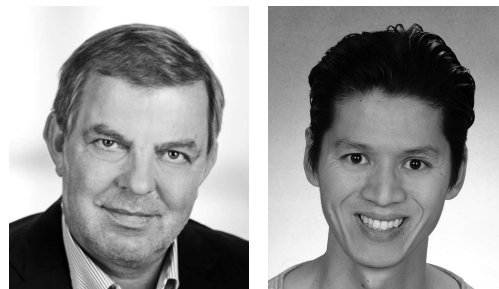


Smoking — Does It Affect Rheumatoid Arthritis Activity? Does It Matter?



For decades it has been common knowledge that there is a connection between rheumatoid factor–positive and antibodies against citrullinated peptide–positive rheumatoid arthritis (RA) and smoking¹. Cigarette smoking is regarded as one of the major environmental factors suggested to play a critical role in the development of a variety of disorders including autoimmune diseases such as RA, systemic lupus erythematosus, systemic sclerosis, multiple sclerosis, and Crohn's disease². It is safe to say that there is a widespread appreciation of the odiousness of smoking. However, does smoking also have an effect on actual disease activity and on the prognosis of patient outcome? Some statistical procedures, as well as some people, may nourish the illusion that there really is such a thing as a one-and-only risk factor. However, is this the case in reality? Is life really that simple?

Many aspects should be considered in relation to smoking and its consequences for patients with RA. Cigarette smoke represents a mixture of more than 4000 toxic substances including nicotine, polycyclic aromatic hydrocarbons, organic compounds, solvents, gas substances (primarily carbon monoxide), and free radicals. Extensive data suggest that smoking has a modulator role in the immune system contributing to a shift from Th type 1 to Th type 2 immune response³. Although there is consensus that smoking is highly likely to play a role in the pathogenesis of RA, does it also influence disease activity? The respective data are conflicting, but in the main they favor the hypothesis that cigarette smoking is associated with poorer responses. While some results indicate a weak but significant negative effect on function⁴, other publications report higher disease activity index levels in smokers than in nonsmokers, but with no effect of smoking cessation on RA activity⁵. In an early RA cohort current smoking status was associated with a 4-fold higher risk for not achieving an American College of Rheumatology 50 response after adjustment for low level of formal education, sex, age in years, and Clinical Disease Activity Index baseline value⁶. In the BARFOT cohort,

significantly fewer current smokers were in remission at 1 year compared to previous smokers or those who never smoked. Current smoking at inclusion independently predicted poor European League Against Rheumatism response during up to 12 months of followup. However, most intriguingly, stopping smoking did not make a difference in treatment response⁷.

In this issue of *The Journal*, Inoue, *et al* demonstrated an effect of smoking status on remission proportions between male and female RA patients and concluded that both sex and smoking status should be considered before treatment decisions are made⁸.

Aside from the fact that the therapeutic scope of inflammatory rheumatic diseases, and of RA in particular, has increased dramatically over the last 20 years, leading to much better chances for the patients, the question of which medication would be optimal for an individual patient has not yet been even partially answered. Thus any support in that respect would be very much appreciated by rheumatologists. However, any of these possibly discriminating factors has to be critically evaluated before being introduced into the therapeutic considerations. With regard to smoking and to the methods of disease activity assessment, some thoughts are provided to contribute to discussions that one hopes would bring us a few steps closer to the personalization of RA therapy.

Regarding cigarette consumption, the prevalence of smoking in Austria in 2006 was 27% in males and 19% in females, with an increasing trend over the last decades. Given that the prevalence of RA in Austria is 0.62%, it can be calculated that there are about 5000 female and 6800 male patients with RA who smoke⁹. The respective numbers from Japan in 2011 show that roughly 34% of the male and 11% of the female population are smokers¹⁰. Given the prevalence of RA in Japan, derived from the same cohort as the remission proportions¹¹, which is comparable to the one in Austria, and indeed in contrast to previous publications, it

See Sex differences and smoking, page 1083

can be assumed that about 124,000 male and 41,800 female patients with RA in Japan are smokers. The comparison of both numbers reveals a remarkable difference. While in Austria the absolute number of male and female RA patients who smoke differs only to a small extent, in Japan 3 times more male than female RA patients smoke. This underlines the sociological differences and thereby the significance that smoking status may exert in different cultures, making direct transferability of the results difficult in a disease preferentially affecting women. Thus, sex differences, (e.g., current female smokers show insignificant but lower disease activity score results vs current male smokers), as described in the article by Inoue, *et al*, may express sociological changes in the population to a greater extent than smoking-dependent issues, which is indeed discussed by the authors and can only be elucidated by a longterm observation⁸.

This leads to another important aspect of the relationship between smoking and RA. Position in society, income, professional position, educational status, familial circumstances, and other issues are well known to be related to smoking and RA prevalence, as well as to RA disease activity¹². Thus, it could be the case, at least on an individual basis, that changes in these socioeconomic factors could contribute to either RA remission and/or smoking status.

Although those risk factors are mostly regarded as sex-independent and may therefore be of lesser significance for the question of whether smoking exerts a sex-dependent effect on RA, the answer is not yet conclusively given to the question of whether males have milder disease *per se* or are simply “favored” by the activity assessment instruments most frequently applied in studies.

We and others have shown unequivocally that female patients have significantly higher Disease Activity Score 28 levels than males and this also holds true for all the other instruments applied in routine RA disease activity assessment^{13,14,15}. In our observations the respective difference is a result of significantly higher joint counts, patient’s assessment of global health, and erythrocyte sedimentation rate values in females. These results could support the idea that, in general, males have milder RA. Interestingly, however, patients’ self-pain rating did not differ significantly between female and male patients, and the C-reactive protein levels were found to be in the same range, with the latter indicating no differences in systemic inflammatory activity.

Whatever the reasons for the sex-related differences in disease activity index levels (i.e., sex-dependent variations in disease activity itself or just confounding factors), applying the same thresholds for RA activity in females and males should be thoroughly discussed in the light of personalized treatment strategies.

Irrespective of all the arguments discussed above, cigarette smoking remains one of the most important risk factors for cardiovascular diseases in general; and RA itself is regarded as a major risk factor for cardiovascular

diseases¹⁶. Therefore, aside from the possible effects on disease activity and regardless of whether there are smoking and sex-related differences, the only advice for patients is to quit cigarette smoking if they want to improve their health and life expectancy.

BURKHARD F. LEEB, MD,

2nd Department of Medicine,
Center for Rheumatology, Lower Austria,
State Hospital Stockerau;
Karl Landsteiner Institute for Clinical Rheumatology, Stockerau;
Department for Rheumatology and Immunology,
Medical University of Graz, Graz;

HARSONO T.H. MAI, MD,

2nd Department of Medicine,
Center for Rheumatology, Lower Austria,
State Hospital Stockerau;
Karl Landsteiner Institute for Clinical Rheumatology,
Stockerau, Austria.

Address correspondence to Dr. B.F. Leeb, 2nd Dept. of Medicine, Center for Rheumatology, Lower Austria, Landstrasse 18, Karl Landsteiner Institute for Clinical Rheumatology, Stockerau, A-2000, Austria.
E-mail: burkhard.leeb@stockerau.lknoe.at

REFERENCES

1. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther* 2014;16:R61.
2. Costenbader KH, Karlson EW. Cigarette smoking and autoimmune disease: what can we learn from epidemiology? *Lupus* 2006; 15:737-45.
3. Baka Z, Buzás E, Nagy G. Rheumatoid arthritis and smoking: putting the pieces together. *Arthritis Res Ther* 2009;11:238.
4. Lu B, Rho YH, Cui J, Iannaccone CK, Frits ML, Karlson EW, et al. Associations of smoking and alcohol consumption with disease activity and functional status in rheumatoid arthritis. *J Rheumatol* 2014;41:24-30.
5. Fisher MC, Hochberg MC, El-Taha M, Kremer JM, Peng C, Greenberg JD, CORRONA Investigators. Smoking, smoking cessation, and disease activity in a large cohort of patients with rheumatoid arthritis. *J Rheumatol* 2012;39:904-9.
6. Rojas-Serrano J, Pérez LL, García CG, Moctezuma F, Álvarez-Hernández E, Vázquez-Mellado J, et al. Current smoking status is associated to a non-ACR 50 response in early rheumatoid arthritis. A cohort study. *Clin Rheumatol* 2011;30:1589-93.
7. Söderlin MK, Bergman S; BARFOT Study Group. Absent “window of opportunity” in smokers with short disease duration. Data from BARFOT, a multicentre study of early rheumatoid arthritis. *J Rheumatol* 2011;38:2160-8.
8. Inoue Y, Nakajima A, Tanaka E, Inoue E, Kobayashi A, Hoshi D, et al. Impact of smoking on remission proportions differs between male and female rheumatoid arthritis patients: a study based on the IORRA. *J Rheumatol* 2015;42:1083-9.
9. Statistik Austria. Smoking [in German]. [Internet. Accessed May 4, 2015.] Available from: www.statistik.at/web_de/statistiken/gesundheit/gesundheitsdeterminanten/rauchen/
10. Knoema data atlas. Smoking [German]. [Internet. Accessed May 4, 2015.] Available from: <http://knoema.de/atlas/Japan/topics/Gesundheit/Risikofaktoren/Raucherpr%C3%A4valenz-Frauen>
11. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort. *Mod Rheumatol*

- 2014;24:33-40.
12. Schnohr C, Hojbjerg L, Riegels M, Ledet L, Larsen T, Schultz-Larsen K, et al. Does educational level influence the effects of smoking, alcohol, physical activity, and obesity on mortality? A prospective population study. *Scand J Public Health* 2004;32:250-6.
 13. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther* 2009;11:R7.
 14. Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Disease activity score-28 values differ considerably depending on patient's pain perception and sex. *J Rheumatol* 2007;34:2382-7.
 15. Rintelen B, Haindl PM, Maktari A, Nothnagl T, Hartl E, Leeb BF. SDAI/CDAI-levels in rheumatoid arthritis patients are highly determined by patient's pain perception and gender. *Scand J Rheumatol* 2008;37:410-3.
 16. Crowson CS, Liao KP, Davis JM III, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. *Am Heart J* 2013;166:622-8.e1

J Rheumatol 2015;42:1072-4; doi:10.3899/jrheum.150491