## EXTENDED REPORT

# Molecular markers of cartilage breakdown and synovitis at baseline as predictors of structural progression of hip osteoarthritis. The ECHODIAH* Cohort

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**Objective:** To determine whether systemic markers of bone, cartilage, and synovium can predict structural progression of osteoarthritis (OA).

**Methods:** Patients with painful hip OA were treated with diacerein or placebo in a multicentre, prospective, double blind, 3 year follow up trial. The following information was collected at entry: demographics, characteristics of hip OA, and 10 markers: N-propeptides of collagen types I and III, cartilage oligomeric matrix protein, YKL-40, hyaluronan (sHA), matrix metalloproteinases-1 and -3, C reactive protein, C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II). Radiographs were obtained at entry and every year. Structural progression was defined as a joint space decrease ⩾0.5 mm or requirement for total hip replacement. Grouped survival analysis was performed with time to structural progression as dependent variable, and clinical data, radiographic findings, treatment groups (diacerein versus placebo), and markers as explanatory measures.

**Results:** In the 333 patients in whom all markers were measured, high functional impairment, a joint space width <2 mm, and lateral migration of the femoral head at baseline increased the risk of progression, but diacerein had a protective effect (relative risk=0.75; 95% confidence interval (CI) 0.54 to 0.96). In addition, patients in whom uCTX-II and sHA were in the upper tertile had a relative risk of progression of 3.73 (95% CI 2.48 to 5.61) compared with patients with markers in the two lower tertiles.

**Conclusion:** In this large cohort, combined measurements of uCTX-II and sHA were a new predictor of the structural progression of hip OA.

T he emerging concept of structure modifying drugs in osteoarthritis (OA) has led to the recommendation of methods[1][2] to be used in studies evaluating these drugs.[3][4] The currently accepted primary outcome is a structural variable: joint space width (JSW), measured by the interbone distance at the narrowest point with a graduated eyepiece[5][6] or by computerised analysis of digitised radiographs.[7]

Radiography, however, directly depicts only gross osseous changes, which tend to occur late in the disease. Cartilage loss can be only indirectly inferred by the development of joint space narrowing, which can be highly unreliable even with careful attention to proper technique.[8]

Another way of assessing structural changes in OA is by measurement of molecular markers. These markers are molecules released into biological fluids during the process of tissue turnover. During normal metabolism, joint tissue macromolecules or fragments thereof are released into the synovial fluid, then into the blood and urine, and can be detected by assays. Several biochemical markers of bone, cartilage, and synovium which have been described in OA may be useful for identifying patients at high risk for progression of the disease and for assessing therapeutic responses, because they show change more rapidly than radiographic assessment.[9][10] These biomarkers are easy to measure and commercial kits are now available. On the other hand, they reflect changes in the metabolism of all the bones

and of all the cartilages of the body. As OA may be a local disease, are the changes induced by degeneration of one or a small number of joints sufficient to be detected in serum or urine? Would measurement of several markers help to achieve this goal?[11–13]

The significance of markers has not been assessed in large populations of patients with hip OA. The current study aimed at measuring a number of biomarkers in the serum and urine of a well defined cohort of patients with hip OA[3][14–18] and examining whether one or several of them might be predictive of the severity of the disease, as assessed by measurement of progressive narrowing of the joint space on radiographs as recommended by the Barcelona consensus.[19]

## PATIENTS AND METHODS
### Study population, recruitment, and data collection
This was a multicentre, prospective, longitudinal 3 year study, approved by the ethics committee of our institution, and patients gave their written informed consent before participation. The study group has been described

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* **ECHODIAH**: **E**valuation of the **CHO**ndromodulating effect of **DIA**cerein in osteoarthritis of the **H**ip.

previously.[15] Briefly, outpatients who fulfilled the American College of Rheumatology criteria for hip OA[20] were recruited by rheumatologists for the study if they were aged between 50 and 75 years, experienced pain during daily activities (0–100 mm visual analogue scale (VAS) ⩾30 mm), and if the JSW was >1 mm at the narrowest point on radiographs. Secondary hip OA was an exclusion criterion (history of hip fracture, inflammatory joint disease, osteonecrosis or Paget's disease of bone) as was femoral head migration on radiographs. Patients were treated either with diacerein (100 mg/day) or placebo during the whole of the 3 year follow up, as previously reported.[3]

At baseline, the following characteristics were noted: demographic data (age, sex), body mass index, history of hip OA (date of first symptoms for calculation of the symptomatic duration of the disease), radiographic pattern of OA (classified as superolateral, superointermediate, superomedial or concentric),[21] severity (Kellgren-Lawrence grading system),[22] bilaterality (American College of Rheumatology criteria), and polyarticular involvement according to the articular score derived from the Landsbury index.[23]

Each patient was evaluated at entry and every 3 months for:

- Pain during daily activities (0–100 mm VAS)
- Functional disability assessed by the Lequesne index[24] and based on the four questions relating to physical activities (0 = easy to perform; 0.5 = performed with some difficulty; 1 = performed with difficulty; 1.5 = performed with great difficulty, and 2 = impossible to perform) giving a score from 0 to 8
- Patient's global assessment (0–100 mm VAS)
- Pain at night assessed by the Lequesne index (0 = no pain; 1 = pain on movement; 2 = pain at rest), and morning stiffness assessed by the same index (0 = no stiffness or stiffness of less than one minute; 1 = stiffness between 1 and 15 minutes; 2 = stiffness >15 minutes).

### Radiological evaluation

At entry, once a year, and when possible just before hip surgery, a weightbearing anteroposterior pelvic radiograph was obtained, then examined by a single observer (ML) who was unaware of the patient and date. The interbone distance was measured using a 0.1 mm graduated magnifying glass.[5] The smallest detectable difference was 0.5 mm.[14] This means that a change of more than 0.5 mm in the JSW between two radiographs is a change not related to a measurement method error. We also noted the presence (1) or absence (0) of osteophytes, and sclerosis and cysts of the subchondral bone. Structural progression of OA in the current study was defined either as a joint space decrease ⩾0.5 mm according to the smallest detectable difference or as requirement for total hip arthroplasty.

### Decision for surgery

The decision for total hip arthroplasty was made by the patient, the rheumatologist, and the orthopaedic surgeon on the basis of signs and symptoms, with no reference to radiographic change, although both physicians had the opportunity to evaluate the most recent follow up x ray findings.

### Molecular biomarkers

Fasting blood samples were collected in all patients between 7 and 10 am. Second morning void urine samples were also collected in plastic containers. Several aliquots of serum and urine were obtained and stored centrally at −20°C until assay.

Ten markers were measured. Eight markers were measured in serum: N-propeptides of collagen type I (sPINP) and type III (sPIIINP), cartilage oligomeric matrix protein (sCOMP), cartilage glycoprotein 39 (sYKL-40), hyaluronan (sHA), matrix metalloproteinases (sMMP-1 and sMMP-3), and ultrasensitive C reactive protein (sCRP). Two markers were measured in urine: C-terminal crosslinking telopeptide of collagen type I (uCTX-I) and type II (uCTX-II); their levels were corrected by the urinary creatinine concentration (measured by a standard colorimetric method).

Two markers reflected bone metabolism. uCTX-I, a marker of bone destruction, was measured by enzyme linked immunosorbent assay (ELISA) (Crosslaps, Nordic Bioscience, Herlev, Denmark), which used a polyclonal antiserum raised against the β-isomerised EKAHβDGGR sequence of the C-telopeptide of α1 chains of human type I collagen.[25] Intra- and interassay coefficients of variation (CVs) were less than 6% and 9%, respectively. sPINP was measured by electrochemiluminescence immunoassay based on monoclonal antibodies raised against purified human PINP and detecting both intact monomeric and trimeric forms, but not fragments, using an automated analyser (Elecsys, Roche Diagnostics, Germany). Intra- and interassay CVs were less than 2% and 4%, respectively.[26]

Two markers assessed cartilage metabolism. sCOMP was assayed by ELISA (COMP ELISA kit, AnaMar Medical, Lund, Sweden) with a solid phase, two site enzyme immunoassay, based on the direct sandwich technique, in which two monoclonal antibodies are directed against separate antigenic determinants on the COMP molecule.[27] Intra- and interassay CVs were below 7% and 8%, respectively. uCTX-II is a marker of type II collagen degradation and was measured by an ELISA based on a mouse monoclonal antibody raised against the EKGPDP sequence of human type II collagen C-telopeptide (Cartilaps, Nordic Bioscience, Herlev, Denmark). This sequence is found exclusively in type II collagen.[28] Intra- and interassay CVs were less than 8% and 10% respectively.

Two markers reflected synovial metabolism. sHA, as a major product of synovial cells, is considered a marker of synovitis. sHA was measured by radioimmunoassay (RIA; Pharmacia HA test, Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) based on the use of specific hyaluronic acid binding protein isolated from bovine cartilage.[29] Intra- and interassay CVs were lower than 10%. sPIIINP was measured by RIA based on a polyclonal antibody (PIIIP-RIA kit, Farmos Diagnostica, Oulunsala, Finland). The assay detects the authentic propeptide and other larger related antigens, but is insensitive to the degradation products of the propeptide.[30] Intra- and interassay CVs ranged from 6% to 8%.

Three markers were markers of both cartilage and synovium turnover. sYKL-40 was measured by a two site ELISA (Chondrex, Metra Biosystems Inc, Mountain View, CA, USA) using antibodies raised against YKL-40 purified from supernatants of the MG63 human osteosarcoma cell line.[31] Intra- and interassay CVs were lower than 4% and 6%, respectively. sMMP-1 and sMMP-3 were assayed with a two site ELISA using two monoclonal antibodies raised against human MMPs (human RNP 2610 and human RNP 2613; Kit Biotrak, Amersham Pharmacia Biotech, Buckinghamshire, UK). These assays recognise proMMPs, active MMPs, and complexes of MMPs and their tissue inhibitors. Intra- and interassay CVs were lower than 8% and 13%, respectively.

Finally, sCRP, which is not joint specific, provides useful information about the general inflammation process. It was assayed using an ultrasensitive immunonephelometry method (N Latex CRP mono; Behringwerke AG, Marburg, Germany) on a BNA Behring nephelometer.[29] Intra- and interassay CVs were lower than 5% and the detection limit was 0.2 mg/l.

All measurements were carried out centrally with the patient's identity, clinical and radiographic data blinded in

**Table 1**  Main baseline characteristics of the two groups of patients

| Variables | Patients included in the analysis (n = 445) | Patients with all variables recorded and all biological markers measured (n = 333) | Patients with missing data (n = 112) |
|---|---|---|---|
| *Demographic data* | | | |
| Age (years) | 62.3 (6.9) | 62.1 (6.9) | 62.8 (6.9) |
| Sex (% female) | 59 | 59 | 59 |
| BMI (kg/m$^2$) | 25.8 (3.5) | 25.7 (3.5) | 26.2 (3.6) |
| *Disease duration (years)* | 4.4 (4.7) | 4.4 (4.6) | 4.7 (5.0) |
| *Symptoms* | | | |
| Pain on movement (VAS) | 45.3 (20.0) | 44.0 (19.5) | 49.4 (20.8) |
| Total Lequesne's index | 7.8 (2.6) | 7.6 (2.4) | 8.6 (2.9) |
| Functional impairment | 2.3 (1.2) | 2.3 (1.2) | 2.6 (1.3) |
| Night pain and/or morning stiffness (%) | 91 | 89 | 95 |
| *Radiography* | | | |
| Femoral head migration (%) | | | |
|   Superolateral | 60 | 60 | 60 |
|   Superomedial | 31 | 31 | 30 |
|   Concentric | 9 | 9 | 10 |
| Joint space width (mm) | 2.3 (0.8) | 2.3 (0.9) | 2.3 (0.8) |
| *Treatment* | | | |
| Placebo/diacerein (No of patients) | 227/218 | 176/157 | 51/61 |

Results are shown as mean (SD) unless stated otherwise.
BMI, body mass index.

the following laboratories: (*a*) Synarc, Lyon, France (Dr P Garnero) for sPINP, sPIIINP, sHA, sCRP, uCTX-I, and uCTX-II; (*b*) Laboratoire d'immunologie CHU Toulouse-Hôpital Rangeuil, Toulouse, France (Professor M Abbal) for sMMP-1, sMMP-3; (*c*) Service de Biochimie 3, Hôpital de la Grave, Toulouse, France (Professor J-P Salles) for sYKL-40; and (*d*) AnaMar Medical AB, Lund, Sweden (Dr C Freiburghaus) for sCOMP.

## Statistical analysis

All data concerning the markers are expressed as the mean (SD) and the median because distribution analysis showed that these markers were not normally distributed.

Using the Cox regression model,[32] analyses were performed with time to structural progression as dependent variable and clinical data, radiographic findings, treatment groups (diacerein versus placebo), and molecular markers as explanatory measures. A first analysis was performed with baseline clinical and radiographic variables only, a second one with

**Table 3**  Mean and SD according to sex for the molecular markers in which there was a significant difference between men and women (p<0.0001)

| Markers | Men (n = 136) | Women (n = 197) |
|---|---|---|
| sMMP-3 (ng/ml) | 37.8 (40.17) | 16.4 (13.10) |
| sPINP (ng/ml) | 35.8 (12.97) | 46.2 (20.41) |
| uCTX-I (μg/mmol crea) | 145 (65) | 214 (112) |
| uCTX-II (ng/mmol crea) | 245 (138) | 374 (240) |

treatment options, and a final one with markers after adjustment for all the previous variables. For markers, the risk of progression in patients with levels in the highest tertile was compared with those of patients with markers in the two lower tertiles.

Statistical analyses were carried out with SAS software (SAS, release 8.02; SAS Institute Inc, Cary, NC, USA).

**Table 2**  Mean, median, interquartile ranges, and minimum and maximum values of the different molecular markers at baseline in the 333 patients with all clinical variables recorded and all biological markers measured

| Markers* | Mean (SD) | Median | Interquartile ranges (25–75%) | Min–max |
|---|---|---|---|---|
| sMMP-1 (ng/ml) | 6.34 (4.54) | 5.15 | 3.05–8.80 | 0.10–28.05 |
| sMMP-3 (ng/ml) | 25.1 (29.5) | 19.3 | 10.5–32.0 | 0.1–429.6 |
| sCOMP (U/l) | 10.7 (2.7) | 10.5 | 9.0–12.4 | 2.4–24.1 |
| sPINP (ng/ml) | 42.0 (18.4) | 40.9 | 28.2–51.0 | 0.2–139.5 |
| sPIIINP (ng/ml) | 4.28 (1.98) | 4.01 | 3.37–4.82 | 1.61–31.10 |
| sHA (mg/l) | 130 (102) | 98 | 63–160 | 21–750 |
| sCRP (mg/l) | 3.11 (4.73) | 1.60 | 0.80–3.30 | 0.10–41.30 |
| sYKL-40 (mg/l) | 83.8 (81.0) | 63.0 | 41.6–100.0 | 4.8–855.0 |
| uCTX-I (μg/mmol crea) | 186 (101) | 168 | 121–226 | 32–675 |
| uCTX-II (ng/mmol crea) | 321 (214) | 262 | 170–408 | 22–1262 |

sMMP-1, matrix metalloproteinase-1; sMMP-3, matrix metalloproteinase-3; sCOMP, cartilage oligomeric matrix protein; sPINP, N-propeptides of collagen type I; sPIIINP, N-propeptides of collagen type III; sHA, hyaluronic acid; sCRP, C reactive protein; sYKL-40, Chondrex; uCTX-I, C-terminal crosslinking telopeptides of collagen type I; uCTX-II, C-terminal crosslinking telopeptides of collagen type II (s = serum; u = urine).

**Table 4** Relative risks of the biomarkers influencing disease progression*

| Variables (upper tertile compared with the two lower tertiles) | Relative risk (95% confidence intervals) | p Value |
|---|---|---|
| sMMP-1 >7.20 ng/ml | 0.977 (0.718 to 1.328) | 0.8817 |
| sMMP-3 >27.4 ng/ml | 1.174 (0.846 to 1.629) | 0.3377 |
| sCOMP >11.4 U/l | 0.826 ( 0.613 to 1.112) | 0.2078 |
| sP1NP >46.4 ng/ml | 1.255 (0.922 to 1.709) | 0.1493 |
| sPIIINP >4.56 ng/ml | 1.097 (0.814 to 1.480) | 0.5425 |
| sHA >137 mg/ml | 1.747 (1.297 to 2.353) | <0.0002 |
| sCRP >2.7 ng/ml | 0.782 (0.568 to 1.076) | 0.1313 |
| sYKL-40 >88 mg/l | 0.950 (0.694 to 1.302) | 0.7504 |
| uCTX-I >198 µg/mmol crea | 1.360 (1.000 to 1.850) | 0.0500 |
| uCTX-II >346 ng/mmol crea | 2.058 (1.529 to 2.770) | <0.0001 |

*Disease progression was defined as joint space decrease ⩾0.5 mm or requirement for total hip arthroplasty at 3 years (univariate analysis after adjustment for age, sex, BMI, and treatment).

## RESULTS
### Clinical, radiological, and biochemical data at baseline

Five hundred and seven patients were recruited initially, of whom 445 were included in the current analysis as they had at least two pelvic *x* ray examinations (at baseline and at 1, 2 or 3 years) or required total hip arthroplasty (censored survival data). Only 333 patients had all clinical variables recorded and all markers measured. This subgroup did not differ significantly from the first group, although those who did not have all the data were more likely to have a higher Lequesne's index and greater night pain or morning stiffness (table 1). The percentage of progressors was 65% and 64% in each group, respectively.

Table 2 presents the mean, median, and variability of the molecular markers. No significant difference was found in marker levels between male and female patients with OA for sMMP-1, sPIIINP, sHA, sCRP, sCOMP, and sYKL-40. For the following markers there was a significant difference between men and women (table 3): sMMP-3, sPINP, uCTX-I, and uCTX-II (p<0.0001 for each marker).

### Relationship between baseline levels of molecular markers and progression of joint damage

The first set of analyses was performed to look for clinical and radiological predictors of disease progression. Univariate analysis detected the significant variables and selected their most accurate cut off points (data not shown). Subsequent multivariate analysis showed that female sex, age ⩾66 years, functional impairment ⩾2, JSW <2 mm, and lateral/concentric migration of the femoral head were significantly associated with structural changes or total hip arthroplasty requirement and explained 9% of the interindividual variance of progression. When treatment modalities were added to the model, there was no significant change in the previous conclusions. Treatment with diacerein had a protective effect (p<0.0234) and the relative risk was 0.75 (95% confidence interval (CI) 0.54 to 0.96).

The second set of analyses was performed to look for molecular markers predictive of progression after adjustment for age, sex, body mass index (BMI), and treatment modalities. Univariate analysis detected the following variables as significant predictors of progression (table 4): uCTX-I (p = 0.05), uCTX-II (p<0.0001), and sHA (p<0.0002). The relative risk of progression was calculated by comparing their highest tertile with their two lower tertiles. Multivariate analysis showed that two markers were always significant predictors: uCTX-II (p<0.0001) and sHA (p<0.0001) when

**Table 5** Relative risks of the clinical, radiographic measures at baseline, treatment modalities, and molecular markers levels influencing disease progression*

| Variables | % OA progression | Relative risk (95% CI) | p Value |
|---|---|---|---|
| **Sex** | | | |
| Male | 57% (77/136) | | |
| Female | 62% (123/197) | 1.20 (0.88 to 1.63) | 0.2504 |
| **Age (years)** | | | |
| <66 | 56% (118/211) | | |
| ⩾66 | 67% (82/122) | 1.21 (0.90 to 1.63) | 0.2099 |
| **Functional impairment** | | | |
| <2 | 50% (56/112) | | |
| ⩾2 | 65% (144/221) | 1.52 (1.10 to 2.07) | 0.0101 |
| **Joint space width (mm)** | | | |
| ⩾2 | 54% (114/210) | | |
| <2 | 70% (86/123) | 1.36 (1.02 to 1.82) | 0.0373 |
| **Femoral head migration** | | | |
| Superomedial/concentric | 45% (47/105) | | |
| Lateral | 67% (153/228) | 2.34 (1.66 to 3.30) | <0.0001 |
| **Treatment modalities** | | | |
| Placebo | 64% (113/176) | | |
| Diacerein | 55% (87/157) | 0.72 (0.54 to 0.96) | 0.0274 |
| **CTX-II (ng/mmol crea)** | | | |
| ⩽346 | 51% (113/220) | | |
| >346 | 77% (87/113) | 2.00 (1.49 to 2.70) | <0.0001 |
| **sHA (mg/ml)** | | | |
| ⩽137 | 54% (120/223) | | |
| >137 | 73% (80/110) | 1.69 (1.25 to 2.27) | 0.0006 |

*Disease progression was defined as joint space decrease ⩾0.5 mm or requirement for total hip arthroplasty at 3years (multivariate analysis).

comparing their upper tertiles (>346 ng/mmol creatinine and 137 mg/l respectively) with their two lower tertiles. After adjustment for baseline clinical, radiological, and treatment variables, age and sex were no longer significant predictors, but functional impairment, radiological measures, treatment modalities, and increased levels of uCTX-II and sHA still predicted the risk of progression with similar relative risks (table 5). If only these two significant markers were taken into account, together with clinical and radiographic measures, they explained up to 16% of interindividual variance of progression (increasing it by 76%).

As there was no interaction between the two markers (p = 0.85), patients with both markers in the upper tertile presented a relative risk of progression of 3.73 (95% CI 2.48 to 5.61) as compared with patients with both markers in the two lower tertiles.

## DISCUSSION

In a previous study we found that female sex, age >66, functional impairment over 2, joint space width <2 mm, and lateral or concentric migration of the femoral head at entry were predictive factors of structural progression of the disease.[14] In the current study, we add the molecular markers in the multivariate analysis of this progression. Not only were the previous predictors always validated but the two above-mentioned markers were also predictive factors of this progression. Finally, treatment by diacerein was also a protective factor of this progression. This finding was not surprising when considering the results obtained in this double blind, placebo controlled study, where the narrowing of the joint space was less in the diacerein group than in the placebo group.[3]

### Molecular markers at baseline

When the normal ranges published in similar populations without OA were used,[29] the increase of sPIIINP, uCTX-II, and sHA and the slight decrease of uCTX-I levels in this group of patients with hip OA is similar to that seen in a population of patients with knee OA,[29] even after adjustment for age, sex, and BMI. This study was unable to confirm any increase of some markers which were previously reported to be raised in OA: sCOMP[33 34] and sYKL-40[31] were within strictly normal ranges, as were sMMP-1 and sMMP-3 (normal values given with the kit). These comparisons are to be made with caution, as biomarker data cannot be compared across different studies without very careful checks of the methodology, calibration samples, definition of the populations, etc.

uCTX-II is a marker of cartilage destruction, and sHA and sPIIINP are considered as markers of synovitis, but they are not tissue specific. Joint destruction in OA is a complex process, probably non-linear, but occurring mainly during a flare up of the disease when synovitis and/or effusion are often present,[34] which may explain the increase of these three markers together.

### Predictive value of the markers

High levels of urinary CTX-II and serum HA were predictors of joint space decrease or total hip arthroplasty requirement. As far as we know, this is the first study investigating a panel of molecular markers as predictors of joint damage progression in a homogeneous and well characterised cohort with hip OA for periods of up to 3 years.

JSW is the ''gold standard'' for assessing structural progression of the disease.[19] Other radiographic measures were tested (Kellgren and Lawrence staging,[22] osteophytes or subchondral bone sclerosis), but no correlations were found.

Patients with knee OA with higher basal serum levels of HA had a faster radiological progression.[35]

The concentration of CTX-II in urine is significantly higher in patients with knee and hip OA than in controls matched for age.[36] CTX-II was recently reported to be a good marker of the progression of OA of hip and knee,[38] and the risk of progression was 8.4 in patients with hip OA when the CTX-II level was in the upper quartile compared with patients with CTX-II levels in the lowest quartile. In the current study, we have studied all the population, comparing the patients with marker in the upper tertile with those in the two lower tertiles. Under such conditions, the association between baseline levels of the markers and radiological progression was significant but modest. This suggests that although higher baseline levels of these markers are associated with a greater progression of joint destruction, molecular markers cannot accurately predict the absolute rate of progression in a given patient. It has been reported in rheumatoid arthritis that time integrated CRP levels are better predictors of radiological progression than is a single baseline assessment, probably because disease activity is likely to vary over time.[39] The same is probably true in OA and for other markers.

Our study has some limitations. Although we assayed 10 molecular markers in both serum and urine, the potential markers which may be relevant in assessing the OA process are more numerous.[11] For instance, we did not assay newly developed molecular markers of type II collagen metabolism such as N-propeptide of type IIA procollagen (PIIANP), which was shown to be decreased in knee OA. Furthermore, an uncoupling index of both PIIANP and CTX-II seemed to be a better predictor of joint damage.[40]

In summary, it is important for the clinician to identify patients who are at a high risk of progression of their hip OA. We found that patients whose baseline levels of uCTX-II and sHA were in the highest tertile of the population had a progression rate 3.7 times higher than that of patients whose baseline levels of these markers were in the lower tertiles. Multivariate regression analysis gave concordant results and indicated that uCTX-II and sHA together with, but independently of, high functional impairment, JSW <2 mm, and treatment modalities, are the most important risk factors for progression. Further studies should use these markers to confirm their validity and to assess their usefulness in assessing treatment efficacy, especially the efficacy of drugs with potentially chondroprotective properties.

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