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Subchondral bone attrition may be a reflection of compartment-specific mechanical load: the MOST Study

Tuhina Neogi[1], **Michael Nevitt**[2], **Jingbo Niu**[1], **Leena Sharma**[3], **Frank Roemer**[4], **Ali Guermazi**[1], **Cora E Lewis**[5], **James Torner**[6], **Kassim Javaid**[2], and **David Felson**[1]

[1]Boston University School of Medicine, Boston, Massachusetts, USA

[2]University of California at San Francisco, San Francisco, California, USA

[3]Northwestern University, Chicago, Illinois, USA

[4]Klinikum Augsburg, Kommunalunternehmen, Germany

[5]University of Alabama at Birmingham, Birmingham, Alabama, USA

[6]University of Iowa, Iowa City, Iowa, USA

Abstract

Introduction—Subchondral bone attrition (SBA), a feature of osteoarthritis, may be caused by excess focal load to bone, and/or inadequate bone quality to withstand loads through the joint. This study evaluated the effects of malalignment, which can cause focal excessive load, and systemic bone density on the presence and incidence of SBA.

Methods—The Multicenter Osteoarthritis Study is a cohort of individuals who have or are at high risk of knee osteoarthritis. Baseline alignment and bone mineral density (BMD) measures were assessed. Baseline and 30-month knee magnetic resonance images were graded for SBA (grade 0–3) using the whole-organ magnetic resonance imaging score. The study evaluated the association of alignment in medial and lateral compartments, respectively, and systemic BMD with baseline presence of SBA and incident SBA using logistic regression and adjusting for age, sex and body mass index.

Results—Of 1253 participants (mean age 62 years, mean BMI 30, 61% women), 33% had baseline SBA and 44% had knee osteoarthritis. Associations between the presence and incidence of SBA with malalignment in both compartments were noted (odds ratios (95% CI) 2.9 (2.1 to 4.0) and 1.9 (1.2 to 2.9), respectively, for varus knees in the medial compartment; 4.5 (2.8 to 7.1) and 2.1 (1.1 to 4.1), respectively, for valgus knees in the lateral compartment). Low BMD was not associated with SBA.

Conclusions—The presence and incidence of SBA are associated with malalignment in a compartment-specific manner, but not with low BMD. SBA may be a marker of increased load

Correspondence to Dr Tuhina Neogi, Boston University School of Medicine, 650 Albany Street, Clinical Epidemiology Unit, Suite X-200, Boston, MA 02118, USA; tneogi@bu.edu.

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experienced by overlying cartilage, which may contribute to increased forces transmitted to the cartilage due to alteration in subchondral bone.

Subchondral bone probably plays an important role in osteoarthritis. Surgical specimens from persons with osteoarthritis have demonstrated that subchondral bone changes, including subchondral bone attrition (SBA), which is a flattening or depression of the subchondral bony surface unrelated to gross fracture, are common.[1] A number of animal models have demonstrated subchondral bone changes very early after the induction of disease,[2 3] and in magnetic resonance imaging (MRI) studies, SBA has been shown to be present in human knees with early osteoarthritis and even pre-radiographic osteoarthritis.[4] Whereas bone marrow lesions (BML) have been the primary lesion of the subchondral bone studied in osteoarthritis,[5–7] SBA has also been associated with pain in knee osteoarthritis measured by radiography and MRI, including independently of BML.[8–10] In addition, the presence of SBA within a subregion of a knee predicts further cartilage loss in that same subregion.[11]

Malalignment is associated with an increased risk of radiographic progression in knees with existing osteoarthritis and with cartilage loss in the compartment that is subjected to excess load by the malalignment.[12] In a small cross-sectional sample, it has been associated with SBA in knees with existing osteoarthritis,[13] suggesting the possibility of altered focal contact stresses potentially contributing to the occurrence of SBA. Because SBA is likely to represent remodelling of the envelope of the subchondral bone, leading to changes in bone shape or bone loss,[14] it is possible that bone quality, as reflected by systemic bone mineral density (BMD) may be an important determinant of the occurrence of SBA. The loss of bone at the joint surface as seen in SBA may be suggestive of bone resorption, and raises the possibility of increased bone turnover. Intriguingly, antiresorptive drug use has been associated with significantly less SBA.[15]

We examined the association between the baseline presence of malalignment and systemic BMD with the presence and incidence of SBA in a large cohort of individuals with or at high risk of knee osteoarthritis.

METHODS

Study sample

The Multicenter Osteoarthritis (MOST) Study is a prospective cohort study of 3026 individuals aged 50–79 years with or at high risk of knee osteoarthritis. All MOST subjects were recruited from two communities in the US, Birmingham, Alabama and Iowa City, Iowa. Details of the study population have been published elsewhere.[16] For this study, eligible participants had to have knee MRI, systemic BMD, and knee alignment measures available for analyses. MRI readings had been performed for one or more of three substudies in MOST evaluating risk factors for radiographic osteoarthritis progression consisting of randomly selected knees with patellofemoral or tibiofemoral osteoarthritis, incident radiographic osteoarthritis and new onset of consistent frequent knee pain.

The study protocol was approved by the institutional review boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Center.

MRI assessments

At baseline and 30 months, knee MRI was performed using a 1.0 T OrthOne extremity scanner (ONI Medical Systems Inc, Wilmington, Massachusetts, USA) with axial and sagittal proton density fat-suppressed and coronal STIR sequences. MRI was scored for SBA on a 0–3 scale using the whole-organ magnetic resonance imaging score (WORMS)[17] and subregions by two

musculoskeletal radiologists (inter-rater weighted κ=0.68). The presence of SBA was defined as any SBA score greater than 0 at baseline in any subregion within the compartment of interest (medial tibiofemoral or lateral tibiofemoral). Incident SBA was defined as any SBA score increase from 0 at baseline within the compartment of interest. To be eligible for incident SBA, a knee had to have an SBA score of 0 in all subregions within that compartment (medial tibiofemoral or lateral tibiofemoral) at baseline.

Alignment

Full-limb radiographs of both legs were obtained at baseline using a previously described method.[12] The hip–knee–ankle mechanical axis was defined as the angle formed by the intersection of a line from the centre of the femoral head to the centre of the femoral notch, and a second line from the centre of the talus to the centre of the tibial spines (interobserver ICC 0.99). Varus alignment was defined as an angle less than 179°, 179–181° was considered neutral and valgus alignment was defined as an angle greater than 181°.[18]

Systemic BMD

Whole body BMD (g/cm^2) was assessed using Hologic QDR 4500A DXA scanners (Hologic Inc, Bedford, Massachusetts, USA) and categorised into age and sex-specific tertiles.[19]

Radiographic assessment

All participants underwent bilateral weight-bearing fixed-flexion posteroanterior and lateral radiographic evaluation of the knee.[20] Radiographs were scored for Kellgren and Lawrence (KL) grade (0–4).[21–23]

Other covariates

Age and sex were recorded at the baseline clinic visit. Body mass index (BMI) (kg/m^2) was computed as $weight/height^2$. The use of bone-modulating agents was assessed by an interviewer-administered questionnaire.

Statistical analyses

We evaluated the association of baseline alignment with both the presence of baseline SBA and incident SBA using logistic regression for each compartment (medial tibiofemoral, lateral tibiofemoral) separately. For systemic BMD, the presence and incidence of SBA in the tibiofemoral joint, irrespective of compartment, per age and sex-specific tertile of BMD was assessed, with the lowest tertile acting as the referent group. All analyses were adjusted for age, sex and BMI. Analyses in which systemic BMD was also evaluated also adjusted for the use of bone-modulating agents. Because we noted similar associations for the presence and incidence of SBA in the medial compartment of varus knees as for the lateral compartment of valgus knees, and for the lateral compartment of varus knees as for the medial compartment of valgues knees, we combined analyses for what could be considered the `more loaded' compartments and the `less loaded' compartments, respectively.

To determine whether any effects noted were related to the presence of late-stage osteoarthritis, analyses for incident SBA were repeated among knees without radiographic osteoarthritis (ie, KL grade <2). Finally, we examined whether systemic BMD modified the effects of alignment on the presence or incidence of SBA.

RESULTS

Of the 1428 knees with available MRI reading data, 1253 subjects (one knee/subject) had no missing values of SBA, alignment and BMD. Their mean age was 62 years, with a mean BMI

of 30 (table 1). Sixty-one per cent were women. Of the 1253 knees studied, 44% had radiographic knee osteoarthritis at baseline (KL grade ≥2) and 33% had SBA present at baseline in the tibiofemoral joint. Approximately 31% were neutrally aligned, 49% were varus and 20% were valgus malaligned.

Varus malalignment was associated with baseline SBA in the medial compartment and valgus malalignment was similarly associated with SBA in the lateral compartment (table 2). As expected, valgus malaligned knees had lower odds of having SBA in the medial compartment because mechanical load is predominantly transmitted through the lateral tibiofemoral compartment in these knees. A similar effect was seen for varus malaligned knees in the lateral tibiofemoral compartment.

A total of 1185 knees was eligible for the incident SBA analyses. Varus malalignment was associated with incident SBA in the medial compartment (odds ratio (OR) 1.9, 95% CI 1.2 to 2.9; table 2). Valgus malalignment had a similar association (OR 2.1, 95% CI 1.1 to 4.1) in the lateral compartment.

The highest tertile of systemic BMD was associated with the baseline presence of SBA anywhere in the tibiofemoral joint (adjusted OR 1.5, 95% CI 1.1 to 2.1). The highest tertile of systemic BMD was similarly associated with 1.6 times the odds of incident SBA compared with the lowest tertile of systemic BMD (table 3).

When limited to the knees without any radiographic osteoarthritis at baseline, the magnitudes of effect for each of the associations of malalignment with incident SBA in the respective compartments were similar to the main analyses, but none of the associations were statistically significant, reflective of the smaller numbers in this subset analysis limiting our ability to estimate these effect estimates precisely (table 4). In contrast, high systemic BMD remained associated with the incidence of SBA among knees without radiographic osteoarthritis (adjusted OR 1.5, 95% CI 0.8 to 3.0; adjusted OR 2.4, 95% CI 1.3 to 4.7 for the middle and highest tertiles, respectively, compared with the lowest BMD tertile).

When we performed analyses using the combined approach, evaluating the `more loaded' and `less loaded' compartments, respectively, similar associations were noted, although with better precision due to the combined sample size.

Finally, when we evaluated for potentially modifying effects of systemic BMD on alignment, neither the interaction terms nor the stratified analyses demonstrated any substantial modification of the alignment effect estimates for the presence of baseline SBA or incident SBA by systemic BMD (data not shown).

DISCUSSION

In this large cohort study, alignment was associated with the presence and incidence of SBA in a compartment-specific manner, with similar magnitudes of effect seen even among knees without radiographic osteoarthritis. In particular, SBA was more likely to occur in the compartment that experienced greater mechanical load, and was less likely to occur in the compartment that experienced less load. Furthermore, systemic BMD was associated with the presence and incidence of SBA.

These findings are in keeping with the association of malalignment with knee osteoarthritis. A number of animal models provide evidence that damage to subchondral bone through loading can lead to cartilage damage.[24–28] Malalignment has been associated not only with cartilage loss, but also with ipsilateral BML in humans,[13 29] another abnormality of subchondral bone. As malalignment imposes abnormal mechanical load across the joint, SBA may well be a

marker for this increased abnormal load transmitted through both cartilage and underlying subchondral bone.

In contrast to our hypothesis, lower systemic BMD was not associated with SBA. In fact, higher systemic BMD was associated with SBA in cross-sectional and longitudinal analyses, even among knees without radiographic osteoarthritis. Why might this be? In osteoarthritis, there exists decreased mechanical properties of subchondral bone related to abnormalities of bone architecture and density, indicating poor bone quality.[30] From a material standpoint, this osteoarthritis subchondral bone is less highly mineralised bone than that from age-matched or younger controls.[31 32] As a result, osteoarthritis bone is less stiff for a given density, with reduced mineral content compared with normals.[33] This altered bone quality, however, may only be present in localised areas and therefore does not necessarily reflect systemic bone abnormalities, with more heavily loaded areas being stiffer and having greater apparent density than more lightly loaded areas.[33]

Systemic BMD is thus not a specific enough marker for abnormal bone turnover or bone quality, and that for attrition, systemic bone quality may not be an issue; rather local bone quality is likely to be more important. To provide further insight into the role of bone abnormalities in osteoarthritis, bone quality may need more direct assessments, such as can be afforded by microcomputed tomography or peripheral quantitative computed tomography, which has demonstrated alterations in trabecular structure and organisation in osteoarthritis models.[34] Instead, perhaps systemic BMD can be thought of as a marker for the overall load experienced through the joints over a lifetime. That higher systemic BMD was associated with the presence and incidence of SBA and did not modify the effects of alignment supports the possibility that systemic BMD reflects load experienced through a joint. Finally, the association between systemic BMD and incident SBA among knees without osteoarthritis suggests that SBA is a pathological feature that occurs early in the process, in contrast to it being thought of as a late feature of existing osteoarthritis.[35]

In summary, malalignment was associated with SBA in a compartment-specific manner. In addition, higher systemic BMD was associated with SBA. Taken together, these findings support the hypothesis that SBA may be a reflection of mechanical load experienced through the knee joint.

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Table 1

Participant characteristics

Participant characteristics	N=1253
Mean age (SD, range), years	62.3 (7.9, 50–79)
Female, n (%)	763 (60.9)
Mean BMI (SD, range), kg/m^2	30.0 (4.9, 18.0–55.8)
Baseline tibiofemoral osteoarthritis (KL ≥2), n (%)	550 (43.9)
Baseline presence of SBA, n (%)	416 (33.2)
Alignment, n (%)	
Neutral (179–181°)	392 (31.3)
Varus (<179°)	612 (48.8)
Valgus (>181°)	249 (19.9)
Whole body BMD, g/cm^3 (SD, range)	
Women	1.10 (0.11, 0.80–1.45)
Men	1.24 (0.12, 0.92–1.69)

BMD, bone mineral density; BMI, body mass index; KL, Kellgren and Lawrence grade; SBA, subchondral bone attrition.

Table 2

Association of alignment with presence of baseline SBA and incident SBA, respectively, in the medial tibiofemoral and the lateral tibiofemoral compartments

	Medial compartment		Lateral compartment	
	N/total	Adjusted OR (95% CI)	N/total	Adjusted OR (95% CI)
Presence of baseline SBA				
Neutral	66/392	1.0 (ref)	32/392	1.0 (ref)
Valgus	28/249	0.6 (0.3 to 0.9)*	74/249	4.5 (2.8 to 7.1)*
Varus	229/612	2.9 (2.1 to 4.0)*	36/612	0.7 (0.4 to 1.1)
Incident SBA				
Neutral	34/367	1.0 (ref)	17/367	1.0 (ref)
Valgus	13/239	0.5 (0.3 to 1.0)*	23/239	2.1 (1.1 to 4.1)*
Varus	94/579	1.9 (1.2 to 2.9)*	19/579	0.7 (0.4 to 1.4)

OR, odds ratio; SBA, subchondral bone attrition.

* $p<0.05$.

Table 3

Association of systemic BMD with presence of baseline SBA and incident SBA in the tibiofemoral joint

	Presence of baseline SBA (1253 knees)		Incident SBA (1185 knees)	
	N/total	**Adjusted OR (95% CI)**	**N/total**	**Adjusted OR (95% CI)**
Systemic BMD				
Lowest tertile	126/416	1.0 (ref)	55/399	1.0 (ref)
Middle tertile	131/419	1.1 (0.8 to 1.5)	58/400	1.1 (0.7 to 1.6)
Highest tertile	159/418	1.5 (1.1 to 2.1)*	75/386	1.6 (1.1 to 2.3)*

BMD, bone mineral density; OR, odds ratio; SBA, subchondral bone attrition.

* $p<0.05$.

Table 4

Association of alignment with incident SBA in the medial and lateral tibiofemoral compartments among knees without radiographic tibiofemoral osteoarthritis

	Medial compartment (n=671 knees)	Lateral compartment (n=671 knees)
Alignment		
Neutral	1.0 (ref)	1.0 (ref)
Valgus	0.7 (0.2 to 1.9)	1.5 (0.6 to 3.8)
Varus	1.6 (0.8 to 3.4)	0.7 (0.3 to 1.9)

Values are adjusted OR (95% CI).

OR, odds ratio; SBA, subchondral bone attrition.