Effect of Minodronic Acid Hydrate on Hip Geometry in Japanese Women with Postmenopausal Osteoporosis

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Abstract

Dual-energy X-ray absorptiometry (DXA)-based hip structural analysis was performed to evaluate the effect of a bisphosphonate, minodronic acid hydrate, on geometry of the proximal femur in Japanese patients with osteoporosis. The subjects were 103 postmenopausal patients (average: 63.9±6.4 years old) with primary osteoporosis. Minodronic acid hydrate was administered orally at a dose of 1 mg/day for 12 months. Significant early responses at 3 to 6 months after the start of administration were observed in all three regions of the proximal femur (narrow neck, intertrochanter, and shaft) in terms of bone density, geometry, and bone strength indices. The outcomes of therapy included a reduction of the internal diameter of the cortical bone (-0.1%, -0.6%, and -0.2% in the neck, intertrochanter and shaft, respectively, at 12 months; not significant) and a significant increase in cortical thickness (3.1%, 3.7%, and 2.0% in the respective regions at 12 months). Furthermore, minodronic acid hydrate induced a significant enlargement of the cross-sectional bone area, which is related to compressive strength; a significant increase in cross-sectional moment of inertia (CSMI) and section modulus (SM: 4.9%, 5.8%, and 2.9% in the neck, intertrochanter and shaft, respectively, at 12 months; p<0.001), which are related to the bending strength; and a significant reduction in buckling ratio (BR: -3.0% (p<0.001), -4.2% (p<0.001), and -1.4% (p<0.05) in the respective regions at 12 months), which reflects improved cortical stability. These findings show that minodronic acid hydrate reduces age-related endocortical bone resorption, leading to increased cortical thickness and sustained or enhanced bone strength.
Introduction

Bone geometry refers to bone tissue distribution and alignment, which are critical for both the structural and biomechanical properties of bone [1]. For those parts of the skeletal system with a complex shape, such as the proximal femur, bone geometry plays a particularly important role in biomechanical assessment. In this context, the hip structure analysis (HSA) algorithm was developed for noninvasive clinical evaluation of dual X-ray absorptiometry (DXA) of the proximal femur [2]. Three prominent prospective epidemiological studies demonstrated the position in the ability to predict hip fracture using the analysis of hip geometry. In a prospective case-control study of 71 female and 25 males aged more than 60 years old [3], the femoral neck diameter, cross-sectional moment of inertia (CSMI), and section modulus (SM) were identified as independent predictors of hip fracture risk after adjustment for bone mineral density (BMD) in both women and men. However, the contribution of these measures to hip fracture prediction over and above BMD is likely modest. A part of the Rotterdam study including 147 incident hip fracture cases in 4806 participants [4], the geometrical parameters did not have a better discrimination than BMD, and the buckling ratio did not offer additional predictive value. Among 7474 women from the Study of Osteoporosis Fracture (SOF) with hip DXA at baseline, there were 635 incident hip fractures recorded over 13 years [5]. HSA showed any geometrical parameters and biomechanical parameters derived from them were not beyond BMD to predict of hip fracture.

This limitation may be linked to the *ex vivo* measurement of the cross-sectional femoral neck geometry and bone density using high-resolution computed tomography (CT), which has shown that site-dependent cortical thickness and a shifted centroid are
important geometrical parameters related to bone strength [6]. HSA based on the
two-dimensional bone density distribution is limited to an evaluation of the morphology
of the cross-section of the femoral neck, including the local cortical thickness and
centroid in the cross-sectional femoral neck. Moreover, the HSA program is also limited,
since most of the derived geometrical parameters depend on assumptions regarding the
cross-sectional shape and on fixed percentages of cortical bone, and all of the
parameters are derived from bone density.

The evaluation of hip fracture risk following drug intervention requires a different
point of view from that taken in epidemiological studies. The purpose of a prospective
epidemiological study is to identify risk factors (e.g., geometry, BMD) that have a
significant association with a future fracture. In contrast, the purpose of an intervention
study is to determine whether the assessment tool (i.e. HSA) can detect a change in
bone geometry and density of individual patient after treatment, and to show whether
the intervention induces an enhancement of bone strength. Taking bone geometry and
BMD into account may improve the accuracy of an assessment of bone strength, since
an anti-osteoporotic drug may modify bone geometry as well as density. A
treatment-induced increase in bone density, which involves an overall change in bone
mass, bone size and bone mineralization also affects bone biomechanical properties.
The DXA-BMD value is influenced by all of these changes, but does not afford a means
to determine how much the medication may influence bone biomechanical properties,
since an observation of elevation in bone mass/mineralization may be offset by an
increase in bone size. Therefore, evaluation of changes in bone density and geometry
based on simultaneous measurement of different indices is required to properly gauge
the response to treatment.
Minodronic acid hydrate is a new 3rd-generation bisphosphonate with potent pharmacological activity that has been developed in Japan. Non-clinical studies have shown that this agent is a strong inhibitor of bone resorption at low doses [7], with inhibitory effects on the reduction of bone density or strength that are comparable with those of other bisphosphonates [8-9]. A clinical study showed that administration of minodronic acid hydrate at 1 mg/day for 12 months produced increases of 6.0% in average lumbar bone density (L2-4) and 3.6% in total bone density of the proximal femur in Japanese postmenopausal female patients with osteoporosis [10]. This trial also provided the first evidence that minodronic acid hydrate was superior to a placebo in preventing vertebral body fracture, with two-year cumulative incidences of vertebral body fracture of 10.4% in the treatment group and 24.0% in the placebo group, corresponding to a 59% reduction in the relative risk of vertebral body fracture over two years [11]. In the present study, we report the effects of minodronic acid hydrate on hip geometry in Japanese female patients with osteoporosis, the first report of HSA results in a multicenter clinical trial in Japan.

Materials and methods

Subjects

The subjects were 103 postmenopausal female ambulatory patients with osteoporosis (age >45 years old, average age: 63.9±6.4 years old) who were enrolled at 43 centers. Osteoporosis was defined by the criteria of the Japanese Society for Bone and Mineral Research [12-13]. The exclusion criteria have been given elsewhere [10]. One hundred and three patients were not selected on purpose from the original clinical trial. The other 32 hip DXA data cases were obtained by the previous version of the QDR4500 series,
or the DXA data was not adapted for the HSA program. The characteristics of the subjects at baseline and 12 months after the start of administration are shown in Table 1, which show the subjects in the present study were not a deliberately selected subgroup from the original clinical trial [10]. The subjects were asked to take 1 mg minodronic acid hydrate tablets for 12 months once daily, and to remain in an upright position for 30 min before the first food or beverage of the day after taking the medication. In addition to the study medication, all subjects received a 1.6 g oral dose of Ca lactate (200 mg elemental Ca) once a day after the evening meal. Vitamin D was not supplied as a supplement.

The study was conducted with consideration for the protection of subjects as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects gave written informed consent before undergoing examinations or study procedures, which were conducted in compliance with Good Clinical Practice.

Methods

The BMD of the proximal femur was measured by DXA at baseline and 3, 6, 9 and 12 months after administration. All DXA devices were of the Hologic QDR Series and each machine was adjusted for differences by calibration with standard phantoms to verify the reproducibility of the measurements within ±1.5% during the study period. DXA image data for the proximal femur were analyzed using the HSA program (Version 12.7.3.1) and all analyses were conducted by the same technician (T.T.) in the Department of Nuclear Medicine, Kawasaki Medical School.

The HSA algorithm is based on a principle first articulated by Martin and Burr [14], who demonstrated that mineral profiles created during a single photon absorptiometry
bone density scan are a projection of the corresponding bone cross-section and can be used to define its geometry. As described previously [15-17], the HSA algorithm derives the conventional BMD (g/cm²), the outer diameter (OD, cm), the endocortical diameter (ED, cm), the average cortical thickness (CoTh, cm), the total mineralized bone area in the cross-section (CSA, cm²), the cross-sectional moment of inertia (CSMI, cm⁴), and the section modulus (SM, cm³) directly from the mass profiles. SM is computed as CSMI/dₘₐₓ, where dₘₐₓ (cm) is the maximum distance between the center of the mass (centroid) and the outer cortex. Another parameter, the buckling ratio (BR), is estimated as the ratio of dₘₐₓ to the estimated average CoTh derived from an annulus model of the cross-section using the measured OD, assuming that a fixed proportion of CSA is in the cortex. CSA and SM are indices of resistance to axial compressive and bending loads, respectively, and BR is an index of susceptibility to local buckling under bending loads.

The HSA software generates profiles of pixel values traversing the proximal femur at three locations: the narrow neck (NN) across the femoral neck at its narrowest point, the intertrochanter (IT) along the angle bisector defined by the neck and shaft axes, and across the shaft at 30 mm below the most prominent portion of the lesser trochanter. To avoid variation in the visualization of the lower border of the lesser trochanter depending on the inner rotation of the hip joint, the distance from the highest part of the lesser trochanter was made constant to improve the reproducibility of bone shaft regions and to correctly determine the region of interest (ROI). At each of these locations, five parallel profiles were generated, spaced one pixel apart, proximal and distal to the three defined locations. The five profiles are averaged within each region and the BMD, CSA, OD, ED, CoTh, CSMI, SM, and BR are reported. The reproducibility of the HSA
parameters was calculated using two measurements at a one or two month interval from 30 women (age; 56-86 years old (71.8±7.6))(Table 2).

Statistical analysis

For each case, the change (%) from baseline was calculated for each parameter and summary statistics were obtained at individual time points. These are expressed as average values and standard deviations (SD). Comparison of the findings before and after administration of minodronic acid hydrate was performed by Wilcoxon test assuming a two-sided level of significance of 5% (p<0.05).

Results

Changes in BMD from baseline

Percentage changes in BMD of individual femoral regions from baseline are shown in Fig. 1. The BMD significantly increased in all regions after 3 to 6 months administration of minodronic acid hydrate, and increased by 3.2% (p<0.001), 4.1% (p<0.001), and 1.6% (p<0.001) in the NN, IT, and shaft, respectively, after 12 months. The largest change was observed in the trochanteric region. The femoral BMD, geometry and bone strength indices at baseline and 12 months are shown in Table 3.

Changes in bone geometry from baseline

Percentage changes in bone geometry from baseline are shown in Fig. 2. CSA significantly increased in all the femoral regions starting 3 months after administration and increased by 3.3% (p<0.001), 3.9% (p<0.001), and 2.0% (p<0.001) in the NN, IT, and shaft after 12 months. The changes in OD from baseline were 0.1%, -0.2%, and 0.4% in the NN, IT, and shaft, respectively, at 12 months after administration, with none
of these changes reaching a significant level, except for OD in the shaft at 12 months
(p=0.015). ED deceased from baseline by -0.1%, -0.6%, and -0.2% in the NN, IT, and
shaft, respectively, after 12 months, showing a trend for a decrease but without
significance in any region. CoTh significantly increased from baseline at 3 months after
administration, and increased by 3.1% (p<0.001), 3.7% (p<0.01), and 2.0% (p<0.001)
in the NN, IT, and shaft, respectively, after 12 months. Overall, the most significant
changes were observed in IT.

Changes in bone strength indices from baseline

Percentage changes from baseline in CSMI, SM and BR, all of which are bone
strength indices for the femoral region, are shown in Fig. 3. CSMI and SM showed
significant increases in all of the femoral regions examined 3 months after
administration; and CSMI increased by 4.8% (p<0.001), 4.9% (p<0.001), and 3.2%
(p<0.001) and SM by 4.9% (p<0.001), 5.8% (p<0.001), and 2.9% (p<0.001) in the NN,
IT, and shaft, respectively, after 12 months. BR significantly decreased at 3 months after
administration in the IT and at 6 months after administration in the NN and shaft. BR
significantly decreased by -3.0% (p<0.001), -4.2% (p<0.001), and -1.4% (p=0.028) in
the NN, IT, and shaft, respectively, after 12 months.

As seen for BMD and the geometry indices, the effects of minodronic acid hydrate on
the bone strength indices most significantly appeared in the IT, followed by the NN, and
then the shaft.

Discussion

The present study demonstrates that minodronic acid hydrate, a new bisphosphonate,
improves bone strength indices in the proximal femur in patients with osteoporosis. The comparison of femoral geometry and bone strength indices before and after administration allows investigation of the mechanism of drug action in the prevention of fracture. Specifically, most changes in the indices for bone density, geometry and strength were observed in all femoral regions starting from an early stage (three to six months) after administration of minodronic acid hydrate. The strongest effect occurred in the femoral trochanteric region due to the dominant action of the bisphosphonate on cancellous bone. No significant increase in the outer diameter, which is reported to typically occur with aging, was observed during the 12-month follow-up period; in contrast, it is of interest that there was a slight decrease in endocortical diameter (-0.1% in the NN, -0.6% in the IT, and -0.2% in the shaft) was observed, which is generally thought to increase with aging. This might be caused by an inhibition of endocortical resorption by minodronic acid hydrate, resulting in a significantly increased CSA (3.3% in the NN, 3.9% in the IT, and 2.0% in the shaft) and CoTh (3.1% in the NN, 3.7% in the IT, and 2.0% in the shaft). The bone strength parameters calculated by the HSA algorithm include the cortical CSA as an index of strength against axial compressive load, CSMI and SM as strength indices against bending load, and BR as an index for predisposition to local buckling due to thinned cortices. In the present study, we found a significant change in CSMI, SM (4.9% in the NN, 5.8% in the IT, and 2.9% in the shaft at 12 months), and BR (-3.0% in the NN, -4.2% in the IT, and -1.4% in the shaft at 12 months). These improvements were observed at 3 months after administration, suggesting that potent inhibition of endocortical resorption results in an increase in cortical thickness so as to sustain or improve bone strength. These effects of the bisphosphonate appeared in high metabolic turnover regions such as the cancellous and
endocortical bone.

A clinical study based on HSA-based assessment of the effects of alendronate (ALN) or estrogen (EST) reported the effects on SM for IT and NN to be 9.1% and 7.3%, respectively, with ALN; 5.8% and 6.9%, respectively, with EST; and 3.4% and 3.2%, respectively, with a placebo [18]. BR increased with the placebo, whereas no change or a decrease occurred with ALN or EST (p<0.05). This study was performed in 373 women over the age of 65 years for three years. In the Fosamax Actonel Comparison Trial (FACT study), ALN and risedronate (RIS) were administered once weekly (70 and 35 mg/week, respectively) for two years, and HSA-based assessment showed that both bisphosphonates improved bone geometry [19]. ALN and RIS increased SM by 6-7% and approximately 4%, respectively, while ALN decreased BR by approximately 2% and RIS increased BR by approximately 1% in the narrow neck. It is difficult to compare the result in the present study with previous studies on bisphosphonates because of differences in the race and age of the subjects, the criteria for diagnosis of osteoporosis in patients with low bone density, dose, and administration method (daily or weekly). However, prominent effects of minodronic acid hydrate were observed that were similar to those reported for other bisphosphonates.

The current study has the limitation that no control group was included; however, the multicenter design should help to limit any bias in the findings. Furthermore, several previous papers have reported there are no positive effects on HSA parameters in the placebo group receiving calcium supplementation at one year [20-23]. Data were collected for one year, and the effects of the agent may increase over a 2-year time-course based on changes in bone biomarkers and bone density [10-11]. The beneficial effect on hip BMD is thought to be an important preventative factor for not
only hip fracture but also vertebral fractures [24], and the early significant effects on hip
BMD and HSA parameters are thought to be important for the near term as well as
longer term preventive effect. The next few years of follow-up, to see the incidence of
hip fracture in the HSA-based assessment of intervention studies, will ultimately reveal
whether geometry derived by HSA effectively serves as a surrogate marker of hip
fracture. In fact, a review of reports using HSA in evaluation of the efficacy of
anti-osteoporotic agents [18-23] suggests that potent increase in bone strength indices
derived from HSA does have an association with reductions in the incidence of hip
fracture [25-27].

Previous HSA-based studies of bisphosphonate effects on the proximal femur have
only included Caucasian patients. Since there may be a racial difference in hip geometry,
bone size and bone density, HSA results might differ among races. Only one study using
HSA assessment in Japanese patients has been performed to investigate the effects of an
anti-osteoporotic agent (raloxifene) [28], and therefore our study provides the first
multicenter evidence of the efficacy of a bisphosphonate on hip geometry in a Japanese
population. We conclude that minodronic acid hydrate may prevent hip fracture by
inhibiting aging-related endocortical resorption, resulting in increased cortical thickness
and improved bone strength indices in the proximal femoral region.

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Pacific Edit reviewed the manuscript before submission.
References


DXA-based hip structural analysis of once-weekly bisphosphonate-treated postmenopausal women with low bone mass. Osteoporos Int 20: 911-921


Table 1. Characteristics of subjects at baseline and after the administration of minodronic acid hydrate for 12 months

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.9±6.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>50.0±6.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>152.3±4.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>49.9±3.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²)</td>
<td>0.648±0.051</td>
<td>0.688±0.060</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.635±0.078</td>
<td>0.657±0.077</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Conventional neck BMD (g/cm²)</td>
<td>0.542±0.072</td>
<td>0.555±0.070</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip axis length (mm)</td>
<td>99.9±5.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neck shaft angle (°)</td>
<td>125.6±5.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bone biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine NTX (nmol BCE/mmol Cr)</td>
<td>53.2±18.6</td>
<td>19.8±9.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine total DPD (pmol/mmol Cr)</td>
<td>9.3±2.8</td>
<td>4.5±1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum BALP (U/L)</td>
<td>30.1±10.0</td>
<td>14.6±4.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum osteocalcin (ng/mL)</td>
<td>9.3±2.7</td>
<td>4.2±1.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

BMD: bone mineral density, HAS: hip structure analysis, NTX: urine type I collagen N-telopeptide, DPD: urine total deoxypyridinoline, BALP: serum bone-specific alkaline phosphatase. Each value is shown as the mean±SD.
Table 2. Reproducibility of HSA parameters in the three regions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV (%)</th>
<th>neck</th>
<th>trochanter</th>
<th>shaft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross Sectional Area</td>
<td></td>
<td>1.91</td>
<td>2.88</td>
<td>1.72</td>
</tr>
<tr>
<td>Subperiosteal Width</td>
<td></td>
<td>2.15</td>
<td>1.40</td>
<td>0.65</td>
</tr>
<tr>
<td>Endocortical Width</td>
<td></td>
<td>2.47</td>
<td>1.53</td>
<td>1.63</td>
</tr>
<tr>
<td>Cortical Thickness</td>
<td></td>
<td>3.87</td>
<td>3.11</td>
<td>2.31</td>
</tr>
<tr>
<td>CSMI</td>
<td></td>
<td>6.10</td>
<td>4.80</td>
<td>2.17</td>
</tr>
<tr>
<td>Section Modulus</td>
<td></td>
<td>3.50</td>
<td>4.11</td>
<td>1.81</td>
</tr>
<tr>
<td>Buckling Ratio</td>
<td></td>
<td>5.54</td>
<td>3.11</td>
<td>2.74</td>
</tr>
</tbody>
</table>

CV: coefficient of variation

The reproducibility was calculated using two measurements at one or two month intervals from 30 women.
Table 3. Femoral BMD, geometry and strength indices at baseline and after the administration of minodronic acid hydrate for 12 months

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narrow Neck (NN)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.661±0.091</td>
<td>0.681±0.092</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSA (cm²)</td>
<td>1.933±0.237</td>
<td>1.993±0.229</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Outer Diameter (OD)(cm)</td>
<td>3.085±0.231</td>
<td>3.088±0.231</td>
<td>0.812</td>
</tr>
<tr>
<td>Endocortical Diameter (ED)(cm)</td>
<td>2.834±0.250</td>
<td>2.829±0.253</td>
<td>0.345</td>
</tr>
<tr>
<td>Cortical Thickness (CoTh)(cm)</td>
<td>0.126±0.018</td>
<td>0.130±0.019</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSMI (cm⁴)</td>
<td>1.585±0.337</td>
<td>1.650±0.327</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Section Modulus (SM)(cm³)</td>
<td>0.899±0.154</td>
<td>0.937±0.141</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Buckling Ratio (BR)</td>
<td>14.389±2.895</td>
<td>13.922±2.874</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Intertrochanter (IT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.639±0.099</td>
<td>0.664±0.098</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSA (cm²)</td>
<td>3.135±0.488</td>
<td>3.250±0.485</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Outer Diameter (OD)(cm)</td>
<td>5.162±0.310</td>
<td>5.150±0.307</td>
<td>0.672</td>
</tr>
<tr>
<td>Endocortical Diameter (ED)(cm)</td>
<td>4.612±0.331</td>
<td>4.581±0.329</td>
<td>0.096</td>
</tr>
<tr>
<td>Cortical Thickness (CoTh)(cm)</td>
<td>0.275±0.044</td>
<td>0.284±0.046</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSMI (cm⁴)</td>
<td>7.718±1.811</td>
<td>8.047±1.798</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Section Modulus (SM)(cm³)</td>
<td>2.520±0.531</td>
<td>2.652±0.525</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Buckling Ratio (BR)</td>
<td>11.464±2.327</td>
<td>10.956±2.172</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Shaft</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>1.204±0.149</td>
<td>1.222±0.150</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSA (cm²)</td>
<td>3.080±0.362</td>
<td>3.141±0.370</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Outer Diameter (OD)(cm)</td>
<td>2.697±0.200</td>
<td>2.709±0.205</td>
<td>0.014</td>
</tr>
<tr>
<td>Endocortical Diameter (ED)(cm)</td>
<td>1.817±0.297</td>
<td>1.813±0.304</td>
<td>0.745</td>
</tr>
<tr>
<td>Cortical Thickness (CoTh)(cm)</td>
<td>0.440±0.072</td>
<td>0.448±0.072</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CSMI (cm⁴)</td>
<td>2.209±0.473</td>
<td>2.278±0.492</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Section Modulus (SM)(cm³)</td>
<td>1.570±0.244</td>
<td>1.616±0.255</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Buckling Ratio (BR)</td>
<td>3.278±0.694</td>
<td>3.228±0.693</td>
<td>0.026</td>
</tr>
</tbody>
</table>

BMD: bone mineral density, HAS: hip structure analysis, CSMI: cross-sectional moment of inertia. Each value is shown as the mean±SD
**Figure Legends**

Figure 1. Percentage changes from baseline of BMD in the femoral neck, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE (n=103); *p<0.05 vs. baseline (Wilcoxon test). BMD: bone mineral density, NN: narrow neck, IT: intertrochanter.

Figure 2. Percentage changes from baseline of the cross-sectional area, outer and endocortical diameters, and cortical thickness of the femoral head, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE (n=103); *p<0.05 vs. baseline (Wilcoxon test). CSA: cross sectional area, OD: outer diameter, ED: endocortical diameter, CoTh: cortical thickness, NN: narrow neck, IT: intertrochanter.

Figure 3. Percentage changes from baseline of bone strength indices (CSMI, SM, BR) of the femoral neck, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE (n=103); *p<0.05 vs. baseline (Wilcoxon test). CSMI: cross-sectional moment of inertia, SM: section modulus, BR: buckling ratio, NN: narrow neck, IT: intertrochanter.
Figure 1

BMD (% BMD) over time (n=103)

- NN
- IT
- Shaft

Significant differences marked with asterisks (*)
Figure 3

(n=103)