

Serum hyaluronic acid as a potential marker with a predictive value for further radiographic progression of hand osteoarthritis

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Summary

Objective: To compare serum levels of hyaluronic acid (HA) between patients with erosive and non-erosive hand osteoarthritis (HOA), and investigate its association with morphological changes and radiographic progression over 2 years.

Methods: Fifty-five women with erosive and 33 women with non-erosive HOA were included in this study. All underwent clinical examination, which included assessment of pain, swelling, deformity and deviation of small hand joints and completed health assessment questionnaires. Serum levels of HA were measured by ELISA. Three-phase bone scintigraphy was performed at baseline. Radiographs of both hands were performed at baseline and after 2 years and scored according Kallman grading scale.

Results: Serum levels of HA were significantly higher in patients with erosive than with non-erosive HOA ($P < 0.01$). It correlated significantly with the number of hand joints with deviations and deformities. HA adjusted for age and disease duration significantly correlated with radiographs at baseline and after 2 years in all patients with HOA ($r = 0.560$ and $r = 0.542$, $P < 0.01$ for both correlations). Although there was an association between HA and radiographic score in erosive disease, after adjustment for confounders it remained no longer significant. HA adjusted for confounders correlated significantly with the late phase in all patients with HOA ($r = 0.412$, $P < 0.01$) and in patients with erosive disease ($r = 0.320$, $P < 0.05$).

Conclusion: HA is increased in patients with erosive HOA and could be proposed as a surrogate marker with a predictive value for further radiographic progression of HOA in general. Further investigation is necessary to confirm these results.

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Key words: Hyaluronic acid, Biomarkers, Hand osteoarthritis, Erosive disease, Scintigraphy.

Introduction

Erosive osteoarthritis (OA) is a subset of hand OA (HOA) with prominent local inflammation of hand joints defined radiographically by subchondral erosion, cortical destruction and subsequent reparative change¹. There is a strong familial predisposition and most typically middle-aged women are affected. OA is commonly classified as a “non-inflammatory” arthropathy, however, serum C-reactive protein (CRP) has been found to be moderately increased compared to healthy population and has been proposed as a marker of disease severity in patients with OA of the hips and knees^{2,3}. Although systemic levels of CRP may be increased by synovial inflammation, conclusive evidence that CRP corresponds to the activity of the erosive disease is still missing^{4–7}.

The diagnosis of OA is generally based on clinical and radiographic findings, which occur fairly late and are insufficient for the prediction of disease progression. Biological markers of the degradation, synthesis or inflammation that play key functional roles in the joint tissue, might help to detect OA at much earlier stages than the imaging techniques or identify patients at high risk of rapidly progressive joint destruction^{8,9}.

Hyaluronic acid (HA) is crucial for the structural and functional integrity of articular cartilage and responsible for unique viscoelastic properties of the synovial fluid^{10,11}. It is generally considered as a marker of synovitis. Higher levels of HA in synovial fluid in comparison with serum were reported in patients with rheumatoid arthritis (RA) and OA, suggesting its local production¹². Moreover, serum HA levels were shown to be elevated in patients with OA^{9,12–14} and demonstrated as a possible predictive factor for further development of OA of the knees and hips^{13,15,16}.

The aim of the study was to compare serum levels of HA between patients with erosive and non-erosive HOA, and investigate its potential association with morphological changes and radiographic progression over 2 years.

Methods

PATIENTS

Eighty-eight women between the ages of 52 and 72 years presenting with HOA were recruited into this study from the out-patient Rheumatology Clinic. All the patients fulfilled the American College of Rheumatology (ACR) criteria for HOA¹⁷ and patients with erosive HOA fulfilled those criteria and had radiographic signs of erosions of the articular surface (Supplementary material). One single erosion of proximal or distal interphalangeal joint was sufficient to consider the disease erosive. We extended the group of patients with HOA that had been studied in our previous work¹⁸. Patient's characteristics at the study entry are given in Table 1. Written informed consent from each patient was obtained prior to enrollment and the study was approved by the local ethic committee.

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All patients were subjected to health assessment questionnaires. To evaluate HOA pain, stiffness and difficulties with daily activities during the preceding 48 h, Australian Canadian OA hand index (AUSCAN) was performed¹⁹. The functional index for HOA (FIHOA), a 10-item investigator-administered questionnaire, was evaluated²⁰. Clinical examination was performed by skilled rheumatologists. Positive hand joints for swelling, pain, deformity and deviation were evaluated by clinical examination at baseline. The deformity included both Heberden and Bouchard nodes. The deviation was assessed as any difference between the normal, natural axis of the joint and the actual direction of a finger either ulnar or radial.

IMAGE ANALYSIS

Postero-anterior plain radiographs of both hands were performed at baseline and after 2 years of follow-up and were scored by trained reader according to Kallman grading scale²¹. Individual joints were assessed for the presence of osteophytes (graded 0–3), joint space narrowing (0–3), subchondral sclerosis (0–1), subchondral cysts (0–1), lateral deformity (0–1), and collapse of central joint cortical bone (0–1). For radiographic imaging of the knees, a technique with knee in extension was used as described earlier²² and scored according to the Kellgren and Lawrence (K–L) grading system, Steinbrocker's modification²³.

Ultrasonography of both knees was performed by an experienced radiologist at baseline. For the purpose of this study, presence or absence of knee joint effusion and/or synovial edema was evaluated.

Three-phase bone scintigraphy was performed following a bolus injection of 600 MBq of Tc-99m methylene diphosphonate (MDP) into an antecubital vein. Blood pool (second phase) images were obtained after 10 min; late (third phase) images were acquired after 2.5 h after 99Tc-MDP application. All the planar anterior images focused on small hand joints were interpreted by the same radiologist. Following regions of joints of the hand were determined: proximal and distal interphalangeal, metacarpophalangeal, carpometacarpal, intercarpal and radiocarpal joints of both hands. Hand joints were considered inflamed when blood pool images indicated increased indicator uptake. Osteoblastic activity presenting bone remodeling was established by increased indicator uptake in the late phase. For the purpose of this study, total number of positive joints was calculated.

LABORATORY MEASUREMENTS

Peripheral blood was withdrawn at baseline from all patients. Collected blood serum was stored at -80°C until all the samples were analyzed. CRP levels were determined by the immuno-turbidimetric technique (high sensitivity CRP) using biochemical analyzer Olympus (model AU 400, Japan). HA serum levels were measured by commercially available ELISA assays according to the manufacturer's protocol (Corgenix HA Test kit, Corgenix Inc., USA). The absorbance was measured at 450 nm by Enzyme-Linked Immunosorbent Assay (ELISA) reader (Tecan Sunrise, Austria). Normal range of HA provided in the ELISA kit is 0–75 ng/ml.

STATISTICAL ANALYSIS

Data were expressed as means and standard deviation (SD) or standard error of the mean (s.e.m.). The Mann Whitney *U* test was used for the comparison between two variables. *P* values less than 0.05 were considered statistically significant. Spearman's correlation coefficient was used to determine the statistical significance. Pearson correlation coefficient was used after the adjustment of HA levels for confounders (age and disease duration). The analysis was performed using SPSS 13.0 for Windows and the graphs were created by GraphPad Prism 5 (version 5.02; GraphPad Software, La Jolla, CA, USA).

Table I
Initial characteristic of women with erosive and non-erosive HOA

Characteristics	Erosive HOA	Non-erosive HOA	<i>P</i>
Age (years)	64.20 ± 8.05	62.55 ± 9.81	0.572
Sex (F/M)	55/0	33/0	NA
BMI (kg/m ²)	26.83 ± 3.67	26.31 ± 4.78	0.538
Disease duration (years)	10.20 ± 8.61	7.30 ± 5.37	0.207
AUSCAN (15–75)	41.15 ± 10.86	33.27 ± 9.72	0.001
FIHOA (10–40)	18.07 ± 4.56	15.36 ± 4.33	0.001
SYSA DOA (%)	78.18	66.67	0.239
NSAID (%)	20.00	6.06	0.045
hs-CRP (mg/l)	1.93 ± 1.68	2.77 ± 6.09	0.599
ESR	14.74 ± 10.33	15.08 ± 10.10	0.808

NA, not applicable. Values are in means ± SD.

Results

CLINICAL AND DEMOGRAPHIC DATA

Female patients with HOA were divided into two groups that consisted of 33 individuals with non-erosive HOA and 55 individuals with erosive disease. Both groups were comparable in terms of age, disease duration and body mass index (BMI). Moreover, inflammatory marker hs-CRP and erythrocyte sedimentation rate (ESR) were comparable between both groups (Table I). Patients with erosive HOA seem to suffer with more pain, stiffness and restriction in daily activities as assessed by both total AUSCAN score and FIHOA index and more of them were on regular treatment with non-steroidal anti-inflammatory drugs (NSAIDs) compared to patients with non-erosive HOA (Table I). Treatment with symptomatic slow acting drugs in OA (SYSADOA) did not differ between the studied groups. Clinical investigation of the hand joints showed more severe course of the disease in erosive HOA patients manifested by significantly higher number of joints with effusion, pain, deviation and deformity (Table II).

Out of 55 patients with erosive HOA, 42 radiographs were scored according Kallman grading scale at baseline and 31 were available after 2 years of follow-up. Out of 33 patients with non-erosive HOA, 26 hand radiographs were scored according Kallman grading scale at baseline and 22 were available after 2 years of follow-up. Patients with erosive HOA exhibited 1–19 erosions (mean ± SD: 8.18 ± 4.89; Table II). As expected, patients with erosive HOA compared to non-erosive HOA had more severely affected hand joints at baseline and after 2 years. The mean radiographic

Table II
Clinical assessment of small hand joints in women with erosive and non-erosive HOA

Feature	Erosive HOA	Non-erosive HOA	<i>P</i>
Physical investigation (mean count of joints ± SD)			
Deformity	10.53 ± 4.37	8.22 ± 4.43	0.019
Deviation	4.05 ± 2.85	1.56 ± 2.03	0.001
Pain	8.33 ± 4.12	5.53 ± 3.93	0.004
Effusion	3.89 ± 3.68	2.22 ± 2.78	0.028
Radiographs			
Number of radiographs read at			
Baseline	42/55	26/33	NA
After 2 years	31/55	22/33	NA
Kallman score (mean ± SD)			
Baseline	58.30 ± 28.1	26.56 ± 18.28	0.001
After 2 years	60.97 ± 27.86	26.26 ± 18.44	0.001
Δ (progression)	2.41 ± 3.06	0.57 ± 1.07	0.002
Erosions (number ± SD)	8.18 ± 4.89	0	0.001
OA of the knee (present/all)	27/53	18/31	0.530
Arthrosonography of the knee			
Synovial edema (positive/all)	8/54	5/32	0.920
Effusion (positive/all)	21/54	16/32	0.317
Three-phase bone scintigraphy			
Number of scintigrams			
Count of inflamed joints (mean ± SD)	3.06 ± 2.26	1.82 ± 3.02	0.001
Count of remodeled joints (mean ± SD)	8.60 ± 4.74	4.07 ± 4.28	0.001

progression (Δ Kallman score) within 2 years was four times faster in erosive than in non-erosive disease (Table II). Knee radiographs were available in 53 out of 55 patients from the group of erosive HOA patients and in 31 out of 33 patients from the group with non-erosive HOA. Prevalence of OA of the knee between both groups was comparable (Table II). Arthrosonography of the knee was available in 54 out of 55 patients from the group of erosive HOA and in 32 out of 33 patients from non-erosive HOA. Presence of synovial edema and intra-articular effusion of the knees also did not differ between studied groups (Table II). Three-phase bone scintigraphy was performed at baseline in 52 out of 55 patients with erosive HOA and in 29 out of 33 patients with non-erosive HOA. The total count of joints of the hand affected by inflammation and bone remodeling as assessed by blood pool and late phase scintigraphy, respectively, was significantly higher in patients with erosive compared to non-erosive HOA (Table II).

HA AND STRUCTURAL CHANGES IN HOA

HA significantly correlated with both age ($r=0.448$, $P<0.01$) as well as disease duration ($r=0.333$, $P<0.01$), but not with BMI ($r=0.195$, $P=0.09$) or treatment with NSAIDs ($r=-0.074$, $P=0.580$) in all patients with HOA. Serum levels of HA were significantly higher in patients with erosive than in non-erosive HOA [78.53 ± 51.31 vs 50.45 ± 41.25 ng/ml, $P<0.01$; Fig. 1(A)] and this finding remained significant also after adjustment for age and disease duration [78.53 ± 23.59 vs 50.45 ± 22.72 ng/ml, $P<0.01$; Fig. 1(B)]. In all HOA patients, HA levels significantly correlated with the number of positive hand joints for clinically assessed deviations and deformities ($r=0.397$ and $r=0.399$, $P<0.01$ for both correlations). These results remained statistically significant only in the group of patients with erosive disease ($r=0.318$, $P<0.01$ for deviations and $r=0.382$, $P<0.01$ for deformities), but not in patients with non-erosive HOA ($r=0.340$, $P=0.066$ for deviations and $r=0.294$, $P=0.115$ for deformities). On the other hand, HA levels correlated neither with clinically assessed hand joint swelling nor pain (data not shown). Serum levels of HA were not affected by the presence of knee joint effusion or synovial edema as assessed by arthrosonography in patients with erosive as well as non-erosive HOA (data not shown).

Serum HA levels significantly correlated with the total count of joints with osteoblastic remodeling as assessed by late phase scintigraphy ($r=0.291$, $P<0.01$) in all

patients with HOA, but not with the total count of inflamed joints as assessed by blood pool phase. This significant association was demonstrated for both groups together but not for each group separately. After adjustment for age and disease duration, the abovementioned finding remained significant in all patients with HOA ($r=0.412$, $P<0.01$) and became significant in patients with erosive disease ($r=0.320$, $P=0.05$) but not in those with non-erosive disease ($r=0.094$, $P=0.637$). Furthermore, HA levels significantly correlated with radiographic findings assessed by Kallman radiographic score at baseline in erosive and non-erosive HOA patients ($r=0.402$, $P<0.05$ and $r=0.597$, $P<0.01$, respectively). After 2 years it also correlated significantly with the radiographic findings in patients with both erosive HOA ($r=0.391$, $P<0.05$) and non-erosive HOA ($r=0.634$, $P<0.01$). However, after adjustment for age and disease duration, the correlation remained statistically significant in the group of patients with non-erosive disease at both time points ($r=0.416$, $P<0.05$ at the baseline; $r=0.505$, $P<0.05$ after 2 years) but remained no longer significant in erosive HOA patients ($r=0.287$, $P=0.10$ at the baseline; $r=0.334$, $P=0.10$ after 2 years). The correlation between HA and Kallman score in all HOA patients was significant at the beginning and after 2 years of follow-up ($r=0.518$, $P<0.01$; $r=0.519$, $P<0.01$, respectively) and this findings remained significant also after adjustment for age and disease duration ($r=0.560$, $P<0.01$ and $r=0.542$, $P<0.01$; Fig. 2).

Interestingly, CRP was neither elevated in patients with erosive compared to non-erosive HOA nor was associated with scintigraphic assessment of the total count of positive hand joints or radiographic findings in both groups of HOA patients (data not shown).

Discussion

In this study, we demonstrated for the first time higher serum levels of HA in patients with erosive than in non-erosive HOA. In addition, HA was associated with the local morphological and structural changes as well as with the further radiographic progression of the disease.

Pain, swelling, redness, warmth and restricted function of small joints of the hand represent the most characteristic clinical symptoms for the most patients with erosive HOA²⁴. Our clinical assessment could confirm more severe disease course in patients with erosive than non-erosive HOA. This impairment resulted in the significant limitation of daily activities in patients with erosive than in non-erosive

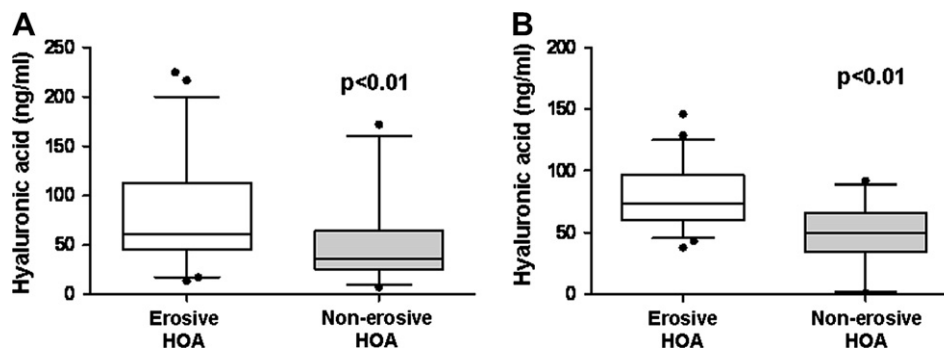


Fig. 1. Increased serum levels of HA in patients with erosive HOA compared with non-erosive HOA without (A) and with (B) adjustment for age and disease duration. Horizontal solid bar within the boxes represents the median, the boxes represent a range of 25% around the median. Vertical bars indicate 95% confidential interval (CI).

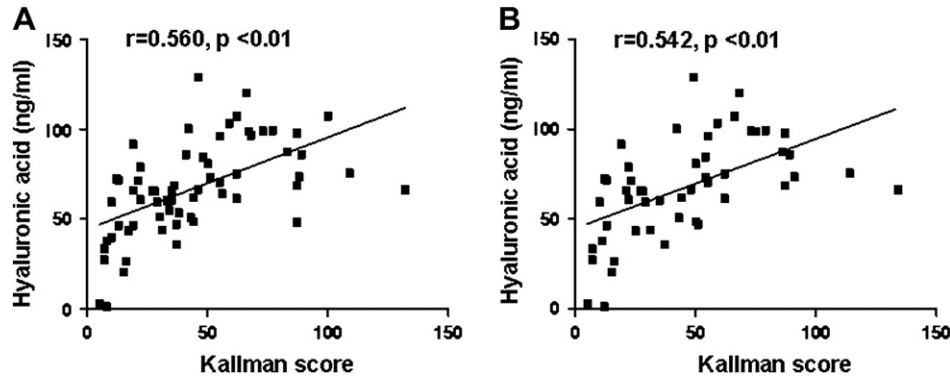


Fig. 2. Association of serum levels of HA adjusted for age and disease duration with Kallman radiographic score of small hand joints at the beginning (A) and after 2 years (B) of the study in the patients with HOA.

HOA as revealed by total AUSCAN score and FIHOA that is in line with another recent study²⁵.

Few studies have investigated biochemical markers in erosive HOA patients. Punzi *et al.*⁶ reported higher levels of CRP in erosive than in non-erosive HOA patients and proposed CRP as a marker of disease activity of erosive HOA as assessed by clinical findings and bone scintigraphy. Contrary, lower systemic inflammatory markers in erosive compared to non-erosive disease have also been previously described⁵. In the present study, we observed no differences in the serum CRP levels between erosive and non-erosive HOA despite the fact that bone scintigraphy revealed significantly more affected small hand joints in erosive disease. We suggest that local inflammatory changes might not be as intensive to induce systemic inflammatory response in patients with HOA, at least in our study.

In normal joint, functional and metabolic activities of HA depend on its high concentration and high molecular weight²⁶. During inflammation, reactive free radicals from neutrophils in synovial fluid damage and depolymerize HA that leads to reduction of its high molecular weight^{27–29}. It contributes to reduction in synovial fluid viscosity and to dialysis of HA fragments and disaccharide monomers into the circulation^{30,31}. Soluble pro-inflammatory cytokines including interleukin (IL)-1 and tumor necrosis factor (TNF)- α can also be responsible for the synovial production of HA³². Small HA oligosaccharides in the joint antagonize with high molecular mass HA, interfere with the normal chondrocyte–matrix interactions^{33,34}, activate production and activity of matrix metalloproteinases, nitric oxide synthesis by articular chondrocytes and inflammatory cells^{35–37}. This process is involved in OA pathogenesis and it can be suggested that increased serum levels of HA in patients with erosive HOA can reflect synovial inflammation and destruction of OA cartilage in erosive disease. Moreover, very recently, Chen *et al.*³⁸ demonstrated increased HA in OA patients associated with clinical phenotypes of HOA or hand symptoms in comparison to those without involvement of hand joints. In fact, there is still lack of studies analyzing biomarkers in erosive and non-erosive HOA³⁹, and to our knowledge, our study is the first report presenting higher levels of serum HA in patients with erosive compared with non-erosive HOA.

Bone scintigraphy was suggested to be useful tool for predicting clinical and radiographic progression in patients with HOA⁵. In the present study, serum HA levels correlated with the total count of small hand joints positive in bone phase scintigraphy and one can thus speculate that this

finding could explain the association of HA with small hand joint morphological changes that were observed. Moreover, age and disease duration seems to affect this result, because after adjustment for these confounders the finding became more significant even in patients with erosive HOA. More interestingly, initial HA levels were significantly associated with the degree of radiographic changes at baseline and also after 2 years of follow-up. These data are in agreement with previous studies demonstrating HA as a surrogate marker with the predictive value for further radiographic progression of the knee and hip OA^{15,16,40,41}. In our study, HA levels were positively associated with the age and duration of the disease. When adjusted for these confounders, positive relationship between HA and radiographic findings remained unchanged in all patients with HOA, but was no longer significant in patients with erosive disease.

However, this study has some limitations. First, OA is often generalized disease and HA serum levels may be elevated due to the contribution of other joints. For this specific reason, we have performed radiographic imaging and ultrasonography of the knees to examine the prevalence of knee OA, effusion or synovial edema. Both studied groups were comparable in terms of these variables. However, we cannot exclude contribution of other joints such as particularly hips or spine, but we were not allowed to assess these joints by radiography due to ethical reasons. Second, HA levels were analyzed only at the beginning and were not available after 2 years of the study. Similarly, we were able to examine less patients by hand radiography after the 2 year follow-up due to loss of some patients mostly due to patient's decision. Thereby, some of our data may remain insignificant. Third, this study does not have healthy controls included. We believe it is unethical to assess radiography of several joint regions in otherwise healthy individuals that may nevertheless, if older than 60 years, suffer from subclinical OA.

In summary, this is the first study showing higher serum levels of HA in patients with erosive compared with non-erosive HOA and demonstrating its association with local morphological and structural changes. We suggest serum HA as a potential surrogate marker with a predictive value for further radiographic progression of HOA. Further studies are necessary to confirm these results.

Conflict of interest

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.joca.2009.06.002](https://doi.org/10.1016/j.joca.2009.06.002).

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