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Original Article

Subchondral bone deterioration in femoral heads in patients with osteoarthritis secondary to hip dysplasia: A case–control study

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ABSTRACT

Objectives: Residual hip dysplasia is the most common underlying condition leading to secondary osteoarthritis (OA) of the hip. Subchondral bone alterations in OA secondary to hip dysplasia (HD-OA) are poorly investigated. The aim of the present study was to analyse the microarchitecture, bone remodelling and pathological alterations of subchondral bone in femoral heads from patients with HD-OA.

Methods: Subchondral bone specimens were extracted from both weight-bearing and non–weight-bearing regions of femoral heads from 20 patients with HD-OA and 20 patients with osteoporotic femoral neck fracture, during hip replacement surgery. Micro-CT and histological examination were performed to assess the microarchitecture and histopathological changes.

Results: The weight-bearing subchondral bone showed significantly more sclerotic microarchitecture and higher bone remodelling level in HD-OA as compared with osteoporosis. In the non–weight-bearing region, the two diseases shared similar microarchitectural characteristics, but higher bone remodelling level was detected in HD-OA. Distinct regional differences were observed in HD-OA, whereas the two regions exhibited similar characteristics in osteoporosis. In addition, HD-OA displayed more serious pathological alterations, including subchondral bone cyst, metaplastic cartilaginous tissue, bone marrow oedema and fibrous tissue, especially in the weight-bearing region.

Conclusions: Osteoarthritic deteriorations of subchondral bone induced by hip dysplasia spread throughout the whole joint, but exhibit region-dependent variations, with the weight-bearing region more seriously affected. Biomechanical stress might exert a pivotal impact on subchondral bone homeostasis in hip dysplasia.

The translational potential of this article: The histomorphometric findings in the project indicate an early intervention for the development of hip dysplasia in clinic.

Introduction

Hip dysplasia is a congenital or developmental deformation of the hip joint, which refers to a spectrum of anatomical abnormalities involving the acetabulum and adjacent femoral head [1]. It is the most common orthopaedic defect in newborns [2,3]. Multifaceted risk factors, including positive family history, female sex and breech presentation, have been assumed to contribute to the pathogenesis of hip dysplasia [4,5]. Once diagnosed, hip dysplasia is normally treated by nonsurgical methods (closed reduction) or surgical methods (open reduction), to achieve and maintain concentric reduction throughout childhood and adolescence [6]. If no treatment is conducted or the primary treatment fails, persistent residual hip dysplasia might ensue, which threatens long-term hip function and leads to the development of osteoarthritis (OA) [7–11]. Residual hip dysplasia has been reported to be the most common underlying condition leading to secondary OA of the hip in

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adults [12–16].

The deficient coverage by the acetabulum over the femoral head in hip dysplasia, which leads to reduced load-transferring areas and abnormally high contact mechanical stress, might have a close relationship with the osteoarthritic degradation [14,17–19]. A study by Kim et al. showed that in patients with hip dysplasia, the biochemical integrity of cartilage correlates with the pain and severity of the dysplasia, suggesting that early OA changes are associated with cartilage integrity in the acetabulum and femoral head [20]. Apart from cartilage, subchondral bone is also an important structure in joint homeostasis, which is actively involved in the initiation and progression of joint degeneration [21,22]. However, in contrast to the wealth of studies concerning subchondral bone in primary OA [23–28], the alterations of subchondral bone in OA secondary to residual hip dysplasia (HD-OA) remain poorly investigated. The sparse studies evaluating subchondral bone in HD-OA were restricted to radiographic imaging assessment [29,30]. Little is known about the relevant bone remodelling status and pathological alterations. In addition, previous studies have typically focused on the weight-bearing region, largely overlooking the non–weight-bearing region.

To address these knowledge gaps, we performed a comparative study between patients with HD-OA and patients with osteoporosis (OP). Microarchitecture, bone remodelling and pathological alterations were analysed in subchondral trabecular bone (STB) from both weight-bearing and non–weight-bearing regions in femoral heads from these patients.

Materials and methods

Patients

20 patients with HD-OA undergoing total hip replacement were recruited in the study (17 females and 3 males, mean age 64.25 ± 5.20 years, age range 58–74 years). As for HD-OA, the criterion for enrolment in the study as a dysplastic hip was radiological evidence of dysplasia with a lateral centre-edge angle less than 20°on the anteroposterior radiograph [31]. When either an anatomic abnormality cannot be determined or other specific causative entities are not identified, primary OA is the diagnosis of exclusion. All these HD-OA patients had radiographic evidence of moderate or severe OA (Grade≥3), according to the Kellgren and Lawrence criteria [32]. Exclusion criteria for HD-OA patients were as follows: 1) patients with primary OA or OA secondary to trauma or other identified disorders; 2) known metabolic or bone disorders other than OA, which could affect bone metabolism, such as severe renal impairment, thyroid or parathyroid disease and malignancy; 3) receiving treatment that affects bone metabolism such as antiresorptive drugs, calcitonin, thyroid or parathyroid hormone therapy, or hormonal replacement therapy; or 4) history of hip osteotomy.

To avoid the disturbance of age and gender, 20 age- and gender-matched patients with OP who underwent prosthetic hip replacement for low-trauma femoral neck fracture were recruited for comparison (15 females and 5 males, mean age 67.15 ± 7.70 years, age range 55–76 years). Exclusion criteria for OP patients were as follows: 1) patients with hip fractures following severe traumas; 2) known metabolic or bone disorders other than OP; or 3) receiving treatment that affects bone metabolism. Owing to the relatively normal joint morphology and mechanical loading, the femoral head from OP patients are normally chosen as a control in previous human studies concerning hip OA [23,24,26,33,34].

Informed consent was obtained from each patient. The study protocol was approved by the Human Research Ethics Committee of The University of Western Australia and complied with the Declaration of Helsinki.

Specimen preparation

One cylindrical specimen of articular cartilage and subchondral bone was extracted from the superior principal compressive weight-bearing region (W region) in each femoral head [26,30,35] (Figure 1). Another cylindrical specimen was extracted from the inferior non–weight-bearing region (N region) [28,35] (Figure 1). According to different disease conditions and extraction regions, specimens were categorised into four groups: 1) specimens from the W region of osteoarthritic femoral heads (OA-W group); 2) specimens from the N region of osteoarthritic femoral heads (OA-N group); 3) specimens from the W region of osteoporotic femoral head (OP–W group); and 4) specimens from the N region of osteoporotic femoral head (OP–N group); each specimen (10 mm in height and 9 mm in diameter) was prepared under continuous water irrigation using a precision bone trephine. STB is defined as the most superficial 5 mm of the specimen, beneath the cartilage and subchondral bone plate [36–38]. Specimens were fixed in 4% paraformaldehyde in phosphate buffered saline (PBS) for 5 days and stored in 70% ethanol.

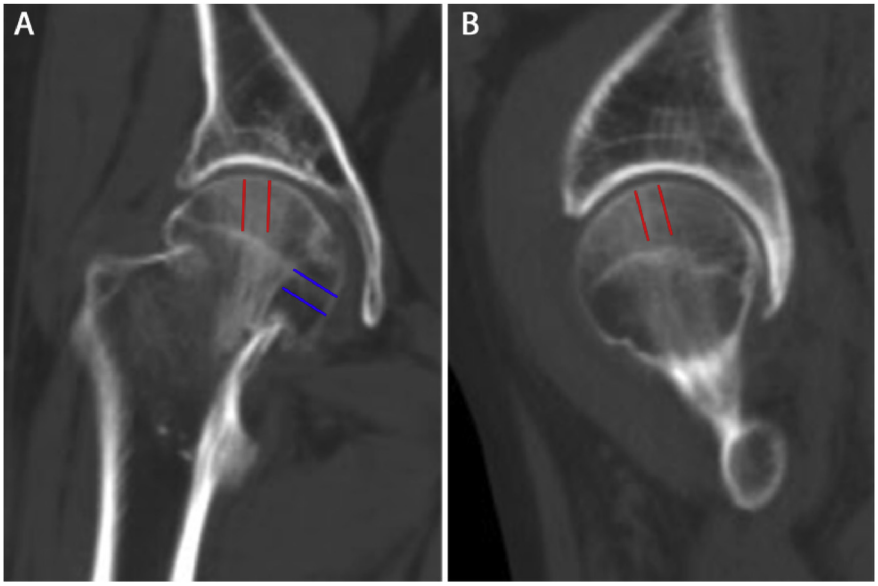

Figure 1. The regions in the femoral head from which cylindrical specimens were extracted: The red and blue parallel lines demonstrated the superior weight-bearing region (W region) and the inferior non–weight-bearing region (N region), respectively. The representative coronal (A) and sagittal (B) CT images were from a patient diagnosed with OP.

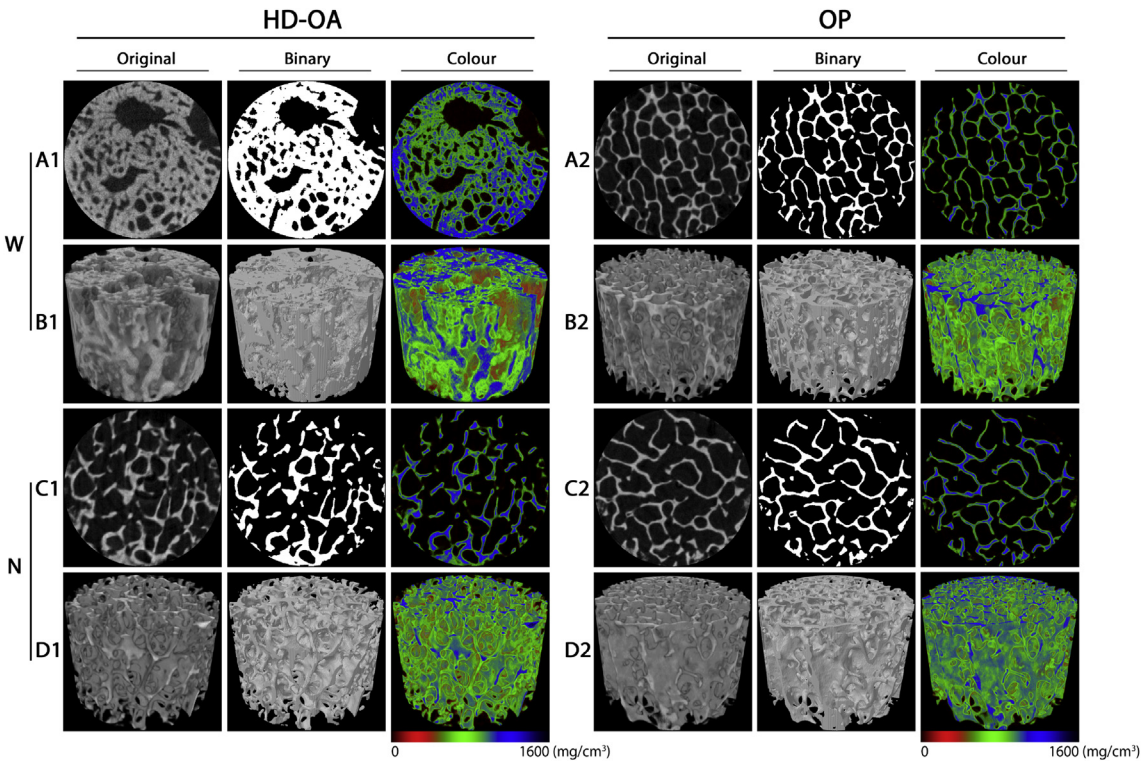

Figure 2. Representative original, binary and colour micro-CT images of STB from the W and N regions in femoral heads from patients with HD-OA (A1–D1) and patients with OP (A2–D2): 2D visualisation of the cross-section of STB from the W region (A1, A2) and the N region (C1, C2), 3D reconstruction of STB (B1, B2) from the W region and the N region (D1, D2). The colour images represent mineralisation distribution in trabecular bone. Red, green, and blue represent low, intermediate, and high mineral density, respectively. W: weight-bearing; N: non–weight-bearing; HD-OA: osteoarthritis secondary to hip dysplasia; OP: osteoporosis; STB: subchondral trabecular bone.

Micro-CT examination

Each specimen was placed in a saline-filled acrylic case for acquisition by a micro-CT scanner (Skyscan 1174, Skyscan, Kontich, Belgium). Imaging acquisition was conducted at a voltage of 50 kV, current of 800 μA, an isotropic pixel size of 14.4 μm (1024 × 1024 pixel image matrix) and with a 0.75-mm-thick aluminium filter for beam hardening reduction. After scanning and reconstruction, the images were transferred with a fixed threshold to binary images for analysis (Figure 2). The measurement region was 8 mm in diameter, which was 1 mm smaller than the diameter of the specimen, to avoid the inclusion of bone debris due to the cutting procedure. The subchondral bone cyst (SBC) was also screened. In samples with SBC, measurement was only conducted in the trabecular region surrounding SBC, rather than the whole specimen. STB microarchitecture was then analysed, using the built-in software.

The following microarchitectural parameters were calculated: bone volume fraction (BV/TV) (%), trabecular thickness (Tb.Th) (μm), trabecular separation (Tb.Sp) (μm), trabecular number (Tb.N) (1/mm), structure model index (SMI), degree of anisotropy (DA), connectivity density (Conn.D) ($1/mm^3$) and bone mineral density (BMD) (mg/cm^3) [39]. BMD was obtained by conversion of x-ray attenuation coefficient, using a calibration curve obtained from phantom specimens of known density.

Histology and histomorphometry

Each specimen was fixed, infiltrated and embedded in methyl methacrylate. All bone blocks were trimmed and sectioned on a microtome (Leica RM 2255, Wetzlar, Germany). Sections, 5 μm thick, were stained by Goldner's Trichrome method. Histomorphometry was performed using Bioquant Osteo Histomorphometry software (Bioquant Osteo, Nashville, TN, USA). The following remodelling parameters were measured in each ROI: thickness of osteoid (O.Th, μm), percentage osteoid volume (OV/BV) (%), percentage osteoid surface (OS/BS) (%), specific osteoid surface (OS/BV) (mm^2/mm^3), percentage eroded surface (ES/BS) (%), specific eroded surface (ES/BV) (mm^2/mm^3) and eroded surface in bone tissue volume (ES/TV) (mm^2/mm^3) [40]. Pathological alterations in the subchondral bone marrow were also assessed.

Statistical analysis

Statistical analyses were performed using the Statistics Package for Social Sciences (SPSS for Windows, version 17.0; SPSS Inc, Chicago, IL, USA). All microarchitecture and bone remodelling parameters were expressed as means and 95% confidence intervals (95% CI). These data were tested for normality using the Shapiro–Wilks test. Subsequently, as applicable, a Student's t test (for data which are normally distributed) or the Mann–Whitney U test (for the data which are not normally distributed) was used to test for significant differences between HD-OA and OP. In addition, the comparisons between OA-W and OA-N, and between OP-W and OP-N were analysed by paired Student's t-test (for the data which are normally distributed) or Wilcoxon test (for the data which are not normally distributed). Concerning pathological alterations, Pearson's chi-square test was used to compare the frequency difference between OA-W and OP-W, and between OA-N and OP-N. The comparisons of pathology frequency between OA-W and OA-N, and between OP-W and OP-N were analysed by McNemar's test. All hypotheses were two-tailed, and $p < 0.05$ were considered statistically significant.

Results

Comparative analysis of microarchitecture and bone remodelling in STB between HD-OA and OP

OP patients did not differ significantly from HD-OA patients in age ($p = 0.104$) and male/female ratio ($p = 0.695$).

In the W region, there were significant differences between HD-OA and OP for all the microarchitecture parameters (Table 1, Figure 2). In HD-OA, there were higher values of BV/TV, Tb.Th, Tb.N, Conn.D and BMD, but lower values of Tb.Sp, SMI and DA. All the bone remodelling parameters were also significantly higher in HD-OA, compared with OP (Table 1, Figure 3). There were higher values of O.Th, OV/BV, OS/BS and OS/BV, indicating a more active bone formation status. Bone resorption activity was also higher, as suggested by higher erosion indexes including ES/BS, ES/BV and ES/TV.

In the N region, none of the microarchitecture parameters differed significantly between HD-OA and OP, with the exception of Tb.N and DA (Table 1, Figure 2). However, all the bone remodelling parameters were significantly different between HD-OA and OP (Table 1, Figure 3). There were higher values of bone formation parameters in HD-OA, including O.Th, OV/BV, OS/BS and OS/BV. Bone resorption parameters, including ES/BS, ES/BV and ES/TV, were also higher in HD-OA.

Table 1
Comparison of microarchitecture and bone remodelling parameters in STB between HD-OA and OP.

Region	Variables	HD-OA (n = 20)	OP (n = 20)	P
W	Microarchitecture			
	BV/TV (%)	60.21 (55.49, 64.92)	20.50 (16.72, 24.28)	**<0.001***
	Tb.Th (μm)	355.79 (333.82, 377.77)	187.14 (169.60, 204.69)	**<0.001***
	Tb.Sp (μm)	358.89 (305.63, 412.15)	703.42 (650.10, 756.75)	**<0.001***
	Tb.N (1/mm)	1.69 (1.60, 1.78)	1.07 (0.94, 1.19)	**<0.001***
	SMI	−0.88 (−1.47, −0.29)	1.28 (1.02, 1.53)	**<0.001**
	DA	1.51 (1.38, 1.65)	1.87 (1.74, 2.00)	**<0.001**
	Conn.D (1/mm^3)	19.74 (15.55, 23.94)	8.71 (7.43, 10.00)	**<0.001**
	BMD (mg/cm^3)	580.65 (539.94, 621.36)	204.88 (161.53, 248.22)	**<0.001***
	Histology			
	O.Th (μm)	11.71 (9.97, 13.46)	3.86 (3.21, 4.50)	**<0.001***
	OV/BV (%)	6.17 (4.66, 7.69)	0.99 (0.69, 1.28)	**<0.001***
	OS/BS (%)	66.51 (60.33, 72.69)	14.90 (10.93, 18.87)	**<0.001***
	OS/BV (mm^2/mm^3)	5.20 (4.50, 5.91)	2.12 (1.55, 2.68)	**<0.001***
	ES/BS (%)	15.98 (12.27, 19.69)	3.17 (2.19, 4.15)	**<0.001**
	ES/BV (mm^2/mm^3)	1.26 (0.96, 1.57)	0.46 (0.30, 0.62)	**<0.001**
	ES/TV (mm^2/mm^3)	0.59 (0.45, 0.72)	0.08 (0.06, 0.12)	**<0.001**
N	Microarchitecture			
	BV/TV (%)	20.17 (15.06, 25.27)	21.28 (18.88, 23.68)	0.234
	Tb.Th (μm)	207.80 (177.65, 237.94)	193.99 (179.47, 208.51)	0.665
	Tb.Sp (μm)	725.13 (635.95, 814.31)	686.02 (641.35, 730.69)	0.419*
	Tb.N (1/mm)	0.95 (0.79, 1.11)	1.10 (1.01, 1.19)	**0.048**
	SMI	1.55 (1.26, 1.85)	1.31 (1.14, 1.47)	0.135*
	DA	1.61 (1.44, 1.77)	2.05 (1.88, 2.21)	**<0.001***
	Conn.D (1/mm^3)	11.11 (7.97, 14.24)	8.85 (7.53, 10.17)	0.534
	BMD (mg/cm^3)	202.35 (146.01, 258.69)	222.38 (193.93, 250.82)	0.267
	Histology			
	O.Th (μm)	5.41 (4.69, 6.14)	3.40 (2.95, 3.85)	**<0.001***
	OV/BV (%)	2.10 (1.35, 2.86)	0.76 (0.51, 1.02)	**<0.001**
	OS/BS (%)	23.94 (18.60, 29.29)	13.87 (10.03, 17.70)	**0.002**
	OS/BV (mm^2/mm^3)	3.44 (2.49, 4.40)	1.88 (1.25, 2.50)	**0.002**
	ES/BS (%)	4.90 (3.31, 6.49)	3.05 (1.19, 4.92)	**0.005**
	ES/BV (mm^2/mm^3)	0.69 (0.45, 0.93)	0.39 (0.19, 0.60)	**0.008**
	ES/TV (mm^2/mm^3)	0.15 (0.08, 0.22)	0.08 (0.03, 0.13)	**0.002**

Data are expressed as means (95% CI). Bold indicates statistically significant difference. * indicates the data which are normally distributed.
W = weight-bearing; N = non–weight-bearing; HD-OA = osteoarthritis secondary to hip dysplasia; OP = osteoporosis; STB = subchondral trabecular bone.

Comparative analysis of microarchitecture and bone remodelling in STB between W and N region

In HD-OA, all the microarchitecture parameters were significantly different between the W and N region, except for DA (Table 2, Figure 2). In STB from the W region, there were higher values of BV/TV, Tb.Th, Tb.N, Conn.D and BMD, but lower values of Tb.Sp and SMI, compared with that from the N region. Concerning bone remodelling, all the parameters were also significantly higher in the W region (Table 2, Figure 3). There were higher values of bone formation parameters, including O.Th, OV/BV, OS/BS and OS/BV. Bone resorption was also more active in the W region, as indicated by higher values of ES/BS, ES/BV and ES/TV.

In OP, none of the microarchitecture parameters were significantly different between the W and N region, which was reciprocal to the situation in HD-OA (Table 2, Figure 2). Similarly, there were no significant differences for all bone remodelling parameters between the W and N region, except for ES/TV (Table 2, Figure 3).

Pathological alterations in subchondral bone

A variety of histologic features were detected in subchondral bone (Table 3, Figure 4), including SBC, metaplastic cartilaginous tissue, bone marrow oedema, fibrous tissue and normal bone marrow.

Specimens from the OA-W group exhibited the highest incidence of SBC, metaplastic cartilage, and fibrous tissue. A small proportion was detected with bone marrow oedema, and no specimen was identified with normal bone marrow. Specimens from the OA-N group showed the highest incidence of bone marrow oedema, together with relatively lower frequency of SBC, fibrous tissue and normal bone marrow. No metaplastic cartilage was detected in this group. Specimens from the OP-W and OP-N groups manifested similar histological characteristics, with high frequency of normal bone marrow and high incidence of bone marrow oedema. No other pathological lesions were found in the two OP groups.

Discussion

In this study, we analysed simultaneously the microarchitecture, bone remodelling and pathological alterations in subchondral bone from both weight-bearing and non–weight-bearing regions in HD-OA and OP. Our results indicated that the weight-bearing subchondral bone exhibited a more sclerotic microarchitecture and higher bone remodelling level in HD-OA as compared with OP. In the non–weight-bearing region, the two diseases shared similar microarchitectural characteristics, but higher bone remodelling level was detected in HD-OA. Distinct regional differences were only observed in HD-OA, whereas the two regions exhibited similar characteristics in OP. In addition, HD-OA displayed more serious pathological alterations, especially in the weight-bearing region.

Mechanical loading is widely reported to play a vital role in bone metabolism and structural adaption [26,41]. Interrupted load distribution and high contact stress might contribute to the abnormal subchondral bone alterations in HD-OA, especially in the weight-bearing region [18,29,42]. In concordance with the limited studies concerning subchondral bone in HD-OA [29,30], our results showed that the weight-bearing subchondral bone in HD-OA was more sclerotic in microarchitecture when compared with OP, with higher bone volume fraction, narrower trabecular space, more and thicker trabeculae, and higher BMD. In addition, as indicated by higher Conn.D, lower SMI and DA, the weight-bearing subchondral bone in HD-OA exhibited a more

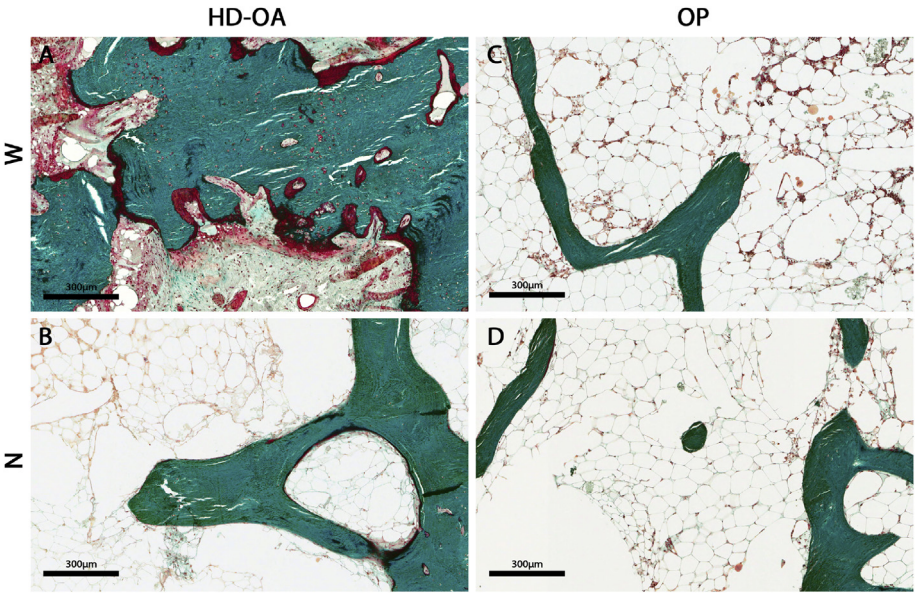

Figure 3. Representative bone remodelling photomicrographs of STB from the W and N regions in femoral heads from patients with HD-OA (A, B) and patients with OP (C, D). Stain: Goldner's Trichrome; magnification: × 100. W: weight-bearing; N: non–weight-bearing; HD-OA: osteoarthritis secondary to hip dysplasia; OP: osteoporosis; STB: subchondral trabecular bone.

Table 2
Comparison of microarchitecture and bone remodelling parameters in STB between W and N regions.

Variables	HD-OA (n = 20)			OP (n = 20)		
	W	N	P	W	N	P
Microarchitecture						
BV/TV (%)	60.21 (55.49, 64.92)	20.17 (15.06, 25.27)	**<0.001**	20.50 (16.72, 24.28)	21.28 (18.88, 23.68)	0.636*
Tb.Th (μm)	355.79 (333.82, 377.77)	207.80 (177.65, 237.94)	**<0.001**	187.14 (169.60, 204.69)	193.99 (179.47, 208.51)	0.502*
Tb.Sp (μm)	358.89 (305.63, 412.15)	725.13 (635.95, 814.31)	**<0.001***	703.42 (650.10, 756.75)	686.02 (641.35, 730.69)	0.405*
Tb.N (1/mm)	1.69 (1.60, 1.78)	0.95 (0.79, 1.11)	**<0.001***	1.07 (0.94, 1.19)	1.10 (1.01, 1.19)	0.765
SMI	−0.88 (−1.47, −0.29)	1.55 (1.26, 1.85)	**<0.001**	1.28 (1.02, 1.53)	1.31 (1.14, 1.47)	0.772*
DA	1.51 (1.38, 1.65)	1.61 (1.44, 1.77)	0.391	1.87 (1.74, 2.00)	2.05 (1.88, 2.21)	0.052*
Conn.D (1/mm^3)	19.74 (15.55, 23.94)	11.11 (7.97, 14.24)	**0.001**	8.71 (7.43, 10.00)	8.85 (7.53, 10.17)	0.847*
BMD (mg/cm^3)	580.65 (539.94, 621.36)	202.35 (146.01, 258.69)	**<0.001**	204.88 (161.53, 248.22)	222.38 (193.93, 250.82)	0.346*
Histology						
O.Th (μm)	11.71 (9.97, 13.46)	5.41 (4.69, 6.14)	**<0.001***	3.86 (3.21, 4.50)	3.40 (2.95, 3.85)	0.233*
OV/BV (%)	6.17 (4.66, 7.69)	2.10 (1.35, 2.86)	**<0.001**	0.99 (0.69, 1.28)	0.76 (0.51, 1.02)	0.052
OS/BS (%)	66.51 (60.33, 72.69)	23.94 (18.60, 29.29)	**<0.001***	14.90 (10.93, 18.87)	13.87 (10.03, 17.70)	0.627
OS/BV (mm^2/mm^3)	5.20 (4.50, 5.91)	3.44 (2.49, 4.40)	**0.019**	2.12 (1.55, 2.68)	1.88 (1.25, 2.50)	0.332
ES/BS (%)	15.98 (12.27, 19.69)	4.90 (3.31, 6.49)	**<0.001**	3.17 (2.19, 4.15)	3.05 (1.19, 4.92)	0.079
ES/BV (mm^2/mm^3)	1.26 (0.96, 1.57)	0.69 (0.45, 0.93)	**0.010**	0.46 (0.30, 0.62)	0.39 (0.19, 0.60)	**0.044**
ES/TV (mm^2/mm^3)	0.59 (0.45, 0.72)	0.15 (0.08, 0.22)	**<0.001**	0.08 (0.06, 0.12)	0.08 (0.03, 0.13)	0.145

Data are expressed as means (95% CI). Bold indicates statistically significant difference. * indicates the data which are normally distributed.
W = weight-bearing; N = non–weight-bearing; HD-OA = osteoarthritis secondary to hip dysplasia; OP = osteoporosis; STB = subchondral trabecular bone.

honeycomb-like structure, with plate-like trabeculae oriented along a preferred direction [30,43]. In the present study, there was also an abnormally high bone remodelling level in HD-OA. The active bone remodelling might be a manifestation of reparative processes within the areas of abnormally high stress [44,45]. Bone formation activity probably outweighs that of bone resorption, culminating in a more sclerotic microarchitecture in HD-OA [21]. Dysregulated osteoblast, osteoclast and osteocyte phenotype might contribute to the abnormal alterations in osteoarthritic subchondral bone [46–48]. In OP, the weight-bearing subchondral bone showed a low bone remodelling level, which was consistent with previous histomorphometric studies undertaken on transiliac bone biopsies [49–52]. In these studies, no significant difference was found in bone remodelling between OP and normal controls. However, the existing low bone remodelling rate could not explain the poor microarchitecture in OP. It has been proposed that elevated bone turnover and high bone loss rate in OP may occur earlier in life, which is long before the manifestation of osteoporotic fracture in later stage [50,51].

The inferior non–weight-bearing region is an habitual non-contact area, without high compressive stress from the acetabulum [35]. In a study by Crane et al. [53], patients with primary OA showed similar bone volume fraction in the non–weight-bearing subchondral bone, compared with old normal control (age>50 years). In the present study, HD-OA and OP also demonstrated similar microarchitecture characteristics in this region. Despite the structural similarity, elevated bone remodelling, including bone formation and resorption, was observed in HD-OA. This phenomenon indicated that the osteoarthritic alteration of subchondral bone induced by hip dysplasia might involve the whole joint, although the non–weight-bearing subchondral bone deterioration was not as serious as that in the weight-bearing region. Our result was consistent with previous studies [45,54], in which the non–weight-bearing subchondral bone also showed elevated remodelling activity in OA than normal. The increased bone formation activity may counteract the simultaneously elevated resorption activity in HD-OA, leading to the structural similarity between the two diseases.

Table 3
Histological findings in the bone marrow.

Histologic finding	HD-OA (n = 20)		OP (n = 20)	
	W	N	W	N
SBC	16 (80%)*,**	2 (10%)	0	0
Metaplastic cartilaginous tissue	14 (70%)*,**	0	0	0
Bone marrow oedema	5 (25%)*,**	13 (65%)	12 (60%)	10 (50%)
Fibrous tissue	20 (100%)*,**	5 (25%)***	0	0
Normal bone marrow	0*,**	6 (30%)	8 (40%)	10 (50%)

*p < 0.05 compared with OP-W.
**p < 0.05 compared with OA-N.
***p < 0.05 compared with OP-N.
W = weight-bearing; N = non–weight-bearing; HD-OA = osteoarthritis secondary to hip dysplasia; OP = osteoporosis; STB = subchondral trabecular bone.

Different regions within a joint might differ in the microarchitectural pattern, reflecting different types and magnitudes of mechanical loadings [35,55]. In the normal joint, a moderate higher bone volume fraction has been observed in the weight-bearing subchondral bone, compared with the non–weight-bearing region [53,56,57]. In primary OA, the regional difference was highly significant, with more sclerotic microarchitecture, elevated bone remodelling activity, higher apparent and mineral density in the weight-bearing region [28,35,44,45,53,57,58]. In HD-OA, our study also suggested a significant regional difference in both microarchitecture and bone remodelling. This distinct regional variation might be due to the abnormal metabolic response of relevant cells trying to maintain the load-bearing capability, resulting in a greater sensitivity to the pathologically high mechanical stress in the weight-bearing region [28,35]. However, in OP, no significant regional difference was found in either microarchitecture or bone remodelling. This might be attributed to the more serious bone deterioration in the weight-bearing region than in non–weight-bearing region in OP, which offsets the original regional difference observed in normal joint. It has been reported that bone loss in OP was more severe in weight-bearing skeletal sites, compared with non–weight-bearing counterparts [59–61].

A variety of pathological lesions, including SBC, metaplastic cartilaginous tissue, bone marrow oedema and fibrous tissue, were observed in subchondral bone. The pathology severity was lowest in both weight-bearing and non–weight-bearing regions of OP, greater in the non–weight-bearing region of HD-OA, and highest in the weight-bearing region of HD-OA. The altered/disrupted biomechanical milieu may contribute to these changes [37,62]. The pathological lesions may give rise to the upregulation of proinflammatory cytokines and matrix metalloproteinases, subsequently leading to the bone remodelling and structural alterations in osteoarthritic subchondral bone [63–65].

One limitation of the present study is the absence of normal subjects. The old age of patients with terminal-staged HD-OA and OP undergoing hip replacement makes the acquisition of age-matched normal specimens difficult. Cadaveric specimens are not satisfactory, as the degenerative changes with ageing process are often observed in “normal” hip joint [66]. Another limitation of our study is the lack of inclusion of early-stage patients with both diseases. This was unavoidable, because hip joint replacement is not the treatment of choice in the early stage. In this sense, the reflection of subchondral bone characteristics observed in the study is not representative for the whole progression of both diseases. The third limitation was the cross-sectional design and lack of dynamic bone

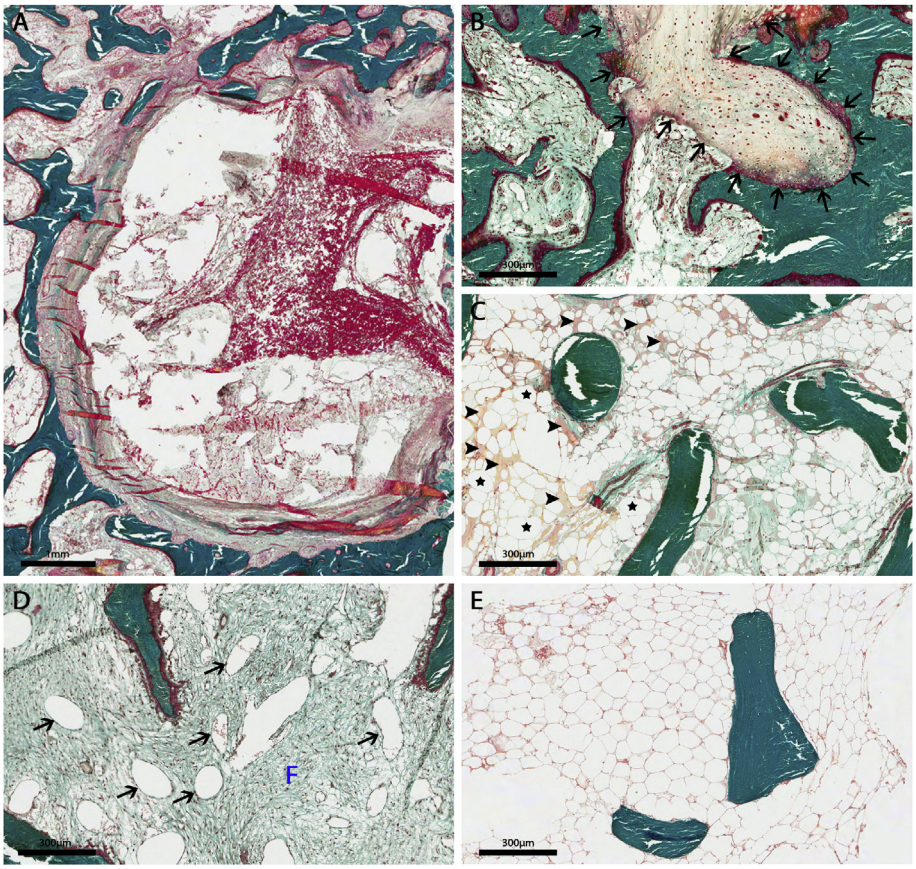

Figure 4. Representative histological findings in subchondral bone. (A) Subchondral bone cyst. (B) Metaplastic cartilaginous tissue (indicated by arrows). (C) Bone marrow oedema with swollen adipocytes (indicated by ★) and accumulation of extracellular fluid (indicated by arrowheads). (D) Fibrous tissue (indicated by F) with collagen texture and thin-walled blood vessels (indicated by arrows). (E) Normal bone marrow. Stain: Goldner's Trichrome.

remodelling assessment. A prospective study with both static and dynamic bone remodelling parameters is needed in the future. Finally, no comparative study was conducted between patients with primary OA and patients with HD-OA in the present study. Subchondral bone difference between OA patients with different etiologies could be illuminated in future studies.

In conclusion, we observed highly significant differences in the microarchitecture, bone remodelling, and pathological alterations in the weight-bearing subchondral bone, between HD-OA and OP. In the non–weight-bearing region, the two diseases shared similar microarchitecture characteristics, but higher bone remodelling level and higher pathology severity were observed in HD-OA. These phenomena suggest that the osteoarthritic deteriorations of subchondral bone induced by hip dysplasia spread throughout the whole joint, but exhibit region-dependent variations, with the weight-bearing region more seriously affected. Biomechanical stress might exert a pivotal impact on subchondral bone homeostasis.

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Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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References

[1] de Hundt M, Vlemmix F, Bais JM, Hutton EK, de Groot CJ, Mol BW, et al. Risk factors for developmental dysplasia of the hip: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2012;165(1):8–17.
[2] Patel H, the Canadian Task Force on Preventive Health C. Preventive health care, 2001 update: screening and management of developmental dysplasia of the hip in newborns. CMAJ: Can Med Assoc J 2001;164(12):1669–77.
[3] Furnes O, Lie SA, Espehaug B, Vollset SE, Engesaeter LB, Havelin LI. Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987-99. J Bone Jt Surg Br 2001;83(4):579–86.
[4] Lehmann HP, Hinton R, Morello P, Santoli J. Developmental dysplasia of the hip practice guideline: technical report. Committee on quality improvement, and subcommittee on developmental dysplasia of the hip. Pediatrics 2000;105(4):E57.
[5] Shipman SA, Helfand M, Moyer VA, Yawn BP. Screening for developmental dysplasia of the hip: a systematic literature review for the US Preventive Services Task Force. Pediatrics 2006;117(3):e557–76.
[6] Albinana J, Dolan LA, Spratt KF, Morcuende J, Meyer MD, Weinstein SL. Acetabular dysplasia after treatment for developmental dysplasia of the hip. Implications for secondary procedures. J Bone Jt Surg Br 2004;86(6):876–86.
[7] Cooperman DR, Wallensten R, Stulberg SD. Acetabular dysplasia in the adult. Clin Orthop Relat Res 1983;175:79–85.
[8] Malvitz TA, Weinstein SL. Closed reduction for congenital dysplasia of the hip. Functional and radiographic results after an average of thirty years. J Bone Jt Surg Am 1994;76(12):1777–92.
[9] Hartofilakidis G, Karachalios T, Stamos KG. Epidemiology, demographics, and natural history of congenital hip disease in adults. Orthopedics 2000;23(8):823–7.
[10] Wedge JH, Wasylenko MJ. The natural history of congenital disease of the hip. J Bone Jt Surg Br 1979;61-B(3):334–8.
[11] Terjesen T. Residual hip dysplasia as a risk factor for osteoarthritis in 45 years follow-up of late-detected hip dislocation. J Children's Orthop 2011;5(6):425–31.
[12] Dezateux C, Rosendahl K. Developmental dysplasia of the hip. Lancet 2007; 369(9572):1541–52.
[13] Sugano N, Noble PC, Kamaric E, Salama JK, Ochi T, Tullos HS. The morphology of the femur in developmental dysplasia of the hip. J Bone Jt Surg Br 1998;80(4): 711–9.
[14] Jacobsen S, Sonne-Holm S. Hip dysplasia: a significant risk factor for the development of hip osteoarthritis. A cross-sectional survey. Rheumatology 2005; 44(2):211–8.
[15] Nicholls AS, Kiran A, Pollard TC, Hart DJ, Arden CP, Spector T, et al. The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case-control study. Arthritis Rheum 2011; 63(11):3392–400.
[16] Lievense AM, Bierma-Zeinstra SM, Verhagen AP, Verhaar JA, Koes BW. Influence of hip dysplasia on the development of osteoarthritis of the hip. Ann Rheum Dis 2004; 63(6):621–6.
[17] Mavcic B, Slivnik T, Antolic V, Iglic A, Kralj-Iglic V. High contact hip stress is related to the development of hip pathology with increasing age. Clin Biomech 2004;19(9): 939–43.
[18] Sampson TG. Hip morphology and its relationship to pathology: dyplasia to impingement. Oper Tech Sport Med 2005;13(1):37–45.
[19] Jessel RH, Zurakowski D, Zilkens C, Burstein D, Gray ML, Kim YJ. Radiographic and patient factors associated with pre-radiographic osteoarthritis in hip dysplasia. J Bone Jt Surg Am 2009;91(5):1120–9.
[20] Kim YJ, Jaramillo D, Millis MB, Gray ML, Burstein D. Assessment of early osteoarthritis in hip dysplasia with delayed gadolinium-enhanced magnetic resonance imaging of cartilage. J Bone Jt Surg Am 2003;85-A(10):1987–92.
[21] Burr DB, Gallant MA. Bone remodelling in osteoarthritis. Nat Rev Rheumatol 2012; 8(11):665–73 [Eng].
[22] Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis Res Ther 2013;15(6):223.
[23] Zhang ZM, Li ZC, Jiang LS, Jiang SD, Dai LY. Micro-CT and mechanical evaluation of subchondral trabecular bone structure between postmenopausal women with osteoarthritis and osteoporosis. Osteoporos Int 2010;21(8):1383–90 [eng].
[24] Chappard C, Peyrin F, Bonnassie A, Lemineur G, Brunet-Imbault B, Lespessailles E, et al. Subchondral bone micro-architectural alterations in osteoarthritis: a synchrotron micro-computed tomography study. Osteoarthr Cartil 2006;14(3): 215–23 [eng].
[25] Li Z-C, Dai L-Y, Jiang L-S, Qiu S. Difference in subchondral cancellous bone between postmenopausal women with hip osteoarthritis and osteoporotic fracture: implication for fatigue microdamage, bone microarchitecture, and biomechanical properties. Arthritis Rheum 2012;64(12):3955–62.
[26] Sun SS, Ma HL, Liu CL, Huang CH, Cheng CK, Wei HW. Difference in femoral head and neck material properties between osteoarthritis and osteoporosis. Clin Biomech 2008;23(suppl 1):S39–47.
[27] Li B, Aspden RM. Mechanical and material properties of the subchondral bone plate from the femoral head of patients with osteoarthritis or osteoporosis. Ann Rheum Dis 1997;56(4):247–54 [eng].
[28] Li B, Aspden RM. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J Bone Miner Res 1997;12(4):641–51 [eng].
[29] Chiba K, Nango N, Kubota S, Okazaki N, Taguchi K, Osaki M, et al. Relationship between microstructure and degree of mineralization in subchondral bone of osteoarthritis: a synchrotron radiation microCT study. J Bone Miner Res 2012; 27(7):1511–7 [eng].
[30] Chiba K, Ito M, Osaki M, Uetani M, Shindo H. In vivo structural analysis of subchondral trabecular bone in osteoarthritis of the hip using multi-detector row CT. Osteoarthr Cartil 2011;19(2):180–5.
[31] Rogers BA, Garbedian S, Kuchinad RA, Backstein D, Safir O, Gross AE. Total hip arthroplasty for adult hip dysplasia. J Bone Jt Surg Am 2012;94(19):1809–21.
[32] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16(4):494–502.
[33] Fazzalari NL, Parkinson IH. Femoral trabecular bone of osteoarthritic and normal subjects in an age and sex matched group. Osteoarthr Cartil 1998;6(6):377–82 [eng].
[34] Shen Y, Zhang Z-M, Jiang S-D, Jiang L-S, Dai L-Y. Postmenopausal women with osteoarthritis and osteoporosis show different ultrastructural characteristics of trabecular bone of the femoral head. BMC Muscoskelet Disord 2009;10. 35-35.
[35] Issever AS, Burghardt A, Patel V, Laib A, Lu Y, Ries M, et al. A micro-computed tomography study of the trabecular bone structure in the femoral head. J Musculoskelet Neuronal Interact 2003;3(2):176–84.
[36] Wright DA, Meguid M, Lubovsky O, Whyne CM. Subchondral bone density distribution in the human femoral head. Skelet Radiol 2012;41(6):677–83 [eng].
[37] Hunter DJ, Gerstenfeld L, Bishop G, Davis AD, Mason ZD, Einhorn TA, et al. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. Arthritis Res Ther 2009;11(1):R11.
[38] Li G, Ma Y, Cheng TS, Landao-Bassonga E, Qin A, Pavlos NJ, et al. Identical subchondral bone microarchitecture pattern with increased bone resorption in rheumatoid arthritis as compared to osteoarthritis. Osteoarthr Cartil 2014;22(12): 2083–92.
[39] Bouxsein ML, Boyd SK, Christiansen BA, Guldberg RE, Jepsen KJ, Muller R. Guidelines for assessment of bone microstructure in rodents using micro-computed tomography. J Bone Miner Res 2010;25(7):1468–86.
[40] Dempster DW, Compston JE, Drezner MK, Glorieux FH, Kanis JA, Malluche H, et al. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res 2013;28(1):2–17.
[41] Turner CH. Biomechanics of bone: determinants of skeletal fragility and bone quality. Osteoporos Int 2002;13(2):97–104.
[42] Inui A, Nakano S, Yoshioka S, Goto T, Hamada D, Kawasaki Y, et al. Subchondral cysts in dysplastic osteoarthritic hips communicate with the joint space: analysis

using three-dimensional computed tomography. Eur J Orthop Surg Traumatol : Orthop Traumatol 2013;23(7):791–5.
[43] Podsiadlo P, Dahl L, Englund M, Lohmander LS, Stachowiak GW. Differences in trabecular bone texture between knees with and without radiographic osteoarthritis detected by fractal methods. Osteoarthr Cartil 2008;16(3):323–9 [eng].
[44] Batra HC, Charnley J. Existence and incidence of osteoid in osteoarthritis femoral heads. A preliminary report. J Bone Jt Surg Br 1969;51(2):366–71.
[45] Grynpas MD, Alpert B, Katz I, Lieberman I, Pritzker KP. Subchondral bone in osteoarthritis. Calcif Tissue Int 1991;49(1):20–6 [eng].
[46] Sanchez C, Deberg MA, Bellahcene A, Castronovo V, Msika P, Delcour JP, et al. Phenotypic characterization of osteoblasts from the sclerotic zones of osteoarthritic subchondral bone. Arthritis Rheum 2008;58(2):442–55 [eng].
[47] Logar DB, Komadina R, Prezelj J, Ostanek B, Trost Z, Marc J. Expression of bone resorption genes in osteoarthritis and in osteoporosis. J Bone Miner Metab 2007; 25(4):219–25 [eng].
[48] Jaiprakash A, Prasadam I, Feng JQ, Liu Y, Crawford R, Xiao Y. Phenotypic characterization of osteoarthritic osteocytes from the sclerotic zones: a possible pathological role in subchondral bone sclerosis. Int J Biol Sci 2012;8(3):406–17 [eng].
[49] Arlot M, Edouard C, Meunier PJ, Neer RM, Reeve J. Impaired osteoblast function in osteoporosis: comparison between calcium balance and dynamic histomorphometry. Br Med J 1984;289(6444):517–20.
[50] Kimmel DB, Recker RR, Gallagher JC, Vaswani AS, Aloia JF. A comparison of iliac bone histomorphometric data in post-menopausal osteoporotic and normal subjects. Bone Miner 1990;11(2):217–35.
[51] Steiniche T. Bone histomorphometry in the pathophysiological evaluation of primary and secondary osteoporosis and various treatment modalities. APMIS 1995;103(S51):5–44.
[52] Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Investig 1997;100(6): 1475–80.
[53] Crane GJ, Fazzalari NL, Parkinson IH, Vernon-Roberts B. Age-related changes in femoral trabecular bone in arthrosis. Acta Orthop Scand 1990;61(5):421–6 [eng].
[54] Boivin G, Meunier PJ. Changes in bone remodeling rate influence the degree of mineralization of bone. Connect Tissue Res 2002;43(2–3):535–7.
[55] van der Harst MR, Brama PA, van de Lest CH, Kiers GH, DeGroot J, van Weeren PR. An integral biochemical analysis of the main constituents of articular cartilage, subchondral and trabecular bone. Osteoarthr Cartil 2004;12(9):752–61.
[56] Parkinson IH, Fazzalari NL. Interrelationships between structural parameters of cancellous bone reveal accelerated structural change at low bone volume. J Bone Miner Res 2003;18(12):2200–5.
[57] Reimann I, Mankin HJ, Trahan C. Quantitative histologic analyses of articular cartilage and subchondral bone from osteoarthritic and normal human hips. Acta Orthop Scand 1977;48(1):63–73.
[58] Reimann I, Christensen SB. A histochemical study of alkaline and acid phosphatase activity in subchondral bone from osteoarthrotic human hips. Clin Orthop Relat Res 1979;140:85–91.
[59] Davis JW, Ross PD, Wasnich RD, Maclean CJ, Vogel JM. Comparison of cross-sectional and longitudinal measurements of age-related changes in bone mineral content. J Bone Miner Res 1989;4(3):351–7.
[60] Mazess RB, Barden HS, Ettinger M, Johnston C, Dawson-Hughes B, Baran D, et al. Spine and femur density using dual-photon absorptiometry in US white women. Bone Miner 1987;2(3):211–9.
[61] Ribot C, Tremollieres F, Pouilles JM, Louvet JP, Guiraud R. Influence of the menopause and aging on spinal density in French women. Bone Miner 1988;5(1): 89–97.
[62] Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology 2000;215(3):835–40 [eng].
[63] Guzman RE, Evans MG, Bove S, Morenko B, Kilgore K. Mono-iodoacetate-induced histologic changes in subchondral bone and articular cartilage of rat femorotibial joints: an animal model of osteoarthritis. Toxicol Pathol 2003;31(6):619–24 [eng].
[64] von Rechenberg B, Guenther H, McIlwraith CW, Leutenegger C, Frisbie DD, Akens MK, et al. Fibrous tissue of subchondral cystic lesions in horses produce local mediators and neutral metalloproteinases and cause bone resorption in vitro. Vet Surg : Vysokomol Soedin 2000;29(5):420–9.
[65] Hulejova H, Baresova V, Klezl Z, Polanska M, Adam M, Senolt L. Increased level of cytokines and matrix metalloproteinases in osteoarthritic subchondral bone. Cytokine 2007;38(3):151–6.
[66] Byers PD, Contepomi CA, Farkas TA. A post mortem study of the hip joint. Including the prevalence of the features of the right side. Ann Rheum Dis 1970;29(1):15–31.