Patient-Specific Finite Element Analyses Detect Significant Mechanical Therapeutic Effects on Osteoporotic Vertebrae During a Three-Year Treatment*

Daisuke TAWARA**, Jiro SAKAMOTO***, Hideki MURAKAMI****, Norio KAWAHARA***** and Katsuro TOMITA****

** Department of Mechanical and Systems Engineering, Faculty of Science and Technology, Ryukoku University, 1-5 Yokotani, Seta, Otsu, Shiga 520-2194, Japan
*** School of Mechanical Engineering, College of Science and Engineering, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan
**** Department of Orthopedic Surgery, Kanazawa University Hospital, 13-1 Takara, Kanazawa 920-8641, Japan
***** Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa, 920-0261 Japan

E-mail: datawara@rins.ryukoku.ac.jp

Abstract

Analyses of the bone mass alone of osteoporotic vertebrae are not sufficient to predict fracture risks and assess the recovery of bone strength during drug treatment. Instead, finite element analyses (FEAs) is superior, because changes in the vertebral strength are strongly dependent on the inner vertebral stress distribution, which is related to the individual bone shape and bone density distribution in cancellous and cortical region. To investigate how FEAs can detect drug effects, we performed patient-specific FEAs of the first lumbar vertebra of osteoporotic patients at five time points (before therapy, and after 6 and 12 months and 2 and 3 years of therapy) during a 3-year drug treatment with alendronate and vitamin D, in four osteoporotic female patients in this study. The FEAs revealed notable decreases in the compressive principal strains in cancellous bone, but these decreases did not necessarily correspond to increases in the bone densities. In addition, statistical analyses by Friedman’s test (nonparametric analysis) showed that evaluation based only on the average compressive principal strains over the 3-year treatment identified drug effects significantly, suggesting that compressive principal strain is an useful indicators for monitoring drug effects. Our data implied that compressive fracture of the vertebrae may be prevented as a result of the drug treatment, in a manner that was optimally detectable by patient-specific FEAs.

Key words: Computational Biomechanics, Finite Element Method, Bone Strength, Therapeutic Effect, Patient-Specific Modeling, Vertebra, Osteoporosis

1. Introduction

Bone compression fractures in the vertebrae, especially in elderly people, occur because of decreases in the vertebral bone mineral mass with decreases in the vertebral strength caused by osteoporosis[1-3]. Once elderly people have vertebral fractures in advanced state of osteoporosis, it is difficult to maintain their quality of life and they can become confined to bed, which results in higher rates of increases in mortality. Therefore, prediction of the
bone fracture risks and treatment to increase the amount of bone mineral mass are essential. For patients suffering from osteoporosis, orthopedic surgeons usually prescribe a drug treatment to increase the bone mass\(^4\)\(^-\)\(^6\) and vertebral strength. Clinically, the typical methods available for assessing the severity and recovery of bone mass in osteoporosis during drug treatment involve quantification of the bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA)\(^7\)\(^-\)\(^8\). However, this technique is of limited value for estimating vertebral behavior, because the BMD does not always exhibit a good correlation with the mechanical strength\(^9\)\(^-\)\(^1\)\(\) which is the stiffness relating to structure and material strength of bone. The fracture risks of a vertebra are related to the stress distribution depending on the three-dimensional vertebral shape, density distribution of cancellous and cortical region and loading conditions. Therefore, finite element analyses (FEAs) have been considered to be a more effective way to evaluate vertebral strength and provide a better prediction of fracture risks of bone than DEXA\(^1\). In addition, some researchers have reported that computed tomography (CT)-based FEAs can predict vertebral fracture sites and estimate the fracture risk\(^1\)\(^2\)\(-\)\(^5\) based on consideration of the morphology and density distributions of bone. These reports suggest the potential of using FEAs to elucidate the effects of drug treatment.

As one of the powerful techniques for FE modeling, voxel FE-meshed modeling based on high-resolution CT images\(^6\)\(^-\)\(^9\) is widely used in bone stress analyses\(^1\)\(^0\)\(-\)\(^1\)\(\). However, this technique still has problems associated with clinical application because of the X-ray dosages from the CT scanner to the patients for actual size models. Therefore, we have regarded general (not voxel) FEAs using image-based modeling techniques\(^2\)\(^1\)\(-\)\(^2\)\(\) as strongly required methods for evaluating vertebral strength in clinical cases.

In our previous study, we investigated the potential of FEAs to evaluate the effectiveness of drug treatment with alendronate and vitamin D for osteoporosis by performing patient-specific general FEAs of osteoporotic vertebrae\(^2\)\(^5\). We considered the three-dimensional vertebral shapes and bone density distributions based on CT images over time of patients undergoing a 1-year drug treatment with assessment at three time points in the analyses. FEAs of the vertebral models at the three time points indicated that the decrease in compressive principal strain with increases in bone density were notable in some models, suggesting their usefulness for the prognosis of osteoporosis. To apply our vertebral modeling and FEAs to more realistic clinical practice, FEAs for identical patients on a longer time scale, an extension of the previous study\(^2\)\(^5\) with follow-up increased to a 3 year period, and with statistical appraisal of the mechanical quantity are indispensable.

In the present study, as a development to a longer time scale relative to the previous study, we performed patient-specific FEAs over time for osteoporotic vertebrae in four patients undergoing a 3-year drug treatment. FE models of the first lumbar vertebrae of the four patients in each period were constructed based on CT images and subjected to FEAs. We then evaluated the applicability of the FEAs to detect the mechanical recovery of the vertebrae by comparisons of the relative bone densities and compressive principal strain distributions of the vertebral models at five time points (before therapy, and after 6 and 12 months and 2 and 3 years of therapy) and analyzed the statistical significance of their differences. The purpose of this study was to ascertain whether FEAs can quantitatively identify the effects of drug therapies on the mechanical strength recovery of osteoporotic vertebrae compared with evaluations based on bone densities (such as BMD values).

2. Methods

2.1 Analysis target

The permission and cooperation of four osteoporosis patients who visited the University Hospital at Kanazawa University as well as their written informed consent were
obtained. All four patients were Japanese females and they were undergoing 3 year drug treatment with alendronate and vitamin D. Their ages were 53, 61, 72 and 73 years old, respectively. We focused on the first lumbar vertebra (L1) as the analysis target because L1 is a frequent site of osteoporotic fractures owing to its location near an inflection point of the spine.

2.2 Patient-specific FE modeling

For FE modeling, we used the Mechanical Finder™ (MF) (RCCM Co. Ltd., Japan) software program. This software program enables analyses of bone strength with consideration of individual complex bone shapes and heterogeneous bone density distributions based on multiple and continuous CT images. Heterogeneous bone density distributions are related to the Young’s modulus of bone, and vary among cancellous bone and around the regions between cortical and cancellous bone. Notably, the heterogeneity of the Young’s modulus within a vertebra changes depending on the degree of the seriousness and recovery of osteoporosis in a patient, and affects the total stiffness and stress distribution of the vertebra. To reflect this heterogeneity in the FEAs, the MF software program calculates the apparent bone density, and determines the Young’s modulus of each element separately based on the relationships provided in previous reports\(^{(23,26,27)}\). The procedure of our FEA is shown in Fig. 1.

![Fig. 1 Procedure of a patient-specific FEA on the MF software program](image)

To create FE models, we took X-ray CT images of L1 using a medical CT scanner (Hitachi Medical Corp., Japan) with a 120-kVp X-ray power voltage, 0.39-mm pixels and 512 × 512 matrices for each patient along the cephalocaudal axis of the body at 1-mm intervals over 20 seconds at five time points. We also scanned the bone mass phantoms (B-MAS200; Kyoto Kagaku Co. Ltd., Japan), which have five 15-mm wide rods corresponding to hydroxyapatite of 0, 50, 100, 150 and 200 mg/cm\(^3\) with 30-mm intervals between the rods, in the vertebrae from the twelfth thoracic vertebra (T12) to the second lumbar vertebra (L2) of the patients. Then we constructed three-dimensional patient-specific FE models using the extracted bone edges of the region of interest in individual CT images in a row, which are provided by one CT scan of the vertebra. The FE models of the four patients designated F53, F61, F72 and F73 are shown in Fig. 2.

![Fig. 2 Patient-specific L1 FE models of the four patients at 3 years after the initiation of therapy](image)
numbers in the model names represent the ages of the patients. Because the FE models have complex vertebral shapes and were constructed based on CT images at 1-mm intervals, we used tetrahedral linear elements and set the representative element length at 1 mm for FE meshing (Table 1).

2.3 Calculation of the bone density distributions in the FE models

Before calculating the bone density of each finite element based on the CT images, we calibrated the relationship between the bone density value and the CT value in HU (Hounsfield Units). The bone density of each finite element by the calibrated relationship was obtained as follows:

\[
\rho = \begin{cases} 
0.0 & (HU < -1) \\
(0.733 \times HU + 4.51) \times 10^{-3} & (-1 \leq HU)
\end{cases}
\]

where \( \rho \) g/cm\(^3\) denotes the apparent bone density determined as the average value of HU obtained for a total of 17 points composed of the center point and four points distributed on four lines connecting the center point to each of the apexes of the tetrahedral element in the MF software program\(^{(28)}\). We determined the apparent Young’s modulus of each finite element using the relationship between the apparent Young’s modulus and the bone density provided by Keyak et al.\(^{(23)}\) as follows:

\[
E = \begin{cases} 
0.001 & (\rho = 0.0) \\
33900\rho^2 & (0.0 < \rho \leq 0.27) \\
5307\rho + 469 & (0.27 < \rho < 0.6) \\
10200\rho^{1.01} & (0.6 \leq \rho)
\end{cases}
\]

where \( E \) MPa denotes the Young’s modulus. Since the Young’s modulus is defined by the individual elements one by one as described above, we can reflect the heterogeneity of the Young’s modulus in the vertebra in the FE model. Poisson’s ratio was set to a constant value of 0.4 by reference to Keyak et al.\(^{(23)}\), Reilly and Burstein\(^{(29)}\) and Van Buskirk and Ashman\(^{(30)}\).

2.4 FEAs and mechanical evaluation of the vertebrae

We set a simple compressive loading condition for the vertebral models in which an inferior surface of the vertebra was fixed and a downward uniform load of 1000 N in total was added to an upper face in the vertical direction\(^{(15,31,32)}\) as shown in Fig. 3. Then we performed a linear elastic analysis of each model over time using the five time points and compared the bone density and compressive principal strain distributions during the drug

![Fig. 3](image)

**Table 1** Number of nodes and elements in the FE models

<table>
<thead>
<tr>
<th>Model</th>
<th>F53</th>
<th>F61</th>
<th>F72</th>
<th>F73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nodes</td>
<td>52814</td>
<td>39935</td>
<td>56387</td>
<td>56999</td>
</tr>
<tr>
<td>Number of elements</td>
<td>255471</td>
<td>192395</td>
<td>273887</td>
<td>277247</td>
</tr>
</tbody>
</table>
To quantitatively assess the changes over time, we calculated the average values of the bone density $\rho_{ave}$ and compressive principal strain $\varepsilon_{ave}$ as follows:

$$\rho_{ave} = \frac{\sum_{i} \rho_i V_i}{\sum_{i} V_i}$$  \hspace{1cm} (3)$$

$$\varepsilon_{ave} = \frac{\sum_{i} \varepsilon_i V_i}{\sum_{i} V_i}$$  \hspace{1cm} (4)$$

where $\rho_i$ and $\varepsilon_i$ denote the bone density and compressive principal strain of the $i$-th finite element, respectively, $V_i$ denotes the volume of the $i$-th finite element and $n$ denotes the total number of finite elements in the model. The changes were statistically assessed by Friedman’s test (nonparametric test) to identify the significant effects of the treatment.

3. Results

3.1 Bone density and compressive principal strain distributions

The bone density and compressive principal strain distributions in the anterior view from the right angle and cross-sections of the mid-sagittal plane in cancellous bone of the four models at the five time points are shown in Figs. 4 and 5, respectively. All the models responded to the drug treatment by changing their contours qualitatively. In particular, the F61 model showed significant therapeutic effects. The high-density areas were increased around the anterior and lateral cortical surfaces during the first year after the initiation of therapy (Fig. 4 (i), (ii) and (iii)), while several high compressive principal strain distributions of the cancellous areas were decreased (Fig. 5 (i), (ii) and (iii)). After 2 years of therapy, the total bone densities were higher in the cortical areas as well as in the cancellous areas. The bone densities at the posterior aspect of the vertebrae were also increased (Fig. 4 (iii) and (iv)). Simultaneously, several local lower-density regions in the cancellous areas observed after 1 year had disappeared after 2 years of treatment and their distributions changed to relatively uniform conditions while the strains at the upper and lateral sides of the vertebra decreased (Fig. 5 (iii) and (iv)). After 3 years of therapy, the F61 model maintained high bone density conditions in both the cortical and cancellous areas and showed marked decreases in the high strain areas. Comparisons between the data before treatment and after 3 years of treatment prominently showed that the low bone densities, especially at the lateral side, and high strain areas had been reduced (Figs. 4 and 5 (i) and (v)). While the F61 model constantly showed drug effects during the drug treatment, the contour changes of the densities and strains in the other models did not seem to be proportional, but were still dominant in the final 2 years. In the F53 model, although the bone density and strain distribution did not change dramatically and higher strains actually occurred in the cancellous area after 2 years of therapy, high bone density over the whole cortical area was observed and the strain contours in the cancellous area decreased and changed to a uniform strain condition after 3 years. In the F72 model, no significant changes in either the density or the strain were observed over time during the first year, but the density at the top of the vertebra slightly increased and the model showed reduced occurrence of strain predominantly in the cancellous area. In the F73 model, the bone density on the whole surface of the vertebra (i.e. the cortical area) increased although it showed almost no changes in the cancellous area, and the widely distributed high strain areas in the cancellous bone eventually declined (Figs. 4 and 5 (iv) and (v)).
3.2 Average bone densities and compressive principal strains

The changes in the average bone densities and compressive principal strains defined by Eqs. (3) and (4) over time for the four models are shown in Figs. 6 and 7. In addition, their values and percentage changes during the therapy compared with those before the treatment are shown in Tables 2 and 3. In the final two years of the treatment, the average bone densities in the F61 model were dramatically increased (+14%) after 3 years and this buildup was maintained from 1 year to 3 years (equivalent to a +9% increase from 1 year).

Fig. 4 Bone density distributions in the anterior view and cross-sections of the mid-sagittal plane of the four models at the five time points ((i): before therapy, (ii): 6 months, (iii): 12 months, (iv): 2 years and (v): 3 years).
In the F53 and F73 models, the densities increased with the same percentage changes after 3 years compared with those before treatment (+7%). The F53 model was already saturated after 1 year, while the F73 model approached the amount after repeatedly decreasing or increasing the bone density until 2 years after the initiation of therapy. On the other hand, although there was a tendency for an increase in density after 2 years (+20%) in the F72 model, the overall percentage change in the density was only +2% after 3 years. However,

Fig. 5  Compressive principal strain distributions in the anterior view and cross-sections of the mid-sagittal plane of the four models at the five time points ((i): before therapy, (ii): 6 months, (iii): 12 months, (iv): 2 years and (v): 3 years).
the changes in the compressive principal strains in the final 2 years (from 1 year to 3 years) were significant in all models. The F61 and F72 models curbed the strain occurrences sequentially in the final 2 years (equivalent to -28% in the F61 model and -21% in the F72 model) and reached -40% in the F61 model and -31% in the F72 model compared with the untreated values. The F53 and F73 models showed decreased strains, especially in the final 1 year, and reached small strain values (-16% in the F61 model and -24% in the F72 model).

Fig. 6  Change in average bone densities calculated by Eq. (3) for the four models at the five time points ((i): before therapy, (ii): 6 months, (iii): 12 months, (iv): 2 years and (v): 3 years).

Fig. 7  Change in average compressive principal strains calculated by Eq. (4) for the four models at the five time points ((i): before therapy, (ii): 6 months, (iii): 12 months, (iv): 2 years and (v): 3 years).

Table 2  Average bone densities and their percentage changes during the therapy compared with those before the treatment

<table>
<thead>
<tr>
<th>Model</th>
<th>Bone density (g/cm³)</th>
<th>Percentage change (%)</th>
<th>Bone density (g/cm³)</th>
<th>Percentage change (%)</th>
<th>Bone density (g/cm³)</th>
<th>Percentage change (%)</th>
<th>Bone density (g/cm³)</th>
<th>Percentage change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before therapy</td>
<td>0.179</td>
<td>-</td>
<td>0.208</td>
<td>-</td>
<td>0.157</td>
<td>-</td>
<td>0.236</td>
<td>-</td>
</tr>
<tr>
<td>6 months</td>
<td>0.189</td>
<td>+6</td>
<td>0.230</td>
<td>+11</td>
<td>0.164</td>
<td>+4</td>
<td>0.223</td>
<td>-6</td>
</tr>
<tr>
<td>12 months</td>
<td>0.191</td>
<td>+7</td>
<td>0.218</td>
<td>+13</td>
<td>0.157</td>
<td>0</td>
<td>0.228</td>
<td>-3</td>
</tr>
<tr>
<td>2 years</td>
<td>0.177</td>
<td>-1</td>
<td>0.234</td>
<td>+13</td>
<td>0.189</td>
<td>+20</td>
<td>0.237</td>
<td>0</td>
</tr>
<tr>
<td>3 years</td>
<td>0.192</td>
<td>+7</td>
<td>0.238</td>
<td>+14</td>
<td>0.160</td>
<td>+2</td>
<td>0.252</td>
<td>+7</td>
</tr>
</tbody>
</table>
compared with the untreated values. This tendency that the changes in the average bone densities were not strictly coincident with those in the average compressive principal strains was manifestly apparent, as shown in Figs. 6 and 7. This is likely to arise because the average values were computed for all FE elements of the models, in which the load was applied to the anterior part.

### 3.3 Analysis of the statistical significance of the drug effects

Table 4 shows the evaluations of the statistical significance of the drug effects based on Friedman’s test. *P*-values were determined based on the $\chi^2$ values obtained in Friedman’s test and the mean probabilities of the null hypothesis that the changes in the densities or strains were random (not significant) after the initiation of drug treatment. As shown in Table 4, the *p*-value using only the average compressive principal strains after 3 years of therapy was small at 0.02 (2%). This indicated statistically that the strain values changed over time because of a drug effect, unlike the *p*-values using the average bone densities and

### Table 3  Average compressive principal strains and their percentage changes during the therapy compared with those before the treatment

<table>
<thead>
<tr>
<th>Model</th>
<th>F53</th>
<th>F61</th>
<th>F72</th>
<th>F73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain</td>
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<td></td>
</tr>
<tr>
<td>(x10^{-3})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
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</tr>
<tr>
<td>change (%)</td>
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<td>Strain</td>
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<td>(x10^{-3})</td>
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<td>Percentage</td>
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<tr>
<td>change (%)</td>
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<tr>
<td>Before</td>
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</tr>
<tr>
<td>therapy</td>
<td></td>
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<tr>
<td>6 months</td>
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<td>12 months</td>
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<td>3 years</td>
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</table>

### Table 4  Evaluations of statistical significance of the drug effects based on the average bone densities and the average compressive strains analyzed by Friedman’s test

<table>
<thead>
<tr>
<th></th>
<th>Bone density</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td><em>p</em>-values</td>
</tr>
<tr>
<td>Before</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>therapy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 months</td>
<td>1.50</td>
<td>$p (\chi^2 = 1.50) &gt; 0.05 (\chi^2 = 6.50)$</td>
</tr>
<tr>
<td>2 years</td>
<td>2.70</td>
<td>$p (\chi^2 = 2.70) &gt; 0.05 (\chi^2 = 7.80)$</td>
</tr>
<tr>
<td>3 years</td>
<td>7.00</td>
<td>$p (\chi^2 = 7.00) &gt; 0.05 (\chi^2 = 9.49)$</td>
</tr>
</tbody>
</table>
the strains of other periods during the drug treatment. These findings suggest that evaluation by the average compressive principal strains alone during a 3-year drug treatment can specifically indicate the drug effects. At the same time, these findings suggest that the vertebrae were strengthened structurally by the treatment.

4. Discussion

4.1 Evaluations using average compressive principal strains

There are three reasons why we used the “average compressive principal strain” to evaluate the mechanical effects of drug therapy. First, the “compressive” principal strain is regarded as a reasonable indicator because compressive forces toward osteoporotic vertebrae cause compression fractures. Second, the “average” strain is not very dependent on the local finite element shape and size in FEAs. Although the magnitude of the maximum strain is a matter for estimating the risk of failure in vertebrae, the maximum strain is a singular value for vertebrae in FEAs that is affected depending on a finite element. We previously reported that changes in the maximum strain have no correlation with changes in the average strain (25). The average strain would be good for evaluating the whole material performance of the vertebra in this case. Additionally, the evaluation of the average compressive principal strain of narrowed area such as vertebral anterior part would be useful, but the average strain of the whole vertebra is reasonable because it is difficult to determine the narrowed area on the same basis between the models which have individual complicated shapes of vertebra. Third, the “strain” is one of the best indicators, because the other physical amounts are not actually sufficiently sensitive to show the drug effects. For example, the possibility of a fracture is sometimes estimated by the magnitude of the stress-strength ratio, which is the ratio of stress against the unit strength, but particular changes in the stress-strength ratio cannot be seen during drug therapy. According to the report by Keyak et al. (23), bone strength is also related to the bone density, and stress depends on the Young’s modulus. The stress-strength ratio would have weak response to the mechanical conditions of the vertebrae in this case because both the stress and the strength will change with changes in the bone density during the drug therapy process. Other physical indicators such as area of vertebral cross-section and average Young’s modulus which was calculated as a nonlinear relation of the bone density had also weak response to the mechanical conditions of the vertebrae in this case. On the contrary, the vertebral inner compressive principal strain can be used to represent the drug effects on the purely mechanical conditions of the vertebra. In addition, the yield strain of bone is fairly constant even as the apparent BMD changes (33) and it is considered that the FEAs based on the displacement method used in this study approximate the strain of the bone tissue for high porosity cancellous bone. Besides, the strain values shown in Table 3 are physically reasonable. The strain values in all the models were higher than 800 microstrains, which are suitable levels between the orders of 800 microstrains during walking and 2000 microstrains during running (25,34,35). The strain values are reasonable considering the osteoporosis severities in the patients.

4.2 Drug effects on the changes in the bone densities and compressive principal strains

The increases in the bone densities and decreases in the compressive principal strains that were observed at not only the cancellous area but also the vertebral surface (i.e. the cortical area) in all patients indicated that the drug treatment strengthened the vertebrae. Because the drug therapy for all patients in this study was oral intake of alendronate and vitamin D, which suppress the activities of osteoclasts and enhance calcium absorption from the intestine (5,36), these actions can indirectly accelerate the buildup and improvement of the load capacity of cancellous bone itself by reducing the stress concentration in the cortical
In addition, the lateral anterior side of the vertebra before therapy, which is a frequent site of bone fractures in osteoporosis, had higher compressive principal strains, such that increases in the bone density on the cortical anterior side by drug treatment directly help to avoid bone fractures by increasing the Young’s modulus and leading to stiffness on the anterior side. However, it is not necessarily the case that increases in the bone densities correspond to decreases in the strains. In fact, in the F53 model, the average bone density did not change (+7% constant; Table 2) from 1 year to 3 years after the initiation while the average strain decreased further (-7% to -16%; Table 3), suggesting that the strain is more appropriate for evaluating the changes in the mechanical conditions of osteoporotic vertebrae under drug therapy. Changes in the strain distributions with remodeling of the trabecular structures in the cancellous area and the surface shape of the cortical bone were probable, even though changes in the average bone density did not appear\(^\text{25}\). The average strains are expected to reflect the morphological changes in the trabecular bone emphatically compared with the bone density. In fact, the average strains in all the models kept decreasing even at 3 years after the initiation of therapy.

### 4.3 Interpretation of the statistical consequences

The statistical findings obtained using Friedman’s test revealed that evaluation based only on the average compressive principal strains for the 3-year treatment was able to identify drug effects (Table 4). This means that the average strain is one of the intelligible indicators that can emphasize the drug effects. It is also worth mentioning that the drug effects for osteoporosis should be evaluated for at least 3 years based on the patient-specific FEAs in this study, because the vertebrae were able to respond to the continuous 3-year drug treatment. According to the data in Table 4, it was not until the evaluation of the average strains after 3 years that the drug effects were detected. Responses to the drug therapy for 3 years depended on the individual patients. The average bone densities of the younger patients (F53 and F61 models) exhibited responses at earlier stages (Table 2) while the average bone densities of the older patients (F72 and F73 models) increased slowly in total. This possibly arose because the osteoblasts and osteoclasts in the younger patients are probably more active, and the drug treatment depresses the activities of osteoclasts but does not speed up the activities of osteoblasts directly, thereby preventing a decrease in the bone density. Relatively, it is considered that remodeling of the trabecular bone caused by osteoblast actions is not straightforward for increasing the bone density, and their effects on the vertebral strains should therefore be evaluated for longer periods. Strictly, a comparison between a long-term consecutive drug therapy case described above and a cessation of drug therapy case would be necessary.

The present results indicate that precise estimation of the changes in vertebral stiffness caused by drug therapy is difficult measuring only the bone densities (such as BMD values), although it is provided by DEXA for the prognosis. Consequently, the mechanical performances of the vertebral models in this study suggest that patient-specific FEAs are requisite for assessing the mechanical therapeutic effects of drug therapy on osteoporotic vertebrae.

### 4.4 Limitations of the FEAs

There are some limitations to the FEAs in this study. The FEAs included some errors. Since simple uniform loading is applied directly to the vertebral models, higher strain is expected to occur in the FEAs. In vivo, skewed distribution loads may be applied to the vertebrae owing to spinal S-curves, and the intervertebral disks ease the loading and fixation. Large deformations, nonlinear characteristics and anisotropy of the intervertebral disks can also affect the vertebral mechanical responses. However, we assume that simple boundary conditions of the FEAs are proper for relative comparisons of vertebrae over time.
during drug treatment. In addition, the element size and material property of the FEAs would also affect the mechanical responses of the vertebrae. The 1-mm size elements used in our FEAs for cortical bone of ≤1-mm thickness may straddle the interface between the cortical and cancellous areas and lead to the inclusion of some errors for calculation of the Young’s modulus. Although mesh size affects the vertebral performance because each element in the macroscale includes heterogeneous features such as the morphology and quality of the trabecular bone in the microscale, we regard the constant 1-mm mesh size as reasonable because the CT scanning resolution (intervals) was 1 mm. Alternatively, use of shell elements on the surface of the cortical bone for the thin cortical shell(28) is appropriate. In addition, our isotropic finite elements should be considered to reflect the anisotropy of bone caused by its properties such as the actual trabecular morphology and orientation of biological apatite. In addition, the number of models for statistical evaluation should be increased. Friedman’s test indicates statistical superiority despite the number of patients and periods of time points used to evaluate the drug effects in this study. For more realistic evaluation, patients of the opposite sex, with wider ranges of age, body height and body weight, and with treatment periods of longer than 3 years should be involved for statistical tests. Comparisons with a control group (healthy group) are also desired.

4.5 Clinical application of the patient-specific FEAs

Overall, the proposed patient-specific FEAs comprise one of the effectual methods that can faithfully consider the bone conditions of patients to evaluate changes in the mechanical strength of osteoporotic vertebrae for current clinical use. Regarding the remaining challenges for clinical application of our mechanical analyses, we should solve some limitations by improving our FEAs as described above and also evaluate the changes in the bone densities and compressive principal strains in different parts of the vertebrae to examine the relationships between structural changes and the vertebral fracture risk.

In conclusion, we have demonstrated that patient-specific FEAs can provide helpful information for the prognosis of osteoporosis. The important findings were that changes in the bone densities do not always correspond to changes in the compressive principal strain during a 3-year drug treatment and that evaluation based on the average compressive principal strains alone can prove the drug effects statistically. These findings imply that our FEAs have the capability to assess drug effects and that patient-specific mechanical evaluation is warranted to discern the effects of drug treatment on osteoporotic vertebrae.

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