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Coll2-1, Coll2-1NO2 and myeloperoxidase serum levels in erosive and non-erosive osteoarthritis of the hands

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SUMMARY

Objective: Erosive osteoarthritis of the hand (EHOA) is thought to be an aggressive variant of hand osteoarthritis (HOA) characterised by prominent local inflammation and radiographic aspects of bone erosions in interphalangeal (IP) joints. However, rare studies have until now investigated the value of biomarkers in these patients. Thus, we determined Coll2-1, a marker of type II collagen denaturation, its nitrated form (Coll2-1NO2) and myeloperoxidase (MPO) levels in serum of patients with EHOA vs non-EHOA and subsequently evaluated their relationships with disease indices of severity and activity.
Methods: Coll2-1, Coll2-1NO2 and MPO were measured using specific immunoassays in 82 patients, 57 with EHOA, all females, median age 59 (41–74 yrs) and 20 with non-EHOA, all females, median age 55 (43–73 yrs), fulfilling the American College of Rheumatology (ACR) criteria for hand OA. EHOA was characterized by the presence of at least one central bone erosion on radiograph in the IP joints. Patients were also evaluated for disease duration, number of affected (swollen and painful or tender) joints, radiographic score (RS) by Kallman scale and high sensitivity C-reactive protein (hsCRP).
Results: Serum levels of MPO were higher in EHOA (230.0 ± 152.1 ng/ml) than in non-EHOA (160.2 ± 111.5 ng/ml, $P = 0.037$). Coll2-1NO2 levels trended towards an elevation in EHOA compared non-EHOA (0.40 ± 0.86 vs 0.22 ± 0.14 nmol/l, $P = 0.06$), while Coll2-1 levels were not different. Correlations were found for disease duration and both MPO ($R^2 = 0.48$, $P = 0.001$) and Coll2-1NO2 ($R^2 = 0.73$, $P = 0.01$) after the splitting of the population in subgroups according to a cut off value above the 50th percentile. A correlation was found between hsCRP and MPO ($R^2 = 0.57$, $P = 0.01$).
Conclusions: This study clearly demonstrates an elevation of some serum biomarkers in EHOA, in comparison with non-EHOA. In particular, MPO, hsCRP and the ratio Coll2-1NO2/Coll2-1 discriminated the two subsets of hand osteoarthritis (HOA), and a trend was also observed for Coll2-1NO2. These data suggest that these biomarkers could be helpful for the diagnosis of EHOA.

Introduction

Erosive hand osteoarthritis (EHOA) targets interphalangeal (IP) joints and is characterized by an abrupt onset, a severe pain and functional impairment, inflammatory symptoms and signs, including stiffness, soft tissue swelling, erythema, paraesthesiae, and worse outcomes than non-erosive hand osteoarthritis (OA) (non-EHOA)[1–8]. Diagnosis is uniquely based on the radiographic aspects of subchondral articular surface erosion, which may progress to marked cartilage and bone attrition, joint instability and bone ankylosis, associated with the classical features of OA[1,4,5,9–11]. The recent EULAR recommendations and clinical trials suggest that EHOA should be considered as a subset of HOA[5,9,10], although some authors have questioned this interpretation, suggesting that EHOA merely represents a phase in the evolution of classical HOA[12]. In the absence of a well defined phenotype, the analysis of some biochemical markers may contribute to better characterize EHOA. To the best of our knowledge, only few studies have considered this aspect. Higher serum levels of high sensitivity C-reactive protein (hsCRP) in patients with EHOA in comparison with non-EHOA have

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been found by our group[13] but not confirmed by others[14]. In another study, patients with EHOA showed increased levels of soluble receptor of interleukin-2 (sIL-2R) a marker of lymphocyte activity[15]. The C-telopeptide of type II collagen (CTX II) was found to be increased in serum and urine of EHOA in comparison with nodal non-EHOA[16]. CTX I was also found elevated in the urine of EHOA compared to non-EHOA[17,18]. Finally, serum levels of hyaluronic acid (HA), considered as marker of synovitis, were significantly higher in EHOA in comparison with non-EHOA[19].

Type II collagen is the major structural protein in cartilage, making up approximately 50% of the extracellular cartilage matrix. Type II collagen-derived fragments have been extensively investigated as potential markers of cartilage remodelling in OA and rheumatoid arthritis (RA). No differences in serum levels of type II collagen degradation biomarkers were observed between patients with EHOA and non-EHOA in a study conducted in Canada some years ago[20]. Recently, Henrotin and collaborators have developed two new immunoassays for the measurement of type II collagen-derived fragments. One assay was specific for the sequence ^{108}HRGYPGLDG^{116} derived from the triple helical region of type II collagen (Coll2-1) and the other for its nitrated form (Coll2-1NO2). The development of a specific immunoassay for the measurement of nitrated type II collagen fragments in biological fluids seems relevant to study the impact of the oxidative damage in cartilage pathophysiology. These assays have been validated in serum of healthy subjects and of patients with OA and RA[21]. Plasma myeloperoxidase (MPO) is the predominant protein present in primary granules of circulating polymorphonuclear cells. It is a member of the human peroxidase family, heme-containing enzymes that play a role in host defence against infection, hormone synthesis, and in the pathogenesis of some diseases. MPO is the major enzymatic source of leukocyte-generated oxidants, released by activated neutrophils and used as a marker of leukocyte recruitment and function and subsequent inflammation. Moreover, MPO concentration is related to inflammatory activity and could play an important role in the maintenance of oxidative stress in RA[22]. MPO was found to be elevated in patients with knee and hip OA candidates for prosthesis[23].

The aim of this study was to determine Coll2-1, Coll2-1NO2 and MPO levels in serum of patients with EHOA and compare these with the levels in non-EHOA. Furthermore, we investigated the possible relationships between these biomarkers and the clinical and radiological indices of disease severity and activity.

Methods

Patients

Seventy seven consecutive patients, 57 with EHOA (57 women, median age 59 yrs, range 41–74 yrs) and 20 with non-EHOA (20 women, median age 58 yrs, range 43–73 yrs), fulfilling American College of Rheumatology (ACR) criteria for HOA[24] were included in the study. EHOA was defined as hand OA with at least one central bone erosion in IP joints, while patients with erosions in metacarpophalangeal joints and/or thumb base joint were excluded. We also excluded patients with other known arthropathies, personal and/or familial history of psoriasis and with active bone scan in lower limb and in sacroiliac. Patients were also evaluated for disease duration in years, number of clinically active (swollen and painful or tender) joints (NCAJ), radiographic score (RS) by Kallman scale[25] (Table I). The radiological assessment was performed by one single experimented reader on all joints at the exception of the thumb base joints according a previously described protocol[13]. The intra-observed precision was less than 10%. Non-EHOA patients were selected out of 30 consecutive patients referred to our clinical centre with active disease but without radiological signs of bone erosion in IP joints. After an informed consent, these patients were submitted to bone scan and those with active bone scan in lower limbs and in sacroiliac joints, were subsequently excluded. Out of the 30 consecutive patients, 10 were excluded for positive bone scan. Non-EHOA group was limited to 20 patients for ethical reasons.

Table I
Main characteristics of patients with EHOA and with non-EHOA

	EHOA	Non-EHOA	*P*
Women, no.	57	20	–
Age: years, median, range	59 (41–74)	58 (43–73)	0.37
Disease duration: years, M ± SD	8.9 ± 6.6	4.5 ± 3.6	0.048
NCAJ	12.0 ± 5.0	8.3 ± 4.5	0.005
RS	71.1 ± 28.5	29.6 ± 15.4	0.009
Number of erosions	4.5 ± 2.6	–	–

Immunoassays

Coll2-1 and Coll2-1NO2 concentrations were measured by two new competitive and specific immunoassays (Enzyme-linked immunosorbent assay (ELISA))[26]. The Coll2-1 immunoassay only measured the amino acid sequence ^{108}HRGYPGLDG^{116} in its linear form while the Coll2-1NO2 immunoassay quantified with a high specificity and affinity the nitrated amino acids sequence. Coll2-1NO2/Coll2-1 is the ratio of nitrated Coll2-1 which reflects the oxidative stress occurring in cartilage. The limits of detection were 17 nM for Coll2-1 immunoassay and 25 pM for Coll2-1NO2 immunoassay. The intra- and inter-assays CVs were lower than 10% and the dilution curves were parallel to the standard curve for both assays. The analytical recoveries were in mean 104.7% and 121.9% for Coll2-1 and Coll2-1NO2 assays, respectively.

MPO was determined by a commercially available ELISA kit (ELIZEN MPO, Zentech SA, Liège, Belgium).

hsCRP values were assessed by a highly sensitive immunonephelometric method (DADE Behring, Milan, Italy) on a BN II Analyzer. The lower limit of detection was 0.175 mg/l (analytical sensitivity 0.04 mg/l).

Statistical analysis

Quantitative variables were summarized as mean (M) ± standard deviation (SD) for those showing normal distribution and by median and range for non-normal ones. Analysis of variance, *t* test and Wilcoxon for unpaired samples were used to compare values among groups and Chi square test for categorical distributions. For differences statistically significant at the univariate analysis, age adjustment was performed with analysis of covariance (ANCOVA) applying general linear models entering age and EHOA type as independent variables and MPO or hsCRP as dependent ones.

For the analysis of the correlation between biomarkers and disease duration, the population was divided in subgroups according to cut off values above the 50th percentile, namely MPO = 214.0 ng/ml and Coll2-1NO2 = 0.30 nmol/l. All statistical analyses were performed using statistical package for the social sciences (SPSS) (SPSS, vers 16 Inc Illinois, USA).

This protocol was approved by the ethical committee of the University of Padova (1686P/13.10.08).

Results

Main characteristics of the patients were reported in Table I. EHOA and non-EHOA populations were statistically different for: NCAJ (12.2 ± 5.2 vs 8.3 ± 4.5 respectively, $P = 0.005$), RS

(72.6 ± 28.4 vs 29.6 ± 15.4, $P = 0.0095$) and, obviously, number of erosions (4.5 ± 2.6 vs 0.0). Serum levels of MPO were higher in patients with EHOA (230.3 ± 152.1 ng/ml) than in those with non-EHOA (160.2 ± 111.5 ng/ml, respectively; $P = 0.037$). hsCRP was also significantly higher in EHOA than in non-EHOA (4.7 ± 3.3 vs 2.1 ± 1.1; $P = 0.001$). Coll2-1NO2 levels trended towards an elevation in EHOA patients compared with non-EHOA (0.40 ± 0.8 nM vs 0.19 ± 0.14 nmol/l, $P = 0.06$), while Coll2-1 levels were not significantly modified (115.2 ± 65.4 vs 114.9 ± 55.0 nmol/l, $P = 0.1$). Median and range were shown in Table II. The ratio Coll2-1NO2/Coll2-1 was higher in EHOA than in non-EHOA patients, but difference was not significant ($P = 0.07$). When the EHOA population was divided in subgroups according to a cut off value above the 50th percentile, correlations were found for disease duration and both Coll2-1NO2 ($R^2 = 0.73$, $P = 0.01$) and MPO ($R^2 = 0.48$, $P = 0.001$). A correlation was found between hsCRP and MPO ($R^2 = 0.57$, $P = 0.01$) (Fig. 1), but not between hsCRP and Coll2-1NO2/Coll2-1 ratio or Coll2-1NO2. No correlations were found between each of these biomarkers and NCAJ or RS.

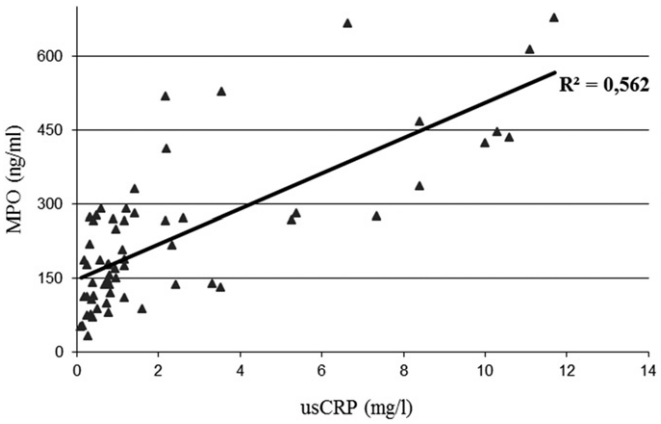

Fig. 1. Correlation between hsCRP and MPO.

Discussion

Our study demonstrates that serum levels of MPO and the ratio Coll2-1NO2/Coll2-1 are higher in EHOA than in non-EHOA. Furthermore, although not significantly, a trend was also observed for increased values of Coll2-1NO2 in EHOA compared to non-EHOA. In contrast, Coll2-1 levels were not significantly different. These results contribute to a better understanding of pathophysiological changes associated with this subset of HOA, still in search of a more precise characterization.

Coll2-1NO2 is the nitrated form of collagen-derived fragments and probably reflects the impact of the oxidative damage in cartilage pathophysiology. During local inflammatory reaction, reactive oxygen and nitrogen species are produced by macrophages, neutrophils but also by chondrocytes in response to cytokines or products of tissue degradation. Reactive oxygen and nitrogen species, mostly peroxynitrite (−ONOO) and HOCl/OCl− produced by MPO, are involved in type II collagen breakdown and nitration[27–29].

The increased levels of MPO and Coll2-1NO2 suggest that EHOA is associated with an oxidative degradation of joint. Anyway, there were only few studies demonstrating some changes in OA biomarkers[13,16–19].

In this context, serum levels of hsCRP were measured in a previously published case control study examining 67 patients with EHOA and 31 patients with non-EHOA[13]. hsCRP levels were higher in the EHOA group and the correlations between hsCRP level, radiographic severity scores and number of joints involved supported hsCRP as an indicator of disease activity. However, the results of this study were in contrast with those previously reported by Olejarova *et al.*, who found in EHOA higher values for the erythrocyte sedimentation rate but lower values for serum CRP[14]. The discrepancies between these two studies may be due to several reasons, including differences in the number of EHOA patients examined, 67 vs 28 in the second study, and in the method for CRP detection. However, in the present study, our previous data on higher hsCRP in EHOA have been confirmed. Furthermore, we found a correlation between hsCRP and MPO, which suggests the role of inflammation in EHOA[6].

As regards as the value of other biomarkers in EHOA, in a very recent study, Filková *et al.* found that serum levels of HA, considered as a marker of synovitis, were significantly higher in 55 women with EHOA in comparison with non-EHOA[19]. Furthermore, HA levels correlated with the number of hand joints showing deviations and deformities and, when adjusted for age and disease duration, with radiographs at baseline and after 2 yrs in all patients with HOA. These results indicate that HA may be a marker of synovitis and of radiographic progression in EHOA. The presence of synovitis in patients with HOA, both EHOA and non-EHOA, has been matter of discussion for many years. In some studies performed in EHOA by mean of a power-Doppler ultrasonography, the findings of synovial membrane thickening and increase vascularity indicative of active synovitis were found in the vast majority of patients with EHOA[30–33]. The percentages of distal IPs and proximal IPs with active synovitis on the right and left hands were 50% and 44.3% and 14.8% and 21.6%, respectively. These findings are thus consistent with the term “inflammatory form of OA” that has been attributed to this subset of HOA[6]. In this context, the inflammatory signs more expressed in our patients with EHOA than in those with non-EHOA seem in agreement with the increased value of serum MPO. Obviously, further studies are necessary to better understand the process underlying the high production of MPO in EHOA.

With respect to the other biomarkers analysed in this study, no difference was found in Coll2-1 values between EHOA and non-EHOA. However, due to the limited cartilage articular surface of hand joints, which is further reduced with the disease progression, it is possible that the amount of Coll2-1 released from hand joints was not enough to influence the systemic Coll2-1 level. On the other hand, our results corroborate those of a previous study performed with other type II collagen epitopes[20]. No differences in serum levels of type II cartilage biomarkers were observed between 30 patients with EHOA and 29 patients with non-EHOA. MPO,

Table II
Serum levels (median, range) of biomarkers analysed in patients with EHOA and non-EHOA

	Age matched non-OA subject ($n = 77$)	EHOA ($n = 57$)	Non-EHOA ($n = 20$)	P
Coll2-1 nmol/l	107.79 (28.77–296.94)	108.0 (33.0–367.5)	106.5 (34.5–245.5)	0.15
Coll2-1NO2 nmol/l	0.26 (0.05–0.71)	0.26 (0.03–6.3)	0.19 (0.025–0.59)	0.06
Coll2-1NO2/Coll2-1 ratio	–	0.0022 (0.0005–0.02)	0.0016 (0.0007–0.003)	0.07
MPO ng/ml	57.7 (<0–216.74)	186.6 (33.3–678.4)	119.8 (35.9–450.0)	0.03
hsCRP mg/l	–	4.7 (2.4–6.9)	2.1 (0.5–4.9)	0.001

Coll2-1NO2 and the ratio Coll2-1NO2/Coll2-1 were correlated with the radiological and clinical severity of the disease. This indicates that these are biomarkers of the burden of EHOA. Furthermore, Coll2-1NO2 but not Coll2-1 was significantly correlated with CRP in serum of patients with EHOA, suggesting that Coll2-1NO2 could be a promising specific marker of arthritic HOA disease activity.

This study suffers of major limitations including the small number of non-EHOA patients. These limitations were mainly due to the use of bone scan as a selection criterion. Subsequently, we were obliged for ethical raisons to limit the number of non-EHOA participants submitted to bone scan. Although this is a major caveat of the study, it allows us to carefully exclude patients with subclinical involvement of lower limbs OA, which may have a relevant influence in the biomarker evaluation. Ideally, to discriminate non-EHOA and EHOA with an 80% power for the assumed effect, 45 non-EHOA was required. Another limitation is the heterogeneity of the distribution of the biochemical factors which deviate from normality. This can be explained by the heterogeneity in the activity, the extent and the severity of the disease.

In conclusion, this study gives insight in a better understanding of EHOA, both for the pathogenesis and for clinical characterization of EHOA.

Authors' contribution

L Punzi: protocole writing, patients inclusion; R Ramonda: patients inclusion; M Deberg: biomarkers analysis, data interpretation; P Frallonardo: patients inclusion; C Campana: data analysis and interpretation; E Musacchio: patient inclusion, data analysis; Y Henrotin: manuscript writing, data interpretation.

Conflict of interest

L Punzi: none; R Ramonda: none; M Deberg: none; P Frallonardo: none; C Campana: none; E Musacchio: none; Y Henrotin: he is the founder and shareholder of the University spin-off Artialis SA.

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