J Musculoskelet Neuronal Interact 2012; 12(3):136-143

Hylonome

Original Article

Whole body vibration exercise improves body balance and walking velocity in postmenopausal osteoporotic women treated with alendronate: Galileo and Alendronate Intervention Trail (GAIT)

J. Iwamoto[1,2], Y. Sato[3], T. Takeda[1], H. Matsumoto[1]

[1]Institute for Integrated Sports Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan; [2]Department of Orthopaedic Surgery, Keiyu Orthopaedic Hospital, Gunma, Japan; [3]Department of Neurology, Mitate Hospital, Tagawa, Fukuoka, Japan

Abstract

A randomized controlled trial was conducted to determine the effect of 6 months of whole body vibration (WBV) exercise on physical function in postmenopausal osteoporotic women treated with alendronate. Fifty-two ambulatory postmenopausal women with osteoporosis (mean age: 74.2 years, range: 51-91 years) were randomly divided into two groups: an exercise group and a control group. A four-minute WBV exercise was performed two days per week only in the exercise group. No exercise was performed in the control group. All the women were treated with alendronate. After 6 months of the WBV exercise, the indices for flexibility, body balance, and walking velocity were significantly improved in the exercise group compared with the control group. The exercise was safe and well tolerated. The reductions in serum alkaline phosphatase and urinary cross-linked N-terminal telopeptides of type I collagen during the 6-month period were comparable between the two groups. The present study showed the benefit and safety of WBV exercise for improving physical function in postmenopausal osteoporotic women treated with alendronate.

Keywords: Whole Body Vibration Exercise, Flexibility, Body Balance, Walking Velocity, Osteoporosis

Introduction

Osteoporosis most commonly affects postmenopausal women, placing them at a significant risk of fractures. Alendronate (ALN) is widely used for the treatment of postmenopausal osteoporosis. The Fracture Intervention Trial (FIT) demonstrated the efficacy of ALN against vertebral, non-vertebral, hip, and wrist fractures in postmenopausal women with osteoporosis[1,2]. Furthermore, a recent systematic review analyzing 11 randomized controlled trials (RCTs) representing 12,068 women confirmed that ALN treatment resulted in both clinically important and statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures for secondary prevention (gold-level evidence)[3]. RCTs in postmenopausal Japanese women with osteoporosis also revealed that short-term (1-3 years) ALN treatment suppressed bone turnover, increased the bone mineral density (BMD), and reduced the incidence of vertebral fractures[4-7]. ALN is regarded as a first-line drug for the treatment of osteoporosis in Japan.

Because most nonvertebral osteoporotic fractures occur as a result of falls, physicians must plan strategies for preventing falls even in patients treated with potent anti-fracture medicines such as ALN. Clinically, the impairment of muscle strength and muscle power of the lower extremities, balance/postural control, and walking ability have been recognized as important risk factors for falls[8]. However, muscle strength should be distinguished from muscle power; muscle strength is defined as the maximal force that a muscle can produce against a given resistance, while muscle power is defined as the product of force and speed[8,9]. The former is related to bone strength, whereas the latter is related to falling[8-11]. Thus, the improvement of muscle power, rather than muscle strength,

The authors have no conflict of interest.

Corresponding author: Jun Iwamoto, Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
E-mail: jiwamoto@a8.keio.jp

Edited by: J. Rittweger
Accepted 5 June 2012

would appear to be important for the prevention of falls.

Exercise is generally accepted to be effective for the prevention of falls in the elderly. A meta-analysis study has demonstrated that exercise is effective for lowering the risk of falls in the elderly and that the consequent reduction in the incidence of fall-related injuries reduces health care costs[12]. Previously, we reported that an exercise program aimed at improving flexibility, body balance, muscle power, and walking ability reduced the incidence of falls in the elderly[13].

Recently, whole-body vibration (WBV) exercise has been developed as a new modality in the field of physiotherapy and has been used to improve physical function in the elderly[14-16]. Several available systematic reviews and meta-analyses have discussed the effectiveness of WBV exercise[17-20]. Rogan et al.[17] concluded that vertical sinusoidal WBV revealed only small effects on static and dynamic balance, while side-alternating WBV showed small to moderate improvements in the same balance requirements in elderly subjects. Slatkovska et al.[18] clarified that WBV exercise resulted in small improvements in BMD in postmenopausal women and children and adolescents, but not in young adults. Lau et al.[19] found that WBV exercise was beneficial for enhancing leg muscle strength among older adults but had no overall treatment effect on BMD in older women. However, Conway et al.[20] reported that WBV exercise acted to degrade the majority of goal-related activities, especially those with high demands on visual perception and fine motor control.

Although there is a lack of long-term studies that have used an adequate number of elderly subjects with robust methodological structures (e.g., inclusion of placebo and control groups), the effects of WBV exercise seem to be modest. To our knowledge, the effect of WBV exercise on physical function in postmenopausal osteoporotic women has rarely been investigated using RCTs. Thus, an RCT was conducted to determine the effect of 6 months of WBV exercise on physical function in postmenopausal osteoporotic women treated with ALN.

Subjects and Methods

Study subjects

Fifty-two ambulatory postmenopausal women with osteoporosis who visited the Department of Orthopaedic Surgery of two hospitals and nine Orthopaedic Clinics in Japan during a one-year period between October 2009 and September 2010 were recruited to our trial. The inclusion criteria were an age of more than 50 years, a fully ambulatory status, the diagnosis of postmenopausal osteoporosis according to the Japanese diagnostic criteria[21,22], an osteoporosis treatment-naïve status, and the ability to measure the physical function parameters described below. The exclusion criteria for the exercise were severe gait disturbance requiring some form of walking aid, a severe rounded back because of osteoporotic vertebral fractures, clinical fractures because of osteoporosis, sciatica because of lumbar spinal canal stenosis, symptomatic osteoarthritis of the knee or hip, rheumatoid arthritis, acute phases of other diseases, and severe cardiovascular disease. The exclusion criteria for ALN treatment for osteoporosis were a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, or bone diseases including cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, multiple myeloma, Paget's disease of the bone, rheumatoid arthritis, or osteogenesis imperfecta. The physical activity level at baseline was considered to be comparatively low in all the participants because none of them had been laborers or had been engaged in any regular or leisure-time sporting activities. Age, height, body weight, body mass index, history of falls in the past 3 months, fractures after the age of 50 years, and physical function were assessed at the start of the trial. Blood and urine samples were also obtained in the morning for biochemical analysis.

The subjects (mean age: 74.2 years, range: 51-91 years) were randomly divided into two groups: an exercise group and a control group (n=26 in each group). For the exercise group, the WBV exercise was supervised and performed in the clinics or hospitals two days per week. Consequently, the compliance with the exercises was 100%. For the control group, no exercise was undertaken. All the subjects were treated with ALN (35 mg weekly). The doses of 5 mg daily and 35 mg weekly are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective[4-7]. The subjects did not receive either elementary calcium or natural vitamin D supplementation, although they were instructed with the aid of brochures to achieve daily intakes of 800 mg of calcium and 800 IU of vitamin D through food consumption. The period of this study was 6 months. Physical function and the incidence of falls and fall-related fractures were assessed 6 months after the start of the trial. At the same time, blood and urine samples were also obtained in the morning for biochemical analysis. In particular, information regarding falls and fall-related fractures was obtained every week by directly asking the participants. Informed consent was obtained from all the participants. The protocol was approved by the Ethical Committee of Keiyu Orthopaedic Hospital.

Blood and urinary biochemical tests

Serum and urine samples were obtained from each patient and the following biochemical analyses were performed. The serum calcium and phosphorus levels were measured using standard laboratory techniques. The serum alkaline phosphatase (ALP) level was measured using the JSCC reference method. The urinary cross-linked N-terminal telopeptides of type I collagen (NTX) level was measured using an enzyme-linked immunosorbent assay (ELISA).

Assessment of physical function

Indices for flexibility (finger-floor distance [FFD] with the body flexed in the anterior, right, and left directions), body balance (tandem standing time, unipedal standing time, and 3-m timed up & go [TUG]), muscle power (3-m TUG and chair-rising time [5 times]), and walking ability (10-m walking time and step number) were assessed. TUG reflects both dynamic body balance and muscle power. Apart from muscle strength, muscle power can be evaluated without using any machines by measuring the chair-rising time and TUG. FFD in the lateral flexions, tandem standing time, and unipedal standing time were determined by obtaining the mean values for the right and left sides.

Whole body vibration (WBV) exercise

WBV exercise was performed using a Galileo machine (G-900; Novotec, Pforzheim, Germany). The Galileo machine 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 legs upwards and downwards, thereby promoting the lengthening of 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 with no serious adverse events. Each WBV exercise session was set at a frequency of 20 Hz and a duration of 4 minutes. This frequency was thought to be comfortable and safe for postmenopausal women with osteoporosis.

Statistical analysis

An intention-to-treat (ITT) analysis was performed except for the comparison of the percentage changes in parameters between the two groups. The percentage changes in parameters were calculated using only the data of participants who completed the 6 months of trial and a per-protocol analysis was adopted. Data were expressed as the means ± standard deviation (SD). An unpaired t-test was used to compare baseline anthropometry, biochemical markers and physical function parameters at baseline and after 6 months of treatment, and percentage changes in assessed parameters between the two groups. A one-way analysis of variance (ANOVA) with repeated measurements was used to analyze the longitudinal changes in physical function parameters within a group. The Fisher's exact test was used to compare the percentages of fallers in the past 3 months and patients with prior clinical fractures and the incidence of falls and fall-related fractures between the two groups. All statistical analyses were performed using the Stat View J-5.0 program (SAS Institute, Cary, NC, USA). The significance level was set at $P<0.05$ for all the comparisons.

Results

Baseline anthropometry, biochemical markers, and physical function of the study subjects

Table 1 shows the baseline anthropometry of the study subjects. The mean age did not differ significantly between the two groups (72.4 years in the exercise group and 76.0 years in the control group). The years since menopause were ≥10 years for 22 women, 5-10 years for 2 women, 1-5 years for 1 woman, and unknown for 1 woman in the exercise group, and ≥10 years for 23 women, 5-10 years for 2 women, and 1-5 years for one woman in the control group. There were no significant differences in any other baseline characteristics including height, body weight, or body mass index. There were 6 fallers (23.1%) in the exercise group and 7 fallers (26.9%) in the control group in the past 3 months. There were 4 patients (15.4%) with a history of clinical fractures after 50 years of age in the exercise group (vertebral fracture in 2 patients and distal radius fracture in 2 patients) and 5 patients (19.2%) with a history of clinical fractures after 50 years of age in the control group (vertebral fracture in 1 patient, distal radius fracture in 2 patients, proximal humerus fracture in 1 patient, and rib fracture in 1 patient). No significant difference in the percentage of subjects who had experienced falls in the past 3 months and the percentage of subjects with a history of clinical fractures after 50 years of age was seen.

Table 2 shows the baseline biochemical markers of the study subjects. No significant differences in any of baseline biochemical marker levels including serum calcium, phosphorus, ALP, and

	Exercise	Control	P value
N	26	26	
Age (years)	72.4±8.1	76.0±7.4	N S
Height (m)	1.51±0.07	1.51±0.06	N S
Body weight (kg)	50.7±7.4	47.9±8.3	N S
Body mass index (kg/m^2)	22.3±3.5	20.8±2.9	N S
Faller in the past 3 months (%)	23.1	26.9	N S
History of clinical fracture (%)	15.4	19.2	N S

Data are expressed as means±SD. An unpaired t-test was used to compare anthropometry data between the two groups. The Fisher exact test was used to compare the percentages of fallers in the past 3 months and patients with prior clinical fractures between the two groups. NS: not significant.

Table 1. Baseline anthropometry of study subjects.

	Exercise	Control	P value
Calcium (mg/dL)	8.8±1.6	9.0±1.3	N S
Phosphorus (mg/dL)	3.5±0.5	3.4±0.5	N S
ALP (IU/L)	275±70	264±69	N S
Urinary NTX (nM BCE/mMCr)	47.1±19.4	43.6±16.6	N S

Data are expressed as means±SD. An unpaired t-test was used to compare biochemical markers between the two groups. Normal ranges of serum calcium, phosphorus, and ALP were 8.4-10.2 mg/dL, 2.5-4.5 mg/dL, and 100-340 IU/L. Standard range of urinary NTX was 9.3-54.3 nM BCE/mM Cr, and cut-off values of BMD loss and vertebral fracture risk were 35.3 and 54.3 nM BCE/mM Cr, respectively.ALP: alkaline phosphatase, NTX: cross-linked N-terminal telopeptides of type I collagen, BCE: bone collagen equivalent, Cr: creatinine, NS: not significant.

Table 2. Baseline biochemical markers.

	Exercise	Control	P value
FFD Anterior flexion (cm)	8.8±5.0	8.0±8.3	N S
Lateral flexion (cm)	40.0±9.2	39.3±7.8	N S
Unipedal standing time (sec)	48.2±50.5	48.7±57.8	N S
Tandem standing time (sec)	74.7±73.0	72.6±70.6	N S
Timed up & go (sec)	7.9±3.3	8.7±5.4	N S
Chair rising time (sec)	12.8±6.0	15.2±9.7	N S
10-m walking time (sec)	11.2±5.0	13.5±8.2	N S
10-m walking step number (#)	18.7±7.4	22.3±8.3	N S

Data are expressed as means±SD. An unpaired t-test was used to compare physical function Paremeters between the two groups. FFD: finger floor distance, NS: not significant.

Table 3. Baseline physical function. (Flexibility, body balance, muscle power, and walking ability indices).

	Exercise	Control
Calcium	N S	N S
Phosphorus	N S	N S
ALP	<0.0001	<0.01
Urinary NTX	<0.0001	<0.0001
FFD Anterior flexion	N S	N S
Lateral flexion	<0.05	N S
Unipedal standing time	N S	N S
Tandem standing time	<0.01	N S
Timed up & go	N S	N S
Chair rising time	<0.001	N S
10-m walking time	<0.01	N S
10-m walking step number	N S	N S

A one-way ANOVA with repeated measurements was used to analyze the longitudinal changes in biochemical markers and physical function parameters within a group.ANOVA: analysis of variance, ALP: alkaline phosphatase, NTX: cross-linked N-terminal telopeptides of type I collagen, FFD: finger floor distance, NS: not significant.

Table 4. One-way ANOVA with repeated measurements.

urinary NTX were seen between the two groups. The mean serum calcium, phosphorus, and ALP levels were within the normal ranges in both groups. The mean urinary NTX levels were higher than the cut-off value for BMD loss (35.4 nM BCE/mM Cr)[23,24].

Table 3 shows the baseline physical function of the study subjects. No significant differences in any of the baseline physical function indices for flexibility (FFD in the anterior and lateral flexions), body balance (unipedal standing time, tandem standing time, and TUG), muscle power (TUG and chair rising time), or walking ability (10-m walking time and step length) were seen between the two groups.

Number of subjects who completed the 6 months of trial

All the participants in the exercise group completed the 6 months of trial. In the control group, however, 3 participants dropped out of the trial because of non-compliance, 1 participant withdrew because of canker sores caused by ALN treatment, 1 participant withdrew because of the need for a extraction of a tooth (fear of osteonecrosis of the jaw), and 1 participant withdrew because of the occurrence of a non-traumatic clinical vertebral fracture during the 6-month study period.

Changes in biochemical markers

The serum calcium and phosphorus levels did not change significantly, but the serum ALP and urinary NTX levels decreased significantly in both groups (Tables 4 and 5). Table 5 shows the percentage changes in the biochemical markers. No significant differences in the percentage changes in the serum calcium, phosphorus, ALP, and urinary NTX levels were observed between the two groups. The mean reduction in the serum ALP level was 21.7% in the exercise group and 17.5% in the control group, while the mean reductions in the urinary NTX level were 41.8% and 40.0%, respectively.

Changes in physical function parameters

The FFD for the lateral flexions, the 10-m walking time, and the chair rising time decreased significantly and the tan-

	Exercise	Control	P value
Calcium	0.9±3.6	1.0±4.3	N S
Phosphorus	0.9±15.7	1.5±20.0	N S
ALP	-21.7±14.9	-17.5±16.0	N S
Urinary NTX	-41.8±19.2	-40.0±19.6	N S

Data are expressed as means±SD. The unpaired t-test was used to compare percentage changes in biochemical markers between the two groups. ALP: alkaline phosphatase, NTX: cross-linked N-terminal telopeptides of type I collagen, NS: not significant.

Table 5. Percentage changes in biochemical markers.

	Exercise	Control	P value
FFD Anterior flexion	-3.5±64.0	17.2±63.0	N S
Lateral flexion	-14.0±27.3	3.1±13.1	<0.05
Unipedal standing time	159.9±291.2	14.4±64.5	<0.05
Tandem standing time	150.0±246.1	27.2±56.0	<0.05
Timed up & go	-5.7±43.7	-0.6±13.6	N S
Chair rising time	-17.1±21.2	-7.5±19.3	N S
10-m walking time	-13.3±15.4	-1.9±17.0	<0.05
10-m walking step number	5.9±18.2	4.4±22.4	N S

Data are expressed as means±SD. An unpaired t-test was used to compare percentage changesin physical function parameters between the two groups. FFD: finger floor distance, NS: not significant.

Table 6. Percentage changes in physical function parameters.

dem standing time increased significantly in the exercise group, whereas none of the indices for flexibility, walking ability, body balance, or muscle power walking ability improved significantly in the control group (Tables 4 and 6). Table 6 shows the percentage changes in the physical function parameters. The percentage changes in the FFD for the lateral flexions, the unipedal standing time, the tandem standing time, and the 10-m walking time were significantly greater in the exercise group than in the control group, but no significant differences in the percentage changes in the FFD for the anterior flexion, the TUG, the chair-rising time, or the 10-m walking step number were observed between the two groups. In particular, the unipedal standing time and the tandem standing time were dramatically increased in the exercise group (mean increase rates: 159.9% and 150.0%, respectively).

Incidence of falls and fall-related fractures

Three participants in the control group and one participant in the exercise group experienced one fall each during the 6-month intervention period. The incidence of falls during the study period did not differ significantly between the two groups (11.5% in the control group vs. 3.8% in the exercise group). The four above-mentioned falls resulted in bruises or sprains of the upper extremities, requiring no intensive treatments and healing within several days. There were no fall-related fractures reported in either group.

Adverse events of WBV exercise

During the study period, no serious adverse events, such as severe fall-related injuries or adverse cardiovascular effects, were observed in the exercise group.

Discussion

Muscle power of the lower extremities, balance/postural control, and walking ability are key physical function parameters for the prevention of falls. An RCT was conducted to determine the effect of 6 months of WBV exercise on the physical function parameters in postmenopausal osteoporotic women treated with ALN. The focus of discussion was: 1) whether ALN would successfully reduce bone turnover markers in postmenopausal women with osteoporosis; 2) whether 6 months of WBV exercise (4 minutes per day, 2 days per week) would be safe and would improve physical function parameters in postmenopausal osteoporotic women treated with ALN; and 3) whether the improvement in the physical function parameters, if any, would be useful for preventing falls and fractures.

An RCT (Phase III study) showed that ALN (5 mg daily or 35 mg weekly) similarly reduced urinary NTX levels (approximately -45% at 6 months) in Japanese patients with involutional osteoporosis[6]. Another RCT (Phase III study) showed that ALN (5 mg daily) reduced serum ALP levels (about -30% at 6 months) in Japanese patients with osteoporosis[7]. In the present study, after 6 months of treatment with ALN (35 mg weekly), the serum ALP levels were reduced by 21.7% in the exercise group and 17.5% in the control group, and the urinary NTX levels were decreased by 40.0% and 41.8%, respectively. Our clinical practice-based studies showed that the reduction rates in urinary NTX and the serum ALP levels after ALN treatment were 40.2-43.6% at 3 months and 17.1-19.0% at 6 months, respectively[25,26]. The discrepancy between our present and previous studies and strictly conducted RCTs regarding the reduction in the serum total ALP levels, which are affected by bone, intestine, and liver diseases, may be attributable to the characteristics of the study subjects. The exclusion criteria in the present study were not as strict as those used for strictly conducted RCTs; therefore, more frail patients might have been enrolled.

The similar reductions in the serum ALP and urinary NTX levels after 6 months of ALN treatment in the exercise and control groups suggest no significant effect of WBV exercise on bone turnover. Our previous study showed that WBV exercise and ALN did not have any additive effects on the lumbar spine BMD and the urinary NTX and serum ALP levels in postmenopausal women with osteoporosis[27]. Chilibeck et al.[28] reported that etidronate increased the lumbar spine BMD and strength training resulted in greater increases in the muscular strength and lean tissue mass and greater loss of fat mass in postmenopausal women, but that there was no interaction between exercise and etidronate. Experimental studies using ovariectomized rats (a model of postmenopausal osteoporosis) examined the effects of bisphosphonates and running exercise on bone mass and strength. Lespessailles et al.[29] reported that zoledronic acid and running exercise did not produce any additive effects on bone mass and strength, whereas Fuchs et al.[30] showed that combination of running exercise and ALN was more beneficial in preventing declines in bone mass and strength than either intervention alone. Thus, it is certain that bisphosphonates increase bone mass or strength while exercises improve physical function and body composition. However, it remains uncertain whether simultaneous application of bisphosphonates and exercises produces synergetic or additive effects on bone parameters. The effect of WBV exercise on BMD and bone turnover markers could possibly be masked by the strong influence of bisphosphonates.

We administered WBV exercise to the subjects two days per week at a frequency of 20 Hz and for a duration of 4 minutes. The intensity and frequency of the exercise program were considered to be reasonable for postmenopausal osteoporotic women (mean age, 74.2 years), enabling the exercise to be continued without any fatigue or difficulty for 6 months. WBV exercise was not only effective for improving physical function, i.e., the indices for flexibility, body balance, and walking velocity, but also was well tolerated. No serious adverse events, such as fall-related injuries or adverse cardiovascular effects, were observed in any of the subjects during the exercise program, suggesting the safety of WBV exercise.

WBV exercise significantly improved the FFD for the lateral flexions in terms of lateral flexibility. This outcome may have contributed to the prevention of falls resulting from staggers. Our previous study showed that WBV exercise was useful for reducing chronic back pain, probably by relaxing the back muscles in postmenopausal osteoporotic women treated with ALN[27]. The relaxation of the back muscles caused by the WBV exercise, in which the right and left legs are thrust upwards and downwards, might have partly contributed to the improvement in lateral flexibility. However, the WBV exercise did not significantly improve the FFD for anterior flexion. Anterior flexibility is affected by the tightness of the hamstrings. Because the WBV exercise promotes lengthening predominantly of the extensor muscles of the lower extremities, tightness of the hamstrings might have been less relaxed by the exercise, resulting in no improvement in anterior flexibility.

The WBV exercise resulted in a significant and dramatic improvement in the unipedal standing time and the tandem standing time in terms of static body balance. This outcome may have contributed to the prevention of falls, since the unipedal standing balance exercise performed with open eyes reportedly reduced the cumulative number of falls among Japanese elderly individuals (mean age: 81.6 years)[31].

Although the WBV exercise significantly improved the 10-meter walking time in terms of walking velocity, it did not significantly improve the chair-rising time or the TUG in terms of muscle power and dynamic body balance. Chair-rising/sitting and the walking velocity may be affected by type II muscle fiber function, in terms of the speed of muscle contraction. A chain of rapid muscle contractions during WBV exercise may be sufficient to influence the type II muscle fiber function, resulting in the improvement of walking velocity. However, the length of each muscle contraction during the WBV exercise is substantially smaller than that observed during chair-rising/sitting. Thus, squatting on the rocking platform of the Galileo machine during the WBV exercise would be required to improve the chair-rising time and the TUG.

Despite a favorable improvement in physical function, including gait and balance[32], the incidence of falls was not significantly reduced by the WBV exercise (11.5% in the control group vs. 3.8% in the exercise group), probably because of an inadequate statistical power. The study period was 6 months, and the sample size was 52 (n=26 in each group). Furthermore, the SDs of some physical function parameters were high because the groups are heterogeneous, especially in age which certainly influences muscle mass. Long-term exercise is needed to reduce the life-time risk of falls and fall-related injuries in postmenopausal women with osteoporosis. However, because our exercise program proved easy for our subjects (mean age: 74.2 years) to continue without any difficulty, we believe that it could be continued under the instruction of general practitioners.

The present study had several strengths. First, the RCT was strictly performed not by exercise-related experts, but mainly by general practitioners (compliance with the exercises: 100%) without the need for any special machines to evaluate physical function. Second, the exercise program was safe and well tolerated. These strengths suggest the clinical usefulness and convenience of the exercise program for improving physical function in postmenopausal osteoporotic women treated with ALN.

The limitations of the present study should also be discussed. First, the study period was short and the sample size was small, as discussed above. Second, we did not evaluate vitamin D insufficiency/deficiency by measuring the serum 25(OH)D levels and we did not provide calcium/vitamin D supplements to the subjects. In Japan, vitamin D supplementation is uncommon and the measurement of serum 25(OH)D levels is not covered by health insurance. Because low serum levels of 25(OH)D are correlated with an increased risk of falls and vitamin D supplementation reduces the incidence of falls in the elderly[33-35], evaluating the vitamin D status is important. Third, it is important to evaluate muscle mass as well as muscle function in elderly people because sarcopenia is an increasing problem in the aging society[36,37]. Sarcopenia is an age-related condition defined by the combined presence of reduced muscle mass, that is, a T score of muscle mass (corrected for height, body weight, or fat mass) of 2SDs or less, and reduced muscle function measured as gait speed less than 0.8 or 1 m/sec[38]. Fjeldstad et al.[39] reported that resistance training alone and with WBV exercise resulted in positive body composition changes by increasing lean mass in older women, but that only the combination of resistance training and WBV exercise was effective for decreasing percent body fat. von Stengel et al.[40] reported that WBV exercise embedded in a multipurpose exercise program showed minor additive effects on body composition and neuromuscular performance in older women. Thus, it would be of importance to examine the effect of WBV exercise on body composition as well as muscle and fat mass in postmenopausal osteoporotic women. Further studies are needed to resolve these limitations.

In conclusion, an RCT was conducted to determine the effect of 6 months of WBV exercise on physical function in postmenopausal osteoporotic women treated with ALN. The 6 months of WBV exercise (4 minutes per day, 2 days per week) was well tolerated and improved the indices for flexibility and body balance as well as the walking velocity. The present study showed the benefit and safety of WBV exercise for improving physical function in postmenopausal osteoporotic women treated with ALN.

Doctors who participated in the study

The following doctors participated in the study; Hiroyuki Suzuki (Department of Orthopeadic Surgery, Kawakita General Hospital, Tokyo), Hisashi Hirabayashi (Department of Orthopeadic Surgery, Tokyo Adventist Hospital, Tokyo), Takami Kumakubo (Kumakubo Orthopaedic Clinic, Tokyo), Yoshito Kikuchi (Kikuchi Orthopeadic Clinic, Tokyo), Yu Miyazaki (Miyazaki Orthopeadic Clinic, Tokyo), Kazunori Hayashi (Nakasugidori Orthopaedic Clinic, Tokyo), Akira Kawashima (Kawashima Orthopeadic Clinic, Chiba), Michimasa Ui (Ui Orthopeadic Clinic, Chiba), Iwao Ibata (Ibata Orthopaedic Clinic, Chiba), Hiroyuki Okada (Fujinoki Orthopaedics and Internal Medicine Clinic, Gunma), and Tadahiko Aibara (Aibara Orthopeadic Clinic, Ehime).

Acknowledgements

We would like to thank Mr. Toshihiro Yamaguchi (Tokyo Branch of MSD Co. Ltd., Tokyo, Japan) for his assistance in the preparation of the trial.

References

1. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.
2. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
3. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;23(1):CD001155.
4. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H. The efficacy of alendronate in reducing the risk of vertebral fracture in Japanese patients with osteoporosis: A randomized, double-blind, active-controlled, double-dummy trial. Curr Ther Res Clin Exp 2002;63:606-20.
5. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H. Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 2004;22:462-8.
6. Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, Arizono H, Nagata K, Santora AC, Shiraki M, Fukunaga M, Tomomitsu T, Ohashi Y, Nakamura T. 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;23:382-8.
7. Shiraki M, Kushida K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, Kaneda K, Minaguchi H, Inoue T, Morii H, Tomita A, Yamamoto K, Nagata Y, Nakashima M, Orimo H. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. Osteoporos Int 1999;10:183-92.
8. Runge M, Rehfeld G, Resnicek E. Balance training and exercise in geriatric patients. J Musculoskel Neuronal Interact 2001;1:61-5.
9. Runge M, Hunter G. Determinants of musculoskeletal frailty and the risk of falls in old age. J Musculoskel Neuronal Interact 2006;6:167-73.
10. Frost HM. Defining osteopenias and osteoporosis: another view (with insights from a new paradigm). Bone 1997;20:385-91.
11. Schiessl H, Frost HM, Jee WSS. Estrogen and bone-muscle strength and mass relationship. Bone 1998;22:1-6.
12. Gardner MM, Robertson MC, Campbell AJ. Exercise in preventing falls and fall related injuries in older people: a review of randomized controlled trials. Br J Sports Med 2000;34:7-17.
13. Iwamoto J, Suzuki H, Tanaka K, Kumakubo T, Hirabayashi H, Miyazaki Y, Sato Y, Takeda T, Matsumoto H. Preventative effect of exercise against falls in the elderly: a randomized controlled trial. Osteoporos Int 2009; 20:1233-40.
14. Iwamoto J, Otaka Y, Kudo Y, Takeda T, Uzawa M, Hirabayashi K. Efficacy of training program for ambulatory competence in elderly women. Keio J Med 2004; 53:85-9.
15. Kawanabe K, Kawashima A, Sashimoto I, Takeda T, Sato Y, Iwamoto J. Effect of whole-body vibration exercise and muscle strengthening, balance, and walking exercises on walking ability in the elderly. Keio J Med 2007;56:28-33.
16. Kawanabe K, Kawashima A, Sashimoto I, Abe K, Takeda T, Matsumoto H, Iwamoto J. Influence of vibration exercise on the effect of muscle strengthening and balance training in the frail elderly. Jpn J Orthop Sports Med 2008;28:242-8.
17. Rogan S, Hilfiker R, Herren K, Radlinger L, de Bruin ED. Effects of whole-body vibration on postural control in elderly: a systematic review and meta-analysis. BMC Geriatr 2011 (Online publication).
18. Slatkovska L, Alibhai SM, Beyene J, Cheung AM. Effect of whole-body vibration on BMD: a systematic review and meta-analysis. Osteoporos Int 2010;21:1969-80.
19. Lau RW, Liao LR, Yu F, Teo T, Chung RC, Pang MY. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: a systematic review and meta-analysis. Clin Rehabil 2011;25:975-88.
20. Conway GE, Szalma JL, Hancock PA. A quantitative meta-analytic examination of whole-body vibration effects on human performance. Ergonomics 2007;50:228-45.
21. Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, Nakamura T, Kushida K, Tanaka H, Ikai T, Ohhashi Y. Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 1998;16:139-50.
22. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 2001;19:331-7.
23. Nishizawa Y, Nakamura T, Ohta H, Kushida K, Gorai I, Shiraki M, Fukunaga M, Hosoi T, Miki T, Chaki O, Ichimura S, Nakatsuka K, Miura M. Guidelines for the use of biochemical markers of bone turnover in osteoporosis (2004). J Bone Miner Metab 2005;23:97-104.
24. Orimo H. Japanese guideline for prevention and treatment of osteoporosis. Life Science 2011 (in Japanese).
25. Iwamoto J, Miyata A, Sato Y, Takeda T, Matsumoto H. Five-year alendronate treatment outcome in older post-

menopausal Japanese women with osteoporosis or osteopenia and clinical risk factors for fractures. Ther Clin Risk Manag 2009;5:773-9.

26. Iwamoto J, Uzawa M, Sato Y, Takeda T, Matsumoto H. Effects of short-term combined treatment with alendronate and elcatonin on bone mineral density and bone turnover in postmenopausal women with osteoporosis. Ther Clin Risk Manag 2009;5:499-505.
27. Iwamoto J, Takeda T, Sato Y, Uzawa M. 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. Aging Clin Exp Res 2005;17:157-63.
28. Chilibeck PD, Davison KS, Whiting SJ, Suzuki Y, Janzen CL, Peloso P. The effect of strength training combined with bisphosphonate (etidronate) therapy on bone mineral, lean tissue, and fat mass in postmenopausal women. Can J Physiol Pharmacol 2002;80:941-50.
29. Lespessailles E, Jaffré C, Beaupied H, Nanyan P, Dolléans E, Benhamou CL, Courteix D. Does exercise modify the effects of zoledronic acid on bone mass, microarchitecture, biomechanics, and turnover in ovariectomized rats? Calcif Tissue Int 2009;85:146-57.
30. Fuchs RK, Shea M, Durski SL, Winters-Stone KM, Widrick J, Snow CM. Individual and combined effects of exercise and alendronate on bone mass and strength in ovariectomized rats. Bone 2007;41:290-6.
31. Sakamoto K, Nakamura T, Hagino H, Endo N, Mori S, Muto Y, Harada A, Nakano T, Itoi E, Yoshimura M, Norimatsu H, Yamamoto H, Ochi T. Effects of unipedal standing balance exercise on the prevention of falls and hip fracture among clinically defined high-risk elderly individuals: a randomized controlled trial. J Orthop Sic 2006; 11:467-72.
32. Ganz DA, Bao Y, Shekelle PG, Rubebstein LZ. Will my patient fall? JAMA 2007;297:77-86.
33. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, Yoshida H. Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. J Bone Miner Res 2008;23:1309-17.
34. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis 2005;20:187-92.
35. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
36. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011; 12:249-56.
37. Wang C, Bai L. Sarcopenia in the elderly: Basic and clinical issues. Geriatr Gerontol Int 2012;12(3):388-96.
38. Cederholm TE, Bauer JM, Boirie Y, Schneider SM, Sieber CC, Rolland Y. Toward a definition of sarcopenia. Clin Geriatr Med 2011;27:341-53.
39. Fjeldstad C, Palmer IJ, Bemben MG, Bemben DA. Whole-body vibration augments resistance training effects on body composition in postmenopausal women. Maturitas 2009;63:79-83.
40. von Stengel S, Kemmler W, Engelke K, Kalender WA. Effect of whole-body vibration on neuromuscular performance and body composition for females 65 years and older: a randomized-controlled trial. Scand J Med Sci Sports 2012;22:119-27.