Effect of whole-body vibration exercise on lumbar bone mineral density, bone turnover, and chronic back pain in post-menopausal osteoporotic women treated with alendronate

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ABSTRACT. ***Background and aims:*** *Exercise may enhance the effect of alendronate on bone mineral density (BMD) and reduce chronic back pain in elderly women with osteoporosis. The aim of this study was to determine whether whole-body vibration exercise would enhance the effect of alendronate on lumbar BMD and bone turnover, and reduce chronic back pain in post-menopausal women with osteoporosis.* ***Methods:*** *Fifty post-menopausal women with osteoporosis, 55-88 years of age, were randomly divided into two groups of 25 patients each: one taking alendronate (5 mg daily, ALN) and one taking alendronate plus exercise (ALN+EX). Exercise consisted of whole-body vibration using a Galileo machine (Novotec, Pforzheim, Germany), at an intensity of 20 Hz, frequency once a week, and duration of exercise 4 minutes. The study lasted 12 months. Lumbar BMD was measured by dual energy X-ray absorptiometry (Hologic QDR 1500W). Urinary cross-linked N-terminal telopeptides of type I collagen (NTX) and serum alkaline phosphatase (ALP) levels were measured by enzyme-linked immunosorbent assay and standard laboratory techniques, respectively. Chronic back pain was evaluated by face scale score at baseline and every 6 months.* ***Results:*** *There were no significant differences in baseline characteristics, including age, body mass index, years since menopause, lumbar BMD, urinary NTX and serum ALP levels, or face scale score between the two groups. The increase in lumbar BMD and the reduction in urinary NTX and serum ALP levels were similar in the ALN and ALN+EX groups. However, the reduction in chronic back pain was greater in the ALN+EX group than in the ALN group.* ***Conclusions:*** *The results of this study suggest that whole-body vibration exercise using a Galileo machine appears to be useful in reducing chronic back pain, probably by relaxing the back muscles in post-menopausal osteoporotic women treated with alendronate.*

(Aging Clin Exp Res 2005; 17: 157-163)

INTRODUCTION

Bisphosphonates such as alendronate and risedronate have the most compelling evidence as the treatment after osteoporotic fractures (1). It is confirmed that alendronate increases lumbar bone mineral density (BMD) and prevents vertebral fractures in post-menopausal women with osteoporosis in Japan (2, 3). However, osteoporosis causes not only vertebral and non-vertebral fractures and postural deformities, but also acute and chronic back pain, possibly resulting in disability and deterioration of quality of life (QOL) in elderly women (4, 5). Thus, pain control as well as strengthening bone is important in preventing deterioration in activities of daily living and QOL in elderly women. Since back pain associated with spinal osteoporosis may be linked to increased bone resorption (6), drugs affecting bone metabolism such as bisphosphonates, which are anti-resorptive agents, may be useful for pain control in elderly women with osteoporosis. Available evidence suggests that alendronate has the potential to reduce back pain and increase activities of daily living in elderly women with symptomatic vertebral fractures (5), and is efficacious in preventing back pain and subsequent deterioration of activities of daily living in elderly osteoporotic women (7).

Recently, vibration training has been developed as a new modality in physiotherapy. It has been suggested that such training may increase muscle power in athletes and

Key words: Alendronate, bone mineral density (BMD), elderly women, osteoporosis, whole-body vibration exercise.

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Received November 4, 2003; accepted in revised form May 21, 2004.

Table 1 - *Characteristics of study subjects.*

	ALN group	ALN+EX group
Age (years)	70.6±8.7	71.9±8.1
Height (m)	1.46±0.07	1.45±0.07
Body weight (kg)	44.4±8.4	45.5±8.6
Body mass index (kg/m^2)	20.8±3.3	21.6±3.3
Years since menopause	21.5±8.9	22.4±7.9
Lumbar BMD (g/cm^2)	0.569±0.107	0.563±0.114
T score (%)	55.6±10.5	55.1±11.2
Number of prevalent vertebral fractures per patient	2.4±3.0	3.4±4.2
Face scale score	5.6±1.2	5.4±1.2
Serum calcium (mg/dL)	9.4±0.3	9.6±0.5
Serum phosphorus (mg/dL)	3.4±0.6	3.2±0.5
Serum ALP (IU/L)	244±114	248±119
Urinary NTX (nmol BCE/mmol Cr)	75.8±44.9	81.5±46.8

Data are expressed as means±SD. Unpaired *t*-test was used to compare data between groups. There were no significant differences in any baseline characteristics between groups.
BMD: bone mineral density; ALP: alkaline phosphatase; NTX: cross-linked N-terminal telopeptides of type I collagen.

post-menopausal women (8, 9) and muscle blood volume in healthy adults (10), improve muscular performance and body balance in young healthy subjects (11), and reduce chronic back pain and pain-related disability in patients without spinal diseases (12). Thus, we expected that vibration exercises would have the potential to relax the back muscles, increase their blood volume, and reduce chronic back pain even in elderly osteoporotic women. Unlike the case of young athletes, it is difficult to force elderly people to continue intense or vigorous exercise, and low-intensity vibration training once a week was thought to be safe, easy to practice, and easy to continue in the elderly. Because elderly women with osteoporosis should be treated with bisphosphonates, it was difficult to include groups treated only with vibration exercise. The aim of this study was to determine whether exercise consisting of once-weekly whole-body vibration exercise would enhance the effects of alendronate on lumbar BMD and bone turnover and reduce chronic back pain in post-menopausal women with osteoporosis.

METHODS

Subjects

Fifty post-menopausal women with osteoporosis (13, 14), 55-88 years of age, were recruited at our hospital in October 2002. According to the Japanese criteria for osteoporosis in women, patients whose BMD T score was <70 or 70-80% with a history of osteoporotic fractures were diagnosed as having osteoporosis (13, 14). All of them had chronic back pain, but did not need bed-rest treatment. Before their recruitment, patients who had osteoarthritis of the knee, moderate to severe spondylosis or degenerative disc disease of the thoracic and lumbar spine, or other musculo-skeletal diseases than osteoporosis which are considered to cause back pain, or had undergone arthroplasty of the knee or hip joint were excluded. Subjects were randomly divided into two groups of 25 patients each: one on alendronate (5 mg daily, ALN) and one on alendronate plus exercise (ALN+EX). A daily dose of 5 mg of alendronate is recognized as effective for Japanese patients with osteoporosis (1, 2). Exercise consisted of whole-body vibration using a Galileo machine (Novotec, Pforzheim, Germany), at an intensity of 20 Hz, frequency once a week, and duration of exercise 4 minutes. The Galileo is a unique device for applying whole-body vibration/oscillatory muscle stimulation. The subject stands with bent knees and hips on a rocking platform with a sagittal axle, which alternately thrusts the right and left leg 0.7-4.2 mm upwards and downwards at a frequency of 20 Hz, thereby lengthening the extensor muscles of the lower extremities. The reaction of the neuromuscular system is a chain of rapid muscle contractions. This type of training provides reflex muscle stimulation to improve balance and possibly also muscle strength. The study lasted 12 months. None of the subjects suffered from any bone metabolic disease, and none had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to this study. The level of physical activity of all patients at baseline was not considered to be high, because none of them undertook physically demanding work or had been participating in any sports. No subjects had taken medication such as non-steroid anti-inflammatory drugs to relieve chronic back pain, and all were instructed to take 800 mg of calcium daily in food.

Pre- and post-treatment examinations included medical history, physical examination, radiographic examination of the thoracic and lumbar spine, lumbar BMD measurement, biochemical blood and urine tests, and a questionnaire to evaluate chronic back pain. Assessment of vertebral fractures on radiographs and lumbar BMD measurement were performed as described below. Blood samples were collected at approximately the same time in the morning after an overnight fast, and serum calcium, phosphorus, and alkaline phosphatase (ALP) levels were measured with standard laboratory techniques. Urinary cross-linked N-terminal telopeptides of type I collagen (NTX) levels were measured as described below. Table 1 shows subjects' characteristics. There was no significant difference in any parameter between the two groups.

Informed consent was obtained from each of the subjects, and all of them completed this trial (no participants dropped out). After the start of treatment, lumbar

BMD and urinary NTX level were measured, back pain was evaluated, and serum calcium, phosphorus, and ALP levels were measured every 6 months. Radiographs of the thoracic and lumbar spine were also assessed, not only at the beginning but also at the end of the 12 months of treatment. None of the subjects participated in any sports during the study period. Therefore, there were no significant changes in physical activity during the study period. The primary efficacy end-points were changes in lumbar BMD, urinary NTX and serum ALP levels (bone turnover markers), and back pain. The secondary end-point was the number of falls.

Assessment of vertebral fractures

Radiographs of the thoracic and lumbar spine were taken to find evidence of vertebral fractures. Vertebral fracture was defined according to the vertebral height obtained from lateral X-ray films based on Japanese criteria (13, [illegible]). Briefly, vertebral height was measured at the anterior (A), center (C) and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when; 1) a reduction of more than 20% in vertebral height (A, C, P) compared with the neighboring vertebrae was observed; 2) C/A or C/P was less than 0.8; or 3) A/P was less than 0.75. Assessment of vertebral fractures was performed for the T4-L4 spine.

Measurement of lumbar BMD

BMD of the lumbar spine (L1-L4) in the antero-posterior view was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 1500W instrument (Bedford, MA, USA). The coefficient of variation (CV, 100 × standard deviation/mean) of 5 measurements each time with repositioning within 72 hours was less than 1.2% in 3 persons.

Evaluation of back pain

Back pain was evaluated quantitatively by assessing the mood of patients according to the face scale. The face scale contains ten drawings of a single face, arranged in serial order by rows, each face depicting a slightly different mood. Subtle changes in the eyes, eyebrows, and mouth are used to represent slightly different levels of mood. The drawings are arranged in decreasing order of mood and numbered from 1 to 10, 1 representing the most positive mood and 10 the most negative mood. As the examiner pointed to the faces, the following instructions were given to each patient: "The faces below go from painless at the top to very painful at the bottom. Point to the face that best shows your current level of back pain". Thus, facial expression is used as an indicator of back pain. Although pain is a subjective symptom which is relatively difficult to evaluate, the validity and reliability of the face scale have been demonstrated (15).

Measurement of urinary NTX levels

Urine samples were collected from the second voiding in the morning, and stored at −70°C until assayed. Urinary NTX levels (nmol BCE/mmol Cr) were measured using an enzyme-linked immunosorbent assay (ELISA, Osteomark, Ostex International, Seattle, WA) with a monoclonal antibody against the N-telopeptide to the helix intermolecular cross-linking domain of type I collagen. All samples were measured in duplicate, and samples were analyzed in the same assay to eliminate inter-assay variations. Assay sensitivity was 20 nM bone collagen equivalents. The intra-assay coefficient of variation of 5 measurements was less than 7%.

Statistical analysis

Data are expressed as means ± standard deviation (SD). Data comparisons between the groups were performed by the unpaired *t*-test. The significance of longitudinal changes in lumbar BMD, face scale score, and serum calcium, phosphorus and ALP and urinary NTX levels was determined by one-way analysis of variance (ANOVA) with repeated measurements. In addition, longitudinal changes in these parameters were compared between the groups by two-way ANOVA with repeated measurements. All statistical analyses were performed using the Stat View-J5.0 program on a Macintosh computer. A significance level of $p<0.05$ was used for all comparisons.

RESULTS

Changes in lumbar BMD, face scale score, serum calcium, phosphorus, and ALP and urinary NTX levels

Figure 1 and Table 2 show longitudinal changes in mean lumbar BMD, face scale score, and serum ALP and urinary NTX levels, and Table 2 also shows the longitudinal changes in serum calcium and phosphorus levels. The mean percent change in lumbar BMD at months 6 and 12 compared with baseline was +4.4 and +8.4% respectively, in the ALN group, and +3.8 and +10.2% respectively, in the ALN+EX group, and these changes were significant (both $p<0.0001$, one-way ANOVA with repeated measurements). The corresponding changes in urinary NTX levels were −47.0 and −49.9% in the ALN group, and −50.5 and −49.6% in the ALN+EX group, and these changes were significant (both $p<0.0001$, by one-way ANOVA with repeated measurements). Serum ALP levels and face scale scores also significantly decreased in both groups (serum ALP, $p<0.001$ and face scale score, $p<0.0001$ in both groups, one-way ANOVA with repeated measurements). The longitudinal increase in lumbar BMD and longitudinal decreases in urinary NTX and serum ALP levels were similar in the two groups. However, the longitudinal decrease in face scale score was significantly

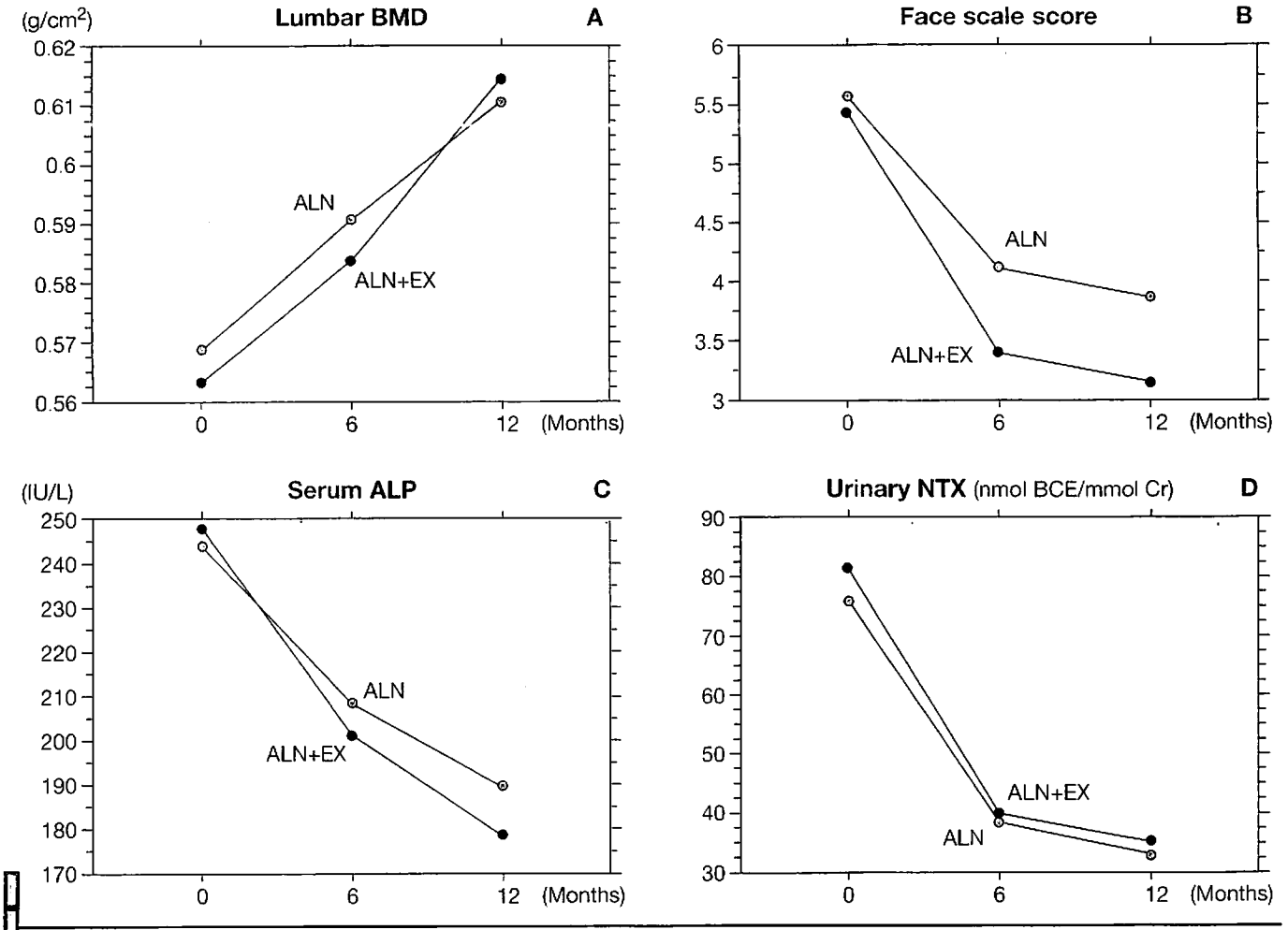

Figure 1a-d - *Changes in mean lumbar BMD, face scale score, and serum ALP and urinary NTX levels. One-way analysis of variance (ANOVA) with repeated measurements was used to determine significance of longitudinal change in parameters. Two-way ANOVA with repeated measurements was used to compare longitudinal changes in parameters between groups. Lumbar BMD significantly increased and serum ALP and urinary NTX levels significantly decreased in both groups similarly. Reduction in face scale score was significantly greater in ALN+EX group than in ALN group. BMD: bone mineral density; ALP: alkaline phosphatase; NTX: cross-lined N-terminal telopeptides of type I collagen.*

greater in the ALN+EX group than in the ALN group ($p<0.05$, two-way ANOVA with repeated measurements). Serum calcium and phosphorus levels did not change significantly in either group (one-way ANOVA with repeated measurements).

Number of falls

During the study period, two patients in the ALN group and one in the ALN+EX group had falls, but no fall-related fracture was observed. Because of the small number of patients who had falls, the efficacy of whole-body vibration exercise for the risk of falls could not be analyzed adequately.

Incidence of vertebral fractures

At the end of the 12 months of treatment, plain X-ray examination of the thoracic and lumbar spine revealed no evidence of new thoracic or lumbar vertebral fractures in any patient. During the 12 months of treatment, no non-vertebral osteoporotic fractures occurred in the hip, wrist or shoulder of any patient.

DISCUSSION

One-year treatment with alendronate (5 mg daily) reduced urinary NTX and serum ALP levels by 49.9 and 8.5% respectively, increased lumbar BMD by 8.4%, and reduced chronic back pain in elderly women with osteoporosis. A double-blind well-controlled study has demonstrated that one-year treatment with alendronate (5 mg daily) reduces urinary deoxypyridinoline levels by 45.0% and increases lumbar BMD by 6.2% in Japanese post-menopausal women with osteoporosis (2). Our results on lumbar BMD were consistent with those of the previous study: treatment with alendronate effectively reduced

bone turnover and increased lumbar BMD in our subjects. Urinary NTX was more sensitive to treatment with alendronate than serum ALP.

Alendronate also reduced chronic back pain. Its therapeutic effect on chronic back pain in patients with osteoporosis has rarely been reported. However, the efficacy of bisphosphonates for bone pain in patients with bone resorption-related diseases has been demonstrated. Short-term treatment with alendronate reduces pain and disability, and improves the standing and walking capacity in patients with avascular necrosis of the hip, due to inhibition of the resorptive action of mature osteoclasts, an increase in osteoclast apoptosis and, probably, a decrease in osteoblast and osteocyte apoptosis (16). Intravenous pamidronate seems to be valuable treatment for back pain, as well as rehabilitating elderly patients suffering from chronic and refractory back pain due to osteoporotic vertebral fractures (17), and it also reduces skeletal pain and biochemical markers of bone resorption in patients with skeletal metastases (18-20). Furthermore, risedronate decreases bone pain in patients with Paget's disease of bone (21). These reports support our view that suppression of bone resorption by alendronate contributes to the relief of chronic back pain.

Another mechanism of the beneficial action of alendronate for chronic back pain may concern prostaglandins and cytokines. Available evidence suggests that the bisphosphonate etidronate decreases pain by suppressing the production of interleukin (IL)-6, IL-12 and prostaglandin E2 (22, 23). Although etidronate was reported transiently to reduce metastatic cancer bone pain in patients with painful bone metastases from primary cancer sites, one explanation for the relief of metastatic cancer bone pain achieved by etidronate is speculated to be the combined effect of suppression of bone resorption and reduced production of interleukins and prostaglandins (24). Alendronate has also been reported to reduce the levels of cytokines such as IL-1, IL-6 and tumor necrosis factor (TNF)-α in patients with early rheumatoid arthritis (25). It is also speculated that alendronate partially reduces chronic back pain by reducing the production of prostaglandins and cytokines (26), which may be produced by microfractures resulting from increased bone resorption in the trabeculae of the spine.

Our training program consisted of once-weekly whole-body vibration using a Galileo machine. The benefit of this whole-body vibration exercise, in addition to the effect of alendronate, was demonstrated by reduced chronic back pain. This information is important, because of the high prevalence and adverse effect of this condition on the QOL of osteoporotic patients. However, lumbar BMD and bone turnover were not affected by whole-body vibration exercise. In this study, we applied whole-body vibration exercise, at an intensity of 20 Hz, frequency once a week, and duration of exercise 4 minutes, and the study lasted 12 months. The intensity and frequency may be low and the duration may be short. This exercise program was simply determined as that which elderly women with os-

Table 2 - *Changes in lumbar BMD, face scale score, and biochemical markers.*

	Baseline	Month 6	Month 12	*p*-value	
				One-way ANOVA	Two-way ANOVA (*vs* M group)
Lumbar BMD (g/cm^2)					
ALN group	0.569±0.107	0.591±0.103	0.611±0.095	<0.0001	NS
ALN+EX group	0.563±0.114	0.584±0.120	0.614±0.102	<0.0001	
Face scale score					
ALN group	5.6±1.1	4.1±0.4	3.9±0.5	<0.0001	<0.05
ALN+EX group	5.4±1.2	3.4±0.6	3.2±0.7	<0.0001	
Serum calcium (mg/dL)					
ALN group	9.4±0.3	9.4±0.3	9.3±0.3	NS	NS
ALN+EX group	9.6±0.5	9.5±0.8	9.5±0.8	NS	
Serum phosphorus (mg/dl)					
ALN group	3.4±0.6	3.5±0.5	3.5±0.5	NS	NS
ALN+EX group	3.2±0.5	3.4±0.5	3.4±0.5	NS	
Serum ALP (IU/L)					
ALN group	244±114	209±72	189±63	<0.001	NS
ALN+EX group	248±119	202±78	179±68	<0.001	
Urinary NTX (nmol BCE/mmol Cr)					
ALN group	75.8±44.9	38.4±25.7	32.9±11.0	<0.0001	NS
ALN+EX group	81.5±46.8	39.6±30.0	35.3±19.4	<0.0001	

Data are expressed as means±SD. One-way analysis of variance (ANOVA) with repeated measurements was used to determine significance of longitudinal change in parameters. Two-way ANOVA with repeated measurements was used to compare longitudinal changes in parameters between groups.
BMD: bone mineral density; ALP: alkaline phosphatase; NTX: cross-lined N-terminal telopeptides of type I collagen.

teoporosis could safely practice and easily continue, but what kind of vibration stimulus would be most effective for the musculo-skeletal system was uncertain. Thus, optimal levels to gain maximum benefit still remain uncertain. Because vibration stimuli can be varied according to intensity, duration and frequency, further studies are needed to confirm the clinical efficacy of whole-body vibration exercise with various kinds of vibration stimuli for osteoporotic bone, performance, and chronic back pain in elderly women.

Increased kyphosis of the thoracic and lumbar spine in terms of a round back in osteoporotic elderly women also causes chronic back pain, partly due to fatigue, spasm, and ischemia in the back muscles. Whole-body vibration exercise elicits muscular activity *via* stretch reflexes and increased metabolic power in the trunk muscles (12). Whole-body vibration exercise has been confirmed to relax the back muscles and increase their blood volume in patients with chronic back pain due to spinal diseases (10). Thus, the benefit of this type of exercise for chronic back pain may result partly from the improvement of spasm and ischemia in the back muscles and subsequent wash-out of fatigue-related substances. We also expected that increased blood volume would also enhance increased lumbar BMD by increasing the calcium supply and subsequently by stimulating skeletal mineralization. However, no benefit of whole-body vibration exercise, in addition to the effect of alendronate on lumbar BMD and bone turnover, was observed.

Torvinen et al. (26) also showed that whole-body vibration exercise in young healthy adults had no effect on mass, structure or estimated strength of bone at any skeletal site, without any changes in serum markers of bone turnover, but it did increase vertical jump height in terms of muscle power. Based on the hypothesis of Rubin et al. (27), they suggested that the non-response of the skeleton to whole-body vibration exercise in young healthy adults was not due to any particular physiological need to adapt themselves to this kind of loading, but that bone response to vibration stimuli may have been seen if the participants had been older or their bone weaker. Thus, our whole-body vibration exercise may have the potential to improve BMD, at least at skeletal sites in the lower extremities such as the femoral neck and calcaneus (clinical BMD measurement sites), because these sites may have received more mechanical stress, i.e., body weight loading and/or muscle force during whole-body vibration exercise, if we extended the study period or optimized the intensity, duration and frequency of the exercise. Rubin et al. (27-30) also showed experimentally that extremely low-magnitude but high-frequency mechanical vibration can greatly influence bone morphology. Thus, whole-body vibration exercise may also have the potential to improve the geometry of the long bones, which cannot be captured by DXA measurements. Further studies are needed to verify the benefit of whole-body vibration exercise in addition to the effect of alendronate on the skeleton.

Whole-body vibration exercise has been developed as a new modality in physiotherapy, but convincing evidence of its safety has been lacking. The danger of long-term exposure to whole-body vibration exercise is well-known, and human studies are needed before any clinical recommendation can be given (26, 31). We believe that our study is the only long-term trial performed on humans regarding the therapeutic effects of this type of exercise, and our results suggest its efficacy for chronic back pain in elderly women with osteoporosis without any serious adverse events such as new vertebral fractures or adverse cardiovascular symptoms. Most of the patients felt refreshed in the leg and back muscles just after whole-body vibration exercise over 12 months; that is, all patients were satisfied. We can show the safety of whole-body vibration exercise in elderly women with osteoporosis.

The limitations of this study, without respect to vibration stimuli, should be discussed. First, there were no placebo controls. Thus, whether the reduction in chronic back pain in the alendronate treatment group reflects a true drug effect is not known. Although the pain relief effect of alendronate treatment in our study is supported by previous studies (5, 7), double-blind placebo-controlled studies are needed to confirm the efficacy of alendronate for back pain as well as BMD and bone turnover in postmenopausal women with osteoporosis. Second, there were no non-alendronate treatment groups. Therefore, the pure effects of whole-body vibration exercise on the skeleton and chronic back pain remain uncertain. It is difficult to include groups treated only with vibration exercise but without bisphosphonate in elderly women with osteoporosis. Thus, further studies conducted on healthy post-menopausal women are needed to examine the pure effects of whole-body vibration exercise on the musculo-skeletal system. Third, the study period may have been too short to detect a small effect of the exercise on the skeleton in such a small sample size. Thus, further studies conducted on a sufficiently large number of subjects with a longer study period are needed, to determine the efficacy of this type of exercise on the skeleton. Fourth, the age of the subjects, in terms of the risk of falls at baseline was too low to evaluate the risk of falls. In fact, among our subjects, only a few patients had falls, and we could not analyze adequately the efficacy of whole-body vibration exercise as regards the risk of falls. Further studies conducted on older patients are needed to determine the efficacy of this type of exercise in fall prevention.

CONCLUSIONS

The results of this study suggest that whole-body vibration exercise using a Galileo machine can reduce chronic back pain, probably by relaxing the back muscles, in postmenopausal osteoporotic women treated with alendronate.

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