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Review article

Influence of periodontal treatment on rheumatoid arthritis: a systematic review and meta-analysis☆

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ABSTRACT

Objective: To evaluate the influence of periodontal treatment on rheumatoid arthritis activity.
Methods: MEDLINE/PUBMED, The Cochrane Library, Clinical Trials, SciELO and LILACS were searched for studies published until December 2014. Included articles were: prospective studies; including patients older than 18 years, diagnosed with periodontitis and rheumatoid arthritis submitted to non-surgical periodontal treatment; with a control group receiving no periodontal treatment; with outcomes including at least one marker of rheumatoid arthritis activity. Methodological quality of the studies was assessed using PEDro scale. Quantitative data were pooled in statistical meta-analysis using Review Manager 5.
Results: Four articles were included. Non-surgical periodontal treatment was associated with a significant reduction of DAS28 (OR: −1.18; 95% CI: −1.43, −0.93; $p < 0.00001$). Erythrocyte sedimentation rate, C-reactive protein, patient's assessment of rheumatoid activity using visual analogical scale, tender and swollen joint counts showed a trend toward reduction (not statistically significant).

☆ Study conducted at Universidade Federal de Minas Gerais, Faculdade de Odontologia e Faculdade de Medicina, Departamento do Aparelho Locomotor, Belo Horizonte, MG, Brazil.

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Conclusions: The reduction of DAS 28 in patients with rheumatoid arthritis after periodontal treatment suggests that the improvement of periodontal condition is beneficial to these patients. Further randomized controlled clinical trials are necessary to confirm this finding.

Influência do tratamento periodontal na artrite reumatoide: revisão sistemática e metanálise

Palavras-chave:
Interações doença periodontal-sistêmica
Periodontite
Artrite reumatoide
Metanálise

R E S U M O

Objetivo: Avaliar a influência do tratamento periodontal sobre a atividade da doença na artrite reumatoide.
Métodos: Pesquisaram-se as bases de dados MEDLINE/PubMed, The Cochrane Library, Clinical Trials, SciELO e LILACS em busca de estudos publicados até dezembro de 2014. Incluíram-se estudos prospectivos que avaliaram pacientes com mais de 18 anos diagnosticados com periodontite e artrite reumatoide submetidos a tratamento periodontal não cirúrgico; os estudos deveriam ter também um grupo controle não submetido a tratamento periodontal. Os resultados dos estudos deveriam contar com pelo menos um marcador da atividade da doença na artrite reumatoide. A qualidade metodológica dos estudos foi avaliada utilizando a escala PEDro. Reuniram-se os dados quantitativos em uma metanálise estatística usando o Review Manager 5.
Resultados: Incluíram-se quatro artigos. O tratamento periodontal não cirúrgico esteve associado a uma redução significativa no DAS-28 (OR: - 1,18; IC 95%: -1,43 a -0,93; p < 0,00001). A velocidade de hemossedimentação, a proteína C-reativa, a avaliação da atividade reumatoide pela escala visual analógica e as contagens de articulações sensíveis e inchadas apresentaram uma tendência de redução (redução não estatisticamente significativa).
Conclusões: A redução no DAS-28 em pacientes com artrite reumatoide após tratamento periodontal sugere que a melhora na condição periodontal é benéfica a estes pacientes. São necessários mais ensaios clínicos randomizados controlados para confirmar este achado.

Introduction

Previous clinical and experimental studies have suggested an association between periodontal disease (PD) and rheumatoid arthritis (RA).[1–9] This association is based on common environmental, inflammatory and genetic pathways shared by RA and PD that include smoking, HLA-DR antigens, inflammatory pattern, tissue destruction pathways. Furthermore, the possible role of periodontopathic bacteria *Porphyromonas gingivalis*, that produces a peptidylarginine deiminase capable of citrullination of human proteins, was demonstrated in RA. A possible role for PD in hampering anti-tumor necrosis factor treatment response in RA has also been suggested.[10–21]

A series of intervention trials to assess the effect of PD treatment on RA have been performed. These trials examined different RA activity parameters, such as Disease Activity Score (DAS 28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient's assessment of rheumatoid activity using visual analogical scale (VAS), tender (TJC) and swollen (SJC) joint counts, cytokines (Interleukin (IL) 1-β, tumor necrosis factor (TNF)-α), antibodies (rheumatoid factor, anti-cyclic citrullinated protein antibodies, antibodies anti-*P. gingivalis*) and/or measures of quality of life. The results were quite controversial, with positive, negative or neutral findings regarding the effect of PD treatment on RA outcomes.[22–31] Therefore, the impact of PD treatment on RA activity remains to be determined.

The present systematic review and meta-analysis aimed to investigate the effects of PD non-surgical treatment in inflammatory parameters and clinical measures of RA activity in adult patients. This review was conducted according to the QUOROM statement for improving the quality of reports of meta-analyses of randomized controlled trials.[32]

Methods

Search strategy

The bibliographical databases MEDLINE/PUBMED, The Cochrane Library, Clinical Trials, SciELO and LILACS were searched for all published studies, from the beginning of the database, until December 2014, without language restrictions.

The search strategy for MEDLINE/PUBMED, The Cochrane Library and Clinical Trials databases was: ((Chronic Periodontitides) OR (Periodontitides, Chronic) OR (Periodontitis, Chronic) OR (Adult Periodontitis) OR (Adult Periodontitides) OR (Periodontitides, Adult) OR (Periodontitis, Adult)) AND ((Rheumatoid arthritis) OR (Arthritis, rheumatoid)).

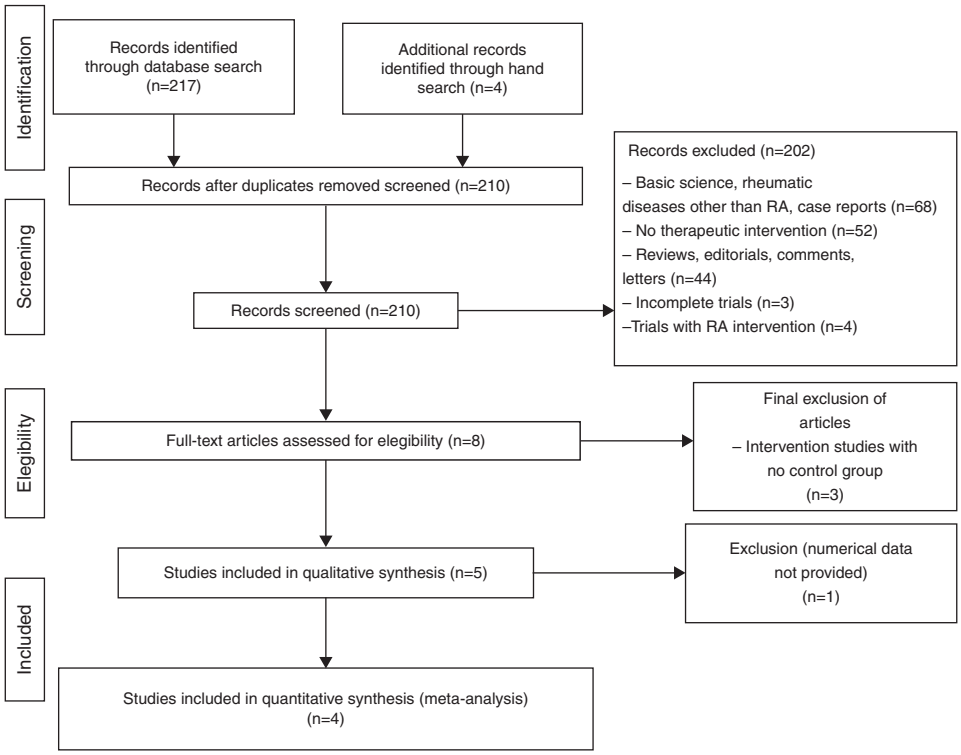

Fig. 1 – Flow diagram for studies retrieved through the searching and selection process. RA, rheumatoid arthritis.

The search strategy for LILACS and SciELO was: ((Chronic Periodontitis) OR (Periodontitis Crónica) OR (Periodontite Crônica)) AND ((Arthritis, Rheumatoid) OR (Artritis Reumatoide) OR (Artrite Reumatoide)).

The search was independently performed by two reviewers (DCC, JDC). Disagreements were solved by discussion. The Kappa between the two reviewers that independently performed the search was 0.764.

In addition to the online search, a hand search of the bibliographies of reviews, comments, letters, case reports, editorials and other papers addressing the relationship between RA and PD was conducted.

The flowchart of the search and selection process is shown in Fig. 1.

Methodological quality of the included studies was assessed using the PEDro scale[33] by two independent reviewers (DCC and JDC) and disagreements were solved through discussion.

Selection criteria

Inclusion criteria

Intervention studies; inclusion of adult patients (older than 18 years) diagnosed with both PD and RA; intervention comprised of non-surgical periodontal treatment; presence of a control group receiving no periodontal treatment for the length of the study; outcome for RA that included at least one of the following: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score (DAS28), tender (TJC) and swollen (SJC) joint counts and patient's assessment of RA activity using a 100 mm-visual analogical scale (VAS); follow-up of at least six 6 weeks.

Exclusion criteria

Case reports, review articles, editorials, comments, letters to the editor, experimental studies/basic science, articles on RA therapeutic interventions and reports about patients with rheumatic diseases other than RA were excluded.

Data collection

Data abstraction was performed in duplicate, by two independent reviewers (DCC, JDC). Attempts were made to contact original authors for missing data, but only the authors of one article provided us the information required (TJC and SJC mean and standard deviation in periodontal disease for treated and non-treated groups at baseline and after follow-up).[29]

Methodological quality assessment

The quality of the studies was peer-reviewed (DCC, JDC) by using a modified version of the PEDro scale for clinical trials.[33] Disagreements were resolved by consensus (Table 1).

Quantitative data synthesis

Quantitative data were pooled in statistical meta-analysis using Review Manager (RevMan) 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).[34]

Table 1 – Estimates of reliability from included studies for each of the 11 items of the PEDro scale.[32]

PEDro scale item	Al-Katma et al., 2007[25]	Pinho et al., 2009[26]	Ortiz et al., 2009[27]	Okada et al., 2013[29]
Eligibility criteria specified	1	1	1	1
Random allocation	1	0	1	1
Concealed allocation	0	0	0	0
Groups similar at baseline	1	1	1	1
Subject blinding	0	0	0	0
Therapist blinding	0	0	0	0
Assessor blinding	1	0	0	0
Less than 15% dropouts	0	1	1	1
Intention-to-treat analysis	1	1	1	1
Between-group statistical comparisons	1	0	1	1
Point measures and variability data	1	1	1	1
Total	7	5	7	7

To assess overall efficacy from all the studies included in the meta-analysis, we calculated mean difference using both fixed-effects and random-effects models, reporting heterogeneity and overall *p*-values. When $I^2 > 50\%$ indicated high heterogeneity between studies, the random-effect model was adopted, and when $I^2 < 50\%$ the fixed effect model was used. Studies that did not report standard deviation were excluded from the meta-analysis. The effect sizes for each study and overall pooled effect sizes were calculated with a 95% confidence interval. Statistical significance was declared if the *p* value was less than 0.05.

Results

Four articles[25–27,29] were included in the meta-analysis (Table 2).

They were single-center interventional controlled studies.

The criteria used for the diagnosis of periodontitis varied. Al-Katma et al.[25] included patients with generalized mild-to-moderate chronic periodontitis according to Armitage[35]; Pinho et al.[26] defined PD according to Machtei et al.[36]: the presence of at least two teeth with CAL ≥ 6 mm and at least one tooth with probing depth ≥ 5 mm. Ortiz et al.[27] included patients with generalized severe chronic periodontitis according to Löe and Sillness,[37] while Okada et al.[29] defined periodontitis as the presence of at least one site with CAL ≥ 4 mm.

Studies were conducted from 2007 to 2013 in different countries: Brazil,[26] Japan[29] and USA[25,27] with participants from different ethnic and cultural backgrounds.

Subjects of these studies presented both RA and PD, and were divided in two groups: one submitted to non-surgical periodontal treatment consisting of scaling/root planning and plaque removal and hygiene instructions (treatment group) and one other group that was only followed up during the period of the study (control group), without periodontal treatment or oral hygiene instruction.

The follow-up period was 6-weeks,[25] 8-weeks[27,29] or six months.[26]

PEDro scores of the studies included in this meta-analysis are shown in Table 1. Quality assessment varied from 7 to 5 points.

Analysis of the pooled data for the outcomes evaluated on this meta-analysis is shown in Table 3.

DAS28 is a composite disease activity score that has been largely used to measure RA activity.[38] A reduction of DAS 28 means that RA has improved. The pooled data of the two studies included in the meta-analysis suggests a discrete, but significant reduction in DAS 28 score following non-surgical periodontal treatment (OR: −1.18; 95% CI: −1.43, −0.93; $p < 0.00001$) (Table 3; Fig. 2).[25,27]

There was no evidence for an effect of periodontal therapy in the blood levels of CRP (OR: −0.16; 95% CI: −0.64,0.33; $p = 0.53$) and ESR (OR: −6.68; 95% CI: −28.57, 15.21; $p = 0.55$); patient's global VAS (OR: −1.56; 95% CI: −8.14, 5.02; $p = 0.84$); TJC (OR: −2.97; 95% CI: −8.76, 2.82; $p = 0.31$) or SJC (OR: −2.53; 95% CI: −5.89, 0.83, $p = 0.14$) (Table 3).[25,26,29]

Discussion

RA and PD share similar pathogenic mechanisms, i.e. inflammatory cells and pro-inflammatory cytokines that drive chronic bone erosion in RA and chronic gum destruction in PD are similar. A role for PD on initiation and maintenance of RA autoimmune inflammatory responses, even in RA patients receiving conventional synthetic disease modifying anti-rheumatic drugs or biologics (specifically TNF inhibitors), has been suggested.[6,10,12–15,21]

The control of local periodontal infection and inflammation by non-surgical periodontal therapy is expected to attenuate systemic inflammatory response which in turn would contribute to improve RA activity. Accordingly, the current meta-analysis shows that, after non-surgical periodontal treatment, there is reduction of DAS28 in RA patients with PD, corroborating the impact of periodontal condition on RA.

In contrast, evaluation of the other variables failed to demonstrate the effect of PD treatment in RA activity. A possible explanation is regarding the complex nature of RA, which disease activity is better evaluated by a composite score like DAS28 instead of individual analysis of inflammatory and clinical markers.

Corroborating these findings, recently, Kaur et al.[22] published a systematic review on the association between PD and RA. The periodontal parameter clinical attachment level (CAL) was greater in patients with RA than in subjects without RA, indicating that PD may be more severe in RA. RA patients also had increased tooth loss when compared to non-RA patients. In line with these findings, some biochemical

Table 2 – Articles included in the meta-analysis.

Article	Study design	Subjects	Losses	Follow-up time	RA outcomes	Results
Al-Katma et al., 2007[25]	IS, C, R, U B[a]	All: RA + P N = 38 Patients: n = 19 Controls: n = 19	Controls: n = 7[b] Patients: n = 2[c]	8 Wk	TJC SJC DAS 28 Global VAS ESR	Improvement of DAS 28 in 13/17 patients (76.4%) and 2/12 controls (16.7%) Improvement of VAS in 10/17 patients (58.8%) and 2/12 controls (16.7%) Greater reduction of DAS 28 and ESR in patients than controls
Ortiz et al., 2009[27]	I, C, U RND BND	All: RA + P N = 20 Patients: n = 10 Controls: n = 10	No losses	6 Wk	TJC SJC Global VAS ESR DAS 28	Improvement of DAS 28, decrease in number of SJC, and global VAS in patients, when compared to controls
Pinho et al., 2009[26]	I, C, U RND BND	All: RA + P N = 30 Patients: n = 15 Controls: n = 15	No losses	6 Mo	ESR CRP DAS 28	No significant differences of ESR and CRP
Okada et al., 2013[29]	I, C, U RND BND	All: RA + P N = 55 Patients: n = 26 Controls: n = 29	No losses	8 Wk	DAS28-CRP CRP TJC SJC Global VAS	Decrease in DAS28-CRP No significant differences for TJC, SJC, VAS, CRP, RF

RA, rheumatoid arthritis; P, periodontitis; DAS 28, disease activity score; DAS28-CRP, disease activity score using C-reactive protein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TJC, tender joint count; SJC, swollen joint count; VAS, visual analogical scale; IS, intervention study; C, controlled; R, randomized; U, unicentric; RND, randomization not described; B, blinded; BND, blinding not described; Wk, weeks; Mo, months.

[a] Rheumatologist blinded to periodontal treatment. Patients: those submitted to non-surgical periodontal treatment. Controls: Those not submitted to periodontal treatment.

[b] Four: absence to evaluations; three: changes in medications for RA.

[c] One: absence to evaluations; one: inability to maintain good level of oral hygiene.

Table 3 – Meta-analysis for outcomes evaluated.

Outcome	OR [95% CI]	I^2; p-value	Number of patients (periodontal treatment/no treatment)	Number of studies (References)
DAS 28	−1.18 [−1.43, −0.93]	0%; <0.00001	27/22	2 (Al-Katma et al.[25]; Ortiz et al.[27])
CRP	−0.16 [−0.64, 0.33]	77%; 0.53	41/44	2 (Okada et al.[29]; Pinho et al.[26])
ESR	−6.68 [−28.57, 15.21]	97%; 0.55	32/27	2 (Al-Katma et al.[25]; Pinho et al.[26])
TJC	−2.97 [−8.76, 2.82]	97%; 0.31	43/41	2 (Al-Katma et al.[25]; Okada et al.[29])
SJC	−2.53 [−5.89, 0.83]	96%; 0.14	43/41	2 (Al-Katma et al.[25]; Okada et al.[29])
Global VAS	−1.56 [−8.14, 5.02]	84%; 0.84	43/41	2 (Al-Katma et al.[25]; Okada et al.[29])

DAS 28, disease activity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TJC, tender joint count; SJC, swollen joint count; VAS, visual analogical scale; OR, odds ratio; CI, confidence interval.

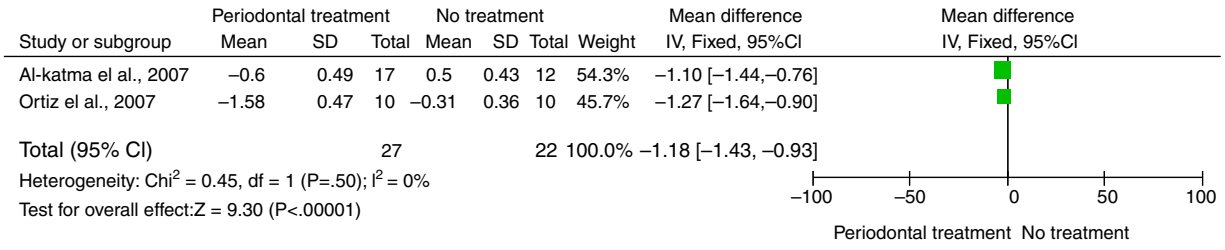

Fig. 2 – Forest plot for Disease Activity Score using a 28 joint count (DAS28).

markers were increased in RA patients with PD (CRP, IL-1β and serum antibodies to *P. gingivalis*), in comparison with patients without PD. Although, no differences in other parameters (ESR, anti-cyclic citrullinated protein antibodies, rheumatoid factor, TNF-α) were observed comparing both groups, a trend toward a decrease in ESR in RA patients after PD treatment was reported.[22]

In another systematic review with meta-analysis, Kaur et al.[23] have also evaluated the influence of PD treatment on RA activity. In their pooled data meta-analysis, DAS28 was not influenced by PD non-surgical therapy. Kaur et al.[23] included, in the pooled meta-analysis of DAS28, the data from the study of Okada et al.,[29] that analyzed DAS28-CRP, another RA activity composite score, slightly different from DAS28 (instead of ESR, it includes CRP), that presents good correlation, but underestimates disease activity when compared to DAS28.[39] For this reason, the results of Kaur et al.[23] might have biased the possible influence of PD treatment on DAS28 and in the present meta-analysis, the data on DAS28-CRP were excluded from the analysis. They have also found a significant reduction of ESR in PD treated patients, what might be explained through the inclusion of the data from Ortiz et al.,[27] since Kaur et al.[23] transformed inter-quartile ranges or ranges in standardized mean difference, assuming a normal distribution curve for this study, increasing the number of patients and improving the detection of small differences.

The four studies eligible for this meta-analysis evaluated a small number of subjects. Randomization was well described in one,[25] cited in two[27,29] and not mentioned in one.[26] Regarding PD treatment, blinding of patients and therapists, is not possible. To overcome this limitation, one alternative is blinding the evaluator. This was mentioned in only one study.[25] One study[25] had a high number of dropouts. Participants had PD diagnosed according to different classification systems. The follow-up period ranged from 6-weeks to 8-weeks in three studies,[25,27,29] which is a relatively short time to assess the impact of therapeutic strategies in RA activity. All studies reported an objective improvement in periodontal clinical parameters, suggesting that the follow-up period was sufficient to observe reduction in infection and inflammation associated with PD. The heterogeneity among studies was high for most outcomes evaluated. These features must be weighted as possible limitations of the present meta-analysis.

The current meta-analysis suggests that non-surgical periodontal treatment might have a beneficial effect on RA activity as evaluated by DAS28. Further randomized controlled clinical trials including a larger number of patients, with appropriate blinding and longer periods of follow-up are necessary to confirm this finding.

Conflicts of interest

The authors declare no conflicts of interest.

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