Antibodies to citrullinated peptides in serum and saliva in patients with rheumatoid arthritis and their association to periodontitis

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Abstract

Objective

A connection between prevalence of rheumatoid arthritis (RA) and periodontitis has been reported. The hypothesis for this association involves increased citrullination in the oral mucosa in patients with periodontitis. Whether ongoing periodontitis has an effect on IgA antibodies to citrullinated peptides (ACPA) in saliva is unknown. We studied IgA ACPA in saliva and serum and their relation to periodontitis and smoking in a population-based elderly RA cohort.

Methods

A population-based cohort of patients with RA ≥61 years of age (n=132) was examined by rheumatologists and a dental hygienist. Analyses of IgG ACPA in serum and IgA ACPA in serum and saliva were performed. The presence of ACPA was compared in patients with RA with and without periodontitis.

Results

IgA ACPA in serum occurred in 35% of RA patients with periodontitis and in 43% of RA patients without periodontitis (p=0.740). IgG ACPA in serum was found in 66% of RA patients with periodontitis, and in 69% without periodontitis (p=0.740). IgA ACPA in saliva occurred in 20% with periodontitis and 55% without periodontitis (p=0.062). A logistic regression analysis adjusting for age, gender and smoking gave an odds ratio (OR) of 0.456 (95% CI=0.183–1.137, p=0.092) for saliva IgA ACPA positive individuals to have periodontitis.

Conclusion

IgA ACPA in serum or saliva was not more common in RA patients with periodontitis. This implies that local production of ACPA by the oral mucosa is not enhanced by periodontal inflammation, in patients with established RA.

Key words

rheumatoid arthritis, periodontitis, epidemiology, smoking, anti-citrullinated peptide antibodies

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Introduction

Mucosal surfaces receive increasing attention as an important part of rheumatoid arthritis (RA) pathogenesis (1). According to this mucosal hypothesis, triggering factors are encountered by mucosal surfaces resulting in activation of the local, mucosal, immune system where antibodies to citrullinated peptides (ACPA) are produced. The lungs (2-4), oral mucosa (5) and gut (6) have all been suggested as possible initiating mucosal compartments. ACPA has been found in sputum from RA patients and at-risk subjects that are positive for ACPA in serum, but also in those who are negative for ACPA in serum (7), which indicates that mucosal immunity with ACPA production may antedate circulating antibodies.

At mucosal surfaces, secretory antibodies are produced by subepithelial B cells and actively transported to the lumen. Secretory IgA antibodies constitute a substantial proportion of salivary proteins (8). Earlier studies report a prevalence of secretory ACPA of 17% (serum) to 22% (saliva) in patients with RA, and that secretory ACPA occur mainly in serum of IgG ACPA positive patients (9, 10). In a pilot study, IgA ACPA levels in saliva from patients with RA have been associated with lower disease activity, and lower prevalence of erosions (9). It is, however, not known if salivary IgA ACPA is related to periodontitis.

Citrullination occurs in many tissues in the presence of inflammation, but the formation of antibodies against these proteins is highly specific for RA (11). One hypothesis regarding this break of tolerance involves citrullination of oral and bacterial proteins by the oral pathogen *Porphyromonas gingivalis*, which is the only prokaryote known to express the enzyme peptidyl arginine deiminase (PAD) enabling citrullination (12). ACPAs binding human citrullinated alpha-enolase have for example been shown to cross-react with *P gingivalis* enolase, which might be one mechanism in the initiation of autoimmunity leading to RA (13). Also, citrullinated proteins have been found in the gingiva of patients with periodontitis (14-16).

The aim of the present study was to investigate the presence and levels of IgA ACPA in saliva and serum in a population-based cross-sectional cohort of elderly RA patients, in relation to clinically verified periodontitis and smoking. Our null hypothesis was that periodontitis was not associated with IgA ACPA in saliva.

Material and methods

All RA patients are recorded in the electronic database at the regional hospitals of Region Blekinge (population 153,000 in 2013). Between October 2013 and January 2015, all individuals with a diagnosis of rheumatoid arthritis (M05 and M06, International Classification of Diseases ICD-10) found in their electronic medical records ≥61 years of age living in Karlskrona city were identified. To be included in the present study, participants must be diagnosed with RA, be ≥61 years of age per October 21, 2013, and be living in the city of Karlskrona (population 64,000 in 2013). The individuals with RA had to have had at least one visit to the rheumatology department after 2006. The Department of Rheumatology provides care for all patients with a diagnosis of RA in Region Blekinge.

Rheumatoid arthritis disease activity

All individuals with RA were examined at the outpatient rheumatology clinic by rheumatologists. Medical records were reviewed by a rheumatologist (author MS). Data on RA disease activity and current anti-rheumatic medications at inclusion were identified at the rheumatologists' visit and confirmed from the Swedish Rheumatology Quality Register online during the visit (www.srq.se). Data on disease duration, previous anti-rheumatic medications, comorbidities, osteoporosis, smoking habits, occupation, body mass index (BMI), the total number of drugs and blood analysis including cholesterol levels, RF (rheumatoid factor) were recorded. Classification of the RA patients was performed according to the 1987 ACR RA criteria (17) and 2010 ACR/EULAR RA criteria (18).

Dental examination

A dental hygienist performed the clinical dental examinations. The examina-

tion included a panoramic radiograph. Panoramic radiographs were chosen to minimise radiation exposure. Such radiographs are commonly used for screening purposes as it has been demonstrated there is a high level of agreement regarding the assessment of alveolar bone levels between panoramic and intra-oral radiographs (19). Radiographs were assessed by a periodontist (author RGP) blinded to clinical dental data as well as to the participants' medical conditions.

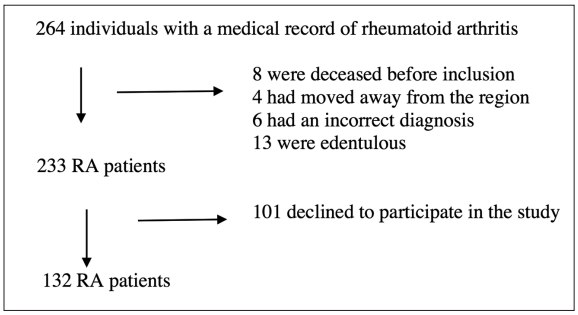
The following dental examinations were performed:

1. Measurements of probing pocket depths at four surfaces at all teeth and dental implants.
2. The extent of bleeding on probing (BOP) was recorded within 30 seconds following probing of probing pocket depth (PPD) measurements and was assessed at the same sites as described above.
3. Dental plaque scores were recorded as described above.
4. Tooth decay was recorded as open decay.
5. The presence/absence of abnormal mucosal conditions was recorded.
6. The number of remaining teeth was registered and confirmed from the radiographs.
7. The extent of alveolar bone loss (mm distance between the cement-enamel junction (CEJ) and bone level at interproximal sites) was assessed from panoramic radiographs. The proportions of sites with a depth ≥4mm and ≥5 mm in relation to the number of assessed interproximal sites were calculated to arrive at a subject based number defining bone loss. The distances were assessed using digital images and the Osirix software v. 9.0 (Pixmeo, SARL, Bernex, Switzerland).

Definition of gingivitis and periodontitis

Gingivitis was defined as having ≥20 % of measured sites with evidence of bleeding on probing. Periodontitis was defined as the clinical presence of bleeding on probing at >20% of recorded tooth surfaces, presence of >2 non-adjacent sites with a PPD ≥5 mm, presence of bone loss at ≥2 sites with a distance between CEJ-to bone level of ≥5 mm, or if evidence of a furcation invasion at molar teeth was found either clinically (grade II), or clearly visible on panoramic radiographs, and bone loss ≥5 mm at ≥30% (20).

Fig. 1. Flow chart of the study.



Antibody analyses

Serum IgG antibodies to citrullinated peptides were analysed using a second generation cyclic citrullinated peptide (anti-CCP) immunoassay (EuroDiagnostica, Malmö, Sweden) using the cut-off limit (25 U/mL) recommended by the manufacturer, corresponding to the 99th percentile among healthy blood donors. Serum IgA antibodies to citrullinated peptides were analysed by using the same immunoassay, but with secondary antibody detecting human IgA (Dako-Cytomation, Glostrup, Denmark) as previously described (21).

Unstimulated whole saliva was collected by 'passive drooling' for 10 minutes. The samples were kept on ice before centrifugation, and then frozen until analysis. Saliva samples were analyzed for IgA ACPA using the same immunoassay as for serum IgA ACPA as previously described (9). Considering the previous finding of unspecific reactivity to the arginine containing control peptide (CAP), all salivary samples were analysed for both IgA anti-CCP and IgA anti-CAP in parallel. All samples were analysed in duplicates. The intra-assay variation was 3.5% and the inter-assay variation 12%. To compensate for inter-assay variation, a reference sample was analysed on each plate and the samples were adjusted for differences in OD values based on the reference sample. The ratio between the OD value for IgA anti-CCP and for IgA anti-CAP was calculated, and IgA anti-CCP positivity in saliva was defined as an anti-CCP/anti-CAP ratio >1.5, corresponding to the 95th percentile of 20 healthy subjects, as previously described (9). Saliva samples were also analysed for levels of total IgA (IBL IgA ELISA, Tecan Nordic AB, Sweden) and total protein (BCA Protein Assay, Thermo Fisher Scientific, Sweden). All samples were stored at -70^{o} C until analysis.

Ethics

The Regional Ethical Review Board at Lund, Sweden, approved the study (LU 2013/323). All study participants gave their written informed consent.

Statistics

Independent student's *t*-tests (equal variance not assumed) were used for continuous variables and Fischer's exact test and chi-square for categorical variables. Mann-Whitney was used for non-parametric data. Two-sided *p*-values <0.05 were considered statistically significant. A binary logistic regression analysis was performed to investigate if periodontitis independently predicted IgA ACPA in saliva. The results are presented as odds ratios (ORs) and 95% confidence intervals (95% CI). Spearman's rho was used to examine correlations between antibody levels in serum and saliva. Statistical calculations were performed using SPSS v. 25.

Results

The flow chart of the study is presented in Figure 1. A total of 132 RA patients were included, giving a catchment of 57%. The 110 RA patients who declined to participate in the study were older (74 *vs*. 70, *p*=0.0001), had a higher mean erythrocyte sedimentation rate (ESR) (27 *vs*. 19, *p*=0.0001), had a higher mean DAS28ESR (3.4 *vs*. 3.0,

Table I. Demographics, disease activity data and comorbidities for patients with RA, stratified for periodontitis.

	RA and periodontitis n=80		RA and no periodontitis n=52		*p*-value
	n	Mean (SD) or percent	n	Mean (SD) or percent	
Age at inclusion, years	80	71 (7.2)	52	69 (5.2)	0.111
Female	80	71%	52	69%	0.80
BMI	80	27 (5.4)	52	27 (4.4)	0.418
Disease duration from diagnosis, years	80	12 (13)	52	12 (11)	0.676
Disease activity					
DAS28 ESR	76	3.0 (1.0)	50	2.8 (1.2)	0.315
DAS28 CRP	78	2.8 (0.9)	52	2.7 (0.9)	0.529
HAQ	69	0.9 (0.8)	50	0.9 (0.7)	0.652
ESR, mm	78	20 (16)	51	18 (16)	0.191
CRP, mg/ml	80	9.4 (8.7)	52	9.4 (9.0)	0.608
SJC (28)	79	1.1 (1.7)	52	1.2 (2.3)	0.510
TJC (28)	79	1.4 (2.1)	52	1.5 (2.8)	0.231
VAS patient's global, mm	79	32 (27)	52	36 (26)	0.263
VAS pain, mm	78	34 (27)	51	38 (30)	0.505
Erosions in hands or feet	77	58%	49	53%	0.537
Treatment					
DMARDs currently	80	65%	52	69%	0.614
Number of previous DMARDs	80	1.3 (1.4)	52	1.4 (1.7)	0.907
Biologics currently	80	21%	52	23%	0.804
Biologics ever	80	36%	52	44%	0.577
NSAID or coxibes currently	80	64%	52	60%	0.714
NSAID or coxibes ever	80	83%	52	94%	0.049
On prednisolone	80	43%	52	54%	0.202
Comorbidities					
Total number of medicines at inclusion	80	10 (4.3)	52	10 (4.5)	0.995
Interstitial lung disease	80	3%	52	8%	0.162
Hypertension	80	70%	52	42%	0.002
Stroke, ischaemic	80	9%	52	8%	0.830
Myocardial infarction	80	8%	52	10%	0.667
Smoking					
Smoker (ever *vs*. never)	80	64%	52	60%	0.714
Current smoker		13%		4%	0.239
Previous smoker		51%		56%	
Never smoker		36%		40%	

VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; SJC (28): swollen joint count 28 joints; TJC (28): tender joint count 28 joints, DAS28ESR: Disease Activity Score (28 joints) calculated with ESR; DAS28CRP: Disease activity Score (28 joints) calculated with CRP; DMARD: disease-modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug; BMI: body mass index.

p=0.005) and were less often on biologics (7% *vs*. 22%), but did not otherwise differ from the RA patients included in the study. 83% of the RA patients fulfilled the 1987 ACR classification criteria and 71% the 2010 ACR/EULAR classification criteria for RA. The period prevalence of RA was 1.5%.

Table I shows that there were no differences in demographics, disease activity, anti-rheumatic treatment, comorbidities or smoking between the patients with and without periodontitis, with the exception of hypertension, being more common in patients with periodontitis. After dental examination, 80/132 (61%) of RA patients were diagnosed with periodontitis.

The total levels of IgA or protein in saliva did not differ between patients with or without periodontitis (Table II).

Association between ACPA and periodontitis

IgG ACPA in serum was found in 66% of RA patients with periodontitis, and in 69% of RA patients without periodontitis (*p*=0.849). IgA ACPA in serum was found in 35% of RA patients with periodontitis, and in 43% of RA patients without periodontitis (*p*=0.461). Saliva IgA ACPA was found in 20% of RA patients with periodontitis, and in 55% of RA patients without periodontitis (*p*=0.062) (Table II).

To further investigate the association between IgA ACPA in saliva and periodontitis, a binary logistic regression analysis, adjusting for age, gender and smoking was performed (Table III), revealing an odds ratio (OR) of 0.456 (95% CI=0.183–1.137, *p*=0.092) for periodontitis independently predicting IgA ACPA positivity in saliva. Female patients with RA had an OR of 0.362 (CI=0.141–0.929, *p*=0.035) for being IgA ACPA positive in saliva. Binary logistic regression analyses adjusting for age, gender and smoking were also performed for periodontitis predicting positivity of ACPA in serum (Table IV), IgG ACPA had an OR of 1.017 (95% CI=0.959–1.078), *p*=0.580 and IgA ACPA had an OR of 0.636 (95% CI=0.299–1.351), *p*=0.636.

The correlation between IgG ACPA in serum and IgA ACPA in saliva was 0.235 (*p*=0.014) and between IgA ACPA in serum and IgA ACPA in saliva 0.208 (*p*=0.030). There were no significant correlations between age and levels of ACPA in serum or saliva (data not shown), and no difference between levels of ACPA in RA patients with or without periodontitis (Table II).

Discussion

In this cohort of established elderly RA patients, no correlation was found between periodontitis and IgA ACPA in saliva. This indicates that local production of ACPA in saliva is not enhanced by periodontitis. To our knowledge, our study is the first to show this. Furthermore, the presence of IgA or IgG ACPA in serum did not correlate to periodontitis, indicating that a systemic reaction to citrullinated peptides is not increased in RA patients with periodontitis. Our hypothesis that periodontitis leads to increased citrullination in the oral cavity, with consequent increase in production of ACPA first locally and then systemically could thus not be confirmed. The present study is, however, a cross-sectional study on established RA patients that were stable

Table II. Prevalence and levels of antibodies to citrullinated peptides in patients with RA, stratified for periodontitis.

	Patients with RA and periodontitis n=80		Patients with RA no periodontitis n=52		*p*-value
Serum	n	Level (SD) or percent	n	Level (SD) or percent	
IgG ACPA level U/mL (SD)	79	609 (944)	51	741 (1110)	0.468
IgA ACPA level AU/mL (SD)	79	201 (441)	51	109 (253)	0.133
IgG ACPA positive, %	79	66%	51	69%	0.849
IgA ACPA positive, %	79	35%	51	43%	0.461
Saliva					
IgA ACPA positive, %	66	20%	45	55%	0.062
IgA ACPA level OD (SD)	66	1.45 (1.58)	45	1.54 (1.59)	0.404
Total IgA level microg/mL	66	99 (74)	45	119 (199)	0.443
Total Protein level microg/mL	66	42.1 (21.6)	45	41.4 (19.2)	0.854

ACPA: antibodies to citrullinated peptides.

Table III. Multivariate binary logistic regression analysis with positivity for IgA ACPA in saliva as outcome. Adjusted for gender, age and smoking status.

Variable	OR	95% CI	*p*-value
Periodontitis	0.456	0.183-1.137	0.092
Female gender	0.362	0.141-0.929	0.035
Age	1.026	0.953-1.104	0.501
Smoking	0.609	0.609-1.310	0.204

Table IV. OR for periodontitis for the different ACPA classes.

	Unadjusted n=130 (serum) n=111 (saliva)		*p*-value	Adjusted for age, sex and smoking n=130 (serum) n=111 (saliva)		*p*-value
	OR	95% CI		OR	95% CI	
IgG ACPA in serum	0.880	0.415-1.868	0.740	1.017	0.959-1.078	0.580
IgA ACPA in serum	0.724	0.352-1.488	0.379	0.636	0.299-1.351	0.636
IgA ACPA in saliva	0.445	0.188-1.051	0.065	0.456	0.183-1.137	0.092

ACPA: antibodies to citrullinated peptides.

in their disease. Thus the association between ACPA and periodontitis before or at the time of the development of arthritis could not be investigated in this study. Furthermore, we do not know if periodontitis preceded RA or how periodontitis has progressed over time since the diagnosis of RA. A recent review of the pathogenesis of RA (22) states that close interaction of a variety of factors are involved, but all at different stages in the disease. Thus, it may well be that we have not captured the stage where a possible association between periodontitis and ACPA formation could be found.

This study shows a correlation between salivary and serum levels of IgA ACPA, indicating a connection between mucosal and systemic immunity in RA. Mucosal ACPA production has been assumed to take place early in the pathogenesis of RA, before manifest arthritis evolves. There are also data implicating that mucosal ACPA is not an early event, but rather a feature of manifest RA (23).

An earlier study of this cohort showed an association between RA and periodontitis with an OR of 2.7 (Renvert *et al*., unpublished observations). Presently, no consensus as to the association between periodontitis and RA exists. Some studies show an association (24-28) whereas some do not (29, 30). These studies have used different study designs, different inclusion and exclusion criteria, different criteria for periodontitis and vary in the choice of controls, and thus are difficult to compare.

Strengths of our study were our systematically recruited population-based cohort, extensive data on demographics, disease activity and comorbidities, and that we used the new modification of the classification system for periodontitis (20). Our RA patients were well treated and stable in their disease. However, our study was small, and we had a high dropout rate most likely resulting in a healthy subject bias. Furthermore, our study was cross-sectional by design, to assess the association between periodontitis and the presence of ACPA, and cannot provide information on the time course or causality. Further investigation in prospective pre-RA cohorts would be valuable.

Conclusions

No correlation was observed between periodontitis and saliva IgA ACPA or between periodontitis and IgA or IgG ACPA in serum. In this cross-sectional cohort of stable patients with established RA, our findings do not support the hypothesis that periodontitis leads to increased formation of IgA ACPA in saliva or serum.

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