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Review

Periodontitis and Rheumatoid Arthritis- Is there a link? - current status of the controlled clinical trials

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Abstract. Aim: To evaluate the current literature regarding the association between periodontal disease (PD) and rheumatoid arthritis (RA). Methods: MEDLINE database was searched for clinical studies published between January 2010 and September 2015 focused on the correlation between these two diseases. Results: Out of 41 articles considered or this review, 35 revealed an association between RA and PD. Significantly increased periodontal attachment loss in periodontal patients with RA as compared to non-RA periodontal patients was reported in 5 studies; 10 studies showed an improvement in RA clinical parameters after periodontal treatment, and 7 studies obtained the improvement of periodontal clinical parameters during the appropriate RA therapy. Conclusion: The current literature seems to sustain a strong association between PD and RA.

Key Words: periodontitis, rheumathoid arthritis, periodontal disease, periodontopathogens.

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Introduction

In the past 20 years, research has focused on evaluating the interrelationship between periodontal disease (PD) and several systemic conditions, including Rheumatoid Arthritis (RA). PD and RA are both chronic inflammatory diseases, sharing a range of similarities like common host-mediated pathogenesis or several similar clinical features (Greenwald et al 1999, Mercado et al 2001, de Pablo et al 2009, Bartold et al 2005, Mercado et al 2003). A bidirectional relationship has been suggested by several authors: periodontitis patients reveal a higher prevalence of RA as compared to periodontally healthy subjects (Dissick et al 2010, Mercado et al 2000, Demmer et al 2011), whereas patients suffering of RA have a higher risk of developing periodontitis (Mercado et al 2001, Kaber et al 1997, Havemose-Poulsen et al 2006, Pischon et al 2008, Dissick et al 2010).

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with a worldwide prevalence of 0.5% (Alamanos et al 2006). It involves the inflammation of synovial joints, resulting in erosion and joint deformity, leading eventually to functional disability. Concomitantly, RA may induce other systemic problems like vasculitis, rheumatoid nodules, lung disease, blood disorders and osteoporosis.

Periodontitis, also a chronic inflammatory disease, affects the tooth supporting structures including soft tissues, root cementum, periodontal ligament and alveolar bone. Periodontitis is the result of a disbiosis in the oral microflora, initiated by specific anaerobic pathogens being eventually characterized by elevated levels of *Aggregatibacter actinomycetemcomitans* (*A. aactinomycetemcomitans*), *Porphyromonas gingivalis* (P. *gingivalis*), *Tannerela forsythia* (*T. forsythia*), *Treponema denticola* (*T. deticola*), and several other anaerobic species (Socransky et al 1987).

A strong association between these two diseases has been suggested in several epidemiologic, clinical and genetic studies (Berthelot et al 2010, Demmer et al 2011, Detert et al 2010, Rutger 2012): some authors investigated a common genetic background (Yoshie et al 2007, Schafer et al 2011, Firatli et al 1996, Katz et al 1987, Marotte et al 2006, Bonfil et al 1999, de Pablo et al 2008) while others looked upon similar environmental risk factors such as smoking (Gonzalez et al 2015, Mikuls et al 2014). Moreover, similar destructive mechanisms of the pro-inflammatory cytokines and inflammatory cells responsible for the periodontal destruction and bone erosion in RA have been reported: overproduction of tumor necrosis factor- alpha (TNF-α), interleukin-6 (IL-6) have been suggested as to be a common cofounding factor for these two diseases (Mercado et al 2003).

The aim of the present review was to offer a current overview upon clinical studies investigating the association of PD and RA published in the last 5 years.

Methods

Study selection

MEDLINE database was searched for articles published between January 2010 and September 2015. Following search terms were employed for study identification: ("periodontal disease" OR "periodontitis" OR "periodontal resorbtion" OR "periodontal

bone resorbtion" OR "periodontal destruction" OR "periodontal retraction" OR "alveolar bone resorption" OR "Periodontal treatment" OR "Periodontal therapy" OR "non-surgical periodontal treatment" OR "scaling and root planning") AND ("rheumatoid arthritis" OR " therapy of rheumatoid arthritis" OR "medication for rheumatoid arthritis" OR "improvement of rheumatoid arthritis").
Case-control, parallel, randomized, longitudinal clinical human studies, evaluating the correlation between PD and RA were included in the present review. Only articles published in English were considered.

Results assessment
Clinical periodontal parameters (e.g. probing pocket depth, clinical attachment level, plaque and gingiva indices) were considered for evaluation of the PD. For RA, parameters like DAS-28 (28 joint disease activity score) and rheumatoid factor were recorded; the citrullination process, erythrocyte sedimentation rate and C-reactive protein were followed. Another outcome of interest was the influence of periodontal disease treatment on the rheumatoid arthritis parameters and vice versa.

Screening procedure
Titles and abstracts resulted from the MEDLINE search, were screened for human studies in English language, published from 2010-2015, reporting on the evaluation and clinical treatment in patients suffering of both RA and/or PD; furthermore, screening of the selected studies included associations for the two investigated diseases. In the next step, all selected studies were thoroughly evaluated based on the full text article considering the endpoints of this review.

Data Extraction and assessment
Following data from the articles were extracted: general information (authors, journal and year of publication), study information (evaluation period, number of patients, treatment groups, main examinations, microbiological and immunological aspects, results). Additional features like sex, age, geographical region or smoking status were taken into consideration. The extracted data was summarized into two tables: studies with and without an association between RA and PD.

Results

MEDLINE search resulted in 489 titles and abstracts with relevant for the present topic; after selecting articles published in the last five years, 121 articles remained for further selection, out of which only 49 studies were conducted in humans. After exclusion of all irrelevant studies regarding the present focused question, 41 articles were finally included in this review.
From the 41 selected studies, 35 found a positive correlation between RA and PD (Table 1)(Gonzalez et al 2015, Okada et al 2011, Kobayashi et al 2014, Yokoyama et al 2014, Kobayashi et al 2014, Rosamma et al 2013, Mirrielees et al 2010, Torkzaban et al 2012, Dev et al 2013, Biyikoglu et al 2013, de Smit et al 2012, Quirke et al 2014, Monsarrat at al. 2013, Shimada et a. 2015, Mittal et al 2015, Hashimoto et al 2015, Silosi et al 2015, Mikuls et al 2014, Lappin et al 2013, Raikarnikar et al 2013, Okada et al 2013, de Pablo et al 2014, Susanto et al 2013, Harvey et al 2013, Chen et al 2013, Sezer et al 2013, Ranade et al 2012, Nesse et al 2012, Ishida et al 2012, Garib et al 2011, Mikuls et al 2012, Debrabrata et al 2015, Erciyas et al 2013, Mayer et al 2013, Ustun et al 2013).

Table 1. Studies that found a positive correlation between rheumatoid arthritis and periodontal disease
1. Authors/ Year: Gonzalez et al 2015
Study Type/ Period: Multicenter case-control / 21 months
Patients: Total n= 617; Test n= 287 RA; Control n= 330 OA; Sex distribution: n.r. ; Smoking distribution: n.r.
Evaluated Therapies: PA: All patients underwent a periodontal evaluation; RA: MTX, prednisone, biologics
Evaluated Parameters: serum ACPA; serum IgG antibody to P.g., F.n., P.i.; ABL; RF; CRP; DAS-28; HAQ; smoking status
Results: Test ACPA had 20% more ABL sites than control (p= 0.03).Other results show high serum ACPA concentration (p= 0.004), DAS28 (p= 0.023), HAQ (p= 0.05), regardless of the smoking status (p< 0.1%).
Association: Increased ABL was associated with increased ACPA, and with findings at articular sites.
2.Authors/ Year: Okada et al 2011
Study Type/ Period: Cohort control study; Period: 5 months
Patients: Total n=150; Test n= 80 RA (male n= 10; female n= 70; smoker n= 6); Control n=38 non-RA (male n= 5; female n= 33; smoker n= 2)
Evaluated Therapies: PA: All patients underwent a periodontal evaluation; RA: DMARD, corticosteroids, NSAID, or TNF antagonists
Evaluated Parameters: serum IgG antibody to P.g., P.i., A.a., E.c; DAS28; Anti-CCP; RF; PD; CAL; BOP
Results: Anti-P.g. and anti-CCP: RA> controls (p= 0.04 and p< 0.0001) Significant association of anti–P.g. and anti–A.a. IgG responses with RA after age, sex, and smoking adjustments (p= 0.005 and p= 0.02). Anti–P.g. titer had a significant correlation with RF levels, PD, and CAL (p= 0.03, p= 0.03, and p= 0.02).
Association: Serum levels of anti-P.g. IgG were associate with RF.
3. Authors/ Year: Kobayashi et al 2014(a)
Study Type/ Period: Clinical control study; Period: 2 months
Patients: Total n= 55; Test n= 28 RA anti IL-6R (male n= 6; female n= 22; smoker n=0); Control n= 27 RA non-TCZ (anti IL-6R) group (male n= 5; female n= 22; smoker n= 0)
Evaluated Therapies: PA: n.r; RA: treatment with TCZ
Evaluated Parameters: serum levels of cytokine; IgG against PA bacteria; GI; BOP; PD; CAL; 3 steps: recruitment; the clinical and laboratory analyses at baseline (T1) for both groups; same analyses 8 weeks from T1 for both groups.
Results: T1: serum IL-6 level differences. Anti–IL6R group: GI, BOP, PD, CAL, IL-6 and (MMP)-3 decreased from T1 to T2 comparing to the control group (p< 0.05); Anti–IL-6R group: significant correlation was found between changes in serum anti-CCP levels and those in PD and CAL (p< 0.05); Both groups: significant association between changes in serum MMP-3 levels and BOP (p< 0.05).
Association: Treatment with or without IL-6R inhibitor shows differences in periodontal and serum parameters between RA and CP.
4. Authors/ Year: Yokoyama et al 2014
Study Type/ Period: Clinical longitudinal control study; Period: 5 months

Patients: Total n=40 (smoking n= 0); Test n=10 RA (male n=1; female n=9); Test n=10 CP (male n=1; female n=9); Test n= 10 RA + CP (male n=1; female n=9); Control n=10 healthy (male n=3; female n=7)
Evaluated Therapies: PA: n.r.; RA: DMARD, corticosteroids, TNF inhibitors were determined at the time of examination
Evaluated Parameters: Serum protein spot volume; Proteins with differences in abundance among the four groups were determined
Results: 7 protein spots out of 1694 obtained in sera were different in abundance among the four groups. Of these, three spots (C3, C factor and Cpl) were significantly different in the RA+CP group compared with the test groups ($p< 0.05$).
Association: C3, C factor and Cpl have different abundance between patients with RA and CP compared with healthy controls and patients with RA only or CP only.
5. Authors/ Year: Kobayashi et al 2014 (b)
Study Type/ Period: Cross-sectional, epidemiological case-control study; Period: 6 months
Patients: Total n= 44; Test n= 22 RA; Control n= 22 healthy; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: n.r.
Evaluated Parameters: missing teeth; PD; CAL; BOP
Results: Number of missing teeth ($p= 0.002$), PD, CAL, ($p< 0.000$), and BOP ($p= 0.001$): RA> controls.
Association: Loss of periodontal CAL and ABL can be detected in patients with RA.
6. Authors/ Year: Rosamma et al 2013
Study Type/ Period: Case-control study; Period: 10 months
Patients: Total n= 212; Test n= 100 RA (male n= 24; female n= 76); Control n= 112 non-RA (male n= 26; female n= 96); Smoking distribution: n.r.
Evaluated Therapies: Comparison of periodontal and systemic parameters in cases and controls
Evaluated Parameters: No. of missing teeth; GI; OHI-S; PD; CAL; DAS28; ESR; CRP
Results: Significant difference in GI, OHI-S, PD, CAL, ESR and CRP levels between RA group and non-RA group ($p= 0.05$). For RA, there was no association between the RA activity and the severity of PA
Association: The occurrence and severity of PA was found to be higher in RA vs. non-RA.
7. Authors/ Year: Mikuls et al 2012
Study Type/ Period: Multi-center prospective cohort; Period: 14 months
Patients: Total n= 284; Test n= 113 ACPA+; Control n= 171 ACPA-; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: ACPA testing and classification of subjects
Evaluated Parameters: ACPA and RF; IgA, IgG, IgM; Antibody to P.g, P.i., and F.n.
Results: Anti- P.g. concentrations were increased in high-RA risk ($p= 0.011$) and ACPA+ ($p = 0.010$) > ACPA-. Anti-P.i. or anti-F.n: no group differences concentrations. Anti-P.g. concentrations significantly associated with ACPA+ and high-RA risk status ($p< 0.05$).
Association: Infection with P.g. could have an important role in the loss of tolerance to self-antigens for the RA.
8. Authors/ Year: Mirrielees et al 2010
Study Type/ Period: Cross-sectional case-control; Period: 6 months
Patients: Total n= 105; Test n= 35 RA; Test n= 35 PA; Control= 35 healthy; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: anti-TNF-α antibody therapy; PA: n.r.
Evaluated Parameters: Medical assessments, periodontal examinations- PI, PD, BOP, CAL, and pain ratings. Unstimulated whole saliva samples were analyzed for IL-1β, MMP-8 and TNF concentrations
Results: Oral disease: RA and control< PA ($p< 0.0001$), RA having more BOP sites than matched controls ($p= 0.012$). Salivary MMP-8 and IL-1β higher in PA ($p\leq 0.002$), and IL-1β: RA> control ($p= 0.002$).RA receiving anti-TNF-α antibody therapy had lower IL-1β and TNF-α levels vs. RA not on anti-TNF-α therapy ($p= 0.016$, $p= 0.024$) and controls ($p< 0.001$, $p= 0.011$).
Association: RA have higher levels of Inf M than healthy controls; increased BOP; anti-TNF-α antibody-based disease modifying therapy significantly lowers salivary IL-1β and TNF-α levels in RA.
9. Authors/ Year: Torkzaban et al 2012
Study Type/ Period: Historical cohort study; Period: 4 months
Patients: Total n= 106 (male n= 48; female n= 58); Test n= 53 RA; Control n= 53, systemically healthy; Smoker n= 0
Evaluated Therapies: PA: n.r.; RA: n.r.
Evaluated Parameters: PI; BOP; CAL; RA: CRP, duration; comparison between periodontal indices in test and controls
Results: Significant correlation between RA and BOP ($p< 0.001$) and between RA and CAL ($p< 0.001$). There was no correlation found between the periodontal parameters and RA. Sex distribution was not correlated to any indices, while age was found to be strongly related to PI, BOP and CAL ($p<0.001$).
Association: Potential effect of RA on periodontal indices.
10. Authors/ Year: Dev et al 2013
Study Type/ Period: Cross sectional study; Period: 3 months
Patients: Total n= 1520; Test n= 852 periodontal group (male n= 462; female n= 390); Control n= 668 healthy group (male n= 340; female n= 328); Smoking distribution: n.r.
Evaluated Therapies: n.r.
Evaluated Parameters: PA based on WHO guidelines (1997); RA based on the American Rheumatism Association (1988)
Results: 4.4% of PA had RA. Females (3.2%) and subjects aged above 50 years (3.5%) showed a higher prevalence vs. their counterparts ($p< 0.001$). Females showed nearly three times ($OR= 2.813$) higher RA risk than males ($p< 0.05$).
Association: Moderate to severe periodontitis patients have an increased RA risk.
11. Authors/ Year: Bryikoglu et al 2013
Study Type/ Period: Single-centered, controlled, follow-up study; Period: 25 months
Patients: Total n= 30; Test RA-P n= 15 (male n= 6; female n= 9; smoker n= 8); Control H-P (systemically healthy, with chronic periodontitis) n= 15 (male n= 9; female n= 6; smoker n= 9)
Evaluated Therapies: PA: non-surgical periodontal treatment; RA: n.r.
Evaluated Parameters: PA recordings, GCF, and blood samples were obtained at baseline, 1, 3, and 6 months after periodontal treatment. GCF, serum IL-1b, TNF-a levels were analyzed; DAS28 was used to assess RA clinical morbidity
Results: RA-P group: DAS28 decreased after PA treatment ($p= 0.01$). Serum TNF-a: H-P> RA-P ($p= 0.01$), while IL-1b levels were similar; Both groups: GCF IL-1b decreased post-treatment

(p= 0.01), while at 6-months, H-P GCF IL-1b- concentrations are lower than at baseline. DAS28 and GCF IL-1b were correlated to clinical PA indices (p= 0.01).
Association: Significant decreases in DAS28 and GCF IL-1b amounts after periodontal treatment.
12. Authors/ Year: De Smit et al 2012
Study Type/ Period: Cross sectional, clinical, microbiological and serological study; Period: 7 months
Patients: Total n= 175; Test n= 95 RA (male n= 27; female n= 68; smoker n= 23); Test n= 44 non-RA (male n= 20; female n= 24; smoker n= 27); Control n= 36 healthy patients (male n= 17; female n= 19; smoker n= 5)
Evaluated Therapies: RA: DMARD, anti-TNF
Evaluated Parameters: Subgingival plaque samples for presence of P.g. IgA, IgG and IgM antibody titers to P.g. were measured by ELISA. Serum and subgingival plaque measures were compared to controls; DAS28; DPSI score-BOP, PD, CAL
Results: increased prevalence of severe PA in RA patients vs. RA controls (27% versus 12%, p< 0.001); RA patients with severe PA had> DAS28 scores vs. RA with no or moderate PA (p<0.001); No differences were seen in IgM, RF or ACPA reactivity; RA patients with severe PA had> IgG- and IgM-anti P.g. titers than controls with severe PA (p< 0.01 resp. p< 0.05).
Association: RA patients with severe PA have an increased antibody response against P.g. than non-RA. Not all RA patients have cultivable P.g.
13. Authors/ Year: Quirke et al 2014
Study Type/ Period: Extended case-control; Period: 3 months
Patients: Total n= 206; Test n= 80 RA (male n= 20; female n= 60); Test n= 44 PD; Control n= 82 non-RA, not screened for PD; Smoking distribution: n.r.
Evaluated Therapies: Cloning and expression of recombinant PPAD and gingipain; Site-directed mutagenesis of PPAD; electrophoresis and Immunoblotting; PPAD enzyme activity; mass spectrometry
Evaluated Parameters: PPAD and an inactivated mutant C351A auto-citrullination of both was examined. ELISAs using PPAD, C351A and another RgpB; Antibody reactivity examined.
Results: Antibodies to PPAD, but not to Rgp, were elevated in the RA sera (median 122 U/ml) compared with controls (median 70 U/ml; p< 0.05) and PD (median 60 U/ml; p< 0.01). The elevated antibody response to PPAD was modified in RA sera when the C351A mutant was used on ELISA.
Association: The specific immune response to PPAD might break tolerance in RA, and could be a target for therapy.
14. Authors/ Year: Monsarrat et al. 2013
Study Type/ Period: Open label, randomized, control trial 36 months
Patients: Total n= 40; Test n= 20 PA+ RA; Control n= 20 RA+PA; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: SRP and systemic antibiotics, oral disinfectants, and oral care advise. At three months, the same for the controls.
Evaluated Parameters: DAS28; HAQ; GOHAI
Results: DAS28 decreased, improving with 20%, 50%, and 70% the rheumatic disease according to American College of Rheumatology criteria.
Association: SRP could meliorate the RA parameters and the quality of life for them.
15. Authors/ Year: Shimada et al 2015
Study Type/ Period: Clinical cohort control study; Period: 30 months
Patients: Total n= 78; Test n= 52 RA (male n= 8; female n= 44); Control n= 26 healthy (male n= 5; female n= 21); Smoker n= 0
Evaluated Therapies: PA: Oral hygiene instruction and supragingival scaling (in RA subgroup). RA: DMARD, corticosteroids, NSAID
Evaluated Parameters: PD; CAL; BOP; PI; DAS28; serum RF, anti-CCP, IgG, CRP, IL-6, TNF and PAD-4 levels using ELISA
Results: Anti-CCP IgG and anti-PPAD IgG: RA group> non-RA group (p< 0.001 and p= 0.03). A positive correlation between the serum levels of anti-PPAD IgG and anti-CCP IgG (p= 0.04). Significant association between anti-PPAD IgG responses and RA after adjustment for age, gender and smoking (p = 0.004). Supragingival scaling significantly improved PA condition and DAS28 (p< 0.05), but failed to decrease the serum levels of anti-CCP IgG, anti-PPAD IgG and PAD-4 after 2 m of treatment.
Association: Association between anti-PPAD IgG and anti-CCP IgG responses, implicating a role for PPAD in protein CTR in patients with RA and PA.
16. Authors/ Year: Mittal et al. 2015
Study Type/ Period: Clinical randomized control study; Period : 6 months
Patients: Total n= 100; Control A n= 25 healthy; Test B n= 25 CP; Test C n= 25 RA; Test D n= 25 CP+RA; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: n.r.
Evaluated Parameters: PI, GI and PD; Panoramic rx seropositivity for RF was assessed. GCF Resistin was evaluated for all groups.
Results: Resistin was found in GFC of all patients. Levels of resistin were found to be least in A group and highest in D group. GCF resistin was correlated to both periodontal and rheumatological parameters.
Association: Resistin levels are increased in both chronic PA and RA.
17. A17. Authors/ Year: Debrabrata et al. 2015
Study Type/ Period: Clinical genetical control study; Period: 3 months
Patients: Test I n= 15 PA healthy; Test II n= 15 CP; Test III n= 15AP; Smoker n= 0; Sex distribution: n.r
Evaluated Therapies: PA: n.r.; RA: n.r.
Evaluated Parameters: Hemogram; Rx; MPO gene polymorphism and telomerase expression were assessed from blood and gingival samples through PCR.; GI, PD, CAL.
Results: AG and AA genotypes were more frequent in the AP subjects than the controls. The m-RNA expression of hTERT was undetectable in the gingival tissue for controls. Its expression in AP subjects was more increased than in CP patients (p< 0.0001).
Association: MPO-463G/A could be correlated with a risk of AP. hTERT level was higher for AP patients than CP and healthy control groups.
18. 18. Authors/ Year: Hashimoto et al. 2015
Study Type/ Period: Prospective cohort study; Period: 20 months
Patients: Total n= 72; Test n= 49 PA; Control n= 23 non-PA; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: RA: MTX
Evaluated Parameters: PA status at baseline. Up to 8 plaque samples and the presence of P.g. was determined by Taqman

PCR; RA treatment with MTX was compared in patients with PA/P.g. versus patients without PA/P.g.
Results: Patients with PA had higher RA activity (p= 0.02) and higher risk for MTX treatment on the diagnosis of RA> non-PA (OR= 2.68, p= 0.03). P.g. was not correlated with RA (p= 0.72) or MTX introduction risk (p= 0.45).
Association: In patients with naive arthralgia, PA, but not P.g., associates with arthritis activity and future MTX treatment on the diagnosis of RA.
19. Authors/ Year: Silosi et al. 2015
Study Type/ Period: Single-centered clinical control study; Period: 12 months
Patients: Total n= 63; Test n= 16 RA (male n= 4; female n= 12); Test n= 14 CP (male n= 6; female n= 8); Test n= 12 RA-CP (male n= 3; female n= 9); Control n= 21 healthy (male n= 7; female n= 14); Smoking distribution: n.r.
Evaluated Therapies: PA: n.r; RA: n.r
Evaluated Parameters: Assessment of serum and GCF concentrations of both active and pro-MMP-9 was done through ELISA
Results: Differences of serum MMP-9 between test groups and control. MMP-9 in serum was similar in RA patients and RA-CP patients. MMP-9 in GCF for RA-CP patients was higher than CP.
Association: RA-CP being characterized by an inflammatory response modification, MMP-9 could contribute to the pathogenesis of RA-CP patients.
20. Authors/ Year: Mikuls et al 2014
Study Type/ Period: Blinded case-control study; Period: 18 months
Patients: Total n= 617; Test n=287 RA; Control n=330 OA; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: PA: n.r.; RA: n.r.
Evaluated Parameters: PA exam; The HLA-DRB1 status. ACPA using ELISA, and subgingival plaque for the presence of P.g.-PCR.; Associations of PD with RA were examined
Results: Presence of PD: RA/ACPA+ (n = 240; determined using anti-CCP-2 test)> controls (35% and 37%, respectively, versus 26%; p= 0.022 and p= 0.006). Levels of anti-P.g.: RA= controls. The anti-P.g. findings showed an association with the findings for both anti-CCP-2 (r= 0.14, p= 0.022) and RF (r= 0.19, p= 0.001). PD was associated with higher SJC (p= 0.004), higher DAS28 using CRP level (p= 0.045), and higher total Sharp scores of rx damage (p= 0.015), and levels of anti-CCP-2 (p= 0.011) and RF (p< 0.001). ACPAs increased in patients with subgingival P.g. and in those with higher levels of anti-P.g., irrespective of smoking status.
Association: Both PD and P.g. appear to shape the autoreactivity of RA.
21. Authors/ Year: Lappin et al 2013
Study Type/ Period: Clinical cross-sectional control study; Period: 6 months
Patients: Total n= 75; Test n= 39 PA (smoker n= 15); Control n= 36 healthy (smoker n= 16); Sex distribution: n.r.
Evaluated Therapies: PA: SRP; RA: n.r.
Evaluated Parameters: PD, CAL, BOP; Serum and plaque before and after SRP and for controls. P.g. by PCR. ACPA was determined by anti- CCP ELISA. Anti-P.g.titres were determined by ELISA.
Results: Anti-CCP antibody titres: Untreated PA> controls [three patients (8%) versus none (0%); p< 0.0001].
Smoker PA demonstrated lower anti-P.g. (15956 ± 4385 versus 2512 ± 1290 Units/ml, p< 0.05), but similar anti-CCP than non-smoking PA (smokers: 1.31 ± 0.35; non-smokers: 1.41 ± 0.32 AU).Anti-CCP titres: non-smokers< healthy smokers< non-smoker PA. Six months recall: significant decrease in anti-CCP (non-smokers p< 0.05) and anti-P.g. (all participants p< 0.01).
Association: In PA patients, P.g. infection may be responsible for inducing autoimmune responses that characterize RA.
22. Authors/ Year: Rajkarnikar et al 2013
Study Type/ Period: Case-control study; Period: 10 months
Patients: Total n= 100; Test n= 50 RA; Control n= 50 non-RA; Smoker n= 0; Sex distribution: n.r.
Evaluated Therapies: PA: Bone loss scoring= P0: no bone loss; P1: 1/3rd- mild bone loss; P2 : 2/3rd- moderate bone loss and P3: >2/3rd- severe bone loss; HAQ = grade 1 -no assistance needed, grade 2 use of an aid or device, grade 3 -assistance from another person; RA: CRP and ESR.
Evaluated Parameters: PA: PI, GI, Rx, ABL score, number of missing teeth; RA: CRP and ESR; HAQ
Results: The average ABL was statistically more severe in RA group than controls although there were similar PI in both the groups. The GI was > in the RA group. ESR and CRP levels of RA patients were associated with the severity of PA.
Association: There was a significant association between RA and PA because of the common modification of the inflammatory response.
23. Authors/ Year: Okada et al. 2013
Study Type/ Period: Clinical randomized control study; Period: 13 months
Patients: Total n= 55; Test n= 26 PA treatment group (male n= 4; female n= 22); Control n= 29 non-treatment group (male n= 5; female n= 24) Smoking distribution: n.r.
Evaluated Therapies: PA: full-mouth supragingival scaling; RA: DMARD, NSAID
Evaluated Parameters: PA and RA parameters and blood levels of citrulline and IgG to P.g. were examined at baseline and after 8 weeks.
Results: The treatment group exhibited a greater decrease in DAS28 (p= 0.02), (HBP)35 IgG (p= 0.04), and citrulline (p= 0.02) as compared to the control group. IgG to HBP35 was correlated with ACPA (p= 0.0002). A correlation was also found for serum IgG and P.g. -sonicated extracts and those of RF (p= 0.02).
Association: Supragingival scaling lowers DAS28 and serum IgG to P.g. (HBP)35 level and citrulline in patients with RA. P.g. may have a role in the protein CTR, which is correlated to the origin of RA.
24. Authors/ Year: De Pablo et al 2014
Study Type/ Period: Clinical case-control study; Period: 4 months
Patients: Total n= 386 (smoker n= 189); Test= PA; Control= non-PA; Sex distribution: n.r.
Evaluated Therapies: n.r. Serum samples were tested for anti-CCP, anti-MCV, anti-CEP-1, anti-cit-vim, anti-cit-fib and their uncitrullinated forms anti-CParg (negative control for anti-CCP), anti-vim and anti-fib antibodies inpatients ±PA and no RA.
Evaluated Parameters: Serum samples were tested for anti-CCP, anti-MCV, anti-CEP-1, anti-cit-vim, anti-cit-fib and their uncitrullinated forms anti-CParg (negative control for anti-CCP), anti-vim and anti-fib antibodies inpatients ±PA and no RA.

Results: PA had a normal frequency of anti-CCP and anti-MCV (~1%) vs. non-PA, but a higher frequency of positive anti-CEP-1 (12% vs 3%; p= 0.02); Positive antibodies against uncitr. fibrinogen and CParg were also more common for PA vs. non-PA (26% vs 3%; p< 0.001, and 9% vs 3%; p= 0.06); Anti-CEP-1: non-smokers with PA> comnon-PA, had significantly higher titres of (103%, p< 0.001), anti-vimentin (87%, p= 0.002), and anti-fibrinogen (124%, p< 0.001).
Association: The antibody response in PA is directed to the unctr. peptides of the RA autoantigens; This autoimmune response in PA evolves into that of RA.
25. Authors/ Year: Susanto et al 2013
Study Type/ Period: Clinical case-control study; Period: 7 months
Patients: Total n= 150; Test n= 75 RA (male n= 15; female n= 60; smoker n= 5); Control n= 75 +-PA (male n= 15; female n= 60; smoker n= 5)
Evaluated Therapies: All patients with RA were on NSAID, unlike the controls.
Evaluated Parameters: PD, GR, PI, BOP, smoking questionnaire, BMI, education, health, drugs, ESR, CRP, RF, ACPA. PA prevalence and 12 severity measures in RA vs. controls.
Results: RA had a significantly decreased surface area of healthy pocket epithelium versus controls (p= 0.008), and a tendency toward higher CRP levels was observed in RA with severe PA vs. RA with no mild or moderate PA (p= 0.063).
Association: Prevalence and severity of PA in RA is comparable to controls but with less healthy pocket epithelium and a higher inflammatory state in patients with RA and severe PA.
26. Authors/ Year: Harvey et al 2013
Study Type/ Period: Clinical case-control study; Period: 3 months
Patients: Total n= 40; Test n= 29 PA (male n= 18; female n= 11; smoker n= 9); Control n= 21 non-PA (male n= 11; female n= 10; smoker n= 2)
Evaluated Therapies: PA: periodontal surgery, after at least one course of SRP and re-evaluation after 3 months; Non-PA: crown lengthening surgery
Evaluated Parameters: Tissue sections were stained using ACPA, PAD-2 and PAD-4. PCR was performed to investigate PAD-2 and PAD-4 mRNA in inflamed and non-inflamed gingival tissues. Anti-CCP antibodies in GCF were detected by ELISA.
Results: Citrullinated proteins, PAD-2 and PAD-4 were detected in gingiva. There was a correlation between them and inflammation. mRNA for PAD-2 and PAD-4 were detected in both inflamed and non-inflamed gingival tissues. Antibodies to CCP were found mostly in the GCF of individuals with PA.
Association: Increased expression of PAD-2 and PAD-4 in inflamed gingiva.
27. Authors/ Year: Chen et al 2013
Study Type/ Period: A nationwide, population-based, case-control study; Period: 60 months
Patients: Total n= 151569; Test n= 13 779 RA+-PA (male n= 3120; female n= 10659); Control n= 137 790 non-RA +-PA (male n= 31200; female n= 106590); Smoking distribution: n.r.
Evaluated Therapies: PA: antibiotic therapy or periodontal surgery, or scaling more than twice per year
Evaluated Parameters: ORs were calculated for subgroups of patients with PA number of visits, cumulative cost, periodontal surgery and time interval between the last PA-related visit and the index date.
Results: An association was found between a history of PA and newly diagnosed RA (OR= 1.16). The association was dose- and time-dependent and was strongest when the interval between the last PA-related visit and the index date was< 3 months (OR= 1.64).
Association: This association is weak and limited to lack of individual smoking status.
28. Authors/ Year: Sezer et al 2013
Study Type/ Period: Cross-sectional comparative study; Period: 4 months
Patients: Total n= 80 (male n= 18, Female n= 62); Test RA-CP n= 20; Test RA-C n= 20; Test CP n= 20; Control C (systemically/ periodontally healthy) n= 20; Smoking n= 0
Evaluated Therapies: PA: n.r.; RA: DMARD, corticosteroids, NSAID or TNF antagonists at the time of the examination
Evaluated Parameters: OSI, lipid hydroperoxide levels, paraoxonase, arylesterase, and ceruloplasmin activity, prolidase level - Pi, PD, CAL, BOP
Results: The OSI values of the RA-CP group were statistically significantly higher than those of the C group (p< 0.05). The prolidase levels of the RA-C, RA-CP groups and the CP group were statistically higher than those of the C group (p= 0.001, p= 0.007, and p= 0.001, respectively).
Association: Increased prolidase levels in patients with RA and CP may be related to increased oxidative tissue damage.
29. Authors/ Year: Ranade et al 2012
Study Type/ Period: Clinical longitudinal control study; Period: 6 months
Patients: Part A: Total n= 80; Test n= 40 RA; Control n= 40 non-RA; Part B: PA treated n= 10; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: PA: SRP, occlusal adjustment, instructions for plaque control
Evaluated Parameters: Their PA indices, RA clinical laboratory parameters were also correlated with PA in group. PA indices were measured pre-operatively and weeks after PA treatment.
Results: High prevalence of mild (12.5%) to moderate (75%) PA in group. Extent severity of PA-RA were positively correlated.; Reduction in parameters postoperatively with concomitant decrease in PA parameters in RA group.
Association: New host modifying medications are developed.
30. Authors/ Year: Nesse et al 2012
Study Type/ Period: Clinical randomized control study; Period: 4 months
Patients: Test n= 15 periodontally compromised /healthy tissue samples; Control n= 6 RA-affected synovial tissue samples; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: Clinically non-inflamed periodontal tissue samples were obtained from 6 patients undergoing prophylactic removal of impacted third molars; Synovial tissue samples of 4 RA and buccal mucosal cell swabs of 3 healthy donors known to be positive for anti-perinuclear factor staining, were used as positive control.
Evaluated Parameters: PA, healthy periodontal and RA-affected synovial tissue samples were collected in addition to buccal swabs, stained for citrullinated proteins using polyclonal (Ab5612) and monoclonal (F95) antibodies. Western blotting with F95 was performed on lysates prepared from PA and synovial tissues.

Results: In PA stroma, increased citrullinated protein presence (80%) was observed compared with control stroma (33%). PA epithelium always stained positive for Ab5612. Only PA-affected epithelium stained positive for F95. All buccal mucosal swabs and 3 of 4 synovial tissue samples stained positive for both Ab5612 and F95. Western blotting with F95 showed presence of similar citrullinated proteins in both PA and RA-affected synovial tissue.
Association: Additional citrullinated proteins are formed in PA, apparently similar to those formed in RA-affected synovial tissue.
31. Authors/ Year: Ishida et al 2012
Study Type/ Period: Clinical case control study; Period: 5 months
Patients: Total n= 90; Test n= 30 RA (male n= 3; female n= 27; smoking n= 3); Test n= 30 CP (male n= 3; female n= 27; smoking n= 0); Control n= 30 (male n= 3; female n= 27; smoking n= 0)
Evaluated Therapies: PA: n.r; Genomic DNA isolated from peripheral blood was modified by sodium bisulfite
Evaluated Parameters: PD; CAL; DNA methylation levels of IL-6 gene were evaluated with direct sequencing. Levels of IL-6 were determined by ELISA; DAS28; CRP
Results: The region of IL-6 gene promoter was shown to contain 19 CpG motifs. The methylation levels of the CpG motif at -74 bp: RA and CP <in controls (p= 0.0001). Both levels of serum IL-6 and IL-6 production by mononuclear cells were significantly different between individuals with and without the methylation at -74 bp (p= 0.03). The +19 bp motif exhibited differential levels of the methylation among the groups, which was not associated with serum levels of IL-6. The other 17 CpG motifs exhibited comparable levels of the methylation between the groups.
Association: Hypomethylated status of a single CpG in the IL-6 promoter region may lead to increased levels of serum IL-6, implicating a role in the pathogenesis of RA and CP.
32. Authors/ Year: Garib et al 2011
Study Type/ Period: Clinical case control study; Period: 6 months
Patients: Total n= 100; Test PD+RA n= 50; Control PD-RA n= 50; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: n.r.
Evaluated Parameters: The PI, CAL, Rx, ABL tooth loss, and TMJ problems were assessed in the 2 groups. Disease duration, level of ESR, HAQ, and Verbal Descriptor Pain Scale score were assessed in the RA group.
Results: RA: predominantly women, with higher illness duration (11.84 years), ESR (32.08 mm/hour), and HAQ scores (0.82). RA: significant increase in CAL (3.24 mm), bone loss (1.79 mm), missing teeth (6.22), and TMJ problems (54%) than controls. Their periodontal status significantly correlated with illness duration, HAQ score, and Verbal Descriptor Pain Scale score. However, no difference in PI was observed between the RA and controls. Pi (1.54) and TMJ deviation (15%): 30-40 old RA> older subjects.
Association: Patients with advanced RA show a higher risk of developing more significant PA and TMJ problems vs. patients with PD and without RA.
33. Authors/ Year: Erciyas et al 2013
Study Type/ Period: Observational prospective cohort study; Period: 3 months
Patients: Total n= 60; Test n= 30 MHDA (moderate to high activity RA+CP); Control n= 30 LDA (low activity RA+CP); Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: All patients: SRP
Evaluated Parameters: RA: DAS28, ESR, CRP, TNF-a levels in serum. DAS28 and PA parameters were evaluated at baseline and at 3 months after treatment.
Results: ESR, CRP, TNF-a levels in serum, DAS28 and periodontal parameters - similar and significant reduction 3 months after the SRP.
Association: SRP may prove beneficial in reducing RA severity in terms of ESR, CRP, TNF-a levels in serum and DAS28in low or moderate to highly active RA patients with CP.
34. Authors/ Year: Mayer et al 2013
Study Type/ Period: Case-control study; Period: 3 months
Patients: Total n= 58; Test n= 10 RA+ IFX; Test n= 12 RA- IFX; Test n= 12 Psoriatic Arthritis; Test n= 12 SSc; Control n= 10 H healthy; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: PA: n.r.; RA: IFX (anti- TNF-α)
Evaluated Parameters: PI, GI, PD, GCF TNF-α, BOP; ELISA
Results: GI: AI> H and RA+ groups (p= 0.0005). BOP: AI> H and RA+ groups (p= 0.0002). PD: AI> H and RA+ (p= 0.0001). GCF TNF-α: AI> H and RA+ (p= 0.0002). A significant positive correlation between PD and GCF TNF-α (p= 0.0002), BOP (p= 0.0001), GI (p= 0.0001).
Association: Anti- TNF- αtreatment decreases PA indices and TNF- α in GCF for patients with AI diseases.
35. Authors/ Year: Ustun et al 2013
Study Type/ Period: Case-control study; Period: 1 month
Patients: Total n= 16 RA; Test n= 9 RA+ IFX; Control n= 7 RA+ ADA; Sex distribution: n.r.; Smoking distribution: n.r.
Evaluated Therapies: PA: n.r.; RA: IFX; ADA
Evaluated Parameters: CAL, PD, BOP, PI, GI; GCF, IL-1β, MCP-1
Results: GCF volume, IL-1β, and IL-8 decreased, without a statistical significance; IL-8 and MCP-1 levels significantly decreased in PA.
Association: TNF blockers may influence the biochemical parameters of the periodontium, in patients with RA.

Five studies revealed significant increased clinical attachment loss or pocket depths in periodontitis patient with RA as compared to those without RA (Okada et al 2011, Kobayashi et al 2014 (b), Rosamma et al 2013, Torkzaban et al 2012, Garib et al 2011). Several studies also highlighted a strong correlation between the presence of RA and clinical oral parameters: increased alveolar bone loss (Gonzalez et al 2015, Javed et al 2014, Rajkarnikar et al 2013, Garib et al 2011), increased number of missing teeth (Garib et al 2011, Rajkarnikar et al 2013, Javed et al 2014, Rosamma et al 2013) or higher prevalence of temporomandibular joint disorders (Garib et al 2011) as compared to patients without RA.
A high number of the studies have evaluated the effect of PD treatment on the RA (Kobayashi et al 2014a, Bryikoglu et al 2013, Mikuls et al 2012, Quirke et al 2014, Okada et al 2013, Monsarrat et al 2013, Sezer et al 2013, Ranade et al 2012, Erciyas et al 2013, Shimada et al 2015) highlighting an improvement of clinical rheumatological parameters like DAS 28 or several immunomarkers (e.g. immunomarker IL-1ß) (Kobayashi et al 2014 a, Bryikoglu et al 2013, Monsarrat et al 2013, Okada et

al 2013, Erciyas et al 2013, Shimada et al 2015);). However, Shimada et al obtained no improvement in RA after treatment of PD (Shimada et al 2015). Seven studies investigated the effect of RA therapy on the periodontal condition evidencing a decrease in periodontal indices (e.g. GI, BOP) and an improvement in the pocket depths and clinical attachment gain (Pers et al 2008, Ortiz et al 2009, Mayer et al 2009, Mayer et al 2013, Ustun et al, 2013, Kobayashi et al 2014a, Kobayashi et al 2014b).
The immunological link between RA and PD was evaluated by correlations between different cytokines/antibodies: anti-citrullinated protein antibodies (Okada et al 2011, Kobayashi et al 2014a, Shimada et al 2015, Mikuls et al 2014, Lappin et al 2013, Susanto et al 2013), TNF-α (Mirrielees et al 2010, Gumus et al 2013, Centikaya et al 2013, Erciyas et al 2013), IL-1β (Centikaya et al 2013, Biyikoglu et al 2013, Mirrielees et al 2010), Ig- G (Okada et al 2011, Kobayashi et al 2014a, de Smit et al 2012, Shimada et al 2015), Ig A or Ig M (de Smit et al 2012), IL-6 (Ishida et al 2012) and clinical periodontal parameters (e.g. PD, CAL, BOP).
Some studies assessed a possible correlation between the presence of certain periodontopathogens (e.g. A.a., P.g, T.d. T.f.) and the severity of RA (Okada et al 2011, Mikuls et al 2012, de Smit et al 2012, Hashimoto et al 2012, Mikuls et al 2014, Okada et al 2013), 5 studies stressing out an association between elevated levels of antibodies against periodontopathogens and the severity of RA (Okada et al 2011, Mikuls et al 2012, de Smit et al 2012, Mikuls et al 2014, Okada et al 2013). However, some authors obtained no correlation between the presence of periodontopathogens and RA (Hashimoto et al 2015).
Eighteen studies presented no microbiological assessment (Yokoyama et al 2014, Rosamma et al 2013, Mirrielees et al 2010, Gumus et al 2013, Mittal et al 2015, Rajkarnikar et al 2013, de Pablo et al 2014, Susanto et al 2013, Harvey et al 2013, Sezer et al 2013, Ranade et al 2012, Nesse et al 2012, Cetinkaya et al 2013, Ishida et al 2012, Esen et al 2012, Garib et al 2011, Erciyas et al 2013), 3 studies performed no immunological evaluation (Kobayashi et al 2014 b, Hashimoto et al 2015), while 6 studies lacked both microbiological and immunological examinations (Dev et al 2013, Debabrata et al 2015, Javed et al 2014, Chen et al 2013).
Smoking was analyzed in several studies: 2 studies found no significant difference between smoker and non-smoker periodontitis patients with RA (Gonzalez et al 2015, Mikuls et al 2014), while other authors mentioned lower P.gingivalis antibodies in smokers, and similar cyclic citrullinated peptide antibodies with non-smoking periodontitis patients (Lappin et al 2013). De Pablo et al (de Pablo et al 2014) showed that non-smoker periodontitis patients with RA had significantly increased antibody titers to citrullinated α-enolase peptide than RA patients without PD. However, only one study used a smoking detailed questionnaire for the smoking assessment (Susanto et al 2013).
Sex and age distribution in patients with periodontitis and RA was evaluated in 2 studies: Torkzaban et al 2012 showed no correlation between gender and the evaluated periodontal and rheumatological parameters, but a strong positive association between age and periodontal clinical parameters (plaque index, bleeding on probing and clinical attachment level). On the other pole, Dev e al. 2013 observed that, females and patients aged above the age of 50 years with PD, had a higher prevalence for RA, female patients showing an almost three times higher risk for RA than male subjects.
Some authors found a further association of patients with PD and RA with several systemic conditions, such as diabetes mellitus and Sjogren sindrom (Chen et al 2013), the body mass index (Susanto et al 2013). Oxidative stress was also related to these patients in 2 of the 38 selected studies: one of them mentioned that RA and periodontitis with an increased level of prolidase could be in relation to an increased oxidative tissue damage (Sezer et al 2013); contrary to these findings, Esen et al 2012 specified that the presence of RA did not affect the local or systemic level of the oxidative stress index in patients with chronic periodontitis.
Six studies showing no association between PD and RA (Gumus et al 2013, Schaefer et al 2014, Javed et al 2014, Cetinkaya et al 2013, Esen et al 2012, Farah et al 2010) obtained no statistical correlation between the evaluated RA and periodontal parameters in patients having both diseases or in patients suffering only of one (Table 2).

Table 2. Studies that did not find a positive correlation between rheumatoid arthritis and periodontal disease

1. Authors/ Year: Gumus et al 2013
Study Type/ Period: Cross-sectional study; Period: 25 months
Patients: Total n= 49; Test n= 17 RA (females with PA); Test n= 19 OPR; Control n= 13SH (females, non-smoker)
Therapies: anti-inflammatory drugs
Evaluated Parameters: GCF and serum samples before any periodontal intervention; Full mouth periodontal measurements; APRIL, BAFF and TNF-a levels were determined by ELISA;
Results: PD differed in site-specific comparisons, but otherwise RA= OPR= SH. TNF-a and concentrations of TNF-a, BAFF and APRIL RA> SH ($p< 0.05$), GCF concentrations of BAFF: OPR> SH. Serum TNF-a and BAFF: RA> SH ($p< 0.05$) and serum TNF-a: RA> OPR ($p< 0.05$).
Association: Whether Increased TNF-family cytokines, result from greater disease activity or contribute to greater disease activity remains unclear.
2. Authors/ Year: Schaefer et al 2014
Study Type/ Period: Case-control; Period: 96 months
Patients: Total n= 843; Test n= 164 AP; Control n= 679; Sex distribution: n.r.; Smoking distribution: n.r.
Therapies: Immunochip genotyping arrays; Affymetrix 500 K Genotyping Arrays
Evaluated Parameters: 47 risk genes of RA and SLE were genotyped in a sample of AP (600 cases, 1440 controls) and Affymetrix 500 K (280 cases and 983 controls). Associations were replicated in 168 Dutch AP cases and 679 controls and adjusted for the confounders smoking and sex.
Results: Variants at IRF5 and PRDM1 showed association with AP. The associations lost significance after correction for multiple testing in the replication. Both genes are implicated in beta-interferon signaling and are also genome-wide associated with SLE and IBD.
Association: Results show no clear evidence for a pathogenic genetic link of PA and RA but suggest IRF5 and PRDM1 as shared susceptibility factors.
3. Authors/ Year: Javed et al 2014

Study Type/ Period: Clinical cohort-control study; Period: 10 months
Patients: Total n= 100; Test n= 50 CP+RA (male n= 15; female n= 35); Control n= 50 CP-RA (male n= 15; female n= 35); Smoking distribution: n.r.
Therapies: n.r.
Evaluated Parameters: Oral health questionnaire; PI, BOP, PD, CAL number of missing teeth, ABL.
Results: There was no significant difference in socioeconomic status, education status, self-perceived oral symptoms, and periodontal parameters among CP patients with and without RA
Association: Self-perceived oral health and PA parameters are given by the CP intensity and the role of RA seems to be secondary.
4. Authors/ Year: Cetinkaya et al 2013
Study Type/ Period: Clinical case-control study; Period: 24 months
Patients: Total n= 49; Test n= 17 RA (male n= 3; female n= 14); Test n= 16 CP (male n= 10; female n= 6); Control n= 16 healthy (male n= 8; female n= 8); Smoker n= 0
Therapies: 15 RA patients were treated with MTX-sulfasalazine combined therapy, and the other 2 with Leflunomid therapy; all patients used NSAID, and 15 used corticoids
Evaluated Parameters: PI, GI, PD, CAL were recorded. IL-1β, IL-4, IL-10, and TNF-α were determined in GCF and IL-1β and IL-10 in serum by ELISA
- ESR, CRP, RA duration
Results: Concentration of GCF IL-1 β, IL-4, IL-10, and TNF-α were similar in RA and CP patients ($p > 0.05$). Although the total amount and concentration of serum IL-10 was not significantly different among the groups ($p > 0.05$), serum IL-1β was lower in the RA group vs. CP patients and controls and was higher in GCF of the RA group vs. CP group.
Association: Immunologic evaluation did not reveal consistent results about pro- and anti-inflammatory cytokine levels. This might due to the use of NSAID drugs and RA agents by patients with RA.
5. Authors/ Year: Esen et al 2012
Study Type/ Period: Multicentric case-control; Period: 11 months
Patients: Total n= 80 (12 males; 68 females); RA-CP n= 20 (male n= 3; female n= 17; former smoker n= 2); RA n= 20 (male n= 1; female n= 19; former smoker n= 1); CP n= 20 (male n= 4; female n= 16; former smoker n= 2); C n= 20 (male n= 4; female n= 16; former smoker n= 2)
Therapies: RA: NSAID, anti-cytokine drugs
Evaluated Parameters: PA: PI, GI, BOP, PD, CAL; RA: DAS28, ESR, VAS; Laboratory: TAS, TOS, OSI
Results: Although all clinical measurements RA-CP and CP> C and RA groups ($p < 0.001$), there were no differences between CP and RA-CP groups ($p > 0.05$). GCF TOS: CP and RA-CP> RA group ($p < 0.05$). GCF OSI: RA-CP> RA group ($p < 0.05$). There were no differences among the groups in terms of serum TOS and OSI values ($p > 0.05$).
Association: Local OSI values in CP groups were higher, while systemic OSI values showed no difference among the groups.
6. Authors/ Year: Farah et al 2010
Study Type/ Period: Observational and analytical case-control; Period: 6 months
Patients: Total n= 202; Test n= 101 PA+ RA (male n= 29; female n= 72); Control n= 101 PA- RA (male n= 35; female n= 66)
Therapies: n.r.
Evaluated Parameters: PD, CAL, BOP, PI; NSJ, NTJ, pain index, RF, CRP; Comparison between the degree of PA and severity of RA
Results: No statistically significant prevalence and severity of PA in both RA/ non-RA groups
Association: RA is not a risk factor for PA

Discussion

The present review evaluated clinical controlled studies focusing on the interrelationship between PD and RA published in the last 5 years. Our research yielded 41 clinical studies performed within the last 5 years addressing this association, 35 of them highlighting a strong bondage between these 2 chronic diseases (Table 1). We highlighted the impact of treatment of these diseases upon clinical and systemic parameters, and on the other hand the link of different cofounds factors upon the severity of RA and PD.
Our findings suggest an increased tooth-loss rate, increased levels of clinical attachment level loss, increased periodontal pocket depths and bleeding indices in patients with RA and PD over patients without RA. These observations are supported by the results of the review of Kaur et al 2013 that included 3 experimental and 16 case-control studies. The calculated overall weighted mean difference for clinical attachment loss in patients with RA versus those without RA was 1.17 (95% CI 0.43-1.90), stressing out the greater attachment loss in patients with RA as compared to those without RA. Moreover, patients with RA had a weighted mean difference for tooth loss over patients without RA of 2.38 (95% CI 1.48-3.29) (Kaur et al 2013).
The majority of the included clinical studies evaluating the effect of periodontal treatment upon RA parameters were case-control studies of short-term duration (3 to 24 months) showing a reduction of the RA disease activity (DAS 28) and systemic inflammation (several interleukines) after completion of non-surgical periodontal treatment. However, these studies have all small sample sizes and this observation might be underpowered. These results are sustained by previous studies reported in the review of Kao et al 2013 (Al-Katma et al 2007, Pinho et al 2009, Ribeiro et al 2005).
Studies showing positive effects of the RA treatment on the improvement of periodontal clinical parameters (pocket depth reduction, clinical attachment level gain) rely on cytokine targeted therapy (TNF-alpha and IL-6 inhibitors) all showing a clinical and systemic improvement (Table 1). As with the other studies, these investigations had small sample sizes and short-time follow-ups. Therefore, more extensive studies with higher number of subjects and long-term follow-ups are needed in order to conclude. These observations are in line with other recent reviews that investigated either the common mechanistic links in the pathogenesis of these 2 diseases (Koziel et al 2014), or similar host responses (Kobayashi & Yoshie 2015) or common clinical diseases features (Payne et al 2015).
The reported similarities (Kobayashi & Yoshie 2015, Koziel et al 2014) in the host response related to PD and RA have also been stressed out in articles reporting on immunological parameters: different authors reported a correlation between elevated levels of TNF-α, several immunoglobulins (-G, - M, -6, -A), IL-1ß and anti-citrullination antibodies and the presence of severe RA (Centikaya et al 2013, Erciyas et al 2013, Centikaya et al

2013, Biyikoglu et al 2013, Mirrielees et al 2010, Okada et al 2011, Kobayashi et al 2014a, de Smit et al 2012, Shimada et al 2015, de Smit et al 2012, Ishida et al 2012). This linkage is in agreement with the obtained results of investigational studies that reported an improvement of clinical periodontal parameters after cytokine targeted therapy (Kobayashi & Yoshi 2015). Another important observation of the included studies, is the correlation between elevated antibodies against certain periodontopathogens (e.g. P. gingivalis) present in chronic periodontitis patients and the presence of RA (Okada et al 2011, Mikuls et al 2012, de Smit et al 2012, Mikuls et al 2014, Okada et al 2013).

Conclusion

According to the clinical evidence published in the past 5 years, a strong correlation between RA and PD may exist. However, clinical controlled studies with a larger number of patients and a longer follow-up period are needed in order to determinate accurate evidence of this relationship.

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Abbreviation list

(HBP)35: Pg hemin binding protein, Aa: Aggregatibacter actinomycetemcomitans, ABL: alveolar bone loss, ACPA: anti-citrullinated antibody, ADA: Adalimumab, AI: autoimmune diseases, Anti-CCP: cyclic citrullinated peptide antibodies, AP: aggressive periodontitis, APRIL: proliferation inducing ligand, BAFF: B cell activating factor, BOP: bleeding on probing, C: complement, CAL: clinical attachment level, CEP-1: citrullinated α-enolase peptide-1, Cit-fib: citrullinated fibrinogen, Cit-vim: citrullinated vimentin, CP: chronic periodontitis, Cpl: ceruloplasmin, CRP: C-reactive protein, CTR: citrullination, DAS-28: 28-joint Disease Activity Score, DMARD: disease modifying antirheumatic drugs, DPSI:Dutch periodontal screening index, Ec: Eikenellacorrodens, ELISA: enzyme-linked immunosorbent assay, ESR: erythrocyte sedimentation rate, Fn: Fusobacterium nucleatum, GCF: gingival crevicular fluid, GI: gingival index, GOHAI: Geriatric Oral Health Assessment Index, GR: gingival recession, HAQ: health assessment questionnaire, HLA-DRB1: class II histocompatibility antigen-beta chain gene, hTERT: human telomerase reverse transcriptase, IBD: inflammatory bowel disease, IFX: Infliximab, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, IL-1β: interleukin-1β, IL-6R: interleukin-6 receptor, Inf M: inflammatory markers, LDA: low disease activity and CP, m-RNA: messenger ribonucleic acid, MCP-1: monocyte chemoattractant protein-1, MCV: mutated citrullinated vimentin, MHDA: moderate to high disease activity and CP, MMP: matrix mettaloproteinase, MPO: Myeloperoxidase, MTX: methotrexate, n: number, n.r. : not reported, NSAID: non-steroidal anti-inflammatory drugs, NSJ: number of swollen joints NTJ: number of tender joints OA: osteoarthritis, OHI-S: oral hygiene index-simplified, OPR: osteoporosis, OR: odds ratio, OSI: oxidative stress index, P.g.: Porphyromonasgingivalis, PA: periodontal disease, PAD-2: peptidylarginine deiminase-2, PAD-4: peptidylarginine deiminase-4, PCR: polymerase chain reaction, PD: probing depth, PI: plaque index, Pi: Prevotella intermedia, PPAD: Porphyromonas gingivalis peptidylarginine deiminase, RA: rheumatoid arthritis, RF: rheumatoid factor, RgpB: Pg protein arginine gingipain, Rx: radiograph, S.D. : standard deviation, Sa: Streptococcus anginosus, SJC: swollen joint counts, SLE: systemic lupus erythrematosus, SRP: scaling and root planning, SSc: systemic sclerosis TAS: total antioxidant status, TCZ: Tocilizumab, Tf: Tannerella forsythia, TNF-α: tumor necrosis factor-α, TOS: total oxidant status.

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