J Orthop Sci (1999) 4:407–412

Journal of
Orthopaedic Science

Prevalence of articular cartilage degeneration in the ankle and knee joints of human organ donors

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Abstract: The prevalence of osteoarthritis (OA) is higher in some joints than in others. Fibrillation and full-thickness cartilage defects in the knee have been considered to be evidence of developing OA (pre-OA). While similar changes have been reported in the ankle (talocrural joint), the frequency of these changes is much higher than expected if the degeneration represents pre-OA. These observations suggest that in the ankle degenerative changes do not proceed to OA. The current study was to determine the prevalence of articular cartilage degeneration in ankles in a population of 470 bone donors with no history of joint disease. Knees from 50 donors were also available. Our data suggest that degeneration in the ankle cartilage does not appear to be a normal part of aging, was more frequent in men than women, increased with age, and occurred most often in both limbs with the same severity. In those donors with degeneration in the ankle, the knee also showed degenerative changes with an equal or higher grade. These data suggest that factors (such as altered mechanics) responsible for degeneration in one limb also cause changes in the contralateral limb and that factors affecting the ankle joints also appear to influence the knee joints.

Key words: human, ankle, knee, articular cartilage degeneration

Introduction

Differences in the prevalence of osteoarthritis (OA) of the knee and ankle joints have been documented based on epidemiological, radiographic, and pathological data. Epidemiological studies have shown that approximately 6% of the adult population is affected by symptomatic knee OA; this percentage increases to almost 10% in those over the age of 65.[8] Symptomatic OA does develop in the ankle, although quite rarely (<1%), and even in advanced age is infrequently present.[23] Both epidemiological and radiographic studies have shown that the knee is slightly more often affected by OA in women than in men, but the difference increases markedly with age. The ankle is more frequently affected in men than in women.[6] Occupations with high knee stress appear to increase the risk of knee osteoarthritis[5]; in the ankle the major risk factor is abnormal mechanics or trauma,[14] although ballet dancers do have an increased risk of ankle OA.[9] Knee trauma also increases the risk for developing OA.[16,24] Participation in some sports was found to result in increased hospital admission rate for both knee and ankle OA.[18] Some forms of OA also appear to have a heritable component as dominant Mendelian traits; it is interesting that even in these individuals some joints appear to be more predisposed to OA than others.[29] Reports of the treatment of ankle OA indicate that primary OA in that joint is rare and that secondary OA that develops following fracture or injury to ligaments is the most common cause of ankle OA.[7,10,13]

Pathological data obtained from the assessment of articular cartilage fibrillation and loss in autopsy specimens or cadavers have been used to estimate the prevalence of degenerative changes that may precede OA in the two joints, although the relationship of the degenerative changes to OA is unclear. Two studies[20,21] reported that full-thickness defects, considered to be evidence of OA, were found in 44% of knee joints and 2% of ankle joints. Another study of the ankle alone[27] reported a much higher prevalence of degeneration (98%), but all changes, including fibrillation, were considered degenerative. Cartilage fibrillation occurs more frequently than full-thickness defects and has been considered a normal feature of an adult synovial joint[1] rather than a sign of degeneration. In this article we have chosen to use the term degeneration rather

Offprint requests to: A.A. Cole
Received for publication on Dec. 2, 1998; accepted on April 22, 1999

than cartilage damage to refer to age-related morphological changes.

In a previous study[22] of cartilage degeneration in the lower extremities of 50 formalin-fixed cadavers (age range, 36–94 years; mean, 76.4 years), we reported that the knee displays the most extensive degeneration (full-thickness defects) in 66% of the joints examined compared to 18% in the talocrural joint. Only 4% of the ankle joints in this cadaveric population were free of signs of degenerative changes. This joint was more often affected in males than in females, and in 56% of the knees and 60% of the ankle joints the degenerative changes were bilateral.

The current study was undertaken to document the degenerative changes present in the ankle joints of a younger population of 470 organ donors available through collaboration with The Regional Organ Bank of Illinois from June 1995 to December 1997. Within this population, a grade was given for both ankle joints and for 50 of the donors from whom both ankles and knees were retrieved. Among these donors, even those over 61 years of age, 38% of the ankle and 4% of the knee displayed no detectable degeneration. This finding would suggest that joint degeneration is not as common a component of aging as previously reported, especially in the ankle. Full-thickness defects were present in 7% of the ankle joints and 18% of the knee joints. The defects were more common in males than in females, and in 12% the defects were bilateral in the ankle and 49% in the knee.

Materials and methods

Joint assessment

A total of 1033 joints were obtained through the Regional Organ Bank of Illinois from 470 donors with no history of joint disease. Age, gender, race, and cause of death were recorded for each donor (age distribution is given in Tables 1, 2). All the donors were tested for hepatitis A and B and HIV. None of the joints used for the study had apparent signs of surgery, and all had intact ligamentous components. For this study only the distal side of the talocrural joint, the talus, was received from 420 donors (total tali, 838). From 50 additional donors both intact knee and ankle joints (197 total joints) were obtained. From 3 of these donors, one knee was unavailable and from 2 donors only one talus was available. Considering the tali only, the mean donor age was 50.8 years (range, 21–74 years). For the matched pairs, the mean age was 54.1 years (range, 21–94 years). The gender distribution for the tali only was 76.4% men, while that of the matched pair donors was 75% men. For the tali only 92.9% were Caucasian; of the donors of the matched pairs, 88.5% were Caucasian. The gender and race distribution reflect the donors available through the Regional Organ Bank of Illinois.

Joint grading scale

Within the matched pairs group, degeneration in both tibiofemoral and patellofemoral compartments of the

Table 1. Distribution of normal joints (grades 0–1) by age

Age in years	21–30	31–40	41–50	51–60	61+
Number of donors	38	58	105	147	122
Number of joints					
Ankle	76	116	210	293	241
Knees	14	14	6	23	40
Number of grade 0 joints					
Ankles (%)	65 (85)	97 (84)	152 (72)	159 (54)	91 (38)
Knees (%)	14 (100)	10 (71)	4 (67)	2 (9)	4 (10)
Number of grade 1 joints					
Ankles (%)	9 (12)	9 (8)	21 (10)	74 (25)	73 (30)
Knees (%)	0 (0)	0 (0)	2 (33)	6 (26)	10 (25)

Table 2. Distribution of Collins' grades 2–4 by age

Age (years)	Tali only (%)	Ankles from matched pairs (%)	Knees from matched pairs (%)
21–30	2/30 (7%)	0/8 (0%)	0/8 (0%)
31–40	6/51 (12%)	1/7 (14%)	2/7 (29%)
41–50	21/102 (21%)	0/3 (0%)	0/3 (0%)
51–60	38/135 (28%)	3/13 (23%)	9/13 (69%)
61+	39/102 (38%)	7/20 (23%)	13/20 (65%)

knee and both the tibial and talar surfaces of the ankle joints were used to determine the overall score in that joint. For the 420 donors from whom tali alone were available, the tibia was retrieved for use by the bone bank, while the talus was dissected out and used for this study. Therefore, within this group of ankles, the entire score was based on the talar articular surface without the accompanying tibial surface. We had previously shown[22] that the largest percentage of joints observed displayed equal degeneration on the talar and tibial components; therefore, the lack of the tibia for scoring should not change the joint scores substantially. The cartilages were inspected for disruptions of the articular surface ranging from fibrillation to full-thickness defects. The joint was then graded on a 5-point scale[4] of Collins based on the appearance of the cartilage and for the knee the presence of osteophytes. Briefly, the scale is as follows: grade 0, no signs of cartilage degeneration or osteophytes; grade 1, limited fibrillation of the articular surface; grade 2, deep fibrillation and fissuring and possible osteophyte formation; grade 3, extensive fibrillation and fissuring of 30% or less of the articular surface eroded to the subchondral bone with osteophytes present; and grade 4, greater than 30% of the articular surface eroded to bone with gross geometric changes including osteophytes. Because the articular cartilages from the joints used in this study were subsequently utilized in metabolic studies, the surfaces of the joints were not coated with India ink to help define fibrillations. However, a thin film of blood often coated the surface, allowing the identification of surface disruptions. For the purpose of this study, joints with grades 0 and 1 were both classified as normal because grade 1 may simply represent normal senescent changes that may not be progressive. Joints with grades 2–4 were classified as showing degenerative changes.

Results

Within the current study population there were normal joints even in advanced age. Of the total 1033 joints that were graded, 599 (58%; 503 tali, 62 ankle joints, and 34 knees) were grade 0 with no detectable degeneration in the cartilage or gross changes in the joint. These normal joints were obtained from donors aged 21–94 years of age. Although the percentage of normal joints decreased with increasing age (Table 1), there were 9 knee/ankle donors whose age was greater than 61 years (including 1 who was 94 years old) with normal joints. For all 50 donors in this group, the ankle joint grade was equal to or less than the knee grade. Of the 1033 joints, 204 received grade 1. By combining grades 0 and 1, the total number of normal joints was increased to 803, or 78%.

With the remaining 231 joints that received grades 2–4 (167 tali, 18 ankles, and 45 knees), degeneration was seen in the articular surface including fibrillation and full-thickness defects as well as osteophyte formation. In the knee, degeneration was found in both the tibiofemoral and patellofemoral articulations and was similar to that previously described.[17,20,22] Full-thickness defects were observed on the patellas of 4 donors; in 3 of these donors the defects were found on the medial facet. In 7 donors, the retropatellar degeneration was present in the patellofemoral compartment with no accompanying visible degeneration in the tibiofemoral joint. Deep fissures (grade 2) were found in 14 donors (19 joints).

In the ankle joint, cartilage degeneration was observed principally on the talus between the malleolar regions of the talar dome (Fig. 1). Early degeneration nearly always involved fibrillation and possibly also fissuring, primarily on anteromedial and superomedial regions of the dome. More extensive degeneration included blistering (loss of superficial cartilage layers) in focal areas of the superior and anterior dome (more frequently medially than laterally) and longitudinal grooves running through the cartilage and occasionally also through the subchondral bone. These longitudinal grooves appeared to be the result of articulation with osteophytes along the anterior border of the articulating tibial plafond. In the joints with less degeneration, these grooves could be found on the median sagittal plane of the superior and anterior articular surface of the talar dome, and in joints with

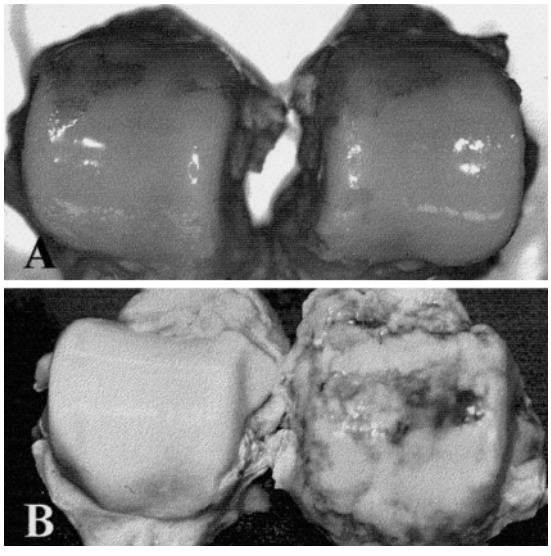

Fig. 1. **A** Tali with bilateral grades of 2 from 42-year-old man. The blistering on the superior dome of the tali is located laterally on one talus and medially on the other talus. **B** Tali from donor with grades 0 and 4 from a 51-year-old man

Table 3. Distribution of Collins' grades by joint

	Collins' grades					
Joints	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Tali only	503 (60%)	168 (20%)	139 (17%)	25 (3%)	3 (0.4%)	838
Matched pairs						
Ankles	62 (63%)	18 (18%)	16 (16%)	2 (2%)	0	98
Knees	34 (35%)	18 (19%)	28 (29%)	11 (11%)	6 (6%)	97
Total	599	204	183	38	9	1033

Table 4. Distribution of Collins' grades 2–4 by gender

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total joints
Tali only						
Men	348 (54%)	142 (22%)	129 (20%)	21 (3%)	4 (0.6%)	644
Women	154 (79%)	26 (13%)	10 (5%)	4 (2%)	0 (0%)	194
Matched pairs						
Men						
Ankles	44 (59%)	16 (22%)	12 (16%)	2 (2%)	0 (0%)	74
Knees	20 (27%)	16 (22%)	25 (34%)	9 (12%)	4 (5%)	74
Women						
Ankles	20 (83%)	0 (0%)	4 (17%)	0 (0%)	0 (0%)	24
Knees	16 (67%)	0 (0%)	4 (17%)	2 (8%)	2 (8%)	24

Table 5. Bilateral grades (symmetrical grades)

	` Bilateral Collins' grades					
Donor joints	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Tali only	227	55	46	4	0	332/418 (79)
Matched pairs						
Ankle	28	5	6	1	0	40/48 (83)
Knees	16	9	13	8	2	44/47 (93)

greater degeneration the grooves were also found across the entire intermalleolar region of the talar dome. These grooves were never present on the most posterior or inferior region.

Degeneration (grades 2–4) occurred less frequently in the ankles than in the knees (Table 3); degeneration in the ankle increased with age (see Table 2) and was more frequent in men than in women (Table 4). Degeneration in the ankle from the matched pairs was nearly equal in men and women, but in the knee the percentage was higher in women. However, in the donors from whom only the tali were received, the percentage of men with degenerative changes was much higher than the percentage of women.

From the 418 donors for whom both tali were available but knees were not available, 79% received identical grades bilaterally (symmetrical grades; Table 5). Of the 48 donors from the matched pairs for whom both ankles were available, the Collins' scores were identical in 40 (83%) of the donors. Of the 86 donors with different grades in the two ankle joints (Table 6), the grade in the majority of the corresponding tali was only one grade higher than the talus with the lower score.

Comparing the ankles and knees within the same limb (right knee with right ankle or left knee with left ankle), we found that the Collin's grade in the ankle was either equal to or lower than the grade in the knee (Fig. 2). Grade 0 in the ankle corresponded with grade 0 in the knee in 58%. From the 18 knees with grade 1, the ankles in the same limb were 78% grade 0 and 22% grade 1. In grade 2 knees, there was a nearly equal distribution of grades 0, 1, and 2 in the ankle. With increasing degeneration in the knee, the distribution of

Table 6. Comparison of asymmetrical grades in donors from whom the tali only were received

Lower grade	Corresponding tali	Number of donors
0	1	29
0	2	13
0	3	5
0	4	1
1	2	24
1	3	3
1	4	2
2	3	9
2	4	0
3	4	0

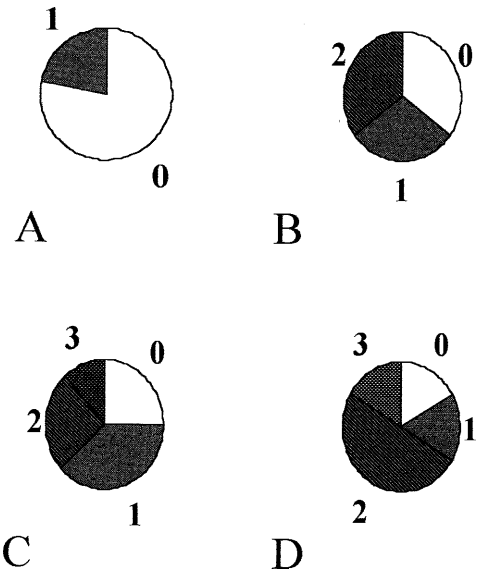

Fig. 2A–D. Collins' grades in the knee joints were greater than or equal to those of the ankle. For each knee grade, the ankle grades in the same limb are shown. **A** Knee Collins' grade 1 (n = 18). **B** Knee Collins' grade 2 (n = 26). **C** Knee Collins' grade 3 (n = 8). **D** Knee Collins' grade 4 (n = 6). *Numbers* demonstrated in the graph are the Collin's grades in the ankle

grade 0 and 1 ankles dropped from 100% (knee grades 0 and 1), 65% (grades 2 and 3), to 33% (grade 4), suggesting that degeneration in the knee may contribute to disturbance of the mechanical balance in the corresponding ankle.

Discussion

The results were obtained through a population-based study of donors available through the Regional Organ Bank of Illinois. Our data show that within this population of donors degeneration of the ankle is not always a component of aging. Although the frequency of degenerative changes did increase with age in both the knee and ankle, there were donors between 61 and 94 years of age with no visible degeneration in either the knee or ankle.

The majority of the tali from the ankles appeared grossly normal (Collins grades 0–1 = 80%). The remaining joints with degeneration (grades 2–4) could represent the early degenerative changes associated with OA as has been reported for the knee, where degeneration increases more dramatically with age. This degeneration in the knee may well have progressed to OA if the donor had lived. However, in the ankle the degeneration is present at a younger age, and although its prevalence does slightly increase with age, the rate is not the same as for the knee. A recently published study concluded that cartilage degeneration observed in the knee at autopsy could be considered a preclinical phase of OA.[28] For this study knee cartilages were obtained from donors and from OA patients. The donor cartilages were divided into normal and degenerative (pre-OA). Two parameters measured were glycosaminoglycan content and matrix metalloproteinase (MMP) activity. The changes in the degenerated cartilages were intermediate between normal and OA. Further biochemical studies on the degenerated ankle cartilage are necessary to determine whether these same and other parameters are intermediate in the ankle.

Studies of cartilages from the two joints have provided evidence that there are metabolic, biochemical, and biomechanical property differences between the two as well the anatomical and evolutionary differences that are well known.[12] When explants of knee and ankle cartilage are cultured with fibronectin fragments, the knee chondrocytes respond by upregulating aggrecanase activity with a loss of 30%–50% of the cartilage proteoglycan; ankle chondrocytes from matched donors do not respond in the same manner to the stimulus.[15] The differences between knee and ankle chondrocytes are even maintained when the cells are isolated from the cartilage and cultured in alginate beads.[11] This study further shows that in the presence of the catabolic cytokine, interleukin-1, both knee and ankle chondrocytes decrease proteoglycan synthesis, but the intensity of the response varies with the knee chondrocytes showing a much stronger response than the ankle chondrocytes. Additionally, the receptor antagonist protein was able to overcome the effects of interleukin-1 in the ankle cartilage but not in that of the knee;[11] this same study reported that ankle chondrocytes contain fewer interleukin-1 receptors than do knee chondrocytes. Expression of one MMP differed between the knee and talocrural cartilages as well[3]; collagenase 2 or MMP-8 mRNA was detectable in

normal knee chondrocytes but not in ankle chondrocytes unless the ankle chondrocytes were stimulated in culture with interleukin-1 or the ankle cartilage showed signs of degeneration in vivo.

Biochemical studies[26] have revealed that the DNA dry weight of the ankle cartilage is significantly lower than that of either the femoral or tibial cartilage while the glycosaminoglycan dry weight is significantly higher. However, the water content in the cartilage of the ankle is significantly lower than that in the femur or tibia. The dynamic stiffness measured at 0.1 Hz is higher in the cartilage of the ankle than in the femur or tibia, while hydraulic permeability is lower. The lower hydraulic permeability would be expected with the higher dynamic stiffness, decreased water content, and higher glycosaminoglycan content. An additional difference between the two joints may reside in differences in the subchondral bone where there is no detectable increased bone density with increasing joint grades,[25] as has been shown for the knee or in animal models of OA.[2,19,30]

Taken together these data suggest that there are significant differences between the two joints that may help to protect the ankle cartilage from the degenerative changes leading to OA that are present in the knee. Further investigations into these differences may lead to therapeutic approaches that could provide a similar protection to the knee.

Acknowledgments. Supported by NIH grant 2-P50-AR-39239, DAAD Fellowship (HK, Germany), Deutsche Forschungsgemeinschaft (DGF; WE) EG 113/1-1; AR45301-01 (CM). We also gratefully acknowledge the assistance of the staff of The Regional Organ Bank of Illinois.

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