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OSTEOARTHRITIS and CARTILAGE

Femoral Trabecular Bone of Osteoarthritic and Normal Subjects in an Age and Sex Matched Group

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Summary

Objective: To describe changes to the cancellous structure of femoral bone from patients with severe primary osteoarthritis by comparison with age and sex matched controls.

Method: Specimens were taken from 18 male and 18 female pairs. One of each pair was a normal control, the other having severe primary osteoarthritis which required hip arthroplasty. Undecalcified cancellous bone blocks were embedded in resin, sectioned and impregnated with silver. Histoquantitation was performed using image analysis. Using a plate model for the trabecular structure of bone, an estimate was made of bone volume, bone surface, trabecular thickness, trabecular separation and trabecular number.

Results: In osteoarthritis, pooled male and female data show a significant decrease in trabecular number together with an increase in trabecular thickness and separation. The statistical variance in the histomorphometric variables for each of the study groups was calculated and expressed as the ratio of osteoarthritic to control. This ratio shows that the variance of the osteoarthritic groups is significantly increased for each variable in the pooled data. The same trend is evident in the male and female groups.

Conclusions: This quantitative study of cancellous bone architecture in the femoral head, infero-medial to the fovea, has found increased trabecular thickness and decreased trabecular number in patients with primary osteoarthritis. Increased morphometric variance has shown that severe osteoarthritis, contrary to osteoporosis, is associated with heterogeneous bone structures. These findings provide some basis for understanding how osteoarthritis may contribute to the prevention of osteoporotic fracture.

Keywords: Cancellous bone, Femoral head, Osteoarthritis, Osteoporosis.

Introduction

Osteoarthritis of the proximal femur results in numerous changes to the articular surface that can be classified according to criteria proposed by Collins [1] or Byers *et al*. [2]. The femoral head surface changes, due primarily to cartilage dysfunction, are traditionally associated with secondary bone changes such as osteophytes and subchondral sclerosis of the underlying bone. It has been postulated that such changes are due to alteration of loading through the joint as a consequence of the articular disease [3]. However, evidence is accumulating that primary osteoarthritis might initially be a bone disease rather than a cartilage disease [4]. Studies of the hip have shown that bone volume in osteoarthritis is increased not because of osteophytes, but as a result of low bone turnover and a high content of growth factors in the bone [5, 6].

Histomorphometry has been used extensively to study morphological changes in cancellous bone. The studies yield parameters, which reflect the structure of the trabecular elements based on mathematical models of plausible structures [7, 8]. Parameters such as bone volume, bone surface, trabecular thickness, trabecular separation and trabecular thickness taken individually, provide information regarding only one aspect of the cancellous structure. However, taken as a group they yield information for spatial visualisation of bone structure [9, 10].

The geometric arrangement of trabeculae in bone is influenced by many factors including the loading forces generated by muscle and body movement [11]. This phenomenon is particularly evident in the femoral head. There are distinctive patterns of trabecular groups which correspond to compressive and tensile areas within the femoral head and radiographs show these phenomena very clearly [12]. In addition, cancellous bone from

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various sites decreases in density with age resulting in parallel changes in structural parameters [13, 14]. These changes differ according to sex, with changes in males being gradual from the age of 50 [15], while in females, the menopause results in a dramatic and rapid decrease in bone density [16].

Cancellous bone infero-medial to the fovea, in the principal compressive region of the femoral head adjacent to the medial cortex, is particularly well suited for the study of primary bony changes, as it is distant from the diseased articular surface but in direct line with transferred loading forces [17]. Thus, alteration in cancellous bone structure associated with osteoarthritis will be reflected in the spatial arrangement of trabeculae in this region. This study investigates structural parameters in the cancellous bone, taken infero-medial to the fovea, of age and sex matched normal control and osteoarthritic subjects. This sampling method also allowed the examination of the effects of osteoarthritis on femoral bone for males and females over the age of 50.

Method

Femoral heads were collected from 18 male and 18 female pairs of age-matched individuals. One of each pair was a normal control, the other having severe primary osteoarthritis.

The control group comprised normal right proximal femora taken at autopsy and immediately placed in 10% neutral buffered formalin. Subjects were only included in this group if there was no evidence of any chronic condition or disease which might have affected bone status. The criteria for exclusion included prolonged bed rest, medication affecting bone turnover, renal dysfunction and endocrine disease affecting bone metabolism.

The osteoarthritic group consisted of patients with severe primary osteoarthritis undergoing total hip replacement. The clinical diagnosis of osteoarthritis is based on radiological investigation and patient history determines whether the osteoarthritis is primary in nature. Patients suspected of having secondary osteoarthritis, inflammatory joint disease, Paget's disease, drug-induced disease or other conditions which may have affected the trabecular bone architecture and quality were excluded from the osteoarthritic group.

A 5 mm coronal slice was cut through the centre of each femoral head. From this slice, a block of cancellous bone (approximately 1 cm^2) was taken infero-medial to the fovea (Figure 1). Using pre-operative patient radiographs, the femoral anatomy and the axial geometry of the resected femoral neck, the coronal plane of the surgical specimens was determined. A contact X-ray of the 5 mm coronal slice was made using a Faxitron X-ray system (75 kVp for 30 seconds). Thus, from the detailed coronal X-ray we were able to obtain autopsy and surgical femoral blocks from reproducible locations. From each of 36 control subjects and 36 osteoarthritic patients, undecalcified tissue blocks were processed into Araldite epoxy resin. Each block was then sectioned on a Jüng K microtome (Reichert, Heidelberg, Germany). Three sections of 8 μm thickness, cut at approximately 200 μm intervals, were stained with silver by the von Kossa/van Gieson technique to distinguish the mineralised bone, the osteoid and the cellular components of the marrow (Figure 2). As a result, a tissue volume of at least 40 mm^3 in the region infero-medial to the fovea was sampled.

Histoquantitation was performed on each section using a Quantimet 720 image analysing computer (Cambridge Instruments Ltd., U.K.) [18, 19]. The microscope objective magnification was ×10. Each section was scanned in the principal direction of trabecular orientation avoiding any osteophytic bone overlying the original medial cortex. Using the plate model for trabecular structure of bone [8], bone volume per total volume

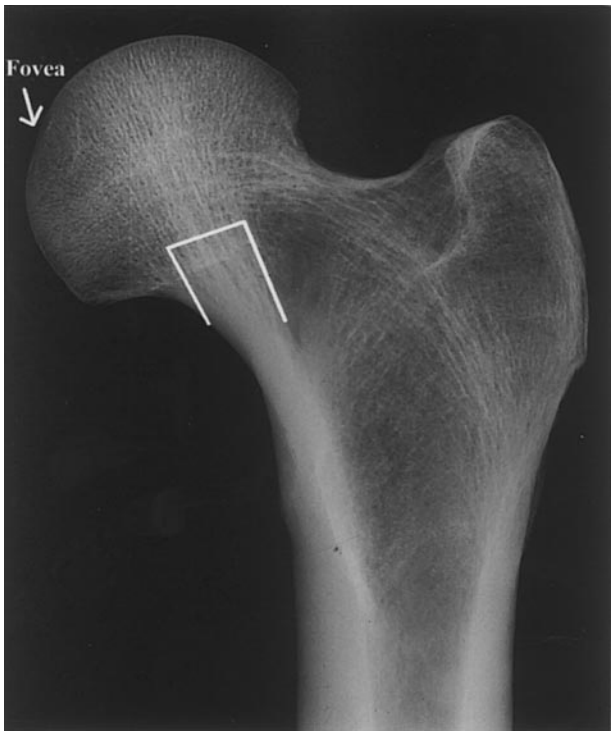

FIG. 1. Radiograph showing the site of cancellous bone sampling, infero-medial to the fovea in the principal compressive region of the femoral head adjacent to the medial cortex.

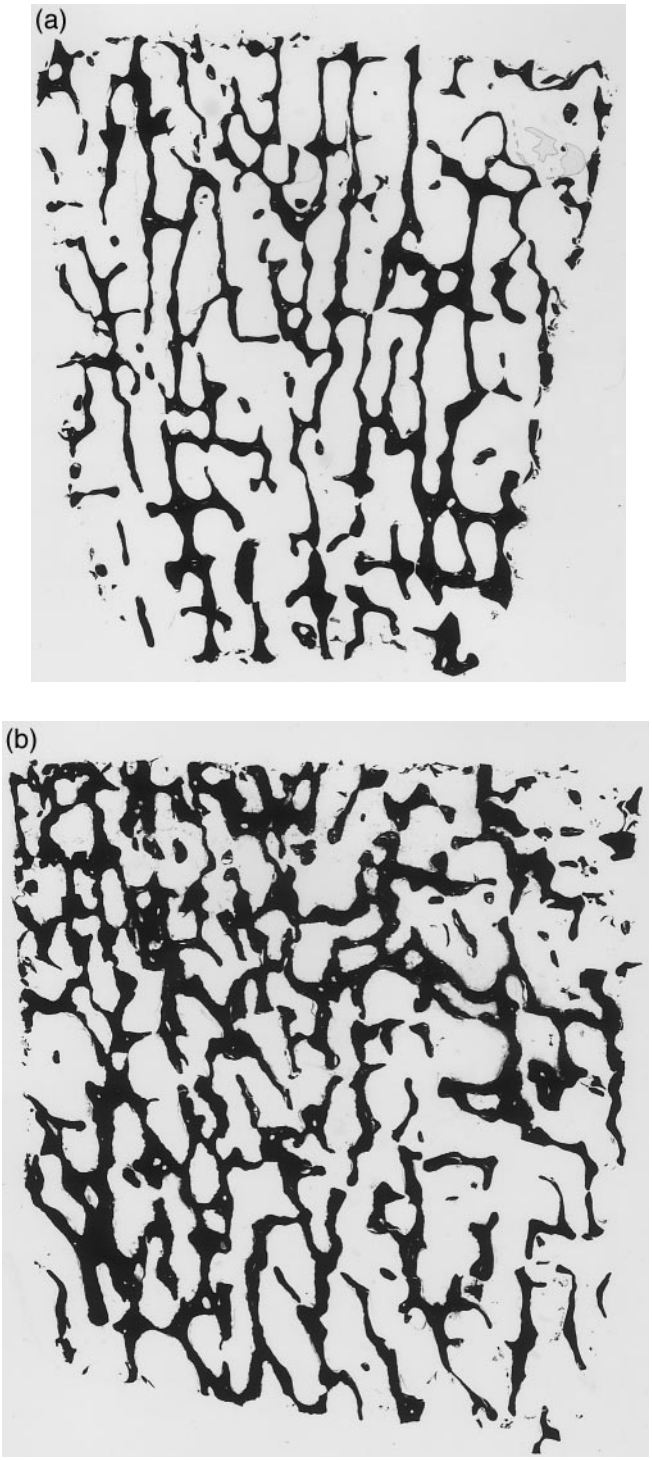

FIG. 2. Photomicrographs of cancellous bone infero-medial to the fovea. (a) Control (b) Osteoarthritic.

(BV/TV) and bone surface per total volume (BS/TV) were measured and trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and trabecular number (Tb.N) were calculated and are presented as a mean of the three sections analysed per block.

Inter and intra operator error was measured according to Parkinson and Fazzalari [20] and found not significant.

STATISTICS

Statistical analysis of the data was performed using parametric statistical models. Student's *t*-test was used to compare means, taking the pooled sample variance as the estimate of the *t*-distribution variance. A logarithmic transformation of the data was necessary to obtain a normal distribution for BS/TV, Tb.Th and Tb.Sp. The critical value for statistical significance was set at $P < 0.05$ for the study.

Results

The age range was 52–90 years for the 36 pairs of subjects (69 ± 9 years) (Mean $\pm$ Standard Deviation). The total group comprised 18 male and 18 female pairs. The age range of the males was 53 to 87 (68 ± 7 years) and the females 52 to 90 (71 ± 10 years). The age of male and female groups was not significantly different.

The pooled male and female BV/TV data decreases significantly with age ($N = 18$, $r = -0.50$, $p < 0.002$), females ($N = 18$, $R = -0.63$, $p < 0.005$) showing a greater dependence on age than males ($N = 18$, $R = -0.49$, $p < 0.04$) in the control group. The osteoarthritic group shows no age dependence for BV/TV. A significant decrease occurs in BS/TV and Tb.N together with an increase in Tb.Th and Tb.Sp for the osteoarthritic group. This is a trend reflected in both the male and female group data.

Comparison of male versus female data in the control and osteoarthritic groups only shows a significant difference in BV/TV ($P < 0.04$) and Tb.Sp ($P < 0.02$) for the osteoarthritic group. The females with osteoarthritis have less BV/TV and greater Tb.Sp than the males (Table 1).

The statistical variance in the histomorphometric variables was calculated and expressed as the ratio of osteoarthritic to control. It shows that the variance of the osteoarthritic group is significantly increased for each variable in the pooled data (Table 2). In the male and female groups the same trend is evident in the data.

Discussion

The pooled data results are consistent with the reported architectural changes of cancellous bone infero-medial to the fovea [9] and the reduced age dependence of BV/TV in the proximal femur with severe osteoarthritis [21]. Unlike those studies

Table 1. Cancellous bone structure morphometry for Osteoarthritic and Control groups (mean ± standard deviation)

		Male (n = 18)	Female (n = 18)	Pooled (n = 36)
Bone Volume/Total Volume (%)	Control	26.29 ± 4.62	28.29 ± 4.62	27.34 ± 5.22
	Osteoarthritic	29.28 ± 10.90	22.31 ± 8.22*	25.79 ± 10.20
Bone Surface/Total Volume (mm^2/mm^3)	Control	3.99 ± 0.88	3.90 ± 0.70	3.94 ± 0.79
	Osteoarthritic	3.17 ± 1.20*	2.64 ± 0.97*	2.91 ± 1.11*
Trabecular Thickness (mm)	Control	0.13 ± 0.03	0.15 ± 0.03	0.14 ± 0.03
	Osteoarthritic	0.19 ± 0.04*	0.19 ± 0.10	0.19 ± 0.07*
Trabecular Separation (mm)	Control	0.41 ± 0.11	0.39 ± 0.12	0.40 ± 0.11
	Osteoarthritic	0.48 ± 0.19	0.68 ± 0.24*	0.58 ± 0.24*
Trabecular Number (#/mm)	Control	2.00 ± 0.44	1.95 ± 0.35	1.97 ± 0.39
	Osteoarthritic	1.59 ± 0.60*	1.29 ± 0.47*	1.44 ± 0.55*

*Where the difference between Osteoarthritic and Control groups reaches statistical significance.

these data are age and sex matched. This study provides added evidence for the trabecular structure transformations of increased Tb.Th and Tb.Sp that have been reported for this region, adjacent to the medial cortex and remote from the marked subchondral bone changes of severe osteoarthritis. These results are consistent with the suggestion that patients with primary osteoarthritis and osteoporosis represent morphologically different populations with characteristic cancellous bone architectures responsible for the inverse relationship between osteoarthritis and osteoporosis [4, 9]. If osteoarthritic subjects develop osteoporotic fracture, generally it occurs at a later age than expected suggesting that osteoarthritis or a related factor has a protective effect on the progression of osteoporosis [22]. Recent studies have demonstrated that the relationship between Tb.Th and mechanical strength was such that relatively small increments in thickness were associated with disproportionately large gains in strength [23]. Hence, the increased Tb.Th in severe osteoarthritis can strengthen bone and compensate for the decrease in bone quality attributed to increased Tb.Sp and decrease in Tb.N, generally associated with osteoporotic fracture [24].

There are no significant differences between male and female data except for a reduction in the BV/TV and increase of Tb.Sp in the female osteoarthritic group. However,the reduced BV/TV in the female group does not put that group at risk of fracture. Tb.N decrease, a significant trend, is consistent with decreased BV/TV and increased Tb.Sp. This suggests that the reduced BV/TV and increased Tb.Sp in females is due to the perforation of trabecular plates [24]. Trabecular plates have a high surface to volume ratio and perforation will modulate the decrease in Tb.N and Tb.Th, while causing a decrease in BV/TV and increase in Tb.Sp.

The control group show no sex difference in the region of femoral trabecular bone infero-medial to the fovea. This is not the case for the iliac crest, as reported by others [25, 26].

For each of the histomorphometric variables, BV/TV, BS/TV, Tb.Th, Tb.Sp and Tb.N, the variance of the osteoarthritic group is markedly increased compared with the control group. This means the osteoarthritic group has a wider range of values for each parameter than the normal control group. This increased variance is perhaps indicative of the different time of onset of the osteoarthritis or the heterogeneous nature of the underlying bone morphology in cases with severe osteoarthritis. This variance heterogeneity is present in both male and female groups. There is also a view that osteoarthritis is a final common pathway for a number of aetiologies [3] and this could contribute to the increased variance in bone morphometry. A number of aetiologies acting to cause primary osteoarthritis can have a diverse range of outcomes for trabecular structure. In a

Table 2. Ratio of variance for Osteoarthritic versus Control groups

(n = 18)	Male (n = 18)	Female	Pooled (n = 36)
Bone Volume/Total Volume ratio	5.58*	3.17*	3.82*
Bone Surface/Total Volume ratio	1.86	1.97	1.97*
Trabecular Thickness ratio	1.78	11.11*	5.44*
Trabecular Separation ratio	4.37*	3.36*	5.17*
Trabecular Number ratio	1.83	1.82	1.96*

*Where the variance ratio of Osteoarthritic versus Control groups is significantly different to 1.

previous study, Fazzalari *et al*. [27] have reported the identification of osteoarthritic subgroups based on trabecular bone structure and the incidence of trabecular microfractures. Alternatively, if osteoarthritis has a single cause the increased variance may be due to variable patient response at the time of onset of osteoarthritis. This diverse patient response, particularly in mechanical loading of the hip joint through change in walking patterns could stimulate various degrees of bone remodelling [3, 28]. Bone remodeling activity has been shown to vary in the femoral head between regions of highest and lowest weight-bearing [29]. We have studied trabecular bone remote from the articular lesion, which would not be affected directly by locally altered biochemical or cellular dynamics [17]. Given this approach, it is reasonable to assume that changes in trabecular bone structure remote from the articular lesion can be biomechanically influenced. Adjacent to the OA articular cartilage, the reactive subchondral bone changes that occur in severe osteoarthritis influence the strain experienced by the region infero-medial to the fovea. This would result in increased variation in femoral trabecular structure.

The physiological mechanisms, which maintain the structural geometry of femoral trabecular bone, within a fairly narrow range over time, are disrupted in osteoarthritic subjects. The age dependent changes have been significantly minimised or rescheduled. The significant alteration to the normal remodeling process may partly be due to a low bone turnover and a high content of growth factors [5, 6] in the bone or the changes in the loading pattern through the entire proximal femur, with the onset of painful symptoms from the osteoarthritis. This study has shown that quantifying cancellous bone architecture of osteoarthritic femurs contributes to our understanding of the prevention of osteoporotic bone fracture by osteoarthritis.

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