Periodontitis in early and chronic rheumatoid arthritis: a prospective follow-up study in Finnish population

Lee a [illegible] e ,[1] Ma a a Le [illegible] -Re ,[2] A [illegible] K [illegible] a a,[3] K [illegible] A a,[1]
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To cite: Äyräväinen L, Leirisalo-Repo M, Kuuliala A, *et al*. Periodontitis in ea and chronic rheumatoid arthritis: a prospective follow-up study in Finnish population. *BMJ Open* 2017;**7**:e011916. doi:10.1136/bmjopen-2016-011916

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011916).

Received 20 March 2016
Revised 15 December 2016
Accepted 19 December 2016

(DMARDs), biological DMARDs and low-dose oral glucocorticoids. Patients with RA have an increased risk for infections. In addition, the treatments, especially biological DMARDs, used to suppress the activity of RA are associated with increased risk of infections.[12 13]

Periodontitis seems to have an association with RA and it has even been suspected to be a triggering factor for RA eruption.[14 15] Bacterial cultures from subgingival pockets of patients with periodontitis have identified increased proportions of bacteria, such as *Porphyromonas gingivalis, Bacteroides forsythus, Campylobacter rectus, Selenomonas noxia, Prevotella intermedia, Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans*.[16 17] Recent studies suggest an association of oral bacterial infections and RA, most of which were evaluated by bacterial gene identification or serum titre measurement.[14 18 19]

Susceptibility to periodontitis and RA shares similarities regarding genetic and other factors such as obesity, smoking and socioeconomic status.[20 21] Periodontitis and RA are chronic inflammatory diseases with varying activity due to imbalance in the immune-inflammatory response; their severity and loss of function also increase with disease duration.[18] Furthermore, both diseases have similarities in morphology and histopathology.[22] Humoral immune response to oral bacteria has been suggested to be linked to the pathogenesis of RA.[23] However, RA typically presents in middle-aged women whereas periodontitis affects patients of any age and gender, even adolescents.[24] RA is nevertheless an inflammatory autoimmune disease,[9] while periodontitis is an immune-inflammatory disease of bacterial origin.[25]

Most of the previous studies on periodontitis and RA are cross-sectional and have focused on chronic RA (CRA) with analysis of clinical signs of periodontitis, or microbiological findings, and the treatment with DMARDs has not been well characterised or not mentioned at all. Therefore, we aimed to study prospectively periodontitis in well-characterised patients with RA before and after therapy with first synthetic DMARDs or first biological DMARD. We compared patients with early untreated RA before and after treatment with synthetic DMARDs and those with chronic active RA on synthetic DMARDs before and after treatment with biological DMARDs. We analysed the changes in periodontal and microbiological findings with respect to antirheumatic therapy during a follow-up. The hypothesis was that there indeed is an association between RA and periodontitis and that RA treatment affects periodontal disease.

METHODS

Study design

This was a prospective follow-up study on three groups of participants: (1) patients with early DMARD naïve RA (ERA), (2) patients with CRA with inadequate response to synthetic DMARDs (CRA) and (3) population controls. We included patients with RA aged 18–70 years. Edentulous patients were excluded. The patients underwent dental and rheumatological examinations before and after the start of synthetic DMARDs and biological DMARDs, respectively. The controls were examined once. According to the classification by Hartling *et al*,[26] the study design is interrupted time series. The dental and medical examinations were conducted from September 2005 to May 2014; twice in patients with RA,

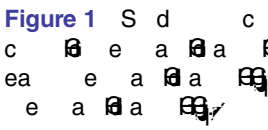

Figure 1 S d c . CRA, c e a a a ERA, ea e a a a RA, e a a a

(PD) and clinical attachment loss (AL) were assessed at four sites per tooth from every tooth excluding the third molars. All sites with PD≥4 mm were recorded, as well as PD with 5 mm and ≥6 mm, respectively. Number of teeth with 5 mm PD was counted according to 0–1 and ≥2 teeth. Degree of periodontitis was defined according to the Center for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP)[28] In brief, severe periodontitis was defined as two or more teeth with AL≥6 mm at interproximal sites and one or more teeth with PD≥5 mm at interproximal sites. Moderate periodontitis was diagnosed when two or more teeth with AL≥4 mm at interproximal sites or two or more teeth with PD≥5 mm at interproximal sites were detected. Mild periodontitis was diagnosed as ≥2 interproximal sites with AL≥3 mm and ≥2 interproximal sites with PD≥4 mm (not on the same tooth) or one site with PD≥5 mm.[29] 'No periodontitis' was recorded when the criteria for severe, moderate or mild disease were not fulfilled. Visible Plaque Index (VPI) and Bleeding on Probing (BOP) were reported as percentages (positive sites/all sites). Periodontal Inflammatory Burden Index (PIBI) was calculated.[30] Number of teeth was also calculated. In the total number of teeth third molars and dental implants were excluded.

Periodontal bacteria

Subgingival plaque samples were taken for analysing periodontal bacteria *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *Tannerella forsythia*, *Parvimonas micra* and *C. rectus*. Samples were pooled from the four to six deepest periodontal pockets at baseline and from the patients with RA again 1 year later. By sampling, sterile paper points were inserted in each chosen periodontal pocket. The paper points were then immediately transferred into a tube containing viability-maintaining microbiostatic medium, anaerobically prepared (Viability Medium Goteborg Aga (VMGA) III) containing 5% bacto gelatine, 0.05% thione E-peptone, 0.2% washed Bacto Agar, 0.05% thioglycolic acid, 0.05% L-cysteine-HCL, 1.0% Na glycerophosphate, 0.0005% phenylmercuric acetate, 0.0003% methylene blue, 0.024% $CaCl_2$ $6H_20$, 0.042% KCl, 0.1% NaCl, 0.01% $MgSO_4$ $7H_2O$. The samples were delivered for microbiological analyses in our hospital laboratory within 6 hours after sampling.

Medical examinations

Patients with RA were examined by a rheumatologist according to our hospital protocol. The number of swollen (66 joint count and 28 joint count) and tender (68 joint count and 28 joint count) joints were recorded. The patient's global assessment of disease activity (PGA) was based on a 100 mm visual analogue scale. Disease Activity Score (DAS28) was calculated from the number of tender and swollen joints (28-joint count), PGA and erythrocyte sedimentation rate (ESR).[31]

Medication in the case of patients with early untreated RA was introduced by the rheumatologist examining the patient. Medication in the case of patient with CRA was planned by the treating physician at the Department of Rheumatology. In each case, the treatments were started after the dental examination. The medications used by the patients during follow-up were collected from the patient files and by asking the patients during the follow-up examination.

Laboratory measurements

Blood samples were analysed for plasma rheumatoid factor (RF) by immunoturbidimetric assay (Roche/Hitachi Modular P. Roche Diagnostics, Mannheim, Germany), normal <14 IU/mL, plasma C reactive protein (CRP) by immunoturbidimetric assay (Roche/Hitachi Modular P. Roche Diagnostics, Mannheim, Germany), normal <3 mg/L, ESR by automatic modified Westergren method of EDTA blood diluted with citrate.[32] Serum antinuclear antibody (ANA) was measured by the

indirect immunofluorescence technique on a HEp-2 cell substrate (Inova Diagnostics, San Diego, California, USA). The serum was initially screened at a 1:80 dilution, and positive samples were further diluted to 1:160, 1:320, 1:640, 1:1280 and 1:5120. A titre of 1:320 or higher was considered a positive result.

Antirheumatic treatment

After the baseline examinations, patients with ERA started treatment with synthetic DMARDs comprising methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) either as monotherapy or in different combinations. Monotherapy was used in 37.0% of patients with ERA (mostly MTX, two patients had LEF), double DMARD therapy (MTX+SSZ, MTX+HCQ, SSZ+HCQ or combinations with LEF) in 39.1% and triple DMARD therapy (MTX+SSZ+HCQ) in 19.1% of patients with ERA. In addition, low-dose (≤10 mg prednisolone) oral glucocorticoids were started in 28.3% of the patients with ERA. CRA cases started biological DMARDs consisting of tumour necrosis factor α (TNF-α) inhibitors (such as adalimumab in 9/27 (33.3%) of patients with CRA, etanercept in 17/27 (63.0%), golimumab in 2/27 (7.4%) and certolizumab pegol in 1/27 (3.7%) of patients with CRA) or non-TNF-α biologicals such as interleukin-1 inhibitor (anakinra in 1/27 (3.7%) of patients with CRA) or anti-B-cell agent (rituximab in 2/27 (7.4%) of patients with CRA) mainly combined with MTX, 3 patients with CRA had LEF. Different biological DMARDs were used during the follow-up; in brief TNF-α inhibitor was used in 85.2% of patients with CRA and non-TNF-α biologicals in 7.4%, respectively. Low-dose prednisolone was used by 74.1% patients with CRA. Intra-articular glucocorticoid injections and non-steroidal anti-inflammatory drugs (NSAIDs) were used if needed to improve physical function and quality of life.

Questionnaires

All the study participants filled out a structured questionnaire. Questions concerned general health and systemic medication, education, health habits (smoking, use of alcohol) as well as daily oral hygiene habits, dental visits, self-assessed oral health and oral symptoms. The questionnaire is a standard form at our clinic, and used in several other studies.[33 34]

Statistical methods

The results are given as medians with IQRs (25–75%; non-parametric distribution) or in means with SDs (parametric distribution). Continuous variables were compared between groups with analysis of variance and Student's t-test when possible, or non-parametric Kruskal-Wallis and Mann-Whitney tests when comparing independent samples. The baseline and follow-up values were analysed with non-parametric Wilcoxon test comparing related samples. Categorical variables were compared between the groups with χ^2 test and between baseline and follow-up values with McNemar's test. Binary logistic regression model was performed to establish odds for periodontitis according to variables such as RA (early and chronic), tooth brushing, smoking, gender and age. Statistical analyses were performed with SPSS V.22 and $p<0.05$ was considered statistically significant.

RESULTS

RF was present in 79.2% of patients with ERA, 69.2% of patients with CRA and in 3% of control individuals ($p<0.001$). CRA participants had suffered from RA for a mean of 176±116.8 months while the duration of disease in patients with ERA was 10.4±17.1 months ($p<0.001$). At baseline, ESR values were in median (IQR 25–75%) 20 (11–34) mm/hour in ERA, 20 (9–46) mm/hour in CRA and 2 (2–10) mm/hour in the control group ($p<0.001$). CRP values were 6 (3–14) mg/L in ERA, 18 (5–30) mg/L in CRA and 2 (2–3) mg/L in the control group ($p<0.001$), respectively.

Patients with RA had a history of hypertension, thyroid disease, bronchial asthma, depression, cancer and diabetes as comorbidities. Compared with patients with CRA and controls, the patients with ERA had more often asthma (19% vs 0% in CRA, 5% in controls ($p=0.046$)).

There were no statistically significant differences between the study participants with respect to age, gender, smoking, alcohol use and level of education. Background characteristics of the study groups are given in more detail in table 1.

Self-reported oral health habits are given in table 2. Control participants reported better oral hygiene habits, especially more frequent approximal tooth cleaning, when compared with patients with RA. At baseline, the patients with RA reported having received less periodontal treatments than controls, but in the re-examination mean 16 months later the number of patients with RA having periodontal treatment increased. The specific determination of profession (hygienist, dentist, periodontist) for periodontal treatment was not available from the patients' questionnaire.

Periodontal status parameters are given in table 3. Periodontal findings in patients with RA differed significantly from the corresponding control cases in values of VPI, BOP, PD≥4 mm, AL<3 mm, ≥3 mm<5 mm, AL≥5mm and PIBI. Sixty seven per cent of the patients with ERA and 64% of the patients with CRA had moderate periodontitis at the time of entry to the study. In the controls, the corresponding frequency was 39.5% as given in table 3. CRP values in patients with ERA with periodontitis (mild, moderate or severe) were in median with IQR 6 (3–14) mg/L, in CRA participants with periodontitis 17 (5–30) mg/L and in controls 2 (2–2) mg/L ($p<0.001$) at baseline. However, in ERA cases with severe periodontitis CRP values were 7 (3–15) mg/L, in patients with CRA with severe periodontitis CRP values

Table 1 Bac g d c a ac e f e d g a ba e

	ERA (N=53)	CRA (N=28)	Controls (N=43)	p Value
W e , N (%)	45 (85)	23 (82)	38 (88)	0.758
Age (ea) ea SD	51 15	52 11	56 13	0.160
N be f ee , ed (IQR)	27 (23–28)	27 (22–28)	27 (25–28)	0.628
R e a fac e (%)	42 (79.2)	18 (69.2)	3 (8.1)*	**<0.001**
D ea d a ( ) ea SD	10.4 17.1	176 116.8		**<0.001†**
ESR (/), ed (IQR)	20 (11–34)	20 (9–46)	2 (2–10)*	**<0.001**
CRP (g/L), ed (IQR)	6 (3–14)	18 (5–30)	2 (2–3)*	**<0.001**
DAS28, ed (IQR)	4.0 (3.2–4.8)	4.1(3.0–4.9)		0.974
Ed ca , N (%)‡				
L e	20 (37.7)	9 (36.0)	16 (61)	0.174
Sec da	27 (50.9)	12 (48.0)	6 (23.1)	
H e	6 (11.3)	4 (16.0)	4 (15.4)	
S g, N (%)				
Ne e	35 (66.0)	23 (82.1)	36 (83.7)	
F e	7 (13.0)	2 (7.0)	1 (2.0)	
C e	11 (21.0)	3 (11.0)	6 (14.0)	0.197
A c , N (%)				
Se d / e	28 (52.8)	12 (42.9)	13 (30.2)	
M / ee	25 (47.2)	16 (57.1)	30 (69.8)	0.084

*N=37, g da a f c a a .
† a e ba ed b - a a e K a-Wa e c a g a ERA a d CRA.
‡M g da a: 3 a CRA a d 17 c a a f ea
Va e b c ab a g χ^2 ac e d g
CRA, c e a a a ; CRP, C eac e e e ; DAS28, D a Ac Sc e (28- c); ERA, ea e a a a ; ESR, e c e ed e a a e; N, be f a

32 (21–42) mg/L and in the one control patient with severe periodontitis 2 mg/L (p=0.029), respectively. At follow-up examination, the periodontal status in patients with RA was similar to the baseline.

Table 4 gives results from the cultivation of the periodontal bacteria. At baseline periodontal bacteria were more frequently detected in the patients with ERA compared with patients with CRA, and after the follow-up, the prevalence of periodontal bacteria in CRA group was further diminished. In RA, *P. gingivalis* was observed only in patients with ERA (p=0.043, table 4).

Figure 2 shows the results for *P. gingivalis* in the participants who had PD≥4 mm. The culture for *P. gingivalis* was positive in 11 participants (21.2%) in the ERA group at baseline, compared with 3 participants (7.0%) in the controls (p=0.009). In patients with CRA no *P. gingivalis*-positive cases were found.

In patients with ERA, synthetic DMARDs were instituted first after the clinical and dental examinations. There were no statistically significant changes in the periodontal parameters between baseline and follow-up examination (table 3). The patients with CRA examined at baseline continued their baseline synthetic DMARD (s) on which a biological DMARD was added on after the baseline examination. Despite the biological DMARD, no statistically significant difference was found in the periodontal parameters either in the patients with CRA during the follow-up (table 3).

Of periodontopathic bacteria, *P. gingivalis* was less frequently cultivated in patients with ERA at follow-up examination, but with respect to other microbes, there were no statistically significant chances during the follow-up (table 4).

After multivariate analysis for odds of periodontal disease, age, gender, smoking and tooth brushing were not statistically significantly associated with periodontitis. Significant association was observed between CRA versus controls, OR 5.3 (95% CI 1.1 to 25.6; p=0.044) and ERA versus controls, OR 3.6 (95% CI 1.1 to 11.6; p=0.036). Figures are given in table 5.

DISCUSSION

Periodontal health in RA

The main result in our study was that periodontal health indeed was poorer in patients with RA in general compared with population controls. Nearly 80% of patients with ERA and 85% of patients with CRA suffered from periodontitis vs 40% of controls at the baseline of this study. These findings confirmed earlier observations by Wolff *et al*,[35] and Ranade and Doiphode.[36] The poorer periodontal health could be the result of a weakened immune defence in the host due to RA and further, increase in systemic inflammation may initiate or enhance the severity of periodontitis as pointed out by Payne *et al*.[37] Periodontitis in turn may have an impairing influence on RA treatment response. Although our results are based only a limited number of patients with RA, they can be applied to Finnish patients with RA in general, as our study populations are in line with two

Table 2 Se f- e ed a ea abB d Bg e d

	Baseline				Follow-up			
	ERA (N=53)	CRA (N=28)	Controls (N=43)	p Value*	ERA (N=47)†	p Value‡	CRA (N=26)†	p Value‡
T b Bg								
T Be a da , N (%)	35/53 (66.0)[b]	22/28 (78.6)[a b]	38/43 (88.4)[a]	0.035	37/47 (78.7)	00.125	20/25 (80.0)	1.000
O ce a da e N (%)	18/53 (34.0)[b]	6/28 (21.4)[b]	5/43 (11.6)[a]		10/47 (21.3)		5/25 (20.0)	
A Ba ee c ea Bg, N (%)	28/53 (52.8)[a]	15/28 (53.6)[a]	34/43 (79.1)[b]	0.018	28/47 (59.6)	1.000	15/25 (60.0)	0.250
De a a Be <2 ea N (%)	43/53 (81.1)[b]	28/28 (100)[a]	41/43 (95.3)[a]	0.009				
De a ea e , N (%)								
Pe Bd a	10/53 (18.9)[a]	4/28 (14.3)[a]	28/43 (65.1)[b]	0.000	21/46 (45.7)	0.001	11/25 (44.0)	0.109
Re a Be fBg	27/53 (50.9)[b]	21/28 (75.0)[a]	21/43 (48.8)[b]	0.063	22/46 (47.8)	0.424	10/25 (40.0)	0.004

*T e a e a eba d c ab a B χ^2- e
†A ERA g Bd - a CRA g ee d - f e a ea
‡ERA a d CRA a e c a ed a ba e Be a d f - , a e b - a a e B McNe a' e e a ed a e
T e fBg e a e fe e ce B (N= be f a B) B e ce age
[a b]Eac b e B e de e a b f d g ca eg B e c B d dffe g B a f eac e a e 0.05 e e.
CRA, c B e a B a B ; ERA, ea e a B a B

recent reports from Finland. Rannio *et al*[38] described all patients with DMARD-naïve early RA (n=310) treated at Jyväskylä Central Hospital rheumatology outpatient clinic between 2008 and 2011. The centre covers rheumatology care in the healthcare district with a population of 275 000. The demographic data of our patients with ERA are comparable with those of the Jyväskylä cohort: mean age 51 vs 60 years, women 81% vs 69%, duration of symptoms 10 vs 6 months, disease activity (DAS28) 4.0 vs 4.3. As to the patients with CRA starting biological treatments, we can compare our patients with CRA with those reported from the National Register for Biologic Treatment in Finland, which is a prospective cohort study designed to monitor the effectiveness and safety of biological drugs in the treatment of rheumatic diseases. The register covers about 70% of patients with RA treated with biologics in Finland. Recently, Aaltonen *et al*[39] reported data collected from year 2003 onwards from this register. The demographic data of our patients with CRA are comparable with those reported from the The Finnish Register of Biological Treatment (ROB-FIN) registry: mean age 52 vs 54 years, women 82% vs 79%, disease duration 14.6 vs 11 years, disease activity (DAS28) 4.1 vs 4.4 before the start of biological DMARD.

RA and periodontitis

An association between RA and periodontitis has been suggested in several earlier studies.[19 40–44] Of special interest is that patients with early untreated RA had even worse periodontal health compared with patients with CRA, and further patients with RA both in early and chronic stages suffered more frequently particularly from moderate periodontitis when compared with population controls in our study. The frequencies of periodontitis in RA and control populations vary from study to study. According to a recent review with meta-analysis, the risk for periodontitis in RA versus controls is 1.13.[45] The prevalence of periodontitis in the US population aged over 30 years is 47%. The risk factors include smoking, age, dental hygiene, minority status and socioeconomic status.[46]

Many authors, such as Loos,[47] have suggested that periodontal lesions may be the origin for daily bacteraemia and even raise systemic inflammation reflected in markers such as CRP. In our study, patients with CRA with severe periodontitis had higher CRP values compared with corresponding ERA participants. Interestingly, during the follow-up, no improvement could be observed in periodontal status among the patients with RA in either group.

RA and *P. gingivalis*

An association between infection at early arthritis phase and the subsequent development of chronic rheumatic complications has been discussed previously as reviewed by Leirisalo-Repo.[48] The presence of *P. gingivalis* in patients with ERA, as observed in our study among the patients with PD≥4 mm, may be a combining link between periodontal disease and RA. Rutger Persson[49] suggested that *P. gingivalis* infection through citrullination has a role in RA. And further, Mikuls *et al*[50] reported that periodontal inflammation with *P. gingivalis*

Table 3 Pe Bd a aa ee a ba eBe a d afe f - Bd g

	Baseline ERA N=52	Follow-up ERA N=46	p Value*	Baseline CRA N=28	Follow-up CRA N=26	p Value*	Controls N=43	p Value†
MedBa B ‡								
DMARD e a	0	17/46 (37.0%)		8/28 (28.6%)	0			
D be DMARD e a	0	18/46 (39.1%)		11/28 (39.3%)	0			
T Be DMARD e a	0	9/46 (19.6%)		7/28 (25.0%)	0			
DMARD( )+TNF B BB	0	0		0	23/27 (85.2%)			
DMARD( )+ -TNF B BB	0	0		0	3/27 (11.1%)			
Pe Bd a deg ee, N (%)								
MBd	0	1 (2.2)	0.297	2 (7.1)	1 (4.0)	0.398	1 (2.3)	**0.001**
M de a e	35 (67.3)	34 (73.9)		8 (64.3)	14 (56.0)		17 (39.5)	
Se e e	6 (11.5)	5 (10.9)		4 (14.3)	3 (12.0)		1 (2.3)	
N be f ee	27 (23–28)	27 (22–28)	**0.024**	27 (22–28)	27 (22–28)	0.317	27 (25–28)	0.628
VPI e ce Pe edBa (IQR)	12 (5–25)	8 (4–20)	0.076	9 (5–19)	8 (3–19)	0.467	5 (2–11)	**0.020**
BOP e ce Pe edBa (IQR)	15 (10–26)	13 (6–21)	0.124	9 (5–19)	8 (3–22)	0.903	4 (2–8)	**0.000**
PD≥1 Pe B ≥4 , N (%)	45 (86.5)	43 (95.6)	0.083	25 (89.3)	21 (84.0)	0.564	28 (65.1)	**0.013**
0–1 Pe B ≥6	49 (94.2)	43 (95.6)	0.564	24 (85.7)	22 (88.0)	0.317	42 (97.7)	0.131
≥2 Pe B ≥6	3 (5.8)	2 (4.4)	0.366	4 (14.3)	3 (12.0)	1.000	1 (2.3)	0.067
<2 ee B ≥5	39 (75.0%)	37 (80.4%)		23 (82.1%)	21 (80.8%)		40 (93.0%)	
≥2 ee B ≥5	13 (25.0%)	9 (19.6%)		5 (17.9%)	5 (19.2%)		3 (7.0%)	
AL<3	5 (9.6)	3 (6.7)	1.000	2 (7.1)	5 (20.0)	0.083	14 (32.6)	**0.004**
≥3<5 N (%)	47 (90.4)	42 (93.3)	1.000	26 (92.9)	20 (80.0)	0.083	29 (67.4)	**0.004**
≥5	22 (42.3)	21 (46.7)	0.257	10 (35.7)	8 (32.0)	0.317	8 (18.6)	**0.045**
PIBI, edBa (IQR)	10 (3–18)	9 (9–19)	0.907	5 (3–15)	4 (1–16)	0.856	1 (0–3)	**0.000**

l VPI a d BOP Bd e d 4 Pe a e e .
Def BBB f deg ee f e Bd a dBea e acc dBg e Ce e f DBea e C a d P e e B a d e A e Ba Acade f Pe Bd g (CDC/AAP; Page a d E e, 2007),[8] Bd e Bd BBB.[29]
* Va eb - a a e B W B e c a Bg ea ed a e a ba eBe a d f - a Ba .
† Va eb c ab a B B χ^2 c a Bg a d g a ba eBe a eb - a a e B K a -Wa B e
‡DMARD e a : MTX, 2 a B ad LEF; d be e a : MTX+SSZ, MTX+HCQ, SSZ+HCQ, c bBa B B LEF; Be e a : MTX+SSZ+HCQ; TNF B BB : ada B ab B 9/27 (33.3%) a B B CRA, e a e ce B 17/27 (63.0%), g B ab B 2/27 (7.4%) a d ce B ab eg B 1/27 (3.7%) a B B CRA; -TNF-α bB g B c a B e e B-1 B BB (a a B a B 1/27 (3.7%) a B B CRA) a B-ce age (B B ab B 2/27 (7.4%) a B B CRA) a B c bBed B MTX, 3 a B B CRA c bBed B LEF.
AL, c Bda a ac e BOP, B edBg P bBg Bd ; CRA, c B e a Ba B DMARD, dBea e- dB Bg a B e a B d g; ERA, ea e a Ba B HCQ, d c Be; LEF, ef Be; MTX, e a e; N, be f a B PD, e Bd a c e de ; PIBI, Pe Bd a l fa a B B de l d ; SSZ, fa a Be; TNF, ; ec fac r; VPI, VBa P a e l d .

Table 4 P e a e ce f e d a bac e a ba e ea d afe f - d a a PD≥4

	ERA (N=46) Baseline	CRA (N=25) Baseline	Controls (N=27)	p Value*	ERA (N=43) After follow-up	CRA (N=21) After follow-up	p Value†
Med a							
DMARD e a	0	8/28 (28.6%)			17/46 (37.0%)	0	
D b e DMARD e a	0	11/28 (39.3%)			18/46 (39.1%)	0	
T e DMARD e a	0	7/28 (25.0%)			9/46 (19.6%)	0	
DMARD( )+TNF ‡	0	0			0	23/27 (85.2%)	
DMARD( )+ -TNF	0	0			0	3/27 (11.1%)	
Bac e a							
A.a N (%)	4 (8.7%)	0	5 (18.5%)	0.074	2 (4.9%)	0	0.298
P.g	11 (23.9%)	0	2 (7.4%)	0.12	7 (17.1%)	0	**0.043**
P.	15 (32.6%)	8 (33.3%)	10 (37.0%)	0.925	19 (46.3%)	5 (22.7%)	0.054
T.f	2 (4.3%)	1 (4.2%)	0	0.550	1 (2.4%)	1 (4.5%)	0.248
P.	12 (26.1%)	6 (25.0%)	4 (14.8%)	0.514	10 (24.4%)	3 (13.6%)	0.329
C.	2 (4.3%)	1 (4.2%)	0	0.550	3 (7.3%)	0	0.199

* Va e b c ab a χ^2.
† Va e b a ed - a a e K a -Wa e c a g de e de a e d g ba e e–f -).
‡DMARD e a : MTX, 2 a ad LEF; d b e e a : MTX+SSZ, MTX+HCQ, SSZ+HCQ, c b a a LEF; e e a : MTX+SSZ+HCQ; TNF : ada ab 9/27 (33.3%) a CRA, e a e ce 17/27 (63.0%), g ab 2/27 (7.4%) a d ce ab eg 1/27 (3.7%) a CRA).
N -TNF-α b g c a e e -1 (a a a 1/27 (3.7%) a CRA) a B-ce age (ab 2/27 (7.4%) a CRA) a c b ed MTX, 3 a CRA c b ed LEF.
A.a, *Aggregatibacter actinomycetemcomitans*; C. , *Campylobacter rectus*; CRA c e a a -DMARD, d a d g a e a d g; ERA, ea e a a -HCQ, d c e; LEF, ef e; MTX, e a e; N be f a a PD, e d a c e de ; P.g, *Porphyromonas gingivalis*; P. *Prevotella intermedia*; P. , *Parvimonas micra*; SSZ, fa a e; T.f, *Tannerella forsythia*; TNF, ec fac .

may modify the autoreactivity of RA. Bacterial culture methods were used in this study for practical reasons, being routine in the hospital laboratory. The association of oral pathogens and periodontal activity might have been higher if we had performed bacterial gene identification by real-time PCR or measured serum antibodies to oral pathogens.

Antirheumatic medication and oral health

We also focused on the effect of the use of antirheumatic medication on periodontal parameters. Therefore, we included patients with early untreated RA at baseline. After the examination, the patients started treatment with synthetic DMARDs. Patients with CRA on the other hand had suffered from the disease for about 14 years and because of insufficient response to synthetic DMARDs, treatment with biological DMARDs was started. Both synthetic and biological DMARDs were, if necessary, combined with glucocorticoids or NSAIDs to suppress the disease symptoms and to improve quality of life.

Recently, Beeraka *et al*[51] reported an association between the use of corticosteroids and higher levels of AL and deepened periodontal pocket depth. We did not observe any statistical difference in periodontal parameters when comparing the baseline values to corresponding figures after the mean 16 months follow-up in the ERA and CRA groups. Our results on patients with ERA show that periodontitis was observed in patients with RA already in the early untreated phase and that conventional antirheumatic treatment did not enhance the inflammation or oral pathogenic microbes. This is in line with a previous study, where MTX had no effect on dental status.[52]

Most studies on the association between treatment of RA and severity of periodontitis have focused on biological DMARDs. A recent meta-analysis included four reports on the effect of anti-TNF-α therapy in patients with RA.[53] In three out of the four reports, the treatment was suppressing periodontal inflammation. Three more publications have reported the suppressive effect of adalimumab, tocilizumab and rituximab on periodontitis.[54–56] Contrary to these findings, periodontal parameters remained stable during the 6-month treatment of 18 patients with RA with various anti-TNF-α therapies.[57] Our results show that biological DMARDs can be used in patients with chronic active RA, as they do not worsen periodontitis in these patients. In fact, there was a trend for improvement in pocket depths in the CRA group.

However, while periodontitis does not usually need pharmacological treatment, mechanical periodontal treatment is required time after time.[15]

Health habits

Patients with RA in both groups reported poorer approximal teeth cleaning and less periodontal dental

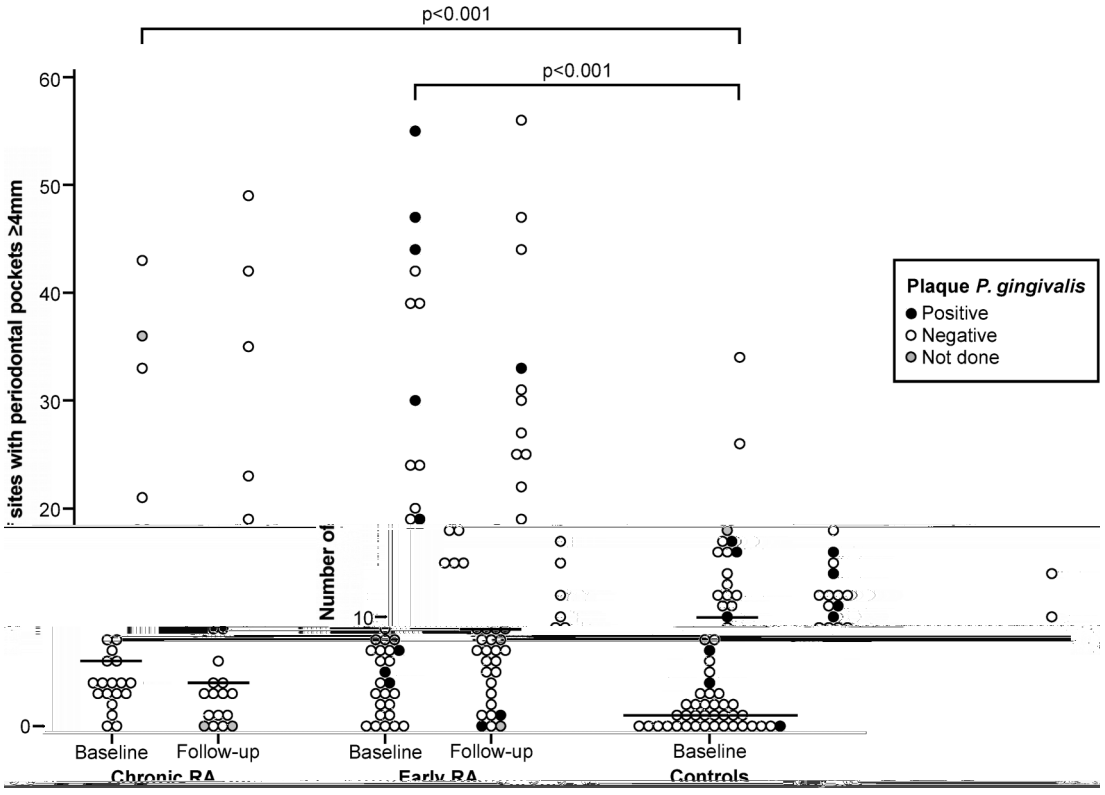

Figure 2 N be f e PD≥4 a d e d a bac e a RA g a d c T e b ded a a ea g ed de ed b a e T e g e e c a ed g Ma -W e e T e de a a e c e f *Porphyromonas gingivalis* a e e 11 a a (21.2%) e ea RA g a ba e, c a ed 3 a a (7.0%) e c g (=0.009, χ^2 e). T e be f ca e f *P. gingivalis* c RA g a . PD, e d a c e de ; RA, e a a

Table 5 B a g eg e f dd f e d

Variable	OR (95% CI)	p Value
G		
CRA	5.3 (1.1 25.6)	0.044
ERA	3.6 (1.1 11.6)	0.036
C	1	
B g a ea e da	0.7 (0.4 6.2)	0.657
S g (c e)	0.3 (0.06 1.5)	0.134
S (a e)	2.7 (0.3 24.5)	0.368
Age (e ea)	1.1 (1.0 1.1)	0.011

CRA, c e a a ERA, ea e a a

treatment compared with the population controls (see table 2). Impaired oral health habits rather than weakened immune defence could partly explain the differences in plaque accumulation and gingival inflammation in patients with RA. This also reflects in higher frequencies of VPI and BOP sites. However, the weakened manual dexterity may have a role in oral hygiene habits and thus these patients need special attention in controlling oral hygiene with suitable individual dental hygiene equipment combined with proper periodontal treatment.

Against all expectations smoking or use of alcohol did not seem to affect the results. This might be explained by the fact that there is a decreased prevalence of smoking among Finnish population in general.[58]

Strengths and limitations

The strengths of our study were the prospective follow-up study of two well-characterised patient groups with RA, the inclusion of control participants and the homogeneous ethnicity of the population. All participants were from the population base of the Helsinki University Hospital with more than 1.5 million inhabitants. Our study patients are representative of the patients with RA in Finnish population.[38 39]

The weakness was the fairly small number of patients although we recruited all eligible patients during nearly 10 years (2005–2014). Furthermore, for practical reasons, it was not possible to conduct follow-up examination in the controls.

To conclude, our study revealed poor periodontal health in patients with early and CRA compared with population controls. The periodontal parameters were throughout higher in patients with early RA compared with patients with RA with long disease history. We did not observe any effect of synthetic or biological DMARDs on the periodontal health parameters. Taking

into account the inflammatory burden of periodontitis combined with the challenge of RA disease itself, these patients should be under supervised oral health with

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