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Association between bone marrow lesions detected by magnetic resonance imaging and knee pain in community residents in Korea

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SUMMARY

Objective: To describe the frequency of bone marrow lesions (BMLs) detected by magnetic resonance imaging (MRI), and to examine the association of BMLs with knee pain severity in community residents in Korea.
Methods: Participants were randomly chosen from the population-based Hallym Aging Study, irrespective of whether they had knee osteoarthritis (OA) or pain. Demographic and knee pain data were obtained by questionnaire. Radiographic evaluations consisted of weight-bearing knee anteroposterior radiographs and 1.5-T MRI scans. MRI was performed in the dominant knees of subjects without knee pain and in the more symptomatic knees of subjects with knee pain. BMLs were graded according to the whole-organ MRI score.
Results: The mean age of the 358 study subjects was 71.8 years, and 34.5% of subjects had radiographically detected knee OA. The prevalences of BMLs and large BMLs in the tibiofemoral compartments were 80.3% and 40.4%, respectively. After adjusting for age, sex, and body mass index, total and medial compartment BML scores were significantly associated with the presence of knee pain, and the association was stronger as the summary score for BML increased. In proportional regression analysis, knee pain severity increased with BML severity in any compartment and in the medial compartment.
Conclusion: BMLs detected by MRI were highly prevalent in this elderly Asian population. BMLs were significantly linked to knee pain, and BML severity correlated with knee pain severity. BMLs may be important surrogate targets for monitoring pain and structure modification in OA therapeutics.

Introduction

Knee pain is a common musculoskeletal problem in older adults, and its prevalence increases with age[1]. Osteoarthritis (OA) is a leading cause of knee pain and physical disability[2]. Although degeneration of articular cartilage is the hallmark of OA, cartilage is aneural, whereas subchondral bone is richly innervated with nociceptive pain fibers[3]. Thus, subchondral bone could be a source of pain in subjects with knee OA.

Previous reports have implicated subchondral bone marrow lesions (BMLs) detected by magnetic resonance imaging (MRI) in the pathogenesis of knee OA and knee pain[4–10]. These lesions appear as ill-defined decreased signal intensity on T1-weighted images and as increased signal intensity in water-sensitive sequences, such as T2-weighted, proton density-weighted, and short-tau inversion recovery (STIR)[11]. Abnormalities of subchondral bone marrow have been reported in various painful conditions, including posttraumatic contusions, transient osteoporosis, infectious and inflammatory arthropathies, insufficiency fractures, spontaneous osteonecrosis, and OA[12,13].

The presence of BMLs is associated with the presence and severity of knee pain in subjects with knee OA. For example, subjects with knee OA and BMLs were shown to have an odds ratio (OR) of 3.3 for knee pain compared with those without BMLs, after adjusting for confounders[4]. Moreover, BMLs were significantly related to knee pain severity after adjusting for age and body mass index (BMI) in patients with knee OA[7]. Changes in BMLs were associated with fluctuations in knee pain in patients with knee OA, with pain resolution occurring frequently when BMLs diminished[14]. Although some studies failed to demonstrate a relationship between BMLs

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and knee pain[15,16], a recent systematic review demonstrated with a moderate level of evidence that BMLs are associated with knee pain[17]. In addition, in patients with established knee OA, BMLs have been shown to be associated with cartilage loss, progression of knee OA, and increased risk of knee joint replacement[5,6,18].

Most studies of BMLs have focused on symptomatic populations with established knee OA, and few studies to date have targeted community based samples. Importantly, BMLs can be detected in adults without knee OA[19–23]. Furthermore, recent studies have showed that the presence of BMLs in asymptomatic adults with no clinical OA was associated with the development of pain and progression of cartilage defects[19,20].

Limited data on the relationship between knee pain and BMLs in the general population are available. Therefore, we examined the prevalence of BMLs and the association with knee pain severity in elderly community residents in Korea.

Method

Subjects

The Hallym Aging Study is a prospective cohort study investigating the health of elderly community residents in Chuncheon, a city approximately 120 km east of Seoul, Korea. This ongoing study commenced in 2004, with follow-up examinations scheduled every 3 years. The study methods have been described in detail elsewhere[24]. Briefly, 1489 subjects among 71,061 residents with age ≥50 years in Chuncheon were randomly selected. Subjects were invited by telephone and mail to participate in the study with the following announcement: "This is a study evaluating the general health and physical function in the elderly." Knee pain or arthritis was not mentioned in the study advertisement. A total of 918 subjects participated in the first triennial examination in 2004, and 702 subjects from the second triennial examination were eligible for this study. A total of 129 subjects refused to undergo the OA substudy. Subjects who refused to undergo the OA substudy were significantly older than those who participated (72.3 vs 70.4 years); however, the sex ratio did not differ. Of the 573 remaining subjects, 400 were randomly chosen for knee MRI, regardless of the presence or absence of knee pain or radiographic knee OA. Thirty-six subjects declined to undergo knee MRI, three had previously undergone bilateral total knee replacement, and three had contraindications to MRI, leaving 358 subjects who underwent knee MRI. The Ethics Committee of Hallym University approved the study protocol. Written informed consent was obtained from all study participants.

Data collection

Demographic information was collected using a standard questionnaire. Knee pain was assessed by asking, "Did you have pain, aching, or stiffness in either of your knees last month?" Those who answered "yes" were asked additional questions about their more symptomatic knee, including the rating of pain severity using a 100-mm visual analog scale and inquiries about previous knee injuries. History of knee injury was elicited with the following question: "Have you ever had a knee injury requiring the use of crutches or a cane?" All subjects were also evaluated using the Western Ontario and McMaster Universities (WOMAC) OA Index for evaluating pain and self-reported functional status[25].

Radiographic assessment

Radiographic evaluations consisted of 14 × 17-inch anteroposterior radiographs taken during weight bearing with a semiflexed knee. A Plexiglas frame (SYNARC, San Francisco, CA, USA) was used to standardize knee positions according to the manufacturer's recommendations. Each knee was graded using the Kellgren–Lawrence (K–L) grading scale[26]. Radiographic knee OA was defined as present if the subject had a radiographic K–L grade ≥2 in the tibiofemoral (TF) joint. All radiographs were read twice at an interval of at least 2 weeks by one reader, an academically based rheumatologist (HAK) who was unaware of the knee pain status or MRI findings. The intra-reader reproducibility of assessments was high, with weighted kappa values of 0.86 [95% confidence interval (CI), 0.80–0.91] for the K–L grade and 0.89 [95% CI, 0.83–0.94] for K–L grades 0–1 (non-OA) vs K–L grade ≥2 (OA). Images that were assigned different K–L grades at the two readings were adjudicated by consensus between the original reader and a second reader (DJH). The weighted kappa value for inter-reader reliability was 0.84 for non-OA vs OA (95% CI, 0.67–1.01).

MRI and evaluation of BMLs

Each subject underwent MRI of one knee. If both knees were symptomatic, the more symptomatic knee was chosen. For subjects without knee pain, the dominant knee was selected for imaging. Knee dominance was determined by the following question: "When you start to kick a ball, which foot would you use first?" MRI scans of the knee were obtained with a 1.5-T scanner (Philips, Andover, MA, USA) with a phase-array knee coil. The imaging protocol included sagittal 3D water-select excited cartilage three fluid images (repetition time, 20 ms; echo time, 7.8 ms; slice thickness, 3.0 mm; interslice gap, 1.5 mm; field of view, 150 × 150 mm; matrix, 304 × 304), sagittal T2 fat-suppression images (repetition time, 2789.6 ms; echo time, 60 ms; slice thickness, 4.0 mm; interslice gap, 0.4 mm; echo spacing, 13.3 ms; field of view, 160 × 160 mm; matrix, 208 × 166), sagittal proton density fat-suppression images (repetition time, 2000 ms; echo time, 15 ms; slice thickness, 4.0 mm; interslice gap, 0.4 mm; echo spacing, 15 ms; field of view, 160 × 160 mm; matrix, 224 × 224), coronal water-select excited cartilage three fluid images (repetition time, 20 ms; echo time, 7.7 ms; slice thickness, 3 mm; interslice gap, 1.5 mm; field of view, 160 × 160 mm; matrix, 304 × 304), and axial T2 fast-field-echo images (repetition time, 439.2 ms; echo time, 13.8 ms; slice thickness, 4 mm; interslice gap, 0.4 mm; field of view, 140 × 140 mm; matrix, 256 × 256).

The MRI scans were read by a musculoskeletal radiologist (MDC) who was unaware of subjects' characteristics and clinical and radiographic data. BMLs were assessed on sagittal T2-weighted fat-suppressed images, and defined as ill-defined areas of increased signal intensity adjacent to the subcortical bone at the distal femur or proximal tibia. BMLs were assessed in each of five subregions of the medial and lateral TF compartments (central and posterior femur; anterior, central, and posterior tibia) using the Whole-Organ MRI Score (WORMS)[27]. BMLs were scored as follows: 0, none; 1, <25% of the region; 2, 25–50% of the region; and 3, >50% of the region. BMLs were defined as grade ≥1 for any region and large BMLs were defined as grade ≥2 for any region. We summed the BML scores for all five subregions of the medial compartment (range, 0–15), of the lateral compartment (range, 0–15), and both TF compartments (range, 0–30). Then, we divided the summary scores into five categories for BML (0, 1, 2–3, 4–5, 6–21) for subsequent analysis. A random subset of images ($n = 38$) was re-read to determine intra-observer reproducibility (κ for BML in the various compartments = 0.69–1.0).

Statistical analysis

We calculated the prevalences of both BMLs and large BMLs according to sex and the presence of radiographic knee OA.