Tibial plateaux size is related to grade of joint space narrowing and osteophytes in healthy women and those with OA
Anita E Wluka, Yuanyuan Wang, Susan R. Davis, and Flavia M. Cicuttini

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Tibial plateaux size is related to grade of joint space narrowing and osteophytes in healthy women and those with OA

Extended report

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Abstract

Objective
Bone is an integral component in the pathogenesis of knee osteoarthritis (OA), however, the relationship of bone size to radiographic severity of disease is unknown.

Methods
One hundred and forty nine women (81 healthy and 68 with knee OA) underwent knee radiography and magnetic resonance imaging (MRI) on their symptomatic or dominant knee. Tibial plateau bone area was measured at baseline and follow up.

Results
Women with OA had larger medial and lateral tibial plateau bone area (mean ± SD, 1850 ± 240 mm² and 1279 ± 220 mm², respectively) than healthy women (1670 ± 200 mm² and 1050 ±130 mm², p < 0.001 for both differences). For each increase in grade of osteophyte, an increase in bone area was seen of 146 mm² in the medial compartment and 102 mm² in the lateral compartment. Similarly, for each increase in grade of joint space narrowing, tibial plateau bone area increased by 160 mm² in the medial compartment and 131 mm² in the lateral compartment (Significance of regression coefficients all p < 0.001). These relationships persisted after adjusting for the potential confounders with the exception of the association between grade of medial osteophytes and medial plateau area.

Conclusion
With increasing severity of radiographic knee OA, tibial plateau size increases. Whether this bone increase has a role in the pathogenesis of OA remains to be determined.

KEYWORDS: bone, knee osteoarthritis, bone size
Introduction/Background
Osteoarthritis (OA) is a common, chronic disease, resulting in degeneration of articular cartilage, changes in subchondral (sclerosis and cyst) and periarticular bone (osteophytes) and cysts. Whether the primary defect of OA occurs in subchondral bone or articular cartilage is unclear(1). We have shown that subjects with knee OA have less knee cartilage than normal subjects and that tibial bone size is an independent predictor of the amount of knee cartilage in an individual (2-5). A recent study showed that those with grade 1 osteophytes had increased medial and lateral tibial plateau bone area compared to those with no evidence of OA (6). Those with a higher grade of osteophytes were not included in that study. No relationship between tibial plateau area and joint space narrowing was observed. If there is a concomitant reduction in knee cartilage volume with an increase in bone size with increasing severity of OA, this is likely to have a major impact on knee cartilage thickness and potentially on load distribution and pathogenesis of knee OA.

We performed a cross-sectional study to explore the hypothesis that a relationship exists between tibial plateau area and the features of radiographic OA in that joint compartment across the spectrum of knee OA, from the normal joint to grade 3 radiographic osteophytes and joint space narrowing. We restricted the study to women in order to deal with the confounding effect of gender.

Patients and Methods
Female subjects aged over 40 years who had been involved in studies in which a radiograph and MRI of the knee was performed in our unit were included in this study. Subjects had been recruited through the Jean Hailes Centre (a women’s health clinic), private consulting clinics (Rheumatologists, orthopaedic surgeons, general practitioners) and through advertising in the local media.

Subjects included those with established knee OA and healthy non-osteoarthritic subjects. Those without OA had been initially recruited for a study of healthy aging and had no significant pain at baseline, we have previously described this group (2). Subjects with OA had pain attributable to knee OA and radiographic evidence of OA (osteophytes in the knee) (4), so that these met ACR clinical and radiographic criteria for knee OA (7). The study was approved by the ethics committee of the Alfred and Caulfield Hospitals in Melbourne, Australia. All subjects provided informed consent.

The exclusion criteria were: inflammatory arthritis, previous knee joint replacement, malignancy, fracture in the last 10 years and contra-indication to MRI (eg pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel in strategic locations, metal in the eye, and claustrophobia), inability to walk 50 feet without the use of assistive devices, hemiparesis of either lower limb and planned total knee replacement.

All subjects completed a questionnaire to obtain information regarding demographic data, current physical activity (8) and smoking history (ever versus never smoked). Weight was measured to the nearest 0.1kg (shoes and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1cm (shoes removed) using a stadiometer. Body mass index (BMI) (weight/height² kg/m²) was calculated. General health status was assessed by SF-36 (Short Form 36) (9). Knee pain and function were assessed using the knee specific WOMAC (Western Ontario and Mc Master Universities Osteoarthritis Index) (10).
At study entry, each subject had a weight-bearing antero-posterior tibiofemoral radiograph, taken in full extension. In asymptomatic healthy subjects, the dominant knee was imaged. The dominant knee was defined as the lower limb from which she stepped off when walking. In subjects with OA, the symptomatic knee was imaged, but where both were symptomatic, both knees were imaged, and the knee with the least severe radiographic OA was used as the study joint. These radiographs were independently scored in duplicate, by a trained observer who used a published atlas to classify disease in the tibiofemoral joint (11). The radiological features of tibiofemoral OA were graded in each compartment, on a four point scale (0-3) for individual features of femoral osteophytes, tibial osteophytes, and joint space narrowing (JSN), where 0 designates no evidence of OA, and 3 designates severe radiographic disease (11). In the case of disagreement between readings, the films were reviewed with an independent observer. The intraobserver reproducibility as measured by kappa statistic was 0.92 for tibial and 0.90 for femoral osteophytes and 0.82 for medial and 0.80 for lateral joint space narrowing (kappa statistic).

Each subject had an MRI performed on the study knee. Knees were imaged in the sagittal plane on the same 1.5-T whole body magnetic resonance unit (Signa Advantage HiSpeed GE Medical Systems Milwaukee, WIS) using a commercial receive-only extremity coil, using the previously described sequence (5). One trained reader did the measurements in duplicate. Medial and lateral tibial plateau bone areas were determined by means of image processing on an independent workstation using the software program Osiris, by creating an isotropic volume from the input images which were reformatted in the axial plane, then areas were directly measured from these axial images, as previously described(4). To measure the tibial plateau bone area, we selected the first image which showed both tibial cartilage and subchondral bone. The area of medial and lateral tibial plateau bone was measured on this image and the next distal image manually (Figure 1). An average of the 2 areas was used as an estimate of the tibial plateau bone area. The coefficient of variation for the medial and lateral tibial plateau areas were 2.3% and 2.4%, respectively, for the repeated image analysis(4).

Descriptive statistics for characteristics of the subjects were tabulated. Independent t-tests were used for comparison of means. Fishers exact test was used to compare categorical characteristics between the groups. Tibial bone area in healthy and OA women was compared using independent T-tests. The effect of potential confounders on the relationship between bone area and radiographic OA was explored by calculating estimated marginal means, using ANOVA methods. Regression techniques were used to examine the relationship between tibial plateau area and maximum grade of osteophyte and joint space narrowing in the medial and lateral tibiofemoral compartment. The effect of potential confounders was examined using logistic regression, with estimated marginal means calculated for the different radiographic grades. A p value < 0.05 (2 tailed) was regarded as statistically significant. All analyses were performed using the SPSS statistical package (version 11.0.0, SPSS, Cary, NC).

Results
Complete data was available for 81 healthy women and 68 women with OA (Table 1). Compared to the healthy women, those with OA were significantly older (p < 0.001), heavier (p = 0.001), had higher BMI (p < 0.001), experienced more pain (p < 0.001),
had a lower level of physical function (p < 0.001), higher level of mental function (p = 0.02) and a lower level of physical activity (p < 0.001).

Table 1: Clinical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal women N = 81</th>
<th>OA women N = 68</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>57 (5.8)</td>
<td>63 (10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, m*</td>
<td>1.63 (0.07)</td>
<td>1.62 (0.06)</td>
<td>0.12</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>70.2 (13.8)</td>
<td>78.3 (15.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>26.3 (5.1)</td>
<td>30.0 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain (WOMAC)*</td>
<td>1.7 (2.8)</td>
<td>83.3 (46.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical function (SF-36)*</td>
<td>5.2 (6.2)</td>
<td>37.2 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental health function (SF-36)*</td>
<td>49.1 (9.0)</td>
<td>52.9 (9.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical activity level*</td>
<td>7.2 (1.7)</td>
<td>5.8 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kellgren Lawrence ≥ 2</td>
<td>1 (1%)</td>
<td>17 (26%)</td>
<td>&lt;0.001#</td>
</tr>
</tbody>
</table>

*mean (SD)

# Fisher’s exact test

Women with OA had larger medial and lateral tibial plateau bone area (mean ± SD, 1850 ± 240 mm² and 1279 ± 220 mm², respectively) than healthy women (1670 ± 200 mm² and 1050 ±130 mm², p < 0.001 for both differences, Table 2). These results remained significant after accounting for potential confounders including age, BMI, pain and physical activity level (Table 2).
Table 2: Tibial plateau area in normal subjects compared to those with OA

<table>
<thead>
<tr>
<th></th>
<th>Crude analysis*</th>
<th>P value</th>
<th>Adjusted results†</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal women n = 81</td>
<td>OA women n = 68</td>
<td>Normal women n = 81</td>
<td>OA women n = 68</td>
</tr>
<tr>
<td>Medial tibial area, mm²</td>
<td>1670 (200)</td>
<td>1850 (240)</td>
<td>&lt;0.001</td>
<td>1660 (30)</td>
</tr>
<tr>
<td>Lateral tibial area, mm²</td>
<td>1050 (130)</td>
<td>1270 (220)</td>
<td>&lt;0.001</td>
<td>1080 (30)</td>
</tr>
</tbody>
</table>

*mean (SD)
†mean (SE), adjusted for age, BMI, pain, physical activity level
In the initial analyses, in which the effect of covariates was not considered, a positive relationship was observed between tibial plateau bone area and grade of osteophytes and JSN in each compartment (all \( p < 0.001 \)) (Table 3). There was an increase in medial and lateral tibial plateau area of 146 mm\(^2\) and 102 mm\(^2\) for every increase in grade of osteophyte in the respective compartment. There was an increase in medial and lateral tibial plateau area of 160 mm\(^2\) and 131 mm\(^2\) for every increase in grade of JSN in the respective compartment. In multivariate analyses after adjusting for the potential confounders including age, height, weight and grade of osteophytes/JSN, higher grade of medial JSN was associated with an increased medial tibial plateau bone area (\( p < 0.001 \)). Higher grade of lateral osteophytes (\( p = 0.002 \)) and JSN (\( p = 0.04 \)) were all associated with an increased lateral tibial plateau bone area. The association between grade of medial osteophytes and medial plateau area was not significant after accounting for covariates (\( p = 0.70 \)). For each increase in grade of tibial or femoral osteophyte or grade of joint space narrowing there was an increase in the respective tibial plateau bone area (Table 4).

Table 3: The relationship between tibial plateau area and individual radiographic characteristics of OA

<table>
<thead>
<tr>
<th></th>
<th>Crude Regression Coefficient(^1) (95% CI)</th>
<th>P value</th>
<th>Adjusted regression Coefficient(^2) (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial Tibial Plateau area</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of osteophyte</td>
<td>146 (81, 212)</td>
<td>&lt;0.001</td>
<td>18 (-41, 78)(^3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>160 (120, 201)</td>
<td>&lt;0.001</td>
<td>145 (103, 186)(^4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Lateral Tibial Plateau area</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of osteophyte</td>
<td>102 (72, 132)</td>
<td>&lt;0.001</td>
<td>58 (22, 95)(^3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>131 (85, 177)</td>
<td>&lt;0.001</td>
<td>57 (2, 113)(^4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\( ^1 \) Change in tibial plateau area for each change in grade of osteophyte or joint space narrowing (mm\(^2\))

\( ^2 \) Change in tibial plateau area for each change in grade of osteophyte or joint space narrowing, after accounting for potential covariates

\( ^3 \) Adjusted for age, height, weight, grade of joint space narrowing

\( ^4 \) Adjusted for age, height, weight, grade of osteophyte
Table 4: The relationship between tibial plateau area and individual radiographic characteristics of OA

<table>
<thead>
<tr>
<th></th>
<th>Medial tibial plateau area</th>
<th>Lateral tibial plateau area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude* P value</td>
<td>Adjusted† P value</td>
</tr>
<tr>
<td>Femoral osteophyte grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1730 (220)</td>
<td>1740 (20)</td>
</tr>
<tr>
<td>I</td>
<td>1810 (360)</td>
<td>1750 (90)</td>
</tr>
<tr>
<td>II</td>
<td>2090 (330)</td>
<td>2060 (100)</td>
</tr>
<tr>
<td>III</td>
<td>--‡ 0.002</td>
<td>--‡ 0.01</td>
</tr>
<tr>
<td></td>
<td>1530 (70)</td>
<td>1390 (130)</td>
</tr>
<tr>
<td>Tibial osteophyte grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1730 (220)</td>
<td>1730 (20)</td>
</tr>
<tr>
<td>I</td>
<td>1960 (360)</td>
<td>1920 (90)</td>
</tr>
<tr>
<td>II</td>
<td>2050 (140)</td>
<td>2010 (160)</td>
</tr>
<tr>
<td>III</td>
<td>--‡ 0.008</td>
<td>--‡ 0.03</td>
</tr>
<tr>
<td></td>
<td>1550 (40)</td>
<td>1410 (120)</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1700 (190)</td>
<td>1700 (20)</td>
</tr>
<tr>
<td>I</td>
<td>1750 (180)</td>
<td>1750 (50)</td>
</tr>
<tr>
<td>II</td>
<td>2060 (220)</td>
<td>2040 (90)</td>
</tr>
<tr>
<td>III</td>
<td>2220 (260)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2190 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1430 (80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1350 (110)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* Mean (SD)
† Estimated marginal mean (SE), results adjusted for age, BMI, pain, exercise level
‡ No result in group
**Discussion**

We have shown that women with established knee OA have larger tibial plateaux area than healthy women. These differences were not attributable to the baseline differences between the groups. We also found that tibial plateau bone area was related to the radiographic severity of OA; tibial plateau bone area increased with increased grade of joint space narrowing in both medial and lateral compartments, whilst only lateral tibial plateau bone area increased with a increased grade of osteophyte.

Bone size has been shown to increase with age and also with OA (12, 13). Two previous studies have compared femoral neck size in subjects with OA to normal subjects. Although a more recent MRI study found femoral neck area to be larger in men with hip OA than healthy controls matched for age and sex (14), an earlier smaller anatomical specimen study, of 28 subjects with OA and 16 controls, found no difference, possibly due to lack of power (15).

Bone size, both adjacent to and distant to affected joints, has been shown to correlate with the severity of OA. A recent study which examined the relationship between tibial plateau area and early changes of radiographic knee OA found a positive association between grade one osteophytosis and tibial plateau area(6). However, this study found no relationship between tibial plateau area and joint space narrowing, perhaps because only healthy subjects with a limited spectrum of disease were examined, with no more than grade one osteophytosis or joint space narrowing. Another study which compared femoral neck area in men with unilateral or bilateral hip OA, found femoral neck size was greater in the hip with higher OA grade (14). However, since a composite score was used to grade OA, the authors were unable to comment on the relationship between bone size and the individual radiographic characteristics of OA. Upper limb indices of bone area have been linked to lower extremity OA. For instance, radial width was found to be associated with severity of knee OA in a large study in 430 men, but not in women, suggesting OA may have systemic manifestations or aetiology (16). Indeed, in support of this hypothesis, the biochemical composition of bone in the iliac crest in women with hand OA differed to that in women without hand OA (17, 18).

Some aspects of the current study need consideration. In order to deal with the confounding effect of gender, we only examined women. Whether these results are generalisable to men is to be determined. Bone area is the only marker of bone size we used. However, we have shown this method to be reproducible, and similar to the methods used by other investigators (14). In this study we did not examine other measures of bone quantity such as density which may also be important. There were significant differences between the healthy women and those with OA, including age, weight, BMI, pain, physical activity level, etc. However, these factors have been accounted for in the analysis.

The increased tibial plateau area we observed in OA may occur as a compensatory response to biomechanical factors, or may be the primary abnormality. With increasing grade of OA the tibial bone area increased in size while the amount of knee cartilage decreased (3). This results in less articular cartilage, spread over a larger
area, which may result in abnormal forces through the joint. This may further enhance cartilage loss in OA.

This study shows that in women, tibial plateau area may be related to the severity of radiographic knee OA. It also provides further evidence that subchondral bone may be worthy of further investigation to identify factors influencing the progression of OA.

Acknowledgements
We would like to acknowledge Judy Hankin, Vicki White and Judy Snaddon for subject recruitment and duplicate measurements. We would like to acknowledge the Shepherd Foundation and NHMRC for support. Special thanks to the participants who made this study possible.

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Figure 1: Axial T1-weighted fat saturated 3D MRI image showing the method of measuring the tibial plateau bone area: The area of medial (Roi 2) and lateral (Roi 1) tibial plateau bone is measured manually on the image on the left, which shows both tibial cartilage and subchondral bone and the next image distal to the joint, shown on the right. An average of the 2 areas is used as an estimate of the tibial plateau bone area.
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