

experience increases in blood flow and shear stress during aerobic exercise bouts [25,26], whereas carotid blood flow does not appear to change during resistance exercises [27,28]. Consistent with this, endothelial function is improved with regular aerobic exercise [29,30] as well as with combined resistance and aerobic training [31,32]. Resistance training alone, however, appears to have no effects on flow-mediated vasodilation [33]. One possibility is therefore that the combined aerobic and resistance training may have increased nitric oxide bioavailability, which in turn may have negated the opposing effects of resistance training on the arterial wall. Future studies will be needed to determine the physiological mechanisms underlying the influence of resistance and aerobic training on carotid arterial compliance.

Although endurance training performed concurrently with resistance training prevented the stiffening of carotid arteries, the magnitude of increases was larger in the combined training group than in the moderate-intensity training group in all exercises except for the leg curl. The strength gains were consistently smaller in the combined training group compared with the previously studied high-intensity resistance training alone [9], especially in the lower limbs. This occurred despite the fact that the same training intensity and volume were prescribed to both groups. These results are consistent with a number of previous studies demonstrating that subjects who perform a combination of endurance and strength training achieve lower strength gains than subjects performing weight training alone [34–36]. It should therefore be noted that simultaneous endurance and resistance training may prevent arterial stiffening, but could attenuate optimum gains in muscular strength. In order to minimize the antagonistic effects of endurance training on strength gains, it is recommended that strength and endurance training be performed on alternate days [36]. A smaller strength gain in the combined training group might confound the interpretation of our findings. The moderate-intensity resistance training that achieved much smaller strength gains, however, experienced a similar magnitude of arterial stiffening to the high-intensity training group. The effect of resistance training on arterial compliance therefore does not appear to be dependent upon the training intensity or strength gains.

There are several limitations of the present study that should be emphasized. First, the combined training group that performed moderate-intensity resistance training was not included in the present study. Because simultaneously performed endurance training negated the effects of ‘high-intensity’ resistance training, however, it is fairly reasonable to assume that it would negate the effects of ‘moderate-intensity’ (i.e. lesser stimuli) resistance training as well. Second, although arterial compliance and blood pressure often change simultaneously with interventions,

changes in arterial compliance were not associated with the corresponding changes in blood pressure in the present study. Because changes in the elastic property of arteries appear to precede changes in blood pressure [37], it is possible that a longer duration of resistance training may have increased blood pressure. Third, we studied relatively small numbers of subjects in each group ( $n = 11–16$ ), and included only young healthy men. Future studies targeting high-risk populations (e.g. the elderly) are needed.

In light of the current recommendation that resistance training should be incorporated into exercise prescription [5–7], the effects of resistance training to stiffen large elastic arteries are of particular concern. We examined two strategies that potentially prevent arterial stiffening associated with resistance training. We demonstrated that moderate-intensity resistance training produced significant reductions in arterial compliance. In contrast, combined resistance and aerobic training did not result in decreases in carotid arterial compliance. These results suggest that in order to negate and prevent the stiffening of carotid arteries caused by resistance training, aerobic training should be performed simultaneously with resistance training.

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## Effects of Isoflavone and Exercise on BMD and Fat Mass in Postmenopausal Japanese Women: A 1-Year Randomized Placebo-Controlled Trial

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**ABSTRACT:** The combined intervention of isoflavone intake and walking exercise over 1 year in postmenopausal Japanese women exhibited a trend for a greater effect on prevention of bone loss at the total hip and Ward's triangle regions.

**Introduction:** The additive effects of isoflavones and exercise on bone and lipid metabolism have been shown in estrogen-deficient animals. In this study, we determined the effects of isoflavone intake, walking exercise, and their interaction on bone, fat mass, and lipid metabolism over 1 year in postmenopausal Japanese women.

**Materials and Methods:** A total of 136 postmenopausal women at <5 years after the onset of menopause were randomly assigned to four groups: (1) placebo, (2) walking (45 minutes/day, 3 days/week) with placebo, (3) isoflavone intake (75 mg of isoflavone conjugates/day), and (4) combination of isoflavone plus walking. BMD, fat mass, serum lipid, and serum and urinary isoflavone concentrations were assessed.

**Results:** A significant main effect of isoflavone on the reduction in trunk fat mass was obtained at 12 months. Significant main effects of walking on the reduction in fat mass in the whole body and the trunk were observed at 3, 6, and 12 months and that in the legs and arms at 6 and 12 months. Serum high-density lipoprotein (HDL)-cholesterol concentration significantly increased by 12 months after the walking and the combined intervention. After 12 months, a significant main effect of isoflavone on BMD was observed only at Ward's triangle. Walking prevented bone loss at the total hip and the Ward's triangle to significant degrees. The effect of the combined intervention on BMD at total hip and Ward's triangle regions was greater than that of either alone. No significant interaction was observed between isoflavone and walking in any measurements recorded during the study.

**Conclusions:** Our study suggest that combined intervention of 75 mg/day of isoflavone intake and walking exercise 3 times/week for 1 year showed a trend for a greater effect on BMD at total hip and Ward's triangle regions than either alone. Intervention with isoflavone in postmenopausal Japanese women showed a modest effect on BMD compared with those in Westerners. Further studies over longer treatment duration that include assessment of BMD at various regions are necessary to ascertain the clinical significance of the combined intervention of isoflavone plus walking in postmenopausal women.

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**Key words:** isoflavones, walking exercise, BMD, fat mass, postmenopausal women

### INTRODUCTION

ESTROGEN DEFICIENCY OFTEN increases the risk of several chronic diseases such as osteoporosis, cardiovascular disease, and obesity.<sup>(1–4)</sup> Hormone replacement therapy (HRT) is an effective regimen that prevents these diseases in postmenopausal women.<sup>(5,6)</sup> However, the HRT trial carried out by the Women's Health Initiative (WHI) found that long-term use of HRT (follow-up, 5.2 years) poses se-

rious risks and may increase the risk of heart attack and stroke.<sup>(7)</sup> Follow-up studies with the WHI will likely provide insight as to whether the increased risks and benefits of HRT therapy decline after the end of the therapy and the time at which this decline occurs as well as evaluation of the dose.<sup>(8)</sup>

Recently, there has been an increased interest in the role of phytoestrogens in preventing osteoporosis and hypercholesterolemia.<sup>(9)</sup> Soybean is a rich source of the isoflavones, genistein, and daidzein, which shows weak estrogenic effects in several organs.<sup>(10)</sup> A number of studies have

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previously reported that soybean isoflavones dose-dependently inhibited bone loss in both female and male osteoporotic animal models without causing notable effects on the reproductive organs.<sup>(11–13)</sup> However, the results obtained from several observational clinical studies are still conflicting. The discrepancies between the results may be caused by the variation in factors such as the duration of intervention, the bone sites measured, dietary intake, isoflavone intake among subjects and controls, and its metabolism.

On the other hand, the effects of exercise on the prevention of bone loss, fat accumulation, and hypercholesterolemia in women around the menopausal period have been previously studied.<sup>(14–17)</sup> An exercise program designed for postmenopausal women should be safe and easy to perform and continue. Although high-intensity exercise could possibly increase the bone mass in pre/postmenopausal women, such exercise is also often associated with stress fractures, particularly in individuals with fragile skeletons.<sup>(18)</sup> Walking is a relatively safe exercise that is commonly performed by elderly people. Thompson et al.<sup>(14)</sup> indicated an inverse association between body composition variables and daily walking steps in middle-aged women. However, walking exercise has a relatively low impact on bones, and therefore, cannot be used exclusively for preventing bone loss in postmenopausal women.<sup>(15)</sup> Thus, a few studies have examined the effects of a combination of exercise and HRT on bone mass and body composition in postmenopausal women. Kohrt et al.<sup>(16)</sup> and Cheng et al.<sup>(17)</sup> assessed the independent and combined effects of exercise and HRT on the increase in BMD and the reduction in fat mass in postmenopausal women. Because the risk to benefit ratio of HRT continues to be debated,<sup>(19)</sup> other interventions that combine therapies using phytoestrogens with exercise training may be preferred. Therefore, we hypothesized that isoflavone intake combined with walking exercise would have beneficial effects on the bone and fat mass and serum lipid concentration in postmenopausal women. We have previously reported that, with regard to the prevention of bone loss and fat gain in estrogen-deficient animals, the effects of moderate-intensity exercise combined with isoflavone administration were better than those observed when either was used exclusively.<sup>(20–22)</sup>

In this study, we report the effects of soy isoflavone intake and/or walking exercise for 1 year on bone mass, body composition, and serum lipid concentration in postmenopausal Japanese women.

## MATERIALS AND METHODS

### *Subjects*

Subjects were recruited for this study through advertisements in local newspapers, and those who fulfilled the following criteria were enrolled for the study. Healthy postmenopausal women 45–60 years of age who were within 5 years of natural onset of menopause (defined as at least 12 months since the last menstrual cycle occurred) were enrolled in the study. The subjects had no history of previous use of HRT, lipid-lowering medications, antibiotics, or any

other medication known to affect the skeleton. They provided written informed consent to participate in the study. The protocol was approved by the institutional review board of the NIH and Nutrition of Japan, and the study was performed in accordance with the guidelines of the Declaration of Helsinki.

In this study, 145 women who fulfilled the required criteria were called for the screening examination. The criteria for the invitation were as follows: willingness to participate, clinically healthy (no cardiovascular, musculoskeletal, respiratory, or other chronic diseases that might limit walking exercise), sedentary life style (no regular sports activities for at least 2 years), nondieting, nonsmoking, and having no apparent occupational responsibilities or leisure time activities that might impede their participation. Nine participants were excluded after the medical screening because of high serum estradiol (E2) concentrations (>20 pg/ml). Thus, 136 women were randomly assigned to four groups: (1) placebo, (2) placebo plus walking, (3) isoflavone, and (4) isoflavone plus walking. However, 28 women withdrew from the study because of illness, family problems, or they thought that participating in the study was troublesome. The remaining 108 subjects completed the 12-month study, and their data were included in the per protocol analysis (Fig. 1).

### *Intervention*

Placebo or isoflavone capsules were blindly allocated to researchers and subjects throughout the study. Participants from the two groups, isoflavone and isoflavone combined with walking, received two capsules that contained a total of 75 mg of isoflavone conjugate (47 mg as aglycone form; Fujiflavone P40; Fujicco Co., Kobe, Japan) with dextrin, daily in the morning. The isoflavone conjugate weighing 75 mg contained daidzin (38.3 mg), malonyldaidzin (0.2 mg), acetyldaidzin (2.1 mg), daidzein (0.6 mg), genistin (8.6 mg), acetylgenistin (0.6 mg), genistein (0.2 mg), and glycitin (23.4 mg) with glycitein (1.0 mg). The remaining subjects were assigned to receive two placebo capsules containing only dextrin, daily in the morning.

Participants who were randomized into the walking groups were expected to attend three 1-h-long exercise classes each week. The exercise program consisted of a 10-minute warm-up period, a 45-minute supervised walking exercise session, and a 5-minute cool down period. Participants were given instructions with regard to the proper manner of walking to eliminate possible injury. The participants were instructed to maintain the speed of walking at 5–6 km/h, and this was monitored by a pedometer.

The nonwalking group participants did not engage in sports training and were asked to continue their normal activity levels. All participants were instructed to record their daily number of steps walked that were continuously monitored by the pedometer, and their diaries were obtained and checked once a month to ensure that they were up-to-date.

### *Questionnaire interview*

Individual information was collected by trained interviewers in face to face interviews based on a structured and

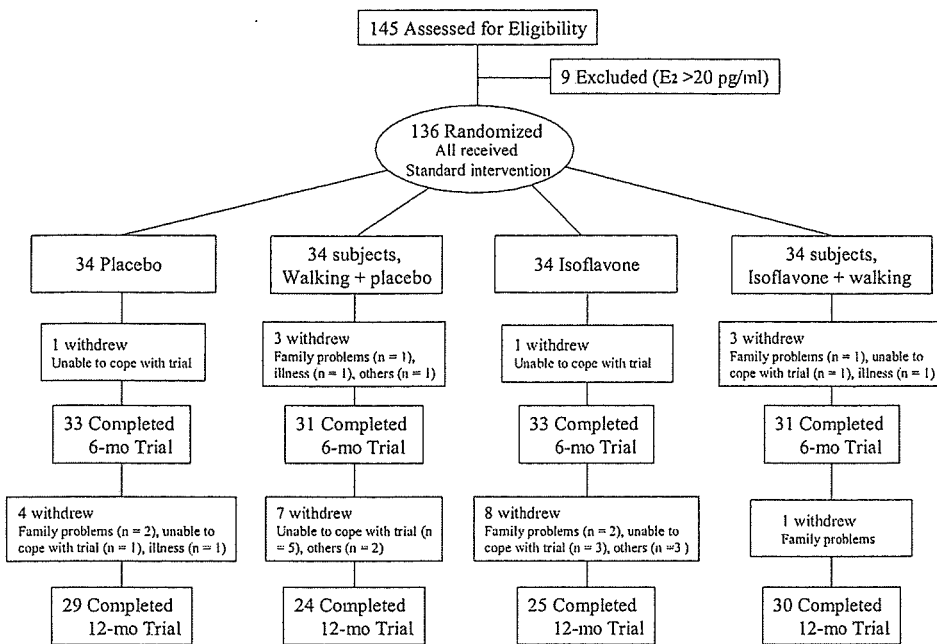


FIG. 1. Flow chart with details of the participants.

previously validated questionnaire that included the following: socio-demographic data; years since menopause; physical activities, including hours spent sitting, standing, walking, sports, and leisure activities; medications; smoking and drinking alcohol; and other factors that may have possible confounding effects on the relation between dietary isoflavone consumption and metabolism of bone and lipid. The participants were instructed to record the contents of daily meals, snacks, and beverages in the diet diary. The diary was collected continuously for 3 days to confirm the meal intake, and, if necessary, the participants were immediately instructed to adhere to the dietary regimen. Daily intakes of soy isoflavones, calcium, vitamin D, total energy, and protein were calculated from the daily record by the dietitian on the basis of the Fifth Revision of the Standard Tables of Food Composition in Japan.<sup>(23)</sup>

#### Blood and urine samples

Before BMD measurement, fasting (>12 h) blood samples were collected by venipuncture in EDTA-containing tubes, refrigerated immediately, and centrifuged at 1500 rpm for 30 minutes at 4°C within 2 h. Serum samples from each participant were stored frozen at -20°C. Serum concentrations of total cholesterol (TC) and triacylglycerol (TG) were determined using commercial kits (cholesterol C-test and triglyceride G-test, respectively; Wako Pure Chemical Industries, Osaka, Japan). Serum high-density lipoprotein (HDL)-cholesterol was measured by an enzymatic method (HDL-cholesterol test; Wako Pure Chemical Industries). Serum low-density lipoprotein (LDL)-cholesterol levels were calculated as follows: total cholesterol (mg/dl) - HDL-cholesterol (mg/dl) - TG (mg/dl) × 0.2. Estradiol (E2) was assessed by radioimmunoassay (Amersham Biosciences, Piscataway, NJ, USA). Serum bone-specific alkaline phosphatase (BSALP; Alkphase-B; Metra Biosystems, Mountain View, CA, USA) was measured by

using a microplate coated with an anti-BSALP monoclonal antibody. Serum intact osteocalcin (OC) was measured by using a sandwich enzyme immunoassay (EIA) that uses polyclonal antibodies against 20 N-terminal residues (amino acids 1-20) and against 7 C-terminal residues (amino acids 43-49; Biomedical Technology, Stoughton, MA, USA). Urine samples were collected from a second voiding at the same time as blood collection, and they were stored at -20°C. Urinary deoxyypyridinoline (DPD) was measured using a sandwich EIA (Pyrilinks-D Assay; Metra Biosystems).

#### Measurement of serum and urinary isoflavones

Concentrations of isoflavones in serum and urine samples were determined for each subject by reverse-phase high-performance liquid chromatography (HPLC). Duplicate samples of serum and urine were incubated with sulfatase (EC 3.1.6.1; Sigma Chemical) and β-glucuronidase (EC 3.2.1.31; Wako Pure Chemical Industries) at 37°C for 2 h to release the aglycones of the isoflavones; this was followed by purification of reactants using a Sep-Pak C18 cartridge (Waters Co., Milford, MA, USA). Isoflavones were separated at 35°C by reverse-phase HPLC on a 4.6 × 250-mm Capcell Pak C18 column (Shiseido Co., Tokyo, Japan) using a Tosoh CCP and 8020 system with a diode array detector PD8020 (Tosoh Co., Tokyo, Japan). Elution was performed at a flow rate of 1 ml/minute with a linear gradient of acetonitrile solution (10-35%) containing a constant 0.1% concentration of acetic acid. Data were simultaneously acquired at 254 nm (daidzein, genistein, glycitein) and 280 nm (equol).

#### BMD and body composition

BMD of the lumbar spine (L<sub>2</sub>-L<sub>4</sub>), left hip, and subwhole body regions (excluding head region) and body composition were assessed by DXA at baseline and after 3, 6, and

TABLE 1. CHARACTERISTICS OF SUBJECTS OF DIFFERENT STUDY GROUPS AT BASELINE AND 12 MONTHS\*

		Placebo (n = 33)	Walking (n = 31)	Isoflavone (n = 33)	Isoflavone + walking (n = 31)
Age (years)		54.9 (2.9)	55.2 (2.8)	53.8 (2.9)	54.4 (2.9)
Years since menopause		3.7 (2.1)	3.6 (1.8)	2.7 (1.4)	3.2 (1.4)
Height (cm)	Baseline	156.7 (6.3)	155.3 (6.3)	155.8 (4.3)	154.8 (5.5)
	After 12 months	156.3 (6.3)	154.8 (6.0)	155.3 (4.4)	154.7 (5.3)
Weight (kg)	Baseline	51.4 (7.1)	54.1 (7.3)	51.5 (5.4)	52.9 (5.3)
	After 12 months	51.7 (6.9)	52.6 (7.3)	51.2 (5.7)	51.8 (5.0)
BMI (kg/m <sup>2</sup> )	Baseline	20.9 (2.2)	22.4 (2.9)	21.3 (2.5)	22.1 (2.0)
	After 12 months	21.2 (2.5)	21.9 (2.8)	21.3 (2.6)	21.7 (2.0)
Daily intake					
Isoflavone (mg) <sup>†</sup>	Baseline	48.1 (30.6)	47.7 (25.0)	44.4 (26.9)	49.4 (25.0)
	After 12 months	49.4 (35.0)	48.1 (24.1)	37.4 (26.9)	48.3 (26.7)
Calcium (mg)	Baseline	671.5 (190.9)	723.8 (221.5)	695.8 (253.5)	691.5 (213.3)
	After 12 months	620.3 (176.6)	687.9 (191.0)	597.1 (209.0)	709.6 (232.2)
Vitamin D (μg)	Baseline	9.2 (5.9)	12.3 (13.1)	9.8 (5.9)	9.2 (5.0)
	After 12 months	8.4 (5.1)	9.5 (6.9)	7.6 (4.9)	8.6 (5.8)
Vitamin K (μg)	Baseline	429.8 (172.2)	463.6 (207.0)	376.3 (211.0)	438.3 (181.9)
	After 12 months	378.2 (177.9)	504.1 (260.8)	365.2 (209.0)	439.8 (200.6)
Protein (g)	Baseline	75.0 (13.5)	79.5 (17.4)	72.4 (14.3)	73.5 (13.5)
	After 12 months	69.7 (14.3)	74.8 (14.2)	67.3 (16.0)	74.8 (14.3)
Total energy (kcal)	Baseline	1980.8 (327.5)	1992.8 (327.0)	1923.0 (361.0)	1995.9 (339.7)
	After 12 months	1861.2 (379.2)	2015.6 (305.2)	1811.4 (371.2)	2020.3 (285.4)
Average numbers of steps/day <sup>‡</sup>	During 12 months	6397 (2166)	8047 (2169) <sup>§</sup>	6111 (2395)	9024 (3113) <sup>§</sup>

\* Mean (SD). There were no significant differences among the four groups for any of these characteristics at baseline and 12 months, except the number of steps walked. There were no significant differences between the baseline and after 12 months in each group.

<sup>†</sup> Excluding the isoflavone capsules used in the study.

<sup>‡</sup> Significant main effect of walking ( $p = 0.0004$ ) on the number of steps recorded by pedometer monitoring was analyzed using the two-factor ANCOVA model.

<sup>§</sup> The walking and isoflavone intake plus walking groups were significantly different from the placebo and isoflavone intake alone groups ( $p < 0.05$ ).

12 months using a Hologic QDR-4500A scanner (Hologic, Waltham, MA, USA). To minimize interobserver variation, all the scans and analysis were carried out by the same investigator, and the day-to-day CVs of his observations were <0.5, 1.9, 0.7, 0.3, 1.9, and 0.8% for BMD in the spine, femoral neck, trochanter, total hip, Ward's triangle, and whole body, respectively. Long-term precision was 0.35% by testing the spine phantom daily over the previous 1 year.

The whole body scans were divided into several regions such as arms, legs, trunk (pelvis, spine, and ribs), and head. The body compositions were analyzed by using manual DXA analysis software (version 11.2.3). The arm region was defined as the region extending from the head of the humerus to the distal tip of the fingers. The reference point between the head of the humerus and the scapula was positioned at the glenoid fossa. The leg region was defined as the region extending from the inferior border of the ischial tuberosity to the distal tip of the toes. The subwhole body was defined as the region extending from the shoulders to the distal tip of the toes. We selected a reference point that could be clearly visualized on the DXA system terminal.

### Statistical analysis

All values are expressed as mean  $\pm$  SD. Differences in baseline characteristics between the different groups were tested by one-factor analysis of covariance (ANCOVA). To determine whether the change over the course of the study was significantly different from the baseline in each group,

paired *t*-test with Bonferroni adjustment was performed. The percent change in BMD, body composition, serum lipid, and biomarkers of bone turnover were calculated  $\{[(\text{post intervention} - \text{baseline values})/\text{baseline values}] \times 100\}$  for each group. Two-factor ANCOVA was performed to determine the main effects of isoflavone intake, walking exercise, and their interactions at 3, 6, and 12 months. Significant differences of the percent change in BMD and fat mass among the different groups were determined by ANCOVA with time as the repeated measure, without the use of the intention-to-treat principle. To adjust for the possible confounding, the body weight, height, and daily intake of calcium, vitamin D, protein, and total energy were used as covariates in the analyses of body composition, BMD, and serum biomarkers. Statistical analyses were performed using SPSS for Windows (version 13.0J), and a *p* value was set at <0.05.

## RESULTS

### General

There were no significant differences among the groups at baseline with regard to the subject characteristics (Table 1). The 1-year intervention of isoflavone intake and walking did not affect these parameters. At the beginning of the study, the average dietary isoflavone (glycoside form) intake was 48.1, 47.7, 44.4, and 49.4 mg/day in the placebo, walking, isoflavone, and isoflavone plus walking groups, re-

TABLE 2. SERUM ESTRADIOL, BIOMARKERS OF BONE TURNOVER, AND LIPID CONCENTRATIONS OF DIFFERENT STUDY GROUPS AT BASELINE AND 12 MONTHS\*

		Placebo	Walking	Isoflavone	Isoflavone + walking
Estradiol (pg/ml)	Baseline	11.78 (2.64)	13.75 (6.55)	11.71 (3.48)	11.99 (3.08)
	After 12 months	12.17 (3.12)	12.63 (4.06)	12.43 (3.12)	12.40 (3.41)
	Percent change	4.83 (26.60)	3.07 (25.91)	9.73 (23.15)	7.88 (34.17)
Osteocalcin (ng/ml)	Baseline	10.51 (2.40)	10.47 (2.88)	9.23 (2.09)	9.50 (2.42)
	After 12 months	9.86 (2.44)	9.60 (2.15)	8.80 (2.15)	9.14 (2.27)
	Percent change	-7.78 (15.63)	-3.52 (20.77)	-2.87 (12.04)	-4.19 (12.29)
BSALP (U/liter)	Baseline	30.37 (11.61)	29.03 (6.65)	27.77 (8.63)	29.26 (8.26)
	After 12 months	29.19 (8.58)	30.38 (6.94)	27.27 (8.19)	28.01 (6.80)
	Percent change	-4.81 (12.40)	10.16 (32.36)	0.89 (18.93)	-3.68 (15.84)
DPD (nM/mM creatinine)	Baseline	7.76 (1.83)	7.65 (1.68)	7.30 (2.37)	6.88 (1.63)
	After 12 months	6.25 (1.47)	6.71 (1.76)	6.28 (1.60)	6.22 (2.17)
	Percent change	-14.02 (24.53)	-10.60 (25.17)	-8.33 (28.19)	-9.82 (23.11)
Total cholesterol (mg/dl)	Baseline	227.4 (33.4)	232.8 (31.5)	227.9 (29.5)	230.7 (35.2)
	After 12 months	231.2 (28.6)	227.2 (26.9)	232.9 (35.8)	228.3 (34.4)
	Percent change	-0.48 (9.71)	0.22 (7.94)	0.58 (11.07)	-0.14 (10.08)
HDL-cholesterol (mg/dl)	Baseline	71.7 (14.9)	71.0 (18.6)	74.2 (18.3)	66.2 (13.5)
	After 12 months	76.8 (14.7)	72.0 (18.1) <sup>†</sup>	76.0 (17.5)	71.3 (12.5) <sup>†</sup>
	Percent change	2.38 (9.33)	7.78 (10.74) <sup>‡</sup>	2.39 (10.36)	8.78 (11.02) <sup>‡</sup>
LDL-cholesterol (mg/dl)	Baseline	138.7 (29.2)	133.8 (24.0)	136.2 (27.6)	143.6 (31.0)
	After 12 months	136.0 (27.2)	133.1 (21.4)	135.1 (27.2)	142.3 (31.8)
	Percent change	0.30 (15.2)	0.62 (14.4)	0.58 (17.5)	0.28 (16.0)
TG (mg/dl)	Baseline	102.5 (49.0)	114.2 (70.2)	83.9 (38.5)	106.7 (55.1)
	After 12 months	87.6 (33.0)	103.2 (44.1)	87.4 (48.1)	81.6 (31.8)
	Percent change	-2.13 (29.72)	-5.71 (45.16)	6.17 (34.98)	-12.16 (32.75)

\* Mean (SD).

<sup>†</sup> Significantly different from the baseline values,  $p < 0.05$ .<sup>‡</sup> Significant main effect of walking exercise on percent change in HDL-cholesterol ( $p = 0.003$ ) was analyzed using the two-factor ANCOVA model. BSALP, bone-specific alkaline phosphatase; DPD, deoxypyridinoline; TG, triacylglycerols.

spectively. At the end of the study, there was no significant difference in the dietary isoflavone intake among the groups and when compared with the intake at baseline in each group. The number of steps recorded by the pedometer during the 1-year study was significantly higher in the two walking groups than in the nonwalking groups (Table 1).

#### Serum estradiol, lipids, and bone biomarkers

Serum concentrations of estradiol, lipids, and biomarkers of bone turnover at both baseline and 12 months of the study are shown in Table 2. Statistically significant differences were not observed with respect to serum concentrations of estradiol, lipids, and biomarkers of bone turnover at baseline among the groups. When these indices at 12 months were compared with those at baseline, serum E2, TC, and TG concentrations, urinary biomarker of bone resorption (DPD), and serum biomarker of bone formation (osteocalcin and BSALP) were observed to be unaffected by walking, isoflavone intake, and the combined intervention. At the end of the study, the HDL-cholesterol concentration significantly increased from baseline by 7.78% and 8.78% in the walking group and the isoflavone intake plus walking group, respectively. By using the two-factor ANCOVA analysis, we observed a significant main effect of walking ( $p = 0.003$ ), but not of isoflavone intake ( $p = 0.53$ ), on the percent change in HDL-cholesterol. On the other hand, there were no significant main effects on TC and LDL-cholesterol concentrations.

#### BMD and body composition

There was no significant difference among the four groups at baseline with respect to fat and lean mass in the whole body; fat mass in the trunk, arms, and legs regions; and BMD in subwhole body, lumbar spine, and hip regions (Table 3). Analysis by two-way ANCOVA model, walking exercise induced a significant reduction in the percent change in fat mass in the whole body and trunk region at 3 ( $p = 0.001$  and  $p = 0.005$ , respectively), 6 ( $p = 0.001$  and  $p = 0.006$ , respectively), and 12 months ( $p = 0.0002$  and  $p = 0.001$ , respectively; Figs. 2A and 2B). The intervention with walking exercise also induced a significant reduction in the percent change in fat mass in the legs after 6 and 12 months ( $p = 0.003$  and  $p = 0.0001$ , respectively; Fig. 2C). A significant main effect of walking exercise on suppression of fat mass gain in the arms was observed after 6 and 12 months ( $p = 0.019$  and  $p = 0.001$ , respectively; Fig. 2D). Isoflavone intake significantly suppressed the percent change in fat mass gain in the trunk region after 12 months ( $p = 0.027$ ); however, no interaction was observed between the effects of isoflavone intake and walking exercise (Fig. 2B). Analysis by ANCOVA with time as the repeated measure revealed that the percent change in fat mass in the whole body, trunk, and legs regions was significantly different in the walking alone and the isoflavone plus walking groups compared with that in the placebo group ( $p < 0.05$ ). The percent change in fat mass in the arms in the isoflavone

TABLE 3. BMD AND BODY COMPOSITION OF DIFFERENT STUDY GROUPS AT BASELINE\*

	Placebo (n = 33)	Walking (n = 31)	Isoflavone (n = 33)	Isoflavone + walking (n = 31)
Whole body fat mass (kg)	15.1 (4.5)	16.8 (4.3)	15.0 (4.1)	16.1 (3.5)
Trunk fat mass (kg)	6.5 (2.5)	7.9 (2.6)	6.8 (2.4)	7.7 (2.3)
Arms fat mass (kg)	0.9 (0.2)	1.0 (0.3)	0.9 (0.3)	1.0 (0.2)
Legs fat mass (kg)	2.9 (0.9)	2.9 (0.7)	2.7 (0.7)	2.7 (0.6)
Whole body lean mass (kg)	36.9 (3.7)	37.9 (4.2)	37.1 (3.2)	37.5 (3.2)
Subwhole body BMD (g/cm <sup>2</sup> ) <sup>†</sup>	1.002 (0.096)	0.979 (0.100)	1.003 (0.108)	1.008 (0.070)
Lumbar spine BMD (g/cm <sup>2</sup> )	0.907 (0.130)	0.879 (0.122)	0.891 (0.123)	0.909 (0.097)
Total hip (g/cm <sup>2</sup> )	0.787 (0.126)	0.780 (0.114)	0.777 (0.125)	0.807 (0.089)
Femoral neck BMD (g/cm <sup>2</sup> )	0.676 (0.114)	0.671 (0.116)	0.668 (0.106)	0.699 (0.094)
Trochanter BMD (g/cm <sup>2</sup> )	0.599 (0.122)	0.592 (0.097)	0.591 (0.089)	0.600 (0.078)
Ward's triangle (g/cm <sup>2</sup> )	0.544 (0.153)	0.523 (0.151)	0.542 (0.151)	0.534 (0.134)

\* Mean (SD). There were no significant differences among the four groups for any measurements at baseline.

<sup>†</sup> The subwhole body was defined as the region extending from the shoulders to the distal tip of the toes.

plus walking group was significantly different from that in the placebo group ( $p < 0.05$ ).

On analyzing the percent change in BMD, walking showed significant main effects on the preservation of BMD in the total hip region after 12 months ( $p = 0.039$ ; Fig. 3A). Interventions with isoflavone and walking showed significant main effects on the preservation of BMD at Ward's triangle after 12 months ( $p = 0.044$  and  $p = 0.0001$ , respectively; Fig. 3B); however, no interaction effect was observed between the two interventions. There were no significant effects of either isoflavone or walking on the percent change in BMD in the femoral neck, trochanter, lumbar spine, and subwhole body regions (Figs. 3C–3F).

#### Serum and urinary isoflavones concentrations

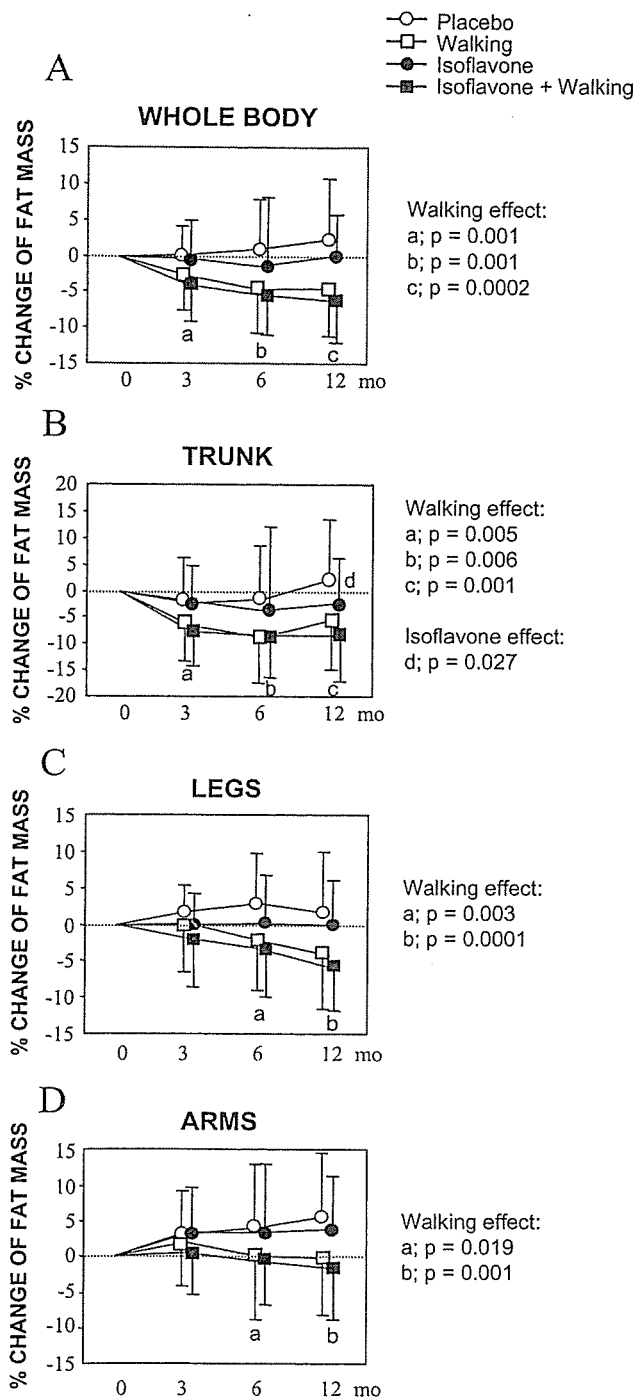
Table 4 shows the serum and urinary concentrations of isoflavones at baseline and 12 months. At baseline, there were no significant differences in the concentrations of serum isoflavones among the four groups. Compared with baseline values, the administration of isoflavones showed a marked increase in the serum concentrations of daidzein, glycitein, and equol, but not in the concentration of genistein. In contrast, the placebo treatment did not modify the concentration of circulating isoflavones. Using the two-factor ANCOVA model, we found significant main effects of isoflavone intake on serum concentrations of daidzein ( $p < 0.005$ ), glycitein ( $p < 0.005$ ), and equol ( $p < 0.001$ ) after 12 months. Similar patterns were observed in the concentrations of urine isoflavones among the four groups.

## DISCUSSION

The major novel findings of this study are as follows: (1) walking exercise for 6 months can significantly decrease the fat mass in the whole body, trunk, legs, and arms regions; (2) isoflavone intake significantly reduced fat mass in the trunk region and decreased bone loss at Ward's triangle region after 1 year; and (3) the combined intervention of isoflavone and walking exercise for 1 year showed a trend for a greater effect on BMD at total hip and Ward's triangle regions than either alone in postmenopausal Japanese women.

Important changes in the body composition of a female occur around the menopausal period. These changes include a decrease in bone mass and an increase in fat mass that may be managed by either replacement of estrogen, exercise, or by their combined intervention.<sup>(24)</sup> Although several animal experiments have consistently indicated the positive effects of soy isoflavone in retarding bone loss caused by estrogen deficiency, the results obtained from studies on humans are still controversial.<sup>(9)</sup> The results of the clinical trials varied from an improvement of BMD in the lumbar and femoral neck after 1 year<sup>(25,26)</sup> to no effect.<sup>(27)</sup> In one study, the loss of BMD in the lumbar spine, but not in the hip, in women who consumed a red clover-derived isoflavone supplement, 45 mg of aglycone form daily, was significantly lower than in those consuming a placebo.<sup>(25)</sup> Furthermore, Morabito et al.<sup>(26)</sup> reported that 54 mg/day of genistein treatment for 1 year significantly increased the BMD of the lumbar spine and the femoral neck in Italian women. On the other hand, daily intake of soy extracts containing 80 mg of isoflavones, but not 40 mg, significantly increased the BMC, but not BMD, of the trochanter after 1 year in postmenopausal Chinese women; however, this effect was observed only in those women with low initial bone mass.<sup>(27)</sup>

To the best of our knowledge, this is the first observational study on the effects of isoflavone intervention on BMD in Japanese women who were followed up for 1 year. We found that soybean isoflavones prevented a decrease in BMD in Ward's triangle in postmenopausal women after 1 year. However, at other regions such as the lumbar spine, total hip, and subwhole body, the main effects of isoflavone intake were not observed despite the fact that the serum and urine concentrations of isoflavones were high compared with those in the previous study.<sup>(26)</sup> A putative explanation is that Ward's triangle is the area that is probably the most sensitive to estrogen because of its higher trabecular bone content compared with that of other regions.<sup>(28)</sup> Among the different regions of interest (ROIs), Ward's triangle in many studies has shown the largest age-related bone loss.<sup>(29,30)</sup> The ability to predict osteoporotic fractures for Ward's triangle has been at least as good as for the femoral neck ROI.<sup>(31,32)</sup> However, it is suggested that the



**FIG. 2.** The percent change in fat mass ( $\pm$ SD) from the baseline to 12 months of the study. The changes shown by the walking exercise and isoflavone intake plus walking exercise groups were significantly different from the placebo group ( $p < 0.05$ ) with regard to (A) the whole body, (B) trunk, and (C) leg regions. (D) The isoflavone intake plus walking exercise group was significantly different from the placebo group ( $p < 0.05$ ) with regard to the arm region. There was a significant main effect of walking exercise on (A) the whole body and (B) trunk region after 3 months, and on (C) the arm and (D) leg regions after 6 months. (B) There was significant main effect of isoflavone intake after 12 months on the trunk region. All  $p$  values were calculated using ANCOVA with time as the repeated measure. The main effects of isoflavone intake and walking exercise over 12 months were determined by two-factor ANCOVA.

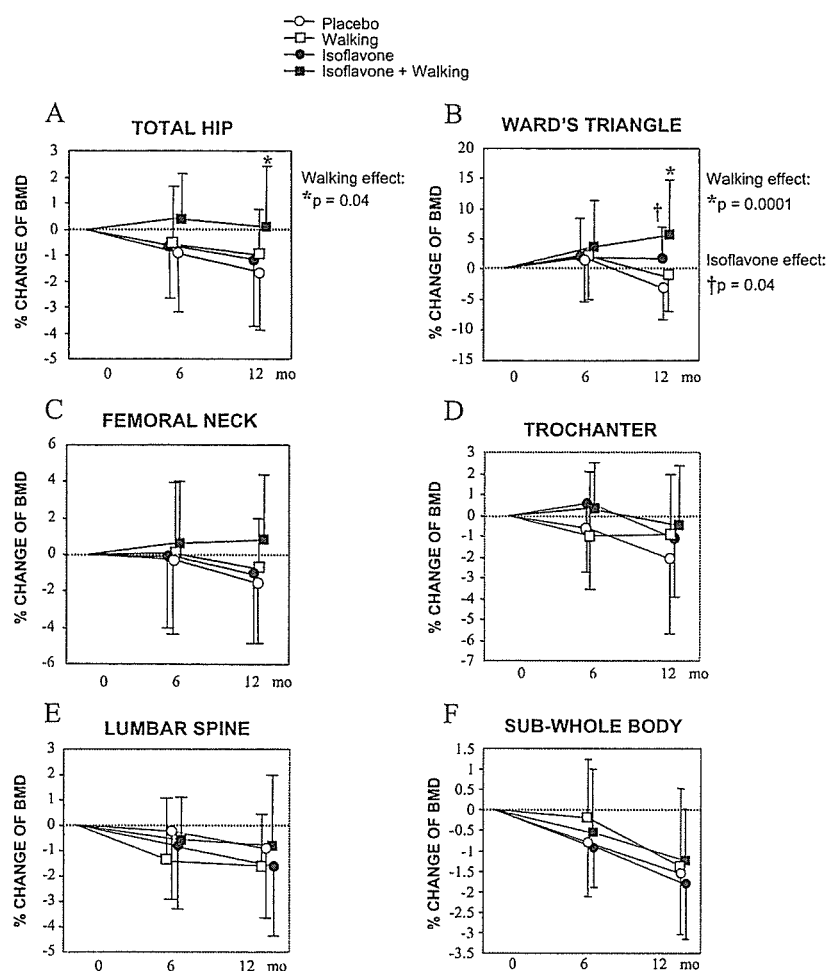
measurement of BMD in the Ward's triangle is unreliable. In this study, the hip scan was analyzed carefully using the comparison software that enables adaptation to a position and an angle at the first measurement. Therefore, it is believed that the results of this study reflect the change in BMD in the Ward's triangle.

It is known that daidzein can be metabolized to equol, which is biologically more active than its precursor, and could ultimately influence the effect on the subject's health.<sup>(33)</sup> Although rodents are constitutive equol producers, equol production in humans depends on the intestinal microflora of an individual.<sup>(9)</sup> Thus, assessment of the correlation between equol status of the subjects and bone effects of isoflavone might be necessary to know the actual clinical effectiveness of isoflavone.

In this study, we expect that the combined intervention of isoflavone and walking exercise would provide a greater benefit than either intervention used exclusively. The combined intervention resulted in a positive change in BMD in the Ward's triangle after 1 year. By using the two-factor ANCOVA model, we found significant main effects of both interventions at this site, although the interaction was not observed. We also found that the combined intervention trend more effective than either intervention used exclusively for preventing bone loss in the total hip region. It is reported that a low estrogen level in females may decrease the sensitivity of bones for detecting mechanical loads.<sup>(34)</sup> Research on ovariectomized animals have shown that combining isoflavones with exercise training can be beneficial in increasing BMD to a greater extent than either intervention used exclusively.<sup>(20,22,35)</sup> In addition, several clinical trials have shown that a combination of exercise and HRT results in an increase in BMD that is more than either intervention used exclusively.<sup>(36)</sup> This study is the first to suggest that the combined intervention of isoflavone and walking exercise for 1 year may partly prevented bone loss in postmenopausal women. It is necessary to focus on the fact that BMD in Ward's triangle increased by 5% in case of the combined intervention, whereas it decreased by 2.5% in the case of placebo-administered controls. This benefit may show a clinically significant reduction in the number of fractures.<sup>(37)</sup>

In this study, we also indicated that any isoflavone intake, walking exercise, and combined intervention decreased body fat mass in postmenopausal women. We noticed that isoflavone intake significantly reduced fat mass in the trunk region but not in the other regions. There is evidence that estrogens modulate central body fat deposition in women. This evidence includes observations that menopause triggers an increase in central adiposity (i.e., trunk fat mass)<sup>(38)</sup> and that fat accumulation in postmenopausal women is attenuated by replacement of estrogens, exclusively or in combination with progestins.<sup>(15,39,40)</sup> Although isoflavones may play a role in the prevention of regional fat mass deposition as a natural alternative to estrogens or HRT, further studies are required to clarify dose-response relationships and the mechanisms leading to this effect. As expected, walking exercise and walking combined with isoflavone intake resulted in reductions in total and regional fat mass after 3, 6, and 12 months. These findings are con-





**FIG. 3.** The percent change in BMD ( $\pm$ SD) from baseline to 12 months of the study. (A) There was a significant main effect of walking exercise on the total hip region after 12 months. (B) There were significant main effects of walking exercise and isoflavone intake on the Ward's triangle after 12 months. There were no significant main effect on (C) the femoral neck, (D) trochanter, (E) lumbar spine, and (F) subwhole body. The subwhole body refers to the whole body scan excluding the head region. The main effects of isoflavone intake and walking exercise over 12 months were determined by two-factor ANCOVA.

**TABLE 4.** SERUM AND URINARY ISOFLAVONE CONCENTRATIONS OF DIFFERENT STUDY GROUPS AT BASELINE AND 12 MONTHS\*

		Placebo	Walking	Isoflavone	Isoflavone	Isoflavone + walking	Main effects <sup>†</sup> Walking isoflavone
<b>Serum isoflavone</b>							
Daidzein (nM)	Baseline	159.7 (143.0)	142.1 (146.0)	166.7 (128.7)	242.5 (360.0)		
	After 12 months	413.2 (611.4)	390.3 (564.6)	1270.7 (1698.4) <sup>†</sup>	903.3 (1097.9) <sup>†</sup>	NS	$p < 0.005$
Genistein (nM)	Baseline	180.7 (136.1)	164.3 (183.8)	220.0 (199.9)	304.2 (371.9)		
	After 12 months	443.6 (628.2)	454.7 (704.3)	633.9 (959.2)	470.7 (413.8)	NS	NS
Glycitein (nM)	Baseline	63.8 (43.6)	54.3 (46.3)	66.8 (43.0)	65.5 (59.4)		
	After 12 months	74.5 (111.4)	88.4 (109.7)	272.7 (408.8) <sup>†</sup>	178.2 (182.3) <sup>†</sup>	NS	$p < 0.005$
Equol (nM)	Baseline	73.8 (201.7)	37.2 (79.4)	93.9 (196.1)	97.8 (232.3)		
	After 12 months	143.4 (330.9)	275.3 (463.0)	515.8 (528.8) <sup>†</sup>	503.3 (507.8) <sup>†</sup>	NS	$p < 0.001$
<b>Urinary isoflavones</b>							
Daidzein ( $\mu$ M)	Baseline	8.38 (12.13)	8.53 (10.57)	6.73 (9.93)	7.29 (10.53)		
	After 12 months	7.30 (9.28)	8.17 (13.41)	16.97 (17.78)	22.22 (39.33) <sup>†</sup>	NS	$p < 0.01$
Genistein ( $\mu$ M)	Baseline	3.39 (5.17)	3.96 (7.40)	2.92 (3.32)	3.12 (5.12)		
	After 12 months	3.01 (3.49)	3.39 (7.09)	3.84 (3.58)	5.09 (6.42) <sup>†</sup>	NS	NS
Glycitein ( $\mu$ M)	Baseline	1.66 (2.38)	1.90 (4.86)	1.11 (1.32)	1.25 (1.62)		
	After 12 months	1.50 (2.67)	2.59 (4.25)	7.04 (6.92) <sup>†</sup>	8.32 (14.78) <sup>†</sup>	NS	$p < 0.0005$
Equol ( $\mu$ M)	Baseline	1.82 (4.06)	5.09 (10.86)	3.01 (5.71)	1.98 (3.59)		
	After 12 months	3.68 (9.20)	4.14 (8.45)	8.28 (10.01) <sup>†</sup>	8.52 (9.81) <sup>†</sup>	NS	$p < 0.05$

\* Mean (SD).

<sup>†</sup> Significantly different from the baseline values,  $p < 0.05$ .

<sup>‡</sup> Significant main effect of isoflavone on serum and urinary daidzein, glycitein, and equol concentrations at 12 months were analyzed using the two-factor ANCOVA model.

NS, not significant.

sistent with the evidence reported by several clinical trials that assessed the combined effects of exercise and HRT on fat mass.<sup>(15,40,41)</sup>

In addition to bone and fat mass, walking exercise significantly increased HDL-cholesterol concentration. This finding is consistent with our previous study.<sup>(22)</sup> However, there was no significant main effect with respect to LDL-cholesterol concentrations. This lack of an effect is in agreement with other studies<sup>(42,43)</sup> examining the effects of soy isoflavones on LDL-cholesterol in postmenopausal women.

Our study had several limitations. First, with regard to our Japanese subjects, intake of soy products during this study was not controlled, because soy products are included in most Japanese foods. Compared with American and European women, Asian women consume a diet that is higher in isoflavones (average conjugated isoflavone intake of each group was 44.4–49.4 mg/day in our subjects). High dietary isoflavone intake might increase the threshold for the skeleton to respond to isoflavone supplementation. Thus, this might moderate the effect of isoflavone intervention in Japanese women. Second, a short-duration study cannot adequately assess the benefits related to bone quality, because bone is a slowly responding organ. A complete bone remodeling cycle takes ~180 days, and therefore, studying only one cycle with regard to the effect of any intervention on bone is not sufficient. Thus, the duration of our study (1 year) was not sufficient to test the clinically relevant changes, which require a longer trail that lasts for at least 2 years. Third, the time at which the biomarkers for bone metabolism are tested may differ from that of other studies. In this study, no significant differences were observed with regard to the serum and urinary biomarkers between the baseline and 1 year in each group. Although, there is a clinical study showing that the bone formation marker (BSALP) was not affected by isoflavone intervention,<sup>(38)</sup> other trials reported that the bone markers changed at 4–8 weeks after the treatment with isoflavone in the postmenopausal Japanese women.<sup>(44,45)</sup> Thus, these bone markers may have been assessed early during the study.

In conclusion, combined intervention of 75 mg/day of isoflavone intake and walking exercise 3 times/week for 1 year showed a trend for a greater effect on BMD at total hip and Ward's triangle regions than either alone. Intervention with isoflavone in postmenopausal Japanese women showed a modest effect on BMD compared with those in Westerners. Walking exercise prevented bone loss at total hip and Ward's triangle and also reduced the fat mass in the whole body. These results suggest that the walking exercise or combined with isoflavone intake over 1 year may offer a potential regimen for primary prevention of osteoporosis and lifestyle-related disease in postmenopausal women. Further studies over longer treatment duration that include the assessment of BMD at various regions are necessary to ascertain the clinical significance of the combined intervention of isoflavones plus walking in postmenopausal women.

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# 生活習慣病の予防・改善のための運動療法 ーベンチステップ運動を用いた無作為化比較試験

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## 要約

**目的：**従業員の定期健康診断で生活習慣の改善を指示された人を対象に、ステップ台を用いた8週間の運動プログラムを実施し、その前後での運動能力や体重、腹囲、総コレステロール値、血圧などを測定することでベンチステップ運動の有効性を検討する。**方法：**対象者33名を無作為に2群に振り分け、運動群には運動負荷試験により決定した乳酸閾値に相当する台高と昇降頻度でのベンチステップ運動（踏み台昇降）を行った。運動は10分連続を1単位として1日3単位、週21単位の運動を指示し、試験期間中の食事指導や食事制限は行わなかった。**結果：**運動群では8週間の試験終了後に運動能力の有意な向上のほか、腹囲や総コレステロール値に有意な改善が認められた。予定されたプログラム（週21単位）の完全実施率は11.8%のみであり、週14単位以上実施した人を合わせても42.2%の実施率であった。しかし週14単位以上実施した人では有意な体重減少が認められ、高血圧の人も全例に血圧の低下が認められた。**結論：**乳酸閾値でのステップ運動を8週間継続することで腹囲や高コレステロール血症者の総コレステロール値の有意な低下が示された。またこの運動を週14単位以上行うことで体重減少や血圧低下も認められ、生活習慣病を予防・改善するための運動量としては乳酸閾値でのステップ運動を1日2単位、週14単位以上行うことが推奨される。

## キーワード

生活習慣病、運動療法、ベンチステップ運動、無作為化比較試験〔人間ドック21(4)：18-23, 2006〕

## はじめに

近年の急速な人口高齢化の進展に伴い疾病構造も変化し、虚血性心疾患、脳血管疾患、糖尿病などの生活習慣病を持つ人の割合が増加し大きな問題となっている。これらの生活習慣病を予防・改善することが健康づくりのための重要課題と考えられており、厚生労働省の標語にも「1に運動、2に食事、しっかり禁煙、最後にクスリ」と示されている。しかし「平成15年国民・健康栄養調査」によると、わが国では運動習慣を持つ者の割合は男性28.3%、女性24.1%であり、国民の3分の2以上が運動習慣を身につけていない状態にある。この原因の一つに、最も効率的な運動の強度や量、頻度などに関して明確に示したものが少ないことが考えられる。今回我々は、乳

酸閾値で決定された台高と頻度を用いた自宅で行うステップ運動プログラムの有用性を検討するため、無作為化比較試験を計画した。

## 対象と方法

平成17年秋に行われた飯塚病院の従業員定期健診で、肥満度（body mass index：BMI）25以上、血圧：収縮期血圧135mmHg以上かつ/または拡張期血圧85mmHg以上、総コレステロール220mg/dl以上、中性脂肪150mg/dl以上、HDLコレステロール39mg/dl以下のうち1項目以上を満たし、産業医および保健師により生活習慣の改善が必要であると指示された67名を対象に、本試験の主旨を説明し文書による同意を得られた者について研究を行った。

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活動性の感染症合併例や狭心症などの心疾患の疑われる例、重症の糖尿病合併例、膝関節疾患など下肢の運動障害のある例は除外された。文書同意の得られた33名は年齢、性、BMI、総コレステロール値を層別化因子として運動群とコントロール群の2群に無作為に振り分けられた(表1)。

トレーニングを行う際の運動強度には乳酸閾値(lactate threshold: LT)を利用した。方法としては20cmのステップ台を用い、初回負荷40回/分で20回づつ漸増させる各負荷4分間の運動負荷試験を行った。各負荷終了30秒前に心拍数を記録し、負荷終了直後に耳朶採血を行い、ラクテート・プロ(アークレイ社製)を用いて血中乳酸濃度を測定した。LT強度はAyabe<sup>1)</sup>らの開発した方法で求めた。対象者全員に運動負荷試験を行い、運動群に対しては個々人の乳酸閾値を基に調節した台高と昇降頻度でのステップ運動を1回に連続10分を1単位として、1日3単位以上を目標とした。運動は自宅での実施を基本としたが、週に1回職場内でインストラクターをつけた運動を全員で行うことを推奨した。また各自の運動実施状況を記録してもらい、週に一度回収した。尚、全試験期間を通じて食事制限や指導は行わないことにし

た。

トレーニングの前後において、運動負荷試験、脚伸展パワー測定、身体測定(身長、体重、腹囲、血圧、脈拍数)、血液検査(血算、血液生化)、血管内皮機能検査を行った。血管内皮機能はPeripheral arterial tonometryを用い、上腕血流を5分間駆血し駆血解放後1分間の血管の拡張反応を人差し指につけたプローブで細小動脈の血流拍動の高さを反対側の血流拍動をコントロールとしてコンピューター解析した<sup>2)</sup>。統計学的解析にはpaired t-testを用いた。

なお、本研究は試験前に飯塚病院内で開催された倫理委員会の承認を得て実施された。

## 結 果

8週間の運動プログラム実施状況を表2に示す。指示通りの1日3単位、週21単位以上実施者は2名のみ(11.8%)で1日平均2回、週14単位以上実施者を合わせても42.2%の実施率であった。各々の測定値の変化を表3に示す。運動群においては乳酸閾値が5.5METsから6.2METsへと有意に( $p=0.001$ )上昇し、脚伸展パワーも863Wから959Wへと上昇が認められた。腹囲異常者14

表1 プログラム参加者の背景

	運動群			コントロール群		
	男	女	合計	男	女	合計
参加人数	10	7	17	10	6	16
年齢	46.5	43.0	45.1	46.0	42.3	44.6
body mass index	27.7	29.1	28.2	27.2	29.0	27.9
総コレステロール値(mg/dl)	221	205	215	225	214	221

表2 プログラム実施状況

実施回数(単位/週)	実施人数(%)
0-7	5 (29.4%)
7-14	5 (29.4%)
14-21	5 (29.4%)
21以上	2 (11.8%)

表3 運動による各種パラメーターの変化

項 目	振り分け	参加者数	運動前値	運動後値	p値
乳酸閾値 (METs)	T	17	5.5±0.3	6.2±0.3	0.001
	C	15	5.5±0.4	5.4±0.3	
脚進展力 (W)	T	17	863±111	959±113	0.011
	C	15	1,110±123	1,087±119	
腹囲 (cm)	T	14	98.2±2.2	95.9±2.0	0.007
	C	15	97.2±1.7	96.9±1.9	
body mass index	T	14	28.8±0.7	28.8±4.9	0.019
	C	13	28.7±0.6	28.8±0.6	
総コレステロール値 (mg/dl)	T	9	237±5.9	228±4.9	0.019
	C	9	250±9.1	248±9.0	
血管内皮機能	T	13	2.13±0.18	2.45±0.08	0.079
	C	12	1.89±0.13	1.90±0.17	

T; 運動群

C; コントロール群

名についても運動群では98.2cmから95.9cmへと平均2.3cmの有意な ( $p=0.007$ ) 改善が認められた。また血管内皮機能も2.13から2.45へと改善傾向にあった。高コレステロール血症者9名の総コレステロール値は237mg/dlから228mg/dlへと有意に ( $p=0.019$ ) 低下した。一方コントロール群ではいずれも有意な変化は示されなかった。BMIや血圧については運動群でも有意な改善は認められなかった。しかし、ステップ運動を週14単位以上実施した人だけを取り上げれば、体重減少が認められ(図1)、高血圧であった者は全員に収縮期、拡張期ともに血圧低下が認められた(表4)。

### 考 察

国民の疾病構造の変化により糖尿病、高血圧、高脂血症等の生活習慣病が問題となっている。このような病態の基礎病態としてメタボリックシンドロームという疾患概念が提唱され<sup>3)</sup>その後わが国でも診断基準が示された<sup>4)</sup>。これは内臓脂肪肥満を重要視したもので、ウエス

ト周囲径が男性85cm以上、女性90cm以上(内臓脂肪面積が100cm<sup>2</sup>以上)のある人で中性脂肪150mg/dl以上かつ/またはHDLコレステロール40mg/dl未満、収縮期血圧130mmHg以上かつ/または拡張期血圧85mmHg以上、空腹時血糖110mg/dl以上の内2つ以上満たすものと定義された。メタボリックシンドロームに該当する人の頻度は一般人口の10-25%であり、これらの人は運動や食事などの生活習慣を改善する必要があるとされており、特に運動の重要性が注目されている。高脂血症ガイド2004年版<sup>5)</sup>では運動療法は動脈硬化性疾患やメタボリックシンドロームの予防・治療効果があり、HDLコレステロールの増加、トリグリセリドの減少、インスリン感受性を改善するだけでなく、ストレス解消や骨密度を高め、Quality of Lifeを改善すると示されている。そして運動の種類としては大腿筋や大臀筋など大きな筋肉をダイナミックに動かす有酸素運動が推奨されており、運動強度としては50%最大酸素摂取量付近の運動が効果と安全性から適しているとされている。運動時間と頻度としては10~20分以上連続して運動を行い、1日30分以上の運動を毎日続けることが望ましいとされ、最低週3回以上、合計で180分/週以上が目標として掲げられている。また高血圧のガイドライン2004<sup>6)</sup>によると、一般に運動をする人は血圧が低いとされており、ここでも運動の種類は有酸素運動(50%最大酸素摂取量)が推奨されている。運動量は1日30分以上とされているが、軽症高血圧では比較的少ない運動量で降圧効果を認める報告もあり、運動を続けると10週間で50%は収縮期血圧20mmHg以上、拡張期血圧で10mmHg以上の降圧効果(平均降圧11/6mmHg)と記載されている。今回の試験では運動群全体でみると血圧の低下に有意差は認められなかったが、これは運動

表4 運動実施者(14単位以上)の8週後の血圧変化

収縮期血圧 (mmHg)	運動前	運動後	低下率 (%)
	150	123	18.0
	156	141	9.5
	133	122	8.3
	153	130	15.0
拡張期血圧 (mmHg)	運動前	運動後	低下率 (%)
	85	80	7.0
	93	83	10.8
	91	75	17.6

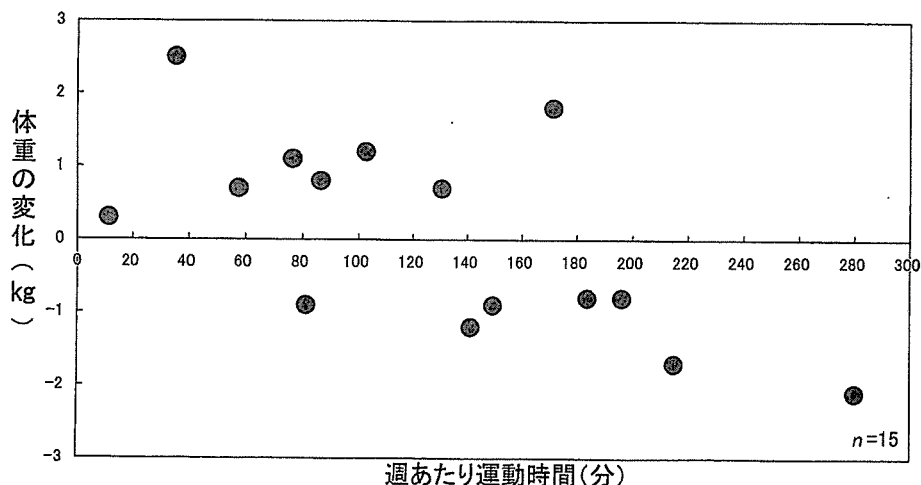


図1 1日の運動時間と体重変化

量の平均が週に11.3単位と少なかったためであろう。実際に週14単位以上の運動を行った者は全員に収縮期、拡張期とも降圧効果が認められ4人中3人の血圧が正常となり、十分な運動量が確保できれば8週間のステップ運動で良好な血圧コントロールが得られる可能性が高いと考えられる。

有酸素能力、即ち一般に全身持久力といわれるものは最大酸素摂取量で評価され、その50%に相当する強度でのトレーニングが、高脂血症などの生活習慣病の改善に効果的であると報告されている<sup>7)</sup>。疲労物質とも指摘されている乳酸はある運動強度までは、ほとんど蓄積が認められず、最大酸素摂取量の50%あたりから指数関数的に急増する。乳酸が急増し始める強度は乳酸閾値 (LT) とよばれ、LT 以下の強度の運動であれば息切れを起こすことなく余裕を持って運動を継続することが出来る。実際にマラソンの平均スピードは一流選手から市民ランナーまで LT に近似していることが示されている<sup>8)</sup>。Motoyama<sup>9) 10)</sup> らは LT 強度でのウォーキングにより、血圧や HDL コレステロールが有意に改善したと報告している。通常最大酸素摂取量の測定には自転車エルゴメーターやトレッドミルなどの高価な機械や特殊な技術が必要である。また一度に測定できる人数にも限りがあり、健診受信者や地域住民を対象とした運動処方として一般化することは容易ではない。一方 LT は Ayabe<sup>1)</sup> らの開発したステップテストによる判定法で安価に且つ簡便に測定可能であるため、今回の研究ではこの方法を用いて運動処方を行った。

身体活動量の単位として MET が知られている。MET は運動時酸素摂取量/安静時酸素摂取量として表され、安静時の酸素摂取量 (3.5ml/分/kg) が 1 MET であり、健康づくりのための身体活動量の基準値としては 23METs・時/週 (運動強度が 3 METs 以上の活動で 1 日当たり約 60 分。歩行中心の活動であれば 1 日当たり、およそ 8,000-10,000 歩に相当)、また運動量の基準値としては 4 METs・時/週 (速足で約 60 分、ジョギングやテニスで約 35 分) とされている<sup>11)</sup>。しかし、一般的には身体能力の多い人は体力が高く、また体力を高めるための運動強度には下限があるため<sup>12)</sup>、これらの漠然とした数値の運動処方では不十分で、個々人の体力に合わせた最も効率的な運動強度と時間による具体的な推奨運動処方が望まれる。ステップ運動はステップ台を昇り降りする単純な運動で、台の高さと 1 分間の昇降回数を変えることで容易に運動強度を変えることができる。台高 20cm でのステップ運動

は昇降頻度 60, 80, 100, 120 回/分はそれぞれおよそ 4, 5, 6, 7 METs に相当する<sup>13)</sup>。

今回我々の試験結果でステップ台を用いたステップ運動が最も効率的な運動処方の一つであることが示された。すなわち乳酸閾値を測定することで決定された台高と昇降頻度で 1 回 10 分、1 日 3 回のトレーニングを指示することで、食事制限を指示しなくても、腹囲や総コレステロール値の有意な低下を示した。実際には指示された運動量を実施できない例も多かったにも係らず運動群全体でみたこれらの指標の変化は、本運動方法の呼びかけの有用性を示している。また週 14 単位 (1 日平均 20 分の運動) 以上のトレーニングを実施した者については、この他に体重の減少や血圧の低下が認められた。このことから今回のステップ運動の推奨量は、この運動強度で 1 日 2 単位以上と考えられる。14 単位以上の運動群で 1 人のみ体重増加した例があったが、これは試験期間中の他の作業で肉離れをおこし運動の継続が 2 週間途切れ、その間食量が増加したとの自己申告があった。このことは運動の継続性の重要性を示唆するものと考えられる。

血管内皮機能は血管の拡がりやすさを表す指標で、血管の内面を覆っている血管内皮細胞という一層の細胞の機能を表す。これらの内皮による血管拡張反応も高血圧や加齢、糖尿病などで障害され動脈硬化が促進されるとされている<sup>14)</sup>。今回の血管内皮機能の測定では運動群において血管内皮機能は改善傾向にあったが、この正常値は 1.67 以上とされており、運動群では測定値が上昇して弾力性のある血管になっている可能性があるが、正常値の範囲の変化であり、現状では評価は困難で今後の研究の進展を見ていく必要があると思われる。

今回の我々の検討では対象者が少なく、今後も対象者数を増やして検討する必要があるが、ステップ運動は自宅で手軽に行える運動であり、器具も安価で、天候の影響も受けず、時間の制約も少ない。また手軽に水分補給や休憩もとれ安全に実施できる。自宅でテレビを見ながら他人の目も気にせず実行できるという利点もある。単調な運動であり実施の継続が懸念されるが、体重の減量効果が現れれば運動を継続するモチベーションは高まるものと考えられる。本試験に参加を呼びかけた 67 人中実際の参加者は 33 名 (49.3%) でその中で週 14 単位以上の運動実施者は 41.2% であった。すなわち生活習慣の改善の必要な人に本運動を呼びかければ約 20% が週 14 回の運動を行う可能性があり、その効果は今回示された通りで

ある。単純にこの数値が実行されれば、かなりの人たちの病院受診や薬物投与が不要になる可能性がある。医療費に占める生活習慣病の割合は、わが国では平成15年度で10.2兆円に上り、国民医療費の約3割を占めている。本運動プログラムを呼びかけ、普及させることにより、国民の健康増進そして増大する医療費の削減が期待される。

本研究においては運動療法単独での効果をみるため改めて食事指導は行わなかったが、生活習慣病の予防・改善のためには食事療法も重要であり、実地では食事療法も併せて指導することでより大きな効果が得られると思われる。

## まとめ

乳酸閾値で決定した運動強度を用いたステップ運動の有効性を示した。自宅でも手軽に行える本運動プログラムは生活習慣病の予防・改善に有効であり、このプログラムの呼びかけにより国民健康の増進と医療費削減が期待できる。

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## An Exercise Program for Prevention and/or Improvement of Lifestyle Related Disease: A Randomized Controlled Trial Using a Bench Step Exercise

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### Abstract

**Objective:** For the prevention or improvement of lifestyle related disease an 8-week exercise program involving a bench step exercise was arranged. **Methods:** Thirty-three employees who had been recommended to change their lifestyle following a routine health check were enrolled. Before and after the program, their physical performance was evaluated, and their waistline, total cholesterol value and blood pressure was recorded and compared. There were no dietary restrictions. The 33 subjects were randomly divided into two groups: an exercise group and a control group. The exercise group was instructed to execute a bench-stepping exercise over ten consecutive minutes three times a day (i.e. twenty-one times a week) at a bench height and stepping rate that varied depending on each individual's lactate threshold as determined by an exercise stress test. **Results:** Only 11.8% of the participants completed the step exercise program as planned (21 times/week), but 42.2% executed it 14 or more times a week. These participants showed not only an improved physical performance, but experienced a significant reduction in weight, waistline size and total cholesterol value. Furthermore, the blood pressure of those participants suffering from hypertension was lowered. **Conclusion:** The step exercise over 8 weeks at the lactate intensity threshold leads to a significant reduction in waistline, total cholesterol value and blood pressure. We recommend executing the step exercise at the lactate intensity threshold more than twice a day (i.e. 14 or more times/week).

**Key words :** lifestyle related disease, bench step exercise, randomized control trial

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