Rapid Evidence Product

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The Association Between Outcomes and Dental Services in Persons with Autoimmune Disease Treated with Biologics and Other Immunosuppressants: A Rapid Response Review

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) is expanding its portfolio to include rapid evidence products. The program has begun to develop a range of rapid evidence products to assist end users in making specific decisions in a limited timeframe.

In 2014, AHRQ produced a taxonomy of rapid evidence products produced by leading organizations around the world. This taxonomy now informs the development of rapid evidence products. Based on levels of synthesis, the report classified products as evidence inventories, rapid responses, and rapid reviews. On one end of the spectrum, evidence inventories offer an assessment of the quantity and type of evidence without presenting results. On the other end, rapid reviews adapt and streamline traditional systematic review methods to provide a limited evidence synthesis. Rapid responses fall between the two; through examination of the literature but no formal evidence synthesis or conclusion, rapid responses aim to offer the end-user a solution to a targeted problem based on the best available evidence.

To shorten timelines, reviewers must make strategic choices about which processes to abridge. Common adaptations to provide rapid evidence include narrowly focusing questions, limiting the number of databases searched and/or modifying search strategies, using a single reviewer and/or abstractor with a second to provide verification, and restricting to studies published in the English language. However, the adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used, the resulting limitations of the evidence synthesis, and the strength of evidence of included studies is extremely important. While tradeoffs will likely differ for each topic, they are described so readers can adjudicate the limitations of the findings and conclusions of the review.

While rapid evidence products are often sufficient for decision making on their own, at other times they can uncover a large, complex literature base that encourages end-users to seek a full review. Rapid evidence products can provide a map of the evidence and assist decision makers in targeting resources to areas of highest interest and greatest potential value.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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The Association Between Outcomes and Dental Services in Persons with Autoimmune Disease Treated with Biologics and Other Immunosuppressants: A Rapid Response Review

Key Messages

Purpose of Review

This review is undertaken to answer the following questions:
Key Question 1: What is the effectiveness of dental services before or during treatment with biologics and other immunosuppressants for autoimmune conditions on disease-related outcomes?

Key Question 2: What are the clinical practice guidelines or standards for dental care for people with autoimmune diseases treated with biologics and other immunosuppressants?

Key Messages

- The body of evidence that was synthesized for the effect of dental services on autoimmune disease-related outcomes focused on patients with rheumatoid arthritis (RA) who received non-surgical periodontal treatment (NSPT). Evidence on other autoimmune disease populations is sparse, and evidence on other dental services is lacking.
- All included studies examined the effect of NSPT during autoimmune treatments. No evidence evaluating the impact of NSPT prior to immunosuppressive treatment was available.
- The evidence reported here has been extracted from 3 systematic reviews (SRs) (1 fair and 2 poor quality SRs) and 10 primary studies (3 good, 2 fair and 5 poor quality).
- Most of the included studies had patients who were on either conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs), or mixed type of therapies.
- Disease-activity: The evidence generally supports the effectiveness of NSPT in reducing disease activity scores for RA (3 SRs of 1 fair and 2 poor quality, 5/7 primary studies of 1 fair and 4 poor quality) and psoriasis (PSO) (2/2 good quality randomized controlled trials (RCTs)) with follow-up times ranging from 8 weeks to 6 months.
- Tender/Swollen joints: There is inconsistent evidence for the reduction of the number of tender/swollen joints after NSPT (1 fair quality SR, 1 fair and 2 poor quality RCTs).
- Inflammatory markers: There is moderate evidence that C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) levels are decreased post-NSPT in RA and systemic lupus erythematosus (SLE) and no evidence about these markers for PSO. There is weak evidence for lowering of other inflammatory markers like Tumor necrosis factor alpha (TNFα), Interleukin-6 (IL6) (in 1 RA SR of fair quality and 1 PSO RCT of good quality.)
- Quality of life outcomes: There is inconsistent evidence showing no effect on QoL measures for RA (2 RCTs of fair quality) and PSO (1 RCT of good quality).

- Other outcomes: We find weak evidence for other outcomes like anti-citrullinated protein autoantibodies (ACPAs), rheumatoid factor (RF), life impact measure and Musculoskeletal ultrasound (MSUS), which are reduced in less than 3 studies.
- Adverse events: None of the included studies reported on the impact of NSPT on adverse effects of therapies for autoimmune conditions.
- Future studies to evaluate dental services other than non-surgical periodontal treatment, and studies that include patients with autoimmune diseases other than rheumatoid arthritis, may enrich our understanding on the potential inextricable link between dental services and autoimmune disease treatment.
- Of the 31 clinical practice guidelines that were identified from our searches, only one official clinical practice guideline on dental care was available. This guideline focused on Sjogren's syndrome.
- The American Dental Association published a practice guide that outlined various aspects of dental management for RA, lupus, Sjogren's syndrome, and scleroderma.
- The British Dental Association provided a review and guidance for oral health management for patients with RA.
- The National Scleroderma Foundation published a patient-oriented fact sheet that included description and treatment of common oral health issues among patients with scleroderma.

Contents

1.Background

The American Autoimmune Related Diseases Association (AARDA) has identified over 100 autoimmune (AI) diseases affecting more than 50 million people in the United States.[1] Development of autoimmunity is multifactorial with effects localized to specific organs or manifesting systemically. Oral symptoms and lesions are often early signs of AI disease.[2] Conversely, patients with autoimmune diseases frequently exhibit markers of poor oral health (e.g., increased plaque index, gum disease, and edentulism) compared to healthy individuals.[3–6] For example, a 2020 report noted that between 2011 and 2016, lack of functional dentition was >50% in persons with rheumatoid arthritis (RA). These RA patients are more likely to have missing teeth and temporomandibular joint diseases than healthy controls.[7]

Various chronic autoimmune and inflammatory diseases are also correlated with an elevated risk for periodontitis,[8–14] an inflammatory gum disease that damages local tissue and can promote systemic inflammation.[10] For some autoimmune diseases (i.e. systemic lupus erythematosus (SLE), RA, and limited cutaneous systemic sclerosis (lcSSc), the co-occurrence of periodontitis has been associated with increased autoimmune disease severity.[4,15–17] For example, patients with both periodontitis and lcSSc had greater arterial stiffness and disease activity compared to healthy individuals with periodontitis.[15] A bidirectional relationship has been proposed for SLE where the dysregulated immune system exacerbates oral inflammation and dysbiosis of the oral microbiota, and in turn, oral infections contribute to systemic inflammation and SLE disease progression.[18]

The Centers for Disease Control and Prevention (CDC) recommends daily oral hygiene with regular professional dental care to reduce rates of tooth decay and oral inflammation.[19] For patients with AI diseases, dental treatments may have a significant impact on disease outcomes, although the relationship likely varies across AI conditions and dental treatments. Since host immune responses are critical in limiting oral dysbiosis and controlling inflammation,[20] preventative oral care to reduce overall plaque, a precursor to periodontitis, may be especially beneficial to AI patients with dysregulated inflammatory responses. **Figure 1** depicts a potential causal model representing the interplay between RA and oral health.

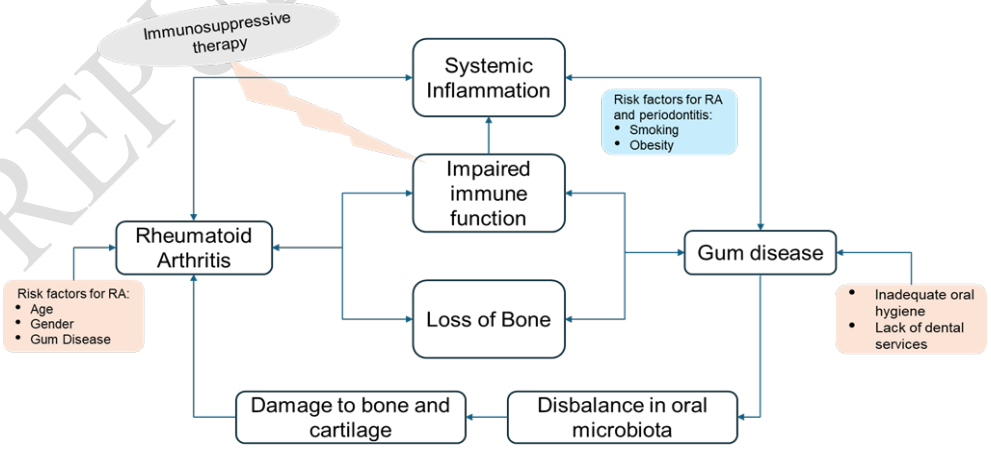


Figure 1. Schematic representation of a causal model depicting the relationship between rheumatoid arthritis and oral disease. Smoking and obesity are common risk factors for the two diseases. Single headed arrows represent the directionality of the specified outcome while double headed arrows signify the common causes and outcomes for both conditions.

There are many therapies available to manage RA and other autoimmune diseases. A class of therapeutic agents called DMARDs (disease-modifying anti-rheumatic drugs) has been in use to treat several autoimmune conditions. DMARDs were first used to treat RA and over time, they have shown effectiveness in the treatment of several autoimmune conditions. Conventional DMARDs are small molecule drug therapies (e.g., methotrexate) while a new class of DMARDs, which are biologics, have gained more prominence as therapies for autoimmune conditions. Both types of DMARDS have an immunosuppressive action albeit via differing mechanisms of action. In general, conventional DMARDS act by inhibiting pathways in the inflammasome, while each DMARD may have a different mode of action depending on which targets they may inhibit in the inflammatory cascade. Biologics are more selective in their action since they are antibodies binding to their host protein selectively, and include inhibition of cytokine function, B-cell depletion, inhibition of T-cell signaling or other similar mechanisms of action. For example, rituximab, a monoclonal antibody for CD20 depletes B cells.[21] For ease of reference, we will use the term DMARD to refer to conventional DMARDs and the term biologics to refer to biologics DMARDs.

Most autoimmune conditions are graded for their severity using disease activity scores made up of many components. For example, the disease activity score in RA, DAS28,[22] contains 4 components – the number of tender joints, the number of swollen joints, a visual analog scale of the patient's assessment of their overall health and ESR, an inflammation marker. DAS28-CRP and DAS28-ESR are two different types of disease activity scores which take into account the levels of CRP and ESR respectively.[23]

To date, the overall impact of preventative or necessary dental care before or during immunosuppressive therapy across multiple AI disease outcomes has not been fully investigated. As a result, Centers for Medicare and Medicaid Services (CMS) has partnered with the Agency for Healthcare Research and Quality (AHRQ) to identify dental services substantially linked to health outcomes of Medicare-covered medical services for people being treated for AI diseases.

This rapid response aims to summarize the current literature evidence on the impact of dental services and oral health management on autoimmune disease outcomes, specifically in people treated with biologics and other immunosuppressants. This review was guided by 2 key questions (KQs) outlined below:

Key Question 1: What is the effectiveness of dental services before or during treatment with biologics and other immunosuppressants for autoimmune conditions on disease-related outcomes?

Key Question 2: What are the clinical practice guidelines or standards for dental care for people with autoimmune diseases treated with biologics and other immunosuppressants?

2. Methods

This rapid review used the following methods as part of the process:

- Literature search
- Study screening and selection
- Data extraction of primary studies and systematic reviews
- Risk of bias (RoB) assessment for primary studies using RoB2[24] and ROBINS-I[25], and for systematic reviews, AMSTAR2[26]
- Data synthesis, i.e., evidence mapping to key questions and qualitative synthesis

2.1 Literature Search

We conducted literature searches across the following biomedical databases for peer-reviewed randomized clinical trials (RCTs), systematic reviews (SRs), controlled observational studies, gray literature (such as conference and poster abstracts), and clinical practice guidelines: OVID MEDLINE®, EMBASE, PsycINFO, Biosis, and Science Citation Index. An experienced librarian conducted these searches.

An additional gray literature search was performed to minimize publication bias. Resources included OpenGrey, Google, Google Scholar, and the websites of relevant societies and institutions, professional society websites, and clinical practice guidelines from inception to the present. A study team member conducted this search. The search strategies used a combination of medical subject headings (i.e., controlled vocabularies) and keywords, adapted to the syntax of each database. The search strategies used terms for the intervention and condition, along with Boolean operators. All search results were limited to the English language and human subjects. Searches were restricted to May 2016 to May 2024 to ensure the literature was relevant to current trends in treatment of autoimmune conditions.

The initial search was intended to cover the last 5 years (May 2019 – May 2024). However, we estimate that studies may have been canceled or postponed during the period of 2020–2022 due to the pandemic. Therefore, we extended our search period to 8 years, from May 2016 to May 2024.

A detailed search strategy is included in Appendix A. Systematic reviews were also searched, and their citations cross-referenced to ensure that no relevant articles were missed in the initial searches.

To ensure that we adequately address key question 2, we conducted a manual search for clinical practice guidelines or standards for dental care in the following professional organization websites: American Dental Association, American College of Rheumatology, European Alliance of Associations for Rheumatology, American Association of Immunologists, American Academy of Allergy, Asthma, and Immunology, British Society for Immunology, International Union of Immunological Societies, American College of Gastroenterology, American Gastroenterological Association, National Institute for Health and Care Excellence, Centers for Disease Prevention and Control, and the World Health Organization.

2.2 Study Screening and Selection

We used Covidence[27] to manage the screening of the articles. One team member reviewed 100% of the titles and abstracts, with 10% of the abstracts randomly selected and reviewed by a second reviewer. Any conflicts were resolved through discussion and consensus. In the second step, the full texts of abstracts categorized as relevant or potentially relevant were retrieved and reviewed. Study selection was based on the predefined Population, Intervention, Comparator, Outcome(s), Timing, and Setting (PICOTS) inclusion and exclusion criteria depicted in **Table 1**. Exclusion reasons were documented at the full-text level.

Full-text screening was conducted by two reviewers to ensure that as many relevant articles as possible were captured. At this stage, we excluded articles that did not describe dental treatments, used healthy controls as the comparator group, or focused on periodontal outcomes rather than AI outcomes. The project manager provided a final review of the included and excluded studies. Clinical subject matter experts (SMEs) reviewed the list of eligible inclusions to ensure that no influential or landmark publications within the clinical community were missed and to identify publications that lacked clinical applicability for exclusion.

Table 1. Study eligibility (PICOTS) criteria

	Inclusion Criteria	Exclusion Criteria
Population	Non-pregnant adults >18 years with AI inflammatory conditions such as but not limited to Sjogren's, RA, psoriatic arthritis, inflammatory bowel disease, SLE, scleroderma	● Pregnant persons ● Persons with oral cancer
Intervention	● Routine professional preventative dental services (exam/cleaning) or ● Any dental treatment ● Before, during, or after treatment for AI including but not limited to: o Anti-Tumor Necrosis Factor biologics: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab o B-cell inhibitors such as belimumab, rituximab o Interleukin inhibitors such as anakinra, canakinumab, tocilizumab o Selective costimulation modulator: abatacept o Monoclonal antibodies o Steroids o Conventional DMARDs, including hydroxychloroquine, methotrexate, sulfasalazine, leflunomide, azathioprine o Calcineurin inhibitors such as cyclosporin and tacrolimus o Janus kinase inhibitors o mTOR inhibitor(s)	● Interventions other than professional dental services ● Home oral hygiene practices
Comparator	No dental services before, during, or after treatment for AI disease	Studies were excluded if they did not report any of the specified comparators.
Outcome(s)	● Disease activity ● Remission ● Quality of life ● Radiographic joint damage ● Adverse effects of pharmacologic treatment: infection, including sepsis, abscesses and cellulitis; oral ulcers ● Serious infection ● Mucositis	● Studies were excluded if they did not report any autoimmune disease related outcomes. ● Dental health outcomes and dental procedure outcomes were excluded.
Timing	Any follow-up duration Before or during immunosuppressive treatment for AI disease	-
Setting	● Inpatient and outpatient settings in the United States (or its territory, embassy, or military installation) ● Other countries may be included if sufficient studies (at least 10 studies and/or systematic reviews) are not available from the US alone.	-
Study Design	● RCTs ● Controlled observational studies ● SRs with MAs ● Clinical practice guidelines	● Reviews without MA ● Non-controlled observational studies ● Laboratory studies ● Animal studies ● Non-clinical publications ● Conference abstracts
Language	English language publications	Non-English language publications
Publication dates	● RCTs and controlled observational studies: 2016 - July 2024 ● SRs with MAs: 2020 - 2024 ● Clinical practice guidelines: 2016 – 2024	-

Abbreviations: AI: autoimmune; MA: meta-analysis; RA: rheumatoid arthritis; RCT: randomized controlled trial; SLE: systemic lupus erythematosus; SR: systematic reviews.

2.3 Data Extraction

Data extraction was performed by one reviewer and verified by another. Preliminary data extraction included study characteristics (e.g., study design, country where study was conducted, and center), population characteristics, details on dental service interventions, and AI outcomes.

For each included primary study, we extracted the following information as available:

- General study characteristics: author, year of publication, country, autoimmune disease and associated medication for treatment
- Study design: study design, sample size, follow-up duration
- Intervention: dental services including routine professional dental care (exam/cleaning), any dental treatment, any patient education on oral health by a dentist or dental professional, timing of dental services including information of the timing of services with respect to treatment for the autoimmune indication.
- Outcomes of interest: as listed in **Table 3.**

For each included SR, we extracted the following information:

- Date ranges of the literature search
- Number of component studies
- The primary conclusions
- Any strength of evidence assessment that was performed.
- Outcomes of interest: as listed in **Table 3.**

2.4 Risk of Bias Assessments

Methodological quality of included primary studies was assessed using the AMSTAR2 quality rating tool for systematic reviews,[26] Cochrane Risk of Bias (RoB2) for randomized controlled trials,[24] and ROBINS-I for controlled interventions.[25] AMSTAR2 classified systematic reviews as high, moderate, low, or critically low confidence; RoB2 determined RCTs to have low risk of bias, some concerns, or high risk of bias; and ROBINS-I gave non-randomized controlled interventions a score of low, moderate, serious, or critical risk of bias. To facilitate better comprehension, the quality of evidence across the three different tools was mapped to the United States Preventive Services Task Force (USPSTF) 3-point scale of good, fair, and poor quality,[28] as shown in **Table 2** below:

Table 2: Mapping quality terms from risk of bias assessments of included studies

	Rating		
USPSTF quality term used in this report	*AMSTAR2*	*ROBINS*	*RoB2*
Good	High confidence	Low risk of bias	Low risk of bias
Fair	Moderate confidence	Moderate risk of bias	Some concerns
Poor	Low confidence	Serious risk of bias	High risk of bias
	Critically low confidence	Critical risk of bias	n/a

2.5 Data Synthesis

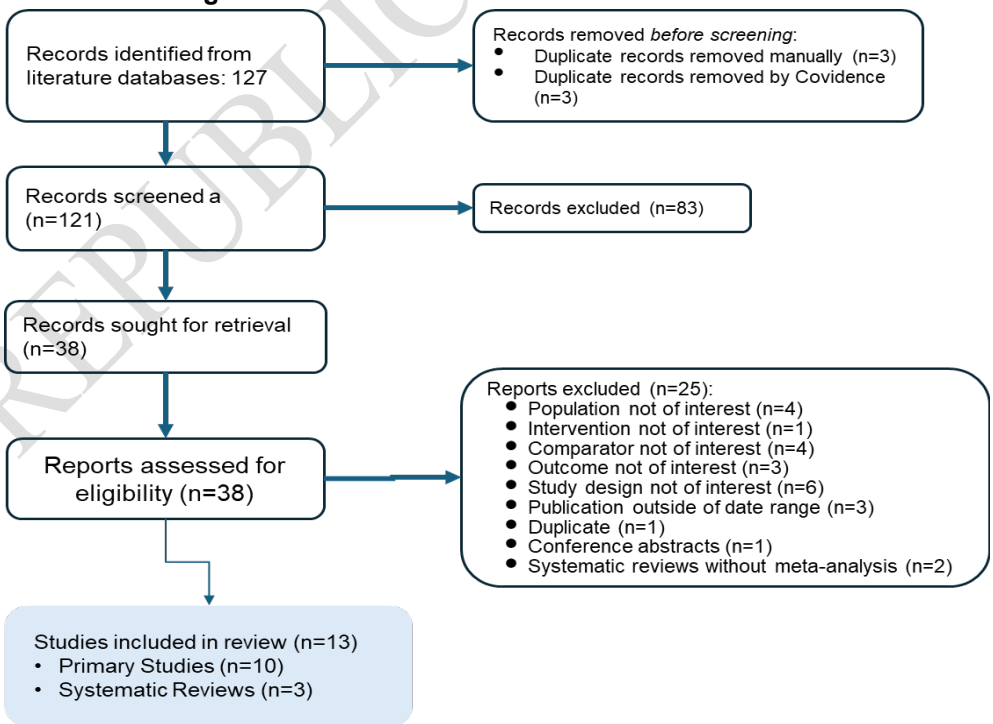
A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram[29] was developed to illustrate the number of studies involved in the literature search and each step of the study selection process. Data was compiled into evidence tables and synthesized narratively and visually, utilizing the AHRQ provided template. In addition to qualitative synthesis, summary tables were organized by key questions and by outcome of interest. We highlighted any gaps in evidence, with attention given to direct comparisons between receipt of dental care and autoimmune disease related outcomes. The subgroup analysis was narrative and done for outcomes reported in at least 3 studies. We consulted our content experts to answer KQ2 by using select references from the literature and/or from clinical practice guidelines. We provided key information and data from these references in our report. The clinical SME reviewed the final report to ensure accurate clinical contextualization of any findings.

3. Results

3.1 Literature Search Findings

Figure 2 depicts the PRISMA flow diagram summarizing the results of the literature search. An electronic database search conducted in Medline and Embase on Aug 21, 2024, yielded 127 citations. After deduplication, 121 titles and abstracts were screened for eligibility, of which 83 were excluded. Of the 38 full-text articles retrieved and reviewed for eligibility, 25 articles were excluded. Thus, a total of 13 unique publications, including 10 primary studies and 3 systematic reviews with meta-analyses, were included, extracted, and synthesized in this rapid response review.[30–42] A list of references excluded at the full-text level along with their reasons for exclusion is available in Appendix B.

Figure 2: PRISMA flow diagram



The literature searches for clinical practice guidelines for dental care and management for patients with autoimmune diseases in response to KQ2 yielded 31 articles, of which 1 was an official clinical guideline for oral management of Sjogren's syndrome and 3 were other relevant guidance publications, as shown in Table 7.

3.2 Key Question 1

Key Question 1: What is the effectiveness of dental services before or during treatment with biologics and other immunosuppressants for autoimmune conditions on disease-related outcomes?

3.2.1 Key points

- Disease-activity: The evidence generally supports the effectiveness of NSPT in reducing disease activity scores for RA (3 SRs of 1 fair and 2 poor quality, 5/7 primary studies of 1 fair and 4 poor quality) and PSO (2/2 good quality RCTs) with follow-up times ranging from 6 weeks to 6 months.
- Tender/Swollen joints: There is inconsistent evidence for the reduction of the number of tender/swollen joints after NSPT (1 fair quality SR, 1 fair and 2 poor quality RCTs).
- Inflammatory markers: There is moderate evidence that CRP and ESR levels are decreased post-NSPT in RA and SLE and no evidence about these markers for PSO. There is weak evidence for lowering of other inflammatory markers like TNFa, IL6 (in 1 RA SR of fair quality and 1 PSO RCT of good quality.)
- Quality of life outcomes: There is inconsistent evidence showing no effect on QoL measures for RA (2 RCTs of fair quality) and PSO (1 RCT of good quality).
- Other outcomes: We find weak evidence for other outcomes like ACPAs, rheumatoid factor, life impact measure and MSUS, which are reduced in less than 3 studies.
- Adverse events: None of the included studies reported on the impact of NSPT on adverse effects of therapies for autoimmune conditions.
- All included studies examined NSPT. Evidence regarding other dental services was not available.
- All included studies examined the effect of NSPT during autoimmune treatments. No evidence evaluating the impact of NSPT prior to immunosuppressive treatment was available.
- Most of the included studies had patients who were on either conventional or biologics DMARDs, or mixed type of therapies.

Table 3: Outcomes assessed and their statistical significance in the included systematic reviews and primary studies

Author Year; Country; Quality; Certainty of Evidence	Disease activity	QoL	CRP	ESR	Tender joint	Swollen joint	ACPAs	RF	Other
Systematic Reviews (all RA)									
Sun 2021[32] NA: Fair; NR	↓ DAS28		↓	ns	↓	↓			ns (TNFa) ns (IL6) ↓VAS
Silva 2022[31] NA; Poor; Very Low	↓		↓	↓					↓ Life Impact measure
Del Rei Daltro Rosa 2021[30] Poor NR	↓		ns	↓					
RCTs of patients with RA									
Monsarrat 2019[33] France; Good	ns (DAS28-ESR)	ns	ns	ns	ns	ns			ns (patient's overall assessment) ns (physician's overall assessment) ns (pain scale)
Khare 2016[35] India; Fair	↓ DAS28	↓	↓	↓	↓	↓			
De Pablo 2022[42] England; Poor	NR (DAS28-CRP, DAS28-ESR)	NR	NR	NR	NR	NR			NR (MSUS)
Thilagar 2022[36] India, Saudi Arabia; Poor	↓ DAS28		↓				↑	↑	
Nguyen 2021[37] Vietnam; Poor	↓ DAS28-CRP		ns	ns			ns	ns	

Author Year; Country; Quality; Certainty of Evidence	Disease activity	QoL	CRP	ESR	Tender joint	Swollen joint	ACPAs	RF	Other
Studies other than RCTs, with patients with RA									
Kaushal 2019[38] India; Poor	↓ SDAI		↓				ns	ns	
Atarbashi-Moghadam 2018[39] Iran; Poor	↓ DAS28								
RCTs of patients with psoriasis									
Marruganti 2024[40] Italy; Good	↓ PASI	ns (DLQI)							↓ BSA
Yarkac 2019[34] Turkey; Good	↓ PASI								↓IL-2 ↓ IL-6 ↑sIgA
RCT of patients with SLE									
Maybodi 2022[41] Iran; Fair	ns (SLEDAI)		↓	↓					

↓: significant reduction; ↑: significant increase; ns: not significant

Abbreviations: ACPAs: anti-citrullinated protein autoantibodies; BSA: body surface area; CRP: C-reactive protein; DAS: disease activity score; DLQI: dermatological life quality index; ESR: erythrocyte sedimentation rate; GOHAI: general oral health assessment index; HAQ: health assessment questionnaire; HRQoL: health-related quality of life; IL: interleukin; MSUS: musculoskeletal ultrasound; PASI: psoriasis area and severity index; RA: rheumatoid arthritis; RF: rheumatoid factor; RCT: randomized controlled trial; SDAI: simple disease activity index; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; VAS: visual analog scale.

3.2.2 Systematic Reviews

Table 4 summarizes the characteristics and findings of the 5 included systematic reviews, All 5 systematic reviews examined the effect of periodontal treatments among patients with RA. Silva 2022 aimed to review studies of both surgical and non-surgical periodontal treatments but found only NSPT studies. Meta-analyses were performed in 3 systematic reviews.[30–32]

All 3 meta-analyses included both RCTs and comparative observational studies. The publication time range of these reviews overlapped - De Rei Daltro Rosa 2021 included studies published till 2019,[30] Silva 2022 from 2019 to 2020,[31] and Sun 2021 from inception to 2020.[32] All 3 meta-analyses found statistically significant favorable effects of NSPT on disease activity. However, two meta-analyses reported high I^2, indicating high heterogeneity across studies. All 3 meta-analyses found statistically significant improvement in systemic inflammation markers, per either CRP and/or ESR. Further, Sun 2021 reported significant reductions in tender joint counts, swollen joint counts, and VAS, although significant heterogeneity across studies were observed for these outcomes as well.

Table 4: Characteristics and findings of the included systematic reviews

Author Year; Disease; Dental Intervention; Timing of dental intervention; Type of RA treatment	**Review type Included studies Search dates Quality Certainty of Evidence**	**Outcomes; # of studies for MA**	**Results If applicable: MD [95% CI]**	**I^2**
SR with MA				
Sun 2021[32] RA; NSPT; NR; NR	SR w/MA 9 RCTs or controlled trials Inception - October 2020 Fair NR	DAS28; 7 studies	**MD -0.61, [-0.37, -0.85]*** **	42.5% p=0.108
		CRP; 5 studies	**MD -0.34 [-0.07, -0.64]***	32.8% p=0.203
		ESR; 6 studies	MD 0.57 [-0.09, 1.23]	79.1% p=0.000
		TNF-α; 2 studies	MD 0.26 [-0.21, 0.73]	0% p=0.628
		IL-6; 2 studies	MD 0.38 [-0.10, 0.86]	0% p=0.634
		Tender joint count; 5 studies	**MD -0.65 [-0.37, -0.93] *** **	41.1% p=0.147
		Swollen joint count; 5 studies	**MD -0.67 [-0.18, -1.17] ** **	65.8% p=0.02
		VAS; 5 studies	**MD -0.48 [-0.08, -0.88] ***	49.6% p=0.094
Silva 2022[31] RA; NSPT + OHI/education/antibiotics; during RA treatment where noted;	SR w/MA 9 RCTs, 5 controlled cohort studies	Disease Activity; 7 studies (311 pts)	**SMD -0.88 [-1.38, -0.38]*** **	74%; p=0.003
		Systemic inflammation markers (CRP or ESR); 7 studies (270 pts)	**SMD -0.66 [-1.14, -0.18]*** **	71% p=NR
		ACR20 response; 1 studies	One study reported that patients in the control group had a higher	NA

Author Year; Disease; Dental Intervention; Timing of dental intervention; Type of RA treatment	Review type Included studies Search dates Quality Certainty of Evidence	Outcomes; # of studies for MA	Results If applicable: MD [95% CI]	I^2
DMARDs and/or biologics	April 2019 - December 2020 Poor Very Low		proportion achieving ACR20 response compared with the treatment group (RR 0.57 [0.23, 1.41]).	
		Life impact measure; 5 studies (197 pts)	**SMD -0.49 [-0.79, -0.18]*** **	34% p=NR
Del Rei Daltro Rosa 2021[30] RA; NSPT; during RA treatment; DMARDs or anti-TNF-a	SR w/MA 5 RCTs, 2 prospective observational studies Inception - April 2019 Poor NR	DAS28; 5 studies (290 pts)	**MD -1.10 [-1.84, -0.36]** **	92%; p<0.00001
		CRP; 5 studies (112 pts)	MD -0.67 [-2.04, -0.71]	92%; p=0.0006
		ESR; 6 studies (232 pts)	**MD -8.98 [-16.05, -1.90]***	78%; p=0.003

*p < 0.05, **p < 0.01; ***p < 0.001

Abbreviations: ACPAs: anti-citrullinated protein autoantibodies; CI: confidence interval; CRP: C-reactive protein; DAS: disease activity score; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; IL: interleukin; MA: meta-analysis; mo: month; MD: mean difference; NA: not applicable; NSPT: non-surgical periodontal treatment; RA: rheumatoid arthritis; RCT: randomized controlled trial; RF: rheumatoid factor; RR: relative risk; SMD: standardized mean difference; SR: systematic review; TNF: tumor necrosis factor; VAS: visual analog scale; wk: week.

3.2.3 Primary Studies

3.2.3.1 Study Design and Population Characteristics

Table 5 summarizes the study design and population characteristics of the included primary studies, categorized first by disease population, then by study design. Seven studies enrolled patients with RA,[33,35–39,42] 2 included patients with psoriasis (PSO),[34,40] and one enrolled patients with SLE.[41] The vast majority (8 out of 10) of the included primary studies were RCTs.[33–37,40–42] Of the rest, one study was a non-randomized interventional controlled study,[38] and the other study used a matched cohort design.[39] Sample sizes were small, ranging from 22[33] to 92.[34] Mean age of the study population ranged from 35.9[42] to 61.6 years old.[33] None of the studies enrolled patients in the US; six studies were conducted in Asia[35–39,41] and four were in Europe.[33,34,40,42] Most of the included studies had patients who were on either therapy or even a mix of both therapy types.

All 10 primary studies focused on patients with periodontitis and evaluated the effect of non-surgical periodontal treatment (NSPT). All but one study[39] specified that NSPT was given during autoimmune treatment; no study evaluated the effect of NSPT before autoimmune

treatment. No studies examined preventive dental care or other dental treatments. In four studies, patients in the control group received oral health instructions (OHI),[37,39,41,42] and the other six studies provided no treatment to the control group. Follow-up duration ranged from 8 weeks[34,38] to 6 months.[37,42]

Risk of bias assessment was performed for all included primary studies with full publications. Due to the nature of the intervention, blinding was not feasible in most studies. Details of this assessment are presented in Appendix D.

Table 5: Study design and population characteristics of the included primary studies

Author **Year** **Country** **Funding**	**Study design** **Followup length** **Sample size** (enrolled/analyzed) **Quality** **Periodontitis definition**	**Treatment for autoimmune disease** **Baseline disease activity level**	**Intervention group treatment** **Timing of dental treatment**	**Control group treatment**	**Mean age** **Male %**
RCTs of patients with RA					
Monsarrat 2019[33] France Grant from French Ministry of Health Clinical Research Hospital	RCT 3 mo 22/22 Good 2000 definition	csDMARDS (77.3%), bDMARDS (77.3%), Glucocorticoids (50%), NSAIDS (36%) DAS28-ESR: 4.0	Full-mouth disinfection with SRP, systemic amoxicillin (1.5g/day or 1200 mg clindamycin if allergic for 7 days), OHI, chlorhexidine (0.12%) rinse, OHI During RA treatment	No treatment	61.6 yr 36.4%
Khare 2016[35] India NR	RCT 3 mo 60/60 Fair 1999 definition	NR DAS28: 6.7	SRP, OHI During RA treatment	No treatment	50 yr 15%
De Pablo 2022[42] England NIHR grant	RCT 3 mo, 6 mo 60/49 Poor 2018 definition	DMARDs (47%), Biologics (33%), NSAIDs (15%), Steroids (26.5%) DAS28: 5.1	Subgingival plaque removal, OHI During RA treatment	OHI	58 yr 25%
Thilagar 2022[36] India, Saudi Arabia None	RCT 12 wk	DMARDs, corticosteroids and NSAIDs (NR %)	Oral prophylaxis with supragingival/subgingival SRP with instruction to maintain	No treatment	42.7 yr 17%

Author **Year** **Country** **Funding**	**Study design** **Followup length** **Sample size** (enrolled/analyzed) **Quality** **Periodontitis definition**	**Treatment for autoimmune disease** **Baseline disease activity level**	**Intervention group treatment** **Timing of dental treatment**	**Control group treatment**	**Mean age** **Male %**
	30/28 Poor 1999 definition	DAS28: 3.1	appropriate oral disinfection During RA treatment		
Nguyen 2021[37] Vietnam NR	RCT 3 mo, 6 mo 82/82 Poor 1999 definition	DMARDs, corticosteroids and NSAIDs (NR %) DAS28: 4.2	Supragingival SRP, OHI During RA treatment	OHI	52.4 yr 9.8%
Studies other than RCTs, with patients with RA					
Kaushal 2019[38] India NR	non-RCT 8 wk 40/40 Poor 1999 definition	NR SDAI: 29.7	Full-mouth SRP, OHI During RA treatment	No treatment	41.2 yr 19.9%
Atarbashi-Moghadam 2018[39] Iran Shahid Sadoughi University of Medical Sciences	Age- and sex-matched cohort study 6 wk, 12 wk 56/56 Poor 1999 definition	NR DAS28: 4.3	SRP, OHI NR	OHI	45.1 yr 21.4%
RCTs of patients with psoriasis					
Marruganti 2024[40] Italy NR	RCT 10 wk 74/74 Good	Biologics (anti-TNF-α, anti-IL-17, anti-IL-23) (73.9%), systemic medications (methotrexate or	Supragingival instrumentation, subgingival instrumentation, OHI During psoriasis treatment	No treatment	57.9 yr 68.9%

Author **Year** **Country** **Funding**	**Study design** **Followup length** **Sample size** (enrolled/analyzed) **Quality** **Periodontitis definition**	**Treatment for autoimmune disease** **Baseline disease activity level**	**Intervention group treatment** **Timing of dental treatment**	**Control group treatment**	**Mean age** **Male %**
	2018 definition	cyclosporine) (13.7%), none/topical/phototherapy (12.3%) PASI: 7.1			
Yarkac 2019[34] Turkey NR	RCT 8 wk 92/92 Good 2018 definition	Topical treatment only (medication not listed); none received systemic immunosuppressive therapy PASI: 5.5	Subgingival/supragingival SRP, OHI During psoriasis treatment (topical only)	No treatment	39.4 yr 53.3%
RCT of patients with SLE					
Maybodi 2022[41] Iran Shahid Sadoughi University of Medical Sciences	RCT 3 mo 90/90 Fair 2018 definition	"Standard treatment" for SLE SLEDAI: 3.3	OHI, SRP During SLE treatment	OHI	35.9 yr 12.2%

Abbreviations: csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DMARDs: disease-modifying anti-rheumatic drugs; mo: month; NR: not reported; NSAIDs: nonsteroidal anti-inflammatory drugs; OHI: oral health instruction; RA: rheumatoid arthritis; RCT: randomized controlled trial; SLE: systemic lupus erythematosus: SRP: scaling and root planing; TNF: tumor necrosis factor; wk: week; yr: year.

3.2.3.2 Reported Outcomes

Among the included studies, the most commonly reported outcome was disease activity – in the form of DAS28, DAS28-CRP, DAS28-ESR, simple disease activity index (SDAI) for RA, and psoriasis area and severity index (PASI) scores for PSO. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and quality of life (QoL) of various scales. Both studies of patients with psoriasis reported PASI. The only study of patients with SLE assessed CRP, ESR, and systemic lupus erythematosus disease activity index (SLEDAI). **Table 6** presents the outcomes assessed in the 10 included primary studies.

Table 6: Summary of findings in the included primary studies

Author Year Country	Study design Follow-up length Sample size (enrolled/analyzed) Treatment comparison Quality	Outcomes assessed	Intra-group % change in treatment group	Intra-group % change in control group	Summary of statistically significant findings for the treatment group vs control
RCTs of patients with RA					
Monsarrat 2019[33] France	RCT 3 mo 22/22 Full-mouth disinfection with SRP, systemic amoxicillin (1.5g/day or 1200 mg clindamycin if allergic for 7 days), chlorhexidine (0.12%) rinse, OHI Vs No treatment Good	**Outcome**	**Adjusted Mean Difference**		• No significant difference in any of the outcomes.
		Tender Joints (0-28)	1.94 [−2.34; 6.23]		
		Swollen Joints (0-28)	0.85 [−0.96; 2.65]		
		ESR (mm/h)	2.30 [−12.77; 17.38]		
		CRP (mg/L)	1.68 [−4.39; 7.75]		
		Patient's overall assessment (0-100)	6.25 [−7.20; 19.70]		
		Physician's overall assessment (0-100)	-4.34 [−22.23; 13.56]		
		Pain Scale (0-100)	4.00 [−10.48; 18.47]		
		DAS28-ESR	−0.03 [−0.98; 0.92]		
		GOHAI	0.10 [-0.12; 0.31]		
		HAQ (disability index)	0.06 [−0.54; 0.65]		
Khare 2016[35] India	RCT 3 mo 60/60 SRP, OHI Vs No treatment Fair	**Outcome**	**% change relative to baseline**		• Reduction in all outcomes
			Treated	**Control**	
		ESR	**-22.1***	2.43	
		VAS	**-23.8***	-0.58	
		Tender joints	**-29.8*****	0.689	
		Swollen joints	**-45.7*****	2.21	

Author Year Country	Study design Follow-up length Sample size (enrolled/analyzed) Treatment comparison Quality	Outcomes assessed	Intra-group % change in treatment group	Intra-group % change in control group	Summary of statistically significant findings for the treatment group vs control
		DAS28	**-15.3*** **	0.824	
		CRP	**-32.8***	1.17	
De Pablo 2022[42] England	RCT 3 mo, 6 mo 60/49 Subgingival plaque removal, OHI Vs OHI Poor	**Outcome**	**Relative to control**		• Greater improvement in tender joint count, global VAS, DAS28-CRP, DAS28-ESR, and MSUS scores than the control group after 3 mo of followup. However, no statistical analysis was reported.
		Tender joint count	Improved		
		Swollen joint count	Improved		
		ESR	Improved		
		VAS	Improved		
		CRP	Improved		
		DAS28-CRP	Improved		
		DAS28-ESR	Improved		
		MSUS	Improved		
Thilagar 2022[36] India, Saudi Arabia	RCT 12 wk 30/28 Oral prophylaxis with supragingival/subgingival SRP with instruction to maintain appropriate oral disinfection Vs No Treatment Poor	**Outcome**	**Median (CI)**		• Reduced CRP (p=0.001) • Reduced DAS-28 (p<0.001) • Increased anti-CCP antibodies (p=0.002)
			Treated	**Control**	
		DAS-28	**0.78 (1.26, 0.18)****	**0.05 (0.04, 0.30)**	
		CRP (mg/L)	**7.45 ± 3.45***	**2.16 ± 3.82**	
		Serum RF (IU/mL)	27 (1,160.50)	11 (2,192.75)	
		Serum anti-CCP antibody (U/mL)	**18.20 (5.57, 112.80)***	**1.00 (0.00, 22.00)**	
Nguyen 2021[37] Vietnam	RCT 3 mo, 6 mo 82/82	**Outcome**	**Median (IQR)**		• Reduced DAS28-CRP at 6 months (p=0.013)
			Treated	**Control**	

Author Year Country	Study design Follow-up length Sample size (enrolled/analyzed) Treatment comparison Quality	Outcomes assessed	Intra-group % change in treatment group	Intra-group % change in control group	Summary of statistically significant findings for the treatment group vs control
	Supragingival SRP, OHI Vs OHI Poor				• Increased remission rates (p=0.028) • All other outcomes not significant.
		DAS28-CRP at 3 mo	3.5 (3.0-4.7)	4.0 (3.5-4.7)	
		CRP (mg/L) at 3 mo	3.9 (1.5-12.9)	4.4 (1.2-15.2)	
		RF (IU/mL) at 3 mo	8.0 (8.0-50.8)	8.0 (8.0-49.2)	
		ACPAs (IU/mL) at 3 mo	NA	NA	
		ESR (mm/h) at 3 mo	28 (17-41)	24 (14.5-40.5)	
		DAS28-CRP at 6 mo	**3.2 (2.5-4.0)**	**3.6 (3.3-4.5)**	
		CRP (mg/L) at 6 mo	3.5 (0.7-9.9)	4.4 (1.1-11.8)	
		RF (IU/mL) at 6 mo	12.1 (8.0-65.9)	13.6 (7.9-57.0)	
		ACPAs (IU/mL) at 6 mo	42.7 (7.10-185.0)	102.3 (9.6-794.0)	
		ESR (mm/h) at 6 mo	20.5 (11-28)	20.5 (11-32)	
Studies other than RCTs, with patients with RA					
Kaushal 2019[38] India	non-RCT 8 wk 40/40 Full-mouth SRP, OHI Vs No treatment Poor	**Outcome**	**Mean +/- SD**		• Reduced SDAI.
			Treated	**Control**	
		ACPAs	0.13 ± 0.32	0.18 ± 0.36	
		CRP	0.04 ± 0.02	0.11 ± 0.13	
		RF	0.52 ± 0.51	0.66 ± 0.50	
		SDAI	**11.48 ± 4.21*** **	**4.24 ± 3.30**	

Author Year Country	Study design Follow-up length Sample size (enrolled/analyzed) Treatment comparison Quality	Outcomes assessed	Intra-group % change in treatment group	Intra-group % change in control group	Summary of statistically significant findings for the treatment group vs control
Atarbashi-Moghadam 2018[39] Iran	Age- and sex-matched cohort study 6 wk, 12 wk 56/56 SRP, OHI Vs OHI Poor	**Outcome**	**Mean +/- SD**		• Reduction in DAS28 in both treatment and control groups at both 6 wk and 12 wk. • At 12 wk, the treatment group had significantly lower DAS28 than the control group (p=0.015), but analysis to compare the mean change between groups was not reported.
			Treated	**Control**	
		DAS28 at 6 wk	**3.87 (SD NR)*****	**3.56 (SD NR)*****	
		DAS28 at 12 wk	**3.71 (SD NR)*****	**3.52 (SD NR)*****	
RCTs of patients with psoriasis					
Marruganti 2024[40] Italy	RCT 10 wk 74/74 Supragingival instrumentation, subgingival instrumentation, OHI Vs No treatment Good	**Outcome**	**Adjusted Mean Difference or Odds Ratio**		• Reduced PASI score (p=0.001) • Reduced BSA (p<0.001) • Lower odds of having severe psoriasis per composite score (adjOR=0.2, p=0.005) and moderate-to-severe psoriasis per BSA categorization (adjOR=0.4, p=0.009), compared with the control group. • No difference in DLQI.
		PASI	**−4.9 (95% CI: −6.2, −3.4)****		
		BSA	**−4.7 (95% CI:−6.4, −3.3) ****		
		DLQI	−2.0 (95% CI: −3.2, 0.9)		
		PASI ≥7 (severe disease)	-OR = 0.4 (95% CI: 0.1, 1.1)		
		BSA ≥4% (moderate/severe disease)	**OR = 0.4 (95% CI: 0.1, 0.9)****		
		Composite score ([BSA ≥4% or PASI>10] & DLQI>10)	**OR = 0.2 (95% CI: 0.03, 0.8)**** **23.1**		
Yarkac 2019[34] Turkey	RCT 8 wk 92/92 Subgingival/supragingival SRP, OHI Vs No treatment Good	**Outcome**	**Mean +/- SD**		• Significant changes in all outcomes • At 8 wks, there were significant differences reported between groups in all outcomes, but analysis to compare the mean change between groups was not reported.
			Treated	**Control**	
		PASI	**3.47 ± 2.67*****	**4.80 ± 2.13**	
		Il-2 (pg/mL)	**19.67 ± 1.65*****	**22.97 ± 7.24**	

Author Year Country	Study design Follow-up length Sample size (enrolled/analyzed) Treatment comparison Quality	Outcomes assessed	Intra-group % change in treatment group	Intra-group % change in control group	Summary of statistically significant findings for the treatment group vs control
		IL-6 (pg/mL)	**12.05 ± 4.79****	**15.87 ± 8.97**	
		sIgA (ng/mL)	**13.91 ± 4.08***	**10.79 ± 3.78**	
RCT of patients with SLE					
Maybodi 2022[41] Iran	RCT 3 mo 90/90 OHI, SRP Vs OHI Fair	**Outcome**	**% change relative to baseline**		• No difference in the change in SLEDAI (p=0.89) • Reduced CRP (p=0.004) and • Reduced ESR (p=0.03)
			Treated	**Control**	
		SLEDAI	-28.4	-23.6	
		CRP	**-42.9****	**-13.5**	
		ESR	-28.4*	-10.7	

Statistically significant change from baseline (intra-group) P-value: *≤0.05; **≤0.01; ***≤0.001
Abbreviations: ACPAs: anti-citrullinated protein autoantibodies; BSA: body surface area; CRP: C-reactive protein; DAS: disease activity score; DLQI: dermatological life quality index; ESR: erythrocyte sedimentation rate; GOHAI: general oral health assessment index; HAQ: health assessment questionnaire; HRQoL: health-related quality of life; IL: interleukin; mo: month; MSUS: musculoskeletal ultrasound; NR: not reported; NSPT: non-surgical periodontal treatment; OHI: oral health instruction; PASI: psoriasis area and severity index; RA: rheumatoid arthritis; RF: rheumatoid factor; RCT: randomized controlled trial; SDAI: simple disease activity index; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; SRP: scaling and root planing; VAS: visual analog scale; wk: week.

3.2.3.3 Outcomes for Patients with RA

- The evidence generally supports the effectiveness of NSPT on disease activity and inflammatory biomarkers.
- All included studies examined the effect of NSPT during RA treatments. Evidence regarding the effect of dental services before immunosuppressive treatment was not available.
- One good-quality RCT, 1 fair-quality RCT, 3 poor-quality RCTs, and 2 poor-quality studies of other designs evaluated the effect of NSPT among patients with RA.

Five RCTs,[33,35–37,42] one non-randomized interventional controlled study,[38] and one matched cohort study[39] evaluated the effect of periodontal treatments among patients with RA. These studies reported mixed results.

Nguyen 2021 reported that six months after receiving SRP and OHI, patients in the treatment group had statistically significantly better DAS28-CRP and RA disease activity level,

compared with those who received OHI only.[37] However, significant differences between groups were not found in CRP, ESR, RF, and ACPAs. Similarly, Kaushal 2019, a non-RCT, found statistically significantly greater improvement in disease activity per SDAI in the treatment group compared with the control group, but no difference in CRP, RF, and ACCP.[38] On the other hand, Thilagar 2022 found that compared with patients who received no treatment, those who received the combination of oral prophylaxis, SRP, and OHI had statistically significantly greater improvements in CRP and DAS-28 but worsened anti-CCP antibody levels.[36] Another RCT, Monsarrat 2019, compared the combination of full-mouth disinfection with SRP, oral prophylaxis, OHI, and oral rinse with no treatment, and found no difference in any outcomes after 3 months.[33]

Khare 2016, a RCT with 3-month follow-up, reported statistically significant improvements in all outcomes in the treatment group, but did not provide between-group analyses.[35] Similarly, Atarbashi-Moghadam 2018, an age- and sex-matched observational study reported that at 12 weeks, patients who received SRP and OHI had significantly lower DAS28 than patients who received OHI only.[39] However, statistical analysis to compare the mean change from baseline between groups was not available.

One RCT stated that statistically significant improvements were found among patients who received NSPT, but did not report numeric data.[42]

3.2.3.4 Outcomes for Patients with Psoriasis

- Moderate evidence for improvement in disease activity was seen (two good-quality RCTs) in patients with PSO reported significant improvement in disease activities (PASI), body surface area (BSA), and inflammatory markers (IL-2, IL-6, and sIgA).
- Both RCTs examined the effect of NSPT during PSO treatments. Evidence evaluating the effect of dental services during immunosuppressive treatment was not available.

Two RCTs evaluated the effect of NSPT among patients with psoriasis. Both studies were conducted in Europe and compared the combination of SRP and OHI with no treatment. Both studies followed up patients for less than 3 months.

Marruganti 2024 reported that 10 weeks after intervention, patients who received NSPT had statistically significantly greater decreases in PASI score ($p=0.001$) and BSA ($p<0.001$), compared with those in the control group.[40] In addition, those in the treatment group had lower odds of having severe psoriasis per composite score (adjOR=0.2, $p=0.005$) and moderate-to-severe psoriasis per BSA categorization (adjOR=0.4, $p=0.009$), compared with the control group. There was no statistically significant difference in DLQI.

Among all included primary studies, Yarkac 2019 was the only RCT that measured IL-2, IL-6, and sIgA levels in saliva samples.[34] At the 8-week follow-up, statistically significant changes from baseline were observed for all measured outcomes (PASI, IL-2, IL-6, and sIgA) in the treatment group but not in the control group. However, statistical analysis comparing the changes between treatment and control groups was not available.

3.2.3.5 Outcomes for Patients with SLE

- Insufficient evidence of no effect on disease activity in SLE (1 fair quality RCT)
- Weak evidence for significant improvement in CRP and ESR (1 fair quality RCT)

- This RCT did not evaluate the effect of dental services during immunosuppressive treatment. Evidence regarding the effect of dental services before immunosuppressive treatment was not available.

We identified only 1 RCT that enrolled SLE patients.[41] Maybodi 2022 randomly assigned 90 patients with SLE to either SRP and OHI or OHI alone and followed up after 3 months. Compared with the control group, patients in the treatment group had statistically significant greater decreases from baseline in CRP (p=0.004) and ESR (p=0.03). There was no difference in the change in SLEDAI between groups (p=0.89).

3.3 Key Question 2

Key Question 2: What are the clinical practice guidelines or standards for dental care for people with autoimmune diseases treated with biologics and other immunosuppressants?

3.3.1 Key points

- Of the 31 clinical practice guidelines that were identified from our searches, only one official clinical practice guideline on dental care was available. This guideline focused on Sjogren's syndrome.
- The American Dental Association published a practice guide that outlined various aspects of dental management for RA, lupus, Sjogren's syndrome, and scleroderma.
- The British Dental Association provided a review and guidance for oral health management for patients with RA.
- The National Scleroderma Foundation published a patient-oriented fact sheet that included description and treatment of common oral health issues among patients with scleroderma.

Of the 31 articles that contained clinical practice guidelines pertinent to autoimmune diseases,[43-72] only one official guideline focused on dental care recommendations for patients with autoimmune diseases, specifically Sjögren's Syndrome.[43] Established by the Sjogren's Syndrome Foundation, this clinical practice guideline outlined 4 oral management recommendations, of which only 1 recommendation – the use of topical fluoride – was graded as a strong recommendation.

Several professional organizations provided guidance on oral management among patients with autoimmune diseases. The American Dental Association (ADA) published the ADA Practice Guide which included a chapter on oral management for patients with autoimmune and connective tissue diseases.[70] While the ADA stated that these were not official guidelines, this book chapter outlined various aspects of dental management (evaluation, treatment, modifications, oral lesion diagnosis and management, and risk of dental care) for 4 autoimmune disease patient groups: RA, SLE, Sorgren's syndrome, and scleroderma. The British Dental Association (BDA) produced a guidance article that included an overview of oral care for patients with RA, with emphasis on periodontal diseases, temporomandibular dysfunction, and salivary gland dysfunction.[45] Also, the BDA stressed the importance of communication between dental service providers and rheumatology practitioners for an interdisciplinary collaborative disease management. Lastly, a patient-oriented fact sheet by the National Scleroderma

Foundation provided description and treatment of various common oral health issues among patients with scleroderma, and encouraged patients to seek help from both dental service providers as well as rheumatologists.[44] The three documents, highlighted in **Table 7** below, share a common message regarding the significance of oral health challenges faced by patients across the diverse types of autoimmune diseases, as well as the difficulties in treatment, and the importance of early dental interventions and consistent care in order to manage complications such as periodontal disease as in the case of RA and dental caries with Sjögren's disease.

The remaining 27 articles included 17 clinical practice guidelines and 10 recommendations, across RA, psoriasis, SLE, and other autoimmune diseases, and notably did not include any recommendations for dental care for patients with autoimmune diseases (Appendix C). Eight previous versions of the included guidelines or recommendations were reviewed and also found to not note any dental management recommendations. Notably, practice guidelines from the European Alliance of Associations for Rheumatology (EULAR), the American College of Rheumatology (ACR), the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the National Institute for Health and Care Excellence (NICE) did not mention dental care guidelines for patients across autoimmune diseases.

Table 7: Guidelines for managing patients with autoimmune diseases, and reference dental care

Source	Title	Type of article	Recommendations for dental care
Regarding various autoimmune diseases			
American Dental Association[70] (Rossi 2015)	The ADA Practice Guide. Ch 10. Autoimmune and Connective Tissue Diseases	Practice Guide	This practice guide outlined various aspects of dental management: evaluation, treatment modifications, oral lesion diagnosis and management, and risk of dental care. Specific recommendations were available for RA, lupus, Sjogren syndrome, and scleroderma.
Regarding specific autoimmune diseases			
Sjögren's Syndrome Foundation (Zero 2016)[43]	Clinical practice guidelines for oral management of Sjögren disease: dental caries prevention	Clinical Practice Guideline	Recommendations included: topical fluoride for all patients (strong), increase saliva through stimulation (weak), chlorhexidine (weak), nonfluroide remineralizing agents (moderate).
British Dental Association (Souza 2017)[45]	Managing patients with rheumatoid arthritis	Guidance	This guidance included management for periodontal diseases, temporomandibular dysfunction, and salivary gland dysfunction. Also, communication between dental service provider and rheumatologist was emphasized.
National Scleroderma Foundation (Castillo 2019)[44]	Dental care in scleroderma	Fact sheet	This patient-focused fact sheet included description and treatments of various oral health issues common in scleroderma, and encouraged patients to seek help from both the dentist and the rheumatologist.

4. Discussion

Overview

The aim of this rapid response report proposal was to identify and evaluate the evidence for the effectiveness of dental services on health outcomes on patients with autoimmune diseases treated with biologics DMARDS and non-biologic DMARDS. Most of the included studies had patients who were on either therapy or even a mix of both therapy types.

Two key questions have been posed for this review – first to evaluate recent evidence (KQ1), and second to summarize current clinical guidelines on oral health management among autoimmune diseases (KQ2).

For KQ1, pertaining to the effect of dental services on autoimmune disease outcomes either before or during treatment for the AI condition, our comprehensive literature search for evidence published in the last eight years found a modest amount of primary research data for patients with RA, limited data for patients with psoriasis or SLE, and no data for patients with other autoimmune diseases. Similarly, all of the identified published systematic reviews examined data relevant to patients with RA only. Despite specifically including search terms for the 20 most common AI diseases in our search strategy, we did not identify relevant studies for many AI conditions. Notably, our search identified 4 studies on Sjogren's syndrome that were excluded based on the pre-defined PICOTS criteria. Two studies reported the dental outcomes or the longevity of dental restorations (outcomes not of interest), and did not report AI-treatment related outcomes.[73,74] Another study evaluated the use of a sodium carbonate spray during dental treatment (intervention not of interest).[75] A fourth study of Sjogren's syndrome included healthy controls (comparator not of interest).[76] The current evidence assessing the potential influence of dental care among patients with other autoimmune diseases appears to be lacking.

All included primary studies and systematic reviews assessed the effectiveness of non-surgical periodontal treatment only. We did not identify any literature on the effect of other dental services, such as preventive oral care, routine dental cleaning, regular oral examination, tooth extractions, fillings, or dental implants. Furthermore, all included studies enrolled patients with pre-existing periodontitis and autoimmune disease, and thus, we were unable to assess whether the timing of dental services might affect autoimmune disease outcomes. In almost all included studies, authors noted no change in AI prescriptions or dosage during the course of the study.

To address KQ1, we note that the most commonly reported outcome pertains to disease activity-related outcomes, reported variously as DAS28, DAS28-CRP, DAS28-ESR or SDAI for RA, PASI for PSO and SLEDAI for SLE. The impact of periodontal treatment is a consistent reduction of disease activity outcomes in 3 of the 3 SRs as well as in eight of the 10 included primary studies (**Table 3**). The clinical implications of disease activity score reduction (DASR) are notable. According to the EULAR guidelines, DASR greater than 0.6 signifies a clinically meaningful improvement.[77] In the included RA studies in this review, the median DAS28 score was 4.2 and the reductions in the DAS post-NSPT ranged between 0.7 - 1.2, signifying that in the included RA studies, the DASR indicated a moderate improvement of disease activity. For the 2 PSO studies,[34,40] the reduction in PASI scores post-NSPT ranged between 40 - 60% at 8-10 weeks post-NSPT, depending on the severity of PSO. As a reference, PASI 75 (75% reduction in PASI score) is a common endpoint used in PSO trials.[78] The reductions in PASI scores at 3-6 months post-NSPT may be considered half as effective as a therapeutic meeting the PASI 75 target. In addition, a significant reduction in the BSA score was also concomitantly seen in one of the PSO studies,[40] further offering weak evidence that NSPT results in reduced disease

activity in PSO. In the SLE study[41] included in this review, there was no difference in the disease activity between cases and controls.

In the context of NSPT for patients with RA, PSO or SLE, there is also a consistent, statistically significant reduction in inflammatory outcomes. Since inflammation is one of the primary hallmarks of autoimmune disease, a reduction in the inflammatory state in patients with AI disease could be considered clinically beneficial. We find that 3 of the SRs and 8 of the 10 primary studies also show a significant reduction in one or more of CRP, ESR and various cytokines. Other outcomes like tender or swollen joints, ACPAs, RF, pain index and others were reported sporadically and there is insufficient evidence for these outcomes.

Except for one RCT with 6-month follow-up, all primary studies that provided numeric data followed patients for 3 months or less. Longer term outcomes over 6 months were not available. While statistically significant improvements were reported for disease activity and some inflammatory biomarkers, heterogeneity across studies was high. While most studies reported trends of change from baseline, statistical significance of the differences between the treatment and control groups were often not reported or not found in many of the included studies.

There are reports in the literature of opportunistic infections in persons treated for AI disease.[79,80] In this evidence base, none of the included studies reported on the impact of NSPT on adverse effects of therapies for autoimmune conditions. In one RCT,[33] patients with RA and treated with an unspecified combination of conventional and biologic DMARDS, glucocorticoids and NSAIDS in both arms (6 in the control arm and 8 subjects in the treatment arm) were reported as being hospitalized with a health problem but the article did not specify what the health issues were, and the incidence of these hospitalizations was not significant between the two arms.

There is a lack of consistent and established recommendations and/or protocols for the treatment of dental conditions in patients with RA, psoriasis, SLE, and other autoimmune conditions. Our detailed search of clinical practice guidelines of various autoimmune diseases identified only one guideline on Sjogren's disease that contains dental management guidelines.

Strengths

This rapid response review was strengthened by restricting to study designs that provide comparative evidence (RCTs and other controlled observational studies), the inclusion of data generated outside of the US, and the utilization of estimated risk of bias assessment tools. Our review also highlights the existing research gap. The strength of these studies also lies in the consistent finding across multiple RCTs that periodontal therapy can significantly lower disease activity for RA and PSO, in spite of the underlying heterogeneity of the studies. The inclusion of diverse populations from different countries also adds to the generalizability of the findings, suggesting that the benefits of periodontal therapy for autoimmune disease-relevant outcomes may apply broadly across various demographic groups.

Clinical Implications

The clinical implications of the studies reviewed as part of KQ1 are significant, considering the near-consistent reduction in disease activity and inflammation, upon NSPT. The reduction in disease activity post-NSPT is observed in a majority of the studies and SRs for which evidence is available. However, the mixed results from these studies point to the need for additional higher quality studies with sufficient power to identify any subgroups of the disease

populations that might do better than others upon receiving NSPT. Additionally, it might be important to tease out any differences between biologics and conventional DMARDS to shed light on whether the type of therapy for the patient makes a difference in the lowering of the disease activity post-NSPT.

Limitations

There are several limitations to the current body of evidence. The variability in study designs, including differences in periodontal treatment protocols, follow-up durations, and outcome measures, precludes the ability to draw definitive conclusions about the benefits of periodontal therapy.

Furthermore, many studies had relatively short follow-up periods, which may not fully capture the long-term effects of periodontal therapy on AI disease-related outcomes or evaluate the impact of recurring maintenance treatments in addition to the original NSPT on maintaining reduced disease activity. Longer follow-up periods are necessary to determine whether the observed benefits are sustained over time and whether they translate into meaningful reductions in AI disease-related complications and mortality.

Lastly, the generalizability of the findings may be limited by the specific populations studied. While the inclusion of diverse populations from different countries is a strength, the applicability to the US population is not known due to the different racial and ethnic demographics.[81]

Future studies to evaluate dental services other than non-surgical periodontal treatment, and studies that include patients with autoimmune diseases other than RA, may enrich our understanding on the potential inextricable link between dental services and autoimmune disease treatment.

5. Conclusions

The body of evidence evaluating the effect of dental services on autoimmune disease-related outcomes focused on patients with rheumatoid arthritis who received non-surgical periodontal treatment. Results from both randomized controlled trials and non-randomized controlled studies showed moderate evidence of reduced disease activity and weak evidence for the reduction in inflammatory markers in the short term upon non-surgical periodontal treatment among patients with RA, PSO and SLE. Data on other autoimmune disease populations were absent. There is also a lack of standards for dental care in clinical practice guidelines for patients with autoimmune disease.

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Abbreviations and Acronyms

Acronym	Definition
AARDA	The American Autoimmune Related Diseases Association
ACPAs	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADA	American Dental Association
adjOR	Adjusted odds ratio
AHRQ	Agency for Healthcare Research and Quality
AI	Autoimmune
anti-CCP	Anti-cyclic citrullinated peptide
BSA	Body surface area
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CRP	C-reactive protein
DAS	Disease activity score
DLQI	Dermatological Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
GOHAI	General Oral Health Assessment Index
HAQ	Health assessment questionnaire
HRQoL	Health-related quality of life
IL	Interleukin
KQ	Key question
lcSSc	Limited cutaneous systemic sclerosis
MA	Meta-analysis
mo	Month
MSUS	Musculoskeletal ultrasound
NA	Not applicable
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSPT	Non-surgical periodontal therapy
OHI	Oral health instruction

OHRQoL	Oral-health-related quality of life
PASI	Psoriasis area and severity index
PD	Periodontitis
PICOTS	Population, Intervention, Comparator, Outcome(s), Timing, and Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSO	Psoriasis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RF	Rheumatoid factor
RoB	Risk of bias
RR	Relative risk
SDAI	Simple disease activity index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SME	Subject matter expert
SR	Systematic review
SRP	Scaling and root planing
TNF	Tumor necrosis factor
USPSTF	United States Preventive Services Task Force
VAS	Visual analogue scale
wk	Week
yr	Year

Appendix A.

Literature search strategy (2 tables).

Search strategy #1		
Set#	**Searched for**	**# Results**
S1	MJEMB.EXACT.EXPLODE("autoimmune disease") OR MJMESH.EXACT.EXPLODE("Autoimmune Diseases") OR MJSUB("Autoimmune Disorders") OR TI,AB,SU((autoimmun* OR "auto-immun*" OR inflammatory OR autoinflammatory OR "auto-inflammatory" OR "immune-mediated") N/2 (disease* OR disorder* OR comorbid* OR "co-morbid*" OR condition*) OR "immune-mediated inflammatory disease*" OR IMID*)	2772347
S2	MJEMB.EXACT.EXPLODE("rheumatoid arthritis") OR MJMESH.EXACT.EXPLODE("Arthritis, Rheumatoid") OR MJSUB("Rheumatoid Arthritis") OR TI,AB,SU(((rheumatoid OR rheumatic OR inflammatory) N/2 (arthrit* OR polyarthrit* OR nodul* OR vasculitis)) OR rheumarthritis OR rheumatism OR "Caplan* syndrome" OR "Felty* syndrome" OR "Still* disease" OR "Beauvais* disease")	1043097
S3	MJEMB.EXACT.EXPLODE("inflammatory bowel disease") OR MJMESH.EXACT.EXPLODE("Inflammatory Bowel Diseases") OR TI,AB,SU((("inflammatory bowel" N/1 (disease* OR disorder*)) OR IBD OR Crohn* OR (ulcerativ* N/1 colitis)))	645908
S4	MJEMB.EXACT.EXPLODE("systemic lupus erythematosus") OR MJMESH.EXACT.EXPLODE("Lupus Erythematosus, Systemic") OR MJSUB("Lupus") OR TI,AB,SU("systemic lupus erythematosus" OR SLE OR lupus)	471605
S5	MJEMB.EXACT.EXPLODE("psoriatic arthritis") OR MJMESH.EXACT.EXPLODE("Arthritis, Psoriatic") OR TI,AB,SU(((psoriasis OR psoriatic) N/2 (arthrit* OR polyarthrit*)))	83544
S6	MJEMB.EXACT.EXPLODE("psoriasis") OR MJMESH.EXACT.EXPLODE("Psoriasis") OR TI,AB,SU(psoriasis OR pustulosis)	278914
S7	MJEMB.EXACT.EXPLODE("Sjoegren syndrome") OR MJMESH.EXACT.EXPLODE("Sjogren's Syndrome") OR TI,AB,SU((Sicca OR Sjogren*) N/1 syndrome)	83257
S8	MJEMB.EXACT.EXPLODE("systemic sclerosis") OR MJMESH.EXACT.EXPLODE("Scleroderma, Systemic") OR TI,AB,SU("systemic sclerosis" OR scleroderma)	150135
S9	S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1	4066991
S10	MJEMB.EXACT.EXPLODE("dental procedure") OR MJEMB.EXACT("dental health") OR MJEMB.EXACT.EXPLODE("preventive dentistry") OR MJEMB.EXACT("mouth hygiene") OR MJEMB.EXACT.EXPLODE("dental prophylaxis") OR MJEMB.EXACT.EXPLODE("periodontics") OR MJEMB.EXACT("pulpitis") OR MJEMB.EXACT.EXPLODE("thrush") OR MJEMB.EXACT.EXPLODE("stomatitis") OR MJEMB.EXACT("xerostomia") OR MJEMB.EXACT.EXPLODE("periodontal disease") OR MJEMB.EXACT.EXPLODE("dental caries") OR MJEMB.EXACT("edentulism") OR MJMESH.EXACT.EXPLODE("Dental Health Services") OR MJMESH.EXACT("Oral Health") OR MJMESH.EXACT.EXPLODE("Preventive Dentistry") OR MJMESH.EXACT.EXPLODE("Oral Hygiene") OR MJMESH.EXACT.EXPLODE("Dental Prophylaxis") OR MJMESH.EXACT.EXPLODE("Periodontics") OR MJMESH.EXACT("Pulpitis") OR MJMESH.EXACT("Candidiasis, Oral") OR MJMESH.EXACT.EXPLODE("Stomatitis") OR MJMESH.EXACT.EXPLODE("Xerostomia") OR MJMESH.EXACT.EXPLODE("Periodontal Diseases") OR MJMESH.EXACT.EXPLODE("Dental Caries") OR MJMESH.EXACT.EXPLODE("Mouth, Edentulous")	572904
S11	TI,AB(dental OR dentistry OR periodont* OR gingivitis OR (gum N/2 (disease* OR infection*)) OR ((dental OR tooth OR teeth OR root OR periapical) N/2 (cavit* OR caries OR carious OR decay* OR lesion*)) OR "oral care" OR "oral health*" OR "oral disease*" OR "oral dysbiosis" OR ((DMF OR DMFT OR DMFS) N/2 index*) OR edentul*)	1313578
S12	TI,AB(((dental OR endodont* OR periapical OR periodont* OR *gingival OR tooth OR teeth OR mouth OR oral OR pulpal) N/2 (abscess* OR disease* OR infection* OR loss*)) OR pulpitis OR "oral candidiasis" OR stomatitis OR xerostomia)	376819
S13	TI,AB((dental OR dentistry OR periodont* OR endodont* OR periapical OR root OR *gingival OR edentul*) N/2 (treatment* OR treating OR treated OR therap* OR intervention* OR procedure* OR planing OR scaling OR debridement OR curettage OR preventive OR preventative OR prophylaxis))	252983
S14	S13 OR S12 OR S11 OR S10	1769099

S15	S14 AND S9	79704
S16	S15 NOT (EMB.EXACT("dental care for children") OR EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT("pregnant woman") OR EMB.EXACT.EXPLODE("child") OR EMB.EXACT.EXPLODE("infant") OR EMB.EXACT("adolescent") OR MESH.EXACT("Dental Care for Children") OR MESH.EXACT.EXPLODE("Pregnancy") OR MESH.EXACT("Pregnant Women") OR MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR MESH.EXACT("Adolescent") OR TI,AB(pregnan* OR child* OR infant* OR adolescent* OR teen* OR juvenile* OR baby OR babies))	70132
S17	S16 AND (TI,AB,SU,DTYPE((systematic N/1 review*) OR "meta analys?s" OR "meta-analys?s" OR metaanalys?s))	2224
S18	S16 AND (TI,AB((("case-control" OR clinical OR comparat$3 OR control[*4] OR blinded OR "single-blind[*2]" OR "single blind[*2]" OR "double-blind[*2]" OR "double blind[*2]" OR "triple-blind[*2]" OR "triple blind[*2]" OR crossover OR "cross-over" OR "cross over" OR multicenter[*2] OR "multi-center[*2]" OR "multi center[*2]" OR multicentre[*2] OR "multi-centre[*2]" OR "multi centre[*2]" OR exploratory OR interventional OR observational OR pivotal OR random[*5] OR retrospective OR systematic) N/3 (analys$s OR evaluation[*1] OR review[*1] OR stud[*3] OR trial[*1])) OR (Phase N/1 ("0" OR "1" OR "1a" OR "1b" OR "2" OR "2a" OR "2b" OR "3" OR "3a" OR "3b" OR "4" OR "I" OR "Ia" OR "Ib" OR "II" OR "IIa" OR "IIb" OR "III" OR "IIIa" OR "IIIb" OR "IV"))))	11032
S19	S18 OR S17	11533
S20	S19 AND YR(>=2016)	6784
S21	S20 NOT (TI,AB(cancer* OR neoplasm* OR malignan* OR tumo$r* OR diabetes OR diabetic* OR prediabetic*))	5784
S22	S21 NOT ("animal model[*1]" OR rat OR rats OR mouse OR mice OR gerbil OR gerbils OR "guinea pig" OR "guinea pigs" OR hamster OR hamsters OR rodent OR rodents OR rabbit OR rabbits OR hare OR hares OR dog OR dogs OR puppy OR puppies OR beagle[*1] OR "german shepherd[*1]" OR "labrador retriever[*1]" OR "golden retriever[*1]" OR cat OR cats OR kitten OR kittens OR monkey OR monkies OR monkeys OR baboon[*1] OR macaque[*1] OR simian[*1] OR chimp[*1] OR chimpanzee[*1] OR orangutan[*1] OR "non-human primate[*1]" OR "nonhuman primate[*1]" OR pig OR pigs OR piglet OR piglets OR horse OR horses OR cattle OR cow OR cows OR bull OR bulls OR sheep OR ram OR rams OR ewe OR ewes OR lamb OR lambs OR bird[*1] OR chick[*1] OR chicken[*1] OR poult[*2] OR fish[*2] OR zebrafish[*2] OR "zebra fish[*2]" OR "in vitro" OR transfect[*3] OR "cell line[*1]")	5177
S23	S22 NOT TI,AB(healthy N/1 (control$1 OR volunteer$1 OR participant$1))	4597
S24	S23 NOT TI,SU,DTYPE("erratum" OR "errata")	4589
S25	S24 AND TI,AB(((dental OR dentistry OR periodont* OR endodont* OR periapical OR *gingival OR (oral N/2 (health OR care))) N/2 (therap* OR treatment* OR treated OR treating OR "before and after" OR preventive OR preventative OR prophylaxis)))	660
S26	S25 AND TI(autoimmun* OR "auto-immun*" OR inflammatory OR autoinflammatory OR "auto-inflammatory" OR "immune-mediated" OR rheumatoid OR rheumatic OR arthrit* OR polyarthrit* OR rheumarthritis OR rheumatism OR "inflammatory bowel" OR IBD OR Crohn* OR (ulcerativ* N/1 colitis) OR "systemic lupus erythematosus" OR SLE OR lupus OR psoriasis OR psoriatic OR pustulosis OR Sicca OR Sjogren* OR sclerosis OR scleroderma)	91°

Search strategy #2		
Set#	**Searched for**	**# Results**
S1	MJEMB.EXACT.EXPLODE("autoimmune disease") OR MJMESH.EXACT.EXPLODE("Autoimmune Diseases") OR MJSUB("Autoimmune Disorders") OR TI,AB,SU((autoimmun* OR "auto-immun*" OR inflammatory OR autoinflammatory OR "auto-inflammatory" OR "immune-mediated") N/2 (disease* OR disorder* OR comorbid* OR "co-morbid*" OR condition*) OR "immune-mediated inflammatory disease*" OR IMID*)	2772347
S2	MJEMB.EXACT.EXPLODE("rheumatoid arthritis") OR MJMESH.EXACT.EXPLODE("Arthritis, Rheumatoid") OR MJSUB("Rheumatoid Arthritis") OR TI,AB,SU(((rheumatoid OR rheumatic OR inflammatory) N/2 (arthrit* OR polyarthrit* OR nodul* OR vasculitis)) OR rheumarthritis OR rheumatism OR "Caplan* syndrome" OR "Felty* syndrome" OR "Still* disease" OR "Beauvais* disease")	1043097

S3	MJEMB.EXACT.EXPLODE("inflammatory bowel disease") OR MJMESH.EXACT.EXPLODE("Inflammatory Bowel Diseases") OR TI,AB,SU((("inflammatory bowel" N/1 (disease* OR disorder*)) OR IBD OR Crohn* OR (ulcerativ* N/1 colitis)))	645908
S4	MJEMB.EXACT.EXPLODE("systemic lupus erythematosus") OR MJMESH.EXACT.EXPLODE("Lupus Erythematosus, Systemic") OR MJSUB("Lupus") OR TI,AB,SU("systemic lupus erythematosus" OR SLE OR lupus)	471605
S5	MJEMB.EXACT.EXPLODE("psoriatic arthritis") OR MJMESH.EXACT.EXPLODE("Arthritis, Psoriatic") OR TI,AB,SU(((psoriasis OR psoriatic) N/2 (arthrit* OR polyarthrit*)))	83544
S6	MJEMB.EXACT.EXPLODE("psoriasis") OR MJMESH.EXACT.EXPLODE("Psoriasis") OR TI,AB,SU(psoriasis OR pustulosis)	278914
S7	MJEMB.EXACT.EXPLODE("Sjoegren syndrome") OR MJMESH.EXACT.EXPLODE("Sjogren's Syndrome") OR TI,AB,SU((Sicca OR Sjogren*) N/1 syndrome)	83257
S8	MJEMB.EXACT.EXPLODE("systemic sclerosis") OR MJMESH.EXACT.EXPLODE("Scleroderma, Systemic") OR TI,AB,SU("systemic sclerosis" OR scleroderma)	150135
S9	S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1	4066991
S10	MJEMB.EXACT.EXPLODE("dental procedure") OR MJEMB.EXACT("dental health") OR MJEMB.EXACT.EXPLODE("preventive dentistry") OR MJEMB.EXACT("mouth hygiene") OR MJEMB.EXACT.EXPLODE("dental prophylaxis") OR MJEMB.EXACT.EXPLODE("periodontics") OR MJEMB.EXACT("pulpitis") OR MJEMB.EXACT.EXPLODE("thrush") OR MJEMB.EXACT.EXPLODE("stomatitis") OR MJEMB.EXACT("xerostomia") OR MJEMB.EXACT.EXPLODE("periodontal disease") OR MJEMB.EXACT.EXPLODE("dental caries") OR MJEMB.EXACT("edentulism") OR MJMESH.EXACT.EXPLODE("Dental Health Services") OR MJMESH.EXACT("Oral Health") OR MJMESH.EXACT.EXPLODE("Preventive Dentistry") OR MJMESH.EXACT.EXPLODE("Oral Hygiene") OR MJMESH.EXACT.EXPLODE("Dental Prophylaxis") OR MJMESH.EXACT.EXPLODE("Periodontics") OR MJMESH.EXACT("Pulpitis") OR MJMESH.EXACT("Candidiasis, Oral") OR MJMESH.EXACT.EXPLODE("Stomatitis") OR MJMESH.EXACT.EXPLODE("Xerostomia") OR MJMESH.EXACT.EXPLODE("Periodontal Diseases") OR MJMESH.EXACT.EXPLODE("Dental Caries") OR MJMESH.EXACT.EXPLODE("Mouth, Edentulous")	572904
S11	TI,AB(dental OR dentistry OR periodont* OR gingivitis OR (gum N/2 (disease* OR infection*)) OR ((dental OR tooth OR teeth OR root OR periapical) N/2 (cavit* OR caries OR carious OR decay* OR lesion*)) OR "oral care" OR "oral health*" OR "oral disease*" OR "oral dysbiosis" OR ((DMF OR DMFT OR DMFS) N/2 index*) OR edentul*)	1313578
S12	TI,AB(((dental OR endodont* OR periapical OR periodont* OR *gingival OR tooth OR teeth OR mouth OR oral OR pulpal) N/2 (abscess* OR disease* OR infection* OR loss*)) OR pulpitis OR "oral candidiasis" OR stomatitis OR xerostomia)	376819
S13	TI,AB((dental OR dentistry OR periodont* OR endodont* OR periapical OR root OR *gingival OR edentul*) N/2 (treatment* OR treating OR treated OR therap* OR intervention* OR procedure* OR planing OR scaling OR debridement OR curettage OR preventive OR preventative OR prophylaxis))	252983
S14	S13 OR S12 OR S11 OR S10	1769099
S15	S14 AND S9	79704
S16	S15 NOT (EMB.EXACT("dental care for children") OR EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT("pregnant woman") OR EMB.EXACT.EXPLODE("child") OR EMB.EXACT.EXPLODE("infant") OR EMB.EXACT("adolescent") OR MESH.EXACT("Dental Care for Children") OR MESH.EXACT.EXPLODE("Pregnancy") OR MESH.EXACT("Pregnant Women") OR MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR MESH.EXACT("Adolescent") OR TI,AB(pregnan* OR child* OR infant* OR adolescent* OR teen* OR juvenile* OR baby OR babies))	70132
S17	S16 AND (TI,AB,SU,DTYPE((systematic N/1 review*) OR "meta analys?s" OR "meta-analys?s" OR metaanalys?s))	2224
S18	S16 AND (TI,AB((("case-control" OR clinical OR comparat$3 OR control[*4] OR blinded OR "single-blind[*2]" OR "single blind[*2]" OR "double-blind[*2]" OR "double blind[*2]" OR "triple-blind[*2]" OR "triple blind[*2]" OR crossover OR "cross-over" OR "cross over" OR multicenter[*2] OR "multi-center[*2]" OR "multi center[*2]" OR multicentre[*2] OR "multi-centre[*2]" OR "multi centre[*2]" OR exploratory OR interventional OR observational OR pivotal OR random[*5] OR retrospective OR systematic) N/3 (analys$s OR evaluation[*1] OR review[*1] OR stud[*3] OR trial[*1])) OR (Phase N/1 ("0" OR "1" OR "1a" OR "1b" OR "2" OR "2a" OR "2b" OR "3" OR "3a" OR "3b" OR "4" OR "I" OR "Ia" OR "Ib" OR "II" OR "IIa" OR "IIb" OR "III" OR "IIIa" OR "IIIb" OR "IV"))))	11032
S19	S18 OR S17	11533

S20	S19 AND YR(>=2016)	6784
S21	S20 NOT (TI,AB(cancer* OR neoplasm* OR malignan* OR tumo$r* OR diabetes OR diabetic* OR prediabetic*))	5784
S22	S21 NOT ("animal model[*1]" OR rat OR rats OR mouse OR mice OR gerbil OR gerbils OR "guinea pig" OR "guinea pigs" OR hamster OR hamsters OR rodent OR rodents OR rabbit OR rabbits OR hare OR hares OR dog OR dogs OR puppy OR puppies OR beagle[*1] OR "german shepherd[*1]" OR "labrador retriever[*1]" OR "golden retriever[*1]" OR cat OR cats OR kitten OR kittens OR monkey OR monkies OR monkeys OR baboon[*1] OR macaque[*1] OR simian[*1] OR chimp[*1] OR chimpanzee[*1] OR orangutan[*1] OR "non-human primate[*1]" OR "nonhuman primate[*1]" OR pig OR pigs OR piglet OR piglets OR horse OR horses OR cattle OR cow OR cows OR bull OR bulls OR sheep OR ram OR rams OR ewe OR ewes OR lamb OR lambs OR bird[*1] OR chick[*1] OR chicken[*1] OR poult[*2] OR fish[*2] OR zebrafish[*2] OR "zebra fish[*2]" OR "in vitro" OR transfect[*3] OR "cell line[*1]")	5177
S23	S22 NOT TI,AB(healthy N/1 (control$1 OR volunteer$1 OR participant$1))	4597
S24	S23 NOT TI,SU,DTYPE("erratum" OR "errata")	4589
S25	S24 AND TI,AB(((dental OR dentistry OR periodont* OR endodont* OR periapical OR *gingival OR (oral N/2 (health OR care))) N/2 (therap* OR treatment* OR treated OR treating OR "before and after" OR preventive OR preventative OR prophylaxis)))	660
S26	S25 AND TI(autoimmun* OR "auto-immun*" OR inflammatory OR autoinflammatory OR "auto-inflammatory" OR "immune-mediated" OR rheumatoid OR rheumatic OR arthrit* OR polyarthrit* OR rheumarthritis OR rheumatism OR "inflammatory bowel" OR IBD OR Crohn* OR (ulcerativ* N/1 colitis) OR "systemic lupus erythematosus" OR SLE OR lupus OR psoriasis OR psoriatic OR pustulosis OR Sicca OR Sjogren* OR sclerosis OR scleroderma)	214
S27	MJEMB.EXACT("Addison disease") OR MJMESH.EXACT("Addison Disease") OR MJEMB.EXACT("pernicious anemia") OR MJMESH.EXACT("Anemia, Pernicious") OR MJEMB.EXACT("ANCA-associated vasculitis") OR MJMESH.EXACT("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis") OR MJEMB.EXACT("Behcet disease") OR MJMESH.EXACT("Behcet Syndrome") OR MJEMB.EXACT("celiac disease") OR MJMESH.EXACT("Celiac Disease") OR MJEMB.EXACT("primary biliary cirrhosis") OR MJMESH.EXACT("Liver Cirrhosis, Biliary") OR MJEMB.EXACT("rheumatic polymyalgia") OR MJMESH.EXACT("Polymyalgia Rheumatica") OR MJEMB.EXACT("ankylosing spondylitis") OR MJMESH.EXACT("Spondylitis, Ankylosing") OR MJEMB.EXACT.EXPLODE("giant cell arteritis") OR MJMESH.EXACT.EXPLODE("Giant Cell Arteritis") OR MJEMB.EXACT("polyarteritis nodosa") OR MJMESH.EXACT("Polyarteritis Nodosa") OR MJEMB.EXACT("vitiligo") OR MJMESH.EXACT("Vitiligo") OR TI,AB,SU(Addison* OR (pernicious N/1 an*emia) OR Behcet* OR c*eliac OR ((cirrhosis OR cholangitis) N/1 biliary) OR (rheumatic* N/1 polymyalgia) OR (ankyl* N/1 (spondylitis OR spondylarthritis)) OR (("giant cell" OR temporal) N/1 arteritis) OR "polyarteritis nodosa" OR (("antineutrophil[*2] cytoplasmic antibody" OR "anti-neutrophil[*2] cytoplasmic antibody" OR "anti-neutrophil[*2] cytoplasmic autoantibody" OR ANCA OR "ANCA-positive" OR "ANCA-associated") N/2 vasculitis) OR vitiligo OR Graves* OR Hashimoto* OR "myasthenia gravis")	744468
S28	S27 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1	4494446
S29	S28 AND S14	82909
S30	S29 NOT (EMB.EXACT.EXPLODE("pregnancy") OR EMB.EXACT("pregnant woman") OR MESH.EXACT.EXPLODE("Pregnancy") OR MESH.EXACT("Pregnant Women") OR TI,AB(pregnan*))	81637
S31	S30 AND (TI,AB,SU,DTYPE((systematic N/1 review*) OR "meta analys?s" OR "meta-analys?s" OR metaanalys?s))	2537
S32	S30 AND (TI,AB((("case-control" OR clinical OR comparat$3 OR control[*4] OR blinded OR "single-blind[*2]" OR "single blind[*2]" OR "double-blind[*2]" OR "double blind[*2]" OR "triple-blind[*2]" OR "triple blind[*2]" OR crossover OR "cross-over" OR "cross over" OR multicenter[*2] OR "multi-center[*2]" OR "multi center[*2]" OR multicentre[*2] OR "multi-centre[*2]" OR "multi centre[*2]" OR exploratory OR interventional OR observational OR pivotal OR random[*5] OR retrospective OR systematic) N/3 (analys$s OR evaluation[*1] OR parameter[*1] OR review[*1] OR stud[*3] OR trial[*1])) OR (Phase N/1 ("0" OR "1" OR "1a" OR "1b" OR "2" OR "2a" OR "2b" OR "3" OR "3a" OR "3b" OR "4" OR "I" OR "Ia" OR "Ib" OR "II" OR "IIa" OR "IIb" OR "III" OR "IIIa" OR "IIIb" OR "IV"))))	14071
S33	S32 OR S31	14611
S34	S33 AND YR(>=2016)	8443
S35	S34 NOT (TI,AB(cancer* OR neoplasm* OR malignan* OR tumo*r* OR diabetes OR diabetic* OR prediabetic*))	6958

S36	S35 NOT ("animal model[*1]" OR rat OR rats OR mouse OR mice OR gerbil OR gerbils OR "guinea pig" OR "guinea pigs" OR hamster OR hamsters OR rodent OR rodents OR rabbit OR rabbits OR hare OR hares OR dog OR dogs OR puppy OR puppies OR beagle[*1] OR "german shepherd[*1]" OR "labrador retriever[*1]" OR "golden retriever[*1]" OR cat OR cats OR kitten OR kittens OR monkey OR monkies OR monkeys OR baboon[*1] OR macaque[*1] OR simian[*1] OR chimp[*1] OR chimpanzee[*1] OR orangutan[*1] OR "non-human primate[*1]" OR "nonhuman primate[*1]" OR pig OR pigs OR piglet OR piglets OR horse OR horses OR cattle OR cow OR cows OR bull OR bulls OR sheep OR ram OR rams OR ewe OR ewes OR lamb OR lambs OR bird[*1] OR chick[*1] OR chicken[*1] OR poult[*2] OR fish[*2] OR zebrafish[*2] OR "zebra fish[*2]" OR "in vitro" OR transfect[*3] OR "cell line[*1]")	6284
S37	S36 NOT TI,AB(healthy N/1 (control$1 OR volunteer$1 OR participant$1))	5511
S38	S37 NOT TI,SU,DTYPE("erratum" OR "errata")	5500
S39	S38 AND TI,AB(((dental OR dentistry OR periodont* OR endodont* OR periapical OR *gingival OR (oral N/2 (health OR care))) N/2 (therap* OR treatment* OR treated OR treating OR "before and after" OR preventive OR preventative OR prophylaxis)))	764
S40	S39 AND TI(autoimmun* OR "auto-immun*" OR inflammatory OR autoinflammatory OR "auto-inflammatory" OR "immune-mediated" OR rheumatoid OR rheumatic OR arthrit* OR polyarthrit* OR rheumarthritis OR rheumatism OR "inflammatory bowel" OR IBD OR Crohn* OR (ulcerativ* N/1 colitis) OR "systemic lupus erythematosus" OR SLE OR lupus OR psoriasis OR psoriatic OR pustulosis OR Sicca OR Sjogren* OR sclerosis OR scleroderma OR Addison* OR (pernicious N/1 an*emia) OR Behcet* OR c*eliac OR ((cirrhosis OR cholangitis) N/1 biliary) OR (rheumatic* N/1 polymyalgia) OR (ankyl* N/1 (spondylitis OR spondylarthritis)) OR (("giant cell" OR temporal) N/1 arteritis) OR "polyarteritis nodosa" OR (("antineutrophil[*2] cytoplasmic antibody" OR "anti-neutrophil[*2] cytoplasmic antibody" OR "anti-neutrophil[*2] cytoplasmic autoantibody" OR ANCA OR "ANCA-positive" OR "ANCA-associated") N/1 vasculitis) OR vitiligo OR Graves* OR Hashimoto* OR "myasthenia gravis")	252
S41	S40 NOT S26	30°

Appendix B.

List of excluded studies along with exclusion reasons.

Author Year	Title	DOI	Exclusion reason
Silva 2024	The impact of periodontitis and periodontal treatment on rheumatoid arthritis outcomes: an exploratory clinical trial	10.1093/rheumatology/keae358	Wrong comparator
Kobayashi 2023	Periodontitis and periodontopathic bacteria as risk factors for rheumatoid arthritis: A review of the last 10 years	10.1016/j.jdsr.2023.08.002	Wrong study design
Inchingolo 2023	The Effects of Periodontal Treatment on Rheumatoid Arthritis and of Anti-Rheumatic Drugs on Periodontitis: A Systematic Review	10.3390/ijms242417228	No meta-analysis
Chapman 2023	'It surprised me a lot that there is a link': a qualitative study of the acceptability of periodontal treatment for individuals at risk of rheumatoid arthritis	10.1136/rmdopen-2023-003099	Wrong study design
King 2022	Targeting the reduction of inflammatory risk associated with cardiovascular disease by treating periodontitis either alone or in combination with a systemic anti-inflammatory agent: protocol for a pilot, parallel group, randomised controlled trial	10.1136/bmjopen-2022-063148	Wrong patient population
Posada-López 2022	The Effect of Periodontal Treatment on Clinical and Biological Indicators, Quality of Life, and Oral Health in Rheumatoid Arthritis Patients: A Quasi-Experimental Study	10.3390/ijerph19031789	Wrong study design
Mustufvi 2022	Does Periodontal Treatment Improve Rheumatoid Arthritis Disease Activity? A Systematic Review	10.1093/rap/rkac061	No meta-analysis
Agossa 2021	Periodontal and dental health in inflammatory bowel diseases: a systematic review	10.1080/17474124.2021.1952866	Wrong study design
Moura 2021	Clinical and microbiological effects of non-surgical periodontal treatment in individuals with rheumatoid arthritis: a controlled clinical trial	10.1007/s10266-020-00566-0	Wrong patient population
Benli 2021	Orofacial manifestations and dental management of systemic lupus erythematosus: A review	10.1111/odi.13271	Wrong outcomes
Zamri 2020	Use of TNF Inhibitors in Rheumatoid Arthritis and Implications for the Periodontal Status: For the Benefit of Both?	10.3389/fimmu.2020.591365	Wrong intervention
Silva 2020	Using evidence-based research to design randomised trial on periodontal treatment for individuals with rheumatoid arthritis: a systematic review putting existing research into context	10.1136/annrheumdis-2020-eular.6393	Duplicate
Rahajoe 2019	Cytokines in gingivocrevicular fluid of rheumatoid arthritis patients: A review of the literature	10.1111/odi.13145	Outside publication year range
Anusha 2019	Efficacy of a mouthwash containing essential oils and curcumin as an adjunct to nonsurgical periodontal therapy among rheumatoid arthritis patients with chronic periodontitis: A randomized controlled trial	10.4103/ijdr.IJDR_662_17	Wrong study design

Trivedi 2018	Novel PAradigm to improve Inflammatory burden in end stage Renal disease (rePAIR): study protocol for a randomized controlled trial	10.1186/s13063-018-2760-y	Wrong patient population
Almeida 2017	Dental implants in Sjögren's syndrome patients: A systematic review	10.1371/journal.pone.0189507	Wrong comparator
Calderaro 2017	Influence of periodontal treatment on rheumatoid arthritis: a systematic review and meta-analysis	10.1016/j.rbre.2016.11.011	Outside publication year range
Silvestre 2016	Effect of nonsurgical periodontal treatment in patients with periodontitis and rheumatoid arthritis: A systematic review	10.4317/medoral.20974.	Outside publication year range
Oliveira 2024	Methotrexate and Non-Surgical Periodontal Treatment Change the Oral-Gut Microbiota in Rheumatoid Arthritis: A Prospective Cohort Study		Wrong outcomes
Oliveira 2023	Methotrexate and Non-Surgical Periodontal Treatment Change the Oral-Gut Microbiota in Rheumatoid Arthritis: A Prospective Cohort Study	[53,54]	Wrong outcomes
Oliveira 2022	Are neutrophil extracellular traps the link for the cross-talk between periodontitis and rheumatoid arthritis physiopathology?	http://dx.doi.org/10.1093/rheumatology/keab289	Wrong comparator
Cosgarea 2019	Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis	http://dx.doi.org/10.1007/s00784-018-2420-3	Wrong comparator
AbdulAmeer 2018	The anti-inflammatory effect of the platelet-rich plasma in the periodontal pocket	http://dx.doi.org/10.4103/ejd.ejd_49_18	Wrong patient population
Ambrósio 2017	Effects of periodontal treatment on primary sj̄ögren's syndrome symptoms	http://dx.doi.org/10.1590/1807-3107BOR-2017.vol31.0008	Wrong study design

Appendix C.

List of clinical practice guidelines for patients with autoimmune diseases, organized by those with and without recommendations regarding dental care, and by disease area.

Year	Title	Type of article	Recommendations for dental care
With recommendations regarding dental care			
Regarding various autoimmune diseases			
2015	The American Dental Association: The ADA Practice Guide.Ch 10. Autoimmune and Connective Tissue Diseases	Practice guide	This practice guide outlined various aspects of dental management: evaluation, treatment modifications, oral lesion diagnosis and management, and risk of dental care. Specific recommendations were available for RA, lupus, Sjogren syndrome, and scleroderma.
Regarding specific autoimmune diseases			
2016	Sjögren's Syndrome Foundation: Clinical practice guidelines for oral management of Sjögren disease: dental caries prevention	Clinical Practice Guideline	Recommendations included: topical fluoride for all patients (strong), increase saliva through stimulation (weak), chlorhexidine (weak), nonfluroide remineralizing agents (moderate).
2015	British Dental Association: Managing patients with rheumatoid arthritis	Guidance	This guidance included management for periodontal diseases, temporomandibular dysfunction, and salivary gland dysfunction. Also, communication between dental service provider and rheumatologist was emphasized.

2019	National Scleroderma Foundation: Dental care in scleroderma	Fact sheet	This patient-focused fact sheet included description and treatments of various oral health issues common in scleroderma, and encouraged patients to seek help from both the dentist and the rheumatologist.
Without recommendations regarding dental care			
Regarding rheumatoid arthritis			
2023	2022 ACR Guideline for Exercise, Rehabilitation, Diet, and Additional Integrative Interventions for Rheumatoid Arthritis	Guideline	None mentioned
2022	EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update	Recommendation	None mentioned [*also reviewed 2016 and 2019 recommendations]
2021	ACR Guideline for the Treatment of Rheumatoid Arthritis	Guideline	None mentioned
2019	ACR/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis	Guideline	None mentioned
2018	NICE, Rheumatoid arthritis in adults: diagnosis and management	Guideline	None mentioned
Regarding psoriasis			
2023	EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update	Recommendation	None mentioned [*also reviewed 2019 recommendation]
2020	Joint American Academy of Dermatology and National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies	Guideline	None mentioned
2017	NICE, Psoriasis: assessment and management	Guideline	None mentioned
Regarding systemic lupus erythema			
2023	EULAR recommendations for the management of systemic lupus erythematosus: 2023 update	Recommendation	None mentioned [*also reviewed 2019 recommendation]

2023	EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis	Recommendation	None mentioned
2018	The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults	Guideline	None mentioned
Regarding other autoimmune diseases			
2023	ACG Guidelines Update: Diagnosis and Management of Celiac Disease	Guideline	None mentioned
2023	EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update	Recommendation	None mentioned [*also reviewed 2016 recommendation, and 2017 and 2022 corrections]
2022	NICE, Multiple sclerosis in adults: management	Guideline	None mentioned [*also reviewed 2019 recommendation]
2021	AGA, Medical management of moderate to severe luminal and perianal fistulizing Crohn's disease	Guideline	None mentioned
2020	AGA, Management of moderate-to-severe ulcerative colitis	Guideline	None mentioned
2019	EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies	Recommendation	None mentioned
2019	EULAR recommendations for the management of antiphospholipid syndrome in adults	Recommendation	None mentioned
2019	ACG Clinical Guideline: Ulcerative Colitis in Adults	Guideline	None mentioned
2019	NICE, Ulcerative colitis: management	Guideline	No mentioned
2019	NICE, Crohn's disease: management	Guideline	Not mentioned
2018	EULAR Update of recommendations for the management of Behçet's syndrome	Recommendation	None mentioned

2018	AGA, Management of mild-to-moderate ulcerative colitis	Guideline	None mentioned
2018	ACG Clinical Guideline: Management of Crohn's Disease in Adults	Guideline	None mentioned
2017	Research Program for Intractable Disease of the Ministry of Health, Labor and Welfare (Japan), Clinical practice guideline for Sjögren’s syndrome	Guideline	None mentioned
2016	Assessment of SpondyloArthritis International Society-EULAR 2016 update of management recommendations for axial spondyloarthritis	Recommendation	None mentioned
2016	EULAR Update of recommendations for the treatment of systemic sclerosis	Recommendation	None mentioned

Appendix D.

Risk of bias assessments (RoB2, ROBINS-I, AMSTAR2) with overall scoring and mapped to quality terms included in this report.

Figure D1. Risk of bias assessment evaluated using AMSTAR2 for systematic reviews

Author Year	***Signaling questions***																***Mapping to quality terms used in this report***
Systematic Reviews	D1	**D2***	D3	**D4***	D5	D6	**D7***	D8	**D9***	D10	**D11***	D12	**D13***	D14	**D15***	D16	**Overall confidence**	**Overall USPSTF quality**
Sun 2021	Yes	Partial yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes/ n/a	No	Yes /n/a	Yes	Yes	Yes	Yes	Yes	Moderate	Fair
Silva 2022	Yes	Yes	No	Yes	Yes	Yes	No	Partial yes	Yes/ n/a	No	Yes/ n/a	Yes	Yes	Yes	No	Yes	Critically low	Poor
Del Rei Daltro Rosa 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes/ Yes	No	No/ no	Yes	Yes	No	No	Yes	Critically low	Poor

Figure D2. Risk of bias assessment evaluated by RoB2 for RCTs

Author year	***Risk of bias domains***							***Mapping to quality terms used in this report***
RCTs of patients with RA	D1	D2	D2a	D3	D4	D5	**Overall risk of bias**	**Overall USPSTF quality**
Monsarrat 2019	Low	Low	Low	Low	Low	Low	Low	Good
Khare 2016	Some	Low	Low	Low	Low	Some	Some	Fair
de Pablo 2022	Some	High	High	Low	Low	Low	High	Poor
Thilagar 2022	High	High	Low	Low	Low	Low	High	Poor
Nguyen 2021	Low	High	High	Low	Low	Low	High	Poor
RCTs of patients with psoriasis								

Marruganti 2024	Low	Low	Low	Low	Low	Low	Low	Good
Yarkac 2019	Low	Low	Low	Low	Low	Low	Low	Good
RCT of patients with SLE								
Maybodi 2022	Some	Low	Low	Low	Low	Low	Some	Fair

Figure D3. Risk of bias assessment evaluated by ROBINS for studies other than RCTs

Author year	***Risk of bias domains***								***Mapping to quality terms used in this report***
Studies other than RCTs with patients with RA	D1	D2	D3	D4	D5	D6	D7	**Overall risk of bias**	**Overall USPSTF quality**
Kaushal 2019	Moderate	Low	Low	Low	Low	Serious	Low	Serious	Poor
Atarbashi-Moghadam 2018	Moderate	Serious	Low	Serious	Serious	Moderate	Low	Serious	Poor