Seropositivity combined with smoking is associated with increased prevalence of periodontitis in patients with rheumatoid arthritis

An association between periodontitis and rheumatoid arthritis (RA) has been proposed based on observations of increased risk of periodontitis in patients with RA as well as the presence of antibodies to citrullinated protein antigens (ACPAs) and rheumatoid factor (RF) in serum and gingiva of patients with periodontitis.[1–3] Additionally, smoking is one of the most important risk factors for both periodontitis and RA, and predispose for the development of seropositive RA.[4–6] We have previously reported that smokers with RA have increased prevalence of periodontitis as compared with never smokers in the Swedish population-based case–control study EIRA (Epidemiological Investigation of Rheumatoid Arthritis).[7] The objective of the current study was to further investigate the effects of smoking on the risk of periodontitis in seropositive and seronegative (ACPA/RF) subsets of RA.

Data on periodontal status (years 2008–2012) were retrieved from the Swedish Dental Health Registry (DHR) for 2327 patients with established RA (1469/852 ACPA-positive/ACPA-negative and 1505/822 RF-positive/RF-negative, respectively) included in the EIRA study (years 1996–2009) as previously described.[7] Periodontal diagnosis was based on diagnostic codes for periodontitis, peri-implantitis and increased risk of periodontitis/peri-implantitis, registered by the patients' dentists in the DHR.[7] The diagnosis of RA was confirmed by the rheumatologist at the time of the recruitment into EIRA; blood samples were collected to determine ACPA/RF status.[8] Detailed information on smoking status was collected by a self-administered questionnaire at the time of enrolment to EIRA.[8] For the association between smoking status, seropositive/seronegative RA and periodontitis, we calculated OR with 95% CI adjusted for age, gender, education and residential area.

In ACPA-positive RA, smoking was associated with a significantly ($p<0.05$) higher prevalence of periodontitis, mainly in current smokers (OR=1.9, 95% CI 1.5 to 2.5) (table 1). The

Table 1 Association between periodontal diagnostic codes and smoking habits compared with never smokers in EIRA RA cases, in relation to ACPA status and gender*

		ACPA-positive RA (n=1469)		ACPA-negative RA (n=852)	
Smoking habits		No with periodontitis (%)†	OR (95% CI)‡	No with periodontitis (%)†	OR (95% CI)‡
Total					
	All	773 (100)		458 (100)	
	Women	557 (100)		331 (100)	
	Men	216 (100)		127 (100)	
Never smokers					
	All	196 (25.4)	1.0 (ref)	155 (33.8)	1.0 (ref)
	Women	156 (28.0)	1.0 (ref)	115 (34.7)	1.0 (ref)
	Men	40 (18.5)	1.0 (ref)	40 (31.5)	1.0 (ref)
Ex-smokers					
	All	285 (36.9)	1.7 (1.3 to 2.2)§	140 (30.6)	0.9 (0.7 to 1.3)
	Women	200 (35.9)	1.8 (1.4 to 2.4)§	88 (26.6)	1.0 (0.7 to 1.5)
	Men	85 (39.4)	1.8 (1.0 to 3.1)§	52 (40.9)	0.7 (0.4 to 1.3)
Ever smokers					
	All	577 (74.6)	1.6 (1.3 to 2.0)§	303 (66.2)	1.1 (0.9 to 1.4)
	Women	401 (72.0)	1.6 (1.3 to 2.1)§	216 (65.3)	1.3 (0.9 to 1.7)
	Men	176 (81.5)	1.9 (1.2 to 3.0)§	87 (68.5)	0.8 (0.5 to 1.3)
Current smokers					
	All	232 (30.0)	1.9 (1.5 to 2.5)§	111 (24.2)	1.2 (0.9 to 1.6)
	Women	157 (28.2)	1.8 (1.3 to 2.4)§	85 (25.7)	1.4 (0.9 to 2.0)
	Men	75 (34.7)	2.9 (1.6 to 5.3)§	26 (20.5)	0.7 (0.4 to 1.4)

*The periodontal diagnostic codes include periodontitis, peri-implantitis and increased risk for periodontitis/peri-implantitis.
†Number (%) of ACPA-positive or ACPA-negative RA cases with periodontal diagnostic codes.
‡ORs, with a 95% CI, were adjusted for age, gender, education and residential area.
§p Value <0.05 for association between periodontal diagnostic codes and smoking habits as compared with never smokers among ACPA-positive and ACPA-negative RA cases.
ACPA, anticitrullinated protein antibody; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis; ref, reference group.

Table 2 Association between periodontal diagnostic codes and smoking habits compared with never smokers in EIRA RA cases, in relation to double seropositive or negative antibody status and gender*

Smoking habits		ACPA-positive and RF-positive RA (n=1261)		ACPA-negative and RF-negative RA (n=616)	
		No with periodontitis (%)†	OR (95% CI)‡	No with periodontitis (%)†	OR (95% CI)‡
Total					
	All	667 (100)		328 (100)	
	Women	479 (100)		234 (100)	
	Men	188 (100)		94 (100)	
Never smokers					
	All	162 (24.3)	1.0 (ref)	122 (37.2)	1.0 (ref)
	Women	130 (27.1)	1.0 (ref)	90 (38.5)	1.0 (ref)
	Men	32 (17.0)	1.0 (ref)	32 (34.0)	1.0 (ref)
Ex-smokers					
	All	254 (38.1)	1.8 (1.4 to 2.3)§	94 (28.7)	0.8 (0.6 to 1.1)
	Women	178 (37.2)	1.9 (1.4 to 2.5)§	53 (22.6)	0.8 (0.5 to 1.2)
	Men	76 (40.4)	1.9 (1.1 to 3.4)§	41 (43.6)	0.7 (0.4 to 1.3)
Ever smokers					
	All	505 (75.7)	1.7 (1.4 to 2.1)§	206 (62.8)	1.0 (0.7 to 1.2)
	Women	349 (72.9)	1.7 (1.3 to 2.2)§	144 (61.5)	1.1 (0.8 to 1.5)
	Men	156 (83.0)	2.0 (1.2 to 3.3)§	62 (66.0)	0.7 (0.4 to 1.1)
Current smokers					
	All	200 (30.0)	2.0 (1.5 to 2.7)§	76 (23.2)	1.0 (0.7 to 1.5)
	Women	133 (27.8)	1.8 (1.3 to 2.5)§	61 (26.1)	1.3 (0.8 to 1.9)
	Men	67 (35.6)	3.3 (1.8 to 6.2)§	15 (16.0)	0.5 (0.2 to 1.1)

*The periodontal diagnostic codes include periodontitis, peri-implantitis and increased risk for periodontitis/peri-implantitis.
†Number (%) of ACPA-positive and RF-positive or ACPA-negative and RF-negative RA cases with periodontal diagnostic codes.
‡ORs, with a 95% CI, were adjusted for age, gender, education and residential area.
§p <0.05 for association between periodontal diagnostic codes and smoking habits as compared to never smokers among ACPA-positive and RF-positive or ACPA-negative and RF-negative RA cases.
ACPA, anticitrullinated protein antibody; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis; ref, reference group; RF, rheumatoid factor.

highest prevalence of periodontitis, with almost a threefold increased risk, was observed among current smoking ACPA-positive men (OR=2.9, 95% CI 1.6 to 5.3). For ACPA-negative RA, no convincing association between smoking and periodontitis was observed (table 1). Similar associations ($p<0.05$) were observed in analysis based on RF status (RF-positive current smokers; OR=1.9, 95% CI 1.5 to 2.5) with the highest OR observed in RF-positive current smoking men (OR=2.9, 95% CI 1.6 to 5.2) (table not shown).

Interestingly, the OR for periodontitis increased even further among patients double positive for ACPA and RF antibodies, with OR of 3.3 (95% CI 1.8 to 6.2) observed in current smoking men compared with never smokers (table 2).

We herein demonstrate that the previously observed association between smoking and periodontitis in RA[7] is confined to patients with seropositive RA, especially those with both ACPA and RF antibodies. One reason for the increased risk of periodontitis in seropositive RA may be due to enhanced ACPA and/or RF titres in smokers since smoking is reported to be associated with increased risk for seropositive RA and higher titres of ACPA/RF in RA, and furthermore, periodontitis has been associated with increased levels of ACPA/RF in patients with RA.[1 4 5 9 10] Smoking did not, however, significantly increase the prevalence of periodontitis in ACPA-negative/RF-negative RA, suggesting different pathophysiological mechanisms depending on autoantibody status in patients with RA. Our results are in line with previous findings that seropositive and seronegative RA represent distinct disease subsets differing in several aspects, including the association between seropositive RA with specific genetic and environmental risk factors such as human leukocyte antigen (HLA)-shared epitope and smoking.[4 5] In summary, the highest risk of periodontitis in patients with established RA was observed among seropositive current smokers, especially those double positive for ACPA and RF antibodies, a finding that warrants awareness by clinicians and their patients as well as further investigations on the mechanisms behind this association.

Kaja Eriksson,[1] Lena Nise,[2] Lars Alfredsson,[2,3] Anca Irinel Catrina,[4] Johan Askling,[4,5] Karin Lundberg,[4] Lars Klareskog,[4] Tülay Yucel-Lindberg[1]

[1]Division of Periodontology, Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden
[2]Unit of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[3]Centre of Environmental and Occupational Medicine, Stockholm County Council, Stockholm, Sweden
[4]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden
[5]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence to Dr Tülay Yucel-Lindberg and Dr Kaja Eriksson, Division of Periodontology, Department of Dental Medicine, Karolinska Institutet, Box 4064, SE-141 04 Huddinge, Sweden; tulay.lindberg@ki.se, Kaja.eriksson@ki.se

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