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Brief report
Analysis of cartilage biomarkers in erosive and non-erosive osteoarthritis of the hands

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Introduction

Osteoarthritis (OA) is a degenerative joint disease, characterised by an imbalance between the synthesis and degradation of cartilage. An enhanced breakdown of cartilage matrix and reduced synthesis of matrix components by articular chondrocytes eventually lead to the destruction of the affected tissue[1]. The hand is a frequent site of disease involvement in OA[2]. Typical joints affected are distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints[3]. Cartilage, bone and synovial alterations in OA have been analysed in large joints such as knees and hips, while very few data are available for hand OA. Nevertheless, hand involvement is important as a marker for the tendency to develop OA at other sites such as the knee and hip[4]. Therefore, the availability of tests that can detect molecular changes in cartilage homeostasis in hand OA would be of great advantage.

The two main components of the articular cartilage matrix are type II collagen and aggrecan, both of which are almost tissue-specific[5]. Fragments produced during degradation/synthesis of these molecules are released into biologic fluids (synovial fluid, blood, urine), where they can be measured and subsequently used as predictive markers of disease.

Various biochemical markers have been measured in different biological fluids, predominantly in knee OA: C-terminal crosslinking telopeptide of collagen type II (CTX-II)[6,7], and collagenase cleavage neoepitopes (Col2-3/4C_{short}, Col2-3/4C_{long} or C2C)[8,9], markers of type II collagen degradation, type II procollagen propeptides (PIICP and PIINP)[8–10], marker of type II collagen synthesis, chondroitin sulphate (CS846 epitope)[8,9], marker of proteoglycan turnover.

Increased urinary[6] and synovial fluid[7] CTX-II, increased cartilage release of Col2-3/4C_{short} and CS846 epitope[8], increased serum PIINP and urinary CTX-II[10], have been found, revealing how in OA both synthesis and degradation of cartilage matrix components are present.

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Methods

Following this evidence, we analysed 59 patients, diagnosed by means of clinical and radiological evaluation as having hand OA, according to Altman *et al.*[11]. In particular, subjects were required to have physical evidence of hard tissue enlargement and/or deformity in three or more index hand joints as listed in the criteria. Hand radiographs were used to subdivide hand OA patients into nodal and erosive. Erosive OA was defined by radiographic central erosions ("gull-wing" erosions) and/or ankylosis in the interphalangeal joints in at least three digits, associated with joint-space narrowing, subchondral sclerosis and/or osteophytes. We recruited 29 patients with nodal OA (1 male, mean age 56.3 years (yrs), SD±9.3, range 41–85 yrs), and 30 patients with erosive OA (4 males, mean age 59.2 years (yrs), SD±7.6, range 47–77 yrs). None of the patients presented clinical manifestations of OA in the hip or knee region. Patients with a history of other rheumatic or skeletal degenerative diseases were excluded from analysis. In particular, for patients with erosive OA, subjects with psoriasis or with familial history of psoriasis were excluded. We also analysed 21 ethnically and geographically age-matched healthy individuals.

For each individual enrolled in the study, venous blood was drawn for serum and plasma separation. Soon after collection, vacutainers were centrifuged at 2000 rpm for 10 min in order to obtain serum and plasma, which were stored at −80 °C for further analysis.

Serum concentration of 3 different markers was evaluated by immunoassay using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Ibex Technologies Inc., Montreal, Quebec), according to the manufacturer's instructions. In particular, we analysed Col2-3/4C_{short}, C2C and CS846 epitope. The detection range is, respectively, 0.03–10 μg/mL, 3–1000 ng/mL, and 20–1000 ng/mL.

Statistical analysis was performed by Kruskall–Wallis ANOVA test followed by Mann–Whitney *U* test for unpaired data.

Results and discussion

Figure 1 shows serum concentrations of these three markers in nodal and erosive OA, and healthy controls (CTR). Significant differences were observed only for Col2-3/4C_{short}, since this marker's serum concentration was higher in both nodal and erosive OA, than in CTR (nodal vs. CTR $P=0.005$; erosive vs. CTR $P=0.0005$). Erosive OA showed a slight increase in C2C levels, and a slight decrease in CS864 levels compared to controls, although not significant. No significant differences were seen between nodal and erosive OA.

To our knowledge, this is the first report to analyse serum levels of cartilage metabolism markers in hand OA. Recently, C-telopeptide of type I collagen (CTX-I), a specific marker sensitive to bone resorption, was evaluated in the serum of patients with hand OA and controls[12]. This study showed increased levels of CTX-I in patients with erosive OA compared to nodal OA.

We found a significant increase in serum levels of Col2-3/4C_{short}, a marker of cartilage catabolism, in both nodal and erosive hand OA compared to healthy controls. From these results, it is not possible to speculate about what happens in the joint compartments of OA patients, for serum levels can be influenced by several factors. Nevertheless, some remarks can be made.

First, these data highlight how in hand OA cartilage metabolism is impaired, as shown by several studies analysing knee or hip OA. Second, our data show no significant differences between nodal and erosive OA. Erosive hand OA is considered by some authors as the progression of the nodal form[13], by others as a different subset of hand OA[14]. We support indirectly the hypothesis that these are not two different subsets of the hand involvement. Third, it would be of interest to extend the analysis of biological markers to bone and synovium as well (i.e. pyridinoline crosslinkings, bone sialoproteins, type III collagen) in order to have a total picture of hand joint involvement in OA.

When analysing biological fluids far from the tissue involved (i.e. serum and urine), one should keep in mind that type II collagen and aggrecan are also present in the intervertebral disc, and that in adults there are various

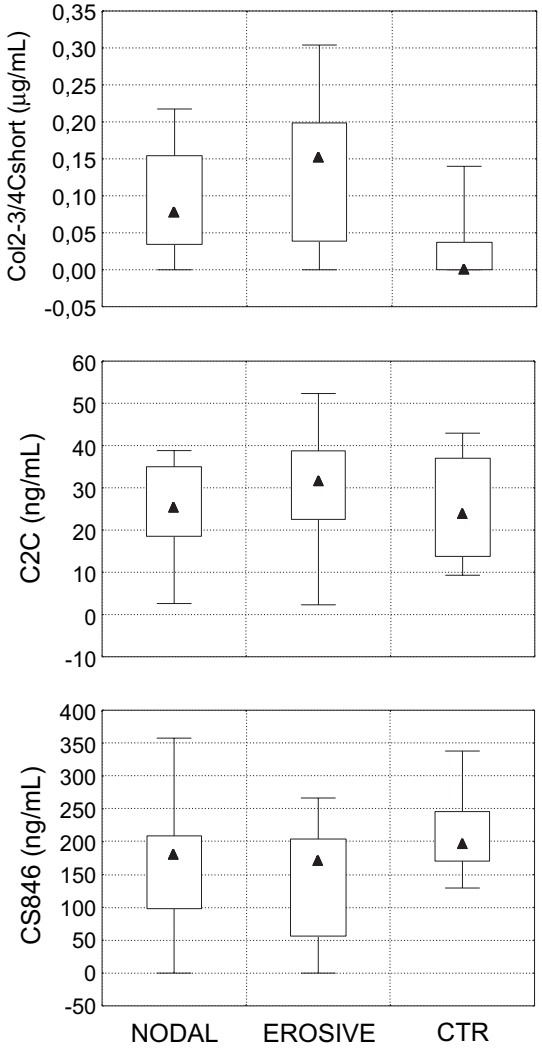

Fig. 1. Serum levels of Col2-3/4C_{short}, C2C and CS846 epitope in patients with nodal OA, erosive OA, and in healthy individuals (CTR). Triangles show median, boxes 25th and 75th percentiles, whiskers 10th and 90th percentiles.

degrees of disc degeneration. Certainly, synovial fluid analysis would be more useful, but both ethically and practically inapplicable. Furthermore, one should consider the possibility that joint damage stimulates a systemic increase in overall collagen metabolism. Nevertheless, the fact that DIP and PIP joint cartilage represents only a small fraction of total articular cartilage in the body makes it particularly impressive that the response to this limited damage can be detected. Thus, serum analysis can still be useful during follow-up or to check the efficacy of new disease-modifying drugs.

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