Cadmium the missing link between smoking and increased rheumatoid disease activity?

Ospelt *et al*¹ have observed a number of important and interesting observations in their paper “Smoking induces transcription of the heat shock protein system in the joints”. It was observed that when synovial fibroblasts were incubated with 5% cigarette smoke extract there was a significant upregulation of the heat shock proteins DnaJA4, DnaJB4, DnaJC6, HspB8 and Hsp70. This important scientific work follows on from the overwhelming epidemiological evidence that smoking is associated with rheumatoid arthritis (RA). A meta-analysis of seven case control and three prospective cohort studies demonstrated a doubling of risk of developing RA (RR 2.07 95% CI 1.15 to 3.73) when comparing those with the highest cumulative exposure versus those with the lowest.²

Ospelt *et al* correctly comment in their paper that cigarette smoke contains potentially hundreds of chemicals that may have a deleterious effect on health. We propose that one such hazardous component of cigarette smoke is cadmium and could account for the observations made by Ospelt *et al*. The mean whole blood cadmium concentration in smokers is reported as double that of in non-smokers ($2.67 \pm 1.21 \mu\text{g/L}$ vs $1.37 \pm 0.45 \mu\text{g/L}$).³ Diet is the main source of cadmium exposure in non-smokers.⁴ Intestinal absorption is increased in those with iron deficiency and higher levels of cadmium are found in women of childbearing age than age-matched men.⁵

Increased cadmium exposure has been observed in men with RA irrespective of smoking history⁶ and is observed in the synovial fluid of patients with RA.⁷ Cadmium inhalation has been linked to the development of chronic obstructive pulmonary disease (COPD).⁸ COPD has a number of striking similarities to RA. COPD and RA are associated with cigarette smoking, upregulation of interleukin (IL)-8 and subsequent neutrophil and macrophage infiltration, activation of matrix metalloproteinases and increased fibroblast activation (reviewed in⁹).

A study of the effects of low cadmium concentrations in HepG2 cells demonstrated an upregulation of Hsp70 and IL-8^{10 11} and it is noteworthy that cigarette smoke extract upregulates IL-8 production by synovial fibroblasts.¹²

It would be interesting to know if the observations made by Ospelt could be reproduced with a solution of cadmium sulfate at a concentration commensurate with the concentration of cadmium observed in the synovial fluid of long-standing smokers with RA. Additionally a cadmium chelating agent could be added to the cigarette condensate used by Ospelt *et al* to determine if their important observations can still be observed independent of cadmium.

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Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Cates M, Hutchinson D. *Ann Rheum Dis* 2015;**74**:e1.

Received 26 August 2014

Accepted 6 September 2014

Published Online First 23 September 2014

► <http://dx.doi.org/10.1136/annrheumdis-2014-206590>

Ann Rheum Dis 2015;**74**:e1. doi:10.1136/annrheumdis-2014-206538

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