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Articular cartilage calcification of the hip and knee is highly prevalent, independent of age but associated with histological osteoarthritis: evidence for a systemic disorder

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SUMMARY

Objectives: Based on the concept of a systemic predisposition for articular cartilage calcification (CC), the aim of this study was to determine the prevalence and amount of bilateral CC of hip and knee joints in an unselected sample cohort by high-resolution digital contact radiography (DCR) and to analyze the association of CC with histological OA.
Methods: Both hip and knee joints of 87 donors (48 m and 39 f; mean age 62) were analyzed by DCR in this post-mortem study of an unselected cohort of donors. Histological OA (OARSI) of the main load bearing area of femoral heads and medial femoral condyles was determined.
Results: The prevalence of CC of the femoral head was 96.6%, of the knee 94.3%. Bilateral calcification was detected in 79.3% of hips and 86.2% of knees. Concomitant CC of all four joints was detected in 69.0% of donors. There was no difference between the amount of CC of hips and knees ($P = 0.47$). The amount of CC of any given hip or knee correlated with that of the contralateral hip ($r_s = 0.54$, $P < 0.001$) or knee ($r_s = 0.50$, $P < 0.001$). There was a correlation between the amount of CC and histological OA (hips $r_s = 0.48$, $P < 0.001$, knees $r_s = 0.30$, $P = 0.004$), but not between CC and age (hips $r_s = -0.09$, $P = 0.42$; knees $r_s = 0.10$, $P = 0.34$).
Conclusions: These data support the concept that articular CC occurs as the result of a systemic disorder. CC appears to be an early element of hip and knee OA pathogenesis independent of age.

Introduction

Ectopic calcification of hyaline articular cartilage and fibrocartilage is considered a pathologic process[1] and is referred to as chondrocalcinosis[2]. The European League Against Rheumatism (EULAR) defines the knee as the target joint[2]. Based on plain radiography, the prevalence of knee cartilage calcification (CC) is reported to be between 7%[3] and 8.5%[4] in the general population. Epidemiological studies have identified the knee as the joint most often affected by CC[5,6]. The sensitivity of detection of CC strongly depends on the imaging method[7–9]. While low resolution imaging (standard radiography, CT or MRI) has limitations in the detection of small initial stages of calcification formations[10], high-resolution digital contact radiography (DCR) has a higher sensitivity to

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detect CC[8]. One disadvantage of DCR, however, is that it can only be applied to tissues *ex vivo*. Using DCR in 106 cadaveric knees from 56 donors of the general population, Mitsuyama *et al.* concluded that CC is present in every examined knee and found that age rather than osteoarthritis (OA) is the predominant factor driving progressive pathologic calcification[11]. However, they did not analyze histological OA grade and did not adjust for OA when calculating the correlation of CC with age. Thus, important questions remain open with regard to the interrelationship between CC, OA and age as well as to the potential systemic nature of CC. Although we have described previously that DCR-detectable calcification exists in 100% severely osteoarthritic hip and knee joints undergoing total joint arthroplasty, no study in the literature has performed a concomitant DCR-based analysis of the prevalence of CC by an intra-individual comparison of several joints[9,12].

Furthermore, the association between radiographic OA and radiographic CC may vary from joint to joint[5,6]. Unlike the knee, radiographic CC of the hip in particular has been described not be associated with radiographic hip OA[13–15]. Given this apparent divergence of the pathophysiology of hips and knees, more sensitive detection methods, such as DCR for CC and histology for OA may help to further confirm or to revise such presumed site-specific differences. In general, the prevalence of hip CC is less well studied than that of the knee and appears to be lower, at least based on plain radiographic assessment. In the literature, there are three epidemiological studies of the elderly population (mean age 66 years or older) that, based on qualitative radiographic assessment without using DCR, reported the prevalence of hip CC to be between 0.4% and 5%, while the prevalence of knee CC in these studies ranged from 8 to 25%[5,6,16].

The aim of this cross sectional post-mortem study was to determine the bilateral prevalence and amount of CC of hip and knee joints in an unselected sample of donors over a wide age range with and without clinical or radiographic OA at a single center by high-resolution DCR and to analyze the interrelationship between CC, histological OA-grade, and age.

Methods

Femoral heads, distal femur and proximal tibia articulating surfaces were obtained from an unselected sample of 87 dead individuals irrespective of the reason for death who underwent autopsy at the Department for Legal Medicine, University Medical Center Hamburg-Eppendorf (hereafter referred to as “donors”). Only donors with bilaterally intact hip and knee joints without any signs of hip or knee disease other than OA were included in this study. The study was approved by the local ethics committee (PV 4570), in compliance with the Helsinki Declaration.

The mean age was 62.02 years (±19.04 standard deviation (SD), range 20–93 years); 39 donors were female and 48 male. Fig. 1 shows the distribution of gender and age by decade. The biometric characteristics of the donors are listed in Table I.

Soft tissue was removed from the joints. For femoral head analysis 4 mm bone and cartilage slabs were cut in the central coronal and axial planes, resulting in three standardized (central, anterior and posterior) slabs per sample. The distal femur was cut along a sagittal plane on the medial and lateral femoral condyle and the trochlear, so that three 4 mm thick bone-cartilage slabs were obtained for each femoral knee joint surface. The tibial head was cut in one 4 mm thick slab along the central coronal plane (Fig. 2).

DCR

All bone-cartilage slabs were washed with physiological saline to remove residual bone debris and sawing dust. Radiographs were taken (25 kV, 3.8 mAs, film focus distance 8 cm) using a high-resolution digital radiography device (Faxitron X-Ray, Illinois, USA). Quantitative computerized analysis of the areas of CC was performed with standard software (ImageJ 1.46, National Institutes of Health, Bethesda, USA) as published previously[9,11]. The mean amount of calcification measured from the three slabs of the femoral head, and the four slabs of the knee per specimen were regarded to be representative for the entire hip and knee joints.

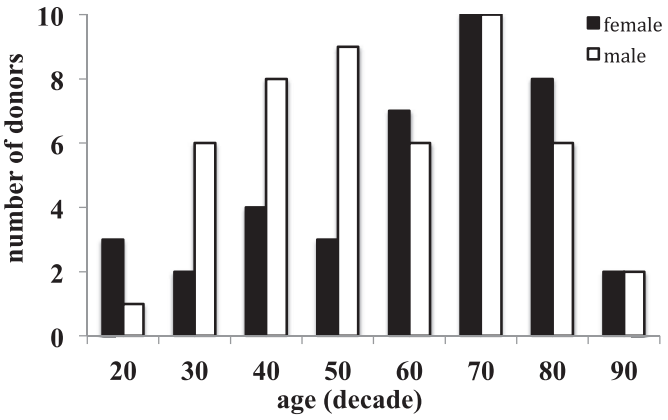

Fig. 1. Study population histogram by decade, comprising 39 female and 48 male donors. The mean age was 62.02 years ± 19.04 SD (range 20–93).

Table I
Biometric characteristics of the study population ($n = 87$)

Age [years]	62.0 ± 19.0
Male	60.0 ± 18.4
Female	64.5 ± 19.7
Height [cm]	
Male	177.0 ± 7.1
Female	164.5 ± 7.9
Body weight [kg]	
Male	83.3 ± 18.1
Female	72.4 ± 20.7
Body mass index [kg/m²]	26.5 ± 5.9

Histologic assessment

Histology was done of the main load bearing zone of each femoral head (central zone, directly adjacent to the central slab plane) and of each medial femoral condyle (central zone, directly adjacent to the sagittal slab plane of the medial femoral condyle). A specimen of full thickness hyaline cartilage was cut to the subchondral bone plate of the load bearing zone. All specimens were fixed in 4% PFA for 24 h, dehydrated in 80% alcohol and embedded in paraffin. 4 μm sections were stained with von Kossa and Alizarin Red (Alizarin Red S staining kit ph-9.0/7.0, Morphisto, Frankfurt, Germany) as well as 1% Safranin-O (Fig. 4) to confirm calcium and phosphate deposition and to evaluate the histological OA grade according to the OARSI osteoarthritis cartilage histopathology assessment system (grade 0–6).[17]

Statistical analysis

The biometric characteristics of donors are reported as mean values ± SDs. For descriptive analysis, mean CC values for each joint were used. Logarithmic transformation was done if appropriate. For categorical data Fisher's and McNemar's test were used. Linear mixed model was used to analyze the difference between the mean amount of CC in hip and knee joints considering side and joint as fixed effects. Subject was used as a random effect with a compound