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

Guangyi Li, Lianzhi Chen, Qiujian Zheng, Yuanchen Ma, Changqing Zhang, Ming Hao Zheng

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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...
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 anti-resorptive 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.
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 micro-architecture 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/mm³) and bone mineral density (BMD) (mg/cm³) [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 Biosquant Osteo Histomorphometry software (Biosquant 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) (mm²/mm³), percentage eroded surface (ES/BS) (%), specific eroded surface (ES/BV) (mm²/mm³) and eroded surface in bone tissue volume (ES/TV) (mm²/mm³) [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

| 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, 421.15) | 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/ mm²) | 19.74 (15.55, 23.94) | 8.71 (7.43, 10.00) | <0.001 |
|        | BMD (mg/cm³) | 580.65 (539.94, 621.36) | 204.88 (161.53, 248.22) | <0.001* |
|        | Histology  |               |             |       |
|        | O.Th (%)  | 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) | 14.09 (10.93, 18.87) | <0.001* |
|        | OS/BV (mm²/ mm³) | 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 (mm²/ mm³) | 1.26 (0.96, 1.57) | 0.46 (0.30, 0.62) | <0.001 |
|        | ES/TV (mm²/ mm³) | 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/ mm²) | 11.11 (7.97, 14.24) | 8.85 (7.53, 10.17) | 0.534 |
|        | BMD (mg/cm³) | 202.35 (146.01, 258.69) | 222.38 (193.93, 250.82) | 0.267 |
|        | Histology  |               |             |       |
|        | O.Th (%)  | 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 (mm²/ mm³) | 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) | 0.006 |
|        | ES/BV (mm²/ mm³) | 0.69 (0.45, 0.93) | 0.39 (0.19, 0.60) | 0.006 |
|        | ES/TV (mm²/ mm³) | 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.

In HD-OA, 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.

### 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, 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...
before the manifestation of osteoporotic fracture in later stage [50, 51].

and high bone loss rate in OP may occur earlier in life, which is long

microarchitecture in OP. It has been proposed that elevated bone turnover

found in bone remodelling between OP and normal controls. However,

bone biopsies [49 – 52]. In these studies, no significant difference was

manifestation of reparative processes within the

area, without high compressive stress from the acetabulum [35]. In a

phenomenon indicated that the osteoarthritic alteration of subchondral

region. Despite the structural similarity, elevated bone remodelling,

volume fraction in the non–weight-bearing subchondral bone, compared

normal. The increased bone formation activity may counteract the

structural similarity between the two diseases.

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 (%)                      | 20.17 (15.06, 25.27) | <0.001       | 21.28 (18.88, 23.68) | 0.636*       |
| Th.Sp (μm)                     | 725.13 (635.95, 814.31) | <0.001*      | 768.02 (641.35, 730.69) | 0.405*       |
| Tb.N (1/μm)                    | 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/μm²)                 | 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) | 0.867* |
| BMD (mg/cm³)                   | 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* |
| OI/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 (18.80, 29.29) | <0.001* | 14.90 (10.93, 18.87) | 13.87 (10.03, 17.70) | 0.627 |
| OS/BV (mm²/mm³)                | 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 (mm²/mm³)                | 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/V (mm³/mm³)              | 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

osteochondral subchondral bone [46–48]. In OP, the weight-bearing sub-

chondral bone showed a low bone remodelling level, which was consist-

ent 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 seri-

ous as that in the weight-bearing region. Our result was consistent with

previous studies [45, 54], in which the non–weight-bearing sub-

chondral 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.

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.
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

### Table 3

| 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  | 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.
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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