Sex differences in the relationship between bone mineral density and tibial cartilage volume

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Abstract

Objective. Although there is a well-established sex difference in the prevalence and severity of OA, the mechanism for this is not clear. The aim of this study was to examine the potential role of BMD and BMC in explaining gender differences in knee cartilage volume.

Methods. A total of 153 subjects aged 25–60 years, 81% female, were recruited. MRI was performed of the dominant knee. Cartilage volume was measured using validated methods. Total body BMD and content was measured using DXA.

Results. Total body BMC and BMD was significantly associated with medial cartilage volume in both sexes. However, the associations were stronger in men for BMC ($B = 0.52; 95\% \text{CI} 0.21, 0.83; P$ for difference $= 0.001$) and BMD ($B=2242; 95\% \text{CI} 443, 4041; P$ for difference $=0.05$). Similar results were obtained in the lateral tibial compartment. No significant association was obtained between total body BMD and BMC and patella cartilage volume in either men or women.

Conclusions. In this relatively healthy population, we found a positive relationship between total body BMD and BMC and tibial cartilage volume in the medial and lateral compartments. These relationships were stronger in men than women. Thus, the results of this study may provide some insight into the sex differences in knee cartilage volume, which may in turn facilitate our understanding of the pathogenesis of OA.

Key words: Sex differences, Bone mineral density, Cartilage volume.

Introduction

OA is a major cause of pain and long-term disability, and is characterized by a loss of articular cartilage volume. Males have significantly more cartilage than females both in childhood [1] and adulthood [2], which may explain why they are at lower risk of OA. The concept that cartilage accrued in younger life may relate to risk of osteoarthritis in later life is analogous to the relationship between osteoporosis (OP) and BMD, in which higher BMD provides protection from age-related OP. Before menopause, the prevalence of knee OA is similar in men and women. However, after menopause the risk is higher in women where oestrogen deficiency is seen [3–5]. Menopause has also been associated with accelerated/increased bone loss and risk of OP. As such, hormonal factors have been considered as an explanation for the well-established sex differences in the prevalence of OA and OP.

Many studies have examined the possible inverse relationship between OA and OP, linking BMD to radiographic change. The prevalence of radiographic knee OA, defined in terms of osteophytes [1–5], has been associated with increasing BMD. The relationship between BMD and osteophytes may in part be attributed to a reduced rate...
of bone loss [6–8] or increased bone size, which will arte-
factually increase areal BMD. However, no relationship
with joint space narrowing, as a proxy for articular cartil-
age, has been demonstrated [9], suggesting that different
mechanisms may be involved in the pathogenesis of the
various radiographic features of OA. Alternatively, it may
be that more sensitive and direct assessments of articular
cartilage are required. A previous study has examined the
relationship between BMD and a direct measure of cartil-
age volume assessed using MRI. In this study, BMD was
positively associated with tibial, but not patella cartilage
volume in a population without knee OA [9]. Whether dif-
fferences in BMD between men and women contribute to
the difference in risk of OA in men and women is un-
known. Indeed, a recent study has shown that subchon-
dral BMD is positively associated with medial cartilage
volume, and that this relationship was stronger in men
than women [10]. Understanding the factors underlying
sex differences in cartilage volume may facilitate develop-
ment of preventive strategies and aid in understanding the
disease process. Thus, the aim of this study was to exam-
ine and compare the relationship between total body BMD
and BMC and medial and lateral tibial and patella cartilage
volume in a relatively healthy population of men and
women.

Patients and methods

Subjects

A total of 153 subjects aged 25–60 years were recruited.
Participants were recruited through local media to take
part in a study of lifestyle factors on knee health.
Subjects were excluded if there was a history of any arth-
ritis diagnosed by a medical practitioner, prior surgical
intervention to the knee including arthroscopy, previous
significant knee injury requiring non-weight-bearing ther-
apy or knee pain precluding weight-bearing activity for
>24 h or prescribed analgesia, malignancy or contraindi-
cation to MRI. The study was approved by Alfred Human
Research and Ethics Committee (HREC), the Monash
Standing Research Ethics Committee, the Austin Health
HREC and the University of Melbourne Central HREC.
Informed consent was obtained from all study participants.

Anthropometric and physical activity data

Weight was measured to the nearest 0.1 kg using a sin-
gle pair of electronic scales. Height was measured to
the nearest 0.1 cm using a stadiometer. BMI (weight/
height$^2$ kg m$^{-2}$) was calculated. Strenuous physical ac-
itivity was assessed by asking ‘On how many days during
the last 14 days did you spend at least 20 minutes doing
strenuous exercise? e.g. bicycling, brisk walking, etc.
that was severe enough to raise your pulse rate, cause
you to breathe faster’ with frequency options: no days, 1–
2 days; 3–5 days; 6–8 days; and >9 days. Participation in
strenuous activity for >3 days was categorized as per-
foming strenuous activity.

DXA measures

Bone mass was measured in all subjects using DXA
(GE Lunar Prodigy, using operating system version 9).
Bone mass was examined as BMC (g), and total body
BMD (g/cm$^2$), which is an approximation of the volumetric
density of bone. The machine has a weight limit of
~130 kg. The coefficient of variation (CV) for total body
BMD was 1.2–1.3% [11].

MRI

MRI of the dominant knee was performed [12]. Knees
were imaged in the sagittal plane on a 1.5-T whole-body
magnetic resonance unit (Philips: Medical Systems,
Eindhoven, The Netherlands) using a commercial trans-
mit–receive extremity coil. The weight limit for the
machine is 150 kg. The following sequence and param-
eters were used: T1-weighted fat saturation 3D gradient
recall acquisition in the steady state (58 ms/12 ms/55°,
repetition time/echo time/flip angle) with a 16 cm field of
view, 60 partitions, 512 x 512 matrix and acquisition time
11 min 56 s (one acquisition). Sagittal images were
obtained at a partition thickness of 1.5 mm and an
in-plane resolution of 0.31 x 0.31 mm (512 x 512 pixels).
A coronal fat-saturated, fast spin echo 3D, T2-weighted
acquisition (2200 ms, 20/80 ms/90° repetition time/echo
time/flip angle) with a slice thickness of 3 mm, a 0.3
inter-slice gap, 1 excitation, a field of view of 13 cm and
a matrix of 256 x 192 pixels was also obtained [13].

Cartilage volume

Cartilage volume was determined by manually drawing
disarticulation contours around the cartilage boundary,
using independent workstation software Osiris (Geneva,
Switzerland). Measurement was done by one trained ob-
server with random cross-checks blindly performed by an
independent trained observer. The CV was 2.1% [14].

Bone area

Plateau area was determined using the independent
workstation Osiris, by creating an isotropic volume from
the input images, which were reformatted in the axial
plane. One trained observer performed the measure-
ments, with random cross-checks blindly performed by
an independent trained observer. The CV was 2.3% [14].

Patella structures

Patella cartilage volume was determined by image
processing on an independent workstation using the
Osiris software. The patellar cartilage volume was isolated
from the total volume by manually drawing disarticulation
contours around the cartilage boundaries on each section.
The measurement was done by two independent observ-
ers with independent random cross-checks blindly
performed by a second trained observer, unpaired and
blinded to subject identification, data collected and the
sequence. The CV for the measure was 2.6%. Patellar
bone volume was calculated by using the same method
as for cartilage volume. Contours were drawn around the
patella boundaries in images 1.5 mm apart on sagittal
views. One trained observer made the measurements, with independent random cross-checks blindly performed by a second trained observer, unpaired and blinded to subject identification, data collected and the sequence. The CV for patellar bone volume measures was 2.2%.

Osteophytes

Osteophytes were measured from MR images, which have been shown to be more sensitive than X-rays [15]. Osteophytes were measured from coronal images by two independent trained observers. In the event of disagreement between observers, a third independent observer reviewed the MRI. Intra- and inter-observer reproducibility for agreement on osteophytes ranged between 0.85 and 0.93 ($k$-statistic), respectively.

Statistical analysis

Cartilage volume was normally distributed. Linear regression was used to assess the relationship between total body BMD and BMC and medial and lateral tibial and patella cartilage volume as a continuous outcome. Multiple regression models were used to adjust for potential confounders including age, gender, BMI and participation in physical activity. The independent samples z-test was used to test for significant sex differences in the relationship between total body BMD and BMC and cartilage volume for men and women. We found there was a significant difference in the relationship between BMC ($P$ for difference $= 0.001$) and total body BMD ($P$ for difference $= 0.05$) and medial and lateral cartilage volume for men and women. Similarly, there was a significant difference in the relationship between total body BMD ($P$ for difference $= 0.03$) and BMC ($P$ for difference $= 0.01$) and lateral cartilage volume for men and women.

Results

Descriptive characteristics of study population

The characteristics of the 153 subjects (81% women) who participated in the study are presented in Table 1. Men had significantly higher total body BMD ($P = 0.007$) and total body BMC ($P < 0.001$) compared with women. Men also had significantly higher tibial cartilage volume in all compartments, larger tibial plateau area and patella bone volume compared with women ($P < 0.001$ for all).

The relationship between total body BMD (g/cm$^2$) and BMC (g) and tibial cartilage volume

In women, total body BMD and BMC were significantly positively associated with medial tibial cartilage volume in univariate analysis. After adjusting for potential confounders, this relationship persisted for BMC. In univariate and multivariate analysis, BMC was significantly associated with increased lateral cartilage volume. No significant association was obtained between total body BMD and lateral tibial cartilage volume in either univariate or multivariate analysis. In men, total body BMD and BMC were significantly associated with increased medial and lateral tibial cartilage volume. After adjusting for potential confounders including age, BMI, tibial plateau area, participation in strenuous activity and the presence of osteophytes, these relationships remained significant (Table 2). Similar results were obtained when subjects with osteophytes were excluded from the analysis (data not shown).

Table 1 Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Men ($n = 29$)</th>
<th>Women ($n = 124$)</th>
<th>$P$-value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46 (9)</td>
<td>47 (10)</td>
<td>0.50</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>30 (8)</td>
<td>33 (9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Presence of osteophytes, %$^a$</td>
<td>2 (7)</td>
<td>22 (18)</td>
<td>0.14</td>
</tr>
<tr>
<td>Participation in strenuous activity, %$^a$</td>
<td>17 (59)</td>
<td>62 (50)</td>
<td>0.40</td>
</tr>
<tr>
<td>Bone measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body BMD, g/cm$^2$</td>
<td>1.282 (0.10)</td>
<td>1.228 (0.10)</td>
<td>0.007</td>
</tr>
<tr>
<td>Total body BMC, g</td>
<td>3437 (460)</td>
<td>2825 (471)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Knee measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial tibial cartilage volume, mm$^3$</td>
<td>1282 (315)</td>
<td>939 (210)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Lateral tibial cartilage volume, mm$^3$</td>
<td>1806 (497)</td>
<td>1194 (251)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Medial tibial plateau area, mm$^2$</td>
<td>2241 (240)</td>
<td>1811 (180)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Lateral tibial plateau area, mm$^2$</td>
<td>1712 (243)</td>
<td>1401 (157)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Patella cartilage volume, mm$^3$</td>
<td>2774 (583)</td>
<td>2032 (411)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Patella bone volume, mm$^3$</td>
<td>14150 (1975)</td>
<td>10021 (1802)</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

Values are reported as mean (s.d.) unless otherwise stated. The t-tests were used for comparison of means. The bold font represents statistically significant results. $^a$Chi-squared tests were used for comparison of proportions. $^*$$P$-value for difference between men and women.
The relationship between total body BMD (g/cm^2) and BMC (g) and patella cartilage volume

In this study, we found a positive relationship between total body BMD and BMC and medial and lateral cartilage volume in men. The relationship between total body BMD and BMC and medial and lateral cartilage volume was significantly stronger in men than women. These results may provide some insight into sex differences in knee cartilage volume, which may in turn facilitate our understanding of the pathogenesis of OA.

The relationship between BMD and OA have been examined in several studies, with some showing a positive association between increasing BMD and the presence of osteophytes [8, 16–19]. Prospective studies have shown that higher BMD is associated with an increased risk of the development of osteophytes [20]. However, no previous study has shown a significant association between BMD and joint space narrowing (JSN) [20], which is used as a surrogate marker for articular cartilage. It may be that the previous studies did not have sufficient power to detect a relationship between BMD and JSN, as the prevalence of JSN is lower in the general population.

In this study, we found a positive relationship between total body BMD and BMC, and medial and lateral cartilage volume in a relatively healthy population of men and women. Most previous studies examining the relationship between BMD and OA have been based on radiological assessment of joints. Cross-sectional studies have shown a relationship between increasing BMD and the presence of osteophytes [8, 16–19]. Prospective studies have shown that higher BMD is associated with an increased risk of the development of osteophytes [20]. However, no previous study has shown a significant association between BMD and joint space narrowing (JSN) [20], which is used as a surrogate marker for articular cartilage. It may be that the previous studies did not have sufficient power to detect a relationship between BMD and JSN, as the prevalence of JSN is lower in the general population.

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### Table 2 Relationship between total body BMD (g/cm^2) and BMC (g) and cartilage volume

<table>
<thead>
<tr>
<th>Characteristics of bone</th>
<th>Men (n = 29)</th>
<th>Women (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate regression coefficient (95% CI)</td>
<td>Multivariate regression coefficient (95% CI)</td>
</tr>
<tr>
<td>Medial a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body BMD</td>
<td>1211 (19, 2402)</td>
<td>2242 (443, 4041)</td>
</tr>
<tr>
<td>BMC</td>
<td>0.41 (0.19, 0.63)</td>
<td>0.52 (0.21, 0.83)</td>
</tr>
<tr>
<td>Lateral a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body BMD</td>
<td>2452 (671, 4233)</td>
<td>2750 (380, 5121)</td>
</tr>
<tr>
<td>BMC</td>
<td>0.69 (0.37, 1.02)</td>
<td>0.60 (0.24, 0.96)</td>
</tr>
<tr>
<td>Patella b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body BMD</td>
<td>31 (–2346, 2408)</td>
<td>2459 (–914, 5832)</td>
</tr>
<tr>
<td>BMC</td>
<td>0.14 (–0.36, 0.63)</td>
<td>0.56 (–0.07, 1.20)</td>
</tr>
</tbody>
</table>

The bold font represents statistically significant results. aMultivariate model adjusted for age, BMI, bone area, participation in strenuous activity and presence of osteophytes. bMultivariate model adjusted for age, BMI, bone volume and participation in strenuous activity. *P-value for difference between men and women.
the regulatory polypeptides TGF-β, interfering with osteoclast and osteoblast coupling and cartilage turnover [21]. Moreover, a decline in oestrogen levels with menopause is associated with alterations in bone including high bone turnover and subsequent bone loss [22]. It is possible that there is a similar effect on cartilage. In support of this, women using long-term oestrogen replacement therapy have been shown to have more knee cartilage volume than controls [23].

The mechanism by which BMD relates to increasing cartilage volume remains unclear. Although it has previously been hypothesized that thickening and stiffening of subchondral bone, reflected by increased BMD, may subsequently lead to degeneration in the overlying articular cartilage [24], we examined relatively healthy subjects, as only 16% of subjects had knee osteophytes. It may be that in subjects without established knee OA, the structural integrity of the bone is maintained. This will need to be tested in longitudinal studies. It is unlikely that the positive relationship between total body BMD and content and tibial cartilage volume observed in this study was simply due to co-inheritance, as we would have expected the positive associations to have been present with patella cartilage as well. This was not the case. It may be that biomechanical factors affect these relationships. Thus, axial loading, has also been demonstrated to relate to higher tibial cartilage volume, such that children who do more physical activity accrued more cartilage volume than those who do not [1]. The importance of biomechanical factors is underscored in contrast to the relationships seen in the patellofemoral compartment, suggesting that other factors influence patellar physical characteristics, as the patella is subject to lower axial loading during weight bearing.

A limitation of this study is that it is a cross-sectional study, hence future longitudinal studies will be needed to confirm these findings. Another potential limitation of this study is the self-report presence of arthritis. Although we did not have knee radiographs, we determined the presence of osteophytes from MRI. This has previously been shown to be a more sensitive method of determining the presence of osteophytes than radiography [15]. We did not have information on vertebral osteophytes. Future studies may be required to measure and examine the potential role of vertebral osteophytes in these relationships. Nevertheless, this was a relatively healthy population, as only 16% of subjects had knee osteophytes. Our findings remained unchanged after adjusting for osteophytes. Furthermore, the relationships between total body BMD and BMC and knee structures were independent of potential confounders including participation in physical activity and body size.

In this study of relatively healthy subjects, we found a positive relationship between total body BMD and BMC and tibial cartilage volume in the medial and lateral compartments. There was a significant sex difference in the relationship between total body BMD and BMC and medial and lateral cartilage volume; this relationship was stronger in men than women. The results of this study may provide some insight into sex differences in knee cartilage volume, which may facilitate our understanding of the pathogenesis of OA.

**Rheumatology key messages**

- The positive relationship between BMD and BMC and tibial cartilage volume was stronger in men than women.
- BMD and BMC may provide insight into the sex differences in knee cartilage volume, and the pathogenesis of OA.

**Acknowledgements**

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**References**


