Serial bone mineral density ratio measurement for fixator removal in tibia distraction osteogenesis and need of a supportive method using the pixel value ratio

Sang-Heon Song\textsuperscript{a,}\textsuperscript{*}, Mandar Agashe\textsuperscript{a,}\textsuperscript{*}, Tae-Young Kim\textsuperscript{c}, Shivam Sinha\textsuperscript{a}, Young-Eun Park\textsuperscript{a}, Seung-Ju Kim\textsuperscript{a}, Jin-Ho Hong\textsuperscript{a}, Sang-Youn Song\textsuperscript{b} and Hae-Ryong Song\textsuperscript{a}

Distraction osteogenesis is one of the common procedures for limb lengthening. However, attempts are being made constantly to establish objective guidelines for early and safe removal of a fixator using a sensitive and quantitative measurement technique. Dual-energy X-ray absorptiometry (DEXA) has been evaluated in the past for understanding callus stiffness, and the present study is a step further in this direction. The purpose of this study was to evaluate the correlation between bone mineral density ratio (BMDR) obtained by a DEXA scan and the pixel value ratio (PVR) on plain digital radiographs at each cortex and various callus pathways and callus shapes as described by Ru-Li’s classification. A retrospective analysis of 40 tibial segments in 23 patients operated upon for various indications for limb lengthening was carried out. There were 11 male and 12 female patients with a mean age of 18 years. The Ilizarov method was applied after monofocal osteotomy, and distraction and consolidation were monitored using digital radiographs and DEXA scanning. BMDR was positively correlated with PVR, and the optimal BMDR for removal of the fixator was found to be 0.511. PVR of all cortices, except the anterior cortex, showed significant positive correlation with BMDR of the regenerate. There was good correlation between BMDR and PVR in the homogenous or heterogenous pathway according to callus shape and pathway. Thus, this study shows that BMD measurement can provide an objective and noninvasive method for assessing the rate of new bone formation during tibial distraction osteogenesis. It can thus function as an effective adjunct to measure callus stiffness, along with PVR, using digital radiographs, especially in cases in which callus maturation and stiffness is doubtful. Further studies especially dealing with callus progression through the lucent pathway as well as those dealing with regenerate fractures may be needed to conclusively prove the efficacy of this method for measurement of callus maturation. J Pediatr Orthop B 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: bone mineral density ratio, distraction osteogenesis, dual-energy X-ray absorptiometry, pixel value ratio

\textsuperscript{*}Department of Orthopaedic Surgery, Institute for Rare Diseases, Korea University Medical Center, Guro Hospital; \textsuperscript{a}Department of Chemistry, Kyunghee University, Seoul and \textsuperscript{b}Department of Orthopaedic Surgery, Hallym University Sacred Heart Hospital, Anyang, Korea

Correspondence to Hae-Ryong Song, MD, PhD, Department of Orthopaedic Surgery, Institute for Rare Diseases, Korea University Medical Center, Guro Hospital, 80, Guro-Dong, Guro-Gu, Seoul 152-703, Korea Tel: +82 2 2626 3086; fax: +82 2 2626 1164; e-mail: songhae@korea.ac.kr

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Introduction

Research is in progress to define callus maturation and corticalization and, hence, the ideal time for removal of the fixator. Early removal of the fixator may lead to fracture of the regenerate, whereas prolonged use leads to joint stiffness, pin-site infection, and discomfort to the patient, as well as delayed complications like subsidence and angulation [1,2].

Indirect quantitative methods measuring callus progression, such as dual-energy X-ray absorptiometry (DEXA) and ultrasonography, have been evaluated in the literature [3,4]. Estimation of the pixel value ratio (PVR) is a recent method for indirect measurement of callus stiffness and was found to correlate well with bone mineral density ratio (BMDR) [5] with respect to Ru-Li’s system of classification of callus pattern [6]. DEXA also used to measure bone mineral accretion rate in the early distraction phase. From an early phase, it can be used to predict the behavior of a given limb segment undergoing lengthening, allowing planning of additional procedures such as bone grafting or adjustment of lengthening rate in later phases [7].

There is no system of classification that shows how the regenerate should progress during lengthening and how its tensile strength and stiffness can be measured. Very few studies have been carried out to measure callus stiffness directly. In addition, to date, no objective criteria have been delineated for deciding the exact time for fixator removal [8,9].

Recently, factors influencing callus subsidence were identified, and callus maturation was assessed using BMDR. BMDR was recommended as one of the criteria for fixator removal [8,9].
to decide the time of fixator removal and prevent delayed callos subsidence [1,10].

Usually, BMD measurements are taken in a single-dimension (anterior–posterior) view, and PVR is measured on a two-dimensional plane (anterior–posterior and lateral). Hence, we sought to determine whether serial BMDR in a single dimension can be used to define corticalization with respect to each cortex separately. We hypothesized that serial BMDR in a single dimension correlates with serial PVR at each cortex in two-dimensional radiograms and that BMDR correlates with PVR in various callus pathways and patterns.

Materials and methods

A retrospective analysis of 40 tibial segments in 23 patients who underwent the tibial lengthening procedure between 2003 and 2006 was carried out. The mean age of the patients was 18 years (range 5–48 years). There were 11 male and 12 female patients, of whom eight were skeletally mature. Indications for limb lengthening were achondroplasia (10 patients), limb-length discrepancy (six patients), and idiopathic short stature (one patient). Of the remaining six patients, one patient each showed other miscellaneous indications like Blount’s disease, hypochondroplasia, genu varum, genu valgum, spondyloepiphyseal dysplasia, and Turner’s syndrome. During the study period, a single pediatric orthopedic surgeon (H.R.S.) at our institute performed the tibial-lengthening procedure on all patients using the Ilizarov external fixator. Routine preoperative planning, intraoperative procedure, and postoperative protocol were followed for all patients.

The purpose of the present study and chances of radiation exposure were explained to the patients and their parents, and the study was carried out after obtaining an informed consent according to the IRB approval.

Measurement of bone mineral density ratio and pixel value ratio

BMD was measured using a Hologic QDR 1000 instrument (Hologic Inc., Waltham, Massachusetts, USA). Three regions of interest (ROIs) were evaluated: proximal (from the osteotomy site to the proximal ring), callus, and distal (between the distal ring and the osteotomy) (Fig. 1). The BMDR was calculated as the ratio of the BMD value of the regeneration area to the average BMD value of the proximal and distal areas using the following formula:

\[ \text{BMDR} = \frac{\text{Regenerate BMD}}{(\text{Proximal BMD} + \text{Distal BMD}) / 2}. \]

PVR was measured on standard radiograms using the STAR PACS PiView STAR 5.0.6.1 software (INFINITT Co. Ltd, Seoul, Korea). The pixel value was measured using the pixel lens included in the tools of the picture archiving communication system workstation (Fig. 2a).

The pixel value of the proximal, distal, and regeneration area was calculated from the mean value of each area using the free line ROI method (Fig. 2b). Care was taken to avoid any metal, such as Ilizarov wires or posts, which might create artifacts and give false values for PVR. For two-dimensional analysis, we evaluated both anterior–posterior and lateral radiographs. We divided medial and lateral cortices on the anterior–posterior radiogram and anterior and posterior cortices on the lateral radiogram, which were between the cortices and anatomical axis (Fig. 3). At the regenerated area, we measured the pixel values of each segment. The PVR of the regenerate was then calculated using the following formula:

\[ \text{PVR} = \frac{(\text{Proximal pixel value} + \text{Distal pixel value})}{2} / \text{Regenerate pixel}. \]

As the raw pixel value was measured and expressed in terms of the monochrome 1 photometric interpretation of the digital imaging communication in medicine protocol, which is inversely related to radiopacity, the raw-pixel value was found to decrease with an increase in radiopacity.

To test interobserver and intraobserver variability of the PVR and BMDR, three observers performed the measurements [one senior pediatric orthopedic surgeon (H.R.S.) and two pediatric orthopedic fellows (S.S. and S.H.S.)]. These three observers evaluated all patients every week during the distraction period and every 4 weeks during the consolidation period. Each digital radiogram was evaluated by them according to the callus shapes and pathways using the classification of Li et al. [6].

The radiographs were reviewed twice by each reviewer, with a minimum interval of 2 weeks. The radiographs were presented in different orders for the second reading by shuffling the identification number list that was supplied. Before beginning the study, reviewers were provided with a written description of the radiographic assessment, with special emphasis on the points for which the value should be measured. The descriptions were presented again before the second set of evaluations.

Follow-up

Three surgeons evaluated all patients clinically and radiologically every week during the distraction phase and every 4 weeks during the consolidation phase. After the desired limb length was achieved, lengthening was stopped. When the PVR reached 1 in all three callus segments after the consolidation phase, the external fixator was removed and the patients were permitted full weight bearing without crutches.

Statistical analysis

The PVR and BMDR were compared using Pearson’s correlation analysis. Intraobserver and interobserver variabilities were also tested using the intraclass correlation analysis.
Under the assumption that changes in the values of PVR are directly due to changes in BMDR, an appropriate statistical analysis called the linear mixed model was used to analyze the relationship of serial PVRs with BMDR values after adjusting for the period of follow-up and laterality of limb (unilateral or bilateral). When using the linear mixed model, we considered the covariance structure as one with compound symmetry or an autoregressive model with an order of 1. Similar analysis was used for each of the various callus shapes and pathways. All statistical analyses based on a two-sided test were carried out using the SAS program (version 9.2; SAS Institute Inc., Cary, North Carolina, USA). We regarded a $P$ value of less than 0.05 as statistically significant.

**Results**

The mean dimension of lengthening was 7.7 cm (range 2.5–10.9 cm). The mean duration of Ilizarov application was 8.2 months (range 5.1–15 months). The mean external fixator index was 32 days/cm.

Two types of calluses were predominantly obtained: cylindrical (68.4%) and fusiform (30.9%). The predominant pathways found in our study were homogenous (52.5%) and heterogenous (42.5%), whereas the percentage of lucent pathway was very low (5%) (Table 1).

The interobserver correlation coefficient was found to be highly significant for the proximal segment (0.917), distal segment (0.879), and posterior cortex (0.929). However, there was poor interobserver reliability for the medial cortex (0.006), anterior cortex (0.004), and lateral cortex (0.048).

The correlation between BMDR and PVR, which was analyzed separately, was significant, and the $P$ value obtained using a statistical method was less than 0.001. According to the correlation equation, $\text{PVR} = 0.8854 + 0.2242 \times \text{BMDR}$ and $R^2$ value = 0.5111, which shows about 51% concordance between the values (Fig. 4).

The relationship between the PVRs of the four cortices of the regenerate measured separately on two-dimensional radiographs with the BMDR of the regenerate in a single dimension was studied. All four cortices showed a positive association with the BMDR, and the linear model analysis revealed a significant $P$ value for lateral ($P < 0.001$), medial ($P < 0.001$), and posterior ($P < 0.001$) cortices. The association was not established between the BMDR and PVR of the anterior cortex ($P = 0.897$) (Table 2) (Fig. 5).

The relationship between the BMDR and PVR according to the callus shape and pathway was statistically analyzed.

<table>
<thead>
<tr>
<th>Region</th>
<th>Area (cm$^2$)</th>
<th>BMC (g)</th>
<th>BMD (g/cm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>2.86</td>
<td>1.34</td>
<td>0.468</td>
</tr>
<tr>
<td>R2</td>
<td>5.02</td>
<td>0.53</td>
<td>0.106</td>
</tr>
<tr>
<td>R3</td>
<td>4.58</td>
<td>2.28</td>
<td>0.498</td>
</tr>
</tbody>
</table>

Image showing the assessment of bone mineral density in different areas. R1, proximal segment; R2, callus regenerate area; R3, distal segment. The chart shows the different values obtained.

Fig. 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Area (cm$^2$)</th>
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<tr>
<td>R3</td>
<td>4.58</td>
<td>2.28</td>
<td>0.498</td>
</tr>
</tbody>
</table>
Significant relationship between cylindrical shape and homogenous pathway ($P = 0.004$), fusiform shape and homogenous pathway ($P = 0.001$), cylindrical shape and heterogenous pathway ($P = 0.003$), and fusiform shape and heterogenous pathway ($P = 0.004$) was found. However, because of the small number of observations in the lucent pathway, no relationship between BMDR and PVR could be established (Table 1) (Fig. 6).
Discussion

Plain radiographic assessment of callus maturation, being highly subjective, has not been regarded as the gold standard until now. Many studies have reported radiographic evaluation of the callus and have tried to obtain guidelines for fixator removal. However, no safe limits have been obtained to date.

In addition to radiologic appearance, bone mineral concentration assessment has been studied by many authors to predict the stiffness of the regenerated segment. The bending rigidity of the newly formed callus was found to correlate closely with the mineral matrix ratio of the regenerate [11], and the calcium content of the callus was found to be a reliable indicator of the mechanical strength of fracture healing [12,13]. This suggests that the strength of a callus can be assessed by measuring the bone mineral density of the callus regenerate.

The DEXA scan has been popularized for its strong reproducibility and strong correlation with torsional stiffness, as well as with the calcium content of the regenerate in animal studies [14,15]. DEXA has previously been used in assessing and monitoring new bone formation during callus lengthening [3,16]. It is a valid and reliable method to quantify bone mineral accretion of the regenerate [17], with good correlation between imaging and biomechanical characteristics [9].

However, owing to its high cost, inability to detect soft tissue changes, and poor measurements in the presence of artifacts, its routine use is not popular.

Recently, Saran et al. [18] used serial DEXA scans and removed the fixator once the BMD had plateaued to a less than 10% increase. With an average of 1.3 (range 0–3) cortices formed at the time of fixator removal, the investigators did not observe postoperative fractures.

However, they cautioned against the sole use of DEXA in deciding the timing, and advised the use of radiographs along with it. In contrast, our study used more sensitive and definite parameters in terms of BMDR and PVR as an objective measure to quantify bone healing using DEXA and radiographs. We advise the use of radiographs only in specific callus patterns (atypical, concave, lateral, and central) and the lucent pathway and have found serial BMDR to be sensitive enough for common pathways followed in most of the lengthening procedures.

Our study is one of the few studies examining the efficacy of serial DEXA measurements to provide guidelines for fixator removal in all diagnoses that require distraction osteogenesis or deformity correction using an

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Table 1 Relationship of pixel value ratio of the regenerate with bone mineral density ratio for each of various callus pathways and shapes

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Shape</th>
<th>No.</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenous (52.5%)</td>
<td>Cylindrical</td>
<td>218</td>
<td>0.104</td>
<td>0.034</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>78</td>
<td>0.563</td>
<td>0.100</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heterogeneous (42.5%)</td>
<td>Cylindrical</td>
<td>155</td>
<td>0.169</td>
<td>0.038</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>83</td>
<td>0.126</td>
<td>0.046</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lucent (5%)</td>
<td>Cylindrical</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

P values were obtained from the linear mixed model of the pixel value ratio on bone mineral density ratio after adjusting for the period of follow-up (or measuring time) and left leg vs. right leg.

---

Table 2 Relationship of pixel value ratio of various cortices with bone mineral density ratio of the regenerate

<table>
<thead>
<tr>
<th>Pixel value ratio</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>0.005</td>
<td>0.041</td>
<td>0.897</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.255</td>
<td>0.056</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medial</td>
<td>0.178</td>
<td>0.028</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.239</td>
<td>0.045</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regenerate</td>
<td>0.129</td>
<td>0.023</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P values were obtained from the linear mixed model of pixel value ratio on bone mineral density ratio after adjusting for the period of follow-up (or measuring time) and left leg vs. right leg.

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Fig. 4

y = 0.2242x + 0.8854

$R^2 = 0.5111$

Linear correlation between the bone mineral density ratio (BMDR; X-axis) and pixel value ratio (PVR; Y-axis).

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In addition to radiologic appearance, bone mineral concentration assessment has been studied by many authors to predict the stiffness of the regenerated segment. The bending rigidity of the newly formed callus was found to correlate closely with the mineral matrix ratio of the regenerate [11], and the calcium content of the callus was found to be a reliable indicator of the mechanical strength of fracture healing [12,13]. This suggests that the strength of a callus can be assessed by measuring the bone mineral density of the callus regenerate.

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Our study is one of the few studies examining the efficacy of serial DEXA measurements to provide guidelines for fixator removal in all diagnoses that require distraction osteogenesis or deformity correction using an
Ilizarov ring fixator. Our study proves that there is a significant correlation between BMDR and PVR and that various pathways and callus patterns show different relationships with respect to BMDR. This knowledge can be applied to monitor callus progression in various pathways, and any decision regarding possible intervention can be taken well in time to avoid complications.

Interoobserver variability was not consistent in any of the four cortices, being poor in medial and anterior cortices.
This signifies that the values of PVR are not interdependent among the four cortices. In addition, a potential error of selection of ROI among the observers might be present. All four cortices showed a significant positive correlation between PVRs and BMDRs of the regenerate, except for the anterior cortex. The probable

Different linear correlation between the bone mineral density ratio (BMDR; X-axis) and the pixel value ratio of each callus shape and pathway (PVR; Y-axis). In homogenous pathways, cylindrical (a) and fusiform (b) callus showed statistically significant relationship between BMDR and PVR. Also in heterogenous pathways, cylindrical (c) and fusiform (d) callus showed significant relationship.
explanation is that mineralization is delayed because of a poor soft tissue envelope around this cortex and poor blood supply as compared with regions having better soft tissue coverage. Even when PVR is poor at the anterior cortex, PVR of the posterior cortex can be higher because of different maturation of the callus with a better blood supply, but BMDR, which was obtained on a single-dimension scan, seems to be high. Thus, we may conclude that supportive use of PVR is essential, especially when BMDR is unexpectedly high, compared with the lateral radiogram, which has poor consolidation.

There may be an optimal time for fixator removal when the regenerate is adequately mineralized; after this, removal avoids further stress protection effects [10]. As seen in our study, BMDR correlates significantly well with PVR; hence, we can decide guidelines for removal of the fixator based on our equation: PVR = 0.8854 + 0.2242 × BMDR or BMDR = (PVR – 0.8854)/0.2242

The optimal PVR suggested recently by Zhao [10] is more than 1 for more than three cortices. Hence, optimal BMDR according to the above-mentioned equation becomes 0.511. We may thus consider it safe to remove the fixator when BMD of the regenerate becomes 51.1% mature in terms of BMD values of the reference cortex; however, supportive use of PVR is recommended.

As our study included patients of varied ages and of different pathologies, there could be a risk of refracture or poor bone quality, which might vary from patient to patient. However, Maffulli et al. [17] showed that bone mineral accretion after removal of the fixator proceeds in a similar manner regardless of the cause of limb length discrepancy. They showed that mineralization of the regenerate after completion of the lengthening process reaches values significantly greater than those at baseline, with an increase of more than 50% in prelengthening values, regardless of the pathology. It is likely that at least part of this increase is due to the normal process of growth and development, before the end of growth [7]. Hence, we can assume that the risk of refracture in our patients is not pathologically dependent.

The major drawback of our study is that none of the patients had refracture as a complication, and hence we could not obtain a control group for comparison. In addition, none of the patients exhibited other patterns of callus (concave, lateral, or central type). Hence, a correlation could not be established with pathways and callus patterns of poor prognosis. Therefore, it was difficult to draw a firm conclusion on how DEXA influences the time in the fixator or the rate of complications. However, the parameters of regenerate fractures and bone healing indices have been reported in multiple other studies [2,19–22], which served as historical controls, but none of these studies used PVR or BMDR as healing indices.

Another drawback of our study is that we did not analyze the BMDR of all four cortices of the regenerate separately, like Eyres et al. did, and presumed our values to be constant throughout the regenerate [16]. Further studies are required to refute this assumption that BMDR is constant for all regions and cortices of the regenerate. However, as previously documented, there was a gradient between the sides where the fixator was applied (medial or lateral) showing low values on the side where the fixator was applied [3,23]. There is no question of such a gradient between medial and lateral cortices in our study, as we have used an Ilizarov circular ring fixator for the distraction osteogenesis in every case.

The advantage of our study is that we propose a serial BMDR, which has a strong correlation with mechanical stiffness [14,15], as a widely available and sensitive option for indirect measurement of callus stiffness. It has a fair association with common pathways followed in callus consolidation and can be used as a parameter to decide time of fixator removal.

We thus conclude that BMD measurement can provide an objective and noninvasive method for assessing the rate of new bone formation during tibia distraction osteogenesis and can provide safe guidelines for fixator removal. It can thus act as a valuable adjunct to plain digital radiographs along with the PVR, especially in conditions in which callus maturation is doubtful and objectivity is needed for decision making with regard to safe fixator removal.

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This study was carried out in the Institute for Rare Diseases, Department of Orthopaedic Surgery, Korea University Medical Center, Guro Hospital, 80, Guro-Dong, Guro-Gu, Seoul 152-703, Korea.

This study is retrospective and nonrandomized.

Conflicts of interest
There are no conflicts of interest.

References


