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ORIGINAL RESEARCH

Effects of short-term combined treatment with alendronate and elcatonin on bone mineral density and bone turnover in postmenopausal women with osteoporosis

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Abstract: The antiresorptive drug elcatonin (ECT) is known to relieve pain in postmenopausal women with osteoporosis. A prospective open-labeled trial was conducted to compare the effects of short-term combined treatment with alendronate (ALN) and ECT on bone mineral density (BMD) and bone turnover with those of single treatment with ALN in postmenopausal women with osteoporosis. Two hundred and five postmenopausal osteoporotic women (mean age: 70 years) were recruited in our outpatient clinic. Forty-six women with back pain were treated with ALN and ECT (intramuscular, 20 units a week), and 159 women without obvious back pain were treated with ALN alone. The lumbar BMD, urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX), and serum levels of alkaline phosphatase (ALP) were measured during the six-month treatment period. The baseline characteristics, except for age, body weight and number of patients with prevalent vertebral fractures, were not significantly different between the two groups. The mean increase rate in the lumbar BMD at six months was similar in the ALN (+4.41%) and ALN+ECT (+5.15%) groups, following similar reduction rates in urinary NTX levels (−40.2% and −43.0%, respectively, at three months) and serum ALP levels (−19.0% and −19.7%, respectively, at six months). These results were consistent even after adjustments for age, body weight, and number of patients with prevalent vertebral fractures. The present study in postmenopausal osteoporotic women confirmed that the effects of short-term combined treatment with ALN and ECT on lumbar BMD and bone turnover in patients with back pain appeared to be comparable to those of single treatment with ALN in patients without obvious back pain.

Keywords: alendronate, elcatonin, osteoporosis, postmenopausal women, back pain

Background

Osteoporosis most commonly affects postmenopausal women, placing them at a significant risk for fractures. Alendronate (ALN) and intramuscular elcatonin (ECT) are widely used for the treatment of postmenopausal osteoporosis in Japan. ALN is a bisphosphonate, which regulates bone turnover through the suppression of osteoclastic activity.[1] Current evidence suggests the antifracture efficacy and safety of ALN in postmenopausal women with osteoporosis.[2–4] On the other hand, ECT is a derivative of eel calcitonin synthesized by substituting an ethylene bond for its disulfide bond.[5] Intramuscular ECT was developed in Japan and has been shown to have biological activity comparable to that of natural eel calcitonin.[5–7] It has also been reported *in vivo* and *in vitro* studies that ECT suppresses bone resorption.[7,8] ECT has been reported to increase metacarpal and forearm bone mineral density

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(BMD) in postmenopausal women with osteoporosis.[9,10] A recent study shows that ECT is useful for relieving pain and improving quality of life in postmenopausal women with osteoporosis.[11] However, there is no evidence showing that ECT significantly reduces the incidence of fractures.[12] Therefore, ECT must primarily be used to relief pain in patients with osteoporosis. Its use is limited to a maximum period of six months in Japan.

Because of the above-mentioned differential effects, combined treatment with ALN and ECT might be useful for preventing fractures and relieving pain in postmenopausal osteoporotic women with back pain. However, combined treatment with two anti-resorptive drugs could induce a severe suppression of bone turnover. The effects of combined treatment with these two drugs on BMD and bone turnover remain to be established in postmenopausal osteoporotic women with back pain. The objective of this prospective open-labeled trial was to compare the effects of short-term (six months) combined treatment with ALN and ECT on BMD and bone turnover in postmenopausal osteoporotic women with back pain with the effects of single treatment with ALN only in those without obvious back pain. The incidence of clinical fractures was also compared between two groups.

Subjects and methods

Subjects

Two hundred and thirty-four postmenopausal women (age range: 48–89 years; mean age: 70.1 years) were recruited in the outpatient clinic of Keiyu Orthopaedic Hospital (Gunma, Japan) during the three-year period between October 2005 and September 2008. Inclusion criteria were postmenopausal women with osteoporosis with or without a history of osteoporotic fractures. Exclusion criteria were histories of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, or bone diseases including primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, multiple myeloma, rheumatoid arthritis, and osteogenesis imperfecta. Subjects who had ever taken medication known to affect bone metabolism were also excluded. None of the subjects included in the present trial participated in regular sporting activities or were heavy laborers.

All the patients had been diagnosed as having osteoporosis according to the Japanese diagnostic criteria.[13,14] Namely, patients with a BMD $<$ 70% of the young adult mean (YAM) or of 70%–80% of the YAM along with a history of osteoporotic fractures were diagnosed as having osteoporosis. A preliminary screening included a medical history, physical examination, plain X-rays of the thoracic and lumbar spine, lumbar BMD measurement, and blood and urinary biochemical tests including serum calcium, phosphorus, and total alkaline phosphatase (ALP) and urinary cross-linked N-terminal telopeptides of type I collagen (NTX).

Fifty-four women with back pain were treated with ALN (5 mg/day or 35 mg/week) and ECT (intramuscular, 20 units a week) (the ALN+ECT group), and 180 women without obvious back pain were treated with ALN alone (5 mg/day or 35 mg/week) (the ALN group). The doses indicated in the parentheses above are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective.[15–17] Daily ALN and intramuscular ECT treatment were available throughout the study period, but weekly ALN treatment only became available after October 2006. All the subjects in both groups were given a pamphlet instructing them to consume about 800 mg of dietary calcium and 400 IU of dietary vitamin D daily during the study period. All of the subjects in the ALN+ECT group were also treated with oral non-steroidal anti-inflammatory drugs (NSAIDs) (zaltoprofen), percutaneous NSAIDs (ointment or compress), and/or trigger point injections of lidocaine hydrochloride due to back pain. The duration of the trial was six months.

The urinary levels of NTX were measured at three months after the start of treatment. The serum levels of calcium, phosphorus, and ALP and the lumbar BMD were measured at six months after the start of treatment. The incidence of clinical fractures, which were diagnosed with radiographs or magnetic resonance images, was assessed during the six-month treatment period. Informed consent was obtained from each participant prior to her participation in the study. This protocol was approved by the Ethics Committee of Keiyu Orthopaedic Hospital.

Assessment of vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture was defined according to the vertebral height on lateral X-ray films.[13,14] Briefly, the vertebral height was measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when (1) a reduction in the vertebral height of more than 20% (A, C, and P) compared with the height of the adjacent vertebrae was observed, (2) the C/A or C/P was less

than 0.8, or (3) the A/P was less than 0.75. The assessment for vertebral fractures was performed at the T4–L4 level.

Measurement of lumbar BMD

The BMD of the lumbar spine (L1–L4) in the anteroposterior view was measured using dual-energy X-ray absorptiometry (DXA) with a Hologic QDR 1500W apparatus (Bedford, MA, USA). The coefficient of variation (100 × standard deviation/mean) of five measurements with repositioning within 72 hours each time was less than 1.2% in three persons.

Measurement of biochemical markers

Urine and blood samples were obtained from the subjects in the morning between 9:00 am and 11:00 am. The urinary levels of NTX were measured using an enzyme-linked immunosorbent assay. The serum levels of calcium, phosphorus, and ALP were measured using standard laboratory techniques.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Cross-sectional data comparisons between the two groups were performed using an unpaired t-test and analysis of covariance (ANCOVA). The significance of longitudinal changes in the parameters in a group was determined using a one-way analysis of variance (ANOVA) with repeated measurements. Longitudinal changes in the parameters were compared between the two groups using a two-way ANOVA with repeated measurements. The ratio of daily to weekly ALN, percentage of women with fractures, and incidence of clinical fractures were compared between the two groups by the Fisher's exact test. All statistical analyses were performed using the StatView-J5.0 program (Windows version; SAS Institute, Cary, NC, USA). A significance level of $p < 0.05$ was used for all the comparisons.

Results

Dropout of study subjects

Twenty (11.7%) women in the ALN group and 8 (14.8%) women in the ALN+ECT group discontinued treatment during the six-month period. The main reasons for the dropout from the trial were difficulty in compliance, epigastric pain, gastric ulcers, heartburn, and tooth treatment (extraction) concerning osteonecrosis of the jaw in the ALN group, and difficulty in compliance, epigastric pain and loss to follow-up in the ALN+ECT group (Table 1). Facial flushing was observed in relation to ECT treatment in three women, but this symptom was mild and required no treatment or withdrawal of the drug treatment. No serious adverse events necessitating hospitalization were observed in either group. The trial was completed in 159 (88.3%) women in the ALN group and 46 (85.2%) women in the ALN+ECT group (age range: 49–89 years; mean age: 70.0 years), and the data for these women were used in the subsequent statistical analyses.

Table 1 Reasons for dropout from the trial

ALN group (n = 20)	ALN+ECT group (n = 8)
Difficulty in compliance (n = 15)	Difficulty in compliance (n = 6)
Epigastric pain (n = 2)	Epigastric pain (n = 1)
Gastric ulcer (n = 1)	Loss to follow-up (n = 1)
Heartburn (n = 1)	
Treatment (extraction) of tooth (n = 1)	

Notes: Twenty (11.7%) women in the alendronate (ALN) group and eight (14.8%) women in the ALN + EC (ECT) group dropped out from the trial because of the above reasons. Namely, 88.3% (159/180) and 85.2% (46/54) of women in the respective groups completed the trial.

Characteristics of the study subjects

Table 2 shows the baseline characteristics of the study subjects who completed the six-month trial. The patients in the ALN+ECT group were older and their body weights were lower than those in the ALN group. The number of vertebral fractures was greater in the ALN+ECT group than in the ALN group. However, no significant differences in the other baseline characteristics were observed between the two groups. The mean levels of urinary NTX in both groups suggested high turnover osteoporosis (the normal range for Japanese women: 9.3–54.3 nmol BCE/mmol Cr).[18]

Changes in lumbar BMD and biochemical markers

Table 3 shows the changes in the lumbar BMD and biochemical markers. Urinary NTX levels were reduced to the normal range for Japanese women (9.3–54.3 nmol BCE/mmol Cr)[18] in both groups. The serum ALP levels stayed within the normal range (135–310 IU/L) during the six-month period of treatment in both groups. The mean increase rate in the lumbar BMD at six months was 4.41% in the ALN group and 5.15% in the ALN+ECT groups. The respective mean decrease rates in the urinary NTX level at three months were 40.2% and 43.0%, and those of the serum ALP levels at six months were 19.0% and 19.7%. No significant differences in the change in the lumbar BMD, serum levels of calcium, phosphorus or ALP, and urinary levels of NTX were observed between the two groups when analyzed using an unpaired *t*-test. The statistical results of

Table 2 Characteristics of study subjects

	ALN group (n = 159)	ALN+ECT group (n = 46)	P values
ALN treatment, Daily: Weekly	92:67	30: 16	NS
Age (years)	68.5 ± 9.7	75.3 ± 8.7	<0.0001
Height (m)	1.49 ± 0.07	1.48 ± 0.06	NS
Body weight (kg)	48.9 ± 7.2	45.7 ± 6.3	<0.01
Lumbar BMD (g/cm^2)	0.660 ± 0.076	0.644 ± 0.080	NS
%YAM of lumbar BMD (%)	65.0 ± 7.5	63.4 ± 7.9	NS
Serum calcium (mg/dl)	9.4 ± 0.4	9.3 ± 0.4	NS
Serum phosphorus (mg/dl)	3.4 ± 0.5	3.4 ± 0.5	NS
Serum ALP (IU/l)	256 ± 65	276 ± 63	NS
Urinary NTX (nmol BCE/mmol Cr)	69.8 ± 22.2	72.2 ± 22.4	NS
Number (%) of women with prevalent vertebral fractures	55 (34.6)	29 (63.0)	<0.001
Number (%) of women with history of nonvertebral fractures	10 (6.3)	1(2.2)	NS

Notes: Data are expressed as the mean ± SD. Data comparison between the two groups was performed using an unpaired t-test. The ratio of daily to weekly ALN and percentage of women with fractures were compared by the Fisher exact test.

Abbreviations: ALN, alendronate; ECT, elcatonin; BMD, bone mineral density; YAM, young adult mean; ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen; BCE, bone collagen equivalent; Cr, creatinine; NS, not significant.

the ANCOVA regarding the percent changes in the lumbar BMD and biochemical parameters were similar even after adjustments for age, body weight and the number of patients with prevalent vertebral fractures.

Incidence of clinical fractures

Six clinical fractures were observed during the six-month treatment period. Vertebral fractures occurred in four women and a wrist fracture occurred in one woman in the ALN group and vertebral fractures occurred in one woman in the ALN+ECT group. The incidence of clinical fractures was 3.14% in the ALN group and 2.17% in the ALN+ECT group, with no significant difference between the two groups.

Discussion

The objective of this trial was to compare the effects of short-term (six months) combined treatment with ALN and ECT on BMD and bone turnover with those of single treatment with ALN in postmenopausal women with osteoporosis. The present study confirmed that the effects of short-term (six months) combined treatment with ALN and ECT on lumbar BMD and bone turnover in patients with back pain appeared to be comparable to those of single treatment with ALN in patients without obvious back pain.

In postmenopausal Japanese women with osteoporosis, studies of ALN showed that ALN (5 mg/day) decreases urinary deoxypyridinoline and serum ALP levels, increases lumbar BMD, and prevents vertebral fractures.[15,16] Our previous studies also showed that ALN (5 mg/day) decreases urinary NTX and serum ALP and increases lumbar BMD.[19–23] The effects of ALN on bone turnover markers and lumbar BMD and the incidence of adverse effects of ALN were reported to be similar for two dosing regimens (5 mg/day and 35 mg/week).[24] These studies imply that ALN (5 mg/day or 35 mg/week) decreases urinary NTX levels by about 36%–45% at three months and serum ALP levels by about 9%–30% at six months, leading to an increase in lumbar BMD by about 3.9%–5.4% at six months. In the present study, treatment with ALN (5 mg/day and 35 mg/week) alone increased lumbar BMD by 4.41% at six months, following reductions in urinary levels of NTX (–40.2% at three months) and serum levels of ALP (–19.0% at six months), which were consistent with the previous reports.[15,19–23]

Weekly intramuscular injections of ECT at a dose of 20 units reportedly increased lumbar BMD by 1.87% from baseline over six months in postmenopausal Japanese women with osteoporosis.[17] The mechanism for this positive effect of ECT on lumbar BMD remains unexplained, since bone turnover markers such as urinary hydroxyproline and serum osteocalcin did not change significantly compared with a control group.[17] In the present study, because an ECT treatment-alone group was not approved by the ethical committee, the effects of administration of ECT alone on bone turnover markers and lumbar BMD remains uncertain. However, because ECT reportedly does not have a significant antifracture effect against vertebral fractures in postmenopausal women with osteoporosis,[12] combined treatment with ECT and a potent antifracture drug, rather than single treatment with ECT alone, might be desirable for the prevention of fractures and the relief of pain.

Table 3 Changes in lumbar BMD and biochemical markers

	Baseline	At follow-up	Percent change	One- and two-way ANOVA
Lumbar BMD(g/cm^2)	0.660 ± 0.076	0.688 ± 0.079	+4.41 ± 4.92	$P < 0.0001$
ALN group (n = 159)	0.644 ± 0.080	0.676 ± 0.084	+5.15 ± 7.74	$P < 0.0001$
ALN+ECT group (n = 46)	NS	NS	NS	NS
Group difference				
Serum calcium (mg/dl)	9.4 ± 0.4	9.3 ± 0.5	−0.94 ± 4.56	$P < 0.01$
ALN group (n = 159)	9.3 ± 0.4	9.2 ± 0.4	−0.96 ± 4.64	NS
ALN+ECT group (n = 46)	NS	NS	NS	NS
Group difference				
Serum phosphorus (mg/dl)	3.4 ± 0.5	3.3 ± 0.5	−2.59 ± 16.8	$P < 0.01$
ALN group (n = 159)	3.4 ± 0.5	3.4 ± 0.4	+0.36 ± 11.7	NS
ALN+ECT group (n = 46)	NS	NS	NS	NS
Group difference				
Serum ALP (IU/l)	256 ± 65	201 ± 53	−19.0 ± 21.1	$P < 0.0001$
ALN group (n = 159)	276 ± 63	221 ± 58	−19.7 ± 20.0	$P < 0.0001$
ALN+ECT group (n = 46)	NS	NS	NS	NS
Group difference				
Urinary NTX (nmol BCE/mmol Cr)	68.9 ± 22.2	39.4 ± 21.6	−40.2 ± 30.0	$P < 0.0001$
ALN group (n = 1 59)	72.2 ± 22.4	38.7 ± 16.4	−43.0 ± 36.9	$P < 0.0001$
ALN+ECT group (n = 46)	NS	NS	NS	NS
Group difference				

Notes: Data are expressed as the mean ± SD. The lumbar BMD and serum levels of biochemical markers were measured at baseline and 6 months after the start of the treatment. The urinary levels of NTX were measured at baseline and 3 months after the start of the treatment. Cross-sectional comparison of the data between the two groups was performed using an unpaired t-test. The significance of longitudinal changes in the parameters within a group was determined using a one-way analysis of variance (ANOVA) with repeated measurements. Longitudinal changes in the parameters were compared between the two groups using a two-way ANOVA with repeated measurements.
Abbreviations: ALN, alendronate; ECT, elcatonin; BMD, bone mineral density; ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen; BCE, bone collagen equivalent; Cr, creatinine; ANOVA, analysis of variance; NS, not significant.

Bone strength reflects both bone mass and bone quality, and bone quality is derived from the bone architecture, turnover, damage accumulation, mineralization, and bone matrix.[25] In particular, a reduction in bone turnover markers has been reported to be important for reducing the incidence of fractures in postmenopausal women with osteoporosis.[26,27] In the present study, both treatment with ALN alone and treatment with ALN and ECT reduced urinary NTX levels to the normal range for Japanese women (9.3–54.3 nmol BCE/mmol Cr).[18] The serum ALP levels stayed within the normal range (135–310 IU/L) during the six-month period of treatment in both groups, even though the level decreased significantly after treatment. The similar increase in lumbar BMD at six months might suggest a similar reduction in bone turnover. Marked reductions in bone turnover markers to below the normal ranges might not necessarily be a concern in the ALN+ECT group when the duration of combined treatment with the two drugs is limited to a maximum of six months. The antiresorptive effect of ECT and the subsequent increase in BMD might have been rather modest, and additional changes in the bone turnover markers and lumbar BMD might have been masked by the potent effects of ALN in the ALN+ECT group.

Calcitonin reduces pain via its action on the central nervous system.[28] The serotonergic system in the spinal cord (dorsal horn) might be involved in antinociception. There are no significant differences in the analgesic effect of eel and salmon calcitonins and their influence on the morphine-analgesia.[29] Estrogen deficiency not only causes bone loss, but also affects the spinal serotonergic system (serotonergic receptor expression), resulting in hyperalgesia. Calcitonin restores this change in the serotonergic system and has an analgesic action in postmenopausal women. Thus, ECT has been used for the treatment of postmenopausal osteoporotic women with back pain. In the present study, the pain relief effect of ECT itself was not assessed, since all of the subjects in the ALN+ECT group were also treated with oral NSAIDs, percutaneous NSAIDs (ointment of compress), and/or trigger point injections of lidocaine hydrochloride.

Twenty women (11.8%) in the ALN group and eight (14.8%) women in the ALN+ECT group dropped out of the present trial. The main reasons for dropout were difficulty in compliance and epigastric problems related to ALN. Facial flushing was observed in relation to ECT treatment in three women, but this symptom was mild and required no additional treatment or withdrawal of the drug. No serious adverse events necessitating hospitalization were observed.

Thus, treatment with ALN alone and treatment with ALN+ECT were both safe and well tolerated in postmenopausal Japanese women with osteoporosis.

The present study has several notable limitations. First, the study was not a double-blind trial but an open-labeled one, and ECT was used to relieve pain only in women with back pain. Therefore, some of the results might be biased. If age, body weight, and number of patients with prevalent vertebral fractures had been matched between the groups, the results of this study might have been different. Second, the number of study subjects was relatively small and not sufficiently large to lend sufficient power to allow a conclusion regarding the effects of these drugs on fractures. Third, it has been reported that NSAIDs such as ibuprofene and acetaminophen affect bone resorption markers including urinary NTX.[30] The simultaneous use of these drugs may modify the effect of ALN and/or ECT on bone markers. Although the effect of zaltoprofen on bone metabolism has not yet been established, its influence on bone markers must have been taken into account in the ALN+ECT group. Fourth, we just recommended for all the participants to consume about 800 mg of dietary calcium and 400 IU of dietary vitamin D daily using a pamphlet. So, we were not able to evaluate how much calcium and vitamin D were exactly consumed by the participants. Thus, a double-blind randomized placebo-controlled study with a sufficient number of subjects is needed to confirm the results of the present study.

In conclusion, the present prospective open-labeled trial in postmenopausal osteoporotic women confirmed that the effects of short-term combined treatment with ALN and ECT on lumbar BMD and bone turnover in patients with back pain appeared to be comparable with those of single treatment with ALN in patients without obvious back pain. Marked reductions in bone turnover markers to below the normal ranges might not necessarily be a concern in the treatment of ALN plus ECT when the duration of combined treatment with the two drugs is limited to a maximum of six months.

Disclosure

The authors report no funding sources or conflicts of interest in this work.

References

1. Rogers MJ, Frith JC, Luckman SP, et al. Molecular mechanism of action of bisphosphonate. *Bone*. 1999;24(5 Suppl):73S–9S.
2. Iwamoto J, Takeda T, Sato Y. Efficacy and safety of alendronate and risedronate for postmenopausal osteoporosis. *Curr Med Res Opin*. 2006;22:919–928.
3. Iwamoto J, Takeda T, Sato Y. Effects of antifracture drugs in postmenopausal, male and glucocorticoid-induced osteoporosis – usefulness of alendronate and risedronate. *Expert Opin Pharmacother*. 2007;8:2743–2756.
4. Iwamoto J, Sato Y, Takeda T, et al. Hip fracture protection by alendronate treatment in postmenopausal women with osteoporosis: a review of the literature. *Clin Interv Aging*. 2008;3:483–489.
5. Morikawa T, Munekata E, Sakakibara S, et al. Synthesis of eel-calcitonin and (asu1,7)-eel-calcitonin: contribution of the disulfide bond to the hormonal activity. *Experientia*. 1976;32:1104–1106.
6. Otani M, Kitazawa S, Yamaguchi H, et al. Biological activity of (asu1,7)-eel-calcitonin. *Clin Med*. 1978;20:2217–2222. [In Japanese]
7. Orimo H. The development of a novel therapy for bone disease, the discovery of elcatonin. In: Christiansen C, Overgard K, editors. *Osteoporosis*. Aalborg, Denmark: Handelstrykkeriet; 1990; p. 2091–2095.
8. Yamamoto I, Morita R, Fukunaga M, et al. Adenylate cyclase activation and competitive binding with renal tissue using synthetic eel calcitonin analog and its fragments. *Endocrinology*. 1981;108:698–702.
9. Fujita T, Inoue T, Orimo H, et al. Low dose intermittent calcitonin in therapy. *J Bone Miner Res*. 1989;179:4s.
10. Fujita T, Inoue T, Orimo H, et al. Effect of elcatonin in osteoporosis: a multicenter, double-blind, placebo-controlled study. *J Clin Exp Med*. 1990;152:261–282. [In Japanese].
11. Yoh K, Tanaka K, Ishikawa A, et al. Health-related quality of life (HRQOL) in Japanese osteoporotic patients and its improvement by elcatonin treatment. *J Bone Miner Metab*. 2005;23:167–173.
12. Asahi-Kasei Co. Ltd. Outline of the results of a clinical trial of intramuscular elcatonin 20S. 2003. Accessed on April 15, 2009. Available from: http://www.asahi-kasei.co.jp/asahi/jp/news/2003/pdf/me030606. [In Japanese].
13. Orimo H, Sugioka Y, Fukunaga M, et al. Diagnostic criteria of primary osteoporosis. *J Bone Miner Metab*. 1998;16:139–150.
14. Orimo H, Hayashi Y, Fukunaga M, et al. Diagnostic criteria for primary osteoporosis: year 2000 revision. *J Bone Miner Metab*. 2001;19:331–337.
15. Shiraki M, Kushida K, Fukunaga M, et al. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. *Osteoporos Int*. 1999;10:183–192.
16. Kushida K, Shiraki M, Nakamura T, et al. The efficacy of alendronate in reducing the risk for vertebral fracture in Japanese patients with osteoporosis: a randomized, double-blind, active-controlled, double-dummy trial. *Curr Ther Res*. 2002;63:9:606–620.
17. Orimo H, Morii H, Inoue T, et al. Effect of elcatonin on involutional osteoporosis. *J Bone Miner Metab*. 1996;14:73–78.
18. Nishizawa Y, Nakamura T, Ohta H, et al. Committee on the Guidelines for the Use of Biochemical Markers of Bone Turnover in Osteoporosis Japan Osteoporosis Society. Guidelines for the use of biochemical markers of bone turnover in osteoporosis (2004). *J Bone Miner Metab*. 2005;23:97–104.
19. Iwamoto J, Takeda T, Sato Y, et al. Determinants of one-year response of lumbar bone mineral density to alendronate treatment in elderly Japanese women with osteoporosis. *Yonsei Med J*. 2004;45:676–682.
20. Iwamoto J, Takeda T, Sato Y, et al. Comparison of effect of treatment with etidronate and alendronate on lumbar bone mineral density in elderly women with osteoporosis. *Yonsei Med J*. 2005;46:750–758.
21. Iwamoto J, Takeda T, Sato Y, et al. Early changes in urinary cross-linked N-terminal telopeptides of type I collagen level correlate with 1-year response of lumbar bone mineral density to alendronate in postmenopausal Japanese women with osteoporosis. *J Bone Miner Metab*. 2005;3:238–242.
22. Iwamoto J, Takeda T, Sato Y, et al. Comparison of the effect of alendronate on lumbar bone mineral density and bone turnover in men and postmenopausal women with osteoporosis. *Clin Rheumatol*. 2007;26:161–167.
23. Iwamoto J, Sato Y, Uzawa M, et al. Comparison of effects of alendronate and raloxifene on lumbar bone mineral density, bone turnover, and lipid metabolism in elderly women with osteoporosis. *Yonsei Med J*. 2008;49:119–128.

24. Uchida S, Taniguchi T, Shimizu T, et al. Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. *J Bone Miner Metab.* 2005;23:382–388.
25. Epstein S. The roles of bone mineral density, bone turnover, and other properties in reducing fracture risk during antiresorptive therapy. *Mayo Cin Proc*. 2005;80:379–388.
26. Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med*. 2002;112:281–289.
27. Hochberg MC, Greenspan S, Wasnich RD, et al. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab*. 2002;87:1586–1592.
28. Shibata K, Takeda M, Ito A, et al. Ovariectomy-induced hyperalgesia and antinociceptive effect of elcatonin, a synthetic eel calcitonin. *Pharmacol Biochem Behav*. 1998;60:371–376.
29. Martin MI, Goicoechea C, Ormazabal MJ, et al. Analgesic effect of two calcitonins and in vitro interaction with opioids. *Gen Pharmacol*. 1995;26:641–647.
30. Head JE, Bryant BJ, Grills BL, et al. Effects of short-term use of ibuprofen or acetaminophen on bone resorption in healthy men: a double-blind, placebo-controlled pilot study. *Bone*. 2001;29: 437–441.

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