Effects of risedronate on cortical and trabecular bone of the mandible in glucocorticoid-treated growing rats

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Introduction: This study was performed to estimate the effects of risedronate on mandibular bone density, bone structure, and bone metabolism in established glucocorticoid-induced osteoporosis in growing rats. Methods: The rats were given oral risedronate at 0, 0.5, or 1.0 mg per kilogram per day for 4 weeks after the administration of oral prednisolone at 30 mg per kilogram per 2 days for 6 weeks. Trabecular and cortical bone masses were analyzed by using peripheral quantitative computed tomography, and bone structure and bone formation were measured by using static and dynamic histomorphometry. Results: In trabecular bone, risedronate improved the prednisolone-induced decreases in bone cross-sectional area and bone mineral content. Risedronate increased bone density and also formed dense bone microarchitecture by reducing the bone turnover rate. In cortical bone, risedronate improved the prednisolone-induced decreases in bone cross-sectional area and bone mineral content without affecting bone density by increasing the mineralizing surface. Conclusions: Risedronate improved prednisolone-induced retardation of trabecular and cortical bone growth, but the bone turnover in these 2 sites was regulated differently in the growing rat mandibles. (Am J Orthod Dentofacial Orthop 2011;139:e267-e277)

Glucocorticoids are used to treat various diseases, such as severe asthma, juvenile rheumatoid arthritis, and chronic renal diseases, but the incidence rate of glucocorticoid-induced osteoporosis is approximately 50% in patients treated for 6 months or longer. In children, not only osteoporosis but also growth retardation occurred with chronic glucocorticoid therapy. Bone mass increases dramatically during childhood and adolescence, peaking in young adulthood (the peak bone mass) plateaus, and finally declines. The bone that must last a lifetime is made between the ages of 10 and 18 years. Patients whose bone mass does not reach the peak during childhood because of glucocorticoid-induced osteoporosis are at permanent risk of suffering fractures. In oral bone tissues, glucocorticoid affects mandibular bone growth and bone strength in humans and animals. However, little is known about bone metabolism and bone microarchitecture of the mandible with glucocorticoid-induced osteoporosis in children and adolescents. Furthermore, no guidelines exist for treating glucocorticoid-induced osteoporosis in children.

Bisphosphonates, which are widely used to manage adults with osteoporosis as first-line therapeutic agents, are divided into 2 classes according to their chemical structure and mechanism of action. The nitrogen-containing bisphosphonates, such as alendronate and risedronate, are markedly more potent inhibitors of osteoclastic bone resorption than nonnitrogen-containing bisphosphonates, such as etidronate and clodronate. Several recent reports described cases of osteonecrosis of the mandible associated with nitrogen-containing bisphosphonate therapy, and controversy is ongoing regarding this issue. A few clinical studies have indicated that bisphosphonate therapy inhibited loss of long bones in children with osteogenesis imperfecta.
and glucocorticoid-induced osteoporosis.17,18 However, the effects of nitrogen-containing bisphosphonates on bone structure and bone formation of the mandible in cases of established glucocorticoid-induced osteoporosis during the growth phase are unknown, and the cause of bisphosphonate-induced osteonecrosis of the jaw has not been clarified.

Peripheral quantitative computed tomography (pQCT) can be used to measure cortical and trabecular parts separately; this is useful for analyzing bone masses and cross-sectional areas, and also provides volumetric data.19 Recently, microcomputed tomography has been applied to quantify trabecular bone structure, such as trabecular bone volume and trabecular thickness.20 However, in the analyses with pQCT and microcomputed tomography, we can evaluate static phenomena of bone metabolism but not those associated with bone formation because the data have a temporal component. Both static and dynamic histomorphometry can be performed with 2-dimensional evaluation by using prepared specimens.

In this study, we evaluated the effects of risedronate, used frequently for treating osteoporosis, on trabecular and cortical bone density with pQCT, and bone structure and bone metabolism with static and dynamic histomorphometry in the mandibles of growing glucocorticoid-treated rats.

**MATERIAL AND METHODS**

In total, 48 male Wistar rats, aged 5 weeks, were purchased from Charles River Japan (Kanagawa, Japan). The animals were housed individually and maintained under a 12-hour light and 12-hour dark cycle at a constant temperature of 22°C ± 1°C with humidity of 50% ± 5%. The animals were given a standard pellet chow containing 1.14% calcium and 1.06% phosphorus (CE-2, CLEA Japan, Tokyo, Japan). The animal procedures were all approved by the Committee for the Care and Use of Laboratory Animals of Kyushu Dental College.

The animals were divided randomly into 6 groups of 8 each as follows: (1) control 6 weeks; (2) prednisolone (pred) 6 weeks; (3) control 10 weeks; (4) pred + saline solution; (5) pred + low risedronate (ris); and (6) pred + high ris (Table I). In the pred + saline and pred + ris groups, prednisolone was administered for 6 weeks followed by vehicle or ris for 4 weeks. Prednisolone sodium succinate (Prednine, Shionogi & Co, Osaka, Japan) was administered orally at 30 mg per kilogram per day or 1.0 mg per kilogram per starting immediately after the 6-week prednisolone regimen. We compared the control 6 weeks group with the pred 6 weeks group to confirm the establishment of osteoporosis induced by prednisolone administration. The effects of risedronate treatment were evaluated in the remaining 4 groups. The doses and durations of prednisolone treatment were determined from the results of a previous study that confirmed mandibular bone deterioration.11 The doses and durations of risedronate were determined from a previous study that demonstrated significant inhibition of bone loss in immobilized rats.21 Both compounds were dissolved in sterile saline solution before delivery so that the required dose was in a volume of 10 mL per kilogram of body weight. Prednisolone and vehicle (saline solution) were administered in the morning. Risedronate and vehicle (saline solution) were administered in the afternoon in animals that had fasted for 4 hours previously and 2 hours after risedronate administration. All rats were given free access to water throughout the experimental period.

Weight was measured weekly. At the end of the experimental period, all rats were deeply anesthetized with diethyl ether and given a lethal injection of thiampylal natrium (Isozole; Mitsubishi Pharma, Osaka, Japan) intraperitoneally at a dose of 90 mg per kilogram of body weight.

For dynamic histomorphometry, all rats were given a subcutaneous injection of calcine (8 mg/kg of body weight; Kanto Chemical, Tokyo, Japan) on days 10 and 3 before they were killed. Bilateral hemi-mandibles were removed from each animal, trimmed of soft tissues, and stored in 70% ethanol. The left hemi-mandible was used for measurement of mandibular bone weight as an index of bone growth and for pQCT analysis. The right hemi-mandible was used for histopathologic evaluation and bone histomorphometry.

Bone density (BD; mg/cm³), cross-sectional area (CSA; mm²), and mineral content (MC; mg/mm) of trabecular (Tr) and cortical (Ct) bone from the left

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>6 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 6 weeks</td>
<td>Prednisolone vehicle (saline)</td>
<td>—</td>
</tr>
<tr>
<td>Pred 6 weeks</td>
<td>Prednisolone vehicle (saline)</td>
<td>—</td>
</tr>
<tr>
<td>Pred + saline solution</td>
<td>30 mg/kg/2 days</td>
<td>Risedronate vehicle (saline)</td>
</tr>
<tr>
<td>Pred + low ris</td>
<td>Prednisolone vehicle (saline)</td>
<td>Risedronate vehicle (saline)</td>
</tr>
<tr>
<td>Pred + high ris</td>
<td>Prednisolone vehicle (saline)</td>
<td>Risedronate 0.5 mg/kg/day</td>
</tr>
</tbody>
</table>
The body weight and mandibular bone weight in the pred 6 weeks group were significantly lower than those in the control 6 weeks group, and these differences did not improve after 4 weeks of treatment with saline solution. However, treatment with risedronate reversed the prednisolone-induced decrease in mandibular bone weight (Table II).

The values of TrCSA, TrBMC, CtCSA, and CtBMC in the pred 6 weeks group were significantly lower than those in the control 6 weeks group, and these decreases did not improve after 4 weeks of treatment with saline solution. Although the mean value of CtBD in the pred 6 weeks group was lower than that in the control 6 weeks group, the difference was not significant. TrBD in the pred 6 weeks group was significantly higher than that in the control 6 weeks group. TrBD increased with risedronate in a dose-dependent manner, but lower doses of risedronate showed a tendency to improve TrCSA and TrBMC, and higher doses of risedronate significantly
reduced these parameters compared with the control 10 weeks group (Table III).

In cortical bone, both doses of risedronate improved the prednisolone–induced decreases in CtCSA and CtBMC (Table IV). Another representative pQCT mandibular bone scan indicated that the trabecular region in the pred 6 weeks group clearly decreased compared with the control 6 weeks group, and risedronate treatment dose-dependently reduced the trabecular bone area and increased the mineralization of trabecular bone (Fig 2).

The results of trabecular microstructural parameters indicated a significantly higher Tb.Sp in the pred 6 weeks group relative to the control 6 weeks group, and risedronate treatment dose-dependently reduced Tb.Sp and increased Tb.N (Table V).

The results of static histomorphometry of trabecular bone indicated that Ob.S/BS, Oc.S/BS, and ES/BS in the pred 6 weeks group significantly decreased compared with the control 6 weeks group (Table V), and osteoblasts with cuboidal morphology were observed in trabecular bone of the pred 6 weeks group (Fig 4). Risedronate decreased Oc.S/BS and ES/BS in a dose-dependent manner. Furthermore, ES/BS, Ob.S/BS, MS/BS, and BFR/BS were significantly lower with risedronate treatment in the control 10 weeks group (Table V). In the double-labeling study, the distance between labels narrowed in the risedronate–treated rats (Fig 3), and risedronate treatment altered the morphology of osteoblasts from cuboidal to a more flattened appearance compared with those in the untreated controls (Fig 4).

The results of dynamic histomorphometry in cortical bone indicated that MAR and BFR/BS in the pred 6 weeks group significantly decreased compared with the control 6 weeks group, and the mean values for MS/BS and BFR/BS in the pred + saline group were lower than those in the control 10 weeks group; these reductions, however, were not statistically significant (Table VI). The distance between double labels was narrowed by prednisolone administration (Fig 5). Risedronate dose-dependently increased MS/BS and BFR/BS, and these values in the pred + high ris group were significantly elevated compared with the control 10 weeks level (Table VI).

**DISCUSSION**

Prednisolone clearly reduced body weight and mandibular bone weight; these findings were consistent with those of other studies indicating that glucocorticoid treatment in growing rats reduced body weight and bone growth.\(^{11,28}\) In addition, prednisolone decreased TrCSA and TrBMC and caused deterioration of the connectivity of trabeculae (Tr.Sp). In contrast, TrBD in

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**Table II. Body weight and mandibular bone weight**

<table>
<thead>
<tr>
<th></th>
<th>Control 6 weeks</th>
<th>Pred 6 weeks</th>
<th>Control 10 weeks</th>
<th>Pred + vehicle</th>
<th>Pred + ris (0.5 mg/kg)</th>
<th>Pred + Ris (1.0 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>135.18 ± 2.89</td>
<td>133.48 ± 2.44</td>
<td>135.88 ± 1.31</td>
<td>136.38 ± 2.55</td>
<td>135.83 ± 1.92</td>
<td>134.75 ± 1.76</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>407.65 ± 11.41</td>
<td>368.63 ± 12.09*</td>
<td>422.80 ± 11.20</td>
<td>378.63 ± 12.46</td>
<td>384.7 ± 17.35</td>
<td>386.43 ± 20.57</td>
</tr>
<tr>
<td>Mandibular bone weight (g)</td>
<td>0.43 ± 0.02</td>
<td>0.40 ± 0.02*</td>
<td>0.52 ± 0.02</td>
<td>0.49 ± 0.031</td>
<td>0.51 ± 0.02</td>
<td>0.50 ± 0.03</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviations.  
*P < 0.05 vs control 6 weeks group (t test); 1P < 0.05 vs control 10 weeks group (ANOVA and Tukey test).

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**Table III. pQCT measurements of trabecular and cortical bone density, cross-sectional area, and mineral content**

<table>
<thead>
<tr>
<th></th>
<th>Control 6 weeks</th>
<th>Pred 6 weeks</th>
<th>Control 10 weeks</th>
<th>Pred + saline</th>
<th>Pred + low ris</th>
<th>Pred + high ris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular bone density (mg/cm³)</td>
<td>608.51 ± 38.91</td>
<td>646.38 ± 35.28*</td>
<td>707.60 ± 16.47</td>
<td>685.13 ± 28.79</td>
<td>684.73 ± 29.32</td>
<td>723.97 ± 26.00</td>
</tr>
<tr>
<td>Trabecular bone cross-sectional area (mm²)</td>
<td>1.56 ± 0.42</td>
<td>1.15 ± 0.24*</td>
<td>1.70 ± 0.38</td>
<td>1.22 ± 0.251</td>
<td>1.35 ± 0.47</td>
<td>1.19 ± 0.23</td>
</tr>
<tr>
<td>Trabecular bone mineral content (mg/mm)</td>
<td>1.01 ± 0.27</td>
<td>0.78 ± 0.20*</td>
<td>1.20 ± 0.26</td>
<td>0.83 ± 0.161</td>
<td>0.92 ± 0.30</td>
<td>0.86 ± 0.17</td>
</tr>
<tr>
<td>Cortical bone density (mg/cm³)</td>
<td>1268.86 ± 9.48</td>
<td>1261.75 ± 11.21</td>
<td>1301.63 ± 14.65</td>
<td>1296.55 ± 9.15</td>
<td>1301.45 ± 8.32</td>
<td>1298.41 ± 9.22</td>
</tr>
<tr>
<td>Cortical bone cross-sectional area (mm²)</td>
<td>6.73 ± 0.67</td>
<td>6.08 ± 0.63*</td>
<td>7.40 ± 0.52</td>
<td>6.74 ± 0.321</td>
<td>7.33 ± 0.331</td>
<td>7.51 ± 0.571</td>
</tr>
<tr>
<td>Cortical bone mineral content (mg/mm)</td>
<td>8.54 ± 0.87</td>
<td>7.67 ± 0.80*</td>
<td>9.62 ± 0.64</td>
<td>8.74 ± 0.361</td>
<td>9.55 ± 0.411</td>
<td>9.75 ± 0.721</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviations.  
*P < 0.05 vs control 6 weeks group (t test); 1P < 0.05 vs control 10 weeks group (ANOVA and Tukey test); 2P < 0.05 vs pred + saline group (ANOVA and Tukey test); 3P < 0.05 vs pred + high ris group (ANOVA and Tukey test).
the pred 6 weeks rats increased significantly compared with the untreated controls.

The major action of glucocorticoids on bone is to reduce osteoblast numbers and function, leading to suppression of bone formation.29 Furthermore, glucocorticoids might function secondarily to increase bone resorption. Glucocorticoids increase the expression of receptor activator of nuclear factor \( \kappa \)B ligand (RANK-L) and decrease the expression of its soluble decoy receptor osteoprotegerin (OPG) in stromal and osteoblastic cells.30 Glucocorticoids might also have direct effects on osteoclasts by suppressing the expression of autocrine cytokines, such as interferon \( \beta \), which normally exerts inhibitory effects on osteoclastogenesis.31

In this study, prednisolone significantly increased bone resorption (Oc.S/BS and ES/BS) but also showed a tendency to increase bone formation (Ob.S/BS and MS/BS). Although this trend was not significant, the differences were inconsistent with those of previous studies.

One possible explanation for those observations is that we simply altered a delicate balance between the activities of osteoblasts and osteoclasts, which generally act in tandem to establish an equilibrium between bone buildup and resorption, respectively. Nakamura et al32 reported that activated osteoblasts with a cuboidal shape were often observed near sites of osteoclast resorption in the trabecular bone of OPG–/– mice.

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indicating that bone formation is tightly coupled with bone resorption. In this study, the presence of similar formative osteoblasts in the trabecular bone from the pred 6 weeks rats suggested that prednisolone-treated growing rats tend to exhibit higher turnover rates in trabecular bone. Furthermore, we used pQCT, which measures the degree of bone mineralization.\textsuperscript{33} We considered that the increase in TrBD by prednisolone could be explained in terms of increased mineralization by prednisolone at sites where osteoblastic bone formation was most active in trabecular regions. The decreases in TrCSA and TrBMC by prednisolone, however, could...
have been the result of increased bone resorption by prednisolone, which in turn accelerated compensatory increases in bone formation.

In a previous study, chronic glucocorticoid treatment increased the rate of orthodontic tooth movement in rats and suggested that the orthodontic force level should be reduced in patients receiving chronic glucocorticoid treatment. This might be due to the increase in bone resorption and the deterioration of the trabecular architecture by glucocorticoid treatment.

In cortical bone regions, prednisolone decreased CtCSA and CtBMC by suppressing the BFR/BS, whereas the bone turnover rate had little effect on CtBD. This suppression caused a decrease in the MAR, generally considered to be an indicator of cellular activity. Thus, a unique suppressive effect of prednisolone on bone formation was found for the periosteal surface in the mandible. These results were consistent with those of recent clinical studies indicating that glucocorticoid treatment has little or no effect on bone mineral density despite an increased fracture risk, and that the cause of glucocorticoid-induced bone deterioration is the decrease in bone quality, such as bone geometry and bone metabolism.

In this study, risedronate treatment was started after 6 weeks of prednisolone administration. In many studies, however, both glucocorticoid and bisphosphonate had been given for the whole experimental period to evaluate the preventive effects of bisphosphonate on glucocorticoid-induced deterioration of bone structure in animals. However, little is actually known regarding whether risedronate improves the bone mass of the mandible or whether sufficient peak bone mass can be accumulated with glucocorticoid administration. In addition, few studies have examined the effects of risedronate on mandibular bone formation in young animals. Therefore, prednisolone was not given for the whole 10-week experimental period to investigate the effects of risedronate treatment alone on prednisolone-induced osteoporosis of the mandible in young rats.

Risedronate treatment improved the deterioration of mandibular bone growth induced by prednisolone. However, differential effects of risedronate on bone formation were seen between trabecular and cortical bone. Risedronate dose-dependently reduced bone resorption (Oc.S/BS and ES/BS). With regard to bone formation, the mean values of Ob.S/BS, BFR/BS, and MS/BS in the risedronate treatment groups were lower than those

**Fig 4.** Histologic evaluations of trabecular bone of the mandible. Original magnification: 400 times. Arrows indicate osteoblasts along the bone surface.
in the saline-treatment group, suggesting that risedronate tended to decrease bone formation. Furthermore, risedronate treatment altered the morphology of osteoblasts from cuboidal to flattened as in bone-lining cells. These results were similar to those of previous studies indicating that risedronate reduced bone formation in ovariectomized rats and caused dedifferentiation of active osteoblasts to flatter cells, more typical of bone lining cells in OPG−/− mice. Furthermore, risedronate dose-dependently increased TrBD and formed dense trabecular bone micro-architecture by decreasing bone turnover, but the higher dose of risedronate did not improve TrCSA or TrBMC. Therefore, we postulated that bisphosphonate-induced osteonecrosis of the jaw might have been due to excessive doses of bisphosphonates that suppressed trabecular bone turnover, which reduced new trabecular bone tissue formation and caused the accumulation of old trabeculae, although no gross

**Table VI.** Bone histomorphometry of cortical bone of the mandible: formative variables

<table>
<thead>
<tr>
<th></th>
<th>Control 6 weeks</th>
<th>Pred 6 weeks</th>
<th>Control 10 weeks</th>
<th>Pred + saline</th>
<th>Pred + low ris</th>
<th>Pred + high ris</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAR (μm/day)</td>
<td>3.20 ± 0.22</td>
<td>2.68 ± 0.24*</td>
<td>2.25 ± 0.02</td>
<td>2.34 ± 0.22</td>
<td>2.17 ± 0.08</td>
<td>2.36 ± 0.43</td>
</tr>
<tr>
<td>MS/BS (%)</td>
<td>65.53 ± 0.87</td>
<td>60.74 ± 7.58</td>
<td>46.13 ± 4.38</td>
<td>37.55 ± 2.31</td>
<td>54.43 ± 7.63</td>
<td>67.78 ± 3.64</td>
</tr>
<tr>
<td>BFR/BS (mm²/cm²/y)</td>
<td>76.66 ± 4.86</td>
<td>59.32 ± 3.63*</td>
<td>37.86 ± 3.98</td>
<td>32.17 ± 5.02</td>
<td>42.96 ± 4.59</td>
<td>58.22 ± 7.61</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviations.

*P < 0.05 vs control 6 weeks group (t test); #P < 0.05 vs control 10 weeks group (ANOVA and Tukey test); ^P < 0.05 vs pred + saline group (ANOVA and Tukey test).

**Fig 5.** Fluorescent micrographs showing double-labeled mineralization in the periosteal surface of cortical bone. Arrows indicate calcein that was taken into the bone formation area. Original magnification: 200 times.
histopathologic findings of osteonecrosis were found in the rat mandibles. Two experimental studies with small animals also showed the positive effects of bisphosphonates on bone healing after tooth movement or distraction osteogenesis. Adachi et al.\textsuperscript{40} reported that risedronate inhibited the relapse of moved teeth by inhibiting alveolar bone resorption in rats, and Tekin et al.\textsuperscript{41} reported that alendronate increased bone mineral density and accelerated bone healing on distraction osteogenesis of rabbit mandibles.

In a study of long-term bisphosphonate therapy, Odvina et al.\textsuperscript{42} discussed the possible adverse effects of long-term alendronate therapy for patients with postmenopausal osteoporosis who sustained spontaneous nonvertebral fractures; some showed delayed healing and histologic evidence of a marked reduction in bone turnover.

These findings suggest that short-term bisphosphonate treatment did not prevent healing of the mandible after orthodontic and surgical treatment, although long-term bisphosphonate treatment might cause detrimental changes in bone. Because the prevalence of osteonecrosis is more frequent in the jaws, we believe that the osteonecrosis is caused by other factors that are specific for jaw bones, in addition to the marked suppression of bone turnover.

Interestingly, Rizzoli et al.\textsuperscript{43} reported that previous histologic studies on bisphosphonate-induced osteonecrosis of the jaw all showed pronounced inflammatory changes. In addition, patients administered glucocorticoids show increased susceptibility to infectious diseases because glucocorticoids have a powerful immunosuppressive effect. Therefore, osteonecrosis of the jaw can occur more frequently when bisphosphonates are given with glucocorticoids because bacterial infection leads to exacerbation of inflammation in the mandible. However, few studies have been conducted regarding the relationship between the analysis of bacteria, such as those involved in periodontal disease and osteonecrosis of the jaw. Further studies are needed to determine whether anaerobic bacteria are involved in these effects.

In cortical bone, risedronate inhibited prednisolone-induced decreases in CtCSA and CtBMC. Furthermore, risedronate treatment increased MS/BS and BFR/BS. Consistent with our findings, bisphosphonate counteracted glucocorticoid-induced bone loss of longitudinal bones in rats.\textsuperscript{28} In contrast, risedronate suppressed periosteal osteoblast activity independent of resorption in rats’ longitudinal bones.\textsuperscript{44} Several studies have suggested that bisphosphonates have a stimulatory effect on osteoblast proliferation and differentiation in vitro.\textsuperscript{45-47} However, there is little evidence to indicate that risedronate increases bone formation in vivo.

Therefore, whether bisphosphonates stimulate or suppress osteoblast proliferation and differentiation, or both, is not yet clear, or whether the balance between proliferation and differentiation is just sensitive, similar to that between formation and resorption. A possible explanation for our findings is that the increase in sLs was greater than the decrease in dLs with risedronate in the bones of growing rats.

Risedronate, however, had no significant effect on CtBD. Consistent with our findings, risedronate prevented bone density loss of the femoral distal metaphysis without affecting bone density of the femoral diaphysis in sciatic neurectomized rats.\textsuperscript{48} Our findings suggest that risedronate had a positive effect on bone geometry but not on cortical bone density of growing rats.

**CONCLUSIONS**

Risedronate improved prednisolone-induced retardation of trabecular and cortical bone growth, but the bone turnover in these 2 sites is regulated differently in the growing rat’s mandible. In trabecular bone, risedronate improved the prednisolone-induced decrease in bone cross-sectional area and bone mineral content, and increased bone density by suppressing bone turnover. However, in cortical bone, risedronate increased the mineralizing surface and improved prednisolone-induced decreases in bone cross-sectional area and bone mineral content with no effect on bone density.

We thank Kiichi Nonaka (Elk Corporation Research Laboratory, Tokyo, Japan) and Hisashi Murayama (Kureha Special Laboratory, Tokyo, Japan) for technical assistance in the bone histomorphometry and helpful discussions.

**REFERENCES**