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Association between biochemical cartilage markers and clinical symptoms in patients with hip osteoarthritis: cohort study with 2-year follow-up

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SUMMARY

Objectives: To assess associations between uCTX-II or uCIIM and severity of hip pain in patients with mild-moderate hip osteoarthritis (OA) over a 2-year period, and establish whether the level of these biomarkers at baseline could estimate a specific trajectory of hip pain.
Design: A cohort study with a 2-year follow-up and 6-monthly measurements of urinary biomarkers (uCTX-II and uCIIM) and symptom severity. Patients were recruited from general practices. The primary outcome was hip pain, measured with the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale and the Visual Analog Scale (VAS). Associations between hip pain and biomarkers were assessed using linear mixed-model analysis for repeated measurements. Five previously identified pain trajectories were used as outcome to investigate whether the level of biomarkers at baseline could estimate membership in one of the trajectories using multinomial regression analysis.
Results: LoguCTX-II and loguCIIM were not associated with WOMAC pain or VAS pain during the 2-year follow-up. Patients in the highly progressive pain trajectory and the moderate pain trajectory were more likely to have a higher loguCTX-II at baseline (OR 6.7; 95% CI 1.6–28.2 and OR 4.8; 95% CI 1.0–22.8, respectively) than patients in the mild pain trajectory.
Conclusion: This study shows that in patients with mild-moderate hip OA the urinary biochemical markers uCTX-II and uCIIM are not cross-sectionally associated with hip pain during the 2-year follow-up. Because the uCTX-II level estimated a progressive or moderate hip pain trajectory, this correlation needs to be confirmed in additional patients with hip OA.

Introduction

Osteoarthritis (OA) is characterized by slowly progressive damage of synovial joint tissues, including cartilage destruction and alterations of the bone and synovial tissue. Signs and symptoms of OA include joint pain, stiffness and disability. Although radiography is used to confirm OA in clinical practice, specific OA signs (such as joint space narrowing) are only visible after significant cartilage degradation has taken place[1].

Biochemical markers, or biomarkers, are defined as characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[2]. The availability of biomarkers that can assist in diagnosing early-stage OA, predicting OA progression, and assessing therapeutic responses could improve early diagnosis and help monitor the effect of OA treatment. In OA, biomarkers of interest originate from bone, synovial tissue, and the articular cartilage[3].

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The articular cartilage is composed of two primary matrix proteins: type II collagen and aggrecan. During cartilage erosion, type II collagen is sequentially degraded by enzymes, as matrix metalloproteinases (MMP). The resulting protein fragments, called neoepitopes, are released into the circulation and excreted in the urine; these fragments could serve as biomarkers. Two of these biomarkers of type II collagen metabolism are type II collagen C-telopeptide (CTX-II) and MMP-derived CIIM. Urinary (u) CTX-II has been investigated most extensively and associations have been shown between uCTX-II and radiographic hip joint space narrowing, and between uCTX-II and hip pain[4,5]. CIIM has recently been identified as a collagen type II neoepitope; serum CIIM levels are reported to be higher in individuals with knee OA than in those without knee OA[6]. Although CIIM was originally identified in urine by mass spectrometry, to date no study has clinically validated the marker in urine as a marker of OA.

Most previous studies have investigated the relationship between biomarkers and symptoms cross-sectionally[5], or studied the relation between biomarkers and prediction of structural damage[7]. Moreover, because the performance of biochemical markers has been investigated more frequently in knee OA than in hip OA, our knowledge on the performance of biomarkers in hip OA is limited[5].

Studying symptomatic progression requires repeated measurements and the ability to discriminate progressing disease from non-progressing disease. Latent class growth analysis (LCGA) has this ability and is a technique that finds clinically meaningful groups of people who are similar in their responses to measured variables, e.g., pain scores[8]. Recently, LCGA applied to a longitudinal dataset of patients with hip OA discriminated between five different pain trajectories over a 2-year period of follow-up, i.e., high pain, moderate pain, mild pain, regularly progressive pain and highly progressive pain[8]. If biomarkers could help in predicting which group patients belong to, this could be of considerable clinical value.

The objective of this study was to assess whether there is an association between uCTX-II or uCIIM and perceived hip pain of patients with mild-moderate hip OA, over a 2-year period with 6-monthly measurements of urinary biomarkers and hip pain. The secondary objective was to assess whether these biomarkers could help to estimate a specific trajectory of hip pain over the 2-year period.

Methods

Study population

The study population consisted of primary care patients diagnosed with hip OA ($n = 222$) who participated in a prospective randomized controlled trial that assessed the effect of glucosamine sulfate (the GOAL trial; ISRCTN54513166)[9–11]. This trial recruited prevalent cases of patients with hip complaints from databases of general practices in the Netherlands. Patients were eligible if they met one of the American College of Rheumatology (ACR) criteria for hip OA[12]. Patients who had undergone or were awaiting total hip replacement (THR) surgery and patients with a Kellgren and Lawrence (KL) score of 4 were excluded[13]. Patients were also excluded if they had renal disease, liver disease, diabetes mellitus, or were already taking glucosamine. Also excluded were patients with a disabling comorbid disease that would make visits to the research center impossible, and those unable to complete questionnaires in Dutch.

Eligible patients were randomly assigned to receive either 1500 mg of oral glucosamine sulfate once daily or placebo over a period of 2 years. The Medical Ethics Committee of the Erasmus University Medical Center approved the study design, and all patients provided written informed consent. A detailed description of the study design and outcomes has been published elsewhere[9–11]. The GOAL trial showed that glucosamine sulfate was not superior to placebo in reducing symptoms and progression of hip OA. One of the secondary outcomes of this trial was biomarker level of CTX-II and a promising new marker CIIM assessed in urine samples[10].

Biochemical markers

The biomarkers uCTX-II and uCIIM were measured in second morning void urine at five time points: at baseline, and at 6, 12, 18 and 24-months follow-up. The samples were stored at −80°C. The samples were collected from September 2003 until March 2006. The samples were analyzed in 2010. Prior to measurement the urine samples were thawed, vortexed and spun down to first mix the samples and pellet potential debris. Prolonged storage test of the assays for up to 12 years showed no effect of storage on the levels of the biomarkers. U-CTX-II was measured by the commercially available Cartilaps® *ELISA (IDS Nordic, Herlev, Denmark)*. Urinary CIIM was measured by an in-house constructed EIA targeting the neo-epitope RDGAAG↓ derived from MMP cleavage of type II collagen[6,14]. For both assays, intra- and inter-assay variations were <8 and <12% for the urine measurement. Samples were run in duplicates and repeated if CV% was >15%. Both markers were normalized for the amount of creatinine (creat) in the urine. If the level of creat was below the lower limit of detection, then the level was set to the lowest detectable level (1 umol/mL creat). In our trial we did not measure CTX-II and CIIM in serum.

Clinical outcomes

The outcome was severity of hip pain reported by the patient. This was measured 3-monthly during the 2-year follow-up with two validated measuring instruments: the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale for hip pain and the Visual Analog Scale (VAS; range 0–100, 0 indicates no pain, 100 indicates unbearable pain)[15]. The WOMAC subscale was converted to a 0–100 score (0 indicates no symptoms, 100 indicates unbearable pain). The WOMAC is recommended by the Osteoarthritis Research Society International for use in clinical trials in patients with hip OA to measure pain severity. The WOMAC asks patients about their pain in the previous 2 days; the VAS pain was scored as the average hip pain during the previous 7 days. If patients had a THR during follow-up, available data were included in the analysis until surgery; data collected after surgery were assumed to be missing.

Pain trajectories

Recently, using the 3-monthly repeated pain measurements during 2-year follow-up, five distinct trajectories of hip pain were identified in the GOAL data[8]. The LCGA differentiated the following trajectories: mild pain ($n = 69$), moderate pain ($n = 31$), high pain ($n = 31$), regularly progressive pain ($n = 48$), and highly progressive pain ($n = 42$). A more detailed description of the determination of these pain trajectories has already been published[8]. Three of these five trajectories started with low baseline pain scores; however, over time the trajectories show important differences. The ‘mild pain’ trajectory stayed at the same low pain level during the 2-year follow-up, the ‘moderate’ trajectory showed a moderate progression in pain score, and the ‘highly progressive’ trajectory showed a rapid progression in pain score.

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