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Title	Effect of periacetabular osteotomy on the distribution pattern of subchondral bone mineral density in patients with hip dysplasia
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2	density in patients with hip dysplasia	
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- 27

28 Abstract

29 Despite the availability of long-term follow-up data, the effect of pelvic osteotomy on the natural 30 history of osteoarthritis is not yet fully understood, partly because there is untapped potential for 31 radiographs to better describe osteoarthritis. Therefore, this study aimed to assess the distribution 32 of subchondral bone mineral density (BMD) across the acetabulum in patients with hip dysplasia 33 immediately (2 weeks) and 1 year after undergoing periacetabular osteotomy (PAO). To that end, 34 we reviewed 40 hips from 33 patients with developmental dysplasia of the hip (DDH) who 35 underwent PAO between January 2016 and July 2019 at our institution. We measured 36 subchondral BMD through the articular surface of the acetabulum using computed tomography 37 (CT) osteoabsorptiometry (OAM), dividing the distribution map into nine segments. We then 38 compared the subchondral BMD between 2 weeks and 1 year after PAO in each area. At 2 weeks 39 after PAO, the high-density area tended to be localized particularly in the lateral part of the 40 acetabulum, whereas 1 year after PAO, the high-density area moved to the central and lateral 41 parts. The percentage ratios of the subchondral BMD for the central-posterior, lateral-central, and 42 lateral-posterior areas relative to the central-central area were significantly decreased at 1 year 43 after PAO, as compared to those at 2 weeks after PAO. These findings suggest that loading was 44 altered by PAO to be more similar to physiological loading. Long follow-up observational study 45 is warranted to confirm the association between early changes in subchondral BMD by PAO and 46 joint degeneration.

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51 Introduction

52 Developmental dysplasia of the hip (DDH) with associated structural instability is one of the more common causes of secondary osteoarthritis^{1, 2}. Deficiency of the bony acetabulum results in 53 54 hip instability and acetabular rim overload with subsequent damage to the labrum and articular 55 cartilage³. Finite element analysis (FEA) has shown that DDH models showed stress 56 concentration in the acetabular edge and contacting femoral head, as compared to the normal hip 57 joint model⁴. As such, reducing articular cartilage contact stress by pelvic osteotomy may delay the appearance or reduce the severity of osteoarthritis^{5, 6}. Multiple types of pelvic osteotomies 58 59 have been described, with intermediate- and long-term clinical and radiographic results, 60 suggesting that these procedures can prevent the progression of DDH to secondary osteoarthritis⁷⁻¹⁰. However, despite the availability of long-term follow-up data, the effect of 61 62 pelvic osteotomy on the natural history of osteoarthritis is not yet fully understood, partly 63 because there is untapped potential for radiographs to better describe osteoarthritis.

64 The pattern of subchondral bone density reportedly reflects the distribution of cumulative 65 stresses acting on a joint surface under actual loading conditions¹¹. As early changes in the 66 subchondral bone can predict subsequent symptoms or disease structural progression, new tools 67 may help clinicians to stratify different osteoarthritis phenotypes based on bone remodeling status¹². Given this theoretical background, Müller-Gerbl et al. have developed a method of 68 69 computed tomography (CT) osteoabsorptiometry (CTOAM) to assess the long-term stress 70 distribution of individual joints in living subjects by measuring subchondral bone density as a surrogate for cumulative stress and loading abnormalities^{11, 13}. Using this method, previous 71 72 studies have evaluated the stress distribution of different joints under various loading conditions, from normal to pathologic or postoperative conditions¹⁴⁻¹⁸. Focusing on the hip joint, a previous 73

study reported significant differences in the severity and patterns of loading based on the severity of dysplasia, as compared to the control group¹⁸. Therefore, CTOAM could detect the effect of pelvic osteotomy, as the subchondral bone mineral density (BMD) changes over time after PAO would be a good surrogate measure for loading changes.

We hypothesized that periacetabular osteotomy (PAO) would change the distribution of subchondral bone density across the acetabulum. In the present study, a modified method of CTOAM was employed to test this hypothesis^{19, 20}. Thus, this study aimed to assess the distribution of subchondral BMD across the acetabulum in patients with DDH immediately (2 weeks) and 1 year after undergoing PAO.

83

84 Methods

85 Subjects

86 This study was retrospective cohort study (level of evidence, level III). This study was 87 conducted in accordance with the ethical standards of the Declaration of Helsinki and was 88 approved by our Institutional Review Board (#017-0508). A total of 41 hips from 34 patients (4 89 males and 30 females) with DDH underwent PAO between January 2016 and July 2019 at our 90 institution. This study only included 40 hips, excluding one patient who delayed rehabilitation 91 due to fracture of the posterior column. The mean age of the patients at surgery was 32.8 years (range, 14-55 years), and the mean body mass index (BMI) was 23.1 kg/m² (range, 17.8-37.9 92 93 kg/m^2) (Table 1). Surgical indications for PAO included acetabular dysplasia with a lateral center of edge (CE) angle $<20^{\circ}$ and discontinuity of the Shenton's line²¹, unsuccessful 6-month 94 95 nonoperative treatment, age <60 years, an excellent or grade of the preoperative joint congruency in abduction according to classification of joint congruency described by Yasunaga²², and no 96

97 pain on hip flexion and extension with the extremity held in abduction²³.

98 Surgery and rehabilitation

99 All osteotomies were performed by one of four board-certified, fellowship-trained 100 orthopedic surgeons at a single institution. The type of PAO used was eccentric rotational 101 acetabular osteotomy $(ERAO)^{23}$, an improved version of rotational acetabular osteotomy²⁴. The operative techniques have been described previously²³. Briefly, a 20-cm curved skin incision was 102 103 made 5 cm proximal to the tip of the greater trochanter. The greater trochanter was then retracted 104 proximally after completion of osteotomy at its base, with an approximate thickness of 10-15 105 mm, and the gluteus minimus and medius muscles were reflected approximately 30 mm from the 106 acetabular rim. The osteotomy site was approximately 15–20 mm or greater from the joint space 107 according to the preoperative planning. Following osteotomy of the ilium and pubis, the 108 acetabular fragment was rotated easily, wherein trimming of the inner cortex of the ilium was 109 essential for medializing the acetabular fragment. Coverage of the femoral head by the rotated 110 acetabular fragment was verified using an image intensifier before fixation of the acetabular 111 fragment with two or three polylactide screws. Afterwards, the greater trochanter was 112 repositioned and fixed with two AO cancellous screws. Postoperatively, one-third partial weight-113 bearing was permitted with a walker after 4 weeks, one-half partial weight bearing was permitted 114 after 6 weeks, and full weight-bearing was allowed after 8 weeks. One year after PAO, the 115 patients underwent surgery to remove the two AO cancellous screws.

116 Clinical and radiological evaluation

117 Clinical evaluations were performed using the Harris hip score (HHS)²⁵ and the Japanese 118 Orthopedic Association Hip-Disease Evaluation Questionnaire (JHEQ)²⁶ preoperatively and 1 119 year after PAO. Range of motion was measured by goniometry. Supine anterior–posterior (AP) 120 pelvic radiographs and CT scans were taken preoperatively, 2 weeks after PAO, and 1 year after 121 PAO (average radiation exposure per examination, 5.5 mSv). The radiographs were obtained using Siebenrock's standardized technique²⁷, and the CE angle, Sharp angle, acetabular head 122 index (AHI)²⁸, and acetabular roof obliquity (ARO) were evaluated²⁹. All digital measurements 123 124 and calculations were performed using the Centricity[™] Web-J 3.0 HD software (GE Healthcare 125 Japan, Tokyo, Japan). Measurements were performed two times with a 3-month interval by the 126 first two authors (T.S. and N.Y.), showing almost excellent intra- and inter-class correlation 127 coefficients (0.943, P < 0.001, and 0.873, P < 0.001; respectively). A high-resolution (pixel 128 matrix, 512 × 512) helical CT scanner (CT High Speed Advantage; GE Medical Systems, 129 Milwaukee, WI, USA) was used to obtain axial images of the bilateral hips with an intensity 130 calibration phantom (B-MAS200, Kyoto Kagaku, Kyoto, Japan). The slice thickness and interval 131 were set to 1 mm each, and the table speed was set to 1 mm/s. Imaging data were analyzed using 132 the Aquilion One image analysis system (Toshiba Medical Systems, Tokyo, Japan), and a three-133 dimensional bone model was generated from the axial image stack. Thereafter, anterior pelvic 134 plane-based coronal views at 1-mm intervals were reconstructed using the multiplanar 135 reconstruction model.

To evaluate subchondral bone density, we used OsteoDens 4.0, a noncommercial software developed at our institution¹⁶⁻¹⁹. The target area was the subchondral bone region of the weight-bearing acetabular surface. In the coronal image, the region-of-interest was manually selected to include the entire subchondral bone layer of the acetabulum in all slices, numbering an average of 102.4 coronal slices (range, 92–115 slices) to capture the acetabulum. After establishing the region-of-interest, we automatically measured the subchondral bone of the undersurface of the acetabular at each coordinate point at 1-mm intervals in Hounsfield units 143 (HU), which is defined as the radiograph attenuation whereby water is 0 and compact bone is 144 1000 (Fig. 1). Measurement and mapping were repeated in each slice, and the data were stacked 145 to create a two-dimensional mapping image showing the distribution of subchondral bone 146 density. We then divided the acetabulum automatically into three equal parts following the front-147 back and medial-lateral directions, and the measured target area was divided into nine regions: 148 medial anterior (MA), medial central (MC), medial posterior (MP), central anterior (CA), central 149 center (CC), central posterior (CP), lateral anterior (LA), lateral central (LC), and lateral 150 posterior (LP) (Fig. 1B). The mean bone density, corrected using the phantom (B-MAS200, 151 Kyoto Kagaku, Kyoto, Japan), was measured for each region. Additionally, to evaluate the 152 distribution, we investigated the ratios of the subchondral BMD of each area to that of the CC 153 area.

154 Furthermore, we calculated the intra- and interobserver reproducibility of the CTOAM 155 based on the five consecutive measurements and based on the measurements of the two 156 orthopedic surgeons (T.S. and N.Y.), respectively. The reliabilities between and within each 157 observer were calculated according to the intraobserver, interobserver, and residual variances 158 estimated by the analysis of variance table based on Proc Mixed in the SAS software (SAS 159 Institute, Cary, NC, USA). The intra-class correlation coefficients for intra- and interobserver 160 reproducibility were 0.86 (95% confidence interval [CI], 0.73-0.97) and 0.79 (95% CI, 0.65-161 0.91), respectively.

162 Statistical analysis

Paired *t*-tests with Bonferroni correction were used to compare the clinical evaluation and BMD of the subchondral bone preoperatively, 2 weeks after PAO, and 1 year after PAO. Correlations between BMI and subchondral BMD were performed using Pearson's product– 166 moment correlation coefficient. All statistical analyses were performed using the IBM SPSS 167 version software (SPSS Inc., Chicago, IL, USA), and statistical significance was set at p < 0.05.

168

169 **Results**

170 Demographic characteristics, clinical score, and radiographic parameters

Table 1 summarizes the longitudinal clinical scores and radiographic parameters in this study. Although internal rotation was limited at 1 year postoperatively (P = 0.005), clinical scores, including the HHS and JHEQ, were significantly improved, as compared to those preoperatively (P < 0.001). The mean CE angle and mean AHI increased, whereas the mean Sharp angle and mean ARO decreased significantly from the preoperative to postoperative values (all P < 0.001).

177 Analysis of patients treated with PAO

178 At 2 weeks after PAO (immediately after surgery), the high-density area tended to be 179 localized in the lateral part of the acetabulum (Fig. 2A), whereas at 1 year after PAO, the high-180 density area moved to the central and lateral parts. In the quantitative evaluation of the 181 subchondral BMD calibrated according to the phantom, mean BMD values in the medial, CA, 182 and CC areas at 1 year after PAO were significantly higher than those at 2 weeks after PAO (Fig. 183 2B). To evaluate subchondral BMD distribution, we investigated the ratios of the subchondral 184 BMD of each area to that of the CC area (Fig. 2C). The percentage ratios of the subchondral 185 BMD for the CP, LC, and LP areas relative to the CC area were significantly decreased at 1 year 186 after PAO, as compared to those at 2 weeks after PAO. No significant associations between BMI 187 and subchondral BMD were observed (Supplemental Table 1).

189 **Discussion**

190 Clinically, PAO has been reported to be an effective treatment for early osteoarthritis in young or active patients with DDH³⁰⁻³². Moreover, this study showed the significant improvement of HHS 191 192 and patient-based clinical outcomes (JHEQ) from preoperative to 1 year after surgery. Despite 193 this, although simulation studies using finite or discrete element analysis showed alterations of 194 contact stress by PAO^{4, 33}, findings on changes in the mechanical environment due to PAO have 195 not yet been fully clarified. In this study using CTOAM, we found that PAO shifted the area with 196 the highest subchondral BMD from the lateral to the central region and reduced the ratio of 197 subchondral BMD in the CP, LC, and LP areas relative to that in the CC area, thus confirming 198 our hypothesis.

199 The finding that the subchondral BMD on the lateral side tended to be higher than that on 200 the medial and center areas at 2 weeks after PAO showed a similar tendency to a previously 201 described study on severe dysplasia subjects¹⁸, suggesting that CTOAM data at 2 weeks after 202 PAO may reflect the preoperative mechanical environment. Moreover, the finding that the 203 subchondral BMD in the central area tended to be higher than that in other areas at 1 year after 204 PAO showed a similar tendency to the control subjects ($25^{\circ} < CE$ angle $< 35^{\circ}$) of that same 205 study¹⁸. Although one of the main limitations of the current study was the indirect measure of 206 mechanical stress with acetabular subchondral BMD using CTOAM, we believe that these 207 findings suggest that loading was altered by PAO to be more similar to physiological loading.

208 Contrary to our expectations and previous reports using FEA^{34, 35}, this study showed that 209 the absolute subchondral BMD in the medial, CA, and CC areas increased significantly from 2 210 weeks to 1 year after PAO. Since PAO transfers the medial part, which is considered to be a 211 lower mechanical stress area, to the central area, it is possible that the subchondral BMD in the 212 medial and central areas were relatively low at 2 weeks after PAO. Furthermore, it is possible 213 that this finding may have been affected by the limitation of weight-bearing immediately after 214 PAO. However, since this study was only a 1-year longitudinal follow-up study, a longer follow-215 up period is necessary to address whether the increase in subchondral BMD from 2 weeks to 1 216 year after PAO would affect future joint degeneration.

217 Despite these findings, this study had a few limitations. First, we could not directly 218 measure the contact stress pressure and stress distribution patterns in the live patients' hips. 219 However, the measurements of BMD were more clinically accessible. Second, although we 220 performed fixation of the acetabular fragment with two or three polylactide screws and compared 221 the CT data on the same setting between 2 weeks and 1 year after PAO, the artifact from the 222 screws could have affected BMD distribution in this setting. Third, postoperative alterations in 223 the pattern of subchondral bone mineralization may depend not only on the biomechanical 224 effects of PAO but also on the individual loading conditions. To clarify this point, we should 225 perform further analysis based on CT data from more patients treated with PAO. Fourth, this was 226 a short follow-up observational study. Although we targeted the early changes in the subchondral 227 bone during PAO, a longer follow-up study is required to understand the association between 228 subchondral BMD and joint degeneration. Finally, because reductions in vascular supply are 229 associated with bone loss³⁶, BMD may also depend on the vascularity of the acetabular fragment. 230 As this study did not investigate the vascularity of the acetabular fragment, further studies should 231 address this concern in the future.

In conclusion, the findings of this study using the CTOAM method suggest that loadingwas altered by PAO to be more similar to physiological loading. Long follow-up observational

 BMD by PAO and joint degeneration. Acknowledgements 	234	studies should be performed to confirm the association between early changes in subchondral
236237Acknowledgements	235	BMD by PAO and joint degeneration.
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- 340

341 Figure legends

Fig. 1. (A) The image shows how the subchondral bone region of the acetabulum was identified automatically using the customized software. In each coronal slice, we measured the Hounsfield units of radiograph absorption in the subchondral bone at each coordinate point in 1-mm intervals. For quantitative analysis, the distribution pattern is represented as a surface-mapping image depicted by a color scale. (B) The image shows segments used for quantitative analysis of the bone density mapping data for the acetabulum.

Fig. 2. (A) The images show the distribution of bone density values across the articular surface of the acetabulum at 2 weeks and 1 year after periacetabular osteotomy. (B) Comparisons of the subchondral bone mineral density between 2 weeks and 1 year after periacetabular osteotomy in each area. (C) Comparisons of the percentage ratio of each area relative to the subchondral bone mineral density in the central center area between 2 weeks and 1 year after periacetabular osteotomy. Data are presented as means \pm standard deviation. Asterisks indicate P < 0.05.

A ## 1.6 0.1 1.2 1.2 0.4 Bone mineral density, g/cm³

В

Medial Anterior (MA)	Central Anterior (CA)	Lateral Anterior (LA)
Medial Central (MC)	Central Central (CC)	Lateral Central (LC)
Medial Posterior (MP)	Central Posterior (CP)	Lateral Posterior (LP)



А