















Current Smoking Is Increased in Axial Psoriatic Arthritis and Radiographic Sacroiliitis

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ABSTRACT. Objective. The effect of smoking in psoriatic arthritis (PsA) is under debate. Our aim was to test whether smoking is increased in axial PsA (axPsA).

Methods. Included in the analysis were 1535 patients from PsArt-ID (PsA-International Database). The effect of smoking on axPsA (compared to other PsA phenotypes) and radiographic sacroiliitis were investigated.

Results. Current smoking was more common in axPsA (28.6% vs 18.9%, $p < 0.001$). It also was found as an independent predictor of axPsA (OR 1.4) and radiographic sacroiliitis (OR 6.6).

Conclusion. Current smoking is significantly associated with both axPsA and radiographic sacroiliitis in patients with PsA. (First Release July 1 2020; J Rheumatol 2020;47:1354–8; doi:10.3899/jrheum.190722)

Key Indexing Terms:

AXIAL PSORIATIC ARTHRITIS

SMOKING

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Psoriatic arthritis (PsA) is a heterogeneous disease, with diverse disease manifestations¹. Several genetic and environmental factors have been implicated as the mechanism underlying PsA, one of the latter being smoking. Although smoking has long been recognized as a risk factor in multiple immune-mediated diseases, there is inconsistent data in the literature regarding its role in PsA. Studies on the general population had demonstrated that smoking increases the risk of PsA^{2,3}. However, looking at the risk of developing PsA in patients with psoriasis, 2 studies had shown that smoking

does not have any effects on the risk of PsA, whereas 2 others demonstrated a decreased risk^{3,4,5,6}.

Smoking has been recognized as a prognostic marker in axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS), with poorer outcomes, more severe disease, and radiographic damage^{7,8}. A population-based study demonstrated that incident AS was associated with current smoking, but not with former smoking⁸. To date, there is no information on the effect of smoking as a risk factor for axial PsA (axPsA).

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We hypothesize that smoking is increased in axPsA, similar to AS. Therefore, in this study we aimed to (1) understand the frequency of smoking in axPsA in comparison to non-axPsA, and (2) investigate risk factors of axPsA, with a focus on smoking.

MATERIALS AND METHODS

Patient selection and data collection. The Psoriatic Arthritis-International Database (PsArt-ID) is a prospective, multicenter registry in PsA that was initially developed in Turkey in 2014, with participation from Canada since 2015 and Italy since 2018⁹. Ethics approval was obtained from the local ethics committees [Hacettepe University Ethics Board, Ankara (GO 14/578); Ottawa Health Science Network Research Ethics Board, Ottawa (20160436-01H); Sacro Cuore-Don Calabria Hospital, Italy (F8MRG)] and all patients gave informed consent prior to data collection. Patients were consecutively placed in the registry with the aim of investigating real-life data using a Web-based system (www.trials-network.org), and the details of the registry have been previously published⁹. In addition, smoking status was categorized as never, current smoker, or ex-smoker at enrollment, with duration and intensity to calculate smoking packs-year. AxPsA definition was clinicians' decision of axPsA, based on inflammatory back pain according to the physician and the clinician's final judgment, but not mandating any imaging. However, whenever possible, radiographs of the sacroiliac joints (SIJ) were read and scored centrally by an experienced rheumatologist (SZA) blinded to the clinical data, and further analyses were made based on the imaging findings. Those readings were done according to the definitions used in the modified New York (mNY) classification criteria¹⁰ and radiographic sacroiliitis defined as \geq grade II both sides or \geq grade III unilaterally.

Statistical analysis. Two group comparisons were made by Fisher's exact, chi-square, Student t, or Mann-Whitney U tests, as appropriate. ANOVA or Kruskal-Wallis test was used in multiple groups' comparisons, with Bonferroni correction. Risk factors for axial disease based on the literature and clinically relevant factors were carried to multivariable analysis; they included age, sex, body mass index (BMI), disease duration, disease subtypes, disease activity scores, function, and C-reactive protein. They were tested in univariable analyses and factors with a significance level of $p < 0.05$. An intraobserver agreement analysis was done on 28 SIJ radiographs by reading the same images 3 months apart, which revealed good intraobserver agreement ($\kappa = 0.79$)¹¹. SPSS software (version 22.0, IBM Corp.) was used to conduct all statistical analyses.

RESULTS

Baseline characteristics. For this study, 1535 patients who had smoking data were included. Among these patients, 562 (36.6%) were male and the mean age was 46.9 (13.4) years. For smoking, 334 patients (21.8%) were current smokers, 324 (21.1%) had quit smoking, and 877 (57.1%) had never smoked (Table 1, and Supplementary Table 1, available from the authors on request).

The effect of smoking on disease outcomes. Current and ex-smokers were more frequently males (Supplementary Table 2, available from the authors on request). Ever-smoking was also more frequent in axPsA (48.2% vs 40.6%, $p = 0.006$). Current smokers were significantly younger than ex-smokers and non-smokers, and also had had more frequent nail disease. BMI was slightly lower in current smokers than ex-smokers and non-smokers (adjusted p value: current vs non-smoker = 0.04; current vs

ex-smoker = 0.05). Current smokers had axPsA more often than ex-smokers and non-smokers (Supplementary Table 2). **Disease characteristics in patients with and without axPsA.** According to the rheumatologist, 454 (29.6%) had axial involvement. Only 7.1% (109/1535) of patients with PsA had axial disease only, without peripheral arthritis. Patients with axPsA were more frequently males and younger compared to patients without axPsA (non-axPsA). There were more current smokers in axPsA patients than non-axPsA participants, compared to ex-smokers and non-smokers. Smoking pack-years were found similar between groups. Patients with axPsA also had more frequent nail disease (Table 1, and Supplementary Table 1, available from the authors on request).

Multivariable analyses for prediction of axial disease. Multivariable analysis to predict axPsA showed that younger age, male sex, current smoking, and nail disease were significant predictors for axPsA, whereas the presence of polyarticular peripheral arthritis and distal interphalangeal joint involvement were protective (Table 2). Ex-smoking did not have any effect on axPsA, similar to non-smokers.

The multivariable analysis was also repeated by excluding patients who did not fulfill the Classification Criteria for Psoriatic Arthritis (CASPAR), which revealed similar results (data not shown).

The effect of smoking on radiographic sacroiliitis. Of the patients with axPsA, 187 (41.2%) had available SIJ radiographs for central reading and 137 (73.2%) of them had radiographic sacroiliitis according to the mNY criteria. Current smoking was more frequent in patients with sacroiliitis (sacroiliitis vs no sacroiliitis: current smoking = 39% vs 20%; ex-smoking = 15.3% vs 20%; non-smoking = 45.3% vs 60%; $p = 0.05$). Smoking pack-years were higher in patients with sacroiliitis [16.7 (13.5) vs 10.9 (11.5), $p = 0.030$]. Patients with sacroiliitis had significantly higher Health Assessment Questionnaire (HAQ) score and lower BMI, whereas age, sex, disease characteristics, and activity scores were similar (Supplementary Table 3, available from the authors on request).

In the multivariable model, current smoking status and higher HAQ scores had increased risk for radiographic sacroiliitis (Table 3).

DISCUSSION

Smoking has been shown to be a risk factor in many immune-mediated diseases¹². There is a clear link between smoking and new bone formation, as demonstrated in AS and axSpA; however, the underlying mechanism has not been clearly understood^{13,14}. Previous studies suggest that smoking has effects on both cellular and humoral components of the immune system, which include leukocytosis, decreased leukocyte function, and increasing some of the cytokines and soluble receptors [interleukin (IL) 15,

Table 1. Demographic features of axial psoriatic arthritis (axPsA) and non-axial PsA (non-axPsA).

Variables	All Patients, n = 1535	AxPsA, n = 454	Non-axPsA, n = 1081	p
Age, yrs, mean (SD)	46.9 (± 13.4)	44.7 (± 13.3)	47.8 (± 13.3)	< 0.001
Male sex	562 (36.6)	201 (44.3)	361 (33.4)	< 0.001
Years of schooling, mean (SD)	9.5 (± 4.7)	10.5 (± 4.7)	9.1 (± 4.7)	< 0.001
Smoking status				
Never	877 (57.1)	235 (51.8)	642 (59.4)	< 0.001
Current	334 (21.8)	130 (28.6)	204 (18.9)	
Ex-smoker	324 (21.1)	89 (19.6)	235 (21.7)	
Pack-yrs, mean (SD)	15.7 (± 13.7)	14.8 (± 13.1)	16.1 (± 14.0)	0.34
BMI, mean (SD)	28.3 (± 5.2)	28.1 (± 5.2)	28.4 (± 5.3)	0.28
Psoriasis duration, yrs, mean (SD)	14.8 (± 11.8)	15.1 (± 11.5)	14.7 (± 11.9)	0.28
Psoriasis type				
Plaque	864/1132 (76.3)	256/351 (72.9)	608/781 (77.8)	0.23
Pustular	158/1132 (14.0)	52/351 (14.8)	106/781 (13.6)	
Plaque and pustular	49/1132 (4.3)	21/351 (6.0)	28/781 (3.6)	
Others	61/1132 (4.3)	22/351 (6.3)	39/781 (5.0)	
PsA disease duration, yrs	5.3 (7.0)	5.7 (7.5)	5.1 (6.8)	0.49
Psoriatic disease family history	534 (34.8)	164 (36.1)	370 (34.2)	0.43
Polyarticular disease	744 (48.5)	195 (43.0)	549 (50.8)	0.005
DIP involvement	230 (15.0)	49 (10.8)	181 (16.7)	0.004
Arthritis mutilans	3 (0.2)	0	3 (0.3)	NA
Nail involvement (ever)	738 (48.1)	246 (54.2)	527 (45.1)	0.005
Dactylitis (ever)	351/1450 (24.2)	99/435 (22.8)	252/1015 (24.8)	0.70
Enthesitis (ever)	364/1421 (25.6)	107/428 (25.0)	257/993 (25.9)	0.94
Achilles enthesitis (ever)	275/1421 (19.4)	87/428 (20.3)	188/993 (18.9)	0.50
Deformity	248/1198 (20.7)	68/359 (18.9)	180/839 (21.5)	0.33
Ankylosis	61/1198 (5.1)	21/359 (5.8)	40/839 (4.8)	0.43
Subluxation	49/1198 (4.1)	15/359 (4.2)	34/839 (4.0)	0.91
Decreased mobility	187/1198 (15.6)	51/359 (14.1)	136/839 (16.2)	0.36
Telescoping finger	6/1198 (0.5)	1/359 (0.3)	5/839 (0.6)	NA
Fulfillment of CASPAR criteria	1326 (86.4)	397 (87.4)	929 (85.9)	0.76

Values are n (%) unless otherwise specified. Values in bold face are statistically significant. BMI: body mass index; CASPAR: Classification for Psoriatic Arthritis criteria; DIP: distal interphalangeal joint; NA: not applicable; PsA: psoriatic arthritis.

Table 2. Univariable and multivariable analysis on factors associated with axial psoriatic arthritis.

Variables	Axial Disease, Present vs Absent			
	Univariable Analysis		Multivariate Analysis, n = 1528	
	OR	95% CI	OR	95% CI
Age	0.98	0.97–0.99	0.98	0.97–0.99
Sex (male vs female)	1.58	1.26–1.98	1.49	1.17–1.89
Smoking				
Current vs never	1.7	1.33–2.27	1.42	1.07–1.88
Ex-smoker vs never	1.03	0.77–1.37	0.97	0.71–1.31
Nail involvement, ever (presence vs absence)	1.41	1.13–1.76	1.43	1.14–1.80
Polyarthritis, ever (presence vs absence)	0.73	0.58–0.91	0.71	0.56–0.89
DIP involvement, ever (presence vs absence)	0.60	0.43–0.84	0.56	0.40–0.80

Values in bold face are statistically significant. DIP: distal interphalangeal joint.

IL-1Ra, IL-6, sIL-6R, and vascular endothelial growth factor receptor 3], as well as generation of reactive oxygen species. Smoking may be triggering the tissue hypoxia and increasing danger signals, similar to the effect of mechanical stress^{15,16}. We hypothesize that a similar relationship between

smoking and structural damage may also be underlying in patients with PsA. Herein we demonstrated that smoking is more linked to a specific phenotype in PsA: axial disease. In addition, current smoking also increased the risk of sacroiliitis with an OR of 6.6. These observations are parallel to

Table 3. Univariable and multivariable analysis of factors associated with radiographic sacroiliitis.

Variables	Radiographic Sacroiliitis, Present vs Absent			
	Univariable Analysis		Multivariable Analysis, n = 147	
	OR	95% CI	OR	95% CI
Smoking				
Current vs never	2.61	1.17–5.83	6.6	2.02–21.6
Ex-smoker vs never	1.01	0.42–2.42	1.05	0.35–3.14
PsA duration	1.07	1.00–1.14	1.05	0.97–1.12
BMI	0.93	0.87–0.99	0.93	0.85–1.01
Morning stiffness	1.01	1.00–1.02	1.00	0.99–1.01
HAQ	1.69	1.01–2.90	2.35	1.14–4.85

Values in bold face are statistically significant. PsA: psoriatic arthritis; BMI: body mass index; HAQ: Healthy Assessment Questionnaire.

what has been observed in AS. The differences across PsA studies can be due to the heterogeneity of the PsA population and representation of different subtypes with different frequencies.

AxPsA does not have a definition that is universally agreed upon. Some studies have used only the clinician's diagnosis¹⁷, whereas others have mandated the presence of sacroiliitis¹⁸. The definition of imaging findings was initially developed in AS. Because differences in imaging findings have been demonstrated in AS and axPsA, whether the same set of imaging criteria can be used in axPsA requires further testing. In addition, the inflammatory back pain (IBP) criteria were also developed for AS and we have previously shown that those criteria lack sensitivities in axPsA, mostly due to age at onset of symptoms. In another study, in axSpA patients with clear imaging findings, a subset of patients with psoriasis had the onset of back pain after the age of 45, raising a concern about the validity of the IBP criteria in axPsA. In the absence of a widely accepted definition, we have chosen the rheumatologists' decisions for axPsA because that would have implications on their management of the disease. The Assessment of Spondyloarthritis international Society and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis are currently working on the definition of axPsA criteria; it is hoped that will standardize future studies and registries.

AxPsA was reported in around 30% in our registry, comparable to the previous reports¹⁹. In addition to the effect of smoking, our study found similar results with the previously demonstrated risk factors for axPsA, such as younger age, male sex, and nail disease, supporting its external validation^{17,19}.

Our study has some limitations. Genetic data or biomarkers were not systematically collected; therefore, the effect of HLA-B27 could not be analyzed. The number of complete sets of spinal radiographs was low and could not be further evaluated. Also due to the cross-sectional design, our results cannot support conclusions on causal relationships.

Both axPsA and radiographic sacroiliitis are more frequent among current smokers, but not ex-smokers,

similar to the observations in AS. The differences between current and ex-smoking are intriguing. If smoking cessation is proven to reduce to risk of axPsA in prospective studies, it can be prioritized for the prevention of axPsA among patients with psoriasis.

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