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The ability of systemic biochemical markers to reflect presence, incidence, and progression of early-stage radiographic knee and hip osteoarthritis: data from CHECK

W.E. Van Spil † *, P.M.J. Welsing †, S.M.A. Bierma-Zeinstra ‡, J.W.J. Bijlsma †, L.D. Roorda §, H.A. Cats ||, F.P.J.G. Lafeber †

† *Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands*
‡ *Department of General Practice, Department of Orthopaedics, University Medical Center Rotterdam - Erasmus Medical Center, PO Box 2040, 3000 CA, Rotterdam, The Netherlands*
§ *Amsterdam Rehabilitation Research Center, Reade, PO Box 58271, 1040 HG, Amsterdam, The Netherlands*
|| *Sint Maartenskliniek, PO Box 9011, 6500 GM, Nijmegen, The Netherlands*

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SUMMARY

Objective: To relate systemic biochemical markers of joint metabolism to presence, incidence, and progression of early-stage radiographic knee and/or hip osteoarthritis (OA).
Method: The cartilage markers uCTX-II, sCOMP, sPIIANP, and sCS846, bone markers uCTX-I, uNTX-I, sPINP, and sOC, and synovial markers sHA and sPIIINP were assessed by enzyme-linked immunosorbent assay or radioactive immunoassay in baseline samples of CHECK (Cohort Hip and Cohort Knee), a cohort study of early-stage symptomatic knee and/or hip OA. Knee and hip radiographs were obtained at baseline and 5-year follow-up. Presence of OA at baseline was defined as Kellgren and Lawrence (K&L) = 1 (maximum observed). Incidence of OA was defined as K&L = 0 at baseline and K&L ≥ 1 at 5-year follow-up. Progression of OA was defined as K&L = 1 at baseline and K&L ≥ 2 at 5-year follow-up.
Results: Data were available for 801 subjects at baseline and for 723 subjects at both baseline and 5-year follow-up. Multiple cartilage and synovial markers showed positive associations with presence and progression of knee and hip OA and with incidence of hip OA, except for negative associations of uCTX-II and sCOMP with incidence of knee OA. uCTX-II and sCOMP showed multiple interactions with other biomarkers in their associations with knee and hip OA. Bone markers were positively associated with presence of radiographic knee OA, but negatively associated with progression of radiographic hip OA.
Conclusion: Especially metabolism in cartilage and synovial matrix appear to be of relevance in knee and hip OA. The role of bone metabolism appears to differ between knee and hip OA.

Introduction

Biochemical markers (biomarkers) of joint metabolism have been proposed as tools that could help along the challenging road to efficacious diagnosis and treatment of OA[1]. Biomarkers are mostly tested in only small study populations and in isolation rather than in combination[2]. Moreover, many studies focus on subjects with advanced OA[2], while it are actually the early-stage disease subjects that would need to take advantage of any future biomarkers the most. They are the ones that are most likely to benefit from disease-modifying drugs and sensitive outcome measures for clinical trials in such early-stage subjects are eagerly awaited.

In the current study, ten systemic biomarkers of joint metabolism were simultaneously assessed in subjects with symptomatic knee and/or hip OA with no or minimum radiographic OA signs from CHECK (Cohort Hip and Cohort Knee). Earlier publications on these biomarkers in CHECK have demonstrated their associations

* Address correspondence and reprint requests to: W.E. Van Spil, Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands. Tel: 31-88-7557063; Fax: 31-30-2523741.
E-mail addresses: w.e.vanspil@umcutrecht.nl (W.E. Van Spil), p.m.j.welsing@umcutrecht.nl (P.M.J. Welsing), s.bierma-zeinstra@erasmusmc.nl (S.M.A. Bierma-Zeinstra), j.w.j.bijlsma@umcutrecht.nl (J.W.J. Bijlsma), l.roorda@reade.nl (L.D. Roorda), h.cats@maartenskliniek.nl (H.A. Cats), f.lafeber@umcutrecht.nl (F.P.J.G. Lafeber).

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with demographic variables[3,4], their mutual associations[3,5], and their associations with radiographic knee parameters and pain[6]. This time, we investigated to what extent these biomarkers reflected concurrent radiographic knee and hip OA and related to future incidence as well as progression of knee and hip OA during 5-year follow-up. With that, we tried to elucidate aspects of the pathogenesis of OA.

Method

Cohort characteristics

CHECK is a longitudinal cohort study of 1002 subjects, age 45–65 years at the time of inclusion, with pain and/or stiffness of one or both knee(s) and/or hip(s)[7]. They had never or not longer than 6 months ago consulted a physician for these symptoms for the first time. Subjects with any other pathological condition that could explain the symptoms (e.g., other rheumatic diseases, previous joint replacement) were excluded. Subjects needed to be sufficiently ambulatory to attend all follow-up visits.

At baseline, CHECK subjects (79.0% female) were age 56 ± 5 years (mean ± SD) and had a median (25–75% percentiles) BMI of 25.5 (23.3–28.4) kg/m^2. Median (25–75% percentiles) WOMAC scores, ranging between 0 and 100 and higher scores representing more complaints, were 25 (10–35) for pain, 38 (25–50) for stiffness, and 21 (10–35) for physical function.

Chronic liver disease was reported by three subjects (0.3%) and chronic renal disease by one subject (0.1%). Excluding these subjects did not change results essentially. Bisphosphonate use was not registered systematically. However, since osteoporosis was reported by only four subjects (0.04%), the use of these agents was presumably low.

Biochemical markers

Biomarker levels were assessed in baseline serum and second morning void urine samples from CHECK, collected once, in a non-fasted state, between 8 and 12 AM. Biomarker levels were assessed by enzyme-linked immunosorbent assay or radioactive immunoassay, as was described in more detail previously[3]. The large-scale assessment was performed over a number of days. Multiple quality controls were included and were unremarkable. Intra-plate, inter-plate, and between-day coefficients of variation (standard deviation/mean*100%) and median (interquartile range) biomarker levels were as follows: C-terminal telopeptide of collagen type II (CTX-II; Urine CartiLaps EIA, Immunodiagnostic systems Ltd., Boldon, UK): 10.0%, 9.3%, and 12.4%; 193 (132–281) ng/mmol. Cartilage oligomeric matrix protein (COMP; AnaMar Med AB, Göteborg, Sweden): 5.0%, 4.0%, and 4.2%; 8.5 (7.2–9.9) U/l. N-terminal propeptide of procollagen type IIA (PIIANP; Millipore Corp, Billerica, MA, US): 15.8%, 7.0%, and 15.7%; 1385 (1087–1771) ng/ml. Chondroitin sulphate 846 (CS846; IBEX, Montreal, Canada): 21.5%, 16.9%, and 15.3%; 70 (54–88) ng/ml. C-terminal telopeptide of collagen type I (CTX-I, Urine CrossLaps EIA, Immunodiagnostic systems Ltd., Boldon, UK): 9.7%, 6.1%, and 2.7%; 152 (100–225) μg/mmol. N-terminal telopeptide of collagen type I (NTX-I, OSTEOMARK NTx Urine, Wampole Laboratories, Princeton, US): 14.9%, 6.6%, and 10.7%; 37 (28–51) nM BCE/mmol. N-terminal propeptide of procollagen type I (PINP, UniQ, Orion Diagnostica, Espoo, Finland): 4.4%, 4.5%, and 6.2%; 42 (32–56) ng/ml. Osteocalcin (OC, N-MID Osteocalcin ELISA, Immunodiagnostic systems Ltd., Boldon, UK): 3.4%, 4.1%, and 4.3%; 13 (10–17) ng/ml. Hyaluronic acid (HA; Corgenix Inc, Westminster, CO, US): 15.1%, 13.0%, and 17.3%; 27 (17–43) ng/ml. N-terminal propeptide of procollagen type III (PIIINP; UniQ, Orion Diagnostica, Espoo, Finland): 5.4%, 3.2%, and 7.2%; 4.1 (3.5–4.9) ng/ml. Urinary biomarker levels were adjusted for urinary creatinine concentrations (automated kinetic assay, UniCel® DxC 800 Synchron® Clinical System, Beckman Coulter).

Radiographic data acquisition

Knee and hip radiography were performed at baseline and 5-year follow-up. Knee radiographs were made in a weight-bearing posteroanterior view, semiflexed. For the hip, weight-bearing anteroposterior radiographs of the pelvis were made with hips in 15° internal rotation. Radiographs were scored by five trained observers according to Kellgren & Lawrence (K&L)[8], in a paired fashion, with known sequence. A random subset of radiographs of 38 subjects was read by all observers, independently of each other, yielding moderate to substantial inter-observer agreement (Cohen's kappa = 0.60 for presence of K&L ≥ 2 in the knees at 5-year follow-up).

Definitions

Knee and/or hip pain were classified as either present or absent according to the history of the patient that was obtained by an experienced rheumatologist.

In each subject one index knee and one index hip were defined at baseline. When only one of both joints was painful that joint was considered the index joint. When both or none of the joints were painful the index joint was randomly selected from both.

Biomarkers were consecutively tested for associations with presence, incidence, and progression of radiographic OA of the index joint. Presence of radiographic OA of the index joint at baseline was defined as K&L = 1 (maximum observed, vs index joints that scored K&L = 0 at baseline). Incident radiographic OA of the index joint was defined as a K&L = 0 at baseline and K&L ≥ 1 at 5-year follow-up for the index joint (vs index joints scoring K&L = 0 at both baseline and 5-year follow-up). Progression of radiographic OA of the index joint was defined as K&L = 1 at baseline and a K&L grade ≥2 in the index joint at 5-year follow-up (vs index joints showing no increase at 5-year follow-up). These definitions were considered most appropriate in these early-stage OA subjects.

Statistical analysis

Cross-sectional associations between biomarkers (independent variables) and presence of radiographic OA in the index joint (dependent variable) were investigated by binary logistic regression, first adjusted for concurrent radiographic OA in the contralateral joint (either present or absent) and in hips or knees (either absent, unilateral, or bilateral) only, and in a next step also adjusted for age, gender, and BMI.

Associations of baseline biomarkers (independent variables) with incidence of radiographic OA or progression of radiographic OA in the index joint during follow-up (dependent variable) were first performed with adjustment for baseline radiographic OA in the index joint and its contralateral joint (present or absent) and in hips or knees (either absent, unilateral, or bilateral) as well as for radiographic OA changes during follow-up in the contralateral joint and hips or knees (occurrence of OA incidence or progression: yes or no). In a next step they were also adjusted for age, gender, and BMI.

To facilitate comparison between biomarkers and between analyses, biomarkers were logarithmically transformed and standardized as z-scores. Z-scores reflect how many standard deviations (SD) raw scores deviate from the population mean. As such, presented odds ratios (OR) indicate the change (ratio) of odds