



## ■ BONE BIOLOGY

# Enhanced angiogenesis and increased bone turnover characterize bone marrow lesions in osteoarthritis at the base of the thumb

**M. Shabestari,  
N. J. Kise,  
M. A. Landin,  
S. Sesseng,  
J. C. Hellund,  
J. E. Reseland,  
E. F. Eriksen,  
I. K. Haugen**

University of Oslo,  
Oslo, Norway

■ M. Shabestari, DDS, Dentist, Department of Biomaterials, Faculty of Dentistry, Institute of Clinical Dentistry, University of Oslo, Oslo, Norway.  
■ N. J. Kise, MD, PhD, Orthopaedic Surgeon, Department of Orthopaedic Surgery, Martina Hansens Hospital, Akershus, Norway.  
■ M. A. Landin, PhD, Dentist, Department of Oral Biology,  
■ J. E. Reseland, PhD, Dentist, Department of Biomaterials, Faculty of Dentistry University of Oslo, Oslo, Norway.  
■ S. Sesseng, MD, PhD, Radiologist, Department of Radiology,  
■ I. K. Haugen, MD, PhD, Rheumatologist, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway.  
■ J. C. Hellund, MD, PhD, Radiologist, Department of Radiology and Nuclear Medicine, Oslo University Hospital, Ullevål, Oslo, Norway.  
■ E. F. Eriksen, MD, DMSc, PhD, Endocrinologist, Department of Endocrinology, Oslo University Hospital, Ullevål, Oslo, Norway and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway.

Correspondence should be sent to M. Shabestari;  
email: maziarg@medisin.uio.no

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### Objectives

Little is known about tissue changes underlying bone marrow lesions (BMLs) in non-weight-bearing joints with osteoarthritis (OA). Our aim was to characterize BMLs in OA of the hand using dynamic histomorphometry. We therefore quantified bone turnover and angiogenesis in subchondral bone at the base of the thumb, and compared the findings with control bone from hip OA.

### Methods

Patients with OA at the base of the thumb, or the hip, underwent preoperative MRI to assess BMLs, and tetracycline labelling to determine bone turnover. Three groups were compared: trapezium bones removed by trapeziectomy from patients with thumb base OA (n = 20); femoral heads with (n = 24); and those without (n = 9) BMLs obtained from patients with hip OA who underwent total hip arthroplasty.

### Results

All trapezium bones demonstrated MRI-defined BMLs. Compared with femoral heads without BMLs, the trapezia demonstrated significantly higher bone turnover (mean SD 0.2 (0.1) *versus* 0.01 (0.01)  $\mu\text{m}^3/\mu\text{m}^2/\text{day}$ ), mineralizing surface (18.5% (13.1) *versus* 1.4% (1.3)) and vascularity (5.2% (1.1) *versus* 1.2% (0.6)). Femoral heads with BMLs exhibited higher bone turnover (0.3 (0.2) *versus* 0.2 (0.1)  $\mu\text{m}^3/\mu\text{m}^2/\text{day}$ ), a higher mineralization rate (26.6% (10.6) *versus* 18.6% (11.9)) and greater trabecular thickness (301.3  $\mu\text{m}$  (108) *versus* 163.6  $\mu\text{m}$  (24.8)) than the trapezia.

### Conclusion

Bone turnover and angiogenesis were enhanced in BMLs of both the thumb base and hip OA, of which the latter exhibited the highest bone turnover. Thus, the increase in bone turnover in weight-bearing joints like the hip may be more pronounced than less mechanically loaded osteoarthritic joints demonstrating BMLs. The histological changes observed may explain the water signal from BMLs on MRI.

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### Article focus

■ Quantitative histological assessment of subchondral bone affected by bone marrow lesions (BMLs) in thumb base osteoarthritis (OA) using dynamic bone histomorphometry.

■ Increased bone turnover in BMLs of osteoarthritic joints may be further enhanced by the biomechanical stress due to weight-bearing.

### Key messages

■ BMLs in thumb base and hip OA show pronounced histological similarities of which the latter exhibited the highest bone turnover.

### Strengths and limitations

■ To our knowledge, this is the first study to assess BMLs histologically in thumb base OA.  
■ Use of identical histomorphometric analyses comparing the two distinct joint

sites with OA omits bias associated with heterogenic measurement methods.

- Lack of control sites without BMLs in the same patients and lack of bone samples from less severe stages of OA are considered the principal limitations of this study.

## Introduction

Bone marrow lesions (BMLs) are frequently seen in joints with osteoarthritis (OA) and represent a treatment target due to the association with progressive cartilage loss,<sup>1-4</sup> pain<sup>5-9</sup> and subsequent joint arthroplasty.<sup>10,11</sup> These diffusely marginated lesions usually show post-contrast enhancement, indicating hypervascularity and repair activity.<sup>12</sup> Previous publications on BMLs offer different histopathological descriptions, and there is no consensus on the tissue changes that explain the MRI findings.

Most histological studies on BMLs have been performed on small biopsies from knee joints. In a qualitative study of nine knee OA patients scheduled for total knee arthroplasty (TKA), BMLs corresponded mainly to fibrous tissue replacing the fatty marrow, and to trabecular thickening.<sup>13</sup> Zanetti et al<sup>14</sup> performed a similar study of 16 patients referred for TKA and showed that BMLs represented areas with a mixture of mainly normal bone, trabecular abnormalities, fibrosis and only 4% marrow oedema. The bone in these lesions appeared sclerotic, with increased bone volume fraction and increased trabecular thickness compared with unaffected regions in the same patient.<sup>15</sup> Shabestari et al<sup>16</sup> demonstrated increased bone turnover and angiogenesis in BMLs of hip OA.

BMLs also occur in the joints of the thumb base,<sup>17</sup> and increased knowledge about their quantitative histopathology may contribute to the development of better treatment strategies. Limited research has been performed on BMLs in hand OA despite their high prevalence, high clinical burden and diminished health-related quality of life compared with healthy controls.<sup>18</sup> Haugen et al<sup>19</sup> have previously reported that BMLs occurred in 28% of the joints with moderate to severe radiological OA, and were infrequent in joints with doubtful or no OA. BMLs were also associated with pain in the same finger joint independent of synovitis or structural OA features in both cross-sectional and longitudinal analyses.<sup>20,21</sup> Significant associations were detected between BMLs at baseline and structural progression five years later.<sup>22</sup> However, earlier studies have focused on the interphalangeal joints and we are not aware of previous studies exploring the biological role of BMLs in thumb base OA.

No data have been published to date to characterize BMLs histologically in hand OA. It remains unclear whether there are histopathologically observable differences between BMLs in joints with and those without weight-bearing. While the interphalangeal joints are rarely

operated on with joint arthroplasty, trapeziectomy is a relatively common procedure for thumb base OA which involves surgical removal of the trapezium bone. Therefore, our primary aim was to quantitatively assess bone turnover and angiogenesis in BMLs in thumb base OA and compare the results with femoral heads with and without BMLs from patients with end-stage hip OA.

## Patients and Methods

**Study populations: cases.** A total of 20 patients with thumb base OA scheduled for trapeziectomy were enrolled in this study. Indications for surgery were pronounced clinical symptoms of OA, including pain, stiffness, dysfunction and demonstration of typical signs of OA on radiographs such as osteophytes, subchondral sclerosis, cysts and joint space narrowing. The number of patients needed was based on previous studies<sup>23</sup> and was specified in the study protocol prior to ethical approval and initiation of patient recruitment. Exclusion criteria were systemic inflammatory joint diseases such as rheumatoid arthritis or psoriatic arthritis, known metabolic bone- or calcium-related disorders including malignant hypercalcaemia, medication that could affect BMLs (anabolic and antiresorptive therapy), contraindications for MRI scans and tetracycline use (hypersensitivity, liver or kidney failure, pregnancy) and known allergy to local anaesthesia or their additives.

Prior to trapeziectomy, patients had conventional radiographs taken, underwent MRI of the thumb base and completed questionnaires about demographic factors, comorbidities, medications and hand symptoms, including the Australian/Canadian (AUSCAN) pain and physical function subscales.<sup>21</sup> An investigator (IKH) with extensive previous experience in scoring hand radiographs for OA scored the first carpometacarpal (CMC-1) and scaphotrapezotrapezoidal (STT) joints for the severity of radiological OA according to the Kellgren–Lawrence (KL) scale<sup>24</sup> (0 = no OA, 1 = doubtful OA, 2 = mild OA, 3 = moderate OA and 4 = severe OA).

**Study populations: controls.** A total of 33 patients with end-stage primary hip OA,<sup>25</sup> who were scheduled for total hip arthroplasty, were recruited at the same hospital. Histological findings in most of the subjects in this cohort have been described previously.<sup>16</sup> Indications for hip arthroplasty were the same as described for trapeziectomy. Among the 33 patients with hip OA, nine femoral heads had no BMLs and these were considered as negative controls. The remaining 24 specimens were considered positive controls in the present study. The tetracycline labelling regimen for these patients was identical to the regimen given to patients planned for trapeziectomy (cases). All patients underwent a double labelling regimen with tetracycline (250 mg, four times a day; Arco, Geneva, Switzerland) that was taken orally during two consecutive days. The dosing was repeated

after two weeks. Subjects were instructed to take each dose one to two hours before a meal or two hours after a meal. Surgery was performed four to five days after the last dosage. The femoral heads were collected four or five days after the last dosage. Both studies were approved by the Regional Ethical Committee (2011/1089/REK), and written informed consent was obtained from all thumb base and hip OA patients.

**MRI: cases.** Prior to trapeziectomy, patients with thumb base OA underwent MRI, with a 1.5T scanner (Philips Achieva, Leiden, The Netherlands), of the affected carpus using a dedicated wrist coil. The MRI protocol included a T1-weighted spin echo (SE) in the coronal, sagittal and axial plane, and a short-tau inversion recovery (STIR) fast spin echo in the coronal and sagittal plane before administration of the contrast agent. A maximum 15 ml of gadolinium (Dotarem 0.5 mmol/mL; Guerbet, Villepinte, France, 0.2 ml/kg bodyweight) was injected intravenously. Following the gadolinium injection, coronal and sagittal T1-weighted (T1W) SE, and coronal T1W SE spectral pre-saturation with inversion recovery (SPIR) scans were obtained. The sesamoid bones at the first metacarpophalangeal joint were used for orientation of the planes.

The STIR images (TI/TR/TE time 160/1960/60 ms, field of view 80 mm, slice thickness 2 mm, slice gap 0.2 mm) were used to identify BMLs. The pre- and post-contrast T1W SE images (TR/TE time 500/20 ms, field of view 80 mm, slice thickness 2 mm, slice gap 0.2 mm) were used to exclude other forms of pathology such as cysts and tumours, and helped in the evaluation of BMLs. Using the T1W SPIR sequence, cartilage loss was scored as 0 = normal, 1 = more than 50% of cartilage volume preserved, 2 = less than 50% preserved and 3 = total cartilage loss.

All MRI scans were independently reviewed by two radiologists (SS and JCH) with 20 and ten years of experience in musculoskeletal radiology, respectively. In the event of a discrepancy, consensus was reached by discussion. The BMLs were described on a standardized chart (supplementary material) for each specimen. BMLs were scored as generalized when more than half of the subchondral bone demonstrated an increased signal. Otherwise, the lesion was described as focal in each trapezium bone. No reliability tests were performed for the assessments of cartilage loss or BMLs.

**MRI: controls.** The MRI acquisition and scoring protocols of BMLs in hip OA patients have been described previously by Shabestari et al.<sup>16</sup> In brief, bilateral hip MRI was performed the day before hip arthroplasty using an Excelart Vantage Atlas-Z 1.5T scanner (Toshiba, Tokyo, Japan). The presence or absence of BMLs was scored on coronal and axial STIR sequences, while location and the maximum cross-sectional area were defined manually on multiple images by one of the principal investigators (EFE) with extensive previous experience.

**Trapeziectomy and total hip arthroplasty.** One orthopaedic surgeon (NJK) confirmed the diagnosis of thumb base OA as the indication for trapeziectomy based on radiographs and hand symptoms, and performed the enrolment and surgery of all patients. The trapezium bone was removed in one piece and the distal joint surface was marked on the dorsal margin with a suture before the specimen was immersed in 70% ethanol. Femoral heads were acquired by routine surgery for total hip arthroplasty. All samples were kept at 4°C before tissue processing for histology.

**Tissue processing and histomorphometry.** Femoral heads and trapezium bones were processed as previously described.<sup>16</sup> In brief, samples were dehydrated before being embedded in methyl methacrylate without decalcification at -20°C. The embedded bone blocks were ground at the distal aspect of the trapezium until subchondral bone was reached. Thin 7 µm sections were cut in a plane perpendicular to the long axis of the diaphysis of the first metacarpal bone. Pairs of sections at least 0.5 mm apart were selected and mounted unstained for quantitative measurements or were subjected to standard Goldner's trichrome stain for qualitative description of marrow fibrosis, woven bone and cartilage loss. Histomorphometric indices, including mineralizing surface (MS), bone formation rate per unit of bone surface (BFR/BS) and mineral apposition rate, were calculated based on random sampling of fluorescent images of the tissue sections. The BFR/BS ratio was considered to be the turnover rate.<sup>26</sup>

As there is no methodological consensus for estimation of non-malignant bone marrow vessels, we estimated vascularity using a protocol developed and validated by our group against angiogenesis markers detected by quantitative immunohistochemistry.<sup>16</sup> In brief, we estimated vascular volume (eV.v) based on the autofluorescence of the tissue. Digital grids with 100 µm intervals were superimposed on random regions of interest which in total corresponded to a minimum of 15 mm<sup>2</sup> of tissue area. Images with the overlaid grids were scored on an LCD screen with a total magnification of 220×. Intersection points within vessel-like structures were counted systematically. Apart from eV.v, which is not a standard parameter, all other histomorphometric indices were measured according to American Society of Bone and Mineral Research (ASBMR) guidelines,<sup>26</sup> and reproduced with coefficient of variation = 6%.

**Statistical analysis.** Analyses were performed in IBM SPSS software version 22 (IBM Corp., Armonk, New York). Normality was checked using the Shapiro-Wilk test and visual inspection of quantile-quantile plots. Data for the MS were log transformed due to skewness and kurtosis of the distributions. For all indices, the trapezia were compared against hips with and without BMLs by one-way analysis of variance followed by Šídák's test for multiple

**Table I.** Characteristics of the study populations

| <b>Patients with BMLs in trapezia (cases, n = 20)</b> |                     |                  |
|---|---------------------|------------------|
| Age, yrs  | 60.6 (7.0)          |                  |
| Female  | 16 (80.0)           |                  |
| Body mass index, kg/m <sup>2</sup>                    | 26.7 (4.2)          |                  |
| AUSCAN pain (0 to 20)                                 | 13.2 (1.9)          |                  |
| AUSCAN stiffness (0 to 4)                             | 1.9 (1.1)           |                  |
| AUSCAN physical function (0 to 36)                    | 24.2 (6.5)          |                  |
| <b>Operated hand</b>                                  |                     |                  |
| Right   | 9 (45.0)            |                  |
| Left  | 11 (55.0)           |                  |
| <b>Radiological OA severity (n = 17)</b>              |                     |                  |
| KL 0 to 1   | <b>CMC-1</b>        | <b>STT</b>       |
| KL 2  | 1 (5.9)             | 12 (70.6)        |
| KL 3  | 3 (17.6)            | 2 (11.8)         |
| KL 4  | 8 (47.1)            | 0 (0.0)          |
|   | 5 (29.4)            | 3 (17.6)         |
| <b>MRI-defined cartilage score</b>                    |                     |                  |
| Grade 0   | <b>CMC-1</b>        | <b>STT</b>       |
| Grade 1   | 1 (5.0)             | 0 (0)            |
| Grade 2   | 4 (20.0)            | 6 (30.0)         |
| Grade 3   | 13 (65.0)           | 12 (60.0)        |
|   | 2 (10.0)            | 2 (10.0)         |
| <b>Patients with hip OA (controls, n = 34)</b>        |                     |                  |
| Age, yrs  | <b>Without BMLs</b> | <b>With BMLs</b> |
| Female, %   | 62.1 (12.1)         | 65.3 (9.1)       |
| Body mass index, kg/m <sup>2</sup>                    | 67                  | 52               |
|   | 27.8 (5.0)          | 25.9 (4.3)       |

Age, body mass index and AUSCAN values are given as mean (SD) and the rest of the data as n (%). AUSCAN, The Australian/Canadian Osteoarthritis Hand Index; OA, osteoarthritis; KL, Kellgren–Lawrence scale; CMC-1, first carpometacarpal joint; STT, scaphotrapeziotrapezoidal joint

comparisons. Values were presented as mean (SD) unless stated otherwise. A p-value < 0.05 was considered statistically significant.

## Results

Characteristics of the patients who underwent trapeziectomy are presented in Table I. The majority were women and their age ranged from 48 to 73 years. The patients reported high levels of pain, stiffness and physical disability of the hands. Pre-surgical radiographs of the thumb base were successfully acquired in 17 patients (85.0%) planned for trapeziectomy. Radiological OA severity is reported for the CMC-1 and STT joints in Table I. Four patients had OA in both CMC-1 and STT joints, whereas the majority (n = 12) had isolated CMC-1 OA. One person with no radiological evidence of OA in the CMC-1 joint had severe radiological OA in the STT joint (KL = 4).

Hip OA patients with and without BMLs in their femoral heads had similar age, body mass index (BMI) and gender distribution (Table I). We found no statistically significant differences in BMI, gender or age between the three groups (data not shown).

**Characterization of BMLs in the trapezia compared with the femoral heads.** BMLs were detected in all trapezia, and all but one trapezium bone demonstrated post-gadolinium enhancement. Focal and generalized BMLs were found in eight (40%) and 12 (60%) of the trapezia, respectively. Comparison of bone formation rates between trapezia with focal *versus* generalized BMLs revealed higher turnover in generalized BMLs (0.3 µm/day (0.1) *versus* 0.1 µm/day (0.1), p < 0.001). The difference between

e.v in the two subgroups was not statistically significant (5.8% (1.0) *versus* 5.4% (1.4), p = 0.9).

The trapezia exhibited a pronounced 22-fold and 13-fold increase of bone turnover and MS (MS/BS), respectively, followed by a four-fold increase of vascularity compared with femoral heads without BMLs. Hips with BMLs demonstrated a doubled bone turnover rate compared with trapezia (Table II). No significant differences were found for the other bone histomorphometric indices and the vascularity index. Femoral heads with BMLs demonstrated higher trabecular thickness compared with that of the trapezia. No statistically significant differences were found for trabecular number or separation (Table II).

Standard histological staining of trapezium bone sections revealed qualitative tissue changes similar to femoral heads with BMLs compared with those without (Figs 1a and 1b *versus* 1c). Fairly large cross-sectional areas of the subchondral bone affected by BMLs in trapezia were covered by woven bone (Fig. 1d). Subchondral regions closer to the articular surface demonstrated higher bone turnover evidenced by an increased proportion of BSs labelled by tetracycline, and larger areas of woven bone. Few signs of inflammation, and no signs of tissue oedema could be detected. Furthermore, moderate to advanced cartilage loss, signs of haemorrhage and fibrosis (Figs 1a and 1b) in the bone marrow and bone cysts were observed in most of the specimens.

## Discussion

To our knowledge, this is the first study investigating bone turnover and vascularity by dynamic bone

**Table II.** Bone histomorphometric data in the trapezia and the femoral heads

|  | Trapezia (with BMLs) n = 20 |                | Hips without BMLs n = 9 |                | p-value* | Hips with BMLs n = 24 |                | p-value† |
|--|-----------------------------|----------------|-------------------------|----------------|----------|-----------------------|----------------|----------|
|  | Median                      | 95% CI         | Median                  | 95% CI         |          | Median                | 95% CI         |          |
| BV/TV (%)                                      | 43.4                        | 38.0 to 49.0   | 30                      | 23.5 to 37.9   | 0.76     | 37.4                  | 33.1 to 52.5   | 0.99     |
| BS/BV (mm <sup>-1</sup> )                      | 12.7                        | 11.4 to 13.2   | 11.7                    | 10.5 to 13.5   | 0.99     | 8.5                   | 8.1 to 10.7    | 0.41     |
| BS/TV (mm <sup>-1</sup> )                      | 5.4                         | 4.9 to 5.8     | 3.5                     | 2.5 to 4.1     | 0.56     | 3.5                   | 3.2 to 3.9     | 0.21     |
| Tb.Th (μm)                                     | 157.9                       | 151.4 to 175.9 | 171.1                   | 148.4 to 189.8 | 0.99     | 270.9                 | 233.7 to 365.0 | 0.008    |
| Tb.N (mm <sup>-1</sup> )                       | 2.7                         | 2.4 to 2.9     | 1.8                     | 1.3 to 2.1     | 0.56     | 2.2                   | 1.7 to 3.3     | 0.99     |
| Tb.Sp (μm)                                     | 213.7                       | 177.3 to 269.0 | 394.3                   | 337.1 to 610.3 | 0.05     | 345.9                 | 247.4 to 426.5 | 0.14     |
| MS (mm)  | 12.3                        | 5.3 to 18.3    | 0.9                     | 0.0 to 1.8     | < 0.001  | 10.1                  | 8.3 to 12.5    | 0.49     |
| MS/BS (%)                                      | 17.1                        | 13.2 to 25.9   | 1.6                     | 0.1 to 2.0     | < 0.001  | 26.6                  | 18.9 to 30.5   | 0.002    |
| MAR (μm/day)                                   | 1                           | 0.7 to 1.1     | 0.6                     | 0.0 to 0.8     | 0.99     | 1.3                   | 1.1 to 1.5     | 0.37     |
| BFR/BS (μm <sup>3</sup> /μm <sup>2</sup> /day) | 0.2                         | 0.1 to 0.3     | 0.01                    | 0.1 to 0.3     | < 0.001  | 0.3                   | 0.2 to 0.5     | < 0.001  |
| eV.v (%)                                       | 5.3                         | 4.8 to 6.0     | 1.1                     | 0.6 to 2.1     | < 0.001  | 5.7                   | 3.9 to 6.8     | 0.99     |

\*Multiplicity-adjusted p-values for trapezia *versus* femoral heads without BMLs.

†Multiplicity-adjusted p-values for trapezia *versus* femoral heads with BMLs.

MS/BS; mineralizing surface/bone surface; MAR, mineral apposition rate; BFR/BS, bone formation rate/bone surface; BV/TV, bone volume/tissue volume; BS/BV, bone surface/bone volume; BS/TV, bone surface/tissue volume; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; eV.v, estimated vascular volume.

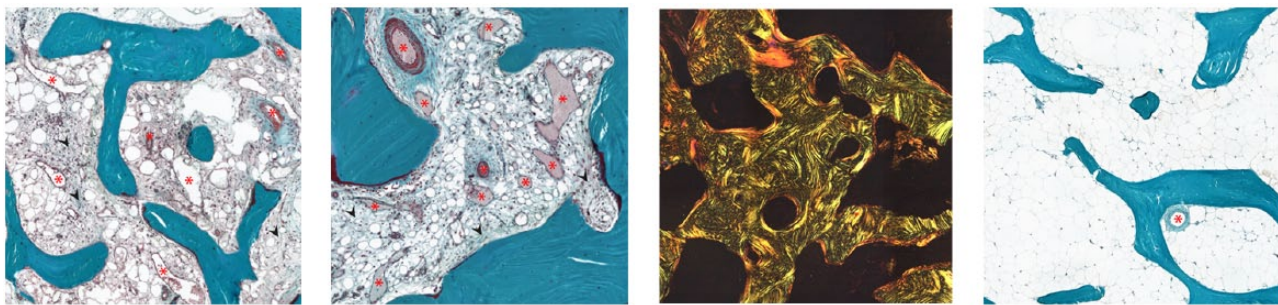


Fig. 1a

Fig. 1b

Fig. 1c

Fig. 1d

Representative histological images of subchondral bone (a, b and c) with and (d) without bone marrow lesions. Image of a section from (a) trapezium bone and (b) femoral head, demonstrating increased vascularity (asterisks) and marrow fibrosis (arrowheads). (d) Trapezium specimen imaged under polarized light showing disproportionately large area of woven bone compared with area covered by lamellar bone.

histomorphometry in patients with thumb base OA. Trapeziectomy is one of the few surgical procedures in the treatment of hand OA where a significant amount of bone is removed from the joint and can subsequently be subjected for bone histomorphometric analysis. The results of the current study show that BMLs in patients with OA in the thumb base joints are characterized by a high bone turnover accompanied by increased vascularity.

The trapezia with BMLs exhibited increased bone turnover compared with osteoarthritic bone without BMLs. The higher bone turnover is likely caused by unfavourable loading in joints demonstrating cartilage loss. In comparison with femoral heads with BMLs, the trapezia demonstrated less bone remodelling and decreased trabecular thickness, which may be due to the absence of weight-bearing in trapezium bones. Although thumb joints do not bear weight, they are subjected to biomechanical stress, especially when performing the functions of a prehensile thumb, meaning higher peak forces with a shorter duration. The two types of loading, however, may have differential effects on the subchondral bone health. It can be speculated that multiple loading cycles

during walking and the longer duration of loading in weight-bearing are more detrimental to the subchondral bone compared with short-term loads of higher magnitude, such as in grip function. This may be true despite both types of biomechanical loading being within the normal physiological threshold, and without causing acute damage.<sup>27,28</sup> The rapid response of bone tissue to altered biomechanical stress was demonstrated when small increases in foot pronation of a group of healthy adults caused BMLs only two weeks post-baseline. When the experimental overpronation was eliminated, BMLs were either reduced or completely diminished at two weeks' follow-up.<sup>29</sup> These findings are in agreement with an increased risk of the presence or progression of BMLs associated with augmented compartmental loads in the knee<sup>30</sup> and therapeutic measures aiming to improve biomechanics in joints affected by BMLs.

Vascularity was measured by histomorphometric assessment of eV.v. This index has been shown to correlate highly with immunohistological quantification of angiogenesis markers CD31 and von Willebrand Factor,<sup>16</sup> and was increased four-fold in the trapezia as compared

with the femoral heads without BMLs in the present study. Increased angiogenesis can be seen as an adaptive response to hypoxia or increased metabolic demands of the bone tissue. The contribution of angiogenesis to inflammation and synovial hyperplasia in rheumatoid arthritis is well recognized, but its importance in OA has not been extensively investigated.<sup>31</sup> Dysregulated tissue growth characteristic of all the affected musculoskeletal tissues in OA can be associated with pathological angiogenesis. Epidemiological studies have indicated a link to atheromatous diseases in patients with end-stage hip OA, suggesting an underlying disease involving systemic and vascular health.<sup>32</sup> The capacity of biomechanical stimulation to modulate vascular growth and remodelling,<sup>33</sup> and the significance of malalignment associated with an increased risk of BMLs are documented.<sup>34</sup> Still, it is not known why some OA patients exhibit BMLs while others do not. Therefore, we hypothesize that the increased angiogenesis may be due to a disproportionate bone healing response initiated by repeated microdamage in the subchondral bone.

The association of BMLs with microfractures<sup>35</sup> and reduced bone mineral density in the hip<sup>36</sup> further strengthens the importance of these lesions as therapeutic targets. The pronounced increase in bone turnover and angiogenesis observed in this study may be relevant for the choice and dosage of antiresorptive medication to reduce BMLs in OA. Bisphosphonates, most commonly used for the treatment of osteoporosis, have a well-documented inhibitory effect on bone remodelling. Previous studies on alendronate and risedronate have suggested a reduction of BMLs<sup>37</sup> but found conflicting results on pain and structural progression.<sup>37-39</sup> Zoledronic acid has been shown to reduce angiogenesis in animal models<sup>40</sup> and circulating vascular endothelial growth factor levels in humans, in addition to its antiresorptive effect.<sup>41</sup> A placebo-controlled trial in knee OA demonstrated reduced pain at six, but not three or 12, months after a single infusion of zoledronic acid.<sup>42</sup> Further research is required to determine whether long-term administration may have more consistent outcomes and whether reduced angiogenesis contributes to the clinical effect observed with bisphosphonate therapy. Due to the dearth of similar clinical trials on hand OA and the aforementioned mixed results, new clinical trials are needed to explore the potentially disease-modifying effects of these drugs on OA.

Magnetic resonance imaging scans detected BMLs in all trapezia, which may be owing to the use of intravenous contrast and a dedicated wrist coil leading to increased sensitivity to detect BMLs in patients scheduled for trapeziectomy. The vast majority of our patients had OA in the CMC-1 joint, whereas one patient had isolated STT OA, which in some cases may be post-traumatic after carpal injuries. Due to acquisition of radiographs of the thumb base only, we do not have any information about

involvement of other carpal joints, but no trauma was reported by the patient. Attempts were made to obtain cancellous bone biopsies from the distal radius at the same time as the trapeziectomy to be used as internal negative controls, but few patients consented. In addition, sufficiently large specimens for meaningful histomorphometric measurements were difficult to obtain from the radius. Consequently, bone turnover and vascularity in hand OA had to be compared with bone obtained from end-stage hip OA in patients with and without BMLs.

We acknowledge that the lack of bone biopsies without BMLs from a distant control site in the patients undergoing trapeziectomy is a limitation of the study, and hip samples were therefore used as controls. While there is known heterogeneity in risk factors for hand and hip OA,<sup>18</sup> our results suggest that the tissue changes underlying BMLs may be similar across phenotypes.<sup>43</sup> Moreover, clustering of OA progression at anatomically distant sites suggests an important role for common systemic and genetic factors.<sup>45</sup> However, there were no significant differences in age, gender and BMI between patients undergoing trapeziectomy and hip arthroplasty. The significance of the current study is related to the histological analysis of BMLs in thumb base OA, which has not been previously explored, and the observation of tissue level changes similar to those of hip OA. Our study is further strengthened by the fact that all patients underwent the same tetracycline-labelling regimen, and samples from both cohorts were processed and analyzed through identical protocols.

In conclusion, observations made in thumb base OA in this study support our previous findings in hip OA of increased bone turnover and increased vascularity, corroborating the notion that BMLs constitute a generalized response to bone injury in OA. The manifestation of higher bone turnover in hip OA than in thumb base OA mediated by BMLs is in line with the established understanding of bone as a highly mechanoresponsive tissue. The thumb base represents an anatomically distant, and physically distinct joint from the hip joint. The similarities between the observed histopathological changes in thumb base and hip joints further strengthen the concept of increased vascularity as the underlying change at the tissue level in subchondral bone affected by BMLs.

### Supplementary material



Examples of the standardized charts describing bone marrow lesions.

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#### Author Contributions

- M. Shabestari: Study conception and design, Performed the histological analyses, Execution of the analyses and interpretation of the data, Drafted the manuscript, Revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- N. J. Kise: Recruited the patients, Performed the trapeziectomies, Read and revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- M. A. Landin: Execution of the analyses and interpretation of the data, Revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- S. Sesseng: Determined the MRI protocols and interpreted the radiological data, Read and revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.

- J. C. Hellund: Determined the MRI protocols and interpreted the radiological data, Revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- J. E. Reseland: Execution of the analyses and interpretation of the data, Read and revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- E. F. Eriksen: Study conception and design, Execution of the analyses and interpretation of the data, Read and revised the manuscript critically, Gave final approval of the version to be published, Agreed to be accountable for all aspects of the work.
- I. K. Haugen: Study conception and design, Execution of the analyses and interpretation of the data, Drafted the manuscript, Read and revised the manuscript

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#### Conflict of Interest Statement

- None declared

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