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Associations between biomarkers of matrix metabolism and inflammation with pain and fatigue in participants suspected of early hip and or knee osteoarthritis: data from the CHECK study

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SUMMARY

Objectives: To assess the associations of biomarkers in serum [highsensitivity C-reactive protein (hs-CRP), serum cartilage oligomeric protein (sCOMP), serum propeptide of type I procollagen (sPINP) and serum osteocalcin (sOC)] and urine [urinary type II collagen telopeptide (uCTX-2)] with the extent and progression of nocturnal pain, pain while walking, and fatigue in participants with hip and/or knee pain suspected to be early stage osteoarthritis (OA).

Methods: hs-CRP, uCTX-2, sCOMP, sPINP and sOC were measured at baseline in 1,002 participants of the Cohort Hip and Cohort Knee (CHECK). Nocturnal pain, pain while walking and fatigue were assessed by self-reported questionnaires at baseline and 2-year follow-up. Associations between these biomarkers and symptoms were examined using logistic and linear regression analyses.

Results: hs-CRP was significantly associated with mild nocturnal pain (OR 1.18 95% CI 1.01−1.37), with mild and moderate pain while walking (OR 1.17 95% CI 1.01−1.35 and OR 1.56 95% CI 1.29−1.90, respectively) and with progression of nocturnal pain (OR 1.25 95% CI 1.07−1.46). uCTX-2 was associated with mild nocturnal pain (OR 1.40 95% CI 1.05−1.85) and with mild and severe-extreme pain while walking (OR 1.35 95% CI 1.04−1.75 and OR 2.55 95% CI 1.03−6.34, respectively). sPINP was associated with severe-extreme nocturnal pain (OR 0.45 95% CI 0.25−0.82). No significant associations were found for sCOMP and sOC, nor for any of the biomarkers and fatigue.

Conclusion: This study of biomarkers in a large cohort of participants with hip and/or knee pain suspected to reflect early stage hip and/or knee OA suggests that inflammation and cartilage matrix degeneration play a role in pain, but not in fatigue.

Introduction

Disability, joint pain and stiffness are commonly reported symptoms of (hip and knee) osteoarthritis (OA)[1]. Many patients with hip or knee OA experience elevated levels of fatigue[2,3], nocturnal pain[1] and pain aggravation during walking[4]. The pathophysiology of OA is more and more viewed as a continuum. The process is characterized by progression from an asymptomatic molecular phase to a final end-stage of hip/knee OA[5]. The phases of OA show slowly progressive damage of synovial joint tissue, including alterations of the bone and synovial tissue and cartilage destruction.

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process, or a pharmacologic response to a therapeutic intervention"[6]. Biomarkers often include biochemical markers that are intended to reflect specific molecular processes. A number of biomarkers of matrix metabolism of inflammation appear to be related to pathobiological mechanism underlying symptoms of hip and knee OA. The most promising markers at this

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moment are, linked to the clinical status of hip OA are urinary type II collagen telopeptide (uCTX-2), serum cartilage oligomeric protein (sCOMP) and serum high-sensitivity C-reactive protein (hs-CRP)[7]. A recent study from the Osteoarthritis Initiative database found COMP and uCTX-2 as clinically useful biomarkers for knee osteoarthritis.[8]

uCTX-2 is a marker of cartilage matrix degradation[9,10] and is also considered as marker of cartilage and bone metabolism[9]. sCOMP is a marker of cartilage and synovial tissue matrix degradation[11]. CRP is an active phase protein that is used as a nonspecific marker of systematic inflammation[12]. Aminoterminal propeptide of type I procollagen (sPINP) and osteocalcin (sOC) are markers of bone matrix synthesis[12–14]. These (bone remodelling) biomarkers might play a role in the pathological process related to nocturnal pain. Bone remodelling is found to be increased in OA joints[15], regulated by the bodies' circadian clock (resulting in daily variations[16]) and could therefore be related to nocturnal pain in hip or knee OA.

Still no OA biomarker has yet been shown to be adequate for clinical use. Most research on biomarkers is focused on participants with advanced hip/knee OA[17], or the incidence and progression of pain symptoms in OA[7]. The relation between OA biomarkers and distinct pain types and fatigue is still unknown. In addition to fatigue and nocturnal pain, we are especially interested in pain while walking, since it is considered a prodromal syndrome for OA[18,19]. Therefore, in the current study, five biomarkers were assessed in participants with complaints suspected to be early hip and/or knee OA from the Cohort Hip and Cohort Knee (CHECK) study. We were interested in exploring the extent to which biomarkers in blood and urine (hs-CRP, uCTX-2, sCOMP, sPINP and sOC) were associated with hip and knee OA symptoms (nocturnal pain, pain while walking and fatigue) and their progression over 2 years. These exploratory analyses might inform about specific pathobiological pathways underlying these symptoms.

Methods

General design

The data for the present study were acquired from the Cohort Hip and Cohort Knee (CHECK) study; details on this cohort are published elsewhere[20]. In short, the CHECK study is a prospective, 10-year follow-up cohort in the Netherlands of 1,002 individuals with hip and/or knee complaints. Individuals entered the cohort between October 2002 and September 2005. The inclusion criteria were: having stiffness and/or pain of the hip and/or knee, aged between 45 and 65 at the time of inclusion, and not yet having consulted a general practitioner for these symptoms or having had a first consultation for these symptoms within 6 months before. Exclusion criteria were having any other condition that could explain the symptoms (e.g., other rheumatic disease, previous hip/knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, etc.), comorbidity that would not allow physical evaluation and/or follow-up of at least 10-years duration, malignancy in the last 5 years, and inability to understand Dutch. For the present study we included all participants, regardless of whether they reported hip or knee pain at baseline. Medical ethics committees of all participating centres approved the study, and all participants gave written informed consent.

Biomarkers

At baseline, biomarker levels were assessed in serum (hs-CRP, sCOMP, sPINP and sOC) and second morning void urine (uCTX-2) samples, collected in a non-fasted state, between 8 and 12 AM. Marker levels were assessed by enzyme-linked immunosorbent assay (ELISA) or radioactive immunoassay (RIA), according to manufacturer instructions, as was described in detail previously[12]. This study demonstrated that quality controls revealed that gathered data were technically reliable and showed that the accuracy of the assessments were relatively good (i.e., low coefficients of variation; ranging between 3% and 12%). This was only not tested for hs-CRP[12]. Urinary biomarker levels were adjusted for urinary creatinine concentrations.

Clinical outcome variables

Nocturnal pain

The presence of nocturnal pain was indicated in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale pain score by the question “at night while in bed, what amount of pain have you experienced during the past 48 h?” (possible responses: none (0), mild (1), moderate (2), severe (3), and extreme (4)). Because of the relative small numbers of participants with severe and extreme pain, we combined those into one category “severe-extreme”. Progression of nocturnal pain was defined as a higher score for nocturnal pain at 2-year follow-up compared to baseline, where participants who reported severe-extreme nocturnal pain at baseline were excluded.

Pain while walking

The presence of pain while walking was indicated in the WOMAC subscale pain score by the question “while walking on a flat surface, what amount of pain have you experienced during the past 48 h?” (possible responses: none (0), mild (1), moderate (2), severe (3), and extreme (4)). Because of the relative small numbers of participants with severe and extreme pain, we combined those into one category “severe-extreme”. Progression of pain while walking was defined as a higher score for pain while walking at 2-year follow-up compared to baseline, where participants who reported severe-extreme pain while walking at baseline were excluded.

Fatigue

Fatigue was determined using the SF-36 Fatigue subscale (also mentioned as Vitality subscale)[21]. The SF-36 Fatigue subscale includes 4 questions (Did you feel full of pep? Did you have a lot of energy? Did you feel worn out? Did you feel tired?) evaluating the past 4 weeks, each item has a 6-level response format, ranging from “all of the time” to “none of the time”. The items are summed and linearly transformed to a range from 0 to 100, with a higher score indicating less fatigue. Progression of fatigue is classified if the score after 2 year follow-up was lower compared to baseline, with at least 10 points difference (scale from 0 to 100) i.e., a lower score is higher levels of fatigue. The suggested minimum clinically important difference (MCID) in SF-36 domains ranges from 5 to 10 points[22,23]; for this study we chose a conservative MCID of $\geq$10 to consider a change as clinically relevant.

Other determinants/covariates

Other information on pain and other joint symptoms was collected by (self-reported) questionnaires and physical examination at baseline and 2 years follow-up. Demographic variables used are age, sex, ethnicity, body mass index (BMI) and education level. The WOMAC questionnaire was also used to measure stiffness (0–8), physical functioning (0–68), pain (0–20) and the total summed score (0–100), with higher scores indicating worse health. During follow-up the participants were asked if they had any hip pain (yes/no) and if they had any knee pain (yes/no).

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	Total study population
Number of participants	1,002
Age in years, mean (SD)	55.9 (5.2)
Female, *n* (%)	792 (79)
Body mass index (kg/m^2), mean (SD)	26.2 (4.0)*
Highest education level (higher), *n* (%)	344 (35)*
Duration of complaints in months, median (IQR)	14 (3–96)**
Nocturnal pain, *n* (%)	*
- None	320 (33)
- Mild	339 (35)
- Moderate	224 (23)
- Severe	78 (8)
- Extreme	11 (1)
Pain while walking, *n* (%)	*
- None	398 (41)
- Mild	402 (41)
- Moderate	149 (15)
- Severe	19 (2)
- Extreme	3 (0.3)
Fatigue (0–100), mean (SD) (higher is less fatigue)	64.2 (16.8)*
Hip pain, *n* (%)	588 (59)
Knee pain, *n* (%)	832 (83)
Both hip and knee pain, *n* (%)	418 (42)
WOMAC, mean (sd) (higher scores is worse)	*
• Pain (0–20)	5.1 (3.4)
• Stiffness (0–8)	2.7 (1.7)
• Physical function (0–68)	16.0 (11.7)
• Total sum score (0–100)	24.7 (16.4)
Radiographic hip OA, either hip, *n* (%)	164 (17)*
Radiographic knee OA, either knee, *n* (%)	159 (16)*
hs-CRP, median (IQR)	1.4 (0.2–14.7)*
uCTX-2, median (IQR)	192.9 (44.5–525.2)*
sCOMP, median (IQR)	8.5 (4.9–14.3)*
sPINP, median (IQR)	42.0 (18.2–96.4)*
sOC, median (IQR)	13.1 (5.9–29.4)*

Mean values with the standard deviation (SD) or median with the Interquartile Range (IQR) or number of participants with percentages.
WOMAC = Western Ontario and McMaster osteoarthritis index, hs-CRP = high sensitive C-reactive protein (mg/l), uCTX-2 = type II collagen telopeptide (ng/mmol), sCOMP = cartilage oligomeric protein (μg/ml), sPINP = type I procollagen (ng/ml), sOC = osteocalcin (ng/ml). *missing values < 4.2% **missing values = 13%.

Table I

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Baseline characteristics

Radiographs: At baseline standardized radiographs were collected: anteroposterior view (AP) pelvis view or unilateral faux profile view (FP) (both hips) of the hips and of the tibiofemoral joints (both knees). Radiographs were centrally scored[24] according to the Kellgren and Lawrence (KL) classification system[25]. For both hips and knees, there was substantial inter-observer reliability on overall KL-scores[26]. Radiographic hip or knee OA (ROA) was defined as KL grade ≥2. To correct for the severity of systemic ROA, we summed all the four separate KL-scores into one overall KL-sum.

Statistical analyses

All analyses were done in the total population. Descriptive analyses were used to describe the baseline characteristics. Logistic and linear regression models were used to examine associations of the biomarkers (hs-CRP, uCTX-2, sCOMP, sPINP and sOC) with the extent of nocturnal pain, pain while walking and fatigue at baseline and the progression of these between baseline and 2 years follow-up. In all analyses, the biomarkers were transformed with the natural log to normalize their distributions. The association of each individual biomarker with the outcome of interest was studied with stepwise adjustment for potential confounders. In model 1, the association of the marker with the outcome of interest was adjusted for sex and age. The next models were only performed when the biomarker had an estimation with P <0.10 in model 1. In model 2, the association was adjusted for sex, age, and BMI. In model 3, the association was adjusted for sex, age, BMI, as well as for the total sum of KL grades for hips and knees (KL-sum), and the presence of hip pain (yes/no) and knee pain (yes/no). All measures of association are presented as odds ratios (OR) when the outcome is categorical (for the extent of nocturnal pain and pain while walking; none was the reference group) or dichotomous (progression of the outcomes), and as standardized betas when the outcome was continuous (fatigue). Statistical analyses were performed using SPSS V24.0 (IBM).

Results

An overview of the baseline characteristics of participants is shown in Table I. The mean age was 55.9 (SD = 5.2) years and 79%

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Model 3: Cross-sectional						
Outcome	Biomarker					
		lnCRP	lnCTX-2	lnCOMP	lnPINP	lnOC
Nocturnal pain	None	Ref	Ref	–	Ref	Ref
	Mild	**1.18 (1.01–1.37)**	**1.40 (1.05–1.85)**	–	0.76 (0.51–1.12)	1.01 (0.67–1.52)
	Moderate	1.04 (0.87–1.24)	1.31 (0.96–1.79)	–	0.80 (0.51–1.24)	1.01 (0.64–1.59)
	Severe-extreme	1.15 (0.91–1.46)	1.25 (0.82–1.90)	–	**0.45 (0.25–0.82)**	0.65 (0.35–1.20)
Pain walking	None	Ref	Ref	–	Ref	Ref
	Mild	**1.17 (1.01–1.35)**	**1.35 (1.04–1.75)**	–	0.79 (0.56–1.13)	1.05 (0.73–1.51)
	Moderate	**1.56 (1.29–1.90)**	1.08 (0.76–1.52)	–	0.65 (0.39–1.07)	0.68 (0.41–1.14)
	Severe-extreme	1.06 (0.68–1.64)	**2.55 (1.03–6.34)**	–	0.65 (0.21–1.95)	1.37 (0.44–4.27)
Fatigue		−0.07 $P = 0.051$	–	–	–	–

Model 3 was only performed when the biomarker had an estimation with P <0.10 in model 1, if the estimation had a P-value ≥0.10 in model 1, we noted a line (–).

Table II

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Adjusted odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models for the extent of nocturnal pain, pain while walking in relation to biomarkers levels or standardized beta's with a ***P***-value from linear regression models for the level of fatigue at baseline in relation to biomarker levels, adjusted for sex, age, BMI, as well as for the total sum of KL grades for hips and knees (KL-sum), and the presence of hip pain and knee pain (model 3)

was female. The median duration of complaints was 14 months, 17% of the participants had radiographic hip OA and 16% had radiographic knee OA (K&L ≥ 2). At baseline, 59% of the participants reported hip pain, 83% reported knee pain, and a total 42% reported both hip and knee pain.

At follow-up, progression of nocturnal pain was reported by 23% (204/879) of the participants. Progression of pain while walking was observed in 22% (193/891). Progression of fatigue was observed in 28% (260/914).

Associations between clinical outcomes and biomarkers

The following biomarkers had an estimation with P <0.10 in model 1: hs-CRP, uCTX-2, sPINP and sOC for both the extent of nocturnal pain and pain while walking and hs-CRP for the extent of fatigue and progression of nocturnal pain (Supplemental Tables S1 and S3). The results of the fully adjusted analyses are presented in Table II (model 3, cross-sectional); other results can be found in Supplemental Tables S1–S5.

Nocturnal pain

At baseline, higher levels of hs-CRP and uCTX-2 were significantly associated with mild nocturnal pain compared to no nocturnal pain (OR 1.18 95% CI 1.01–1.37 and OR 1.40 95% CI 1.05–1.85, respectively). We also found a negative association for PINP with severe-extreme nocturnal pain (OR 0.45 95% CI 0.25–0.82). During 2 years follow-up, hs-CRP was significantly associated with progression of nocturnal pain (OR 1.24 95% CI 1.06–1.45).

Pain while walking

At baseline, higher hs-CRP levels were significantly associated with mild and moderate pain while walking compared to no pain while walking (OR 1.71 95% CI 1.01–1.35 and OR 1.56 95% CI 1.29–1.90, respectively). At baseline also a higher level of uCTX-2 was significantly associated with mild and severe-extreme pain while walking compared to no pain while walking (OR 1.35 95% CI 1.04–1.75 and OR 2.55 95% CI 1.03–6.34, respectively). During follow-up, for progression of pain while walking, we did not observe any significant association with any biomarker.

Fatigue

We did not observe any association between the biomarkers and the extent of fatigue or progression of fatigue (Table II).

Discussion

In participants with symptoms suspected to be early stage of hip and/or knee OA, we found that higher hs-CRP levels (inflammation) were associated with severity of nocturnal pain, with severity of pain while walking, and with progression of nocturnal pain severity. We also found that higher uCTX-2 levels (cartilage matrix degeneration) were associated with severity of both nocturnal pain and pain while walking. Higher levels of PINP (bone synthesis) were associated with severe-extreme nocturnal pain. For sCOMP (matrix metabolism) and sOC (bone synthesis) no associations with any of the symptoms were found. Neither did we found any associations between the biomarkers and fatigue.

We found that higher hs-CRP levels were associated with nocturnal pain, pain while walking and the progression of nocturnal pain. Earlier studies also found associations between hs-CRP levels and pain, although not specific for nocturnal pain or pain while walking[27,28]. One of these is a meta-analysis showing a weak, but statistically significant positive correlation between hs-CRP and pain scores in patients with hip and knee OA[28]. Inflammatory processes cause localized damage to tissue as well as activation and hypersensitivity of peripheral nociceptors in the joint[29,30]. Additionally, patients with knee OA demonstrated increased inflammation in the leg musculature[31]. Both pathways, inflammatory and mechanical, might play a role in the associations between hs-CRP and nocturnal pain, pain while walking and the progression of nocturnal pain.

The associations between uCTX-2 and both nocturnal pain severity and severity of pain while walking in our study are

supported by previous findings that CTX-2 was associated to pain[32,33]. In our study, we further distinguished between nocturnal pain (non-weight-bearing) and pain while walking (weight-bearing). Our results were partly in line with a study from Bihlet *et al.*[34], showing that uCTX-2 was associated with weight-bearing pain, but not with non-weight-bearing pain. Bihlet *et al.* used the WOMAC pain subscale to create combined variables of weight-bearing questions (3 questions) and non-weight-bearing questions (2 questions). As opposed to this study (where a composites of the WOMAC pain sub-scale were constructed), we distinguished between nocturnal pain and pain while walking in particular. Moreover, we used the categorical answer options from the WOMAC question about nocturnal pain and the WOMAC question on pain while walking. This could explain why we found an association between CTX-2 and nocturnal (non-weight-bearing) pain, while Bihlet *et al.* did not.

For severe-extreme nocturnal pain, we found a negative association with PINP. This may indicate that decreased bone turnover is underlying nocturnal pain. However, it is important to realize, that this group of participants with severe-extreme nocturnal pain was relatively small and no similar association with mild or moderate nocturnal pain or for the other bone biomarkers was found. In one other study, a negative association between PINP and early knee OA was found, although this was in a population of premenopausal females[35]. Our study group consisted of 76% of females of whom most were postmenopausal (60%, $n = 475$). In a sensitivity analysis limited to postmenopausal women, no associations were found with PINP, although we lost power due to a smaller population (data not shown). More research is needed to give meaning to this outcome.

We did not find any association between systemic biomarker levels and the extent or progression of fatigue. With that, the etiology of fatigue remains poorly understood. A 2019 review[36] on fatigue in OA, based on two studies only, concluded that there is lack of evidence to characterize the relationship between fatigue and systemic inflammation[36–38]. A study on fatigue in rheumatoid arthritis (RA), characterized by systemic inflammation, concluded that fatigue levels in RA patients did not differ essentially from those in OA. This study also found that fatigue was not related to measures of inflammation (swollen joint count and Erythrocyte Sedimentation Rate)[39].

Although measuring hs-CRP is common in general practice, we do not think there is a clinical implication for the associated biomarkers in daily practice. For now, the association is to weak and causality unknown. Moreover, at present it seems more efficient and informative to just ask the question during consultation whether a patient is suffering from nocturnal pain, pain while walking or fatigue than to determine biomarkers.

Strengths of our study are the large cohort, its longitudinal design, and a number of promising biomarkers that were simultaneously assessed with clinically relevant outcome measures. Moreover, to the best of our knowledge, this study is the first study investigating associations between distinct types of pain and biomarkers. As any study, this study has limitations as well. The first is that biomarkers in serum and urine are not specifically related to one joint, but also relate to systemic metabolism. Although we have data of participants reported hip and/or knee pain on baseline, we believe that stratification for these joints would result in small subgroups and would not add relevant information. A second limitation of our study might be that biomarkers were measured at baseline only and not during follow-up. Information whether repeated measurements of biomarkers has an additional value is lacking. Another possible limitation is the definition of progression of symptoms, especially fatigue. For fatigue, quantified on a scale from 0 to 100, we defined a rise of 10 points (=10%) as clinically relevant. But maybe this was still too small to obtain relevant estimations. We were able to use a big biomarker dataset. There are, however, a number of promising biomarkers for in-tissue inflammation not available (e.g., CRTAC1[40], C1M and C3M[10]). Finally, a comparison between patients with and without any joint symptoms would have been of additive value to see whether the identified associations are specific for OA.

In conclusion, in this study of five biomarkers in a large cohort of participants with hip and knee pain suspected to be early stage of OA, we provide indications of pathobiological processes involved in OA symptoms. hs-CRP and uCTX-2 showed the most consistent association with severity of nocturnal pain and progression of nocturnal pain and severity of pain while walking, indicating that inflammation and/or cartilage degeneration could contribute to these complaints. More research is needed to confirm these findings.

Data availability statement

Datasets analysed during the current study are available from the corresponding author on reasonable request.

Patient and public involvement

This study was conducted without patient and public involvement.

Authors' contributions

ACB, DS, WES, SBZ contributed to the conception and design of this study. ACB, DS, WES and SBZ contributed to the analysis of data. All authors contributed to the interpretation of data. Article draughts were written by ACB and critically revised by all authors. The final version of the article was approved by all authors.

Competing interests

The authors have declared no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2022.08.013.

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