

Is there a bidirectional association between rheumatoid arthritis and periodontitis? A systematic review and meta-analysis

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Abstract

Background: Several lines of evidence suggest a bi-directional association between Rheumatoid Arthritis (RA) and Periodontitis (PD). Our aim was to systematically appraise the evidence on the association between RA and PD in terms of clinical and laboratory outcomes.

Methods: An electronic search of several databases (PubMed, EMBASE, MEDLINE, LILACS, CINHL, Scopus, Web of Science, The Cochrane Library, OpenGrey and Google Scholar) was conducted up to March 2019 (PROSPERO CRD42018107817) by two independent reviewers. Observational studies included in the review were quality-appraised using the Newcastle-Ottawa Scale (NOS) tool. Random effects models were used for quantitative analyses.

Results: A total of 8 case-control studies were identified after the final search of 1491 titles. Following quality assessment, 2 studies were excluded due to the high risk of bias, while the remaining 6 were further analysed. Meta-analyses revealed no substantial effect of RA on the Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL) of patients with PD when compared to controls but high degree of study heterogeneity was found. To the contrary, PD was associated with substantially worse RA disease activity as assessed by an increase in the DAS28 score of 0.74 (0.25–1.24, 95%CI, $p < 0.001$).

Conclusion: There is consistent evidence suggesting that PD is associated with worse RA clinical activity as assessed by DAS28 scores whereas, RA patients do not have worsened PD clinical outcomes.

Key Words: rheumatoid arthritis, periodontitis, periodontal diseases, DAS28, periodontology, systematic review

Introduction

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease characterized by chronic joint inflammation leading to increased morbidity and mortality (1–3). If not adequately managed, RA causes progressive disability and systemic complications to patients leading to early death and it is associated with high cost for society (1,2,4,5).

RA prevalence is estimated between 0.5-1.0% cases in the general population (6). While its cause remains unclear; RA prognosis is heavily influenced by how early diagnosis is made and whether the response to treatment is adequate (1,5). Clinicians use a validated Disease Activity Score assessing 28 selected joints (DAS28) to document and monitor disease activity as well as to guide treatment decisions (7). RA patients frequently exhibit increased serum levels of rheumatoid factor and anti-citrullinated peptide/protein antibodies (ACPAs), which are associated with a more severe disease progression and poorer prognosis (8). The process of citrullination of arginine (the most common citrullinated peptide implicated in the pathogenesis of RA) is catalysed by the enzyme peptidylarginine-deiminase (PAD) and plays a critical role in initiating inflammatory responses in RA (9,10).

Periodontitis (PD) is a chronic non-communicable inflammatory disease characterized by progressive destruction of the periodontal apparatus (11). The disease is thought to be caused by an altered host immune response to a dysbiotic dental plaque biofilm (12–17). PD is one of the most prevalent diseases in the world and is undoubtedly an important public health problem (18). The destructive burden of PD has a significant social and economic impact on society as its worldwide prevalence remains worryingly high (19–22). Recent evidence suggests that PD is more prevalent in patients with other comorbidities including diabetes mellitus, cardiovascular diseases and some types of cancers or chronic inflammatory conditions (23–29).

Though triggered by different aetiological factors, RA and PD share common pathophysiological traits. They are both associated with chronic inflammation characterized by similar cytokines profile and leading to localised bone loss (1,5,30–32). Environmental triggers as well as genetic susceptibility are common features of both disorders (1,5,31,33,34).

Recently a promising research hypothesis emerged linking the pathogenesis of RA to PD based on an autoimmune response to citrullinated proteins produced by *Porphyromonas gingivalis* (Pg) PADs (PPADs) (35). *Pg* is considered as a keystone pathogen implicated in the dysbiotic changes of the dental plaque biofilm but it is not the only potential bacterial trigger linked to RA. Indeed other periodontal pathogens' antibodies responses have been reported in RA including *Prevotella intermedia*, *Prevotella melaninogenica*, *Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans* (Aa) (4,32,35,36).

Over the last two decades, cross-sectional evidence has suggested that PD is more prevalent in patients with RA (33,37–40). Longitudinal studies have reported that PD exposure is associated with increased risk of developing RA (41,42). In addition, a recent systematic review was also found evidence supporting a role of RA in the development/risk of PD (43).

Furthermore, PD was associated with first-degree relatives RA along with obesity and ACPAS, because pre-RA individuals presented significant inflammatory periodontal involvement, which could modulate RA severity and clinical presentation (44,45). Another investigation identified C-reactive protein, baseline periodontal status and RA activity as relevant factors for the progression of periodontitis lesions in interproximal sites of early RA individuals, though disease-modifying anti-rheumatic drugs (DMARDs) contributed to the slow-down of PD progression (46).

Lastly some evidence exists on the potential beneficial effect of periodontal treatment on RA disease activity and inflammatory burden (47,48). There is however inconclusive evidence on the potential role of RA on periodontal tissues (worsen or better gingival condition).

Our aim was therefore to comprehensively review all the evidence linking PD and RA (hypothesizing a bidirectional nature of the association) using a rigorous systematic protocol.

2. Materials and Methods

2.1. Protocol and registration

This systematic review protocol was approved by all authors and registered in the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO>, ID Number: [CRD42018097324](https://doi.org/10.1111/1471-2389.14712389)). This review was conducted according to the Cochrane Handbook of Systematic Reviews of Interventions (49) and reported according to the PRISMA guidelines for papers (50), Supplemental S1) and abstracts (51).

2.2. Eligibility criteria

We set a broad overall research question: “Is there a clinical bidirectional association between PD and RA?”, with the following specific questions:

- 1) “Do RA patients without PD have worse clinical periodontal parameters?”
- 2) “Does RA influence clinical manifestations of PD?”
- 3) “Does PD influence the clinical symptoms of RA?”.

The review followed these respective PI(E)CO statements:

- 1) Adult patients without PD (Patients – P); RA (Intervention/Exposure – I); No RA (Comparison – C); Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL) levels (Outcome – O)
- 2) Adult patients with PD (Patients – P); RA (Intervention/Exposure – I); No RA (Comparison – C); PPD and CAL levels (Outcome – O)
- 3) Adult patients with RA (Patients – P); PD (Intervention/Exposure – I); No PD (Comparison – C); DAS28, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), DAS28-CRP and/or DAS28-ESR (Outcome – O)

Cross-sectional, case-controls and longitudinal studies were included as well as randomized clinical trials (RCTs).

To address the first research question, studies reporting on the presence of PPD and CAL assessment in RA patients and healthy controls without a previous diagnosis of PD, were included. Studies

comparing these two groups of patients without diagnostic confirmation of absence of clinical and radiographic abnormalities in the control group were excluded.

For the second question, studies reporting the presence of PPD and CAL values of RA patients and healthy controls were included.

To address the third question, studies reporting RA outcome measures, such as DAS28, ESR, CRP, DAS28-ESR and DAS28-CRP in RA patients with and without a previous diagnosis of PD were included.

For the second and third questions, studies that have included RA patients and healthy controls without previously knowing their periodontal status following periodontal clinical assessment were excluded due to high risk of reporting bias.

2.3. Information sources search

For the selection of studies included in this systematic review, we searched PubMed, Google Scholar and CENTRAL (The Cochrane Central Register of Controlled Trials) for articles published until March 2019. We merged keywords and subject headings in accordance with the thesaurus of each database and applied exploded subject headings. Our PubMed search strategy was based on the following algorithm (MeSH terms): (chronic periodontitis OR periodontitis, chronic OR adult periodontitis OR periodontitis, adult OR periodontal disease OR alveolar bone loss OR attachment loss, periodontal OR periodontal pocket) and (Rheumatoid arthritis OR RA). In addition, grey literature was searched through the OpenGrey portal (<http://www.opengrey.eu>). The reference lists of included articles and relevant reviews were manually searched. We included both randomized clinical trials (RCTs) and non-RCTs (case-control, cohort studies and cross-sectional) that reported on (A) RA patients with and without associated periodontal diseases and/or (B) patients with periodontitis with and without a concomitant RA diagnosis. There were no restrictions on publication period. Only English language papers were considered. Authors were contacted when necessary for additional data or clarifications.

2.4. Study selection

Study selection was initially conducted by two authors (SBH and JB), who screened the titles and/or abstracts of the retrieved studies. The final selection of studies was independently performed by three authors (SBH, JB and VM) who reviewed the full text of the selected papers based on the inclusion criteria mentioned above. Any disagreements were resolved by discussion.

2.5. Data extraction process and data items

A predefined table was used to conduct data extraction. The extracted data included: the first author's name, publication year, country of origin of the research, study design, study population inclusion/exclusion criteria, number of cases and participants, gender, mean age in years, periodontal diagnostic criteria, and RA diagnosis based on validated classification criteria. Clinical periodontal measures included: PPD, plaque index (PI), missing teeth, bleeding on probing (BOP), and CAL. To assess RA outcome measures the following data were extracted: Disease Activity Score 28 (DAS28),

Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP). All data were independently extracted by three reviewers (SBH, VM and JB) who reached a consensus on all the aspects.

2.6. Risk of bias in individual studies

The Cochrane Collaboration's tool was used to assess the risk of bias of randomized clinical trials (52). Case-control and cohort studies were appraised using the Newcastle-Ottawa (NOS) Scale by two authors (SBH and SAZ). Due to the lack of established standard criteria, authors subjectively considered studies achieving 7 to 9 stars in the scale to be of high quality, studies with 5 to 6 stars of medium quality whilst studies with less than 5 stars were deemed of low methodological quality. Disagreements between reviewing authors over the risk of bias were resolved by discussion.

2.7. Summary Measures & Synthesis of results

Quantitative analyses were performed with studies of similar design. Estimates were calculated in R version 3.4.1 (R Studio Team 2018) using a DerSimonian-Laird random-effects model (53), as previously described (54). Forest plots were produced to visualise estimates and their 95% confidence intervals (CIs). All random-effects meta-analysis and forest plots were performed using 'meta' package (54). Quantity I^2 was measured to assess the degree of dispersion of effect sizes (ES) estimates and the overall homogeneity statistical significance was calculated through the χ^2 test (Higgins et al. 2003). All tests were two-tailed, with alpha set at 0.05 except for the homogeneity test whose significance level cut-off was set at 0.10 due to the low power of the χ^2 test in the context of a limited number of eligible studies. Publication bias analysis was planned to be performed if, at least, 10 or more studies were included (49). Overall ES estimates were reported with 95% confidence intervals (CI).

3. Results

3.1. Study selection

The search strategy identified 2159 potentially relevant publications. After the exclusion of duplicates (668), 1491 papers were analysed further. 68 articles out of 1491 fulfilled the inclusion criteria (1424 articles were excluded). Out of these 68 articles which were subjected to full paper review eligibility, 60 articles were excluded as they did not address the research questions (Supplemental S2), while 8 studies were included in the final analysis of the association between PD and RA and vice versa. After quality assessment, 2 studies were excluded from further analyses due to high risk of bias (55,56), resulting in a final number of 6 observational studies (Figure 1). These studies were characterised by heterogeneity regarding the association between the two diseases and various outcome measures reporting. All studies included information about clinical outcomes and biomarkers for PD and RA, as well as disease treatment and duration.

3.2 Study characteristics

The characteristics of the included studies are shown in Table 1. We identified 6 case-control studies from four different countries, across Europe and Asia. These studies were published between 2012 and 2019. The sample sizes ranged from 36 (57) to 566 participants (58) per study. After risk of bias assessment, a total of 866 participants were included in this review, comprising 271 RA patients with PD, 68 RA patients without PD, 337 patients with periodontitis and 190 healthy controls.

3.3. Assessment of Risk of bias within studies

NOS Scale bias assessment was used for the case-control studies included in this systematic review (Table 2). Two studies were excluded because they have not met the predefined minimum risk of bias level (55,56). The remaining studies which were rated as high quality studies presented adequate case definition for RA, clear definition of controls, and the same method of ascertainment for cases and controls for both RA and PD (n = 6, 100%) (57–62). Furthermore, most studies were characterised by representativeness of RA patients (n = 5, 83.3%), correct selection of controls (n = 4, 66.7%), appropriate comparability of cases and controls on the basis of the design or analysis and for additional factors (n = 5, 83.3%) and equal non-response rate (n = 5, 83.3%). Finally, two studies had unblinded periodontal diagnosis to case/control status (n = 2, 33.3%).

3.4. Synthesis of results

3.4.1. RA effects on periodontal tissues

Five studies which investigated the effect of RA on the periodontal tissues of patients without clinical diagnosis of PD were included. Only four clinical studies involved CAL assessments (59–61) and five studies specified PPD values (58–62). In total, 100 and 128 individuals were investigated for CAL and PPD levels, respectively. Although not statistically significant, the overall results suggested that RA is

associated with increased CAL and PPD levels in patients with no previous diagnosis of PD (Supplementary S3 and S4). A high degree of study heterogeneity was observed in both analyses.

3.4.2. RA effect on PD

Six studies including CAL and PPD measurements were selected to investigate the effect of RA on PD clinical characteristics (57–62). Five studies had CAL measures (57–61), while all six had PPD assessments. No statistically significant association between CAL and PPD levels in patients with and without RA were found, and there was a high heterogeneity among the studies included (Figure 2 and Figure 3).

3.4.3. PD effect on RA

Three studies only were included in this analysis (59,60,62), comprising 116 RA patients (58 with and 58 without PD) which had their DAS28 scores calculated. The analysis confirmed an association between PD and increased RA disease activity, with an average of 0.74 DAS28 score points greater in PD compared to non-PD patients ($p < 0.001$) (MD [95% CI]: 0.74 [0.25–1.24]) (Figure 4). The study heterogeneity was low, revealing a high consistency among the included studies. No other quantitative analysis on other RA outcome measures, such as DAS28-CRP, ESR or CRP was performed due to the lack of data reported.

4. Discussion

4.1. Summary of Main Findings and Quality of the Evidence

This review concluded that RA has no significant effect on periodontal tissues. Our results show that diagnosis of RA might not worsen clinical periodontal parameters (PPD and CAL) in patients with PD versus controls with PD only. On the other hand, PD diagnosis was associated with worse RA disease activity.

These results are in agreement with previous studies reporting that RA patients with PD presented with more missing teeth and higher levels of CAL, ESR, CRP and moderate-high RA activity (63,64). Moreover, we should consider the timing of RA diagnosis, since these results were obtained from studies on established RA cases, and it has already shown that pre-RA cases present higher periodontal inflammation involvement than established RA cases (44).

The mechanisms by which PD influences RA remain to be clarified, although it is proven that this can be partly mediated by the oral microbiota, for instance *Pg* and *Aa* (2,5), since RA patients express higher antibody response to *Pg* (65) and *Aa* (32,36) and can trigger the autoimmunity in RA.

Lately, evidence-based reviews have showed moderate evidence that RA patients have increased risk of developing PD (43,66) and more missing teeth and higher levels of CAL (63) compared to general population. In addition, positive associations between various RA biomarkers and PD, such as

Interleukin-21, Resistin and Adipokines have been established (67–69). Also, it has been confirmed that nonsurgical periodontal treatment has beneficial effects on RA periodontal patients by improving clinical and inflammatory parameters (47,48).

Although there is lack of data regarding the impact of RA treatment on the PD risk and rate of progression, the most used biologic treatment in RA targeting TNF- α has been shown to reduce the local production of inflammatory cytokines and periodontal inflammation in RA patients with PD (46,64,70). It is therefore possible to speculate that conventional and biologic DMARDs, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticoids which are used for RA treatment could potentially have an indirect beneficial effect on controlling PD inflammation at the gingival level (71,72). However, the results of these studies are contradictory since RA drugs had significant (71) and non-significant adjunctive effects with PD treatment (72). Only two studies included in this systematic review have described the type of RA medication used (57,61); however, they have not explored the impact of medication on PD related inflammation as this was beyond the scope of our systematic analysis. Interestingly, a recent study has shown that the presence of periodontal inflammation in patients with RA was associated with poorer response to anti TNF- α therapy (73).

Therefore, further well-designed longitudinal trials are mandatory to allow definitive conclusions regarding RA-PD bilateral relationship and potential therapies with shared benefit. In particular, is necessary to include stratified patients based on background RA medication, various degrees of periodontal inflammation, larger sample sizes and longer follow-ups.

The nonsurgical periodontal treatment (NSPT) effect in RA patients was not an outcome of this review since recent literature found evidence that NSPT improved RA associated parameters, such as DAS28, ESR and inflammatory markers levels (47,48). Nevertheless, these studies had very small sample sizes, hence precluding definitive conclusions.

Overall, the results of this systematic review do not support a bidirectional link between RA and PD but rather point towards a negative impact of PD to RA disease activity. However, we cannot definitively exclude a bidirectional association between both diseases because the studies included in our meta-analysis were associated with high heterogeneity and methodologic variability.

4.2. Potential Limitations and Strengths

There are some limitations we wish to highlight to the reader. Firstly, we identified a high level of heterogeneity between studies which precluded definitive conclusions on the effect of RA on healthy and unhealthy periodontium. This could be due to the large variability of the periodontal diagnostic criteria used in the included studies. Indeed, while three studies (57,58,61) used recognized at the time case definitions the remaining three used other criteria. Studies included in our meta-analyses assessed predominantly female RA patients, as this reflects the natural prevalence of the disease which is two-to-threefold more likely to affect women than men (74). Male gender was associated however with greater prevalence of destructive periodontal diseases (75) and, eventually, may lead to the worsening of RA disease activity and increased morbidity. In the future, gender-related risk factor should be

considered in RA periodontal patients. In addition, we did not investigate the efficacy of RA medication on PD severity or the impact of PD severity on response to RA treatment. Throughout the review process, several articles were excluded because they compared RA patients with healthy controls without a previous periodontal diagnosis. Future investigations should define the PD status of RA and healthy participants.

This is the first systematic review that reported pooled estimates for clinical parameters linking RA and PD, supported by a thorough literature search, meticulous a priori defined protocol, and following recommended guidelines for data reporting. Also, all studies included in our analyses were carried out in hospital settings and, considering the relative low prevalence of RA in general population and the fact that RA patients are followed up in hospital rheumatology departments (2), we can conclude that our results allow comprehensive conclusions. Importantly, the apparent effect of PD on RA activity assessed by a validated outcome measure (DAS28 score) is remarkable. The pooled estimate of DAS28 score was derived from three studies which had very low heterogeneity (59,60,62), despite using different periodontal diagnostic criteria.

5. Conclusion

This systematic review concluded that whilst there is moderate evidence supporting that PD is associated with worse RA disease activity, to the contrary (RA worsening PD status) could not be confirmed based on the available evidence.

Periodontal tissues/PD status of patients with RA should be monitored on a regular basis. Rheumatologists and dental professionals should collaborate to aim at improving the clinical outcomes of their patients. In the future, more efforts are needed to comprehensively assess the association between RA and PD, by taking into consideration additional RA clinical characteristics, and to clarify the effect of RA on periodontitis in studies with better methodology and broader clinical and laboratory biomarkers.

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Competing interests

We declare no competing interests.

Contributors

Syed Basit Hussain screened the titles and abstracts, assessed studies for study quality and inclusion, extracted data, drafted the manuscript and gave final approval.

João Botelho screened the titles and abstracts, assessed studies for study quality and inclusion, extracted data, performed statistical analysis, drafted the manuscript and gave final approval.

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Marco Orlandi drafted the manuscript and gave final approval.

Francesco D'Aiuto drafted the manuscript and gave final approval.

Abbreviation list

PD - Periodontitis

RA - Rheumatoid Arthritis

PPD – Probing Pocket Depth

CAL - Clinical Attachment Loss

BOP - Bleeding on Probing

PI - Plaque Index

CRP - C - reactive protein

DAS28 - Disease Activity Score [HS3]

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Figure and Table legends:

Figure 1. PRISMA flow-chart representing the results of the workflow to identify eligible studies.

Figure 2: Forest plot of studies evaluating CAL levels in PD patients with and without RA (p-value = 0.0685). Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. The size of the squares is proportionate to the study sample size, continuous horizontal lines and diamonds width represents 95% confidence interval. Diamond and the vertical dotted line represent the overall pooled estimate.

Figure 3: Forest plot of studies evaluating PPD levels in PD patients with and without RA (p-value = 0.1064). Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval. Diamond and the vertical dotted line represent the overall pooled estimate.

Figure 4: Forest plot of mean difference in DAS28 scores in RA patients with and without PD (p-value = 0.0035). Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval. Diamond and the vertical dotted line represent the overall pooled estimate.

Table 1: Details of the included studies

Table 2: Case-control studies bias assessment using the Newcastle-Ottawa Scale (NOS).