

Elevated serum levels of alarmin S100A8/A9 in patients with hand osteoarthritis

Sirs,

Hand osteoarthritis (HOA) is one of the major forms of OA. While biomechanical factors arguably play a minor, or different, role compared to knee or hip joints, genetic predisposition (1) and inflammation (2) are major factors in its pathogenesis. In HOA, a well-recognised subset of patients presents with an erosive/inflammatory disease with a high burden of pain and disability (3). To date, the search for circulating inflammatory biomarkers in HOA has been extremely frustrating. Conflicting data on C-reactive protein (CRP) and minor elevations of other markers such as myeloperoxidase and vascular cell adhesion molecule (VCAM)-1 (4-6) have hampered the possible use of biomarkers in detecting and monitoring inflammation in HOA.

S100A8/A9 has been described as alarmin which is secreted by activated phagocytes as monocytes and neutrophils at sites of inflammation. They are part of the molecular paraphernalia of innate immunity (7). Their role in experimental OA is well demonstrated (8, 9) and data supporting a role for the S100A8/A9 alarmin as prognostic biomarker in human OA have been produced (8, 9).

We evaluated levels of circulating alarmins in 294 patients with HOA (mean age \pm SD: 68 \pm 5; female 93%; BMI median, range: 25.3, 17.8–39; disease duration, median, range: 25.3 817.8–39.0). All patients had a radiographic diagnosis: at least one IP joint with Kellgren-Lawrence score \geq 2 was observed. Informed consent from the patients and approval by the ethics committee of our hospital was obtained.

Sera were also obtained from age-matched 100 normal controls (NC). X-ray images from HOA patients were quantified utilising Kellgren-Lawrence and OARSI scores. On the basis of the presence of the characteristic central bone erosions in IP joints, patients were divided into three groups: Group 0 = no central erosion detected, Group 1 = central erosion detected in one IP joint, Group 2 = central erosions detected in 2 or more IP joints. Furthermore, patients were sub-grouped into lone HOA patients = patients without clinical signs of knee and/or hip OA, and generalised OA patients = patients with clinical and/or radiographic OA of the knee and/or hip in addition to HOA. In patients without symptoms and clinical signs of knee and/or hip OA radiographic imaging was not performed due to ethical reasons.

Serum concentrations of S100A8/A9 were determined using a sandwich enzyme-linked immunosorbent assay as previously reported (10). Patients with HOA had serum levels of S100A8/A9 significantly higher than those seen in NCs (Fig. 1). No difference was observed in serum alarmin levels between lone HOA and generalised OA sub-groups, both having higher levels than NCs. Indeed, disease erosiveness was not related to alarmin levels: group 0, 1 and 2 showed similar levels of

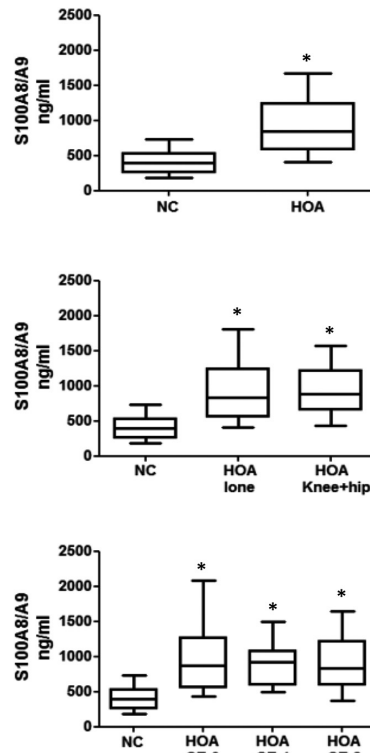


Fig. 1. Serum levels of S100A8/A9 in controls and patients.

The results are expressed as median and boxes indicating the 25th and 75th percentiles. Whiskers indicate the 10th and 90th percentiles. NC: normal controls; HOA: hand osteoarthritis; Lone HOA: patients with only HOA; Knee + hip HOA: patients with generalised OA; CE 0: patients without central erosions CE 1: patients with one central erosion; CE 2: patients with two or more central erosions.

The Mann-Whitney (two independent groups) or the Kruskal Wallis tests (multiple independent groups) were used. When the Kruskal Wallis test was significant, Dunn's post-hoc correction for multiple comparisons was used. * $p < 0.001$ vs. NC.

alarmins which were always higher than those seen in NCs (Fig. 1).

Finally, S100A8/A9 levels did not show correlations with disease duration, osteophyte score, Joint Space Narrowing score (data not shown). A direct association with BMI values was found: ($\rho = 0.141$, 95% CI: 0.021–0.258, $p = 0.018$) (Spearman's correlation analysis).

Our findings show that serum alarmin levels are significantly elevated in patients with HOA, irrespective of the erosiveness of disease and of the involvement of other joints, suggesting that inflammation is a constant feature of HOA and is probably involved in its pathogenesis. Circulating S100A8/A9 alarmin levels probably reflect inflammation more accurately than CRP, due to conflicting results on CRP elevation in HOA (4, 5).

Further studies to confirm our data are necessary and, in particular, studies on patients in the early phase of HOA. In addition, longitudinal studies will provide data on the role of inflammation/innate immunity activation in the pathogenesis of HOA and the role of serum S100A8/A9 alarmin levels as prognostic biomarker, as already suggested in knee or hip OA.

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O. ADDIMANDA^{1,2}, MD
L. PULSATELLI¹, BSc
T. VOGL³, MD
J. ROTH³, MD
L. MANCARELLA¹, MD
E. ASSIRELLI¹, BSc
R. RAMONDA⁴, MD
A. FIORAVANTI⁵, MD
R. MELICONI^{1,2}, MD

¹IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy;

²Dept. of Biomedical and Neuromotor Sciences,

University of Bologna, Italy; ³Institute of

Immunology, University of Münster, Germany;

⁴Division of Rheumatology, Dept. of Medicine

DIMED, University of Padova, Italy; ⁵Division of

Rheumatology, Dept. of Medical Sciences, Surgery

and Neurosciences, University of Siena, Italy.

Please address correspondence to:

Dr Olga Addimanda,

Medicine and Rheumatology Unit,

IRCCS Istituto Ortopedico Rizzoli,

40136 Bologna, Italy.

E-mail: olga.addimanda@ior.it

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