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Associations of markers of matrix metabolism, inflammation markers, and adipokines with superior cam deformity of the hip and their relation with future hip osteoarthritis

W.E. van Spil † *, R. Agricola ‡, K.W. Drossaers-Bakker §, H. Weinans † ||, F.P.J.G. Lafeber †

† *University Medical Center Utrecht, Utrecht, The Netherlands*
‡ *Erasmus Medical Center, Rotterdam, The Netherlands*
§ *Medisch Spectrum Twente, Enschede, The Netherlands*
|| *Technical University, Delft, The Netherlands*

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SUMMARY

Objective: First, to study how markers of matrix metabolism, inflammation markers, and adipokines relate to (superior) cam deformity and (possible) cam impingement of the hip. Second, to investigate whether they can identify subjects with cam deformity that are at risk of future hip osteoarthritis (OA).
Method: In a cohort of 1002 subjects (CHECK), (superior) cam deformity was defined by an alpha angle >60° on anteroposterior pelvic radiographs and (possible) cam impingement by a cam deformity together with internal hip rotation ≤20°. Hip OA at 5-year follow-up was defined by Kellgren and Lawrence grade ≥2 or total hip replacement.
Results: Subjects with (superior) cam deformity and (possible) cam impingement showed lower levels of bone turnover markers (uCTX-I, uNTX-I, sPINP, sOC) than those without. Cam deformity was positively associated with future hip OA, but associations were weaker at high levels of bone turnover. sCOMP and sHA levels were higher in subjects with cam deformity, while other cartilage and synovium markers were not. Some markers of inflammation (pLeptin, pAdiponectin, and erythrocyte sedimentation rate) were lower in presence of cam deformity and cam impingement, but high-sensitivity C-reactive protein was not. Most associations depended largely on gender differences.
Conclusion: Bone metabolism may be relevant in the pathogenesis of (superior) cam deformity and in the development of (superior) cam deformity into hip OA. Subjects with cam deformity and cam impingement surprisingly showed lower levels of inflammation markers and adipokines. Associations of cartilage turnover markers with cam deformity and cam impingement were less obvious.

Introduction

Osteoarthritis (OA) should no longer be considered a single disease entity, but rather a heterogeneous disease with varying features between subtypes[1,2]. In the past decade, it has become apparent that in particular subgroups of patients abnormal hip morphology is an important factor in the development of hip OA[3]. Especially the presence of cam deformity, characterized by extra bone formation at the anterolateral femoral head–neck junction, was found to be strongly associated with future development of hip OA[4].

Still, most individuals with cam deformity will not develop OA. Reported positive predictive values of cam deformity to determine hip OA vary between 6% and 25% and negative predictive values between 98% and 99%[5]. This suggests that although cam deformity is a risk factor for hip OA, additional factors (e.g., sport activities) do influence the probability of developing OA. As the pathophysiology of cam impingement includes gradual changes in cartilage and subchondral bone structure[6,7], serum and urinary biochemical markers of matrix metabolism from these tissues might help in identifying those particular individuals with cam deformity that will develop hip OA.

* Address correspondence and reprint requests to: W.E. van Spil, University Medical Center Utrecht, Utrecht, The Netherlands. Tel: 31-88-75-573-57; Fax: 31-88-75-556-39.
E-mail addresses: w.e.vanspil@umcutrecht.nl (W.E. van Spil), r.agricola@erasmusmc.nl (R. Agricola), w.drossaers@mst.nl (K.W. Drossaers-Bakker), h.h.weinans@umcutrecht.nl (H. Weinans), f.lafeber@umcutrecht.nl (F.P.J.G. Lafeber).

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A few studies have suggested that metabolic changes and inflammation do occur in cam impingement. Plasma levels of cartilage oligomeric matrix protein (COMP) and C-reactive protein (CRP) were increased in athletes with femoroacetabular impingement (FAI; cam-type, pincer-type, or mixed) as compared to control athletes[8]. In line with these findings, gene expression profiles suggested an heightened metabolic state in cartilage of the impingement zone as compared with healthy and osteoarthritic cartilage[6]. However, to the best of our knowledge, epidemiological studies on this subject are currently unavailable. Moreover, no studies have tried to stratify subjects with cam deformity using biochemical markers in order to determine their risk of future hip OA.

In the current study, we measured baseline levels of biochemical markers of matrix metabolism, inflammation markers, and adipokines in CHECK (Cohort Hip and Cohort Knee), a large prospective cohort study of 1002 subjects with early-stage knee and/or hip symptoms. Our first aim was to examine cross-sectional associations of these levels with presence of (superior) cam deformity and (possible) cam impingement, the latter being a combination of a radiographic cam deformity together with clinical signs of impingement. This might elucidate aspects of the pathogenesis of cam deformity and impingement. Our second aim was to investigate whether these levels could predict which hips with a cam deformity continued to develop hip OA in the next five years.

Method

Cohort characteristics

The current study was performed using 5-year data from CHECK, a cohort of subjects age 45–65 years, with pain and/or stiffness of one or both knee(s) and/or hip(s) at baseline, that at the time of inclusion had never or not longer than 6 months ago visited a general physician for these complaints for the first time[9]. Subjects with any other pathological knee and/or hip condition(s) that could explain these symptoms were excluded. For the hip these alternative conditions included other rheumatic diseases, trauma, dysplasia, Perthes disease, subluxation, osteochondritis dissecans, fracture, previous hip surgery, acetabular protrusion, Kellgren and Lawrence (K&L) grade 4 or previous joint replacement, and subjects only having symptoms of bursitis or tendinitis.

Biochemical marker and adipokine assessment

Biochemical marker, high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and adipokine levels were assessed in serum, plasma, and second morning void urine samples, collected in a non-fasted state, between 8 and 12 AM. Biochemical markers and adipokines were assessed by enzyme-linked immunosorbent assay or radioactive immunoassay, according to manufacturer instructions, as was described previously[10]. Intra-plate, inter-plate, and between-day coefficients of variation (standard deviation/mean*100%) 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%. Cartilage oligomeric matrix protein (Anamar Med AB, Göteborg, Sweden): 5.0%, 4.0%, and 4.2%. N-terminal propeptide of procollagen type IIA (PIIANP; Millipore Corp, Billerica, MA, US): 15.8%, 7.0%, and 15.7%. Chondroitin sulphate 846 (CS846; IBEX, Montreal, Canada): 21.5%, 16.9%, and 15.3%. C-terminal telopeptide of collagen type I (CTX-I, Urine Crosslaps EIA, Immunodiagnostic systems Ltd., Boldon, UK): 9.7%, 6.1%, and 2.7%. N-terminal telopeptide of collagen type I (NTX-I, OSTEOMARK NTx Urine, Wampole laboratories, Princeton, US): 14.9%, 6.6%, and 10.7%. N-terminal propeptide of procollagen type I (PINP, UniQ, Orion Diagnostica, Espoo, Finland): 4.4%, 4.5%, and 6.2%. Osteocalcin (OC, N-MID Osteocalcin ELISA, Immunodiagnostic systems Ltd., Boldon, UK): 3.4%, 4.1%, and 4.3%. Hyaluronic acid (HA; Corgenix Inc, Westminster, CO, US): 15.1%, 13.0%, and 17.3%. N-terminal propeptide of procollagen type III (PIIINP; UniQ, Orion Diagnostica, Espoo, Finland): 5.4%, 3.2%, and 7.2%. Leptin (BioVendor, Modrice, Czech Republic): 7.8, 5.7, and 7.0%. Adiponectin (BioVendor, Modrice, Czech Republic): 18.9, 14.3, and 9.0%. Resistin (BioVendor, Modrice, Czech Republic): 7.1, 3.9, and 2.5%. Urinary biomarker levels were adjusted for urinary creatinine concentrations (automated kinetic assay, UniCel® DxC 800 Synchron® Clinical System, Beckman Coulter). Serum levels of hsCRP were assessed by an automated nephelometric assay (BN™ II analyzer, Siemens, routine clinical chemistry laboratory, University Medical Center Utrecht, Utrecht, The Netherlands). ESR was assessed according to clinical practice in each of the ten participating medical centers.

Radiographic and clinical assessments

Weight-bearing anteroposterior pelvic radiographs were obtained at baseline and after 5 years, according to standardized protocols. Feet were positioned such that the medial side of the distal part of the first phalanx touched. A wedge was used to assure 15° internal rotation. The tube to film distance was 100 cm and the beam was centered at the top of the pubic symphysis. On these radiographs, the shape of the proximal femur was then outlined using statistical shape modelling (SSM) software (ASM tool kit, Manchester University, Manchester, UK) so that the alpha angle could be calculated automatically, as was all explained in more detail before[4]. The alpha angle measures the extent to which the femoral head deviates from spherical, as is shown in Fig. 1, and is the most frequently applied parameter for quantifying cam deformity. Osteophytes were excluded while placing the SSM point set from which the alpha angle was quantified.

In the current study, both cam deformity and cam impingement were investigated. Presence of radiographic (superior) cam deformity was defined by an alpha angle threshold of >60° on the anteroposterior radiographs, as was recently validated in the CHECK and Chingford cohorts[11]. (Possible) Cam impingement was defined by the presence of cam deformity together with limited internal hip rotation of ≤20° (as measured in 90° of hip flexion), the latter being a clinical sign suggestive of cam impingement[12].

In addition, all anteroposterior pelvic radiographs were scored for hip OA according to the K&L classification system (grade 0–4)[13]. Presence of hip OA at 5-year follow-up was defined by K&L grade ≥2 changes or total hip replacement. Radiographs of tibiofemoral knee joints were made in a weight-bearing posteroanterior view, semiflexed (7–10 degrees) and were also scored for knee OA according to the K&L classification system, as was explained in more detail before[14].

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

Statistical analysis

In all analyses, hip parameters were included for each hip individually. To take into account the probable dependence between the two hips in one subject we used generalized estimation equation analysis. Logistic models for binary outcomes were created, introducing continuous variables as covariates (age; body mass index; biochemical marker and adipokine levels) and discrete variables as factors (gender; knee pain absent, unilateral, or bilateral; knee OA absent, unilateral, or bilateral; hip OA absent or