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Original Article

Bone Histomorphometry of Femoral Head Cancellous Bone in Patients Who Underwent Total Hip Arthroplasties due to Destructive Hip in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) affects the hip joints. The microarchitecture of the cancellous bone in RA-affected hip joints has been unclear. Here we investigated the bone metabolism changes in the subcapital cancellous bone of destructive hips of RA patients (n = 26 patients; 28 hip joints) which were classified by Larsen grade on X-ray into the groups: destructive hip (Des) (Larsen grade IV, n = 18) and neck fracture (Fx) (Larsen grade 0 or 1, n = 10). The femoral heads of the Des-group showed significantly higher trabecular thickness versus those of the Fx-group (179 ± 30.8 vs. 151 ± 23.5 μm, $p = 0.02$). The Des-group had significantly higher osteoid volume/tissue volume (OV/TV) and osteoid volume/bone volume (OV/BV) ratios than the Fx-group (OV/TV: 0.72 ± 0.70% vs. 0.27 ± 0.32%, $p = 0.028$; OV/BV: 2.96 ± 2.85% vs. 1.24 ± 1.31%, $p = 0.039$). The osteoblast and osteoclast surface areas of the Des-group were remarkably higher than those of the Fx-group (9.80 ± 10.9 vs. 0.15 ± 0.15%, $p = 0.0005$; 0.34 ± 0.48 vs. 0.06 ± 0.06%, $p = 0.0285$, respectively). The T-scores of hip (femoral neck) bone mineral density (BMD) of the Fx-group were significantly lower versus those of the Des-group (−3.1 ± 0.76 vs. −1.6 ± 1.17, $p < 0.01$). Increased osteoid and resorption parameters and higher femoral neck BMD demonstrate a high bone-turnover state in response to destructive changes in the hips of RA patients.

Key words: bone histomorphometry, rheumatoid arthritis, destructive hip, femoral neck fracture, bone turnover

Periarticular osteoporosis, bone destruction (bone erosion), and decreased systemic bone volume are representative characteristics of bone lesions in patients with rheumatoid arthritis (RA) [1,2]. Even in patients with low-severity RA whose condition is maintained on biological disease-modifying antirheumatic drugs (bDMARDs), the persistence of local inflammation in peripheral joints such as finger joints was associated with alteration of the trabecular compartment [3]. For the amelioration of synovitis and arthritis, methotrexate (MTX), an antifolate-type antimetabolite, along with tumor necrosis factor (TNF) inhibitors, anti-interleukin (IL)-6 receptor antibodies, and modulated T-cell costimulatory inhibitors are currently prescribed in clinical practices. These drugs also showed an inhibitory effect on bone destruction in periarticular lesions [4-6]. It was reported that TNF inhibitors improved the upregulation of serum bone resorption-related markers such as the receptor activator of nuclear factor kappa-B ligand (RANKL) and crosslinked telopeptide of type I collagen (CTX-1) [7].

Most importantly, RA affects hip joints, and in some cases of destructive RA, total hip arthroplasty is still required [8]. The pathogenesis and microstructures in subcapital cancellous bone in RA affecting the

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hip joints have been unclear. Bone histomorphometry — a bone microarchitecture characterization method — can be used to analyze bone tissue on the cellular level and quantitatively evaluate the bone metabolism and its dynamics. Generally, the human iliac bone has been used for bone histomorphometry [9], but the femoral head was used in several past studies for assessments of the microarchitecture of bone tissue affected by osteoporosis or osteoarthritis in clinical settings [10-12]. The femoral head is the anatomical zone most affected by the pathologies in question and is considered the most reliable sampling zone. However, no study has yet demonstrated the changes in bone metabolism in the cancellous bone of femoral heads affected by RA. We conducted the present study to investigate how the bone metabolism changes in cancellous bones of destructive femoral heads in patients with RA. For this investigation, we evaluated the findings of bone histomorphometry of cancellous bone in the femoral heads of RA patients with destructive changes and compared the findings with those of RA patients with femoral neck fractures.

Patients and Methods

We enrolled Japanese 26 patients (28 hips, including 2 bilateral cases) between September 2009 and August 2015. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA and were under treatment with MTX and/or bDMARDs at the time of a total hip arthroplasty (THA) for destructive hip secondary to RA or a femoral head replacement (FHR) following a femoral neck fracture. Just after the THA or FHR, the osteotomized femoral heads were extracted and subjected to bone histomorphometry.

We divided the femoral heads into two groups depending on the location of the destruction of the hip joints. Femoral heads showing Larsen grade IV deformity (18 hips) on X-ray were allocated to the destructive (Des) group, and all of the femoral neck fracture cases showing Larsen grade 0 (9 hips) or I (1 hip) on X-ray were allocated to the fracture (Fx) group. There were no Larsen grade II, III, or V cases. One case in the Des-group was complicated with idiopathic osteonecrosis of the femoral head. The evaluated items were as follows: the duration of RA (from diagnosis to the THA or FHR), the patient's age at the time of surgery, the use and average doses of prednisolone (PSL) and MTX, the specific history of bDMARD use, osteoporosis medications (specially bisphosphonates), and the Disease Activity Score-28 C-Reactive Protein (DAS28-CRP) values [3]. Serum CRP, rheumatoid factor (RF), and matrix metalloproteinase-3 (MMP-3) were assessed at the time of hip surgery. In addition, the bone mineral density (BMD) of the hips on the contralateral side was measured using dual energy X-ray absorptiometry (DXA) (Hologic, Tokyo), and the T-scores of the femoral neck sites were evaluated around the hip surgery area for each patient.

Bone histomorphometry. The osteotomized femoral heads were pre-stained for 72 h using Villanueva bone stain. The specimens were dehydrated, defatted, and embedded with methyl methacrylate and stored at 37°C until they were fully polymerized. Embedded biopsy samples were subsequently sectioned at 5 μm thick on a microtome (Leica RM2255; Leica, Nussloch, Germany).

A region of interest (ROI) was set up in a 20-mm^2 region at the center of the femoral head in the maximal plane of the tissue section (Fig. 1). The central region was selected so that the influence of the degeneration of the hip articular cartilage could be ignored. Normal light and fluorescent microscopic findings were evaluated and compared between the Des- and Fx-groups. Bone histomorphometric parameters were measured with an epifluorescence microscope-based system (Olympus BX50; Olympus America, Center Valley, PA, USA) connected to an Epson computer (Shinshu Seiki Co., Nagano, Japan).

Bone histomorphometric parameters. The specimen from each case stained with Villanueva bone stain was observed under a light microscope, and trabecular bones, osteoids, and osteoclasts were measured. The bone histomorphometric parameters were based on a previous report [13]. The scheme of these parameters is provided as Fig. 2. As bone volume parameters, the bone volume/issue volume (BV/TV), trabecular thickness (Tb.Th), and wall thickness (W.Th) were measured. As osteoid parameters (*i.e.*, bone formation parameters), the osteoid volume/tissue volume (OV/TV), osteoid volume/bone volume (OV/BV), osteoid surface (OS/BS), osteoid thickness (O.Th), and osteoblast surface (Ob.S) were measured. As bone resorption parameters, the eroded surface/bone surface (ES), osteoclast surface (Oc.S/BS), and fibrosis volume (Fb.

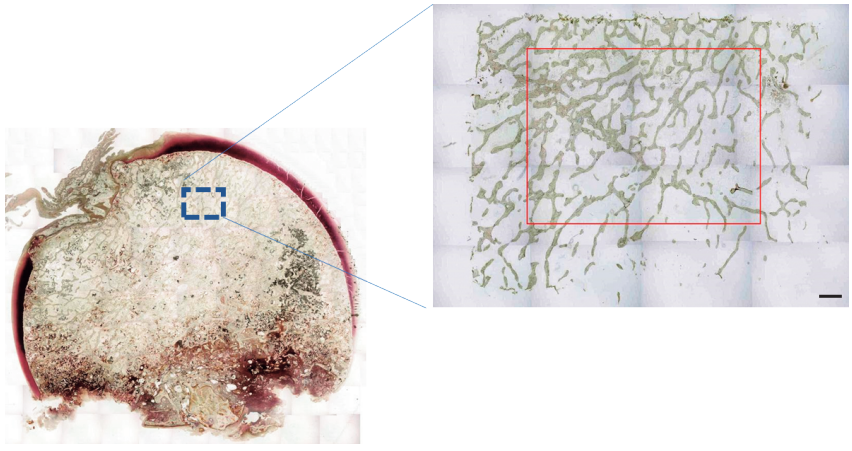

Fig. 1 Region of interest for the bone histomorphometry of the femoral heads. Bar: =1 mm.

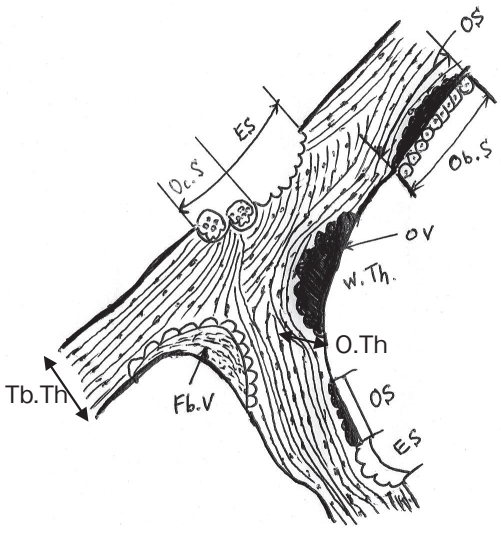

Fig. 2 Scheme of the bone histomorphometric parameters; here, for trabecular bone under a light microscope (reproduced from ref. [13]). Bone tissues consist of bone and bone marrow. Bone is divided into 2 categories; the calcified bone (lamellar structure) and osteoid (*black-colored zone*). BV (bone volume): the area of trabecular bone. Trabecular width (W.Th) and trabecular thickness (Tb.Th): the width and the thickness of trabecular bone, respectively. BV, W.Th, and Tb.Th are bone volume parameters. OV (osteoid volume): the area of osteoid. O.Th (osteoid thickness): the thickness of osteoid. OS (osteoid surface): the length of the surface of osteoid. Ob.S (osteoblast surface): the length of the surface of palisaded osteoblasts. OV, O.Th, OS, and Ob.S are bone formation parameters. Fb.V (fibrosis volume): the area of fibrous tissue. ES (eroded surface): the length of the invaded area of trabecular bone. In an eroded surface, the Oc.S (osteoclast surface) indicates the length of the surface to which osteoclasts are attached. ES, Oc.S, and Fb.V are bone resorption parameters.

V/TV) were measured.

Statistical analysis. An unpaired *t*-test (Student or Welch) or Mann-Whitney test was performed, and a *p*-value <0.05 was considered significant. We performed a correlation analysis to examine the association between the BMD of the femoral neck and each bone morphometric parameter, and *p*-values <0.05 were considered significant. GraphPad Prism 6J software (GraphPad Software, San Diego, CA, USA) was used to perform all statistical analyses.

Ethics. The clinical study was approved by the institutional review board of Niigata University (2018-0377; the clinical study for patients with RA using Niigata University Orthopedic Surgery Rheumatoid Arthritis Database: NOSRAD). Written informed consent was obtained from each enrolled patient.

Results

The 26 patients (28 hips) were 3 men (3 hips) and 23 women (25 hips); average age 66.4±12.5 years (39-87 years). The average RA disease duration was 14.8±12.7 years (0.3-48 years). Bisphosphonates and PSL were used by 38% (n=10) and 50% (n=13) of the patients, respectively. The average dose of PSL was 2.6±3.8 mg/day. MTX was used by 11 patients (42%) with the mean dosage of 2.7 mg/week; bDMARDs were used in 14 cases (54%). No significant difference was detected between the Des-group (18 hips) and Fx-group (10 hips) regarding patient age; RA duration; rates of bisphosphonate, PSL, MTX, and bDMARD use; or the average dose of PSL (3.2±4.0 mg/day vs.

1.6±3.2 mg/day, $p=0.29$) or MTX (2.9±2.9 mg/week vs. 2.4±3.5 mg/week, respectively; $p=0.74$). The clinical characteristics are summarized in Table 1.

The average DAS28-CRP(3) score for all patients was 2.55±0.79; no significant difference was detected between the Des- and Fx-groups (2.55±0.74 vs. 2.54±0.91, respectively, $p=0.95$). There were no significant differences in the CRP, RF, or MMP-3 levels between the Des- and Fx-groups (CRP: 0.62±0.75 vs. 0.67±0.65 mg/dl, $p=0.87$; RF: 346±1,092 vs. 263±449 IU/l, $p=0.82$; and MMP-3: 159±128 vs. 140±90 ng/ml, $p=0.7$, respectively) (Table 1).

Critical histological differences were revealed between the 2 groups by qualitative evaluations. In the Des-group, the osteoid region was observed around the trabecular bone (Fig. 3A, C). In contrast, the trabecular bone had a sparse osteoid region around it in the Fx-group (Fig. 3B, D).

The bone histomorphometry results (Table 2) showed that the trabecular thickness (Tb.Th) was significantly higher in the Des-group than in the Fx-group (179±30.8 vs. 151±23.5 μm, $p=0.02$). However, the bone volume (BV/TV) and wall thickness (W.Th) showed no significant differences between the groups. Both the osteoid volume/tissue volume (OV/TV) ratio and the osteoid volume/bone volume (OV/BV) ratio were significantly higher in the Des-group compared to the Fx-group (OV/TV: 0.72±0.70 vs. 0.27±0.32%, $p=0.028$, and OV/BV: 2.96±2.85 vs. 1.24±1.31%, $p=0.039$). The osteoblast surface area (Ob.S/BS) in the Des-group was remarkably higher than that in the Fx-group (9.80±10.9 vs. 0.15±0.15%, $p=0.0005$). However, the osteoid sur-

Table 1 Demographic data of femoral head cases of the destructive (Des) and fracture (Fx) groups

		All cases	Des-group	Fx-group	*p*-value
Cases		26 cases 28 hips	16 cases 18 hips	10 cases 10 hips	
Male : Female	Cases	3: 23	3: 13	0: 10	0.26
Age	Years old (Min.-Max.)	66.40±12.50 (39-87)	65.10±14.10 (39-87)	68.80±9.15 (54-79)	0.46
Larsen grade on radiograph in hip joint RA disease duration	Grade 0/I/II/III/IV/V	9/1/0/0/18/0	IV; 18 hips	0; 9hips, I; 1 hip	0.09
	Years	14.80±12.70 (0.30-48)	17.80±14 (0.50-48)	9.40±8.30 (0.30-28)	
Bisphosphoate	Cases	10	8	2	0.22
Methylprednisolone	Cases	13	10	3	0.22
Average methylprednisolone dose	mg/day	2.60±3.80 (0-13)	3.20±4.0 (0-13)	1.60±3.20 (0-10)	0.29
Methotrexate	Cases	11	7	4	0.98
Average methotrexate dose	mg/week	2.70±3.70 (0-10)	2.90±3.90 (0-10)	2.40±3.50 (0-8)	0.74
bDMARDs	Cases	14	10	4	0.42
Details, accumulated number of cases	Cases	TCZ, 5 ETN, 5 ADA, 4 IFX, 3 GOL, 2 ABA, 1	TCZ, 5 ADA, 4 ETN, 4 IFX, 2	GOL, 2 ETN, 1 IFX, 1 ABA, 1	
DAS28CRP(3)		2.55±0.79 (1.34-4.80)	2.55±0.74 (1.84-4.80)	2.54±0.91 (1.34-4.35)	0.95
CRP	mg/dl	0.64±0.70 (0.01-2.01)	0.62±0.75 (0.01-2.00)	0.67±0.65 (0.02-2.01)	0.87
RF	IU/L	316±904 (0-4610)	346±1092 (0-4610)	263±440 (9.10-1342)	0.82
MMP-3	ng/mL	150±111 (19.90-488)	159±128 (26.00-488)	140±90 (19.90-297)	0.71

ABA, abatacept; ADA, adalimumab; bDMARDs, biological disease-modifying anti-rheumatic drugs; DAS28CRP(3), Disease Activity Score 28-C-Reactive Protein (3 joints); ETN, etanercept; GOL, golimumab; IFX, infliximab; MMP-3, matrix metalloproteinase-3; RF, rheumatoid factor; TCZ, tocilizumab.

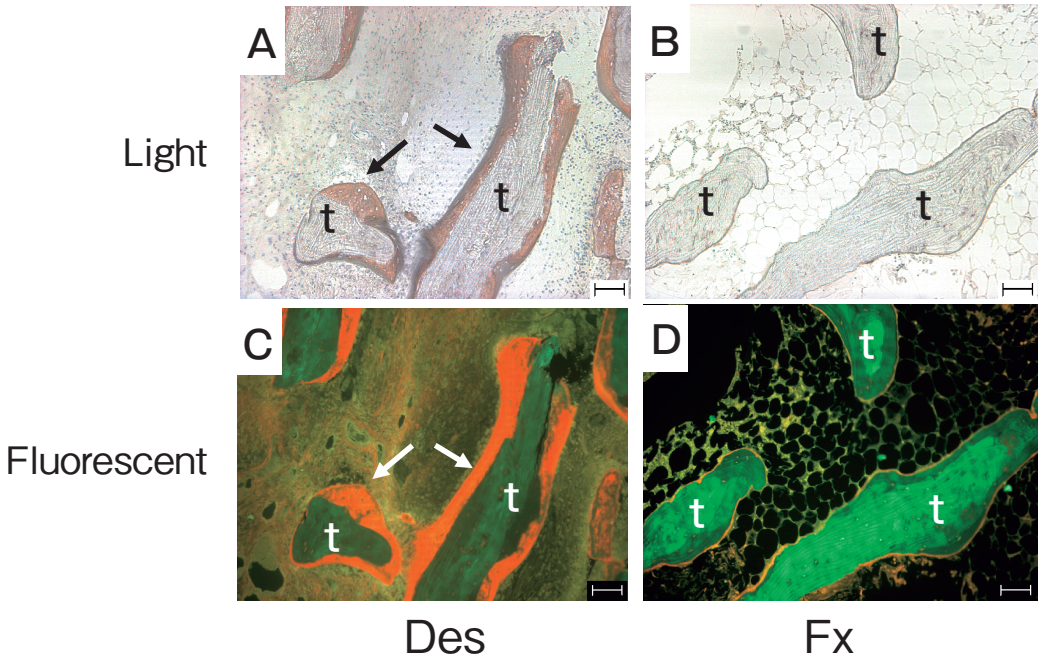

Fig. 3 Histology findings after Villanueva bone staining of subchondral cancellous bone in the femoral heads. More osteoid (*arrows*) was attached to trabecular bone in the destructive (Des)-group (**A**, **C**). A small amount of osteoid was attached to trabecular bone in the femoral head of the fracture (Fx)-group (**B**, **D**). **A**, **B**: normal light. **C**, **D**: Fluorescent light. Bar: 100 μm. t: trabecular bone, *black or white arrows*: osteoid bone.

Table 2 Comparison of the bone histomorphometry findings of femoral head cancellous bone in the Des- and Fx-groups

	Parameter	Abbreviation	Unit	General	Des-group	Fx-group	*p*-value	
Bone	Bone volume	BV/TV	%	23.7 ± 6.43	25.4 ± 5.92	20.8 ± 6.54	0.068	
	Trabecular thickness	Tb.Th	μm	169 ± 31.1	179 ± 30.8	151 ± 23.5	0.02	*
	Wall thickness	W.Th	μm	31.1 ± 9.84	29.4 ± 13.0	32.9 ± 5.64	0.49	
Osteoid	Osteoid volume/Tissue volume	OV/TV	%	0.56 ± 0.62	0.72 ± 0.70	0.27 ± 0.32	0.028	*
	Osteoid volume/Bone volume	OV/BV	%	2.35 ± 2.53	2.96 ± 2.85	1.24 ± 1.31	0.039	*
	Osteoid surface	OS/BS	%	18.2 ± 14.4	20.7 ± 16.3	13.6 ± 9.35	0.22	
	Osteoid thickness	O.Th	μm	10 ± 7.3	11.6 ± 8.26	7.09 ± 4.21	0.069	
	Osteoblast surface	Ob.S/BS	%	6.79 ± 10.0	9.80 ± 10.9	0.15 ± 0.15	0.0005	**
Resorption	Eroded surface	ES/BS	%	1.60 ± 2.15	1.91 ± 2.57	0.99 ± 0.59	0.17	
	Osteoclast surface	Oc.S/BS	%	0.25 ± 0.41	0.34 ± 0.48	0.06 ± 0.06	0.0285	*
	Fibrosis volume	Fb.V/TV	%	0.10 ± 0.32	0.16 ± 0.39	0.00 ± 0.00	0.01	*

*$p<0.05$, **$p<0.01$.

face (OS/BS) and osteoid thickness (O.Th) showed no significant differences between the groups.

Regarding the bone resorption parameters, the osteoclast surface (N. Oc/BS) of the Des-group was significantly higher than that of the Fx-group (0.34 ± 0.48 vs. 0.06 ± 0.06%, $p=0.0285$). The fibrosis volume (Fb. V/TV) of the Des-group was also significantly higher than that of the Fx-group (0.16 ± 0.39 vs. 0.00 ± 0.00%, $p=0.01$). No significant differences were detected in the eroded surface (ES/BS) between the groups (Table 2). In addition, the hip (femoral neck) BMD of the Fx-group was significantly lower than that of the Des-group (T-scores −3.1 ± 0.76 vs. −1.6 ± 1.17, $p<0.01$) (Fig. 4).

In a coefficient analysis, the BMD of the femoral

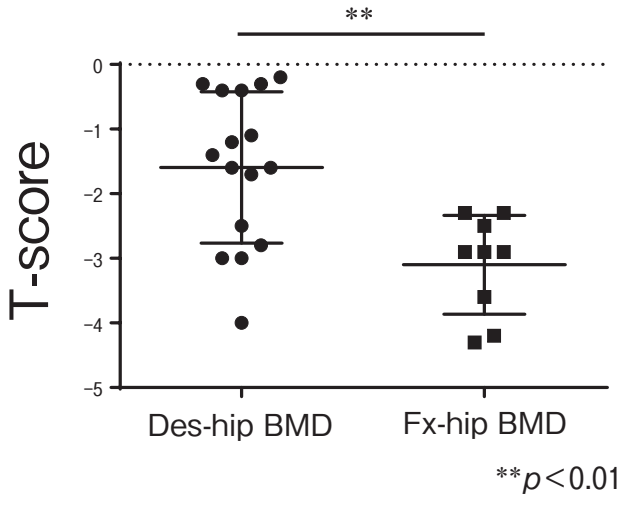

Fig. 4 T-scores of the hip bone mineral density (BMD) of the Des- and Fx-groups. The T-scores of the Des-group (−1.6 ± 1.17) were significantly higher than those of the Fx-group (−3.1 ± 0.76) ($p < 0.01$).

neck in all cases was not closely associated with any bone histomorphometric parameter (bone volume, bone formation, or bone resorption) (data not shown).

Discussion

The results of our present analyses demonstrated that the localized bone turnover in subcapital cancellous bone areas of destructive hip joints of patients with RA was much higher than that of the controls (*i.e.*, the femoral neck fracture group in RA) despite the low disease activity based on DAS28-CRP(3) scores under treatment with bDMARDs. We investigated the histomorphometric characteristics of cancellous bone in the subcapital region of the femoral heads in great detail, and our observations confirmed that both bone formation and resorption parameters were significantly increased in the destructive hip group in response to the destruction itself. The hip BMD values demonstrated that the patients in the fracture group were more susceptible to femoral neck fractures because of the significant decrease in their BMD compared to the patients with destructive RA.

Shimizu *et al.* evaluated the bone histomorphometry of the subchondral bone of 12 RA cases (10 knees, 1 hip, and 1 elbow) and 6 osteoarthritis (OA) cases (4 knees and 2 hips) and they reported that a bone formation (osteoid) parameter and bone resorption parameter were significantly higher in the RA group compared to the OA group [14]. The bone histomorphometry of 3 femoral heads from RA patients was reported; those data indicated that both bone formation and resorption parameters were more increased in the 2 destructive hip cases than in the single nondestructive case [15].

In the present Des-group, since the cancellous bone under the articular cartilage of the hip joints had severely degenerated, the values of the osteoid and resorption parameters were higher. The Fb.V was also higher in the Des-group, indicating high bone turnover; the high bone turnover state probably reflects hyperactive bone remodeling. In both the Des- and Fx-groups, the DAS28-CRP(3) score was comparably low and the disease activity of RA was well-controlled, which suggests that the destruction of femoral heads in the hips of RA patients occurs without any relation to their RA disease activity. In addition, no significant between-group difference was detected in the value of RF or MMP-3.

Another research group compared the femoral heads of 42 RA cases and 61 OA cases, and they reported significantly higher osteoid volumes in the RA group compared to the OA group, but no significant difference was detected between the 2 groups in bone resorption parameters [16]. Li *et al.* examined the histomorphometry findings of superficial and deep zones of the subchondral bone of femoral heads in RA and OA cases, and they demonstrated a significantly higher ES/BS ratio alone in the superficial zone in RA compared to OA. In the deep zone, significant differences between RA and OA were not observed for any parameter, indicating that the microarchitecture of the groups was similar [17]. In comparison, the ROI in our present study seems compatible with the deeper trabecular zone. Our data indicate that (1) in RA femoral heads, bone resorption is increased even in the deeper trabecular zone, and (2) hip destruction (*i.e.*, cartilage degeneration) can affect bone remodeling in the deeper zone of the femoral heads.

Our findings indicate that the BMD was not closely associated any bone histomorphometric parameter (*i.e.*, bone volume, bone formation, or bone resorption parameters). This result suggests that the BMD of the femoral neck of a hip with destruction due to RA does not reflect the degree of destruction in femoral subchondral cancellous bone turnover. Therefore, the results of a histological examination itself may be

important to understand the conditions of localized bone metabolism in RA hips.

The limitations of our study were as follows: (1) the small sample size, (2) MTX and/or bDMARD treatments were controlled to a high extent, (3) the effects of PSL and bisphosphonates on the bone histomorphometric findings were not evaluated, and (4) double labeling by tetracycline was not performed, and thus dynamic histomorphometry parameters could not be evaluated.

In conclusion, the histomorphometry analysis of localized subchondral bone cancellous bone of femoral heads in patients with RA revealed that the osteoid and resorption parameters were considerably increased in the Des-group, indicating that a high bone turnover state probably reflects hyperactive bone remodeling in response to the destructive changes in the hip.

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References

1. Redlich K and Smolen JS: Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov (2012) 11: 234–250.
2. Moon SJ, Ahn IE, Kwok SK, Park KS, Kim HY and Ju JH: Periarticular osteoporosis is a prominent feature in early rheumatoid arthritis: estimation using shaft to periarticular bone mineral density ratio. J Korean Med Sci (2013) 28: 287–294.
3. Kong S, Locrelle H, Amouzougan A, Denarie D, Collet P, Pallot-Prades B, Thomas T and Marotte H: Remaining Local Subclinical Joint Inflammation is Associated With Deteriorated Metacarpal Head Bone Microarchitecture in Rheumatoid Arthritis Patients Low Disease Activity. Joint Bone Spine (2018) 85: 569–572.
4. Lipsky PE, van der Heijde DM, Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR and Maini RN: Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy Study Group. N Engl J Med (2000) 343: 1594–1602.
5. Rich E, Moreland LW and Alarcón GS: Paucity of radiographic progression in rheumatoid arthritis treated with methotrexate as the first disease modifying antirheumatic drug. J Rheumatol (1999) 26: 259–261.
6. Goekoop-Ruiterman YD, de Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JHLM, Lems WF, van Krugten MV, Breedveld FC and Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patient with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum (2005) 52: 3381–3390.
7. Perpetuo IP, Caetan-Lopes J, Rodrigues AM, Campanilho-Marques R, Ponte C, Canhão H, Ainola M and Fonseca JE: Effect of tumor necrosis factor inhibitor therapy on osteoclasts precursors in rheumatoid arthritis. Biomed Res Int (2017) 2690402.
8. Goodman SM and Bass AR: Perioperative medical management for patients with RA, SPA, and SLE undergoing total hip and total knee replacement: a narrative review. BMC Rheumatol (2018) 2: 2.
9. Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, Ott SM and Recker RR: Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res (1987) 2: 595–610.
10. Fazzalari NL, Moore RJ, Manthey BA and Vernon-Roberts B: Comparative study of iliac crest and subchondral femoral bone in osteoarthritic patients. Bone (1992) 13: 331–335.
11. Morini S, Pannarale L, Braidotti P, Marinozzi A and Gaudio E: A morphological study on femoral heads in human hip joint osteoarthritis. Ital J Anat Embryol (1996) 101: 29–43.
12. Fazzalari NL and Parkinson IH: Femoral trabecular bone of osteoarthritic and normal subjects in an age and sex matched group. Osteoarthritis and Cartilage (1998) 6: 377–382.
13. Takahashi HE: Bone histomorphometric parameters of cancellous bones; in Handbook of Bone Morphometry, Takahashi HE eds, 2nd Ed, Nishimura Shoten, Niigata (1997) pp76–82.
14. Shimizu S, Shiozawa S, Shiozawa K, Imura S and Fujita T: Quantitative histologic studies on the pathogenesis of periarticular osteoporosis in rheumatoid arthritis. Arthritis Rheum (1985) 28: 25–31.
15. Ishikawa Y, Kondo N, Sano H et al.: Three rheumatoid arthritis cases in which histomorphometric analysis was performed for cancellous bone in femoral heads. Arch Niigata Soc Orthop Surg (2014) 30: 13–17. (In Japanese).
16. Akesson K, Onsten I and Obrant KJ: Periarticular bone in rheumatoid arthritis versus arthrosis. Histomorphometry in 103 hip biopsies. Acta Orthop Scand (1994) 65: 135–138.
17. Li G, Ma Y, Cheng TS, Landao-Bassonga E, Qin A, Pavlos NJ, Zhang C, Zheng Q and Zheng MH: Identical subchondral bone microarchitecture pattern with increased bone resorption in rheumatoid arthritis as compared to osteoarthritis. Osteoarthritis Cartilage (2014) 22: 2083–2092.