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REVIEW ARTICLE

Does non-surgical periodontal treatment influence on rheumatoid arthritis? A systematic review and meta-analysis

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KEYWORDS

Rheumatoid arthritis;
Periodontal diseases;
Dental scaling;
Systematic review

Abstract *Objective:* The objective of this systematic review was to evaluate the efficacy of non-surgical periodontal therapy on rheumatoid arthritis activity.

Material and methods: Articles published until April 2019 were electronically searched and screened using PubMed / MEDLINE, Scopus, and Cochrane databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). This study was recorded in the international PROSPERO database (CRD42019132205). The PICO question (population, intervention, comparison, results) was: in adult patients with rheumatoid arthritis and periodontitis (P), does non-surgical periodontal treatment (I), as compared to no treatment (C), provides better outcomes in rheumatoid arthritis activity (O).

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Results: After searching the databases, seven articles were selected for qualitative and five for quantitative analysis. The total number of participants included was 292, with an average age of 50.5 years. All patients had rheumatoid arthritis and periodontal disease. Non-surgical periodontal treatment significantly reduced Disease Activity Score 28 ($P = 0.004$; $I^2 = 92\%$) and erythrocyte sedimentation rate ($P = 0.01$; $I^2 = 78\%$), but with no significant effect on C-reactive protein ($P = 0.34$; $I^2 = 92\%$).

Conclusions: It can be concluded that non-surgical periodontal treatment can benefit patients with rheumatoid arthritis.

Contents

1. Introduction

Periodontitis is a bacterial infection-induced chronic inflammatory disease that may initiate and maintain high systemic levels of various cytokines (Tonetti et al., 2013) and may be a risk factor for the development of systemic disorders (Silvestre et al., 2016) such as diabetes, atherosclerosis, myocardial infarction, stroke, and rheumatoid arthritis (RA) (Pinho et al., 2009).

RA is of particular interest as it is a chronic inflammatory disease with many inflammatory mediators similar to periodontitis (Zhao et al., 2018) such as the presence of interleukin-1b (IL-1b), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Yang et al., 2018), in addition to both diseases acting on connective tissue degradation (Al-Katma et al., 2007). Thus, reducing the systemic burden of inflammation through non-surgical periodontal therapy can have beneficial effects on RA activity (Kaushal et al., 2019).

According to the recommendations of the American College of Rheumatology (Anderson et al., 2012), the Disease Activity Score 28 (DAS28), with erythrocyte sedimentation rate (ESR) or C-Reactive Protein (CRP), accurately reflects the activity of RA, is a sensitive change test, and is accepted by most rheumatologists. In the literature, studies such as Bıyıkoğlu et al., 2013, report significant declines in rheumatoid arthritis activity indices, including DAS28, after non-surgical periodontal therapy. However, the results lack consensus because results of other studies using this index were not reported to be influenced by non-surgical periodontal therapy (Pinho et al., 2009; Kaur et al., 2014). Thus, this systematic literature review aims to evaluate the effect of non-surgical periodontal therapy on RA activity. The null hypothesis of this study was that there is no difference in RA activity after non-surgical periodontal therapy.

Although there is a systematic review on this topic (Calderaro et al.,2017), the particular analysis included literature only until 2015, with the most recent study published in 2013 (Okada et al., 2013). Due to the publication of new studies, it is possible to evaluate a larger number of patients, because further analysis are needed to establish the potential benefit of non-surgical periodontal therapy in RA activity (Erciyas et al.,2013).

The aim of this systematic review was to evaluate the efficacy of non-surgical periodontal therapy on rheumatoid arthritis activity.

2. Materials and methods

2.1. Protocol registration

This systematic review followed the criteria established by the - PRISMA and was recorded in the international database of systematic reviews PROSPERO CRD4201913220 5.

2.2. Eligibility criteria

The PICO question (population, intervention, comparison, results) was: in adult patients with rheumatoid arthritis and periodontitis (P), does non-surgical periodontal treatment (I), as compared to no treatment (C), provides better outcomes in rheumatoid arthritis activity (O). Finally, the main outcome was to evaluate the activity indices of rheumatoid arthritis (DAS28) with inflammatory markers (ESR and CRP) as secondary outcomes.

The defined inclusion criteria for the selection of articles were: randomized controlled trials; prospective studies with at least 10 participants who were diagnosed with RA and periodontal disease; at least four weeks of follow-up; studies that evaluated the activity of RA after scaling and root planing using DAS28 and / or the inflammatory measures ESR and CRP.

Exclusion criteria were: studies with patients under 18 years; systemic antibiotic therapy prescribed to patients 3 months before the study or during non-surgical periodontal therapy; studies with smoking or diabetic patients; as well as studies with patients who, during the follow-up period, changed their rheumatoid arthritis medication.

2.3. Search strategy

Two investigators (C.D.D.R.D.R and J.M.L.G) independently performed electronic searches in the PubMed / MEDLINE, Scopus, and Cochrane databases for articles published until April 2019, according to the eligibility criteria.

The descriptors used for the search were: "((("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields]AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields]AND "arthritis"[All Fields]))AND ("periodontitis "[MeSH Terms] OR "periodontitis"[All Fields])) OR (("arthritis, rheumatoid" [MeSH Terms] OR ("arthritis"[All Fields]AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields]AND "arthritis"[All Fields])) AND (non-surgical [All Fields]AND periodontal [All Fields]AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics" [All Fields]))". In addition, a manual search of the most impactful journals of periodontics was performed: Journal of Periodontology, Journal of Dental Research, Journal of Clinical Periodontology, Journal of Periodontal Research, Journal of Dentistry, Journal of the American Dental Association, Periodontology 2000, and Clinical Oral Investigations.

2.4. Data Analysis

One author (C.D.D.R.D.R.) was responsible for collecting relevant information from the included articles, and a second author (C.A.A.L.) reviewed all the collected information. The qualitative data collected were: author of study and year, mean age of the study participants, the comparative groups, RA evaluation methods, number of patients, range of follow-up reported in weeks, and conclusion of the studies. The quantitative data collected was shown as mean and standard deviation (Mean ± SD) of the outcomes: DAS28, ESR, CRP.

2.5. Summary measurements

The *meta*-analysis was based on an inverse variance (IV) method. The primary outcome DAS28, and the secondary outcomes ESR and CRP were considered continuous outcomes and were evaluated using the mean difference (MD) quantified by IV with a 95% confidence interval (CI). The MD values were considered to be significant when $P < 0.05$. For statistically significant ($P < 0.10$) heterogeneity, a random-effects model was used to assess the significance of the treatment effects. When no statistically significant heterogeneity was found, an analysis was performed using a fixed-effects model. The software Reviewer Manager 5 (Cochrane Group) was used for the *meta*-analysis.

2.6. Risk of bias and evaluation of study quality

Two authors (L.M., J.P.J.O.L.) performed risk of bias analysis on the included RCTs using the Cochrane risk of bias tool; the tool verifies selection, performance, attrition, reporting, and other biases. The Newcastle-Ottawa scale (NOS) was used for non-randomized studies. The NOS verifies three elements: selection, comparability, and outcome for cohort studies. The scale classifies studies with a maximum of 9 stars; > 6 stars indicates a low risk of bias, and scores of ≤5 stars indicate a high risk of bias.

2.7. Additional analysis

The inter-examiner test (Kappa) was used as an additional analysis to assess the researchers' agreement on database searches (PubMed / MEDLINE, Scopus, Cochrane). All disagreements were reviewed and resolved by a third reviewer (E.P.P.).

3. Results

3.1. Selection of studies

Searches in the previously selected databases totaled 1510 articles, 628 in Pubmed / Medline, 816 in Scopus, 65 in Cochrane Library, and 1 in manual search. After duplicates removal, 1126 remained and, from those, 1116 articles were excluded after title and abstract reading step because they did not meet the eligibility criteria. Ten studies were eligible for full reading, of which 3 were excluded for the reasons: two studies contained smoking patients (Bıyıkoğlu et al., 2013; Cosgarea et al., 2019) and only one abstract was published from the 2018 American College of Rheumatology Annual Meeting (Mariette et al., 2018). The details of the search strategy are illustrated in Fig. 1.

The kappa test was applied to evaluate the agreement between examiners in the initial search, indicating high levels of agreement: 0.92 for PubMed / MEDLINE, 0.86 for Scopus, and 1.00 for Cochrane Library.

3.2. Characteristics of the selected studies

Detailed data from the selected studies are listed in Table 1. Of the seven selected studies, five were randomized controlled trials (Al-Katma et al., 2007; Ortiz et al., 2009; Pinho et al.,2009; Okada et al., 2013; Khare et al., 2016) and two were prospective studies (Erciyas et al., 2013; Zhao et al.,2018). The total number of participants included was 292, with a mean age of 50.5 years, all of whom were diagnosed with RA and periodontal disease. The follow-up period ranged from 1 to 6 months.

In five studies (Al-Katma et al., 2007; Pinho et al.,2009; Erciyas et al., 2013; Okada et al., 2013; Zhao et al.,2018), the diagnosis of rheumatoid arthritis followed the 1987 revised classification criteria of the American Rheumatism Association (Arnet et al., 1988). In the studies of Khare et al., 2016 and Ortiz et al., 2009 based on value at the beginning of DAS28, patients exhibited moderate and severe rheumatoid arthritis, in the studies by Al-Katma et al., 2007, Pinho et al., 2009, Zhao et al., 2018 patients exhibited moderate disease activity; in the study by Erciyas et al., 2013 patients had low disease activity and moderate plus high disease activity and finally in the study by Okada et al., 2013 they contained patients in the stages of remission, low and moderate disease activity based on DAS-28. Even with different degrees of RA, no prescription changes in RA modifying drug therapy were made by patients during the study to avoid interferences.

For the diagnosis of periodontal disease, three included articles (Al-Katma et al., 2007; Erciyas et al., 2013; Okada et al., 2013) used the criteria according to the American Academy of Periodontology classification (Armitage, 1999). Another study (Pinho et al., 2009) used the criteria of Machtei et al., 1992, the criteria explain that patients with periodontal disease and having 2 or more teeth with clinical attachment loss $\geq$ 6 mm. For Carranza's criteria (Newman et al., 2016) the patient must have one or more teeth with probing pocket depth $\geq$ 5 mm and one included study (Khare et al.,2016) applied this criteria. The study of Khare et al. 2016 study included patients with moderate periodontitis, with 3 to 4 mm loss of clinical insertion and patients with severe

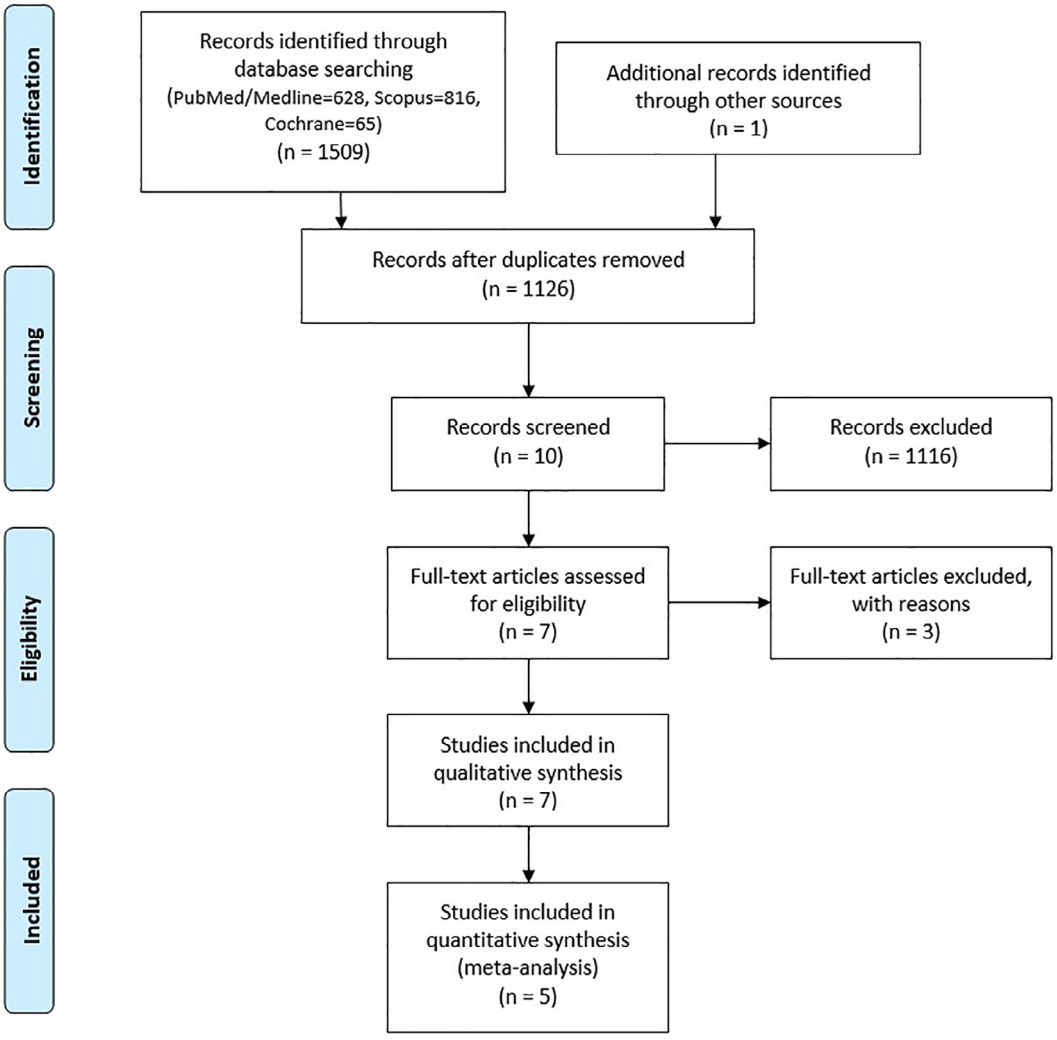

Fig. 1 Search strategy.

Table 1 Summary of characteristics of included studies.

Author	Study Design	Patient, n	Mean age, years	Groups (patient, n)	RA evaluated Methods	Outcomes Results	Conclusion	Follow-up
Zhao X. et al., 2018	EP	18	42.8	PD + RA + SRP (18)	DAS28, ESR, hsCRP	DAS28, ESR and hsCRP were all significantly downregulated (P < 0.001) when compared with baseline	Non-surgical periodontal treatment is effective for improve the clinical outcome of RA and routine use of this therapy is strongly recommended for RA having coexisting PD.	1 month
Khare et al., 2016	RCT	60	50	PD + RA (30)PD + RA + SRP (30)	DAS28, ESR, CRP	DAS28, ESR and CRP were statistically significant in treatment group, when compared at baseline and control group (p < 0.05).	Nonsurgical periodontal therapy may contribute to a reduction in the signs and symptoms of RA.	3 months
Okada et al., 2013	RCT	55	61.7	RA + PD + SS (26) RA + PD (29)	DAS28-CRP, CRP	Showed a significantly greater decrease in DAS28-CRP (P = 0.02), when compared with baseline and control group. No statistical differences in levels of CRP when compared treatment group with baseline and too when compared treatment group with control group.	These results suggest that supragingival scaling decreases DAS28-CRP	8 weeks
Erciyas et al., 2013	EP	60	43.2	HARA + PD + SS (30) LARA + PD + SS (30)	DAS28, ESR, CRP	Statistically significant decreases (P < 0.001) in the DAS28 levels in both groups,CRP and ESR levels significantly decreased in both LARA (P < 0.05) and HARA (P < 0.001) when to compared at baseline.	Effective non-surgical periodontal treatment, which is measured by DAS28, ESR, CRP may reduce RA severity in low or moderate to highly active RA patients with chronic periodontitis.	3 months
Ortiz et al., 2009	RCT	40	55.5	PD + RA + SRP (10) (A) PD + RA (10)(B) PD + RA + SRP + TNF (10)(C) PD + RA + TNF (10)(D)	DAS28, ESR	Subjects receiving periodontal therapy (groups A and C) showed a statistically significant improvement in ESR, DAS28 when compared at baseline. When groups A and C were compared to the control subjects (groups B and D), statistically significant differences in DAS28 were observed among the groups (P < 0.01), whereas ESR was not significantly different among the groups (P = 0.64).	The present findings indicate that scaling and root planing and oral hygiene contribute to a reduction in the signs and symptoms of active RA	6 weeks
Pinho et al., 2009	RCT	30	47.5 (35-60)	PD + RA + SRP (15) PD + RA (15)	DAS28, ESR, CRP	No statistical differences in levels of DAS28, ESR and CRP when compared treatment group with baseline and too when compared treatment group with control group.	It was not possible to verify a direct correlation of the periodontal treatment in the activity of the systemic disease	6 months
Al-Katma et al., 2007	RCT	29	53.3	PD + RA + SRP (17) PD + RA (12)	DAS28, ESR	DAS28 and ESR showed statistically significant reduction in the treatment group compared with the control group ($P < 0.05$). The values of DAS28 and ESR statistically non-significant when compare at baseline for treatment group.	This study indicates the scaling/root planing in subjects with periodontal disease might reduce the severity of RA.	8 weeks

EP = prospective study; RCT = randomized controlled tiral; PD = periodontal disease; RA = rheumatoid arthritis; SRP = scaling and root planing; HARA = highly active RA; LARA = low or moderate active RA; TNF = Anti-tumor necrosis fator; SS = supragingival scaling

periodontitis with 5 mm or more of loss of clinical insertion. Thus, patients had chronic periodontitis to varying degrees: Okada et al.,2013 participants were confirmed to exhibit mild to moderate chronic periodontitis; Al-katma et al.,2007 participants showed generalized mild-to-moderate chronic periodontitis; Erciyas et al.,2013 participants had moderate chronic periodontitis; Khare et al.,2016 participants exhibited moderate-to-severe chronic generalized periodontitis; Ortiz et al.,2009 participants demonstrated generalized severe chronic periodontitis; Pinho et al.,2009 participants had severe chronic periodontitis and Zhao × et al.,2018 participants exhibited chronic periodontitis.

Periodontal treatment in most studies (Al-Katma et al., 2007;Pinho et al., 2009; Ortiz et al., 2009; Khare et al., 2016; Zhao et al., 2018), consisted of oral hygiene instruction along with full-mouth scaling and root planing immediately after the RA baseline and periodontal assessment using manual and / or ultrasonic instruments. In the studies by Okada et al., 2013 and Erciyas et al., 2013, full-mouth supragingival scaling was performed.

The follow-up period ranged from 1 to 6 months. According to D'Aiuto et al.2004, after 2 months of periodontal therapy, a systemic reduction of pro-inflammatory cytokines, such as IL-6, which is also linked to AR activity, can be noticed. In the follow-up period of one month was observed a positive effect of periodontal treatment in decreasing RA activity, showed in Zhao X et al., 2018 and Ortiz et al., 2009 studies. Similar results were found in the 2-month follow-up (Okada et al., 2013; Al-katma et al., 2007) and 3 months (Khare et al., 2016; Erciyas et al., 2013). When assessed at sixth month, in the study by Pinho et al., 2009, there was no effect of periodontal treatment on rheumatoid arthritis.

The most prevalent periodontal clinical parameters in the studies were: probing depth (PD), clinical attachment levels (CAL), and percentage of probing bleeding (BOP). These three parameters were analyzed in five studies (Al-Katma et al., 2007; Ortiz et al., 2009; Erciyas et al., 2013; Okada et al., 2013; Khare et al., 2016), two other studies (Pinho et al., 2009; Zhao et al., 2018) evaluated PD and BOP. What can be seen in all these analyses is that the group that received periodontal treatment showed significant improvement in periodontal parameters, the PD reduced significantly (Al-Katma et al., 2007; Ortiz et al., 2009; Pinho et al., 2009; Erciyas et al., 2013; Okada et al., 2013; Khare et al., 2016; Zhao et al.,2018), there was a significant gain in CAL (Al-Katma et al., 2007; Erciyas et al., 2013; Okada et al., 2013; Khare et al., 2016), and a significant decrease in BOP posttreatment (Al-Katma et al., 2007; Ortiz et al., 2009; Erciyas et al., 2013; Okada et al., 2013; Khare et al., 2016; Zhao et al., 2018). The reduction in PD and improvements in CALs can be attributed to the decreased size of inflammatory components after periodontal therapy, this decrease in inflammation in patients with chronic periodontitis according to Luthra et al., 2019 can be observed 30 days after non-surgical periodontal therapy.

3.3. Risk of bias

For randomized clinical trials, the Cochrane scale was used (Table 2). In general, two domains (random sequence generation and allocation concealment) were at risk of uncertain bias, only Al-Katma et al., 2007 presented how random sequence generation was performed and considered low risk of bias. The other studies did not present data on this domain. In the blinding domain (participants, personnel and outcome assessors), all articles were considered to be low risk of bias, since the analyzes were made from blood tests, the outcome is not altered by the lack of blinding. In other domains (incomplete outcome data; selective outcome reporting and other sources of bias), all articles indicated low risk of bias.

The Newcastle Ottawa Scale was used to assess the risk of bias in prospective studies, analyzing studies for selection, comparison, and outcome criteria. (Table 3). When submitted to analysis, both studies obtained nine stars, indicating a low risk of bias.

3.4. Meta-analysis

Seven studies evaluated DAS28, five of the studies could be included in the *meta*-analysis (Fig. 2A). Comparing the values, the difference was statistically favorable for non-surgical periodontal treatment (P = 0.004, MD −1.10 [CL-1.84 to −0.36], I^2 = 92%, P < 0.00001). The study by Okada et al., 2013 was not included in the *meta*-analysis because it analyzed DAS28-CRP, another composite RA activity score, which includes the value of CRP instead of ESR, and the study by Pinho et al., 2009 did not present standard deviation values.

ESR values were analyzed in six studies, four studies could be included in the *meta*-analysis (Fig. 2B). A significant favorable difference was observed in the ESR for periodontal treatment (P = 0.01, MD −8.98 [CL-16.05 to −1.90], I^2 = 78%, P = 0.003). The studies by Ortiz et al., 2009 and Pinho et al., 2009 could not be included in the *meta*-analysis because they did not show standard deviation values.

Five studies analyzed serum CRP levels, two studies could be included in the *meta*-analysis (Fig. 2C). There was no statis-

Table 2 Risk of Bias of Randomized Controlled Trials- Cochrane Scale.

	Al-Katma et al., 2007	Ortiz et al., 2009	Pinho et al., 2009	Okada et al., 2013	Khare et al., 2016
Sequence Generation	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Allocation Concealment	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Blinding of participants, personnel and outcome assessors	LOW	LOW	LOW	LOW	LOW
Incomplete outcome data	LOW	LOW	LOW	LOW	LOW
Selective outcome reporting	LOW	LOW	LOW	LOW	LOW
Other sources of bias	LOW	LOW	LOW	LOW	LOW

Table 3 Risk of Bias of the Prospective Studies– NewCastle Otawa.

Studies	Selection				Comparability		Outcome			Total
	Exposed Cohort	Non exposided cohort	Ascertainment of exposure	Outcome of interest not present at start	Main Factor	Additional Factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Erciyas et al., 2013	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Zhao et al., 2018	☆	☆	☆	☆	☆	☆	☆	☆	☆	9

tically significant difference in CRP when comparing pre- and post-periodontal treatment (P = 0.34, MD −0.67 [CL-2.04 to 0.71], I^2 = 92%, P = 0.0006). The study by Zhao et al., 2018 was not included in the *meta*-analysis because it presented a high sensitivity CRP test, and the other studies (Pinho et al., 2009; Erciyas et al., 2013) were not included because they did not show standard deviation.

4. Discussion

The null hypothesis of this study was rejected; the *meta*-analysis showed that periodontal treatment promoted significant changes in the DAS28-ESR, reducing the RA activity index. The improvement observed in DAS28 was not related to differences in RA modifying drug therapy as no prescription

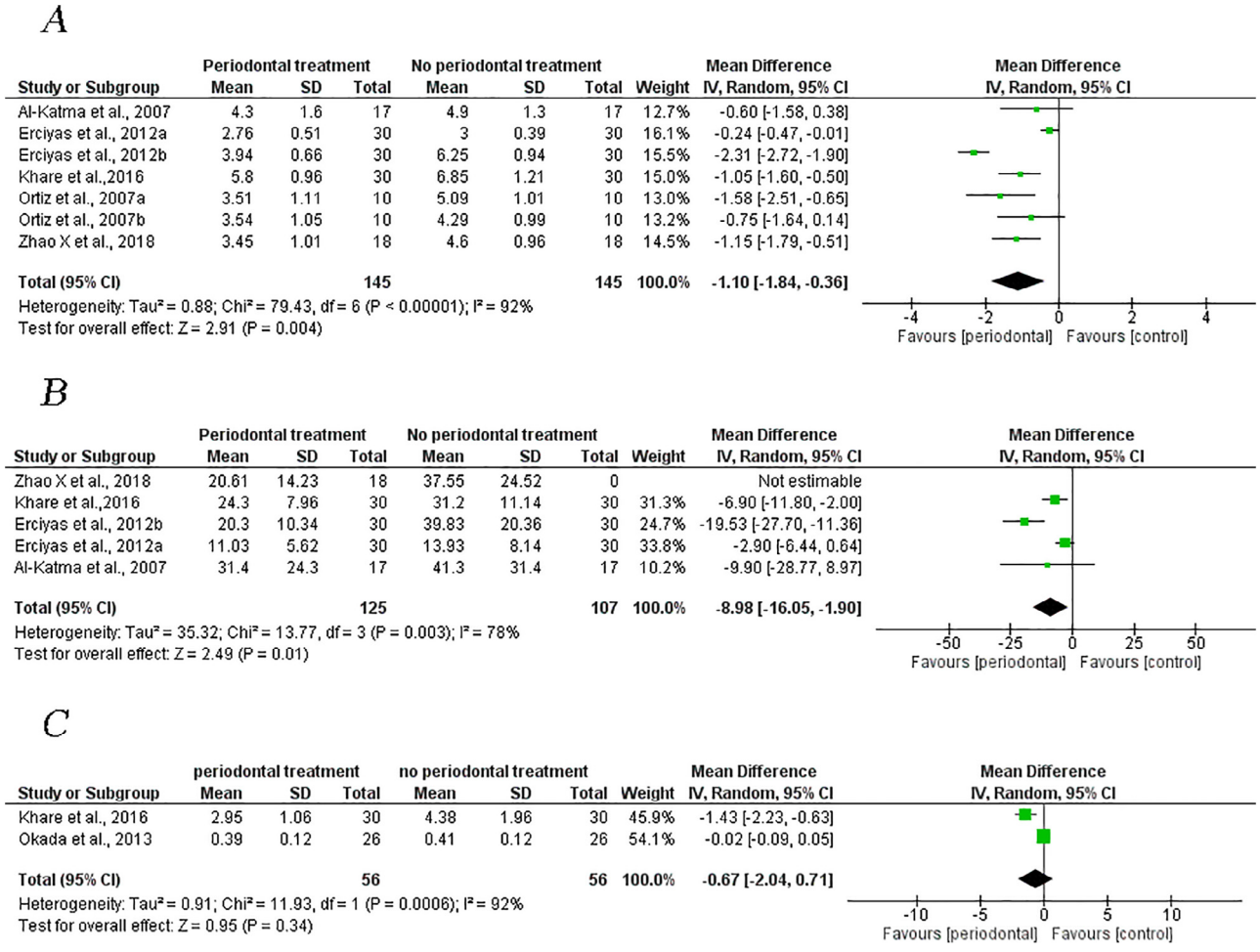

Fig. 2 [A] Forest plot evaluating DAS28. Statistically significant difference ($p < 0.05$) favorable to periodontal treatment. [B] Forest plot of the biochemical marker ESR. Statistically significant difference ($p < 0.05$) favorable to periodontal treatment. [C] Forest plot of the biochemical marker CRP. There was no statistically significant difference ($p > 0.05$).

changes were made during the included studies. Therefore, periodontal therapy is likely to have synergistic effects with medication (Erciyas et al., 2013).

The first drug of choice for the treatment of rheumatoid arthritis comprises several conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (Fleury et al., 2017). When DMARD therapy is not effective and high disease activity is persistent, the preferred treatment option is TNF-α inhibitors (anti-TNF-α) (Swierkot et al., 2015). The literature suggests that anti-TNF-α agents may reduce periodontal inflammation in patients with RA, and therefore, periodontitis (Pers et al., 2008; Mayer et al., 2009). Ortiz et al., 2009 reported that anti-TNF-α therapy without periodontal treatment had no significant effect on the periodontal condition. Results showed that RA patients receiving periodontal treatment had a significant reduction on the mean score of disease activity and ESR, with no significant difference between those treated with DMARDs or anti-TNF-α drugs ($P > 0.05$). This difference may be due to the time of administration of anti-TNF-α agent; in studies that observed medication influence on periodontal state, anti-TNF-α was administered over a long period of time, 8–26 months (Mayer et al.,2009) and 9 months (Pers et al., 2008), compared to the 6 weeks used by Ortiz et al., 2009.

Is expected a pronounced reduction on pocket depth and attachment level around the third month after Non-surgical root debridement (Haffajee et al., 1997). According to D'Aiuto et al.2004, After 2 months of periodontal therapy, a systemic reduction of pro-inflammatory cytokines, such as IL-6, which is also linked to AR activity, can be noticed. In the follow-up period around the third month, was observed a positive effect of periodontal treatment in decreasing RA activity. (Zhao X et al., 2018; Ortiz et al., 2009; Okada et al., 2013; Al-katma et al., 2007; Khare et al., 2016; Erciyas et al., 2013).

CRP and ESR have been used for over 80 years to evaluate inflammation in diseases such as RA (Crowson et al., 2009). Cytokines present in periodontal disease, particularly TNF-α, IL-1, and IL-6 trigger increased hepatic synthesis and rapid secretion of intravascular plasma proteins, including CRP and fibrinogen (Ebersole & Cappelli, 2000). Increased fibrinogen levels elevate ESR concentration (Ribeiro et al., 2005).

Erythrocyte sedimentation has been proposed as the best marker for disease evaluation over time and for monitoring treatment efficacy for bacterial infections and RA (Bray et al., 2016). According to the *meta*-analysis, a significant difference in ESR was observed for periodontal treatment, suggesting a reduction in systemic inflammation following non-surgical periodontal treatment in RA patients, as Kaur et al., 2014 also reported. This is in disagreement with another systematic review (Calderaro et al., 2017) which did not demonstrate significant reductions in ESR levels in patients with RA and periodontitis following non-surgical periodontal treatment. This disagreement can be explained by the number of studies included in the *meta*-analysis. The study by Calderaro et al., 2017 has a smaller amount of patients, making it difficult to detect small differences.

The hypothesis that periodontal infections may independently contribute to the aggravation of chronic diseases, such as diabetes and cardiovascular disease, (Demmer et al., 2013) may be extended to RA, as inflammation is common on both (Chen et al., 2014). Although *meta*-analysis has not shown significant differences for CRP values, it is possible to see a decrease after periodontal treatment (Erciyas et al., 2013; Khare et al., 2016; Kaushal et al., 2019). This tendency may be associated with the lack of specificity of CRP testing (Bray et al., 2016), as CRP may also be associated with obesity, leptin, stress, and other conditions (Yang et al., 2018). To reduce this interference, the high sensitivity CRP (hsCRP) test (Dessein et al., 2004) for rheumatoid arthritis activity has been suggested, as used in the study by Zhao et al., 2018, in which RA patients receiving non-surgical periodontal therapy showed statistically significant improvement in hsCRP, DAS28, and ESR at 3 months, than those who did not receive periodontal therapy.

The bacteria involved in the pathogenesis of periodontitis is known to have a promoting effect on RA severity in patients (Zhao et al., 2018). Kaushal et al., 2019, related 61.1% of patients with periodontal disease and RA had high RA activity, according to the American Rheumatism Association. This high disease activity was significantly reduced to 27.8% after periodontal treatment, while the group that did not received periodontal treatment showed no significant improvement in disease activity. A similar result was also reported by Erciyas et al., 2013. After periodontal treatment, the group with moderate to high RA activity showed a significantly greater decrease in DAS28, ESR, and CRP levels than the group of patients with low RA activity.

A reduction in systemic inflammation may be noted after periodontal treatment (D'aiuto et al., 2005). Removal of microbial biofilm from dental surfaces results in a health-related change in microbiota (Bıyıkoğlu et al., 2013) as there is a decrease in bacteria, bacterial antigens, and proinflammatory mediators entering the circulatory system. Reduced systemic inflammation may contribute to a better clinical outcome of RA (Zhao et al., 2018). It also reduces joint exposure to bacteria and their products (Al-Katma et al., 2007).

Although all studies reported an objective improvement in periodontal clinical parameters, suggesting that the follow-up period was sufficient to observe a reduction in infection and inflammation associated with periodontal disease, the number of patients included in the *meta*-analysis may still be relatively small. Heterogeneity between studies was high for the outcomes evaluated and these characteristics should be considered as possible limitations of the present *meta*-analysis. Other randomized controlled trials including a larger number of patients, with standardization of the severity of periodontal disease and rheumatoid arthritis activity among patients are needed to confirm this finding.

5. Conclusion

The current *meta*-analysis suggests the control of periodontal disease in patients with RA through non-surgical periodontal treatment have a beneficial effect on the clinical marker of RA (DAS28) and the biochemical marker (ESR). These results should be viewed with caution due to the high heterogeneity between studies, and more randomized clinical studies are needed to confirm these findings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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