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Lopez-Oliva, Isabel; De Pablo, Paola; Dietrich, Thomas; Chapple, Iain

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Gums and joints: is there a connection?

PART 1. EPIDEMIOLOGICAL AND CLINICAL LINK

Isabel Lopez-Oliva, Paola de Pablo, Thomas Dietrich, Iain Chapple

Review for BDJ

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ABSTRACT

Rheumatoid arthritis (RA) and chronic periodontitis are common chronic inflammatory diseases that share numerous clinical and pathobiological characteristics. Due to their similarities, despite manifesting at anatomically distinct sites, the relationship between these two diseases has been investigated for many years. This review attempts to summarise the state of the field based on evidence published in the last 10 years.

KEYPOINTS

1. RA and periodontitis are epidemiologically linked
2. The effect of periodontal therapy in RA remains unknown and more rigorous clinical trials are needed
3. Rheumatologist and dentist should be aware of this link and work together for the benefit of the RA patient

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that leads to the destruction of cartilage and bone in the joints. RA and chronic periodontitis are common chronic inflammatory diseases that share numerous clinical and pathobiological characteristics. The exacerbated immune reaction that arises in the gingival tissues of periodontitis patients leading to destruction of connective tissues and ultimately bone, is similar to the one occurring in the joints of RA patients. [1] Furthermore, these two diseases appear to be epidemiologically associated. [2] Due to their similarities, despite manifesting at anatomically distinct sites, the relationship between these two diseases has been investigated for many years.

The link between Rheumatoid arthritis (RA) and Periodontal disease (PD) dates back to Hippocrates who observed that extraction of diseased teeth could cure arthritis. During the 1950s-60s the “total dental clearance” was commonly employed as part of the treatment regime for RA.[3] More recently,

the upsurge in stratified medicine approaches to unravelling diseases mechanisms has brought into focus the link between PD and RA. The international workshop between the European Federation of Periodontology and the American Academy of Periodontology in 2013, lead to a call for more controlled clinical trials in this area and recommended an urgent need for research in this topic. [4] Since this workshop, a significant number of studies have investigated the PD-RA paradigm and this review attempts to summarise the state of the field based on evidence published in the last years.

1.1. Prevalence of RA

The prevalence of RA in the first world is believed to be increasing, currently affecting about 1-2% of the world's population, with a male/ female ratio of 1:3 and a peak incidence in the 4-5th decade of life. In the UK, the economic burden of RA is estimated to be more than £600 million [5] and these patients often suffer from comorbidities such as cardiovascular disease, which increases associated mortality. [6]

1.2. Pathogenesis of RA

Whilst the trigger for the autoimmune reaction that leads to RA remains unknown, our understanding of the pathogenesis of RA has increased substantially over the last decade. The synovium of RA patients exhibits an elevated production of pro-inflammatory cytokines, including Tumor Necrosis Factor (TNF), Interleukins (IL) 1, 6, 15, 17, and granulocyte-macrophage colony-stimulating factor (GM-CSF). In the presence of these cytokines, T-cells and synoviocytes activate osteoclast maturation, which leads to bone resorption in the joint (Figure 1). Moreover, the joint surface is encroached upon and destroyed by an anomalous fibrovascular coating, the pannus. [7, 8] This constant state of inflammation and degradation of the joint structures causes chronic pain, fever, bone deformity, functional impairment and disability, classical features of inflammation.

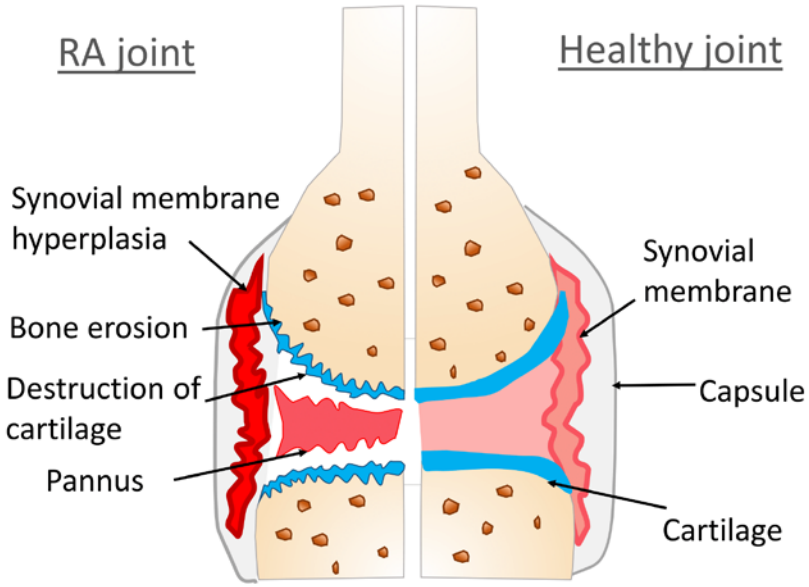

Figure 1. Differences between the joint structure in rheumatoid arthritis (RA) and a healthy joint.

1.3. Diagnosis and treatment of RA

RA typically presents with swollen joints (often symmetrically), generalized pain, morning stiffness and movement limitations that last over an hour, and which can be reduced by gentle movements. These signs and symptoms help rheumatologists differentiate RA from osteoarthritis (OA), which is the most common form of joint disease, caused by cartilage degeneration and mechanical wear and tear. Interestingly, OA has not been found to be associated with chronic periodontitis and OA patients are frequently used as controls in studies that investigate the relationship between RA and PD. [2 9 10]

The latest criteria employed for the diagnosis of RA were formulated in 2010 by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR). This classification uses a score-based algorithm that considers type and number of joints involved, serological parameters (rheumatoid factor and anti citrullinated protein antibodies/ACPAs), acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate/ESR)

and duration of symptoms. [11] While rheumatoid factor can be present in in up to 20% of the general population, antibodies against citrullinated proteins (ACPA) are highly specific for RA. However, these antibodies are not present in all RA patients, therefore all clinical presentations of the criteria need to be considered necessary for the diagnosis of RA. [12]

The treatment of RA is complex and involves pharmacological and non-drug therapies including education, physical activity, occupational therapy and in late disease, joint replacement. The aim of pharmacological treatment of RA is to relieve pain, reduce inflammation and prevent destruction of cartilage and bone. This is usually achieved by the use of a combination of different drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (oral or by injection), conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological therapies, a subcategory of DMARDs which targets specific steps of the inflammatory process, including TNF inhibitors, IL-6 inhibitors and anti-B-cell therapy. [13]

2. CLINICAL EVIDENCE

2.1. Epidemiological association between Periodontitis and RA

For many years studies have investigated the association between periodontitis, tooth loss and rheumatoid arthritis (Table 1). While two of these studies reported negative results, the majority have reported a higher risk and prevalence of periodontitis in rheumatoid arthritis patients and *vice versa* [20, 23].

Cross sectional studies have shown that patients with RA have a significantly increased prevalence of periodontitis compared to systemically healthy controls, with odds ratios (OR) ranging between 1.82 [14] and 8.1 [15]. Furthermore, patients with periodontitis have a higher prevalence of RA, with OR ranging between 1.16 [16] and 2.05. [17] Some of these studies, after adjusting for confounding factors, have demonstrated that the relationship appears independent of smoking [16], oral hygiene (plaque) [18, 15] and genetic factors. [19]

De Pablo and colleagues (2008) investigated this association using the National Health and Nutrition Examination Survey (NHANES), concluding that patients with RA had a higher prevalence of periodontitis (10-16%) compared to non-RA patients with 50% of RA subjects identified as edentulous. Although the cause of tooth loss was unknown, the authors concluded that these edentulous patients may be representative of severe cases of periodontitis, as RA patients had a lower frequency of restorations and caries. [14]

In 2012 the European Federation of Periodontology (EFP) and American Academy of Periodontology (AAP) workshop on periodontal and systemic interrelationships concluded that the evidence of an association between RA and periodontitis was at least minimal but that more research was needed. [4] Since then, more than 150 papers have been published in the field, including a large number of reviews, animal studies and 18 cohort studies. The cohort

studies were conducted in different countries around the world, some using very large data sets and only one reported no relationship. [20]

Using the Taiwanese National Health Insurance Research Database (NHIRD) cohort study which included 1,000,000 patients, a significant and independent association between RA and history of periodontitis was reported. [21] Another cohort study reported that from the 74 RA patients examined, 94% suffered from moderate to severe periodontitis (48% moderate and 46% severe). [22]

In contrast, there are also studies that have not reported such associations. In a large prospective cohort study, using data reported from 91,132 nurses followed over 12 years, there was no evidence of a higher risk of developing RA among patients with periodontitis [23]; however, in this study periodontitis was defined based on history of periodontal surgery through a self-reported questionnaire and no clinical examinations were conducted to diagnose periodontitis. More recently, no difference in the prevalence of periodontitis was observed in a Swedish case-control study including 2,740 RA patients. However, again in this study periodontitis was investigated by self-reporting questionnaire. [20] Thus, these two studies may be biased due to the recruitment methodology, as no clinical examination was used to diagnose periodontitis and therefore their conclusions may be misleading.

The most recent systematic review and meta-analysis exploring the epidemiological evidence from 8 case control studies, concluded that there is a strong and significant association between RA and PD. However, the authors highlight the need for further rigorous studies using consistent case definitions for periodontitis and a more defined population to avoid bias due to invalid control groups. [24]

Although some of these case-control and cohort studies have clear limitations, there are now a large number of studies including thousands of patients from all over the world reporting an association.

Table 1. Summary of observational studies published since 2000 (with study population > 60) analysing the association between rheumatoid arthritis (RA) and periodontitis. Abbreviations: OR, odds ratio; RR, risk ratio; PII, plaque index; GI, gingival index; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide.

Author & Year	Study population	Results	Type of study
Mercado et al., 2000 [25]	1412 patients attending dental hospital	Periodontitis: higher prevalence of RA (3.95%)	Cross sectional
Mercado et al., 2001 [18]	65 patients (RA vs. non-RA)	-RA: higher number of missing teeth, deeper pockets. No difference in bleeding or plaque index	Case control
Marotte et al., 2006 [19]	147 patients (RA)	-Association between periodontal bone loss and wrist bone destruction ($\chi 2 = 11.82$) and shared epitope HLA-DR	Cross sectional
De Pablo et al., 2008 [14]	4,461 patients (NHANES III)	-RA: higher prevalence of periodontitis (OR:1.82), edentulous (OR:2.27), less decay ($p<0.001$)	Cross sectional
Pischon et al., 2008 [15]	109 patients (57 RA, 52 non-RA)	RA: higher prevalence of periodontitis (OR:8.05), statistically significant after adjusting to confounding factors (PI, GI)	Case control
Dissick et al., 2009 [10]	69 RA patients vs. 35 Osteoarthritis (controls) patients	-RA: higher prevalence of periodontitis and more severe -RA patients with periodontitis associated with	Case control

		RF positive and anti-CCP	
Arkema et al., 2010 [23]	81,132 patients (Nurses' Health Study prospective cohort)	No evidence of higher incidence of RA in periodontitis	Cohort study
Demmer et al., 2011 [17]	9,702 patients (NHANNES I)	Periodontitis: higher prevalence of RA (OR:2.05)	Cross sectional
Potikuri et al., 20120 [16]	91 RA (DMARD naive, non-smokers) vs healthy controls	RA: higher prevalence of periodontitis (OR:4.28)	Case control
Smit et al., 2012 [26]	95 RA, 420 matched controls	RA: higher risk of periodontitis (RR: 3.7)	Cross sectional
Chen et al., 2013 [21]	13,779 newly diagnosed RA, 137,790 non-RA	periodontitis: higher prevalence of RA (OR:1.16) ,	Cohort study
Monsarrat et al., 2014 [22]	74 RA patients	94% of RA had periodontitis (48% moderate and 46% severe)	Cross sectional
Eriksson et al., 2016 [20]	2,740 RA cases and 3,942 non-RA	No difference in periodontitis prevalence between groups	Case control
Bello-Gualtero JM, et al., 2016 [27]	119 Pre-RA; 48 early-RA; Matched controls for both	Significant association with periodontal disease and IgG against *Pg*	Cross sectional
Choi IA, et al., 2016 [28]	264 RA and 88 matched controls	Higher prevalence of periodontitis in RA	Cross sectional
Ayravainen L, et al., 2017 [29]	168 RA ad 168 matched healthy controls	RA patients had worse periodontal	Cross section

		condition	
Schmickler J, et al., 2017 [30]	53 RA DMARDs; 28 RA unresponsive to DMARDs; 42 controls	RA patients had worse periodontal condition	Prospective follow up study
Ouedraogo DD, et al., 2017 [31]	43 RA; 86 controls	Prevalence of periodontitis higher in RA	Case-control

2.2. Effects of periodontal treatment on RA

Due to its high prevalence, scientists believe that periodontitis may represent an important modifiable risk factor for RA incidence and severity. If proven, treatment of periodontitis could offer a relatively inexpensive and safe, non-pharmacological treatment with direct benefit for patients with RA.

To date, 10 clinical studies and 3 systematic reviews have investigated the effect of periodontal therapy on RA, analysing different parameters. Their results suggest that treatment of periodontitis may have a significant positive effect on RA severity (Table 2). [32 33] However, most of the published studies are small, have short follow-up times following periodontal therapy, and investigate different outcome measures.

Due to the heterogeneity of design in the various studies connecting RA and periodontitis, only a few parameters could be included for meta-analysis in the first systematic review considering the effects of treatment of periodontitis on RA outcomes; ESR being the only parameter found to be significantly reduced following periodontal treatment. [34] Another systematic review considering those same four studies concluded that although the RA "disease activity score" based on the 28 joint count (DAS28) appeared to be consistently improved following periodontal therapy throughout the four trials, further RCTs were needed. [2] The latest systematic review conducted by Caldeloro included 4 studies from 2005 to 2013 and the authors concluded that there was a significant reduction of DAS28 following periodontal therapy. [35] Since then, three studies have been published, all of them reporting a significant improvement of RA parameters after periodontal therapy. [36-38]

Although these results are promising, some authors have failed to observe this effect. In a case report of one RA patient undergoing periodontal treatment for 15 years, no beneficial effect was reported. [39] Pinho and collaborators conducted a clinical trial in which they observed no reduction in acute phase reactants following periodontal therapy in RA, and systemic

markers of inflammation did not correlate with observed improvements in periodontal health. [40] More recently, Kurgan reported a positive effect of periodontal treatment on gingival crevicular fluid (GCF) levels of a marker of systemic inflammation, plasminogen activator-2, in 15 patients with periodontitis with or without rheumatoid arthritis but he found no effect on RA parameters. [41]

Although in the workshop between the EFP and the AAP in 2013, it was concluded that more rigorous controlled clinical trials and research were needed in the field, [4] the studies published since the workshop continue to utilise a short follow-up period (ranging between 8 weeks and 6 months) and a small sample size (<75 patients). Furthermore, each study employed different definitions of periodontitis and used different parameters to measure RA status, with the DAS28 Disease Activity Score being the most widely reported, based on subjective measures, such as the Visual Analog Scale (VAS) for pain and number of tender joints.

Therefore, although the current evidence suggests that there is an improvement in RA parameters after periodontal therapy, investigators in the field agree that longer and more rigorous randomized controlled trials are necessary to definitively determine the effects of periodontal treatment on RA.

Importantly, a recent systematic review considering the effect of periodontitis upon the response of RA patients to medication, found that persistent periodontal inflammation hampers the effect of anti-TNF drugs. [42] Therefore, the treatment of periodontitis may also benefit the efficiency of pharmacological interventions in RA.

Table 2. Clinical trials evaluating the effect of periodontal therapy in Rheumatoid arthritis (RA). Abbreviations: PD, periodontitis; RA, Rheumatoid Arthritis; RF, Rheumatoid Factor, ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; DAS, Disease Activity Score; VAS, Visual Analogue Scale; TNF, Tumor Necrosis Factor; CRP, C-Reactive Proteins; AAG, alpha-1 acid glycoprotein.

Author&Year	Duration	Patient number	Parameters evaluated	Results
Ribeiro 2005 [32]	3 months	42 RA+PD -16 periodontal treatment -26 oral hygiene and supragingival cleaning	RF, ESR, HAQ	ESR significantly reduced
Al-katma 2007 [43]	8 weeks	29 RA+PD -17 periodontal treatment -12 no treatment	DAS 28, ESR	VAS, DAS 28 and ESR reduced
Ortiz 2009 [44]	8 weeks	40 RA+PD -10 periodontal treatment and DMARDs only. -10 periodontal treatments and DMARDs with anti-TNF drugs. -10 no periodontal therapy, DMARDs only -10 no periodontal treatment, DMARDs with anti-TNF drugs.	ESR, TNF-alpha, signs and symptoms	VAS and DAS 28 improved in treatment groups. ESR not significantly reduced Anti-TNF drugs improved PPD and CAL

Pinho 2009 [40]	6 months	75 patients: -15 RA+PD with periodontal treatment -15 RA+PD no periodontal treatment -15 PD with periodontal treatment -15 PD no periodontal treatment	DAS 28, CRP, ESR, AAG (alpha-1 acid glycoprotein)	No clear relation. AAG, ESR and CRP not significantly reduced with periodontal therapy.
Okada 2013 [45]	8 weeks	55 RA+PD -26 supragingival cleaning -29 no treatment	DAS 28, CRP, anti-CCP, RF, TNF-alpha and levels of IgG to P. gingivalis	Reduction of DAS 28 and levels of IgG to *P.gingivalis* and citrulline.
Erciyas 2013 [33]	3 months	60 RA and PD -30 RA moderate-severe disease activity -30 RA low disease activity	ESR, CRP, TNF-alpha, DAS28	Significant reduction of ESR, CRP, TNF-alpha, DAS28
Biyikoglu 2013 [46]	6 months	15 RA PD, 15 RA healthy	DAS 28, GCF, serum IL-1β, TNF-α	Significant decreases in DAS28 and gingival crevicular fluid interleukin-1
Roman-Torres 2015 [36]	90 days	12 RA and 12 controls	CRP and ESR	Improvement after periodontal therapy (mild periodontitis)
Khare 2016 [37]	3 months	60 RAPD patients	DAS, ESR, CRP	Significant improvement of DAS 28

				and CRP after periodontal therapy
Zhao 2018 [38]	1 month	-18 PD patients -18 RA patients -18 RA with PD patients -10 healthy controls	anti-CCP, CRP, DAS 28, periodontal parameters	Significant decrease of all RA parameters in treatment group

3. SUMMARY AND CONCLUSIONS

Numerous studies have reported an epidemiological link between RA and periodontitis and although some studies did not find such associations, the shortcomings of these studies may well explain their negative results. Although numerous epidemiological studies conducted in the past have employed inconsistent definitions of periodontitis, the most recent studies have overcome this problem and also include larger numbers of patients. Therefore, considering the evidence, there appears to be a clear epidemiological relationship between RA and periodontitis.

Although there is sufficient evidence for an epidemiological link between RA and periodontitis, the directionality of this relationship is not known. Large-scale longitudinal studies are needed to explore whether periodontitis increases the risk of incident RA and *vice versa*. Therefore, future research investigating the oral microbiome, inflammatory response and autoimmune response of patients at risk to develop RA, RA patients and periodontitis patients, is needed to clarify gaps in the literature.

While an increasing number of small clinical studies have shown a trend to an amelioration of surrogate measures of RA following periodontal treatment, controlled clinical trials with longer follow up periods and larger numbers of patients are needed to corroborate this hypothesis. If proven, periodontal therapy could be a relatively inexpensive, non-pharmaceutical method of improving RA in addition to the known local and systemic benefits of maintaining periodontal health.

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