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Factors affecting tibial plateau expansion in healthy women over 2.5 years: a longitudinal study[1]

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Summary

Objective: There is evidence for tibial bone area to increase in response to risk factors for knee osteoarthritis (OA) in healthy subjects and to increase over time in subjects with knee OA. We performed a cohort study to examine whether tibial plateau bone area changes over time in healthy subjects and identify factors influencing the change.

Design: Eighty-one healthy women (age range 50–76 years) underwent magnetic resonance imaging (MRI) on their dominant knee at baseline and approximately 2.5 years later. Tibial plateau bone area was measured at baseline and follow-up. Risk factors assessed at baseline were tested for their association with change in tibial plateau bone area over time using multiple linear regression.

Results: The mean tibial plateau bone area increased from 1733 ± 209 to $1782 \pm 203\,mm^2$ for the medial, and from 1090 ± 152 to $1109 \pm 152\,mm^2$ for the lateral over the study period, representing an annual average increase rate of 1.2% (95% CI 0.03%, 1.6%) and 0.8% (95% CI 0.7%, 1.8%), respectively. Baseline tibial plateau bone area was inversely associated with the increase rate of tibial plateau bone area. There was a trend for static knee alignment to be related to the increase rate of tibial plateau bone area.

Conclusion: In healthy women, tibial plateau bone area increases over time. Baseline tibial plateau bone area is the main factor affecting the rate of increase, with biomechanical factors, such as static anatomical alignment, likely to affect the expansion of tibial plateau. Further work will be needed to determine the effect of subchondral bone change in the pathogenesis of knee OA.

Key words: Bone, Bone size, Knee alignment, Osteoarthritis, Knee.

Introduction

Osteoarthritis (OA) is a disease involving cartilage, bone and soft tissues of the articular joint[1]. It has long been recognised by clinicians that bony expansion is a characteristic of an osteoarthritic joint[2]. Bone changes have been thought to be an important element in the pathogenesis of OA[3–8]. However, whether OA originates in cartilage or bone remains unclear[6].

Bony swelling is recognised as a clinical criterion for OA by the American College of Rheumatology[9], based on expert clinical opinion. More recently, this has been quantified, with subjects with OA having larger bone size than healthy controls[10,11]. The bone size increases with increasing severity of radiographic OA[10,11]. We have shown that tibial plateau bone area increased over time in subjects with established knee OA[12]. Male gender, body mass index (BMI) and baseline grade of medial joint space narrowing (JSN) were positively associated with the rate of medial tibial plateau bone enlargement. Baseline medial tibial plateau bone area was inversely associated with the rate of medial tibial plateau bone area increase[12]. These findings cannot be explained simply by osteophytes or change in osteophytes.

We have shown that risk factors for OA such as obesity and increased adductor moment appear to increase tibial bone area before any effect is seen on knee cartilage[13,14]. These associations were found in people with no evidence of OA, in particular no evidence of osteophytes. In healthy subjects, age, BMI, gender, knee adduction moment and physical activity have been associated with tibial bone size in cross-sectional studies[13–20]. It is well known that femoral bone size in healthy adults undergoes continual remodelling, after growth has ceased[21]. However, whether tibial bone size is static or changes over time in healthy subjects is unknown.

We performed a cohort study of healthy middle-aged women over 2.5 years, to examine whether tibial plateau bone area changes over time and to identify the factors at baseline which might predict the change in bone area. We restricted the study to women in order to deal with the confounding effect of gender.

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Patients and methods

Eighty-one healthy postmenopausal women aged over 50 years, with no symptoms of knee OA (no significant knee pain), were recruited through the Jean Hailes Centre (a women's health clinic), private consulting clinics and through advertising in the local media. We have previously described this group[22]. The exclusion criteria were: inflammatory arthritis, previous knee joint replacement, malignancy, fracture in the last 10 years, contraindication to magnetic resonance imaging (MRI) (e.g., pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel in strategic locations, metal in the eye, and claustrophobia), hemiparesis of either lower limb and planned total knee replacement. The study was approved by the Alfred Hospital Human Research Ethics Committee in Melbourne, Australia. All participants gave written informed consent.

At baseline, subjects completed a questionnaire that included demographic data, reproductive and menopausal history, type and duration of postmenopausal oestrogen therapy (ET), and current physical activity[23]. Weight was measured to the nearest 0.1 kg (shoes, socks and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. BMI (weight/height^2, kg/m^2) was calculated. Knee pain was assessed using the knee specific WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)[24].

At baseline, each subject had a weight-bearing anteroposterior tibiofemoral radiograph taken of the dominant knee in full extension. The dominant knee was defined as the lower limb from which she stepped off when walking. All radiographs were independently scored by two trained observers using a published atlas to classify disease in the tibiofemoral joint[25]. The radiographic features of tibiofemoral OA were graded in each compartment on a four-point scale (0–3) for individual features of osteophytes and JSN[25]. Intraobserver reproducibility was 0.93 for osteophytes and 0.93 for JSN. Interobserver reproducibility was 0.86 for osteophytes and 0.85 for JSN (by kappa statistic)[22].

Knee angles were measured by a single observer, as has previously been described from standing anteroposterior radiographs[26,27]. Lines were drawn through the middle of the femoral shaft and through the middle of the tibial shaft. The angle subtended at the point at which these two lines met in the centre of the tibial spines was based on a modification of the method of Moreland *et al.*[26] recently described by Felson *et al.*[27]. The angle subtended by the lines on the medial side was measured using Osiris software (University of Geneva). Thus, an angle less than 180° was more varus and an angle greater than 180° more valgus. The intraobserver variability was 0.98[28].

Each subject had an MRI performed on her dominant knee, at baseline and approximately 2.5 years later. Knees were imaged in the sagittal plane on a 1.5 T whole body magnetic resonance unit (Signa Advantage Echospeed; GE Medical Systems, Milwaukee, WI) using a commercial transmit–receive extremity coil. The following sequence and parameters were used: a T1-weighted fat suppressed 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 (frequency direction, superior–inferior) × 512 (phase encoding direction, anterior–posterior) matrix; one acquisition, time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 mm × 0.31 mm (512 × 512 pixels). Cross-sectional areas of medial and lateral tibial plateaus were determined by means of image processing on an independent workstation using the software program Osiris (University of Geneva, Switzerland), 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[11,12,17,22,29]. Using this technique, osteophytes, if present, are not included in the area of interest. One trained reader (YW) did the measurements in duplicate. An average of the duplicate results was used for the final results. The scans were measured independently. Each subject's baseline and follow-up MRI scans were measured unpaired and blinded to subject identification and timing of MRI. To measure the tibial plateau bone area, we selected the first image which showed both tibial cartilage and subchondral bone. The areas of medial and lateral tibial plateau bones were measured on this image and the next distal image manually. An average of the two areas was used as an estimate of the tibial plateau bone area (Fig. 1). The coefficients of variation (CVs) (for the repeated image analysis) for the medial and lateral tibial plateau bone areas were 2.3% and 2.4%, respectively[22].

Tibial cartilage volume was determined using the Osiris software as previously described[22,29]. Two trained observers read each MRI, blinded to subject identification. The CVs for cartilage volume measures were 3.4% for medial tibial and 2.0% for lateral tibial cartilage[22].

Descriptive statistics for characteristics of the subjects were tabulated. *t* test for independent samples was used to compare those who completed the study and those who did not. Chi-square test was used to compare nominal characteristics between the groups. The principal outcome measure in the analyses was annual percentage change in tibial plateau bone area. Absolute change in tibial plateau bone area was obtained by subtracting baseline bone area from follow-up bone area. Annual absolute change was calculated by dividing this figure by the time between MRI scans. Annual percentage change was obtained by dividing annual change by the baseline bone area and multiplying by 100 to obtain a percentage. Paired *t* test was used to compare the baseline and follow-up tibial plateau bone areas. Multiple linear regression techniques were used to explore the possible factors affecting annual percentage change in tibial plateau bone area, including age, BMI, knee angle, physical activity, ET, baseline tibial cartilage volume and plateau bone area. A *P*-value less than 0.05 (two-tailed) was regarded as statistically significant. All analyses were performed using the SPSS statistical package (standard version 11.5.0, SPSS, Chicago, IL).

Results

Eighty-one women (mean age 57 years, range 50–76) fulfilled the study criteria and entered this study (Table I). Fifty-seven (70%) women completed the longitudinal MRI component of the study. Of the 24 subjects who failed to complete the study, 10 were unable to be contacted, eight declined to be followed for non-specific reasons, four had ill health/metal implants since baseline, and two moved interstate. There were no statistically significant differences in terms of age (57.3 ± 5.9 vs 56.4 ± 5.7 years, $P = 0.54$, mean ± standard deviation), BMI (26.0 ± 5.1 vs 26.9 ± 5.2 kg/m^2, $P = 0.48$), ET use (51% vs 54%, $P = 0.79$), knee angle (181.4 ± 3.4 vs 181.4 ± 3.2°, $P = 0.99$), tibial cartilage volume (1.53 ± 0.31 vs 1.53 ± 0.26 ml for the

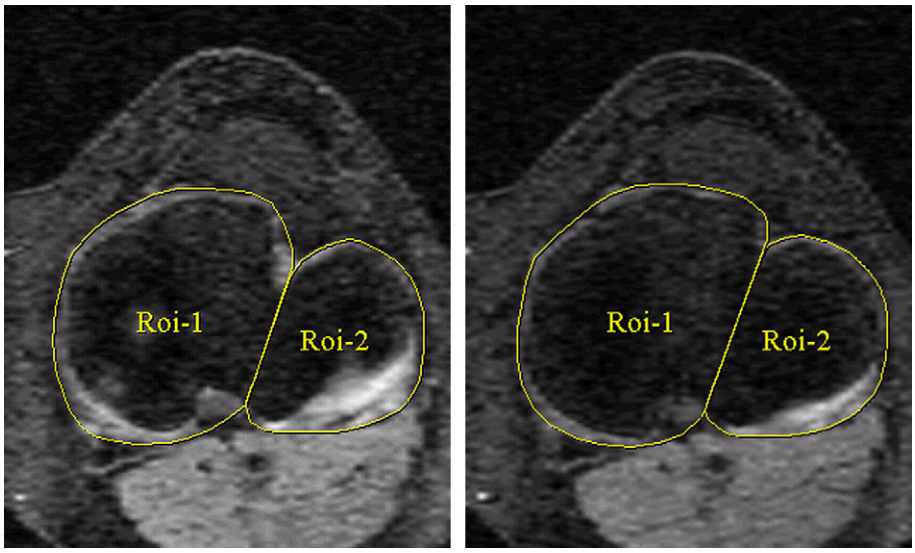

Fig. 1. Axial T1-weighted fat-saturated 3D MRI image showing measurement of tibial plateau bone area. The areas of medial (Roi 1) and lateral (Roi 2) tibial plateau bones are measured manually on the first image that shows both tibial cartilage and subchondral bone (left), and on the next distal image (right). An average of the two areas is used as an estimate of the tibial plateau bone area. MRI, magnetic resonance imaging; Roi, region of interest.

medial, $P = 0.95$; 1.99 ± 0.38 vs 2.12 ± 0.37 ml for the lateral, $P = 0.16$), and tibial plateau bone area (1733 ± 209 vs 1683 ± 184 mm^2 for the medial, $P = 0.29$; 1090 ± 152 vs 1102 ± 120 mm^2 for the lateral, $P = 0.71$), between the subjects who completed the study and those who did not. However, the women who completed the study had higher baseline pain score (0.50 (0.00, 3.20) vs 0.00 (0.00, 0.93), $P = 0.004$, median (interquartile range)) and physical activity level (7.4 ± 1.7 vs 6.6 ± 1.6, $P = 0.03$) than those who did not. Osteophytes were presented in four women. However, only one of them (1%) had radiographic knee OA.

The mean bone area increased from 1733 ± 209 mm^2 to 1782 ± 203 mm^2 (mean $\pm$ SD, $P < 0.001$) for the medial

Table I
Characteristics of the study population

	Total ($n = 81$)	Completers ($n = 57$)	Loss to study ($n = 24$)	P value
Age, years	57.1 (5.8)	57.3 (5.9)	56.4 (5.7)	0.54
Height, cm	163.5 (7.1)	164.0 (7.3)	162.2 (6.5)	0.26
Weight, kg	70.2 (13.8)	70.0 (13.6)	70.8 (14.6)	0.80
BMI, kg/m^2	26.3 (5.1)	26.0 (5.1)	26.9 (5.2)	0.48
Pain score (WOMAC)†	0.00 (0.00, 2.65)	0.50 (0.00, 3.20)	0.00 (0.00, 0.93)	0.004
ET user, number (%)	42 (52%)	29 (51%)	13 (54%)	0.79*
Physical activity level				
Walk	2.9 (1.1)	3.0 (1.1)	2.8 (1.0)	0.56
Job	2.6 (1.0)	2.8 (1.0)	2.4 (0.9)	0.11
Sports	1.6 (0.8)	1.7 (0.9)	1.4 (0.6)	0.05
Total	7.2 (1.7)	7.4 (1.7)	6.6 (1.6)	0.03
Time between scans, years	2.5 (0.2)	2.5 (0.2)	–	–
Radiographic knee OA, number (%)	1 (1%)	1 (2%)	0	0.51*
Average knee angle, degrees	181.4 (3.3)	181.4 (3.4)	181.4 (3.2)	0.99
Tibial cartilage volume, ml				
Medial	1.53 (0.29)	1.53 (0.31)	1.53 (0.26)	0.95
Lateral	2.03 (0.38)	1.99 (0.38)	2.12 (0.37)	0.16
Tibial plateau bone area, mm^2				
Medial	1719 (202)	1733 (209)	1683 (184)	0.29
Lateral	1093 (143)	1090 (152)	1102 (120)	0.71

Except where indicated otherwise, values are presented as mean (SD). WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ET: oestrogen therapy; OA: osteoarthritis.

*Determined by Chi-square test, all others by *t* test.

†Values are presented by median (interquartile range).

plateau, and from $1090 \pm 152\ mm^2$ to $1109 \pm 152\ mm^2$ ($P = 0.08$) for the lateral plateau over the study period. The mean amounts of bone area increase in medial and lateral tibial plateaus were $20\ mm^2$ and $8\ mm^2$ per year, respectively, representing an annual average increase rate of 1.2% (95% CI 0.03%, 1.6%) and 0.8% (95% CI 0.7%, 1.8%). The results remained unchanged when the four subjects with osteophytes were excluded. There was no correlation in the annual change in medial and lateral tibial plateau bone areas (correlation coefficient $r = -0.12$, $P = 0.38$).

Factors affecting annual percentage change in medial and lateral tibial plateau bone areas were similar (Table II). In univariate analyses, medial and lateral baseline tibial plateau bone areas were inversely associated with medial ($P = 0.02$) and lateral ($P = 0.03$) annual percentage changes in tibial plateau area, respectively. In multivariate analyses after adjusting for age, BMI, knee angle, baseline tibial cartilage volume and plateau bone area, these significant inverse associations persisted ($P = 0.05$ and $P = 0.01$, respectively). There was a trend for age to be inversely associated with annual percentage change in medial tibial plateau area ($P = 0.08$). BMI and baseline cartilage volume were not significantly associated with annual percentage change in medial and lateral tibial plateau areas (Table II).

In univariate analyses, height, weight, ET, baseline pain score and physical activity did not show any significant effect on annual percentage change in medial and lateral tibial plateau areas (results not shown), so they were excluded from the multivariate model.

The effect of knee alignment on annual percentage change in tibial plateau bone area was examined (Table II). In univariate analysis, a more varus knee angle was associated with increased rate of expansion of medial tibial plateau and a more valgus angle was associated with increased rate of expansion of lateral tibial plateau, but these results did not reach statistical significance. When these relationships were examined after adjustment for age, BMI, baseline tibial cartilage volume and plateau bone area, the direction of effect remained constant, but the results approached statistical significance (regression coefficient $B = -1.08$, $P = 0.17$ for medial tibial; regression coefficient $B = 2.32$, $P = 0.06$ for lateral tibial).

Using annual absolute change instead of annual percentage change in tibial plateau bone area in the regression equation did not change the findings (results not shown).

Discussion

We found tibial plateau bone area increased over 2.5 years in healthy women with no evidence of knee OA in this cohort study. The medial and lateral tibial plateau bone areas increased by average rates of 1.2% and 0.8% per year, respectively. The baseline tibial plateau bone area was inversely associated with the rate of bone expansion in both medial and lateral tibial plateaus. There was a trend for static knee alignment to be related to the rate of increase in tibial plateau bone area, with the plateau subtended by the more acute angle showing increase.

We showed an increase of tibial plateau bone area in healthy postmenopausal women at average rates of 1.2% for the medial tibia and 0.8% for the lateral tibia per year. At the level of the individual, the minimum detectable change that can be distinguished from measurement error (at a 5% level of significance) is 2.8 multiplied by the CV for an individual bone area measurement, i.e., approximately 6.4% for medial tibial bone area and 6.7% for lateral tibial bone area in this study. We found that two (4%) individuals had a reduction and 12 (21%) individuals had an increase in medial tibial bone area, and six (11%) individuals had a reduction and 10 (18%) individuals had an increase in lateral tibial bone area that was greater than measurement error.

No previous longitudinal studies have examined the change in tibial plateau bone area in normal subjects. However, the rate of increase of medial and lateral tibial plateau bone areas we observed in normal subjects in this study is less than the rate of increase in medial and lateral tibial

Table II
Factors affecting annual percentage change in tibial plateau bone area

	Univariate analysis*		Multivariate analysis†	
	Regression coefficient (95% CI)	*P* value	Regression coefficient (95% CI)	*P* value
Medial tibial plateau area				
Age‡	−0.69 (−1.58, 0.20)	0.13	−0.78 (−1.65, 0.09)	0.08
BMI§	−0.21 (−1.26, 0.85)	0.70	0.07 (−0.96, 1.11)	0.89
Baseline medial tibial plateau area‖	−2.92 (−5.37, −0.48)	0.02	−2.76 (−5.47, −0.05)	0.05
Knee angle¶	−0.99 (−2.57, 0.58)	0.21	−1.08 (−2.62, 0.46)	0.17
Baseline medial tibial cartilage volume#	−0.98 (−2.69, 0.74)	0.26	−0.55 (−2.41, 1.30)	0.55
Lateral tibial plateau area				
Age‡	0.10 (−1.29, 1.49)	0.89	0.07 (−1.33, 1.47)	0.92
BMI§	0.38 (−1.24, 1.99)	0.64	0.82 (−0.79, 2.43)	0.31
Baseline lateral tibial plateau area‖	−5.60 (−10.78, −0.42)	0.03	−8.05 (−13.87, −2.24)	0.01
Knee angle¶	1.50 (−0.91, 3.92)	0.22	2.32 (−0.13, 4.77)	0.06
Baseline lateral tibial cartilage volume#	−0.52 (−2.66, 1.63)	0.63	0.63 (−1.66, 2.91)	0.58

*Change in annual percentage change in tibial plateau area per unit increase in respective variable.

†Change in annual percentage change in tibial plateau area per unit increase in respective variable after adjusting for age, BMI, knee angle, baseline tibial plateau area and tibial cartilage volume in regression equation.

‡Per 10 years change in age.

§Per 10 kg/m^2 change in BMI.

‖Per 1000 mm^2 change in tibial plateau bone area.

¶Per 10° change in knee angle.

#Per ml change in tibial cartilage volume.

plateau bone areas of 2.2 ± 6.9% and 1.5 ± 4.3% per year, respectively, which we previously observed in subjects with knee OA[12].

In this study, we found the baseline tibial plateau bone area was inversely associated with the rate of tibial plateau bone area increase. This suggests that the rate of increase in tibial plateau bone area may be more rapid when the tibial plateau bone area is smaller, and that as the tibial plateau bone enlarges over time, the rate of increase slows down. We also found there was a trend for age to be inversely associated with the rate of increase in medial tibial plateau bone area. Whether this is part of the normal ageing process or represents part of the spectrum of disease in OA is unknown. We have previously shown that tibial plateau bone area increases significantly in subjects with knee OA, but the magnitude of this increase is greater than we showed in these normal subjects[12]. However, the definition of normal that we used in this study includes a radiological component[30]. Recent work has shown that by the time radiological OA can be detected, reductions of knee cartilage volume have already occurred[20]. Thus it is possible that within our normal population there are some people who already have early OA, but it does not fulfill the radiological definition of the disease.

In our previous study of subjects with OA, as in this study of normal subjects, we showed that initial tibial plateau bone area was a significant predictor of the increase in tibial plateau bone area over 2 years[12]. There are no other longitudinal data examining tibial bone size. Some previous work has identified factors associated with tibial bone size in cross-sectional studies[13–20]. However, different measures have been used to assess tibial bone size, and different regions of tibia have been measured as the marker of bone size[13–20,31]. We have shown that tibial plateau bone area assessed by MRI increased with age and BMI in cross-sectional studies in healthy adults[13,15]. However, Dacre *et al.*[31] showed that BMI was not significantly correlated with tibial plateau width measured unidimensionally on radiographs, rather than in 2-dimensions as our study. Bone loading has been shown to increase remodelling to increase bone size as per Wolff's law[32]. In keeping with this, knee adduction moment[14] and physical activity[16] are both positively associated with the tibial bone size in healthy middle-aged women. Cross-sectional studies have shown that men have larger tibial bone size than women[17–19]. Jones *et al.*[20] showed that grade 1 medial osteophytosis was associated with a 10–16% increase in both medial and lateral tibial bone areas after adjustment for age, sex and BMI. These cross-sectional data suggest biomechanical and systemic factors may affect the tibial bone size.

The findings related to the knee angle are complementary, with the tendency of more varus alignment (i.e., more acute angle medially, lower knee angle) being associated with increased expansion of the medial tibial plateau, and a more valgus alignment (i.e., more acute angle laterally, higher knee angle) associated with increased expansion of the lateral tibial plateau. Although the findings related to knee angle do not reach statistical significance, they are consistent across the knee. These findings suggest that the effect of knee alignment on change in bone differs to that on change in cartilage: more varus alignment has been related to increased cartilage loss in the medial compartment, and more valgus alignment has been related to increased cartilage loss in the lateral compartment[28,33]. Thus it may be that the increase in load to the medial compartment attributable to varus malalignment[33] facilitates both the expansion of the medial tibial plateau and also progressive cartilage loss, creating the environment for establishment and perpetuation of the pathological process of OA.

We have shown that the risk factors for OA such as obesity and increased adductor moment appear to increase tibial bone area before any effect is seen on knee cartilage[13,14]. This suggests that changes in the bone may occur early in the pathogenesis of knee OA. These associations were found in people with no evidence of OA, in particular no evidence of osteophytes. We have also previously reported that tibial bone size was an independent predictor of knee cartilage volume[17]. The enlargement of tibial plateau bone in response to risk factors for knee OA may result in attenuation of overlying articular cartilage, with the differential effect of these factors on cartilage and bone contributing to risk of OA. This may result in biomechanical changes at the knee, which may further contribute to the pathogenetic process in knee OA. The mechanism for the bone changes is likely to be a combination of biomechanical, such as knee alignment, and systemic factors. Increased bone size is a potential adaptation to enhance the mechanical competence of bone because a larger cross-sectional area can bear larger compressive loads and cope more efficiently with bending loading[34]. The enlargement of bone may represent a partial compensation against age-related bone loss to maintain adequate bone mechanical competence[18].

There are some limitations of this study. Tibial plateau bone area is the only marker we used to assess tibial bone size. Our measurement of tibial plateau bone area as measured by MRI is averaged on a 2D projection of the tibia. Although the measurement has been shown to be highly reproducible[17,20,22,29], small positional changes in the longitudinal study may have resulted in an increased measurement error which will have underestimated longitudinal change. In order to deal with the confounding effect of gender, we only examined women. Whether these results are generalisable to men will need to be determined. Our subjects were generally healthy, with only one subject having any evidence of radiographic knee OA. Repeating our analyses excluding this subject did not change the magnitude or direction of our findings. These findings cannot be explained by osteophytes since osteophytes are not included in the measurement of bone area. The loss to follow-up in our study may introduce bias. However, there was no significant difference between those who completed the follow-up study and those who did not in terms of previously reported factors affecting tibial bone size (age and BMI)[13,15]. Alignment was measured using weight-bearing knee radiographs and not full limb images. Although these angles are highly correlated[28], use of full limb images may have increased the relationship we observed.

In healthy women, tibial plateau bone area increases over time. Baseline tibial plateau bone area is the main factor affecting the rate of change, with biomechanical factors, such as static anatomical alignment, likely to affect the expansion of tibial plateau. Further work will be needed to determine the effect of subchondral bone change in the pathogenesis of knee OA.

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