PREDICTION OF OSTEOARTHRITIS PROGRESSION USING MOLECULAR MARKERS OF CARTILAGE METABOLISM

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INTRODUCTION

The hallmark of osteoarthritis is the loss of articular cartilage. This loss arises from an imbalance between cartilage synthesis and cartilage degradation over a variable period of time. As the rate of cartilage loss is thought to be unpredictable, increased pain and immobility are considered the most common markers for cartilage progression. We hypothesized that molecular markers reflecting the imbalance of cartilage metabolism could be used to predict whether further cartilage damage will occur. We have developed reagents and a method to reliably measure cartilage metabolism by a combination of markers for cartilage synthesis and cartilage degradation. Detection of Type IIA procollagen N-propeptide is a serum marker for collagen biosynthesis and is lower in patients with osteoarthritis (1) while CTX-II, generated from the C-telopeptide, is a urine marker of collagen breakdown (2). Using these markers together, we find that osteoarthritis progression, over the one year period tested, can be predicted and correlated with X-ray data and arthroscopy.

MATERIALS AND METHODS

Seventy-five patients with medial knee OA (51 women, 24 men; mean age, 63+/-8 yr, mean disease duration: 4.3+/-1.5 yr) were included. At baseline, we measured serum N-propeptide of the long form of type II collagen (IIA) and urine C-telopeptide fragments (CTX-II, Cartilaps™, Osteometer) as markers for type II collagen synthesis and degradation, respectively. Joint space width on X-ray and medial chondropathy by arthroscopy (VAS score, 100 mm) were measured in all patients at base line and in 52 of them in one year. Progression of joint destruction was defined by a decrease in joint space width of 0.5 mm on X-rays and by an increase of chondropathy in VAS score >/= 8.0 between the baseline and one year evaluation.

RESULTS

At baseline, patients with knee OA, compared to 58 healthy controls (C), had decreased serum PIIANP (20 vs 29 ng/ml, p<0.001) and increased urinary CTX-II (618 vs 367 ng/mmol Creatinine, p<0.001) (see Table I). Highest discrimination between OA patients and controls was obtained by combining PIIANP and CTX-II in an Uncoupling Index (UI: Z-score PIIANP) minus a Z-score (SDs from the mean of C) of 4.1.

Table I. Baseline values for collagen synthesis and collagen degradation.

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<tr>
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<th>Baseline PIIANP (Serum marker)</th>
<th>Baseline CTX-II (Urinary marker)</th>
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<tr>
<td>Osteoarthritis patients</td>
<td>20 ng/ml serum</td>
<td>618 ng/mmol Creatinine</td>
</tr>
<tr>
<td>Controls</td>
<td>29 ng/ml serum*</td>
<td>367 ng/mmol Creatinine*</td>
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*p< 0.001 for each

Table II. Changes in one year follow-up.

<table>
<thead>
<tr>
<th>One Year Progression in:</th>
<th>Joint Space Narrowing (X-ray)</th>
<th>VAS Chondropathy Score (arthroscopy)</th>
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<tr>
<td>Yes (n=16)</td>
<td>No (n=36)</td>
<td>Yes (n=16)</td>
</tr>
<tr>
<td>Uncoupling Index (UI)</td>
<td>7.6+/-6.6**</td>
<td>3.0+/-2.9</td>
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<td>6.4+/-4.0***</td>
<td>3.2+/-4.2</td>
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**p<0.02, ***p<0.01

DISCUSSION

Increased Uncoupling Index (UI) at baseline was associated with a higher rate of chondrolysis over one year when evaluated by changes in joint space narrow (r=0.43, p=0.01) or VAS score (r=0.40, p<0.01). As shown in Table II, patients who showed a progression of joint destruction had increased baseline UI. Similarly, patients with both low PIIANP (>/= mean –1 SD of C) and high CT-II (>/= mean+2 SD of C) progressed five-fold more rapidly than the others and had a relative risk of progression of 4.5 (1.01-19.7) for X-ray and 6.1 (1.3-29) for arthroscopy changes.

CONCLUSIONS

Patients with knee OA are characterized by a measurement of type II collagen metabolism which can be detected by assays for anabolism (serum PIIANP) and catabolism (urinary CTX-II). Combination of these two new markers could be useful to identify patients with knee OA at high risk for rapid progression of joint damage. While many potential markers are available for cartilage degeneration, this is the first report of combined use of anabolic and catabolic markers. These markers provide insight into the activity of the disease process and can thereby be used to predict future disease progression. Prediction of OA progress could target a time period for specific interventions.

REFERENCES


***Osteometer Biotech, Herlev, Denmark.
****Hospital Cochin Paris, Paris, France.