessed), tender joint counts (TJCs), swollen joint counts (SJCs), visual analogue scale (VAS), and serum C-reactive protein (CRP) in patients with RA. The review scrutinized the quality of the evidence published, and concluded that due to selection bias and the tendency for RA medication to change regularly, there is still an urgent need for well-designed studies investigating this topic.[22] Therefore, researchers in the field agree that there is gap in the scientific literature and it is

TABLE 1 Randomized Controlled Clinical trials evaluating the effect of periodontal therapy on rheumatoid arthritis (RA).

Author, year	Duration	Patients, group size, interventions	Parameters evaluated	Did periodontal treatment improve any RA parameter?	Details
Ribeiro et al. (2005) [4]	3 months	42 RA + PD • 16 periodontal treatment • 26 oral hygiene and supragingival cleaning	RF, ESR, HAQ	Yes	RF significantly reduced
Al-Katma et al. (2007) [5]	8 weeks	29 RA + PD • 17 periodontal treatment • 12 no treatment	DAS 28, ESR	Yes	VAS, DAS and ESR reduced
Ortiz et al. (2009) [6]	8 weeks	40 RA + PD • 10 periodontal treatment and DMARDs only. • 10 periodontal treatments and DMARDs with anti-TNF drugs. • 10 no periodontal therapy, DMARDs only • 10 no periodontal treatment, DMARDs with anti-TNF drugs.	ESR, TNF-alpha, signs and symptoms	Yes	VAS and DAS improved in treatment groups. ESR not significantly reduced Anti-TNF drugs improved PPD and CAL
Pinho et al. (2009) [7]	6 months	75 patients: • 15 RA + PD with periodontal treatment • 15 RA + PD no periodontal treatment • 15 PD with periodontal treatment • 15 PD no periodontal treatment	DAS 28, CRP, ESR, AAG (alpha-1 acid glycoprotein)	No	No clear relation. AAG, ESR and CRP not significantly reduced with periodontal therapy.
Okada et al. (2013) [8]	8 weeks	55 RA + PD • 26 supragingival PMPR • 29 no treatment	DAS 28, CRP, anti-CCP, RF, TNF-alpha and levels of IgG to *P. gingivalis*	Yes	Reduction of DAS 28 and levels of IgG to *P. gingivalis* and citrulline
Monsarrat et al. (2019) [9]	3 months	22 RA + PD • 11 periodontal treatment+systemic antibiotics • 11 no treatment	DAS28-ESR	No	No change
Kaushal et al. (2019)[10]	8 weeks	40 RA + PD • 20 periodontal treatment • 20 no periodontal treatment	SDAI, CRP, anti-CCP, RF	Yes	Significant reduction of SDAI, no reduction of CRP, anti-CCP or RF
Mariette et al. (2020) [11]	24 months	472 RA (nested RCT) • 81 RA (OHI, mouthwash, scaling 2/year) (41/73 had periodontitis) • 234 RA—control – no intervention	DAS28-ESR	In subgroups with periodontitis or reduction in red complex bacteria	50 patients with RA completed all dental visits Numerical reduction in DAS28-ESR in subgroups
Nguyen et al. (2021)[12]	6 months	82 RA + PD • Control: Oral hygiene instructions • Non-surgical periodontal therapy	ESR, ACPAs, and DAS28-CRP	Yes	Rreduction of DAS and AS after 3 months, reduction of ESR, ACPAs and DAS28-CRP after 6 months

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Healthcare Access and Quality; IgG, Inmunoglobulin G; PD, periodontitis; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity score; TNF-alpha: tumor necrosis factor alpha; VAS, visual analogue score.

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currently not possible to assess changes in RA outcomes following periodontal treatment. There are substantial challenges in designing and executing such trials, highlighted by de Pablo et al.[23] While the gold standard remains the RCT, there is an increasing appreciation that other, novel trial designs may be useful in addressing complex questions such as the relationship between two complex multifactorial diseases.[24]

Non-randomized clinical studies have investigated the changes in RA following periodontal therapy (Table 2). These studies lack randomization and blinding, and thus, are usually excluded from meta-analyses investigating the effect of periodontal treatment on RA outcomes. However, the findings from these studies should be considered alongside the conclusions from RCTs. These studies generally support the beneficial effect of periodontal therapy on RA parameters (Table 2).

Further complicating these "two diseases" trials is the possibility that patients with RA do not respond as well to periodontal treatment. Reassuringly, a systematic review with meta-analysis concluded that RA does not affect the efficacy of periodontal treatment.[25]

In addition to investigating whether periodontal treatment impacts on RA, there are a small number of studies investigating whether periodontitis severity impacts the response to RA medications. It is unknown why some patients with RA are classified as non-responders and researchers have hypothesized that for some of these patients with RA, gingival inflammation might contribute to the limited therapeutic response. In a 1-year retrospective study of 50 patients with RA, both bivariate and multivariate analyses demonstrated that periodontitis severity was associated with poorer clinical response to biological disease modifying anti-rheumatic drug (bDMARD).[26] Given the devastating impact of therapeutic failure for RA, more research is merited to understand whether treating periodontitis can increase the efficacy of RA treatments, or whether different therapies should be targeted for patients with RA with periodontitis.

TABLE 2 Clinical trials (non-RCT) evaluating the effect of periodontal therapy on rheumatoid arthritis.

Author	Duration	Patient number	Aims and parameters evaluated	Results
Balci Yuce et al. (2017) [13]	6 weeks	17 RA + PD, 18 PD, 18 H	Levels of vitamin D and cytokines in GCF and serum	Periodontal treatment decreased GCF RANKL and TNF GCF vitamin D
Kurgan et al. (2017) [14]	3 months	15 RA + PD, 15 PD	GCF tissue/blood vessel-type plasminogen activator (t-PA) and plasminogen activator (PAI-2)	Periodontal treatment decreased PAI-2, which was higher in RA compared to systemically healthy
Zhao et al. (2018) [15]	1 month	18 RA + PD, 18 RA, 18 PD, 18 H	DAS, ACPA, CRP, ESR	Periodontal treatment decreased DAS, ACPA, CRP, ESR
Cosgarea et al. (2019) [16]	3 and 6 months	16 RA + PD	DAS28, ESR, CRP	Significant decrease of serum CRP at 3 months
Kaneko et al. (2021) [17]	2 months	40 RA + PD, 30 PD, 43 H	Serum carbamylated protein and NETs, clinical RA and periodontal paramenters	Periodontal treatment significantly reduced DAS28, CarP and NETs
Bialowas et al. (2020) [18]	4–6 weeks	44 RA, 30 Spondyloarthritis, 39 H	DAS 28, other activity disease indexes, Pg, serum cytokine levels	Periodontal treatment decreased DAS28 and other activity diseases indexes
Moller et al. (2020) [19]	6 months	5 responder to DMARD RA, 3 non-responder—all RA	DAS28, antibodies and periodontal pathogens	Periodontal treatment improved DAS28 in 5/8 patients
Moura et al. (2021) [20]	45 days	30 H, 23 RA, 25 RA + PD, 30 PD	Periodontal pathogens and parameters, DAS28	Periodontal treatment reduced DAS28
Moura et al. (2021) [20]	45 days	19 H, 23 RA, 24 RA + PD	Plasma and salivary markers. RA and periodontal parameters	Periodontal treatment resulted in a significant reduction of Survivin and OPG in plasma and saliva
Elsadek and Farahat (2021) [21]	12 weeks	50 RA + PD (25 received periodontal treatment with photodynamic therapy; 25 only periodontal treatment)	GCF IL-6, TNF, RF, DAS28, ACPA, CRP	Both groups experienced improvement, photodynamic therapy signifficantly reduced GCF cytokines

Abbreviations: ACPA, anti-citrulinated protein antibodies; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; GCF, gingival crevicular fluid; H, health (no RA and no PD); PD, periodontitis; Pg, *P. gingivalis*; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor kappa-B ligand; RF, rheumatoid factor; TNF, tumor necrosis factor alpha.

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3 | CLINICAL EFFECT OF RA THERAPY ON PERIODONTITIS

Understanding of the pathogenesis of RA and the inflammatory processes that occur in the synovium of patients with RA has allowed for important advances in RA treatment. Current therapeutic regimes often involve the use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) which target specific steps of the inflammatory process. It has been hypothesized that by reducing systemic inflammation, these drugs could provide a benefit for periodontitis patients. Researchers have investigated the effect of RA-drugs on periodontal and inflammatory parameters of patients with periodontitis (Table 3). Although these studies generally show limited impact of RA-drugs on periodontitis,[33] the results need to be considered with caution as most of them are not RCTs and they evaluate surrogate measures of inflammation instead of periodontal clinical outcomes. There are immense challenges associated with evaluating the effects of bDMARDS on periodontal health. There are case reports of acute periodontal infection associating with adalimumab (anti-TNF treatment) treatment for psoriasis, which resolved with conventional periodontal treatment and change of medication to secukinumab (anti-IL17 treatment).[34] There are case reports of Secukinumab treatment associating with oral candida infection and oral lichen planus.[35] To date, there is minimal reporting of oral effects of bDMARDS, reflecting the inherent difficulty in measuring changes in oral health in outpatient rheumatology settings. Moreover, there is an ever-increasing variety of bDMARDs available, and the indications for their use can change over time as data emerge. For example, janus kinase (JAK) inhibitors have proved successful in the management of RA[36]; however, the European Medicines Agency subsequently recommended restrictions on the use of JAK inhibitors in patients over 65, those at risk of cardiovascular disease, and smokers.[37,38] Thus, individual patients can change medications and recommendations for the use of certain medications can change—particularly as further data on bDMARDSs arises. This further complicates understanding the impact of bDMARDs on oral health.

The epidemiological relationship between RA and periodontitis is now well-established, and an increasing number of studies suggest that treating periodontitis may be beneficial for patients with RA. However, the evidence to date is not definitive and carefully designed RCTs and novel study designs are required to adequately quantify the effect of periodontal therapy on RA

TABLE 3 Clinical trials evaluating the effect of rheumatoid arthritis drugs on periodontitis.

Author	Duration	Patient number	Aims and parameters evaluated	Results
Jung et al. (2018) [27]	4 weeks	32 RA and 32 systemically healthy patients with periodontitis	Response to nonsurgical periodontal treatment in multiple csDMARDs therapy and addition of NSAIDs and/or steroids to csDMARDs	No statistically significant difference found
Ayravainen et al. (2018) [28]	1 year	53 early untreated RA (eRA), naive to anti-rheumatic drugs (DMARDs), 28 RA candidates for biologic DMARDs and of 43 age- and sex-matched controls	Impact of anti-rheumatic medications on salivary matrix metalloproteinase (MMP)-8 levels and MMP-8/TIMP (tissue inhibitor of MMPs)-1 ratio in patients with rheumatoid arthritis (RA)	The used DMARDs, synthetic or biologic, did not affect salivary MMP-8 concentrations
Ziebolz et al. (2018) [29]	6 months	168 patients with RA divided according to medication (and combinations)	Periodontal clinical parameters and periodontal bacteria	MTX + TNF-alpha antagonists therapy showed higher BOP. Periodontal bacteria showed differences for different medication subgroups
Heredia-P et al. (2019) [30]	1 year	28 eRA	Factors associated with the progression of clinical attachment loss (CAL) in interproximal dental sites of patients with eRA	Combined treatment with DMARDs and corticosteroids exhibited less CAL ($p < 0.0001$)
Ancuta et al. (2020) [31]	24 weeks	21 patients with RA initiating baricitinib	Evaluate the periodontal status in RA with and without baricitinib	Improvement of periodontal status after 24 weeks of baricitinib
de Smit et al. (2021) [32]	2 months for MTX, and 3 and 6 months for the anti-TNF + MTX	14 treatment-naive patients with RA starting with MTX and 12 patients with RA starting with anti-TNF therapy in addition to MTX	Effect of methotrexate (MTX) and anti-tumor necrosis factor-alpha (anti-TNF, etanercept) treatment on the periodontal condition of patients with RA	MTX or anti-TNF treatment did not result in an improvement of the periodontal condition

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; DMARD, disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; eRA, early RA; ESR, erythrocyte sedimentation rate; MMP, matrix metalloproteinases; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor; PD, periodontitis; RA, rheumatoid arthritis; RF, rheumatoid factor.

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outcomes, and response to RA therapies. Unraveling the unanswered clinical questions will be underpinned by understanding of the mechanistic basis underlying the epidemiological link. To date, there remain significant gaps in this understanding. However, several ground-breaking studies have been recently published that are revealing the critical influence of host–pathogen interactions at the mucosal surfaces of the gut and gums in precitating of joint inflammation.[39-42] Human studies investigating the mechanisms linking periodontitis and RA are discussed in the following sections, focusing on the interrelating concepts of (i) citrullination, (ii) anti-citrullinated antibodies, (iii) the microbiota, and (iv) inflammation as potential factors mediating the links between periodontitis and RA. Their findings are summarized in Tables 4–6. Animal studies evaluating both periodontal and arthritis associated features are then considered.

4 | POTENTIAL MECHANISMS LINKING PERIODONTITITS AND RHEUMATOID ARTHRITIS

4.1 | Periodontitis mediated citrullination and carbamylation as a potential link between periodontitis and RA

RA is strongly associated with a genetic background of HLA-DRB1 risk alleles, which predispose to the development of anti-citrullinated autoimmunity, characterized by the presence of anti-citrullinated peptide antibodies (ACPAs). Notably, emergence of ACPA in patient sera pre-dates joint inflammation by up to a decade[80] and strongly associates with specific mucosal insults, such as smoking.[81] These observations indicate that early triggering of RA occurs outside of the joint, most likely at mucosal surfaces. Given the strong epidemiological association with RA, the gingival tissues of patients with periodontitis have been proposed as a possible extra-articular site of disease initiation (Catrina et al.[82]; reviewed Lundberg et al.[83]). Indeed, clinical evidence indicates that the citrullinome of gingival tissues of patients with periodontitis is similiar to that of the inflamed synovium in patients with RA.[84] Thus, the periodontal tissues may be a source of the antigens recognized by the immune system causing anti-citrulline autoimmunity which is characteristic of RA. There is evidence that periodontitis may contribute to post-translational protein modifications, namely, citrullination and carbamylation. The levels of circulating carbamylated proteins but not myeloperoxidase-DNA complexes (a marker for the generation of neutrophil-extracellular traps) were elevated in the serum of 30 systemically healthy periodontitis patients, relative to periodontally healthy controls.[71] Furthermore, the levels of both carbamylated proteins and myeloperoxidase-DNA complexes were reduced in 22 patients with combined RA and periodontitis following periodontal therapy.

In a study of 26 patients with RA and 72 controls with non-RA, there was no evidence of increased citrullination in the GCF according to periodontal status of patients with or without RA.[63] Yet, higher levels of citrullinated proteins were detected in the GCF of patients with *Porphyromonas gingivalis*, and citrullinated protein levels correlated with the levels of anti-*P. gingivalis* antibodies in patients without RA but not in patients with RA.

A few studies have attempted to quantify the extent of protein citrullination in biopsy tissue from patients with periodontitis. Citrullinated histone 3 was detected by immunohistochemistry of biopsies from 9/15 periodontitis patients compared with 0/6 periodontally healthy controls.[60] Citrullinated proteins were detected in 80% (12/15) gingival biopsies from periodontitis patients compared with 27% (4/15) of healthy controls.[61] Furthermore, the expression of peptidyl arginine deiminase-2 (PAD2) and PAD4 were increased in the gingival connective tissue of biopsies from periodontitis patients compared with healthy controls. However, in this group, there was no evidence that the levels of citrullinated proteins or PAD enzymes were associated with the presence of *P. gingivalis* or *A. actinomycetemcomitans*.[61] A small cross-sectional study investigating the extent of citrullination and carbamylation in gingival tissues of 5 patients with RA, 5 with RA and periodontitis, and 5 healthy controls found evidence of increased numbers of cells positive for citrullination and carbamylation in patients with RA and RA combined with periodontitis compared with healthy controls.[66] The study design excluded the potential to investigate the extent of citrullination and carbamylation in periodontitis patients, independent of RA.

Together, these studies suggest that citrullinated and carbamylated proteins can be detected in the gingival tissues of patients with periodontitis, and in patients with combined periodontitis and RA. However, of the above studies only Janssen et al sought to investigate associations between protein modification in gingiva with specific autoantibody production; and found no evidence for increased titres of autoantibodies against citrullinated histone 3 in patients with periodontitis compared with periodontally healthy controls. A recent study undertook a sophisticated approach to investigate whether the gingival tissues are a site involved in triggering the production of autoantibodies.[85] Monoclonal antibodies generated from the immunoglobulin genes of gingival B cells were screened for citrulline reactivity and found to cross-react with a *P. gingivalis* citrullinated peptide and human citrullinated peptides. This study supports the hypothesis that citrullination occurring in the gingiva can induce autoantibody responses.

4.2 | Anti-citrullinated antibodies in periodontitis patients with or without RA

There is clinical evidence suggesting periodontitis is associated with the development of ACPA in systemically healthy individuals.[86-88] In some patients with periodontitis, the ACPA titre may be modulated by periodontal treatment.[89]

Several studies published since 2017 have sought to investigate the relationship between autoantibody levels in serum or oral fluids with the prevalence and/or severity of periodontitis in systemically healthy or patients with RA. These investigations yielded variable results. In 98 patients with RA there was no evidence of an association between

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TABLE 4 Summary of studies investigating autoantibodies as a potential link between periodontitis and RA.

Author	Study population	Method	Results
Che Rahim et al. (2019) [43]	98 patients with RA	Cross-sectional study to investigate the prevalence of periodontitis and correlate with levels of RF, ACPA, and DAS-28	45.9% (45/98) of patients with RA were diagnosed with chronic periodontitis There was no evidence of an association of periodontitis status with RF or ACPA positivity
Loutan et al. (2019) [44]	99 FDR relatives of patients with RA	Nested case–control to investigate periodontitis status (PD, BoP, CAL, GI, and PI) and correlate with levels of ACPA	ACPA positive FDRs ($n=34$) had higher PD, BoP, and CAL compared with ACPA negative FDRs ($n=65$) ACPA positive FDRs had significantly higher prevalence of moderate to severe periodontitis compared with ACPA negative FDRs
Chila-Moreno et al. (2020) [45]	124 FDR relatives of patients with RA and 124 gender and age-matched healthy controls	Cross-sectional case control to investigate association between anti-carbamylated antibodies with PD status and presence of Pg	Anti-carbamylated antibodies were detected more frequently in FDRs compared with controls Periodontal status did not differ between FDRs and controls No evidence that periodontitis or presence of Pg associates with levels of anti-carbamylated antibodies
Gonzalez-Febles et al. (2020)[46]	164 patients with RA	Cross-sectional study to investigate the association between periodontal parameters (PI, BoP, PD, and CAL) with the presence of ACPA	Presence of anti-CCP was associated with higher mean CAL, number of pockets >5 mm, mean PI compared with anti-CCP negative patients Mean anti-CCP titres increased significantly with increasing number of pockets >5 mm
Rahajoe et al. (2020) [47]	72 patients with RA and 151 healthy controls	Cross-sectional study to investigate autoantibodies (ACPA and RF) in serum and GCF according to periodontitis status (PISA)	There was no difference in the prevalence of periodontitis in RA and healthy controls (21% vs. 29%) Mean levels of IgA ACPA was higher in the serum of HC with periodontitis compared with healthy controls without periodontitis
Svard et al. (2020) [48]	132 patients with RA, aged 61 years or older	Cross-sectional study to investigate IgA and IgG ACPA in serum, and IgA ACPA in saliva according to periodontal status	There was no evidence of association of the proportion of IgA or IgG ACPA positivity in serum or saliva of patients according to periodontal status
Manoil et al. (2021) [49,50]	51 healthy FDR controls, 51 FDRs with RA, 51 FDRs with inflammatory arthralgias and 48 FDRs with unclassified arthritis	Cross-sectional study to investigate whether serum IgG antibodies directed against periodontal pathogens associate with ACPA in different cohorts of FDRs of patients with RA	No association between IgGs directed against periodontal pathogens between each group. Significant association between cumulative IgG and ACPA positivity.
Lew et al. (2021) [51]	20 patients with RA, 20 patients with RA + PD, 20 non-RA patients with periodontitis and 20 periodontally and systemically healthy controls	Cross-sectional study to investigate levels of serum ACPA according to periodontal parameters (PPD, CAL, BoP, PI, PISA)	Median levels of serum ACPA were higher in patients with RA and RA with periodontitis compared with healthy controls. There was no evidence of a correlation between periodontal parameters and serum ACPA in each of the groups

Abbreviations: ACPA, anticitrullinated protein antibody; BI, bleeding index; BOP, bleeding on probing; CAL, clinical attachment level; CCP, cyclic citrullinated peptide (diagnositic assay); FDR, first degree relatives; GCF, gingival crevicular fluid; HC, healthy controls; Ig, immunoglobulin; IgG, Inmunoglobulin G; IU, international units; PD, periodontitis; PI, plaque index; RA, rheumatoid arthritis; RF, rheumatoid factor; RA, rheumatoid arthritis.

periodontitis status and ACPA or RF positivity.[43] In a study of 132 patients with RA there was no evidence that the proportion of patients with ACPA positivity of IgA or IgG isotypes associated with a diagnosis of periodontitis.[48] Conversely, a study of 164 patients with RA, ACPA positivity (defined as anti-CCP > 25 UI/mL serum) was associated with higher mean clinical attachment loss, number of pockets >5 mm and mean plaque index compared with anti-CCP negative patients.[46]

In a study of the prevalence of periodontitis among 72 patients with RA and 152 controls with without RA no difference was reported among patient groups for levels of serum IgG ACPA or RF

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TABLE 5 Studies investigating the oral bacterial microbiota in patients with rheumatoid arthritis using next generation sequencing methods and/or DNA-based techniques.

Author	Study population	Method	Results
Scher et al. (2012) [52]	31 New-onset patients with RA	Multiplexed-454 pyrosequencing Anti–*P. gingivalis* antibody testing	Subgingival microbiota profile in patients with new-onset RA was similar to that in patients with chronic RA and healthy subjects whose periodontitis was of comparable severity. Exposure to *P. gingivalis* was similar among the groups
Zhang et al. (2015) [53]	105 dental and 98 saliva samples (dental: 54 treatment-naive RA, 51 controls; saliva: 51 RA, 47 controls; 69 of the subjects had a complete set of fecal, dental and salivary samples)	Metagenome-wide association study	RA status had the strongest effect on the dental and salivary microbiomes among all available phenotypes
Lopez-Oliva et al. (2018) [54]	41 periodontally healthy individuals (22 with RA and 19 without RA)	16S r-RNA sequencing	Subgingival microbiota differed significantly between patients with RA and controls based on both community membership and the abundance of lineages
Beyer et al. (2018) [55]	*N* = 78 patients with RA	16SrDNA amplicon sequencing Pg-specific qPCR	Significantly different microbiota compositions according to gingival bleeding, periodontal probing depth, RA disease status, prednisolone use and smoking
Chen et al. (2018) [56]	110 patients with RA, 67 patients with OA and 155 healthy subjects	16S rRNA gene amplicon sequencing	Eight oral bacterial biomarkers were identified to differentiate RA from OA
Correa et al. (2019) [57]	42 patients with RA	16S rRNA high throughput sequencing	Oral microbiota dysbiosis was linked with more severe RA
Eriksson et al. (2019) [58]	40 patients with RA	16S rRNA sequencing	Subgingival microbial profile related to periodontitis severity
Esberg et al. (2021) [59]	61 patients with early-onset RA	16S rRNA sequencing	Early onset patients with RA demonstrated a distinct oral microbiota, independent of periodontal status

Abbreviations: rRNA ribosomal RNA; rDNA ribosomal DNA; OA - osteoarthritis; qPCR - quantitative PCR; RA rheumatoid arthritis; PD - (scored out - change to periodontitiis).

(IgM or IgA). However, there was a statisically significant increase in serum IgA ACPA in non-RA healthy controls with periodontitis compared with the periodontally healthy non-RA controls.[47]

In a study of 40 patients with RA and 40 patients without RA stratified by periodontitis positive or negative diagnosis (20 each group), levels of serum ACPA were higher in RA + PD and RA only groups compared with systemically and periodontally healthy controls.[51] However, within each group, there was no correlation between periodontal parameters with serum ACPA.

Other investigations have looked at the association between periodontal status and the levels of autoantibodies in first-degree relatives (FDRs) of patients with RA. In a nested case control study of 99 RA FDRs, ACPA positive FDRs had significantly higher prevalence of moderate-to-severe periodontitis compared with ACPA negative RA–FDRs.[44] Due to the cross-sectional design, the direction of this association remains unknown. In the second study, 124 RA–FDRs were age- and gender-matched with 124 healthy controls to investigate association between anti-carbamylated antibodies with periodontal status and the presence of *P. gingivalis*.[45] The prevalence of periodontitis was similar in both RA–FDRs and healthy controls, although anti-carbamylated antibodies were detected more frequently in FDRs compared with healthy controls. There was no evidence that periodontitis status or presence of *P. gingivalis* associated with levels of anti-carbamylated antibodies. A study investigating the antibody response to periodontitis associated bacteria in patients with RA and FDRs (FDRs both with and without RA-related autoimmunity) revealed no association with ACPA positivity and any individual bacteria, but demonstrated that cumulative anti-bacterial IgG levels showed a strong association with the presence of ACPA.[49]

It remains to be determined whether particular human leukocyte antigen (HLA) alleles are associated with initiation and/or maturation of the ACPA response, in particular in the context of challenges at mucosal barriers. Therefore, future studies could attempt to determine whether citrullination or carbamylation occurring locally in the gingival tissues of systemically healthy patients with periodontitis associates with the emergence/maturation of ACPA or anti carbamylated protein (CarP) antibody responses, and crucially whether this precedes RA. This challenging question will require long term longitudinal studies and may prove unanswerable with currently available data sets.

4.3 | The oral bacterial microbiota as a potential link

A number of studies have attempted to understand if differences in the composition of the oral bacterial microbiota are a modifying factor in RA pathogenesis (Table 4).

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TABLE 6 Clinical studies investigating citrullination and/or inflammation as a pathophysiological mechanism linking RA and periodontitis.

Author	Study population	Method	Results
Studies considering citrullination and/or antibodies alongside inflammatory mediators			
Janssen et al. (2017) [60]	84 patients with RA, 131 with PD, and 36 healthy controls	Cross-sectional study to assess serum for the presence of autoantibodies against citrullinated histones Biopsies from 15 periodontitis patients and 6 healthy controls were assessed for citrullinated histone 3 by immunohistochemistry	Sera from patients with RA had significantly higher titres of autoantibodies against citrullinated histone 3 compared with healthy controls and periodontitis sera 60% of periodontitis biopsies were positive for citrullinated histone 3, which was undetected in biopsies from healthy controls
Engstrom et al. (2018) [61]	15 patients with PD and 15 periodontally healthy controls	Cross-sectional study to investigate the extent of citrullination and expression of PAD2 and PAD4 in gingival biopsy tissue, in relation to the presence of Pg and Aa	Citrullinated proteins were detected in 12/15 (80%) periodontitis biopsies compared with 4/15 (27%) healthy biopsies. Staining for PAD 2 and 4 was elevated in the gingival connective tissue, but not epithelium of patients with periodontitis compared with healthy controls. The extent of citrullination and PAD expression did not correlate with the presence of Pg or Aa
Zhao et al. (2019) [62]	128 patients with RA and 109 healthy controls	Cross-sectional study to investigate prevalence of periodontitis (PI, GI, PPD, CAL, and BoP) and correlate with inflammatory markers (ESR and CRP) and autoantibodies (ACPA and RF)	Compared with controls, patients with RA had higher prevalence of periodontitis (OR 4.68) Frequency of ACPA and RF were significantly higher in patients with RA with periodontitis compared with patients with RA without periodontitis
Maldonado et al. (2020) [63]	26 patients with RA and 72 RA controls stratified by periodontal status (aggressive periodontitis, chronic periodontitis, and gingivitis + health)	Cross-sectional study to determine whether the presence of Pg or Aa in subgingival plaque, or antibodies directed against Pg or Aa correlated with levels of citrullination in gingival crevicular fluid	Citrulline levels in gingival crevicular fluid were higher in patients with detectable Pg Citrulline levels correlated with anti-Pg antibodies in patients without RA but not in patients with RA
Panezai et al. (2020) [64]	19 patients with RA, 19 patients with RA + PD, 38 patients with PD and 12 systemically and orally healthy controls	Case–control study to compare the mean serum levels of 98 inflammatory biomarkers by multiplex proximity extension, ACPA, RF, and ESR between each group	17 inflammatory biomarkers, RF and ACPA were elevated in the serum of patients with RA and periodontitis compared with RA only
Karapetsa et al. (2021) [65]	77 RA + PD patients and 43 patients with RA without periodontitis	Cross-sectional study to investigate the prevalence of serum RF and ACPA positivity and mean levels of CRP, ESR and fibrinogen according to periodontitis status (PPD and CAL)	Prevalence of seropositivity in patients with RA with periodontitis was greater than patients with RA without periodontitis No differences were detected in mean levels of serum CRP, ESR, or fibrinogen in patients with RA by periodontitis status
Lee et al. (2021) [66]	5 patients with RA only, 5 with RA + PD and 5 healthy controls	Cross-sectional study to investigate the extent of citrullination and carbamylation in gingival tissues by immunohistochemistry	The proportion of cells stained positive for citrullination and carbamylation was significantly higher in gingival tissues from patients with RA regardless of periodontitis status compared with healthy controls
Studies considering inflammatory mediators			
Gamel et al. (2017) [67]	57 patients with RA, 57 patients with PD and 57 healthy	Cross-sectional study to investigate association of salivary TNFα in patients with RA according to severity of periodontitis parameters (CAL)	No significant difference in mean salivary levels of TNFα in patients with RA, periodontitis, or health. No correlation between salivary TNFα with CAL
Kirchner et al. (2017) [68]	103 patients with RA and 104 healthy controls	Cross-sectional study to investigate association between periodontal status (PPD, BoP, and CAL) presence of certain periodontal bacteria (PCR) and GCF aMMP8 levels (ELISA)	The prevalence of Aa was significantly higher in patients with combined RA and severe periodontal disease compared with patients with RA with moderate and mild periodontitis GCF aMMP8 levels increased with increasing severity of periodontal disease and was significantly higher in patients with RA compared with healthy controls
Silvestre-Rangil et al. (2017) [69]	30 patients with RA and 30 matched controls	Longitudinal case–control study to investigate the association between salivary IL-6 with periodontal parameters (PI, PPD, CAL)	Patients with RA presented with more severe periodontal indices compared with controls Patients with RA had higher levels of salivary IL-6 compared with controls

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TABLE 6 (Continued)

Author	Study population	Method	Results
Ayravainen et al. (2018) [70]	53 early patients with RA, 28 patients with chronic RA and 43 healthy controls	Prospective study to determine whether salivary and serum inflammatory biomarkers (MMP8, TIMP1, and Il-6) associated with periodontal parameters (PIBI)	MMP8 was elevated in the saliva of early patients with RA compared with chronic patients with RA at baseline and correlated with PIBI in early patients with RA at baseline
Kaneko et al. (2018) [71]	40 patients with RA and periodontitis, 30 PD patients and 43 systemically and periodontally healthy controls	Retrospective case–control study to investigate the association between serum levels of carbamylated proteins and neutrophil extracellular traps with periodontal parameters (PPD and CAL)	Increased levels of carbamylated proteins and neutrophil extracellular traps were correlated with more severe periodontal parameters in patients with RA
Panezai et al. (2018) [72]	19 patients with RA, 19 patients RA + PD, 38 patients with PD and 14 systemically and orally healthy controls	Case–control study to compare the mean levels of inflammatory markers (osteopontin, TNF receptors 1 and 2, RANKL and RANKL/OPG ratio) in the serum of patients from each group	Osteopontin and TNF receptor 1 was significantly higher in the serum of patients with combined RA and periodontitis compared with periodontitis only and patients with RA without periodontitis
Schmalz et al. (2019) [73]	56 patients with RA undergoing methotrexate therapy	Cross-sectional study to investigate association between inflammatory markers from serum (MMP8, TIMP1, TGFβ, IFNγ, IL-6 and Il-23), gingival crevicular fluid (MMP-8), and selected subgingival plaque bacteria with periodontal status (PPD, BoP, CAL)	34 (61%) patients were diagnosed with periodontitis MMP8 was significantly higher in the blood and GCF of patients with periodontitis Prevalence of periodontal bacteria was higher in periodontitis patients, while association with serum inflammatory markers was not conclusive
Cheah et al. (2020) [74]	45 patients with RA and 55 RA controls, stratified by periodontitis status (Chronic periodontitis, gingivitis, periodontal health)	Cross-sectional study to correlate levels of serum and salivary LL37 in RA and RA controls by periodontal status	Salivary LL37 was highest in patients with RA with chronic periodontitis Serum LL37 was significantly higher in all RA groups regardless of periodontal status, and RA controls with chronic periodontitis compared with RA controls with gingivitis or oral health
Arvikar et al. (2021) [75]	33 patients with untreated, new-onset RA, 20 non-RA patients with PD and 20 systemically and periodontally healthy controls	Cross-sectional study to investigate periodontitis severity (PPD, CAL, BoP) and a panel of 13 inflammatory mediators in serum, saliva, gingival crevicular fluid and synovial fluid	All periodontal parameters were elevated in Patients with RA compared with healthy controls Compared with healthy controls, saliva and gingival crevicular fluid of patients with RA (with and without periodontitis) and periodontitis only patients contained elevated inflammatory mediators consistent with neutrophilic inflammation.
Inanc et al. (2021) [76]	55 patients with RA, 41 patients with Bechet's disease and 58 healthy controls. In Patients with RA 34 were periodontally healthy and 21 were diagnosed with periodontitis)	Cross-sectional study to compare the mean serum levels of triggering receptor expressed on myeloid cells (TREM-1) and peptidoglycan recognition protein 1 (PGLYRP1) according to periodontitis	Serum levels of TREM-1 and PGLYRP1 were elevated in patients with RA with periodontitis compared with patients with RA without periodontitis
Soderlin et al. (2021) [77]	132 patients with RA	Cross-sectional study to investigate the mean levels of selected cytokines in gingival crevicular fluid in patients with and without periodontitis	No differences in the mean levels of selected cytokines were found in patients with RA according to periodontal status
Xiao et al. (2021) [78]	42 RA + PD patients and 56 non-RA controls with periodontitis	Cross-sectional study to measure the levels of TNF-α and IL-1β in gingival crevicular fluid	TNF-α and IL-1β were higher in the gingival crevicular fluid of patients with combined RA and periodontitis compared with non-RA patients with periodontitis
Yilmaz et al. (2021) [79]	23 patients with RA, 21 periodontitis patients and 23 patients with RA + PD and 22 systemically and orally healthy controls	Cross-sectional study to investigate the levels of macrophage-chemoattractant protein-1 (MCP-1) macrophage migration inhibitory factor (MIF) and fractalkine in saliva and serum	Salivary MCP-1, MIF and fractalkine were higher in patients with RA regardless of periodontal status compared with healthy controls. MCP-1 was higher in serum of patients with combined RA and periodontitis compared with controls Serum fractalkine was higher in patients with combined periodontitis and

Abbreviations: Aa, aggregatibacter actinimycetemcomitans; CAL, clinical attachment loss; CRP, C-reactive protein; ELISA, enzyme linked immune-sorbent assay; ESR, erythrocyte sedimentation rate; GI, gingival index; GCF, gingival crevicular fluid; IFN, interferon; IL-6, interleukin-6; MMP8, matrix metalloproteinase 8; OR, odds ratio; PAD, peptidyl arginine deiminase; PCR, polymerase chain reaction; PIBI, Periodontal inflammatory burden index; Pg, Porphyromonas gingivalis; PI, plaque index; PISI, plaque inflammation score index; PPD, probing pocket depth; RANKL, receptor activator of nuclear factor kappa beta ligand; RF, rheumatoid factor; TIMP1, tissue inhibitor of matrix metalloproteinase-1; TNFa, tumor necrosis factor alpha.

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Studies of the bacterial oral microbiota of patients with RA have identified oral bacterial dysbiosis associated with RA, even in periodontally healthy individuals.[54] However, the association between the composition of the oral bacterial microbiota and RA pathogenesis remains unclear.

Oral mucosal breaches in patients with periodontitis were shown to be associated with RA flares.[39] During RA flares, surface citrullinated oral bacteria disseminated systemically and associated with surges in specific subsets of inflammatory blood monocytes. Furthermore, ACPA from patients with RA cross-reacted with citrullinated oral bacteria. The authors additionally provide data suggesting that (at least in some instances) ACPAs may originate from stimulation with citrullinated bacterial antigens. This study highlights the value of assessing the impact of the microbiome on host responses to identify the mechanisms underpinning the association between RA and periondontitis.

In addition to possible changes in the overall composition of the oral bacterial microbiota, infection with specific oral pathogens are hypothesized to alter citrullination locally within the periodontal tissues and drive the generation of ACPA. *Porphyromonas gingivalis*, *Aggregibacter actinomycetemcomitans*, and *Prevotella intermedia* have been extensively investigated for their roles in the pathogenesis of RA. Studies describing the roles of other bacteria and novel taxa are also described.

P. gingivalis uniquely expresses its own peptidylarginine deiminase (PPAD) and an arginine gingipain (Rgp) capable of cleaving proteins at arginine residues. The combined activity of Rgp and PPAD is sufficient to generate non-endogenous C-terminally citrullinated epitopes. Incubation of RA autoantigens with *P. gingivalis* generates C-terminal citrullinated host derived peptides.[90] We have recently shown how C-terminal citrullination alters CD4 T cell epitope recognition, and demonstrated that immunization of mice with a C-terminally citrullinated model antigen was sufficient to breach immune tolerance for the native antigen.[91]

Substantial clinical and experimental evidence supports an aetiopathogenic role for *P. gingivalis* in the development and/or exacerbation of arthritis (reviewed in[92]). Serum antibodies directed against *P. gingivalis* antigens (Rgp and PPAD) are strongly associated with ACPA-positive RA in clinical studies.[93,94] Exposure to *P. gingivalis* exacerbates the severity of experimental arthritis (reviewed in section on animal studies).

Of the periodontal pathogens, only *A. actinomycetemcomitans* appears to induce hypercitrullination of human neutrophils.[84] *A. actinomycetemcomitans* induces neutrophil hypercitrullination through the secretion of leukotoxin A (LtxA), a bacterial pore-forming toxin that induces calcium influx and subsequent hyperactivation of PAD enzymes in the neutrophil. Patients with RA showed elevated anti-LtxA antibody titres. This study proposed that the impact of human lymphocyte antigen–DRB1 shared epitope alleles on auto-antibody positivity was limited to patients with RA who were exposed to *A. actinomycetemcomitans*.[84] Interestingly, in a geographically distinct population of patientswith RA, although there was evidence of elevated anti-LtxA antibodies, there was no association between LTxA antibodies and the impact of the shared epitope on RA in ACPA positive patients with RA.[95]

Cryptobacterium curtum is a gram-positive, assaccharolytic, anaerobic rod (previously misclassified as *Eubacterium saburreum*). *C. curtum* is enriched in the oral and gut microbiota of early RA cases.[53,96] This species is a member of the core microbiota in patients with RA, demonstrating a 100-fold greater abundance patients with RA when compared to non-RA controls; with 39-fold greater odds of detection in the RA cohort. Early investigations demonstrated that 48% of the variation in alveolar bone loss in patients with RA could be attributed to presence *C. curtum*. These association are not indicative of an etiopathogenetic role for *C. curtum*, however, this organism is a candidate for further studies.[54]

Two novel citrullinated peptides (cTNC5 and cCK13-1) were significantly associated with anti-*P. intermedia* antibodies[97] As *P. intermedia*, does not express PAD nor induce or earthritis. However, *P. intermedia* induces distinct ACPA fine specificities (differently from P. gingivalis). The authors propose that this ACPA induction may be the result of *P. intermedia* degrading neutrophil extracellular traps which releases endogenous PADs.

Fusobacterium nucleatum is an oral pathogen enriched in the gut of patients with RA, and was recently shown to exacerbate collagen-induced arthritis via release of outer membrance vesicles (OMVs) capable of translocating to the joint and activating synovial macrophages.[41] Notably, OMVs are a conserved virulence feature of Gram negative bacteria.[98] Thus, the contribution of OMVs released from periodontal pathogens in the oral cavity on RA pathogenesis is a possible area for future exploration.

Many studies focus on the composition of microbial plaque, or saliva. Conceptually, unattached bacteria in the gingival crevicur fluid have more potential to initiate or exacerbate autoimmunity and/or inflammation via the gingival microcirculation. Studies of this microbiota revealed overrepresentation Megasphera and *Anaeroglobus germinatus* in patients with RA. *Porphyromonas gingivalis* was signficiantly associated with plaque scores, BoP, IgA isotype rheumatoid factor, and with more severe/active RA.[50]

4.4 | Inflammation as a potential link

It is well established that local immune-mediated destruction occurring in the periodontal tissues of patients with periodontitis is accompanied by a systemic inflammatory response.[99] One proposed mechanism linking periodontitis and RA suggests that the systemic inflammatory reaction induced by one disease exacerbates or precipitates the other.[100] Notably, experimental periodontitis was recently shown to induce epigenetic changes in haemotopoietic stem and progenitors cells (HSPCs), licensing HSPCs with enhanced capacity to generate myeloid cells with heightened responses to inflammatory stimuli.[42] Importantly, bone-marrow transfer of periodontitis "trained" HSPCs to naïve recipients was sufficient to exacerbate responses to experimental arthritis. This study provides novel insights into how inflammatory periodontitis contributes to joint inflammation. This common basis of inflammation hyopothesis can potentially support the

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epidemiological findings that RA is associated with a geater burden of periodontitis and the vice-versa relationship that patients with periodontitis appear to be at slightly greater risk of RA. The narrative below considers the evidence in each of these potential directions.

Several recent studies have documented evidence that RA contributes to oral inflammation and the severity of periodontal disease. Patients with RA have higher mean levels of salivary MMP-8 and IL-6 compared with non-RA controls.[28,70] Similarly, MMP-8 was elevated in the gingival crevicular fluid of patients with RA compared with non-RA healthy controls. Notably, MMP-8 levels increased in both groups according to the severity of periodontitis.[68] Further support for MMP-8 as an inflammatory biomarker linking both diseases was reported in a cross-sectional study of patients with RA undergoing methotrexate therapy.[73] Mean levels of MMP-8 in serum and gingival crevicular fluid were higher in patients with RA with moderate to severe periodontitis compared with patients with RA with mild or no periodontitis, suggesting periodontitis can impact on the inflammatory burden associated with RA.

A case control study demonstrated that IL-6 was elevated in the oral fluids of patients with RA.[69] However, patients with RA also had increased severity of periodontitis compared with non-RA controls. As such, the contribution of RA, independent of periodontitis, to salivary IL-6 could not be determined in this study.

A study of 42 patients with RA and 56 non-RA controls sought to investigate the contribution of RA to oral inflammation in patients with periodontitis.[78] Mean levels of TNFα and IL-1β were higher in the gingival crevicular fluid of patients with RA compared with non-RA patients (both groups had periodontitis). Evidence that RA contributes to elevated salivary LL37 in patients with chronic periodontitis independent of age, ethnicity, hypertension, DMARDs, vitamin D, and steroid use was provided from a study of 45 patients with RA and 55 non-RA controls stratified by periodontitis status.[74] Higher levels of macrophage-chemoattractant protein-1, macrophage migration inhibitory factor and fractalkine were detected in the saliva of 23 patients with RA without periodontitis compared with 22 systemically and periodontally healthy controls.[79]

Saliva and GCF were investigated for the levels of 13 inflammatory mediators in 33 patients with untreated new-onset RA, 20 non-RA patients with periodontitis, and 20 systemically and periodontally healthy controls.[75] Levels of IL-8, but not IL-6 were elevated in the saliva and GCF of patients with RA, while MMP-8 and MMP-9 were elevated in the saliva but not GCF of patients with RA compared with healthy controls. Notably, various periodontal parameters (BoP, PPD, and CAL) were elevated in patients with RA compared with healthy controls.

Conversely, some studies found no evidence that RA was associated with oral inflammation. No difference was reported in the levels of salivary TNFα in patients with RA only, RA and periodontitis, or healthy controls.[67] There was no difference in the inflammatory profile (TNFα, MCP-1, and IL-1β) of GCF in patients with RA, aged 65 or older according to the presence or absence of periodontitis.[77]

Two publications arising from a case–control study sought to compare the levels of inflammatory mediators in the serum of 19 patients with RA, 19 patients with RA and periodontitis, 38 patients with periodontitis only and 14 systemically and periodontally healthy controls. Osteopontin, TNF receptor 1, TNF receptor 2, and RANKL were highest in the serum of patients with combined RA and periodontitis compared with all other groups,[72] suggesting that periodontitis contributed to the systemic inflammatory burden associated with RA. In a later publication from the same population, levels of 17/98 inflammatory markers were elevated in the serum of patients with RA and periodontitis compared with patients with RA without periodontitis. Furthermore, the levels of rheumatoid factor and ACPA were also elevated in patients with combined RA and periodontitis compared with periodontitis only.[64]

In 41 patients with RA grouped according to periodontal status, mean levels of triggering receptor expressed on myeloid cells 1 (TREM-1) and peptidoglycan recognition protein 1 (PGLYRP1) were higher in patients with combined RA and periodontitis compared with patients with RA and without periodontitis.[76]

There was no evidence that periodontitis contributed to the serum levels of CRP, ESR, or fibrinogen in a study of 77 patients with RA with periodontitis and 43 patients with RA without periodontitis.[65] However, the prevalence of seropositivity was higher among patients with combined RA and periodontitis compared with RA without periodontitis, suggesting that periodontitis might contribute to the generation of autoantibodies.

Together these studies support the hypothesis that oral tissues are a possible extra-articular site of inflammation associated with RA, and further suggest that the oral inflammation associated with RA might influence the extent of periodontitis. However, the evidence is not conclusive and is influenced by the specific population, the mediators assessed and the study design. Further research is required to define the molecular mechanisms, the specific cells and mediators that cause this apparent bidirectional link—such pathways may prove valuable therapeutic targets.

5 | ANIMAL STUDIES OF THE RELATIONSHIP BETWEEN PERIODONTITIS AND RA

Animal models of diseases are valuable in studying disease pathogenesis, identifying exacerbating factors, treatment targets, and testing novel treatments. Different animal models of the same disease have distinct features, and if used judiciously, different models can be used to untangle component features of a disease.

There are numerous models of both arthritis and periodontitis which are considered to model different elements of the disease (Figure 1). Studying the relationship between two diseases in animal models is fraught with challenges. Within each model, the precise experiment protocols can have myriad permeations, for example, different immunization schedules, doses, and routes. When combining two models, experiment design is further complicated by the nuances of timing of initiation of arthritis in respect of periodontitis. Even within the same animal models, different outcome measures

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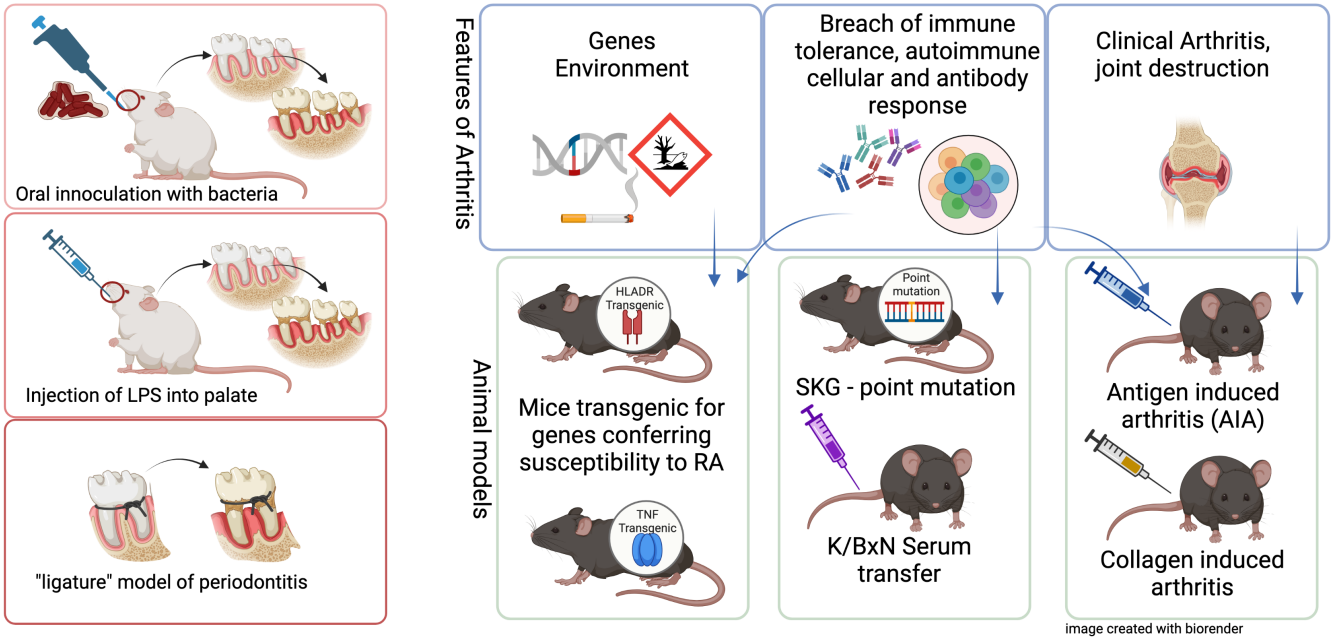

FIGURE 1 Schematics of the murine models of periodontitis and periodontitis used in Table 7.

can be reported, and the same outcome measure can be evaluated differently. Nonetheless, animal models can employ tools such as gene manipulation, and can yield essential proof of concept and preclinical data. For example, infection of DBA1/J mice with wild-type *P. gingivalis* but not a PPAD null mutant strain induced development of ACPA, implicating PPAD in the generation of ACPA.[126]

In the current review we evaluated 26 animal studies, selected for combining periodontitis and arthritis, and which were published since the last review.[2] The studies were highly heterogenous, using different models, in different combinations. In some cases, interventions in the periodontitis or arthritis were included in the experiment design. The studies are summarized in Table 7. It should be noted that not all features of all studies are reported, and the main questions asked are shown in the table headings. Of the 26 studies, 21 combined a model of periodontitis with a model of arthritis. The remaining five studies used a single model (of either periodontitis or arthritis) but evaluated outcomes relevant to pathogenesis of the other disease. Within the 26 studies there was variable reporting of periodontitis and arthritis measures - some studies only evaluated impact of one disease on another, rather than recording any bidirectional effect. From these studies, 23 could be evaluated to see if periodontitis had an impact on arthritis, and out of these 19 reported that periodontitis exacerbated arthritis. The remaining four studies showed no change in arthritis with periodontitis. In 16 of the total 26 studies, it was possible to assess whether arthritis had an impact on periodontitis and 8 out of these 16 studies arthritis exacerbated periodontitis. There was no effect of arthritis on periodontitis in the other 8 studies. Given the heterogeneity of the studies and of the models, it is unsurprising that the results show variations.

Nonetheless, these data show that in some models, disruption of oral homeostasis—by induction of a periodontitis model—can result in distant changes in the joint. It has even been reported that periodontitis alone can result in inflammatory changes in the joint.[110,111] By contrast, other studies showed no impact of periodontitis on RA.[118]

In terms of the impact of arthritis on periodontitis—it appears that in some cases arthritis alone can alter the oral barrier such that alveolar bone loss occurs (e.g., Kim et al.[104]) although this is not a universal finding and other models report no impact of arthritis on alveolar bone levels (Table 5). One advantage of animal models is the potential to look for mechanisms and harvest tissues and intervene with distinct processes. One intriguing finding from some animal studies reviewed here is observation that arthritis compromises barrier integrity—and a proposal that the compromised gut barrier allows oral bacteria (pathogenic ones) to mediate systemic inflammatory effects and exacerbate arthritis.[115,125]

There seems to be a consistent pattern of periodontitis exacerbating RA in the majority of these models; and around half of the models showed that RA exacerbates. Nonetheless, there are clear discrepancies in the findings which may be a reflection of variations in model protocols, differences between strains of animals, and even differences in the same strain of animal held in a different facility with a different diet and different microbiome. Limits on resources and on acceptable use of animals further complicates the design process. Despite these limitations, the animals models provide unparalleled insight into mechanisms - such as the role of PPAD, or changes to the gut microbiome - by which periodontitis and RA relate to each other—the challenge remains to recapitulate these findings in humans.

6 | EUROPEAN CONTRIBUTION TO THE FIELD

A significant proportion of the studies included in this review include European researchers. Globalization facilitates research

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TABLE 7 Overview of recent mouse models investigating the link between rheumatoid arthritis and periodontitis.

Author	Animal model	Periodontitis model	Clinical effect of RA on PD	Clinical effect of PD on RA	Comments
Correa et al. (2017) [101]	Wistar rat, CIA	Ligature	No	Yes	RA + PD: highest ACPA in gingival tissue
de Aquino et al. (2017) [102]	C57BL/6 mice IL-17RA KO, AIA (mBSA)	Oral inoculation with *Pg*	No	Yes	PD + RA: elevated IL-17, TNF. PMN accumulation in RA joints—dependent on IL-17RA
Jung et al. (2017) [103]	DBA1/J Mice, CIA	Oral inoculation with *Pg*	No	Yes	RA exacerbated by Pg strain W83 not 2561
Kim et al. (2017) [104]	DBA1/J Mice, CIA + TNF transgenic spontaneous	*Not done (No PD group)*	Yes (Both CIA & TNF Tg)	*Not done (No PD group)*	Effect on alveolar bone reduced by inhibition of NAMPT
Sato et al. (2017) [105]	DBA1/J Mice, CIA	Oral inoculation with *Pg*	Data not shown	Yes	Pg but not Pi exacerbated CIA -gut microbiota changes, Th17 increased in MLN
Ebbers et al. (2018) [106]	Mice DBA/1 xB10.Q, CIA	Oral inoculation with *Pg*	Data not shown	Yes[a]	Alveolar bone loss with Pg; [a]but exacerbation of arthritis with Fn or Aa—no arthritis exacerbation with Pg
Jeong et al. (2018) [107]	Mice DBA1/J, CIA	Oral inoculation with *Pg*	No	Yes	Exacerbation of CIA Inhibited with anti-FimA Ab
Munenaga et al. (2018) [108]	SKG Mice	Oral inoculation with *Pg*	No	Yes	Elevated C5a in periodontitis and arthritis
Pan et al. (2019) [109]	DBA CIA	Oral and anal inoculation with *Pg*	Yes (RA + PD worse bone loss than PD. No difference RA v ctl)	Yes	Effects of PD/RA/ and RA ameliorated by ctsk inhibitor
Courbon et al. (2019) [110]	Lewis Rat, Induced by Pg alone	Oral inoculation with *Pg*	No RA group	[a]	[a]Pg alone induced signs of early arthritis in the ankle joint and serum CCP
Lubcke et al. (2019) [111]	DBAxB10.Q F1 mice, CIA	Oral inoculation with *Pg*	No RA group	[a]	[a]Treatment of PD with MET or chlorhexidine reduced arthritis Treatment of RA with methotrexate reduced periodontal bone loss
Sakaguchi et al. (2019) [112]	DBA/IJJmcS1c CIA	Oral inoculation with *Pg*	Data not shown	Yes	*E. coli* used as control. No effect PD/RA serum + saliva showed more ACPA than RA
Scanu et al. (2019) [113]	None—perio only	Repeated LPS injection into maxillary gingivae—bone loss shown	N/a	Yes[a]	LPS into tail had no effect LPS injection into maxilla caused paw swelling
Tsurumaki et al. (2019) [114]	Rats mBSA	Ligature	Yes Worse bone loss PD + RA	Not known—all groups had PD	Looking at effect of soyabean unsaponifiables
Flak et al. (2019) [115]	C57BL/6 K/BxN serum transfer	Oral inoculation with *Pg*	Data not shown	Yes	EA promoted gut barrier dysfunction, which facilitated Pg impact on gut
Buschhart et al. (2020) [116]	DBA/B10.Q F1Mice CIA	Oral inoculation with *Pg or Aa*	No	No	PD changed synovial proteome signature
Munoz-Atienza et al. (2020) [117]	C57BL/6, K/BxN serum transfer	Oral inoculation with *Pg*	Data not shown	Yes	Not PPAD dependent—but supports role for gut barrier breakdown
Cardoso et al. (2020) [118]	Wistar rats Collagen/IFA/CFA	Ligature	Not done	No obvious effect PD on RA scores	Showed probiotics could reduce ACPA in RA groups irrespective of PD and implicated changes in gut microbiome
Hamamoto et al. (2020) [119]	SKG/lamarin	Oral inoculation with *Pg*	None		Gut microbiota changes/gut inflammation associated with Pg—gut bacteria transplants

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TABLE 7 (Continued)

Author	Animal model	Periodontitis model	Clinical effect of RA on PD	Clinical effect of PD on RA	Comments
Wei et al. (2020) [120]	DBA/CIA	Oral inoculation with *Pg*	Yes	Yes	Inhibited by ctsk transfection Pg alone increased safarin O staining of joint
Yue et al. (2020) [121]	DBA/CIA	Oral inoculation with *Pg*	Yes More bone loss Pg + CIA versus Pg alone)	Yes More rapid onset	Increased expression of ctsk, TFEB in PD + RA versus PD or RA (in bone of joints)
Gusmao et al. (2021) [122]	Wistar rats CIA	Ligature	No	Not done	Electroacupuncture treatment increased NFKb expression in PDL in RA/EP versus EP
Karydis et al. (2021) [123]	Humanized HLADRB1 mice—challenged with collagen	Oral inoculation with *Pg*	Yes	Yes	Increased IL-17 expressing cells with Pg, + more ACPA
Zhou et al. (2021) [124]	DBA CIA	Oral inoculation with *Pg*	Yes CIA alone caused bone loss equivalent to PG	Yes[a]	[a]PD increased speed of RA onset + increased serum CRP, + increased Th17 + Treg
de Arruda et al. (2022) [125]	C57BL/6 AIA (BSA)	Not done	Yes	Not done	AIA changed oral and gut microbiota. Alveolar bone loss in AIA mitigated by MTX

Abbreviations: ACPA, anti citrullinated protein antibodies; AIA, antigen induced arthritis; CIA, collagen induced arthritis; CRP - creative protein; DBA/ dark brown agoutictsk-cathepsin k; EP - Electroacupuncture; IL-17RA KO, Interleukin 17 receptor alpha knock out; K/BxN, mice expressing transgenic T cell receptor 'KRN' and MHC Class II A9(g7); mBSA, methylated bovine serum albumin; MTX - methotrexate; NFKB-Nuclear factor -kappa beta; PD, periodontitis model; Pg, *Porphyromonas gingivalis*; Pi, *Prevotella intermedia*; RA, arthritis model; SKG, mice with mutation in ZAP-70, resulting in spontaneous T cell driven arthritis; Th17 - T helper 17; Treg - T regulatory; TFEB- transcription factor EB;.

collaborations between universities across the world. Rather than trying to define "European" research (for example by corresponding author, first author, any author, etc.) the main narrative of this review has sought to evaluate recent literature.

Three significant European projects, active from 2010 to 2017, are briefly described below. The findings from these programs have generally been included in earlier reviews so are not covered in detail in the current narrative. Overall, this European effort made significant contribution to understanding the epidemiology of periodontitis and RA, understanding microbiological and immunological mechanisms (in particular the role of PADS/PPAD and citrullination), and developing therapeutics. The groups generated large numbers of publications, theses, conferences and workshops, provided myriad training opportunities and created long-term partnerships (including the three authors of this review).

GUMS AND JOINTS was an EU-FP7 Health Program (ID: 2614650) involving 10 international groups and two SME (small medium sized enterprises), from seven countries, coordinated by The University of Bergen, Norway, from 2010 to 2014. This group sought to investigate the possible causative link between periodontitis and RA. This consortium pioneered studies of *P. gingivalis PPAD*, and analyzed existing cohorts to further understanding of the epidemiology of the two diseases. The group generated over 77 publications, along with conferences and significant impact on media reach. (https://cordis.europa.eu/project/id/261460).

RAPID (Rheumatoid Arthritis and Periodontal Inflammatory Disease) was an EU Initial Training Network (ITN) of 14 partners in 7 European countries, coordinated by the University of Birmingham, UK (290246), active from 2012 to 2016. The ITN aimed to develop multidisciplinary, highly skilled researchers of the future while pioneering new discovery around the relationship between periodontitis and RA. Several of the fellows who trained in the program completed research doctorates. This project generated more than 87 peer-reviewed publications, as well as numerous conferences, workshops, and talks within Europe. The most recently published randomized controlled trial published looking at the effect of periodontal treatment on RA was the OPERA study (Outcomes of PEriodontal treatment on RA) which was funded by the UK National Institute of Health Research and RAPID. (https://cordis.europa.eu/project/id/290246/reporting/).

TRIGGER, from 2013 to 2017 "King of hearts, joints and lungs; periodontal pathogens as etiologic factor in RA, CVD and COPD and their impact on treatment strategies" (ID: 306029), coordinated by Universty of Bergen, involved partners in 9 countries. (https://cordis.europa.eu/project/id/306029).

The full reports from these programs are available in the results sections of the weblinks.

7 | CONCLUSION

This narrative has attempted to capture the recent advances in the study of the relationship between periodontitis and arthritis. There is a clear epidemiological link between these diseases. What

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is also clear is that understanding the link between two complex, multifactorial, remitting, and relapsing diseases is hugely challenging. Optimizing disease prevention and treatment—for both diseases—will offer immense health gains for individuals and substantial socio-economic benefits for individuals and their societies. This will require a variety of bold, pioneering, and innovatively designed studies.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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