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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.

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 change[1]. There is a strong familiar 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].

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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 production[12]. 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 HOA[17] 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 work[18]. Patient's characteristics at the study entry are given in Table I. Written informed consent from each patient was obtained prior to enrollment and the study was approved by the local ethic committee.

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 performed[19]. The functional index for HOA (FIHOA), a 10-item investigator-administered questionnaire, was evaluated[20]. 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 scale[21]. 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 earlier[22] and scored according to the Kellgren and Lawrence (K–L) grading system, Steinbrocker's modification[23].

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 disphosphonate (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	*P*
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
SYSADOA (%)	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	*P*
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	52/55	29/33	NA
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