

Association of Periodontal Disease and Tooth Loss with Rheumatoid Arthritis in the US Population

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ABSTRACT. *Objective.* To test for an association of periodontitis and tooth loss with rheumatoid arthritis (RA). *Methods.* The third National Health and Nutrition Examination Survey (NHANES III) is a nationally representative cross-sectional survey of noninstitutionalized civilians. We included participants aged ≥ 60 years who had undergone both musculoskeletal and dental examinations. RA was defined based on American College of Rheumatology criteria. Dental examinations quantified decayed and filled surfaces, missing teeth, and periodontitis. Periodontitis was defined as at least 1 site exhibiting both attachment loss and a probing depth of ≥ 4 mm. We classified dental health status as (1) no periodontitis, (2) periodontitis, or (3) edentulous (i.e., complete tooth loss). We performed multivariate multinomial logistic regression models with dental health status as the dependent and RA as the independent variables. *Results.* The sample consisted of 4461 participants, of whom 103 were classified as having RA. Participants with RA had more missing teeth (20 vs 16 teeth; $p < 0.001$), but less decay (2% vs 4%; $p < 0.001$) than participants without RA. After adjusting for age, sex, race/ethnicity, and smoking, subjects with RA were more likely to be edentulous [odds ratio (OR) 2.27, 95% confidence interval (CI) 1.56–3.31] and have periodontitis (OR 1.82, 95% CI 1.04–3.20) compared with non-RA subjects. In participants with seropositive RA there was a stronger association with dental health status, in particular with edentulism (OR 4.5, 95% CI 1.2–17). *Conclusion.* RA may be associated with tooth loss and periodontitis. (First Release Nov 15 2007; J Rheumatol 2008;35:70–6)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
TOOTH LOSS

PERIODONTAL DISEASE
EDENTULISM

PERIODONTITIS
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Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation that results in destruction of joint tissues. Periodontitis is a chronic inflammatory disease characterized by loss of the periodontal ligament and alveolar bone, and is a major cause of tooth loss, particularly in the elderly¹. Tooth loss has important clinical consequences, including reduced dietary quality and quality of life^{2,3}.

Periodontitis and RA appear to share numerous characteristics including certain pathogenetic processes^{4,5}, cytokine

profiles⁶, markers of inflammation^{7,8}, association with HLA-DRB1^{9,10}, interleukin 1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) polymorphisms^{11–14}, presence of citrullinated proteins and peptide epitopes⁴, and rheumatoid factor (RF)^{4,15,16}. This suggests that subjects susceptible to RA may also have higher rates of periodontal disease.

Further, there are reasons to suspect that the role of periodontitis in RA might be based on more than just shared susceptibility. For example, induction of adjuvant arthritis in Lewis male rats is associated with periodontal breakdown, increased cytokines and matrix metalloproteinases in gingival tissues, and alveolar bone loss¹⁷.

Studies have also demonstrated an antibody response against oral anaerobic bacteria in synovial tissue¹⁸ and serum¹⁹, and the presence of oral bacterial DNA in the synovial fluid and serum of patients with RA²⁰. Also, periodontal pathogens may express the peptidyl arginine deiminase (PAD) enzyme responsible for citrullination of peptide antigens⁴.

Indeed, several clinical studies suggest a possible association between periodontitis/tooth loss and RA^{21–25}, although some studies did not find a positive association^{26–28}. However, no population-based data on this association have been reported.

Our objective was to compare periodontal disease and tooth loss prevalence in subjects with and without RA in the US population.

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MATERIALS AND METHODS

Data source. Data were derived from the Third National Health and Nutrition Examination Survey (NHANES III), a representative survey conducted between 1988 and 1994 to study the health and nutritional status of the civilian noninstitutionalized US population^{29,30}. In brief, the survey included home interviews and medical and dental examinations performed by a physician and a dentist, respectively, in a mobile examination center. The musculoskeletal examination was performed in subjects aged 60 years or older. Upper and lower extremity examinations documented pain and swelling of the proximal interphalangeal, metacarpophalangeal, wrists, knees, and first metatarsophalangeal joints, and the presence of rheumatoid nodules. Presence and duration of morning joint stiffness for at least 6 weeks, lasting for more than 1 h, and other symptoms of inflammatory arthritis such as joint tenderness and swelling were ascertained by interview.

Clinical dental examinations. The standardized dental health examination consisted of a visual and tactile dental examination performed by a licensed dentist specially trained in the use of specific epidemiologic indices for oral health. The comprehensive dental examination assessed caries, restorations, presence of third molars, number of missing teeth, and periodontal measures. The oral health component of the survey has been described in detail³¹, as have detailed analyses of periodontitis in this sample¹⁰.

Periodontitis was assessed with a periodontal probe that was inserted into the gingival crevice between the teeth and gums. Periodontal measurements (attachment loss and probing depth) were performed at the mesiobuccal and midbuccal site of all fully erupted teeth — except third molars — in 2 randomly selected quadrants. Clinical attachment loss is a cumulative measure of the destruction of the tooth-supporting connective tissue and alveolar bone and is measured as the distance between the cemento-enamel junction and the bottom of the periodontal pocket. Attachment loss due to periodontitis is typically accompanied by a deepening of the periodontal pocket, measured as probing depth, the distance between the free gingival margin and the bottom of the pocket. Periodontitis was defined as the presence of at least 1 site with both attachment loss and probing depth ≥ 4 mm, as described³¹.

Caries was quantified as the proportion of decayed tooth surfaces among all surfaces of all present teeth. Similarly, the proportion of decayed or filled surfaces was calculated as a measure of caries history.

Oral examinations were performed by trained and calibrated examiners. Detailed data regarding the reliability of the oral assessments and measurements have been reported³¹.

Outcome definition. The primary outcome variable was classified in mutually exclusive categories as: (1) dentate without periodontitis (reference group), (2) dentate with periodontal disease, or (3) edentulous (i.e., no natural teeth).

Classification of RA. We defined RA based on a modification of the 1987 American College of Rheumatology (ACR) criteria for classification of RA³². Participants who met at least 3 of 6 available ACR criteria were defined as having RA as described³³, as all of the criteria, except radiographic data, were available from NHANES III. Briefly, Rasch, *et al* evaluated the agreement between 3 different classification methods for RA in NHANES III including the method we used³³. The classification agreement between these methods was excellent ($\kappa = 0.879$ and $\kappa = 0.921$). In addition, we performed a sensitivity analysis using a definition of RA based on the presence of 4 ACR criteria for classification of RA.

ACR criteria included the presence of morning stiffness for at least 1 h for at least 6 weeks; physician's examination findings (presence of arthritis in 3 or more joint areas, presence of arthritis in the joints of the hand, presence of symmetric arthritis, presence of rheumatoid nodules); and positive RF. The presence of RF was determined from blood samples using the Singer-Plotz latex agglutination test. Blood specimens were screened using latex-enhanced nephelometry prior to obtaining a titer³⁴. Participants with ≤ 2 ACR criteria were defined as not having RA.

Other variables. Demographic information included age, sex, race/ethnicity, education level, and poverty index. Race/ethnicity was classified as non-Hispanic White, non-Hispanic Black, and Mexican-American. Education was coded as the number of years of formal education completed. The poverty

income ratio was computed as the ratio of family income versus the poverty threshold as produced annually by the Census Bureau. Thus, the higher the family income relative to the poverty threshold, the higher the poverty income ratio²⁹. Smoking status and diabetes mellitus were assessed during the household interview. Respondents were classified as never-smokers (< 100 cigarettes in their lifetime), former smokers (≥ 100 lifetime cigarettes, not currently smoking), and current smokers (≥ 100 lifetime cigarettes, currently smoking). Current smoking status was further stratified by the number of cigarettes smoked per day (up to 10 and ≥ 11 cigarettes/day). Body mass index (BMI) was calculated as weight/height². Total hip bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry. Physical activity was defined based on leisure-time physical activity. Frequency of dental care was defined based on self-report of the number of visits to dentist per year, and dichotomized as visits to dentist at least once a year versus less frequently.

Statistical analyses. Summary statistics are presented as means \pm standard deviations (\pm SD) for continuous measures and frequencies for all discrete variables. Univariate comparisons were made using the Student t-test or chi-square test as appropriate. The association between RA and periodontal disease/tooth loss was analyzed using multinomial logistic regression models with periodontal disease/tooth loss as the dependent and RA as the independent variables, adjusting for age, sex, and race/ethnicity first, and second, with further adjustment for poverty income ratio, education, smoking, diabetes, BMI, and physical activity. In a secondary exploratory analysis, we further adjusted the multivariate model for BMD. In a sensitivity analysis, we fitted the same models using a more stringent definition of RA, which was based on the presence of 4 ACR criteria for RA classification.

We examined the independent association of RF with periodontal disease/tooth loss in a multinomial logistic regression model, adjusting for age, sex, race, and smoking, in a subset analysis stratified by RA status. With stratification the sample size for each group decreased, thus limiting the number of covariates included in the model. Finally, among dentate participants, we examined the relationship between dental care and RA status using chi-square test.

We performed all statistical analyses with Stata 7.0 (Stata Corp., College Station, TX, USA) accounting for survey clustering and stratification. To obtain population prevalence estimates of periodontitis and tooth loss in RA compared with non-RA participants, sampling weights were used as appropriate.

RESULTS

There were 5302 individuals aged 60 years and older who had a musculoskeletal examination, of whom 4535 had a dental examination including periodontal attachment level measurements. Of these, 74 subjects were excluded due to missing data on the dental clinical assessments and covariates, leaving 4461 individuals for analysis. Among those, 103 participants were classified as having RA. Sociodemographic characteristics, clinical features, and dental health status of RA and non-RA participants are shown in Table 1. Among RA participants, 57% were women, 61% non-Hispanic White, 16% non-Hispanic Black, 23% Mexican-American, and 29% seropositive. There were no differences in smoking habits, physical activity, BMI, and BMD (Table 1).

Dental health status. Table 1 shows the characteristics of the sample. Participants with RA had a higher prevalence of periodontitis (weighted prevalence 16% vs 10%) and edentulism (weighted prevalence 56% vs 34%) compared with non-RA ($p < 0.0001$). Participants with RA also had more missing teeth (20 vs 16 missing teeth; $p = 0.0001$), but a significantly

Table 1. Characteristics of the subjects. Values represent means ± standard deviation (SD) or percentages.

Characteristic	RA, n = 103	Non-RA, n = 4,358
Age, yrs, mean ± SD	73 ± 8.3	72 ± 8.1
Women, n (%)	59 (57)	2,206 (51)
Race/ethnicity, n (%)		
Non-Hispanic White	63 (61)	2,519 (58)
Non-Hispanic Black	16 (16)	874 (20)
Mexican-American	24 (23)	965 (22)
Education, yrs, mean ± SD	9.1 ± 4.2	9.5 ± 4.4
Poverty income ratio	2.1 ± 1.6	2.4 ± 1.8
Smoking status, n (%)		
Never	49 (47)	2,020 (46)
Former	38 (37)	1,663 (38)
Current (≤ 10 cigarettes/day)	9 (9)	305 (7)
Current (11 + cigarettes/day)	7 (7)	370 (8)
Physical activity (MET), mean ± SD	5.1 ± 5.1	6.3 ± 6.2
Sedentary lifestyle, n (%)	36 (35)	1,218 (28)
Body mass index, kg/m ² , mean ± SD	27 ± 5.5	27 ± 5.2
Bone mineral density, g/cm ² , mean ± SD	0.82 ± 0.18	0.85 ± 0.18
Diabetes, n (%)	18 (17)	674 (15)
Positive rheumatoid factor, n (%)*	28 (29)	248 (6)
Increased C-reactive protein (> 1.0 mg/dl), n (%)**	21 (22)	488 (12)
Missing teeth [#] , mean ± SD*	20 ± 10	16 ± 11
Decayed surfaces [†] , %*	2	4
Decayed or filled surfaces ^{††} , %	21	24
Dental care (visits to dentist per year), n (%)*		
At least once a year	22 (23)	1,374 (34)
Less frequently	72 (77)	2,642 (66)
Dental health categories, n (weighted % ± SE)*		
No periodontal disease	34 (28 ± 4.6)	2,222 (56 ± 1.6)
Periodontal disease	16 (16 ± 5.3) ^{##}	642 (10 ± 1.1)
Edentulous	53 (56 ± 6.7)	1,494 (34 ± 1.5)

* $p \leq 0.001$ and ** $p \leq 0.002$ based on chi-square or t-test. [†] Number of decayed tooth surfaces/number of surfaces of all present teeth. ^{††} Number of decayed or filled tooth surfaces/number of surfaces of all present teeth. [#] Total number of missing teeth based on a total of 28 teeth. ^{##} May be statistically unreliable. MET: metabolic equivalent.

lower frequency of decay (2% vs 4%; $p < 0.001$), and a slightly lower frequency of filled or decayed surfaces (21% vs 24%; $p = 0.3$) compared with non-RA (Table 1).

Participants with RA were more likely to be edentulous [odds ratio (OR) 2.27, 95% confidence interval (CI) 1.56–3.31] compared with non-RA subjects. Similarly, among dentate participants, individuals with RA were more likely to have periodontitis (OR 1.82, 95% CI 1.04–3.20), independently of age, sex, race/ethnicity, and smoking (Table 2). These associations were maintained in a multivariate model further adjusting for education, poverty income ratio, smoking, diabetes, BMI, and physical activity (edentulous: OR 2.13, 95% CI 1.35–3.36 and periodontitis: OR 1.74, 95% CI 0.92–3.32).

In a secondary exploratory analysis, the multivariate model further adjusting for BMD showed similar results (edentulous: OR 2.28, 95% CI 1.49–3.51 and periodontitis: OR 1.43, 95% CI 0.69–2.97).

RA definition based on the presence of 4 ACR criteria. In a sensitivity analysis, participants with RA based on presence of 4 ACR criteria showed a stronger association with periodon-

tal disease/tooth loss (edentulous: OR 3.34, 95% CI 1.16–9.64 and periodontitis: OR 4.13, 95% CI 1.30–13.15), independent of age, sex, race/ethnicity, and smoking.

Presence of RF. Participants with seropositive RA were more likely to be edentulous (OR 4.50, 95% CI 1.2–17) than those with seronegative RA, adjusting for age, race/ethnicity, sex, and smoking (Table 3). Participants with seropositive RA had more than twice the odds of periodontitis (OR 2.20, 95% CI 0.4–13.1) than those with seronegative RA, adjusting for age, race/ethnicity, sex, and smoking; however, the difference was not statistically significant due to the reduced sample size. Seropositivity itself was not independently associated with being edentulous (OR 1.20, 95% CI 0.85–1.68) or having periodontitis (OR 1.07, 95% CI 0.73–1.57) among participants without RA (Table 3).

Dental care. Overall, participants with RA had less regular dental care (23% vs 34% visited the dentist at least once a year; $p = 0.03$) than non-RA participants (Table 1). Even when the analysis was confined to dentate participants, those with RA tended to have less frequent dental care than those with-

Table 2. Association of dental health status with rheumatoid arthritis (RA).

	Dental Health Status			
	Periodontal Disease		Edentulous	
	OR (95% CI)*	OR (95% CI)**	OR (95% CI)*	OR (95% CI)**
Non-RA	1	1	1	1
RA	1.82 (1.04–3.20)	1.74 (0.92–3.32)	2.27 (1.56–3.31)	2.13 (1.35–3.36)

* Multivariate multinomial logistic regression model with dental health status as the dependent variable and RA as the independent variable, adjusting for age, sex, race/ethnicity, and smoking. ** Multivariate multinomial logistic regression model with dental health status as the dependent variable and RA as the independent variable, adjusting for age, sex, race/ethnicity, smoking, diabetes, education, poverty income ratio, body mass index, and physical activity, and accounting for survey stratification and clustering. The reference group for the outcome is the group with healthy dental health status (i.e., dentate without periodontal disease).

Table 3. Association of dental health status with seropositivity among participants with and without rheumatoid arthritis (RA).

	No PD [†] N (%)	Dental Health Status			
		Periodontal Disease N (%)	OR (95% CI)	Edentulous	
				N (%)	OR (95% CI)
RA*					
RF-	28 (41)	10 (15)	1	30 (44)	1
RF+	5 (18)	4 (14)	2.2 (0.4–13.1)	19 (68)	4.5 (1.2–17.0)
Non-RA**					
RF-	2017 (52)	568 (15)	1	1280 (33)	1
RF+	115 (46)	36 (15)	1.07 (0.73–1.57)	97 (39)	1.20 (0.85–1.68)

[†] The reference group for the outcome is the group with healthy dental health status defined as dentate without periodontal disease (no PD). * Subset analysis restricted to RA participants. Multinomial logistic regression models with dental health status as the dependent and seropositive RA as the independent variable, adjusting for age, sex, race/ethnicity, and smoking. ** Subset analysis restricted to non-RA participants. Multinomial logistic regression models with dental health status as the dependent and seropositivity as the independent variable, adjusting for age, sex, race/ethnicity, and smoking. RF: rheumatoid factor.

out RA (38% vs 47% visited the dentist at least once a year; $p = 0.1$), and there was no difference in dental care frequency among subjects with periodontitis and those without periodontitis among dentate participants with RA (Table 4).

DISCUSSION

In this population sample, participants with RA (based on 3/6 ACR criteria) were more than twice as likely to have complete

tooth loss compared with non-RA participants. Further, this association was largely preserved after adjusting for a number of potential biases including age, sex, race/ethnicity, income, education, smoking, diabetes, BMI, BMD, and physical activity. RA was also associated with an almost 2-fold increase in the odds of periodontal disease. The association with complete tooth loss was particularly strong for those with seropositive RA. Similarly, the association was stronger in a sensitiv-

Table 4. Distribution of dental care frequency by dental health status among participants with and without rheumatoid arthritis (RA).

Dental Care Frequency*	Dental Health Status		
	No PD n (%)	Periodontal Disease, n (%)	Edentulous, n (%)
RA			
At least once a year	13 (38)	6 (38)	3 (7)
Less frequently	21 (62)	10 (62)	41 (93)
Non-RA			
At least once a year	1118 (52)	193 (32)	63 (5)
Less frequently	1045 (48)	415 (68)	1182 (95)

* Defined as number of visits to dentist per year, and dichotomized as visits to dentist at least once a year versus less frequently.

ity analysis based on a more stringent definition of RA based on the presence of 4 ACR criteria for classification of RA.

The finding that seropositivity among participants with RA was associated with complete tooth loss is intriguing. RF in RA has been associated with a more severe disease course and extraarticular manifestations. Interestingly, previous studies have reported the presence of RF in gingiva, subgingival plaque, and serum of subjects with periodontitis^{15,16}.

A notable observation was that RF was present in 29% among those with RA, while published series of patients with RA indicate a higher prevalence of RF. It is possible that persons with severe RA could have missed the mobile examination evaluation due to severe disability or that a high proportion of participants classified as RA based on 3/7 ACR criteria, instead of 4/7 ACR criteria, have a mild or less severe disease or an early, undifferentiated inflammatory arthritis. Given the stronger association between periodontitis/tooth loss and seropositive RA, our results may therefore underestimate the association between periodontitis/tooth loss and RA. This is also consistent with our findings of a stronger association between periodontitis/tooth loss and RA based on a more stringent definition of 4 ACR criteria for classification of RA. Alternatively, seronegative RA may be more prevalent in this sample. Indeed, biases associated with referral (such as RF detection itself) and classification criteria could have inflated its apparent frequency in clinical samples. Population-based studies have found lower rates of seropositive RA (26% to 60%)³⁵⁻³⁸ and a decline in the prevalence of seropositive RA³⁹⁻⁴¹. In addition, Rasch, *et al* evaluated the agreement between 3 different classification methods for RA in NHANES III including the method we used³³. The classification agreement between these methods was excellent ($\kappa = 0.879$ and $\kappa = 0.921$), which adds to the validity of this approach, as one of the case definition methods incorporated the use of antirheumatic drugs.

In addition to having a common underlying proinflammatory trait, there are several mechanisms that could result in increased periodontitis and tooth loss among individuals with RA, of which low BMD, medications used for RA therapy, xerostomia due to Sjögren's syndrome, and differences in dental healthcare are all strong contenders.

For a number of reasons, including the inflammatory process itself, osteopenia is common in people with RA. Osteoclast activation seems to be the dominant process leading to bone loss in RA, mediated through the receptor activator of nuclear factor- κ B ligand (RANKL)/RANK pathway⁴². Several studies have reported positive associations between osteoporosis or low bone density and alveolar bone loss (i.e., periodontitis), indicating that osteoporosis may be a risk factor for periodontitis⁴³. In addition, studies suggest that in the elderly, maintenance of BMD is associated with improved tooth retention; however, the evidence is still inconclusive⁴⁴. We conducted an exploratory analysis to evaluate if differences in BMD may explain the association between RA and

periodontitis/tooth loss. Adjustment for BMD did attenuate the association only slightly, suggesting that osteoporosis may not be an important factor in the association between RA and periodontitis/tooth loss in this sample, although this does not rule out the possibility of alveolar osteopenia.

Medications used for treatment of RA, rather than the disease itself, could affect the association between RA and periodontal disease/tooth loss. However, most of the drugs used to treat RA are likely to reduce the risk of periodontitis and/or its progression. Indeed, there is robust evidence that nonsteroidal antiinflammatory drugs have beneficial effects on periodontal outcomes⁴⁵. Similarly, more recent evidence from animal models indicates that RA therapy with biologics (i.e., anti-TNF drugs) may improve experimental periodontitis^{46,47}.

Some patients with RA may have secondary Sjögren's syndrome⁴⁸, which has been associated with accelerated decay and tooth loss⁴⁹⁻⁵¹, but it has not been associated with periodontal disease⁵¹⁻⁵⁴. However, in our study, participants with RA had a significantly lower proportion of decayed surfaces and a similar proportion of decayed/filled surfaces compared with non-RA, suggesting that caries (and, by inference, xerostomia) are less likely explanations for our finding of increased tooth loss in RA.

Tooth loss is the final outcome of a multifactorial process, which involves biological processes (i.e., dental disease such as periodontitis and decay) as well as nonbiological processes related to dental treatment including health behaviors, patient preferences, available treatment options, and access to dental care. For example, it is possible that patients with RA might visit dentists less frequently and that dentists might favor extractions of diseased teeth in patients with RA. We found that participants with RA had a lower frequency of regular dental care compared with non-RA participants, even when the analysis was confined to dentate individuals; however, it is possible that these differences are explained by confounding factors such as socioeconomic status.

Strengths of our study include its population-based sample, which minimized the potential for selection bias, and ability to control for many of the potential confounders of the association between RA and periodontal disease/tooth loss. Although causality could not be established, our results suggest that RA, and in particular seropositive RA, is associated with increased periodontitis and complete tooth loss.

Important limitations of our study are the relatively low number of subjects with RA, resulting in wide confidence intervals and limiting our ability to perform subgroup analyses.

Notwithstanding these limitations, our findings have several important implications. First, mechanistic studies into the links between periodontitis and RA and the possible causal role of oral infections in RA pathogenesis are warranted. Second, longitudinal studies are necessary to establish the temporal relationship between RA and periodontitis/tooth loss. Third, regardless of whether the association between RA

and periodontitis/tooth loss is causal or the result of a common proinflammatory phenotype, our findings suggest that periodontitis and tooth loss are highly prevalent in older patients with RA and that regular dental care should be advocated by rheumatologists.

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