Link between rheumatoid arthritis and chronic periodontitis

Związki między reumatoidalnym zapaleniem stawów i przewlekłym zapaleniem przyzębia

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Summary

Chronic periodontitis is an infectious disease associated with the progressive destruction of periodontal tissues. In recent years, more and more data indicate an existing relationship between periodontal disease and rheumatoid arthritis. The link between both diseases has been confirmed in multiple studies. Despite the fact that this association might be based on shared environmental and genetic risk factors, a possible causal relation was advocated by experimental, epidemiological and interventional studies, with the leading role of *Porphyromonas gingivalis*. Individuals with chronic periodontitis are at an increased risk of developing rheumatoid arthritis, as well as rheumatoid arthritis patients are at an increased risk of chronic periodontitis and more severe forms of periodontitis. Furthermore, there is a correlation between the activity in both diseases – patients with more severe periodontitis suffer from more active rheumatoid arthritis. Intervention attempts were also performed, which demonstrated that eliminating periodontal infection and inflammation can affect the severity of rheumatoid arthritis. In this paper, we review the current knowledge about the link between both diseases, focusing on its clinical implications. Will periodontal treatment become a part of standard therapy for rheumatoid arthritis?

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Abbreviations: **ACPA** – antibodies to citrullinated peptides, **CP** – chronic periodontitis, **CRP** – C-reactive protein, **DAS28** – disease activity score, **DMARDs** – disease-modifying antirheumatic drugs, **ESR** – erythrocyte sedimentation rate, **HAQ** – health assessment questionnaire, **HLA-DR** – Human Leukocyte Antigen – antigen D Related, **IL** – Interleukin, **PAD** – peptidylarginine deaminase enzymes, **PD** - probing depth, **PGE2** – Prostaglandin E2, **P.g** – *Porphyromonas gingivalis*, **PI** – plaque index, **RA** – rheumatoid arthritis, **RF** – rheumatoid factor, **RgpB** – arginine gingipain type B, **TNF-α** – tumor necrosis factor alpha, **VAS** – Visual Analogue Scale.

INTRODUCTION

Chronic periodontitis (CP) is a disease which can be associated with other systemic conditions, such as type II diabetes, cardiovascular diseases, osteoporosis, premature birth and low birth weight [46]. Recent epidemiological studies suggest the existence of a link between rheumatoid arthritis (RA) and CP. Despite the fact that this association might be non-causal and based on shared environmental and genetic risk factors, such as smoking [94,99] or genetic alleles [11,34], possible causal relation was advocated by several studies, both epidemiological [15,18,22,24,31,35,58,60] and interventional [2,10,26,48,72,80].

Periodontitis, as one of the most prevalent chronic bacterial infections, is associated with the progressive destruction of periodontal tissues including gingiva, periodontal ligament, root cementum and alveolar bone. According to recent multicenter epidemiological studies carried out among people aged 35 to 44, shallow periodontal pockets were present in 40.7% of people and deep periodontal pockets were noted in 16.5% of people. [32]. Among people aged 65 to 74 years, it is found in 21.8% and 21.9% of these people, respectively [53]. Despite the multifactorial etiology of CP, the main triggering factor is the prevalence of dental plaque being a reservoir of certain pathogenic bacteria. In the chronic form of periodontitis *Porphyromonas gingivalis* (*P.g*), *Tannerella forsythia* and *Treponema denticola* are a group of the most virulent bacteria, collectively named red periodontal complex [92]. The aforementioned bacteria are able to induce an immuno-inflammatory reaction of periodontal tissues in both direct and indirect mechanisms. The activation of macrophages resulting from the presence of bacterial lipopolysaccharide (endotoxin) leads to an increase of cytokines secretion: IL-1, IL-6, TNF-α, PGE2 and matrix metalloproteinases responsible for progressing the destruction of tooth supporting tissues. The imbalance between proinflammatory and anti-inflammatory cytokines is a common feature of both RA and CP, and might result in the inflammatory destruction of disease specific tissues. Progressing bone resorption, initiated by inflammatory mediators including IL-1, TNF-α and PGE2, is observed in both disease entities [7,16]. IL-17 secreting helper CD4 T cells (Th17 cells) act on neutrophils, macrophages, fibroblasts or osteoclasts to induce chronic inflammation in bone and cartilage. Recently, it was suggested that Th17 cells could play a role in the progression of both RA and CP [6,16]. Furthermore, the outer membrane protein of *P. gingivalis* was found to stimulate the secretion of IL-17 by T cells [67].

EPIDEMIOLOGICAL STUDIES

A strong association between RA and CP (independent of age, gender, ethnicity or smoking) was reported in many epidemiological studies (Tab.1) [1,5,7,15,17,18,22,23,24,31,33,39,42,45,47,58,60,61,75,76,79,80,86,87,88,100,104].

Although most of these investigations included cross sectional studies or case control studies with relatively small groups, there are a few cohort studies based on large groups. The first study, conducted by Arkema et al. [4], include 81,132 women from Nurses' Health Study prospective cohort. In multivariable-adjusted models it did not show a significant risk increase of developing RA among those with a history of periodontal surgery (RR=1.24; 95% CI (0.83, 1.83)) nor with a history of tooth loss (RR=1.18; 95% CI (0.47, 2.95)). However, the dental history was based on self-reports, and the patients were asked only about periodontal surgery and tooth loss, not periodontitis, and the dental data was not validated. Also RA group was non-standard – the average age at diagnosis in the RA cases was 64.6 years – due to the exclusion of cases of RA that had been diagnosed at younger ages than after the start of study. The first nationwide population-based cohort study was performed by Chou et al. [18]. It compared 3 cohorts from Taiwanese National Health Insurance Research Database - 628,628 patients with periodontal disease, 168,842 randomly selected individuals without any periodontal disease and 96,542 patients who had an ambulatory visit with a diagnosis of PD and received dental scaling concurrently. A diagnosis of both periodontal disease and RA was retrieved from ambulatory visits ICD codes. PD cohort had a higher risk of RA than the non-PD cohort without or with routine dental scaling (HRs, 1.91 and 1.35; 95% CIs, 1.57–2.30 and 1.09–1.67, respectively). Unfortunately, the data regarding smoking status, important confounding factor in both diseases, was not collected. The last cohort study, by Grasso et al. [33], evaluated a group of Veterans Affairs patients who had at least 4 visits in one of the VA dental clinics for any dental issue – over 25 million patients. 433,674 of them had periodontal disease and 21,442 had RA. Authors concluded that the odds ratio between periodontal disease and rheumatoid arthritis is 1.42 (95% CI, 1.37–1.46). Despite a large study population, the study has a few limitations – about 90% of the patients in the database are male. Also RA was not diagnosed with standard ACR criteria – the study excluded individuals with negative serologic test results – missing a substantial number of patients.

META-ANALYSES

Still, the results of most studies are very consistent, indicating that individuals with CP are at an increased risk of developing RA [18,58,104], as well as RA patients are at an increased risk of CP and more severe forms of periodontitis [1,7,15,17,22,23,31,39,42,45,60,61,75,76,79,80,86,88,100]. The relative risk of periodontitis in RA patients was assessed in two separate meta-analyses. Tang et al. [97] evaluated 8 studies published between 2004 and 2014 involving a total number of 14,556 RA patients and 142,840 healthy controls. Prevalence rates of RA ranged from 15.5% to 100% compared with 10% to 82.1% in controls. This meta-analysis indicated that an increased risk of periodontitis was significantly associated with RA (OR=4.68; 95% CI: 3.11-7.05). Another study analyzed 17

Table 1: Epidemiological correlations between chronic periodontitis and rheumatoid arthritis

Type of study	Groups design	Methods	Results	Name of study
Case control study	RA group = 50 Control group=101	Periodontal status assessment	Prevalence of CP↑; SBI↑ PD↑ CAL↑ missing teeth number↑ compared to control group.	Kasser et al. (1997) [45]
Case control study	RA group = 50 Control group=50	Periodontal and RA status assessment	Prevalence of CP↑; SBI↑, PD↑, CAL↑, calculus↑, missing teeth number↑ compared to control group. Correlation of severity of CP with RA disease duration, number of tender and swollen joints, VAS pain, ESR and CRP levels.	Abou-Raya et al. (2005) [1]
Case control study	RA group = 39 Control group=22	Periodontal status assessment	Number of missing teeth ↑ PI↑ CAL↑ compared to control group.	Ishi et al. (2008) [39]
Case control study	RA group = 50 Control group= 50	Periodontal status assessment	Prevalence of CP↑; CAL↑ compared to control group.	Bakhtiari et al. (2009) [5]
Case control study	RA group = 35 CP group= 35 Control group= 35	Periodontal status and global pain assessment, saliva IL-1β, TNF-α and MMP-8 levels assessment	Prevalence of CP↑; BOP↑, PI↑, PD↑ compared to control group. Saliva IL-1β level↑ compared to control group.	Mirrielees et al. (2010) [61]
Case control study	RA group = 101 Control group=101	Periodontal and RA status assessment	No higher prevalence of CP compared to control group. No correlation of severity of CP with severity of RA.	Farah Vakar et al. (2010) [28]
Case control study	RA group = 91 Control group= 93	Periodontal and RA status assessment	Prevalence of CP↑; PD↑, missing teeth number↑ compared to control group. PD↑ in seropositive RA group compared to seronegative group. No correlation of severity of CP with severity of RA.	Potikur et al. (2011) [76]
Case control study	RA group = 53 Control group= 53	Periodontal status assessment	CAL↑ BOP↑ compared to control group	Torkzaban et al. (2012) [100]
Case control study	New-onset RA group=31 Chronic RA group =34 Control group= 18	Periodontal and microbiological assessment	Prevalence of CP↑ in both RA groups compared to control group. No microbiological differences among groups.	Scher et al. (2012) [86]
Case control study	RA group = 40 Control group= 40	Periodontal and RA status assessment	Prevalence of CP↑; BOP↑, CAL↑, PD↑, PI↑ and mobile teeth number↑ compared to control group. Correlation of severity of CP with number of tender and swollen joints, VAS pain, morning stiffness, grip strength, HAQ, ESR levels.	Ranade et al. (2012) [80]
Case control study	RA group = 95 Control group 1 for CP assessment=420 Control group 2 for microbiological assessment=80	Periodontal, RA and microbiological status assessment	Prevalence of CP↑ compared to control group. IgM anti-P. g↑ compared to control group. IgG- and IgM-anti P. g↑ in RA subgroup with severe periodontitis compared to control subgroup with severe periodontitis. Correlation of severity of CP with DAS28 and CRP levels.	de Smit et al. (2012) [23]
Case control study	RA group = 50 Control group= 50	Periodontal and RA status assessment	Prevalence of CP↑ and GI↑ compared to control group. Correlation of severity of CP with ESR and CRP levels.	Rajkarnikar et al. (2013) [79]
Case control study	New RA group = 13779 Control group= 137790	Periodontal status assessment	Prevalence of CP↑ compared to control group.	Chen et al. (2013) [15]
Case control study	RA group = 100 Control group= 112	Periodontal and RA status assessment	Prevalence of CP↑; GI↑ OHI↑, PD↑, CAL↑ compared to control group. No correlation of severity of CP with severity of RA.	Joseph et al. (2013) [42]

Type of study	Groups design	Methods	Results	Name of study
Case control study	Early RA group = 22 Control group= 22	Periodontal and microbiological status assessment	Prevalence of CP↑; number of missing teeth↑, PD↑, BOP↑ compared to control group. ↑T. forsythia and S. anginosus compared to control group.	Wolff et al. (2014) [104]
Case control study	RA group = 287 Control group= 330	Periodontal, RA and microbiological status assessment	Prevalence of CP↑; PD↑ compared to control group. Anti-F. nucleatum antibody concentration↑ compared to control group. Correlation of severity of CP with swollen joint counts, DAS-28-CRP, radiographic damage, RF and ACPA. Correlation of anti-P. g OMA antibody concentration with ACPA, RF, and CRP levels. ACPA↑ in patients with subgingival P.g and higher anti-P.g antibody levels.	Mikuls et al. (2014) [60]
Case control study	RA group = 44 Control group= 41	Periodontal status assessment	Prevalence of CP↑; PI↑, BOP↑, GI↑, CAL↑, PD↑ compared to control group.	Pons-Fuster et al. (2015) [75]
Case control study	RA group = 287 Osteoarthritis group= 330	Periodontal and microbiological status assessment	Prevalence of alveolar bone loss↑ compared to Osteoarthritis group. Correlation of alveolar bone loss with ACPA, DAS28, HAQ, number of swollen and tender joints.	Gonzalez et al. (2015) [31]
Case control study	RA group = 73 Control group= 73	Periodontal status assessment	Prevalence of CP↑; BOP↑, PI↑, CAL↑, PD↑ compared to control group.	Silvestre-Rangil et al. (2016) [88]
Case control study	RA group=2740 Control group= 3942 from Swedish population-based Epidemiological Investigation of Rheumatoid Arthritis	Periodontal status assessment by linking patients with National Dental Health Registry	No higher prevalence of CP compared to control group, regardless of seropositivity.	Eriksson et al. (2016) [27]
Case control study	RA group = 264 Control group= 88	Periodontal and RA status assessment	Prevalence of CP↑; BOP↑, PD↑, CAL↑, GI↑, PI↑ compared to control group. Correlation of severity of CP with RA disease duration, ESR and ACPA levels.	Choi et al. (2016) [17]
Case control study	Early RA group = 53 Chronic RA group = 28 Control group = 43	Periodontal and RA status assessment,	Prevalence of periodontitis ↑ in RA patients. Prevalence of P. gingivalis ↑ in early RA petients.	Äyräväinen et al. (2017) [5]
Cross-sectional study	1412 patients attending for dental treatment	Periodontal status and self-reported RA status assessment	Prevalence of self-reported RA↑ in group referred for periodontal treatment. Prevalence of moderate to severe CP↑ in group with self-reported RA.	Mercado et al. (2000) [58]
Cross-sectional study	4461 noninstitutionalized civilians	Periodontal status assessment	Prevalence of CP↑, edentulism↑ and number of missing teeth ↑ in patients with RA.	de Pablo et al. (2008) [22]
Cross-sectional study	1520 patients attending for dental treatment	Periodontal status and patients medical record assessment	Prevalence of RA↑ in females and patients aged >50 in group referred for periodontal treatment.	Dev et al. (2013) [24]
Cross-sectional study	196 rheumatology clinic patients	Periodontal and RA status assessment	No correlation of severity of CP with severity of RA.	Khantisopon et al. (2014) [47]
Cross-sectional study	168 RA patients and 168 healthy control patients	Periodontal and RA status assessment	Prevalence of PD↑, CAL↑ and number of missing teeth ↑ in RA patients. CP was more severe in RF-positive patients.	Schmickler et al. (2017) [87]
Cohort study	Cohort of 81131 female nurses	Prospective observation for RA cases from 1992 to 2004	No higher incidence of RA cases in group with history of periodontal surgery or tooth loss.	Arkema et al. (2010) [4]

Type of study	Groups design	Methods	Results	Name of study
Cohort study	Cohorts from 1000000 nationwide, population-based sample. CP cohort = 628628 CP with dental scaling cohort = 96542 Non CP cohort = 68842	Retrospective observation for RA cases from 1999 to 2010	Incidence of RA cases↑ in CP cohort and CP with dental scaling cohort compared to non CP cohort. Incidence of RA cases↑ in CP cohort compared to CP with dental scaling cohort.	Chou et al. (2015) [18]
Cohort study	Cohorts from 25000000 veterans population based sample. CP cohort = 433674 Other dental treatment cohort = 431582	Retrospective observation for RA cases from 1999 to 2012	Incidence of RA cases↑ in CP cohort	Grasso et al. (2015) [33]

ACPA – anti-citrullinated protein antibody, BOP – bleeding on probing, CAL – clinical attachment loss, CP – chronic periodontitis, CRP – C-reactive protein, DAS28 – disease activity score, ESR – erythrocyte sedimentation rate, GI – gingival index, HAQ – health assessment questionnaire, OHI – oral hygiene index-simplified, PD – probing depth, PI – plaque index, P.g – Porphyromonas gingivalis, RA – rheumatoid arthritis, RF – rheumatoid factor, SBI – sulcus bleeding index, TLC – VAS – Visual Analogue Scale

publications involving 153,492 patients proved a statistically significant higher risk of developing periodontitis in RA patients when compared with healthy controls (RR=1.13; 95% CI: 1.04-1.23) [30]. Similar findings were not observed when RA patients were compared with osteoarthritis patients. Both studies were based on numerous studies with a large number of subjects and indicate an association between RA and periodontitis.

Furthermore, a correlation between the activity in both diseases was presented in multiple studies – patients with more severe CP suffer from more active RA [1,17,23,31,60,80]. Conversely, there are a few exceptional studies, which do not show such a correlation [4,42,47,76] or even no association at all [4,27,28].

INTERVENTIONAL STUDIES

Based on our knowledge of the relationship between CP disease and RA, some intervention attempts were performed to determine whether eliminating periodontal infection and inflammation will affect the severity of RA [2,10,26,48,72,74,80,81] (Table 2). Though there were not many clinical trials and most of them were made on a relatively small groups (up to 30 patients in the treatment group), with a short period of observation (up to 6 months), their results are still promising. Most of the studies confirmed that periodontal treatment decreases RA activity [2,10,26,48,72,80].

In all studies patients in the treatment groups received non-surgical periodontal therapy including scaling and root planning, usually with addition of oral hygiene instruction. The treatment decreased significantly RA activity measured by DAS28 score in several trials [2,10,26,48,72], though in a study performed by Al-Katma

et al. [2] it was only due to ESR reduction, as other parameters did not change significantly. The reduction of inflammatory markers serum levels was observed in the treatment groups – ESR [2,26,48,80,81], CRP [10,26,48] or even TNF-α [26,72] do not surprise, and may be explained by the reduction of the local inflammatory process in the oral cavity. A more significant reduction was observed in the number of tender joints [48,80], the number of swollen joints [48,72,80] or the patient's global assessment VAS [48,72,80]. A study by Ranade et al. [80] also showed a significant decrease in mean HAQ score and an increase in mean grip strength (however, in their paper there is no information on how many weeks after treatment a second assessment was performed). Only one small study by Pinho et al. [74] did not reveal a beneficial effect of periodontal treatment in maintaining RA. It compared patients with RA and CP before and after periodontal treatment (n=15) with patients with RA and CP without treatment (n=15). Significant differences were not observed with regard to HAQ, DAS28, Short Form (36) Health Survey nor to ESR, CRP values.

Despite the promising results, randomized clinical trials (there were only two current randomized studies [2,72]) with large study groups and consistent protocols for assessment of RA activity (presented studies differed in study designs) are still missing. One meta-analysis compared the effect of non-surgical periodontal therapy on clinical markers of RA disease activity [46]. Treatment was associated with a statistically significant reduction in erythrocyte sedimentation rate, TNF-α titers and DAS scores. Another meta-analysis included four single-center interventional controlled studies published between 2007 and 2013 that evaluated the effect of non-surgical periodontal treatment in RA patients [13]. Periodontal therapy was associated with a significant reduction of

Table 2. Interventional studies summary – periodontal treatment

Type of study	Groups design	Intervention type	Results	Name of study
Pre-post study	Patients with RA and CP. Group 1 (G1; n=16) Group 2 (G2; n = 26)	G1 oral hygiene instruction and professional tooth cleaning vs G2 additional full-mouth scaling and root planing	ESR↓ in group with additional full-mouth scaling and root planing 3 months after treatment beginning. RA activity has not been evaluated in this study.	Ribeiro et al. (2005) [81]
RCT	Patients with RA and CP. Treatment group n=17 Control group n=12	Scaling/root planing and oral hygiene instruction	DAS28↓ and ESR↓ 2 months after treatment compared to control group	Al-Katma et el. (2007) [2]
RCT	Patients with RA and CP. Treatment group n=20 Control group n=20	Scaling/root planing and oral hygiene instruction	DAS28↓, number of swollen joints↓ and VAS value↓ 6 weeks after treatment compared to control group	Ortiz et al. (2009) [72]
Pre-post study	Patients with RA and CP. Treatment group=15 Control group=15 The study evaluated in addition group with RA and total prosthesis, group with CP and without RA and group of healthy subjects.	Full-mouth conventional scaling and root planning	None difference between treatment and control group	Pinho et al. (2009) [74]
Pre-post study	Patients with RA and CP.(n=10)	Scaling and root planning, occlusal adjustment and instructions for plaque control.	*No information how many weeks after treatment second assessment was done HAQ↓, ESR↓, number of tender joints↓, number of swollen joints↓, VAS↓, morning stiffness↓, grip strength↑	*Ranade et al. (2012) [80]
Pre-post study	Patients with RA and CP (n=10) The study evaluated in addition group with CP but without RA.	Oral hygiene instructions, quadrant-by-quadrant scaling, and root planing	DAS28↓(1, 3, and 6 months), CRP↓ (1 and 3 months) and gingival crevicular fluid IL-1b↓ (6 months) after treatment compared to baseline.	Bıyıkoğlu et al. (2013) [10]
Pre-post study	Patients with RA and CP with low (n=30) and moderate or high RA activity (n=30)	Oral hygiene instructions and supragingival scaling and root planing	DAS28↓, ESR↓, CRP↓ TNF-a↓ after 3 months from treatment in both groups. Greater ↓ of DAS28, ESR and CRP were observed in group with moderate or high RA activity.	Erciyas et al. (2013) [26]
Pre-post study	Patients with RA and CP. Treatment group n=30 Control group n=30	Scaling/root planing and oral hygiene instruction	DAS28↓, VAS↓ number of swollen joints↓ number of tender joints↓ ESR↓ CRP↓ 3 months after treatment compared to control group	Khare et al. (2016) [48]

CP – chronic periodontitis, CRP – C-reactive protein, DAS28 – disease activity score, ESR – erythrocyte sedimentation rate, HAQ – health assessment questionnaire, RA – rheumatoid arthritis, VAS – Visual Analogue Scale patient global assessment.

DAS28 score. The main disadvantage of both meta-analyses was the limited number of articles that met the inclusion criteria and a relatively low quantity of subjects. Thus, as stated by the authors, larger studies are required to discuss the effect of non-surgical periodontal treatment on RA patients. Without them it will be hard to introduce periodontal treatment as a part of standard therapy in RA patients, even though there is a possible biological link between RA and CP.

ROLE OF PORPHYROMONAS GINGIVALIS IN PEPTIDE CITRULLINATION – POSSIBLE BIOLOGICAL LINK

Citrullination is an enzymatic protein modifying the process that involves the conversion of amino acid arginine into amino acid citruline. Peptidylarginine deaminase enzymes (PAD) catalyzing citrullination are common endogenous substances found in various physiological processes [35]. PAD are very important from

a clinical point of view due to its influence on the auto-immune response in the pathogenesis of RA [51]. Antibodies to citrullinated peptides (ACPA) are the key biomarker of RA, present in the majority of patients. Serum ACPA might be detected many years before the onset of RA [41,63] and the titer of ACPA positively correlates with disease radiological severity [40]. One of the links between RA and periodontitis could be the key periodontal bacterium *Porphyromonas gingivalis* that is the only known microorganism able to produce PAD [103]. Nasse et al. [62] reported that citrullinated proteins present in periodontal tissues, similar to those formed in RA-affected synovial tissues, indicate high in vivo activity of bacterial PAD. These bacterial enzymes are capable of inducing citrullination of both host endogenous proteins (such as fibrinogen or α-enolase) and bacterial exogenous proteins [54]. Because citrullination can inactivate epithelial growth factor and C5a protein of complement system and results in the disruption of the healing processes and immune response in periodontal tissues, PAD could be a relevant virulence factor of *P.g.* [77] Maresz et al. [57] conducted an animal study and proved that *P.g* infection was related to high ACPA titer and the progression of collagen-induced arthritis in mice. A clinical analysis of gingival crevicular fluid carried out by Harvey et al. [30] revealed that the presence of ACPA antibodies was almost exclusive to a subset of patients affected with periodontitis. Furthermore, the enzymatic activity of *P.g* in individuals with CP may be the cause of immunization triggering an inflammatory response that can result in ACPA production. Given that *P.g* infection and its citrullinated peptides are an ubiquitous, immunological response to citrullinated proteins at the onset of RA might be promoted in patients with CP, who also have a human leukocyte antigens type suited to the presentation of citrullinated peptides [56,59]. The process potentially triggered in periodontal tissues could lead to a breakdown of tolerance to specific citrullinated peptides and host citrullinated proteins in the inflamed joint [78]. The aforementioned process could be further exaggerated by the enzymatic activity of PAD2 and PAD4 present within synovial membranes [50]. *P.g* also could be responsible for a stronger immune response in patients with RA. Studies conducted by de Smit et al. [23] on patients with periodontitis showed a significantly higher serum *P.g* antibody level in subjects with RA. Kharlamova et el. [49] evaluated serum level of IgG antibodies against *P.g* virulence factor arginine gingipain type B (RgpB) in a large population-based case control study. The antibody levels were significantly higher in RA patients compared to controls without RA and higher in ACPA-positive RA patients compared to ACPA-negative RA patients. Moreover, strong immunization was detected in RF-positive and ACPA-positive individuals with high RA risk (having first-degree relative with RA as a common risk factor). They displayed significantly higher *P.g* antibody levels when compared with the control group. What is more important, the correlation between RgpB antibodies and RA was even stronger than the correlation between RA and smoking. Smoking

is considered as major environmental risk factor for RA [25,43,97] due to peptides citrullination, especially in patients with shared epitope of HLA–DR [52,55,73]. The main hypothesis assumes that smoking causes peptides citrullination, triggering an immune response, with shared epitope contribution to induction of immunity to citrullinated peptides, which in time results in the onset of RA. If smoking itself is estimated for about 20% of all RA cases [43], the role of *P.g* may be even greater [49].

However, not all studies showed a correlation between *P.g* prevalence and the clinical onset of RA. A case-control study conducted on 103 pre-RA cases displayed that risk of RA or pre-RA autoimmunity was not associated with antibody levels to RgpB or *P.g* PAD [29]. Furthermore, an analysis of anti-*P.g* antibodies revealed no differences in exposure to *P.g* among new-onset RA, chronic RA and control group [86].

All this data suggests that *P.g* infection could play a central role in the pathogenesis of RA and may initiate early loss of tolerance to self-antigens before the onset and symptoms of RA. This fact can show previous studies of antibiotics treatment in RA in a new light.

ANTIBIOTICS TREATMENT IN RA

The first attempt of antibiotics treatment in RA was made over 40 years ago because of suspicions that mycoplasmas are one of the etiologic agents in RA [90]. Although the current theory that mycoplasmas cause RA is disregarded, there were many studies in which antibiotics have shown partial efficacy in treating RA [12,64,65,66,68,69,70,71,84,85,98]. Their exact mechanism of action remained unclear. Antibiotics were never widely introduced into rheumatological clinical practice. For some time they were recommended [82] in the treatment of patients with low disease activity and with short disease duration, but currently neither EULAR [91] nor ACR [89] recommend the usage of antibiotics as one of disease-modifying anti-rheumatic drugs (DMARDs), mainly because of the small number of studies regarding their application in RA and the fact that classic DMARDs, such as methotrexate, are effective. Nevertheless, it cannot be denied that antibiotics demonstrated some efficacy in treating RA in many multiple double blind randomized clinical trials [12,64,65,66,68,69,70,71,84,98] with just a few trials showing no effect of antibiotics on RA activity [93,102] (Table 3). These studies can take on a new meaning, given our current knowledge of the relationship between CP and RA.

One of first groups of antibiotics used in clinical trials for RA treatment were tetracyclines [12,66,90,98], minocycline and, to a lesser extent, doxycycline. In a meta-analysis done by Stone et al. [95] tetracyclines, in particular minocycline, were associated with a clinically significant improvement in disease activity in RA with no absolute increased risk of side effects. Tetracyclines are widely used in the treatment of CP, as they are effective against

Table 3. Antibiotic treatment in Rheumatoid Arthritis studies summary

Type of study	Groups design	Intervention type	Results	Name of study
RCT, double blind	Patients with active RA Treatment group=109 Placebo group=110	Minocycline 200mg/daily	Number of swollen joints↓, number of tender joints↓, ESR↓, RF↓ after 48weeks of treatment.	Tilley et al. (1995) [98]
RCT, double blind	Patients with early RA Treatment group=23 Placebo group=23	Minocycline 200mg/daily	Patient VAS global assessment ↓ physician VAS global assessment↓, morning stiffness↓ after 6 months of treatment.	O'Dell et al. (1997) [66]
head to head RCT, double blind	Patients with early RA Minocycline group=30 hydroxychloroquine group=30	Minocycline 200mg/daily or hydroxychloroquine 400mg/daily	ACR 50 response ↑ and patient VAS global status↓in minocycline group compared to hydroxychloroquine group after 2 years	O'Dell et al. (2001) [65]
RTC, double-blind	Patients with active RA Doxycycline group=10 Azithromycin group=11 Placebo group=10	Doxycycline 200mg/ daily IV or azithromycin 250mg/daily	None difference between groups after 84 days	St Clair et al. (2001) [93]
RTC, double-blind	Patients with active RA Treatment groups=48 Placebo group=18	Doxycycline 2x50mg/daily	None difference between groups after 36 weeks	van der Laan et al. (2001) [102]
RCT, double blind	Patients with early RA MTX alone group=24 MTX plus low dose doxycycline=18 MTX plus high dose doxycycline=24	MTX plus doxycycline 40mg/d or MTX plus doxycycline 200mg/d or MTX plus placebo	ACR 50 response ↑ in high dose doxycycline group and morning stiffness↓ in high and low dose doxycycline group compared to MTX plus placebo group after 2 years. There were no differences in MTX dose between groups at the end of the study.	O'Dell et al. (2006) [64]
RCT, double blind	Patients with active RA Treatment group=41 Placebo group=40	Clarithromycin 500mg/ daily	ACR 20, ACR 50, ACR 70 response ↑ VAS pain↓ patient VAS global assessment↓ physician VAS global assessment↓ morning stiffness↓HAQ↓ CRP↓ ESR↓ after 6 months of treatment	Ogrendik (2007) [68]
RCT, double blind	Patients with early RA Treatment group=38 Placebo group=38	MTX plus levofloxacin 500 mg/d or MTX plus placebo	ACR 20, ACR 50, ACR 70 response ↑ number of swollen joints↓, number of tender joints↓VAS pain↓ patient VAS global assessment↓ physician VAS global assessment↓ morning stiffness↓ HAQ↓ CRP↓ ESR↓ after 6 months of treatment with addition of levofloxacine	Ogrendik (2007) [70]
RCT, double blind	Patients with early RA Treatment group=16 Placebo group=15	Roxithromycin 300 mg/d	ACR 20, ACR 50, ACR 70 response ↑ DAS28↓ number of swollen joints↓, number of tender joints↓VAS pain↓ patient VAS global assessment↓ physician VAS global assessment↓ morning stiffness↓HAQ↓ CRP↓ ESR↓ after 3 months of treatment	Ogrendik (2009) [69]
RCT, double blind	Patients with active RA Treatment group=50 Placebo group=50	Roxithromycin 300 mg/d	ACR 20, ACR 50, ACR 70 response ↑ DAS28↓ number of swollen joints↓, number of tender joints↓VAS pain↓ patient VAS global assessment↓ physician VAS global assessment↓ morning stiffness↓HAQ↓ CRP↓ ESR↓ after 6 months of treatment	Ogrendik & Karagoz (2011) [71]
RCT, single blind	Patients with active RA Treatment group=16 Control group=16	Clarithromycin 1000mg/d for 15days and 500mg/d for another 15 days	ACR 20, ACR 50, ACR 70 response ↑ after 1 months of treatment compared to control group	Saviola et al. (2013) [84]

ACR – american college of rheumatology criteria, CRP – C-reactive protein, DAS28 – disease activity score, ESR – erythrocyte sedimentation rate, HAQ – health assessment questionnaire, MTX – methotrexate, RA – rheumatoid arthritis, RF – rheumatoid factor, VAS – Visual Analogue Scale.

different periodontal pathogens. Tetracyclines not only show antibacterial effect, but also inhibit matrix metalloproteinases activity, among others by inhibiting nitric oxide synthesis [3], which could be beneficial in the treatment of both CP and RA. Macrolides [68,69,71,84,85], clarithromycin and roxithromycin were another group of antibiotics studied in RA showing good clinical effect. Macrolides are both active against anaerobic oral bacteria and known for their anti-inflammatory properties [37]. Roxithromycin can inhibit the in vitro production of TNF and IL-6 [101]. Finally, the last studied antibiotic in RA with immunomodulatory effects is levofloxacin [70], quinolone agent. Quinolones are not only effective against anaerobic oral bacteria, but also are capable inhibiting IL-1 and TNF production [20].

Without further research it cannot be concluded that anti-bacterial effect of antibiotics on the oral bacterial flora influenced their value in treating RA patients. Growing evidence suggests that, beside oral microbiota, gut microbiota may play some role in the development of RA [44,83]. Furthermore, it is not known whether the main mechanism of action in the presented studies were the antibacterial or immunomodulatory features of antibiotics. Finally, a question arises regarding the effectiveness of antibiotics in treating CP and, to some extent, in the treatment of RA. Will antibiotics become a part of recommended treatment in RA patients with CP? There are a few ongoing studies assessing the effectiveness of combined antibiotics (amoxicillin plus metronidazole) and non-surgical periodontal treatment in RA [19,38].

Final remarks

Some data may indicate that periodontal treatment affects the course of RA, decreasing the disease activity.

Most of the studies on that matter have limitations as they display small study groups and lack consistency in terms of diagnostic criteria of periodontitis in patients and assessment of RA activity. A short period of observation is another factor to be considered as in nearly all the studies it ranged between 6 weeks to 6 months. The major disadvantage regarding the cross-sectional design of some epidemiological studies is the lack of ability to assess the pattern of disease development. Impaired manual skills of RA patients may contribute to the lack of proper oral hygiene and thus increase the risk of periodontitis. Therefore, the onset or aggregation of periodontitis might be secondary to poor oral hygiene and plaque control resulting from joint inflammation and stiffness observed in patients with RA. However, results obtained by Mikuls et al. [60] showed that CP was more common in patients with ACPA-positive RA, when compared with osteoarthritis control group. This could indicate the existence of an independent relationship between RA and periodontitis, since both compared groups suffered from different types of arthritis. Bartold et al. [8] found in an animal model that existing *P.g* infection promotes the development of adjuvant arthritis in mice. Similar research conducted by Cantley et al. [14] confirmed these results. Mice with pre-existing periodontitis were more susceptible to developing severe experimental arthritis that progressed faster. These two animal studies suggest that the association between RA and CP could be causal. How do genetic and epigenetic factors influence this association? There is no research on this issue, although it is already known that there is an interaction between the shared epitope of HLA-DRB1 and RgpB antibodies [49].

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