Increased cancellous bone and connectivity in coxarthrosis


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Increased femoral neck cancellous bone and connectivity in coxarthrosis (hip osteoarthritis)

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Abstract

Patients with coxarthrosis (cOA) have a reduced incidence of intracapsular femoral neck fracture, suggesting that cOA offers protection. The distribution of bone in the femoral neck was compared in cases of coxarthrosis and postmortem controls to assess the possibility that disease-associated changes might contribute to reduced fragility. Whole cross-section femoral neck biopsies were obtained from 17 patients with cOA and 22 age- and sex-matched cadaveric controls. Densitometry was performed using peripheral quantitated computed tomography (pQCT) and histomorphometry on 10-micron plastic-embedded sections. Cortical bone mass was not different between cases and controls (P > 0.23), but cancellous bone mass was increased by 75% in cOA (P = 0.014) and histomorphometric cancellous bone area by 71% (P < 0.0001). This was principally the result of an increase of apparent density (mass/vol) of cancellous bone (+45%, P = 0.001). Whereas cortical porosity was increased in the cases (P < 0.0001), trabecular width was also increased overall in the cases by 52% (P < 0.001), as was cancellous connectivity measured by strut analysis (P < 0.01). Where osteophytic bone was present (n = 9) there was a positive relationship between the amount of osteophyte and the percentage of cancellous area (P < 0.05). Since cancellous bone buttresses and stiffens the cortex so reducing the risk of buckling, the increased cancellous bone mass and connectivity seen in cases of cOA probably explain, at least in part, the ability of patients with cOA to resist intracapsular fracture of the femoral neck during a fall.

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Introduction

Osteoarthritis (OA) and osteoporosis are the two most common musculoskeletal disorders of the elderly and are associated with considerable morbidity and mortality. Clinical observations generally report an absence of OA of the femoral head in cases of hip fracture, and in cases of osteoarthritis of the hip (coxarthrosis, cOA), intracapsular hip fracture is rare [12,20]. The absence of cOA in patients with femoral neck fractures was initially reported almost 3 decades ago [20] and it has since been shown that a negative correlation exists between cOA and osteoporosis (OP) of the hip [12,36]. It is unclear, however, whether this is due to mechanical influences associated with arthritis or whether the associated biochemical changes cause local alterations in the factors and cytokines that modulate bone remodeling. Radin et al. demonstrated that patients with early OA had stiffer endochondral bone than normal [38] and proposed the hypothesis that OA was consequent upon a primary defect in bone [37]. The femoral heads of patients with cOA show higher...
bone mineral density [33], stiffness, and ability to absorb energy [28]. Certain histomorphometric indices of cancellous bone structure are also higher in cOA, including femoral head trabecular thickness (Tb.Th) [18,26] and trabecular volume (Tb.V) [26,29]. Other indices, such as microcrack density (Cr.Dn) [19,26] and trabecular number (Tb.N) [18], are lower in cOA. Compressive regions in cOA have increased trabecular separation (Tb.Sp) [17], bone volume/tissue volume (BV/TV), bone surface/tissue volume (BS/TV), and bone surface/bone volume (BS/BV) [17].

These studies provided some evidence that cOA-associated changes in bone of the femoral head increase the ability to withstand stress; however, it is not the head, but the neck and the trochanteric regions [2] of the femur that are vulnerable to fracture.

We decided to compare the structural parameters of whole cross sections of bone taken from the femoral neck of patients with cOA with those of unaffected controls because few histomorphometric studies into cOA have focused on this site. Our reasoning was that investigating the distribution, porosity, and connectivity of bone in this region should allow us to assess the potential association of bone structure and density in coxarthrosis with fracture resistance. We were also interested in coxarthrosis as a biological model of hip fracture resistance that might point to novel future approaches to intervening against hip fracture in those without cOA who were vulnerable.

**Materials and methods**

**Subjects**

This investigation was carried out alongside our ongoing study into femoral neck fracture [7] and was approved by the Cambridge District Research Ethics Committee. cOA
samples with a complete or near complete cortical shell were selected. The 17 cOA cases (12 female, 5 male) were aged 51–95 years (mean, 69.9 ± 2.61) (Table 1) and the biopsies were obtained from clinical waste generated during routine surgery for arthroplasty. All the cases were scored either grade 3 or 4 on the Kellgren Lawrence scale [24] (Table 1). Cases were excluded if the patient history indicated the presence of preexisting conditions known to affect bone metabolism.

The control biopsies were selected from our current collection of postmortem control material and were as closely gender and age matched to the cOA cases as possible (17 female, 5 male; 45–87 years; mean, 75.9 ± 2.02) (Table 1). Controls were only excluded on the basis of known local or generalized bone disease using the following criteria: (i) To avoid the early effects of disuse osteoporosis, admission to hospital more than 19 days prior to death (mean, 5.80 ± 1.11) or if they were admitted from other hospitals or residential care. (ii) A history of metabolic bone disease, local bone disease, coxarthrosis, or hip fracture secondary to moderate trauma. Samples were obtained 1–5 days after death (mean, 3.04 ± 0.22). Informed consent to the use of this material for research was given at the time of surgery by the patients themselves or in the case of the postmortem samples by the subjects’ relatives, according to procedures required by the District Ethics Committee and the Hospital Trust.

Sample preparation

Femoral neck biopsies (Figs. 1A–C) were taken during standard arthroplasty using a technique that minimizes mechanical and thermal damage [32]. Control autopsy samples were obtained from cadavers. Samples were dehydrated in ethanol and embedded in methylmethacrylate without prior decalcification [44]. To reduce possible artifacts caused by the surgeon’s saw, the embedded material was trimmed to a depth of at least 100 μm. Ten-micrometer sections (Jung Polycut E microtome, Leica, Milton Keynes, UK), parallel to the face of the biopsy, were cut and stained using the Von Kossa protocol [34], which differentiates between calcified tissue and osteoid.

Image analysis (histology)

Structural analysis of the femoral neck biopsies was assessed on three histological sections (each 60–120 μm apart) per subject using software described previously [5]. Biopsies were analyzed after being magnified to give the largest possible size of image on the monitor screen (~5×). Differences in image magnification in this system do not have a significant effect on reproducibility [5]. For all analysis, manual thresholding and image editing allowed the removal of artifacts prior to the commencement of measurement. For most analyses, cross sections were divided into eight anatomical regions (Fig. 2, top left) and the amount of bone per region was quantified.

The following parameters were assessed; total area (Tt.Ar, mm²), bone area plus marrow space, percentage cortical area (%Ct.Ar, cortical bone area as a percentage of total area), cancellous bone area (%Cn.Ar, cancellous bone area as a percentage of the area of trabecular bone and marrow space), cortical porosity (%Ct.Po), and osteophyte area (absolute area, Op.Ar, and osteophyte area as a percentage of total bone area, %Op.Ar). To account for possi-
ble differences in position along the neck at which the biopsies were taken (see below) %Cn.Ar was also adjusted by the reported change in cancellous bone density (females +5.1%/mm, males +3.9%/mm) proximally along the neck [13]. Mean cortical widths were assessed from 128 measurements taken automatically (every 2.8° of angle) around the femoral neck. Osteophyte was identified as irregular deposits of bone with very high lacunar density on the periphery of the cortex and its area was measured using the public domain NIH Image (v 1.61) software.²

² This software was developed at the U.S. National Institutes of Health and is downloadable from the Internet at http://rsb.info.nih.gov/nih-image.
Connectivity is a precise topological term and is a measure of the degree to which a feature under study is multiply connected [14]. As connectivity cannot be directly assessed using 2-D histological sections, the current study used strut analysis, a method based on the topological definition of struts and denotation of nodes and termini (free ends) [10]. The ratio between nodes and free ends/mm² provides an alternative measure of spatial (trabecular) connectivity [11,35] and was measured automatically using dedicated software [21]. Connectivity was determined in four anatomical regions (Fig. 2, top right). Trabecular width was assessed using NIH Image. Four fields³ per anatomical region (Fig. 2, top right) were examined and trabecular width was assessed as trabecular bone area/ trabecular bone perimeter*²/1.²³⁵ using a semiautomatic procedure. Trabecular number was calculated according to the parallel plate model using the formula (BV/TV)/Tb.Th [35].

**Scanning electron microscopy (SEM)**

To illustrate the biopsy appearance using SEM, a 3-mm-thick section was cut (Struers Accutom 5 saw) from each of two age- and gender-matched embedded biopsies (one cOA, one control). The biopsies were selected because they fell in the mid range for %Cn.Ar in their respective groups. The sections were deplasticized in a xylene/chloroform (50/50, v/v) agitated bath over 5 days. Any remaining methylmethacrylate or fat was washed out using a xylene/chloroform (50/50, v/v) solution (5%, 30 min)) and then washed away in distilled water. The sample was air dried, mounted on aluminium stubs using epoxy resin [8], and coated with a conductive metal (Polaron SEM Sputter Coater equipped with a platinum target). Samples were then viewed in a Jeol 840A SEM operated at 10 kV and images recorded onto Ilford FP4 film.

**pQCT analysis**

Peripheral QCT (pQCT) has recently been used to study the proximal femur and to analyze differences in cortical and cancellous bone in cases of femoral neck fracture compared to cadaveric controls [13]. Tomograms (1 mm thick; 10-cm scan diameter, Densiscan 1000 pQCT, Scanco Medical Ag, Zurich, Switzerland) were made at 0.5-mm intervals along each biopsy and analyzed using a semiautomatic approach [13]. Cortical and cancellous bone areas (mm²) and bone density (mg/cm³) were computed by the Densiscan software. Cortical and cancellous bone masses (mg) for each slice were calculated by multiplying area, slice width (standard for all biopsies), and density. It is important to note that bone density differences between groups may be affected both by bone size and bone porosity or the completeness of mineralization in bone tissue, as well as by bone area differences.

To assess the location of the biopsies along the axis of the neck, the maximum and minimum external diameters of the each of the pQCT slices were measured since this ratio varies predictably along the neck axis [13]. This was significantly higher in the female controls than in the biopsies from female cases of OA (Controls, 1.46 ± 0.03; Cases, 1.32 ± 0.07). For the male cases and controls, although the mean ratios were higher, there was less difference between them (Controls, 1.41 ± 0.16; Cases, 1.43 ± 0.15). This was interpreted as an effect of positioning of the cuts made by the surgeon (cases) or the mortuary technician (controls) to separate the specimen from the more distal part of the femur. Subsequent analyses were done starting at locations where the mean ratio of maximum to minimum external diameters was similar between the sample groups. This corresponded to 2.5 mm toward the femoral head in the case of female controls and 0.5 mm nearer the head in the male cases of cOA (adj. Male cases, 1.41 ± 0.15; adj. Female controls, 1.34 ± 0.02). Analysis of bone areas, density, and mass was restricted to the 4 mm of the neck between that point and the femoral head.

**Statistical analysis**

Preliminary analysis showed that not only were there differences between sexes but the effect of cOA on certain parameters was sex dependent. Therefore, for each group (i.e., controls or cases) the data are presented as the mean ± SEM of the male and female biopsies independently. The data were analyzed using the JMP statistical software package (V.3.2.2, SAS Institute, Cary, NC 27513). Where the data were normally distributed, significance was assessed using a one-way analysis of variance followed by a matching fit model which analyzed the effects of sex or the presence of cOA on the regional bone parameters. Where data were not normally distributed, normalizing by log transformation preceded the above and was in each case successful. For the pQCT analysis, bone area, density, and mass for an individual subject were obtained by averaging the data from each pQCT slice over a distance of 4 mm. The data are presented as the mean ± SEM of individual subjects within each sample group and analyzed by single Anova.

**Results**

**Effects of age**

Because the mean age of the control biopsies was slightly higher than that of the cases, we regressed the indices of cortical and cancellous bone on age to establish if age was a determinant of the parameter in question, strati-
Table 2  
*pQCT Analysis of Bone Area (mm²), Density (mg/mm³), and Mass (mg/mm³)*

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Coxarthrosis</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 20)</td>
<td>F (n = 15)</td>
<td>M (n = 5)</td>
</tr>
<tr>
<td>Tt. Area</td>
<td>756 ± 937</td>
<td>685 ± 21</td>
<td>970 ± 88</td>
</tr>
<tr>
<td>Mass</td>
<td>417 ± 24</td>
<td>372 ± 17</td>
<td>551 ± 88</td>
</tr>
<tr>
<td>Ct. Area</td>
<td>173 ± 8</td>
<td>163 ± 8</td>
<td>202 ± 17</td>
</tr>
<tr>
<td>Density</td>
<td>1.31 ± 0.03</td>
<td>1.29 ± 0.04</td>
<td>1.36 ± 0.06</td>
</tr>
<tr>
<td>Mass</td>
<td>231 ± 14</td>
<td>216 ± 14</td>
<td>276 ± 35</td>
</tr>
<tr>
<td>Cn. Area</td>
<td>690 ± 67</td>
<td>522 ± 25</td>
<td>767 ± 140</td>
</tr>
<tr>
<td>Density</td>
<td>0.31 ± 0.02</td>
<td>0.30 ± 0.02</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>Mass</td>
<td>185 ± 20</td>
<td>155 ± 16</td>
<td>275 ± 112</td>
</tr>
</tbody>
</table>

Bone areas, density, and mass for individual subjects were averaged over a distance of 4 mm after adjusting for the position of the biopsy along the femoral neck. Analysis used 20 of 22 controls versus 15 of 17 cases as the remaining biopsies were no longer available. Data are shown as the mean ± SEM of individual subjects within each of the patient groups.

fying for case/control status. We found no correlation between age and Ct.Wi, %Cn.Ar, Ct.Po, Tb.N, or Nd.Tm ratio (0.06 < P < 0.82). Tb.Wi declined with age in both cases and controls at a similar rate (P for difference = 0.94) of 9.3 μm per decade. Therefore in the following analyses we did not adjust for the effects of age except in the case of Tb.Wi.

**Densitometry**

Although the patients with cOA had higher total bone areas this was not significant when considering the group males and females together. However, analysis of the different genders (Table 2) revealed a significant increase in total bone area in the females (+13%, P = 0.02, ANOVA). Patients with cOA had a significantly higher total bone mass (+41% overall, P = 0.008; males, +55%, P = 0.04; females, +22%, P = 0.004). This increase in bone mass was not related to significant changes in cortical bone mass (Table 2). Cancellous bone mass was increased by 75% in cOA (combined, +75%, P = 0.014; males, +73%, NS; females; +60%, P = 0.002). This increase cancellous bone mass was principally the result of an increased density of cancellous bone in cOA (+45%, P = 0.001), which was evident in both males (+52%, P = 0.04) and females (+40%, P = 0.004).

**Histomorphometry**

**Cortical bone**

There was a significant interaction between disease status and sex (P = 0.0373), with the male cases having 20% thicker cortices than their controls (9 df; NS,) and the female cases 14% thinner cortices than their controls (19 df; NS). Regional analysis of the cortical widths in the males showed a marginally significant increase in Ct.Wi in cOA (P = 0.076; matching fit) but no significant interaction between region and disease (P = 0.8). In females the presence of cOA resulted in a reduction in Ct.Wi (P = 0.017) and there was a close to significant interaction between disease and region (P = 0.052). The effect of cOA was most marked in the inferoanterior region (−33%; P = 0.024; t test). Over the whole biopsy (Fig. 3) cortical porosity (Ct.Po) was significantly increased in cases over controls (P < 0.0001; matching fit model) and this was independent of sex (P = 0.12) or region (P > 0.5).

**Cancellous bone**

Coxarthrosis increased the mean %Cn.Ar by 71% (P < 0.001) or by +65% (P < 0.01) when adjusted for position in the neck. This effect was independent of sex (P = 0.55) but the increase in males was more than twice (adj. +114%; P < 0.05) that in females (adj. +47%; P < 0.05 ANOVA). These effects were independent of region (P > 0.19; Fig 4).

Neither trabecular width (Tb.Wi) or number (Tb.N) was normally distributed, so the statistical analyses were done following normalization by log transformation. Trabecular

![Fig. 3. Percentage of cortical porosity; cases versus controls in males and females. Data were analyzed by ANOVA followed by Tukey Kramer HSD for disease (Males, Ctl, 2.82 ± 0.32; cOA, 8.81 ± 1.48; P < 0.01 (n = 5 Ctl, 5 cOA)); (females, Ctl, 3.74 ± 0.39; cOA, 5.87 ± 0.46; P < 0.05 (n = 10 Ctl, 10 cOA)). Values represent means ± SE.](image-url)
significantly increase mean Ct.Ar (P = 0.13). However, in biopsies where osteophyte was present, a significant positive relationship existed between both the Log e %Op and the Log e %Cn.Ar. (adj. r² = 0.56; P < 0.05) and the Log e Op and the Log e %Cn.Ar; (adj.r² = 0.53; P < 0.05).

Effect of body weight

Only a minority (10/22; 4 males; 6 females) of the postmortem reports and recent clinical notes on the control subjects contained body weights. Therefore, we analyzed the possible statistical effects of weight by comparing those cases whose age and gender matched those of the controls for whom the data on weight were available. In this subset, body weight was higher in the cases (cases, 75.7 ± 3.6; controls, 65.1 ± 4.0 kg, P = 0.067), while Tb.Wi. was 52% (P = 0.007) higher, the same increase as in the whole group. Tb.Wi.:Nd:Tm. Ct.Wi., and %Cn.Ar were modeled as dependent variables, with disease and weight as the independent variables. Both Tb.Wi and Nd:Tm (whole model test; adj. r² > 0.43, P < 0.004) were significantly dependent on disease (P < 0.045) but only marginally dependent on weight (P > 0.059). Ct.Wi (adj. r² = 0.16, P = 0.12) was independent of disease (P = 0.28) but dependent on weight (P = 0.049), while %Cn.Ar. (adj. r² = 0.25, P = 0.06) was dependent on disease (P = 0.029) but independent of weight (P = 0.88).

Osteophyte

Of the 17 patients with cOA, 9 had osteophyte tissue on the femoral neck surface. Deposition of osteophyte did not
Discussion

This study provides evidence from both densitometric and histological methods that strengthening of femoral neck bone in cOA may be conferred principally through structural effects on cancellous bone rather than consistently beneficial effects on the cortex. It was noteworthy that in the female cases of cOA the cortex was thinned to a degree similar to that found in cases of intracapsular hip fracture [6] and a regional analysis revealed a significant reduction in %Ct.Ar in the inferoanterior region. This region lies on the axis of greatest strain during a sideways fall on the hip [30] and in cases of femoral neck fracture, the greatest loss of bone occurs in this region [6]. On the basis of this evidence alone one would expect cOA to have a deleterious effect on the overall strength of the femoral neck. However, in cOA cases, this region of cortex was much better buttressed internally with cancellous bone than is found in cases of hip fracture. In contrast, in the male cases of cOA the cortex appeared to be thicker, although this may be due to the low number of subjects. In both males and females cortical bone strength would have been further reduced by the increased porosity.

Increased fracture resistance might in principle be derived from increases in cortical areas through the deposition of osteophyte. However, the presence of osteophyte in cOA did not significantly increase the %Ct.Ar at either the regional or biopsy level. The recognition that increases in the cortex due to osteophyte deposition are minor, and the knowledge that osteophyte is predominantly disordered immature woven bone of low intrinsic strength, gives weight to the notion that increased fracture resistance seen in cOA is probably only related to osteophyte deposition to a minor extent.

Significant differences in %Cn.Ar between the cases (both males and females) and controls were found at the level of whole cross sections and regionally. In the whole biopsy, the %Cn.Ar was 47 and 114% higher in the female and males cases, respectively. A similar increase was seen in the regional analysis. This increase in Cn.Ar may not only compensate for any loss of Ct.Ar but could provide increased strength, as trabecular bone volume has been shown to be strongly correlated with bone strength in the iliac crest [42] and lumbar vertebrae [15]. Increased trabecular width in both genders would also increase the strength in the femoral neck; a recent study in rats found a significant correlation between trabecular thickness and bone strength at the femoral neck [41]. Additionally, buckling theory argues that the buckling load of a columnar structure, such as a trabecula, is related to the ratio of trabecular thickness to effective length [40]. In the femoral neck, although a greater proportion of strength is derived from the cortex, an important role of cancellous bone is widely thought to be its capacity to buttress the cortex internally and prevent cortical buckling under excessive compression, for example, during a sideways fall on the trochanter [30].

The role of cancellous connectivity in determining bone strength is still somewhat unclear in spite of its theoretical importance derived from Euler buckling theory. Some studies have proposed that in normal cancellous bone, connectivity has limited value for assessment of elastic properties [23] and strength [25], although a relationship between loss of connectivity and loss of elastic modulus has been reported [25]. It has been suggested that skeletal fragility in vertebral osteoporosis is in part due to a loss of trabecular connectivity [39]; a loss of trabecular elements would increase loads and strain on the remaining trabeculae leading to a reduction in fatigue life. Extrapolating from this model, an increase in cancellous connectivity in the femoral neck would confer increased ability to withstand mechanical loads. It is noteworthy that connectivity in our study was greatest in the inferosuperior plane, which bears the principal loads during normal gait and standing [30].

The greater %Cn.Ar, Tb.Th, Tb.N, and connectivity seen in the cases may result from an alteration in the balance between bone formation and bone resorption. Wand et al. [43] found that the presence of coxarthrosis was associated with a reduced rate of loss of trabecular bone in the femoral neck region with increasing age. While it is widely accepted that the response of articular cartilage to degeneration or injury is an important factor in the development and progression of osteoarthritis [9], a significant body of evidence suggests that bone changes may precede the onset of OA [37]. Osteophyte is commonly seen adjacent to bone around the OA joint and this requires an increase in bone formation. In this study, osteophyte was strongly correlated to %Cn.Ar, supporting the idea that the increase in %Cn.Ar seen in cOA is related to an anabolic effect on cancellous bone rather than decreased bone resorption. Bone from patients with OA has been shown to have higher levels of IGF-1, IGF-2 [16], and TGFβ [31], all being potent anabolic modulators of bone modeling/remodeling, and decreased levels of mRNA for the osteoclastogenic cytokines II-6 and II-11 [27]. However, it is not known whether these cytokines and growth factors represent mediators or markers of the disease.

This study has a number of limitations. There were relatively small numbers of cases of cOA studied. However, our results concerning cancellous bone are consistent with those of a previous study which, while not examining complete cross sections of the femoral neck, also showed that cancellous bone volume and strength adjacent to the calcar were increased in cOA [29], and cortical bone in this region was no different than controls [29]. It is recognized that subjects with OA have a higher body mass index (BMI) than unaffected controls. In this study it would have been valuable to compare the BMI of the cases and controls, but unfortunately no information relating to height was recorded in the cases clinical notes. In only approximately 45% of the postmortem controls was the body weight recorded, so it was not possible to examine the potentially confounding effects of weight within the whole study. How-
ever, within the subset of subjects for whom it was available, adjustment for body weight showed that it had only modest effects on differences between cases and controls.

A limitation that arises in the two-dimensional analysis of connectivity is that many of the apparent trabecular termini in the histological image are artifacts caused by the plane of section. This anomaly lends to a major underestimation of connectivity [1] but would affect cases and controls similarly. A recent study on iliac crest material from cases of vertebral fractures with similar cancellous bone volumes to biopsies from subjects without vertebral fractures has highlighted the differences between analyses in 2-D and 3-D [1]. Briefly, a 15% decrease in the node:free termini between the two groups on 2-D images corresponded to a 60% decrease in the number of free termini in the 3-D images. The SEM images of our study would also indicate that connectivity is much higher in cases than in controls. Finally, this was a study of structure. However, in preliminary work we have measured static indices relating to bone formation and resorption and this suggests that increased bone formation is the main cause of increased cancellous bone mass [22]. Dynamic histomorphometry is not practical because it is not possible to obtain tetracycline-labeled control material.

In conclusion, this study provides evidence that the increase in the percentage of cancellous area, trabecular thickness, and connectivity that occurs in cases of coxarthrosis may provide protection against intracapsular hip fracture. There is increasing evidence that a principal adverse consequence of aging bone loss leading to fracture of the hip may be through the increased risk of buckling of the expanding and thinning cortex [3,4]. Therefore, understanding the causes of the structural and mechanical differences highlighted in this study may help in developing novel approaches for preventing osteoporotic bone fracture in the femoral neck by modeling interventions on one or more biochemical consequences of cOA that would mimic the strengthening effect of cOA on the cancellous bone that buttresses the cortex. Also, this study gives further encouragement to study of the mechanical compliance of subchondral bone in cOA and its consequences for cartilage preservation in early coxarthrosis.

Acknowledgments

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References


