The Selective Cyclooxygenase-2 Inhibitor Celecoxib Reduces Bone Resorption, but not Bone Formation, in Ovariectomized Mice in Vivo

YUJI KASUKAWA,1 NAOHISA MIYAKOSHI,1 APURVA K. SRIVASTAVA,2,3 KOJI NOZAKA,1 SHIGETO MAEKAWA,1 DAVID J. BAYLINK,2,3 SUBBURAMAN MOHAN2,3 and EIJI ITOI1

1Division of Orthopedic Surgery, Department of Neuro and Locomotor Science, Akita University School of Medicine, Akita, Japan
2Musculoskeletal Disease Center, Jerry L. Pettis VA Medical Center, Loma Linda, CA, USA
3Department of Medicine, Loma Linda University, Loma Linda, CA, USA

KASUKAWA, Y., MIYAKOSHI, N., SRIVASTAVA, A.K., NOZAKA, K., MAEKAWA, S., BAYLINK, D.J., MOHAN, S. and ITOI, E. The Selective Cyclooxygenase-2 Inhibitor Celecoxib Reduces Bone Resorption, but not Bone Formation, in Ovariectomized Mice in Vivo. Tohoku J. Exp. Med. 2007, 211 (3), 275-283 —— Suppression of increased bone resorption is an important issue in treatment of post-menopausal osteoporosis. Celecoxib is a highly selective inhibitor of cyclooxygenase-2 (COX-2), and inhibits osteoclastogenesis in vitro. In the present study, to test whether celecoxib can suppress elevated bone resorption caused by estrogen deficiency in vivo, celecoxib (4 mg/kg) or its vehicle was administered to sham-operated or ovariectomized (OVX) mice (model of post-menopausal osteoporosis). The treatment with celecoxib or vehicle was started immediately after the sham operation or ovariectomy, and lasted for 4 weeks. At 2 and 4 weeks after surgery, OVX mice administered vehicle had significantly higher levels of C-telopeptide, a marker of bone resorption in serum, than sham-operated mice administered vehicle (37% and 60% higher, respectively; p < 0.01). At 2 and 4 weeks after surgery, celecoxib treatment significantly decreased serum C-telopeptide levels in OVX mice, but not in sham-operated mice (45% and 41%, respectively; p < 0.001). In contrast, in both sham-operated and OVX mice, celecoxib did not significantly affect serum osteocalcin levels (a marker of bone formation) or bone mineral density (BMD) of the femur, which was evaluated by peripheral quantitative computed tomography (pQCT). In conclusion, treating OVX mice with celecoxib significantly suppressed the increase in serum levels of the bone resorption marker, but did not affect levels of the bone formation marker. Also, celecoxib did not prevent the decrease of femoral BMD in OVX mice. The present study suggests the possibility that celecoxib may be used to prevent bone loss caused by estrogen deficiency.

celecoxib; cyclooxygenase-2 (COX-2) inhibitor; ovariectomized mice; bone formation; bone resorption
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Correspondence: Yuji Kasukawa, M.D., Department of Orthopedic Surgery, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan.
e-mail: kasukawa@doc.med.akita-u.ac.jp
Throughout life, the skeleton is continuously renewed by bone remodeling. Osteoporotic conditions are caused by negative bone balance, in which the amount of bone formed by osteoblasts is less than the amount of bone resorbed by osteoclasts. Post-menopausal estrogen deficiency leads to increased bone resorption that is not counterbalanced by a corresponding increase in bone formation (Garnero et al. 1996). Suppression of this increased bone resorption is a key issue in treatment of post-menopausal osteoporosis. In studies of the mechanism of the increased bone resorption caused by estrogen deficiency, cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), have been implicated as mediators of increased osteoclastogenesis that occurs during estrogen deficiency (Kimble et al. 1997).

The effects of inflammatory cytokines and growth factors on osteoclasts during the post-menopausal period may involve prostaglandins, which are produced from membrane phospholipids by sequential actions of phospholipase A2 and cyclooxygenase (COX) (Kawaguchi et al. 1995). Two isoenzymes of COX have been identified: COX-1 and COX-2. COX-1 provides homeostatic levels of prostaglandins throughout the body (Vane et al. 1998), and COX-2 is an inducible enzyme whose expression can be stimulated by inflammation (Muscarat et al. 2000).

Celecoxib, 4-(5-[4-methylphenyl]-3-[trifluoromethyl]-1H-pyrazol-1-yl) benzenesulfonamide, is a highly selective inhibitor of COX-2 that has been shown to have anti-inflammatory effects. A previous in vitro study showed that celecoxib inhibits osteoclastogenesis induced by the inflammatory cytokines IL-1β, TNF-α, and endotoxin lipopolysaccharide (LPS) (Igarashi et al. 2002). However, there have been no reported studies of the in vivo effects of celecoxib on bone resorption. The goal of the present study was to determine whether celecoxib reduced bone turnover in vivo, using serum bone metabolic markers, and to determine whether celecoxib can be used to prevent the bone loss and the increase in bone turnover that occur in ovariectomized mice, which are commonly used as a model of post-menopausal osteoporosis.

**Materials and Methods**

**Animals**

Eight-week-old female C3H mice (CLEA Japan Inc., Tokyo) were pair-fed and allowed free access to water and standard food (CE-2, CLEA Japan Inc.) containing 1.14% calcium, 1.06% phosphorus, and 250 IU vitamin D₃ per 100 g. They were housed in a controlled environment at 22°C with a 12-hr light/dark cycle. Their body weight was measured once per week.

**Experimental protocol**

At 8 weeks of age, mice underwent ovariectomy (OVX; n = 18) or a sham operation (n = 20), under anesthesia by intraperitoneal injection of Ketamine (Sankyo, Tokyo) and Xylazine (Zenoaq, Fukushima). Daily oral administration of celecoxib (Pharmacia, Tokyo, Japan/Pfizer, New York, NY, USA) or its vehicle was started immediately after the operation, and continued for 4 weeks. Celecoxib (4 mg/kg body weight) was diluted with 0.5% carboxymethylcellulose and 0.5 ml of water, and was administered orally once per day using a metal probe. The present dose of celecoxib was based on results of a previous in vivo study of the use of celecoxib to decelerate fracture healing (Simon et al. 2002). The animals were divided into 4 groups according to surgery and celecoxib/vehicle administration: sham-vehicle group, sham-operated with vehicle administration (n = 8); sham-celecoxib group, sham-operated with celecoxib administration (n = 8); OVX-vehicle group, OVX with vehicle administration (n = 5); OVX-celecoxib group, OVX with celecoxib administration (n = 10). At 2 weeks after surgery, blood samples were collected by eye bleeding, under anesthesia with Ketamine and Xylazine (Schnell et al. 2002). Four weeks after surgery, the mice were euthanized by CO₂ inhalation and decapitated, and blood and bilateral femora were collected. Serum samples used to assay bone metabolic markers were stored at –70°C until the biochemical measurements were performed. Before bone density measurement, femur length was measured using a caliper (Shinwa, Niigata). The present animal experimentation protocols were approved by the Animal Committee, Akita University School of Medicine. All animal experiments conformed to the “Guidelines for Animal Experimentation” of Akita University.

**Biochemical assays**

* C-telopeptide ELISA. Serum C-telopeptide levels were measured by mouse C-telopeptide ELISA, using
affinity-purified antibodies generated against the human amino acid sequence of C-telopeptide (Srivastava et al. 2000). The sensitivity of the ELISA was < 0.1 ng/ml. The inter- and intra-assay CVs were < 12%.

**Osteocalcin RIA.** Serum osteocalcin levels were measured using a commercially available mouse osteocalcin assay kit (Biomedical Technologies, Inc, Stoughton, MA, USA) (Srivastava et al. 2000). The sensitivity of the assay was 6.25 ng/ml, and inter- and intra-assay CVs were < 10%.

**Bone mineral density (BMD) measurement and geometric parameters of femur**

BMD and geometric parameters of the harvested femurs were measured by peripheral quantitative computed tomography (pQCT) (XCT-Research SA+, Stratec, Pforzheim, Germany). Previous studies indicate that the femur is an ideal site for evaluation of trabecular and/or cortical BMD as well as geometrical parameters including periosteal or endosteal perimeters using pQCT (Kasukawa et al 2003). A two-dimensional scout view of the femur was obtained first, and a distal growth plate of the femur was identified as a landmark. Measurements were performed at the metaphysis and mid-diaphysis of the femur, at 1.4 mm and 5.5 mm proximal to the growth plate, respectively. Analyses of the scans were performed using the manufacturer-supplied software. Two different thresholds were used for the analysis of scans: a lower threshold of 395 mg/cm$^3$ for the metaphysis; and a higher threshold of 464 mg/cm$^3$ for the mid-diaphysis. We measured total BMD of the metaphysis and mid-diaphysis, and we measured cortical + subcortical BMD and trabecular BMD at the metaphysis. We also measured total area, cortical + subcortical area, and trabecular area at the metaphysis, and we measured cortical area, cortical thickness, periosteal perimeter, and endosteal perimeter.

**RESULTS**

**Body weight and femur length**

Body weight of the OVX-vehicle group was significantly greater than that of the sham-vehicle group (16%, $p < 0.05$) at 4 weeks after surgery (Table 1). Body weight of the OVX-celecoxib group was significantly greater than that of the sham-celecoxib group (6%, $p < 0.05$) at 4 weeks after surgery (Table 1).

Femoral length of the OVX-vehicle group was significantly greater than that of the sham-vehicle group (2.6%, $p < 0.0001$). Femoral length of the OVX-celecoxib group was significantly less than that of the OVX-vehicle group (1.3%, $p < 0.05$) (Table 1).

**Serum bone metabolic markers**

Ovariectomy had significant effects on the levels of serum C-telopeptide and osteocalcin. Celecoxib treatment had significant effects on the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-vehicle ($n = 8$)</th>
<th>Sham-celecoxib ($n = 8$)</th>
<th>OVX-vehicle ($n = 5$)</th>
<th>OVX-celecoxib ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>20.3 ± 0.4</td>
<td>20.1 ± 0.2</td>
<td>20.4 ± 0.3</td>
<td>20.1 ± 0.3</td>
</tr>
<tr>
<td>Start</td>
<td>20.8 ± 0.8</td>
<td>22.3 ± 0.4</td>
<td>24.1 ± 0.4$^4$</td>
<td>23.7 ± 0.4$^{4,AA}$</td>
</tr>
<tr>
<td>4 weeks after surgery</td>
<td>15.4 ± 0.05</td>
<td>15.3 ± 0.07</td>
<td>15.8 ± 0.07$^4$</td>
<td>15.6 ± 0.06$^B$</td>
</tr>
</tbody>
</table>

The values are mean ± s.e.m.

$^4p < 0.05$ vs sham-vehicle group; $^Bp < 0.05$ vs sham-celecoxib group.

$^Bp < 0.05$ vs OVX-vehicle group.
serum levels of C-telopeptide, but not on the levels of osteocalcin (Table 2). However, there was no significant interaction between the effects of ovariectomy or celecoxib treatment on bone metabolic markers and the length of the postoperative period or the length of the treatment period (Table 2).

At 2 and 4 weeks postoperative, serum C-telopeptide levels were significantly higher in the OVX-vehicle group (20.2 ± 1.7 ng/ml and 21.6 ± 1.2 ng/ml, respectively) than in the sham-vehicle group (14.7 ± 0.9 ng/ml and 13.5 ± 1.5 ng/ml, respectively) (37% and 60% higher, respectively; p < 0.01; Fig. 1). At 2 and 4 weeks after surgery, serum C-telopeptide levels were lower in the sham-celecoxib group (11.6 ± 0.6 ng/ml and 9.4 ± 0.5 ng/ml, respectively) than in the sham-vehicle group, but these differences were not statistically significant (21% and 30% lower, respectively). At 2 and 4 weeks after surgery, serum C-telopeptide levels were significantly lower in the OVX-celecoxib group (11.1 ± 1.0 ng/ml and 12.7 ± 0.8 ng/ml, respectively) than in the OVX-vehicle group (45% and 41% lower, respectively; p < 0.001; Fig. 1).

The OVX-vehicle group had a significantly higher serum osteocalcin level than the sham-vehicle group at 4 weeks after the operation (69%, p < 0.01), but not 2 weeks after surgery (Fig. 2). There was no significant difference in serum osteocalcin levels between the sham-vehicle and sham-celecoxib groups or between the OVX-

<table>
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<tr>
<th></th>
<th>OVX</th>
<th>Celecoxib</th>
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<tr>
<td>C-telopeptide</td>
<td>Significance</td>
<td>Interaction</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.05</td>
<td>NS</td>
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<tr>
<td>Osteocalcin</td>
<td>p &lt; 0.001</td>
<td>NS</td>
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</table>

The values represent p levels for the effects of ovariectomy or celecoxib treatment by repeated analysis of variance (ANOVA). NS, not significant.

Fig. 1. Serum levels of C-telopeptide.
Effects of vehicle (Ve) and celecoxib (Ce) treatment on serum C-telopeptide levels in sham-operated (Sham) and ovariectomized (OVX) mice at 2 and 4 weeks after surgery. The values are expressed as mean ± s.e.m. (n = 5-10) A: p < 0.01, compared to the sham-vehicle group. B: p < 0.001, compared to the OVX-vehicle group.
vehicle and OVX-celecoxib groups at 2 or 4 weeks after surgery (Fig. 2).

**BMD**

At the metaphysis, total and trabecular BMD, but not cortical+subcortical BMD, were significantly lower in the OVX-vehicle group than in the sham-vehicle group. The sham-celecoxib group had higher total and trabecular BMD than the sham-vehicle group at the metaphysis (6% and 6%, respectively), but these differences were not statistically significant ($p = 0.06$ and $p = 0.08$, respectively). There was no significant difference in total, cortical+subcortical, or trabecular BMD between the OVX-celecoxib group and OVX-vehicle group at the metaphysis. At the mid-diaphysis, total BMD was lower in the OVX-vehicle group than in the sham-vehicle group (2% lower), but the difference was not statistically significant. There was no significant difference in total BMD at the mid-diaphysis between the sham-celecoxib and sham-vehicle groups or between the OVX-celecoxib and OVX-vehicle groups (Table 3).

**Geometric parameters**

There were no significant differences in total area of the metaphysis among the 4 groups. The

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**Fig. 2. Serum levels of osteocalcin.**

Effects of vehicle (Ve) and celecoxib (Ce) treatment on serum osteocalcin levels in sham-operated (Sham) and ovariectomized (OVX) mice at 2 and 4 weeks after surgery. The values are expressed as mean ± S.E.M. ($n = 5-10$) A: $p < 0.01$, compared to the sham-vehicle group.

<table>
<thead>
<tr>
<th>TABLE 3. Femoral BMD measured by pQCT.</th>
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<tr>
<td>Variable</td>
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<tr>
<td><strong>Metaphysis</strong></td>
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<tr>
<td>Total BMD</td>
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<tr>
<td>Cortical + subcortical BMD</td>
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<tr>
<td>Trabecular BMD</td>
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<tr>
<td><strong>Mid-diaphysis</strong></td>
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<td>Total BMD</td>
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The values are mean ± S.E.M. (mg/cm$^3$)

$^A p < 0.05$, $^B p < 0.001$ vs sham-vehicle group.
cortical + subcortical area of the metaphysis was significantly smaller in the OVX-vehicle group than in the sham-vehicle group (18%, $p < 0.001$). The trabecular area of the metaphysis was significantly larger in the OVX-vehicle group than in the sham-vehicle group (37%, $p < 0.001$). These results suggest that ovariectomy increased bone resorption at the endosteal surface, leading to expansion of the trabecular area at the expense of the subcortical area. The sham-celecoxib group had greater cortical + subcortical area (10%) and less trabecular area (23%) at the metaphysis than the sham-vehicle group, but these differences were not statistically significant. There was no significant difference in cortical + subcortical area or trabecular area at the metaphysis between the OVX-celecoxib and OVX-vehicle groups.

At the mid-diaphysis, there was no significant difference in the cortical area, cortical thickness, periosteal perimeter, or endoosteal perimeter between the OVX-vehicle group and the sham-vehicle group. There was no significant difference in the geometric parameters at the mid-diaphysis between the sham-celecoxib and sham-vehicle groups or between the OVX-celecoxib and OVX-vehicle groups (Table 4).

**DISCUSSION**

The present findings show that celecoxib administration significantly decreased the serum levels of C-telopeptide (bone resorption marker), but not osteocalcin (bone formation marker), in the OVX mice. Because celecoxib decreased serum C-telopeptide levels by 45% in the present OVX mice, we expected that celecoxib would at least partially prevent ovariectomy-induced bone loss in mice. However, we found that celecoxib did not cause a significant increase in BMD in the OVX mice. Although there was an increase in total BMD at the femoral metaphysis in sham-operated mice administered celecoxib, this increase was not statistically significant.

Several previous studies have provided convincing evidence that prostaglandin stimulates bone resorption, and that several systemic and local regulators recruit prostaglandins to mediate their effects on osteoclasts (Suda et al. 1999; Wani

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**Table 4. Femoral geometric parameters measured by pQCT.**

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<thead>
<tr>
<th></th>
<th>Sham-vehicle ($n = 8$)</th>
<th>Sham-celecoxib ($n = 8$)</th>
<th>OVX-vehicle ($n = 5$)</th>
<th>OVX-celecoxib ($n = 10$)</th>
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<tbody>
<tr>
<td><strong>Metaphysis</strong></td>
<td></td>
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<tr>
<td>Total area (mm$^2$)</td>
<td>2.82 ± 0.01</td>
<td>2.78 ± 0.05</td>
<td>2.85 ± 0.04</td>
<td>2.77 ± 0.04</td>
</tr>
<tr>
<td>Cortical+subcortical</td>
<td>1.85 ± 0.03</td>
<td>2.03 ± 0.06</td>
<td>1.52 ± 0.05$^b$</td>
<td>1.54 ± 0.05$^b$</td>
</tr>
<tr>
<td>area (mm$^2$)</td>
<td></td>
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<tr>
<td>Trabecular area (mm$^2$)</td>
<td>0.97 ± 0.04</td>
<td>0.75 ± 0.05</td>
<td>1.33 ± 0.06$^b$</td>
<td>1.23 ± 0.06$^A$</td>
</tr>
<tr>
<td><strong>Mid-diaphysis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cortical area (mm$^2$)</td>
<td>0.98 ± 0.01</td>
<td>1.01 ± 0.01</td>
<td>0.96 ± 0.01</td>
<td>0.96 ± 0.01</td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>0.345 ± 0.005</td>
<td>0.357 ± 0.009</td>
<td>0.341 ± 0.005</td>
<td>0.335 ± 0.007</td>
</tr>
<tr>
<td>Periosteal perimeter (mm)</td>
<td>3.919 ± 0.023</td>
<td>3.952 ± 0.021</td>
<td>3.901 ± 0.015</td>
<td>3.926 ± 0.028</td>
</tr>
<tr>
<td>Endoosteal perimeter (mm)</td>
<td>1.752 ± 0.029</td>
<td>1.709 ± 0.065</td>
<td>1.757 ± 0.018</td>
<td>1.818 ± 0.064</td>
</tr>
</tbody>
</table>

The values are mean ± S.E.M.

$^A p < 0.05$, $^B p < 0.001$ vs sham-vehicle group.
et al. 1999). In a study by Igarashi et al. (2002), celecoxib completely inhibited the osteoclastogenesis induced by IL-1β, TNFα and LPS in vitro, suggesting that the effect of these cytokines on osteoclasts is mediated partly by increased production of prostaglandins. Furthermore, a deficiency in steroid sex hormones can increase osteoclastogenesis via increased production of cytokines such as IL-6, IL-1β and TNFα (Kitazawa et al. 1994; Bismar et al. 1995). Estrogen deficiency has been shown to increase production of prostaglandin E2 (PGE2) in ex vivo cultures of human and rat marrow stromal cells (Bismar et al. 1995; Kawaguchi et al. 1995). Although it is not known to what extent the increased production of PGE2 during estrogen deficiency contributes to increased bone resorption, the present finding that celecoxib treatment decreased serum c-telopeptide levels by 45% in ovariectomized mice after 2 weeks of treatment represents convincing evidence that ovariectomy-induced increases in bone resorption are caused in part by increased prostaglandin production.

We can only speculate as to why celecoxib did not prevent ovariectomy-induced bone loss in the present study. PGE2 is a strong anabolic agent that stimulates bone formation in ovariectomized mice (Keila et al. 2001). Thus, inhibition of COX-2 activity may cause the rate of bone formation to fall below that of bone resorption. Consistent with this idea, Simon et al. (2002) have reported that celecoxib caused a delay in fracture healing in wild-type mice, and that normal fracture healing failed in COX-2 null mice. If celecoxib causes a reduction in bone formation, we would expect osteocalcin levels to be lower in celecoxib-treated mice than in vehicle-treated mice. However, that was not the case in the present study. In a related study, Weinreb et al. (2002) found that inhibition of COX-2 activity did not abolish the anabolic effect of PGE2 on bone formation in vivo or in vitro. Furthermore, the effects of the selective COX-2 inhibitor celecoxib on bone metabolism and remodeling remain controversial. In several studies, celecoxib delayed fracture healing or bone ingrowth into implants (Simon et al. 2002). However, in other studies, celecoxib did not affect fracture healing or bone union (Brown et al. 2004). Further studies are needed to clarify the effects of the selective COX-2 inhibitor celecoxib on bone metabolism and bone healing.

Studies show that the effects of selective COX-2 inhibitors on bone are clinically relevant. Several studies of inhibition of PGE2 have shown that non-steroidal anti-inflammatory drugs (NSAIDs) also inhibit resorptive responses of bone to cytokines and hormones (Akatsu et al. 1989; Shinar and Rodan 1990). Selective COX-2 inhibitors are associated with lower risk of gastrointestinal and platelet side effects and lower incidence of impaired renal function, compared with conventional NSAIDS. That suggests that COX-2-specific inhibitors are more suitable for long-term treatment of older patients, who are at risk for osteoporosis and often suffer from joint pain. However, recent reports indicate that continuous administration of COX-2 inhibitors increases the risk of cardio-vascular events (Juni et al. 2004). Therefore, it is important to evaluate the relative benefits and risks of use of COX-2-specific inhibitors to regulate bone metabolism or bone mineral density, and to pay particular attention to their effects on the cardiovascular system.

The present study had the following 3 major limitations:

1) Celecoxib was administered with a single dosage and duration. The dose and duration of celecoxib used in the present study, 4 mg/kg/BW (which is within the recommended dose range for humans) and 4 weeks, respectively, were based on the results of previous in vivo studies (Simon et al. 2002; Brown et al. 2004), including the finding that celecoxib administration at a dose of 1.5 mg/kg or 7.5 mg/kg does not cause significant changes in bone strength or BMD in rats with renal failure (Kamae et al. 2003). A higher dosage or longer duration of treatment is apparently needed to evaluate effects of celecoxib on bone mineral density or bone strength.

2) The level of PGE2, which plays a key role in the effects of selective COX-2 inhibitors on bone resorption, was not measured after the in vivo administration of celecoxib. McAdam et al.
(1999) reported that celecoxib treatment at a dose of 100 to 400 mg had an inhibitory effect on COX-2 activity, as indicated by levels of endotoxin-induced PGE2, which were reduced to levels that were 75% to 86% of their control levels. Based on those findings, we assume that the PGE2 level in the serum of the present mice was decreased to a certain degree after celecoxib treatment. Measurement of serum levels of PGE2 is needed to elucidate the mechanisms by which celecoxib affects bone resorption before and after treatment in ovariec-tomized mice.

3) Effects of celecoxib on bone resorption and formation were evaluated using only a single metabolic marker each for resorption and formation, and bone histomorphometry was not examined. In order to obtain conclusive results as to whether celecoxib is useful for treatment or prevention of osteoporosis, it is necessary to conduct several other types of research including measurement of BMD at other sites of bone, bone histomorphometry, bone mechanical testing, and human studies.

In conclusion, the present study of in vivo celecoxib treatment of OVX mice revealed that celecoxib significantly suppressed expression of a serum bone resorption marker, but did not suppress expression of a bone formation marker. However, this significant effect on a bone resorption marker did not result in prevention of bone loss in the OVX mice, which had an estrogen deficiency. Further studies are needed to determine whether celecoxib can be used to prevent bone loss that involves increased bone resorption due to elevated PGE2 production.

Acknowledgments

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References


Bismar, H., Dietl, I., Ziegler, R. & Pfeilschifter, J. (1995) Increased cytokine secretion by human bone marrow cells after menopause or discontinuation of estrogen replace-


measurement of bone resorption in mouse serum. Bone, 27, 529-533.