研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Unfavorable Effects of Resistance Training on Central Arterial Compliance

A Randomized Intervention Study

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Background—Reductions in the compliance of central arteries exert a number of adverse effects on cardiovascular function and disease risk. Endurance training is efficacious in increasing arterial compliance in healthy adults. We determined the effects of resistance training on carotid arterial compliance using the intervention study design.

Methods and Results—Twenty-eight healthy men 20 to 38 years old were randomly assigned to the intervention group (n=14) and the control group (n=14). Control subjects were instructed not to alter their normal activity levels throughout the study period. Intervention subjects underwent 3 supervised resistance training sessions per week for 4 months and detraining for a subsequent 4 months. The resistance training increased maximal strength in all muscle groups tested ($P<0.001$). There were no significant differences in baseline arterial compliance and β-stiffness index between the intervention and control groups. In the intervention group, carotid arterial compliance decreased 19% ($P<0.05$), and β-stiffness index increased 21% ($P<0.01$) after resistance training. These values returned completely to the baseline levels during the detraining period. Arterial compliance did not change in the control group. In both groups, there were no significant changes in brachial and carotid blood pressure, carotid intima-media thickness, lumen diameter, and femoral arterial compliance. Changes in carotid artery compliance were significantly and negatively related to corresponding changes in left ventricular mass index ($r=-0.56$, $P<0.001$) and left ventricular hypertrophy index ($r=-0.68$, $P<0.001$).

Conclusions—In marked contrast to the beneficial effect of regular aerobic exercise, several months of resistance training "reduces" central arterial compliance in healthy men. (***Circulation.* 2004;110:2858-2863.)**

Key Words: arteries ■ echocardiography ■ elasticity ■ exercise ■ ultrasonics

Arterial compliance in the central (cardiothoracic) circulation reflects the ability of an artery to expand and recoil during cardiac contraction and relaxation, thereby damping down the fluctuation in arterial pressure and blood flow.[1] Reductions in arterial compliance or increases in arterial stiffness impair this buffering function and contribute to elevations in systolic blood pressure, left ventricular (LV) hypertrophy, coronary ischemic disease, and reductions in arterial baroreflex sensitivity.[2–4] Indeed, higher arterial stiffness is associated with a greater rate of mortality in patients with end-stage renal failure and essential hypertension.[5] Accordingly, the prevention and treatment of arterial stiffness are of paramount importance.

We and others have demonstrated that regular aerobic exercise is efficacious in preventing and reversing arterial stiffening in healthy adults.[6–8] In recent years, resistance exercise, another common exercise modality, has gained widespread acceptance in exercise prescription and cardiopulmonary rehabilitation programs and has become an integral component in the comprehensive health program endorsed by the major health organizations.[9,10] These recommendations are based primarily on the documented impact of resistance training on the attenuation of osteoporosis and sarcopenia and related risks, including falling and functional disability.[9,11] However, there is very little information on the potential influence of resistance training on nonmusculoskeletal components, in particular, cardiovascular function. In marked contrast to the favorable effects of regular aerobic exercise that we observed on arterial compliance, we recently found in a cross-sectional study that strength-trained middle-aged men exhibited rather "decreased" levels of arterial compliance.[12] Given the well-known limitation of cross-sectional study design and the conflicting results between aerobic and strength training, we

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deemed that our previous cross-sectional study should be confirmed prospectively with the interventional approach.

With this information as background, the primary aim of the present study was to determine the effects of strength training intervention on central arterial compliance. On the basis of our previous cross-sectional study,[12] we hypothesized that a period of strength training would decrease arterial compliance in previously sedentary men. In addition, after the strength training period, we used the detraining phase to further confirm that the changes we observed after strength training were indeed because of strength training per se. Our working hypothesis was that changes in arterial compliance would return to the baseline levels when the stimuli of daily weight lifting were removed.

Methods

Subjects

Twenty-eight healthy men were studied for the present study. None of the subjects had participated in any resistance or endurance training on a regular basis. All subjects were normotensive (blood pressure <140/90 mm Hg), nonobese (body mass index <30 kg/m^2), and free of overt chronic diseases as assessed by medical history, physical examination, and complete blood chemistry and hematological evaluation. Candidates who had smoked in the previous 4 years, who were taking medications or anabolic steroids, or who had significant intima-media thickening, plaque formation, and/or other characteristics of atherosclerosis (eg, ankle-brachial index <0.9) were excluded. All subjects gave their written informed consent to participate, and all procedures were approved by the Institutional Review Board. Subjects were subsequently randomized into either the exercise intervention group or the nonexercising control group.

Measurements

The intervention group was studied 5 times: before training (baseline), at 2 months (midpoint of resistance training), at 4 months (at the completion of resistance training), at 6 months (midpoint of detraining), and at 8 months (at the completion of detraining). The control group was studied 3 times: at baseline, at 4 months, and at 8 months. To avoid potential diurnal variations, subjects were tested at a same time of day throughout the study period. Before each testing, subjects abstained from caffeine and fasted for at least 4 hours (a 12-hour overnight fast for determination of metabolic risk factors). Subjects in the intervention group were studied 20 to 24 hours after their last exercise training session to avoid the acute effects of exercise, but they were still considered to be in their normal (ie, habitually exercising) physiological state.

Incremental Exercise

To demonstrate that the subjects had not been sedentary, we measured maximal oxygen consumption during an incremental cycle ergometer exercise.[13] Oxygen consumption (coefficient of variation [CV] 4±1), heart rate, and ratings of perceived exertion were measured throughout the protocol.

Strength Testing

Maximal muscular strength in the intervention group was tested before and after resistance training using the following exercises: half squat, bench press, leg extension, leg curls, lateral row, and abdominal bend. After 10 warm-up repetitions, 1-repetition maximums (1RM) were obtained according to the established guidelines. Because of the potential risks involved in 1RM testing, this test was not performed in the control group.

Metabolic Risk Factors for Coronary Heart Disease

To screen for the presence of coronary heart disease, fasting plasma concentrations of cholesterol and glucose were determined by use of enzymatic techniques.[6]

Arterial Blood Pressure at Rest

Chronic levels of arterial blood pressure at rest were measured with a semiautomated device (Form PWV/ABI, Colin Medical Technology) over the brachial and dorsalis pedis arteries. Recordings were made in triplicate with subjects in the supine position.

Carotid Artery Intima-Media Thickness

Carotid artery intima-media thickness (IMT) was measured from the images derived from an ultrasound machine equipped with a high-resolution linear-array broad-band transducer (5 to 10 MHz; axial resolution of 0.06 mm) as previously described.[12] Ultrasound images were analyzed by use of computerized image analysis software. At least 10 measurements of IMT were taken at each segment, and the mean values were used for analysis. Plaque was considered to be present if a localized irregular thickening was at least 1.5 mm thick. This technique has excellent day-to-day reproducibility (CV, 3±1%) for the carotid IMT.

Artery Stiffness and Compliance

The combination of ultrasound imaging of a common carotid artery with simultaneous applanation of tonometrically obtained arterial pressure from the contralateral carotid artery permits noninvasive determination of arterial compliance.[6,14] Carotid artery diameter was measured from the images derived from an ultrasound machine equipped with a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1 to 2 cm distal to the carotid bulb. To assess the effects of peripheral artery compliance, the same procedure was repeated on the common femoral artery. The computer images were analyzed with the use of image analysis software. All image analyses were performed by the same investigator, who was blinded to the group assignments.

The pressure waveform and amplitude were obtained from the common carotid artery with a pencil-type probe incorporating a high-fidelity strain-gauge transducer (SPT-301, Millar Instruments).[6,15] Because the baseline levels of carotid blood pressure are subjected to hold-down force, the pressure signal obtained by the tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial artery value.[6,12] The pressure waveforms were also used to obtain carotid augmentation index, which has been proposed as an indicator of the magnitude of wave reflections.[8,5] In addition to arterial compliance,[16] we also calculated β-stiffness index, which provides an index of arterial compliance adjusted for distending pressure.[17] Arterial compliance and β-stiffness index were calculated by use of the equations $[(D1-D0)/D0]/[2(P1-P0)]\times\pi\times(D0)^2$ and $(\log P1/P0)/[(D1-D0)/D0]$, where D1 and D0 are the maximal and minimum diameters and P1 and P0 are the highest and lowest blood pressures. The day-to-day CVs were 2±1%, 7±3%, and 5±2% for carotid artery diameter, pulse pressure, and arterial compliance, respectively.[6] The CV for femoral arterial compliance was 7±4%.

LV Dimensions, Mass, and Function

Echocardiography was used to measure LV dimension, wall thickness, and functions according to established guidelines.[18] The LV mass was then calculated.[19] The ratio of average LV wall thickness to LV internal end-diastolic diameter was used as an index of LV hypertrophy (CV, 7±3%).[12]

Body Composition

Body composition was determined by use of the bioelectric impedance method (CV, 4±2%).

Resistance Training Intervention

In the first 4 months of the study period, subjects in the intervention group underwent 3 supervised resistance-training sessions per week. During each training session, subjects completed 3 sets of 8 to 12 exercises at 80% of 1RM in the following order: leg extension, seated chest press, leg curls, lateral row, squat, and sit-ups. Subjects performed 12 repetitions in sets 1 and 2 and as many repetitions as possible to concentric failure in set 3. Resistance was increased for

TABLE 1. Selected Subject Characteristics

Variables	Control	Intervention
No.	14	14
Age, y	22±1	22±1
Height, cm	172±1	173±2
Body weight, kg	68.1±2.1	66.5±2.4
Body mass index, kg/m^2	22.9±0.7	22.2±0.7
Body fat, %	19±1	18±2
Lean body mass, kg	55.2±1.6	54.5±1.5
Heart rate, bpm	58±3	56±2
Total cholesterol, mmol/L	4.26±0.39	4.42±0.13
HDL cholesterol, mmol/L	1.46±0.07	1.62±0.10
Plasma glucose, mmol/L	4.7±0.1	5.0±0.2
Plasma insulin, μU/mL	5.9±0.6	5.4±0.5
$\dot{V}o_2$max, mL · min^{-1} · kg^{-1}	49±3	49±2

Data are mean±SEM. $\dot{V}o_2$max indicates maximal oxygen consumption.

the following exercise sessions when subjects were able to complete at least 10 repetitions in the final set. Recovery time between exercises was controlled at 2-minute intervals. Each training session lasted ≈45 minutes. Trained assistants verbally encouraged the subjects and ensured proper form and technique. Subjects were instructed to refrain from any other regular exercise workouts during the entire study period. Subjects in the control group were instructed not to alter their normal activity levels throughout the study period.

Statistical Analysis

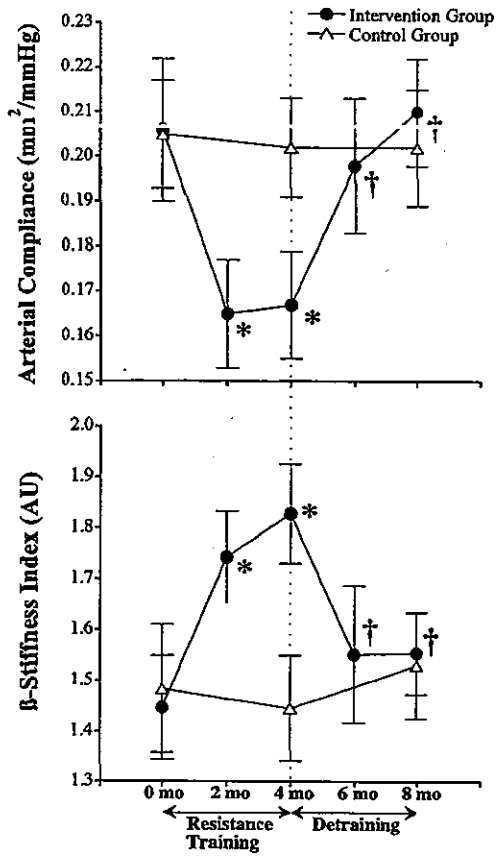
Changes were assessed by 2-way ANOVA (group×period) with repeated measures. In the case of significant F values, a post hoc test (Newman-Keuls method) was used to identify significant differences among mean values. Pearson's correlation and regression analyses were performed to determine the relation between variables of interest.

Results

Before the intervention period, there were no significant differences in any of the variables between the groups (Table 1).

Twelve subjects in the intervention group completed 100% of all training sessions as scheduled (ie, 50 total training sessions in 4 months). For the remaining 2 subjects, the training period was extended by 1 week to ensure that each subject underwent the required 50 training sessions. The resistance training increased 1RM strength in all muscle groups tested ($P<0.001$). Percent increases for each of the exercises were 30% in squat, 20% in bench press, 47% in leg extension, 26% in leg curl, 25% in lat row, and 32% in abdominal bend.

There were no significant differences in baseline arterial compliance and β-stiffness index between the intervention and control groups (Figure). Carotid arterial compliance decreased after 2 months of resistance training ($P<0.01$). No further decreases in arterial compliance occurred between 2 and 4 months of resistance training. After the detraining period, the reduced arterial compliance values returned to the baseline level. Alterations in arterial compliance were primarily a result of changes in arterial distension, because carotid pulse pressure remained unchanged. In general, qualitatively similar results (although inverse in direction) were obtained by use of β-stiffness index ($P<0.01$). There were no



Changes in carotid arterial compliance (top) and β-stiffness index (bottom) in the intervention group (black circles) and control group (white triangles). Values are mean±SEM. *$P<0.05$ vs baseline; †$P<0.05$ vs resistance training period (2- and 4-month values).

changes in arterial compliance or β-stiffness index in the control group throughout the 8-month period. Femoral arterial compliance, an index of the compliance of peripheral muscular artery, did not change. In both groups, there were no significant changes in brachial and carotid blood pressures, carotid augmentation index, carotid IMT, and carotid lumen diameter (Table 2).

There were no significant changes in resting heart rate and stroke volume throughout the study period (Table 2). Resistance training increased LV wall thickness, LV mass index, and LV hypertrophy index ($P<0.001$). The values returned to the baseline levels during the detraining period, because there was no longer a significant difference from the baseline values. In the intervention and control groups, changes in carotid artery compliance during resistance training and detraining periods were significantly and negatively related to the corresponding changes in LV hypertrophy index ($r=0.68$, $P<0.001$) and LV mass index ($r=0.56$, $P<0.001$). There was no significant association between changes in carotid IMT and LV hypertrophy index ($r=0.17$, $P>0.05$).

Discussion

The salient findings of the present study were as follows. First, a few months of resistance training significantly

TABLE 2. Hemodynamic and Cardiovascular Indices

Variable/Group	Baseline	After Training	After Detraining	Interaction
Heart rate, bpm				
Control	57±2	56±2	57±2	F=0.218
Intervention	55±2	54±2	53±2	*P*=0.805
Brachial systolic BP, mm Hg				
Control	118±3	120±2	120±2	F=0.324
Intervention	116±3	116±3	116±3	*P*=0.728
Brachial diastolic BP, mm Hg				
Control	69±2	72±2	73±1	F=2.487
Intervention	69±1	66±1	70±2	*P*=0.093
Brachial mean BP, mm Hg				
Control	87±2.3	89±1.5	90±1.5	F=0.988
Intervention	85±1.6	84±1.9	87±2.2	*P*=0.379
Carotid systolic BP, mm Hg				
Control	100±2	103±2	103±1	F=1.477
Intervention	103±3	104±2	102±3	*P*=0.238
Carotid intima-media thickness, mm				
Control	0.49±0.01	0.52±0.02	0.50±0.02	F=0.400
Intervention	0.47±0.01	0.52±0.02	0.51±0.01	*P*=0.677
Carotid lumen diameter, mm				
Control	5.91±0.11	5.94±0.14	6.02±0.12	F-0.496
Intervention	5.87±0.12	5.98±0.11	6.00±0.10	*P*=0.612
IMT/lumen diameter, mm/mm				
Control	0.084±0.002	0.087±0.004	0.085±0.002	F=0.380
Intervention	0.084±0.003	0.088±0.004	0.084±0.004	*P*=0.686
Carotid augmentation index, %				
Control	−19±3	−18±3	−16±3	F=0.979
Intervention	−18±3	−13±3	−16±2	*P*=0.382
Femoral artery compliance, mm²/mm Hg				
Control	0.09±0.01	0.09±0.01	0.08±0.01	F=0.180
Intervention	0.10±0.01	0.10±0.02	0.09±0.01	*P*=0.836
Stroke volume index, mL/kg				
Control	1.19±0.03	1.26±0.05	1.26±0.09	F=1.150
Intervention	1.21±0.06	1.20±0.06	1.21±0.57	*P*=0.326
LV mass index, g/kg				
Control	3.1±0.2	3.1±0.2	3.1±0.2	F=15.912
Intervention	2.8±0.1	3.4±0.1*	2.9±0.1†	*P*<0.0001
LV hypertrophy index, mm/mm				
Control	19±1	19±1	19±1	F=22.432
Intervention	18±1	21±1*	18±1†	*P*<0.0001

BP indicates blood pressure; LV, left ventricular.
*$P<0.05$ vs Baseline; †$P<0.05$ vs After Training.

reduces central arterial compliance in healthy men. Second, the reduced arterial compliance returned to the baseline levels a few months after the cessation of resistance training, confirming that the change in central arterial compliance was indeed an effect of resistance training per se. Third, effects of resistance training on the compliance of the peripheral muscular artery (ie, femoral artery) were not apparent, indicating that the effect of resistance training involves only central elastic arteries whose cushioning function dampens fluctuations in pressure and flow. Fourth, changes in central arterial compliance induced by resistance training and detraining were significantly associated with corresponding structural changes in LV. Thus, in marked contrast to the beneficial effect of regular aerobic exercise that we observed on arterial compliance, the present findings are not consistent with the idea that resistance training exerts beneficial influences on arterial wall buffering functions.

Previous cross-sectional studies found that individuals who performed resistance training on a regular basis demonstrated lower levels of arterial compliance than their sedentary peers.[12,20] Because the cross-sectional nature of these observations precluded us from attributing the observed group difference to the effects of resistance training per se, we performed the present intervention study. Consistent with the previous cross-sectional findings,[12,20] in the present study, several months of resistance training induced ≈20% reductions in carotid arterial compliance. Moreover, to isolate the effects of resistance training on arterial compliance as much as possible, we also implemented the detraining program at the conclusion of resistance training. We reasoned that if the changes in arterial compliance were mediated by resistance training, such changes should return to the baseline level when the stimuli of daily resistance exercise were removed. Indeed, during the detraining period, arterial compliance, which was reduced with resistance training, was reversed to the baseline values. Taken together, these results would further support the view that resistance training reduces central arterial compliance.

It is generally thought that arterial compliance is a relatively static measure and that it would take years to change the elastic properties of arteries. In marked contrast to this prevailing thought, arterial compliance has a large reserve and can be altered over a much shorter period, even acutely.[21,22] In the present study, we observed an ≈20% reduction in central arterial compliance in the initial 2 months of resistance training, and no further changes were observed between 2 and 4 months of the exercise intervention. The magnitude of the reduction in arterial compliance achieved in the present intervention study is similar to ≈20% difference in arterial compliance between sedentary and resistance-trained young men that we observed in our previous cross-sectional study.[12] These results are consistent with previous pharmacological studies[23] that, in contrast to the prevailing thought, arterial compliance can be altered over a relatively short time period.

It is not clear what physiological mechanisms explain the arterial stiffening with resistance training. During each bout of resistance exercise, arterial blood pressure is known to increase to as high as ≈320/250 mm Hg.[24] These acute intermittent elevations in arterial blood pressure during resistance exercise may have altered the arterial structure and/or the arterial load-bearing properties of collagen and elastin,[25] thereby causing arterial stiffening. Although there were no changes in carotid artery IMT or IMT/lumen ratio, it would not exclude the possibility of some qualitative changes within the arterial wall (eg, fracture of elastic lamellae). Intense resistance training is also known to be a strong stimulus to increase sympathetic nervous system activity,[26,27] which may have acted to reduce arterial compliance by providing chronic restraint on the arterial wall via greater sympathetic adrenergic vasoconstrictor tone.[28] However, because the influence of sympathetic vasoconstrictor tone would be expected to be greater in peripheral muscular arteries, the preferential changes observed in central versus peripheral artery in the present study argue against this possibility. Other potential mechanisms may include impaired endothelial function[29] and increased formation of collagen cross-linking and advanced glycation end products in arterial wall.[30] Because we observed effects of resistance training only on the central elastic artery (carotid artery) but not on the peripheral muscular artery (ie, femoral artery), it is also possible to hypothesize that some mechanical/physical factors may have interacted to reduce arterial compliance. Future studies will be needed to determine the physiological mechanisms underlying the influence of resistance training on central arterial compliance.

The traditional view on the mechanism underlying LV concentric hypertrophy is that the intermittent pressor responses during weight-lifting sessions increase cardiac afterload and LV wall tension, resulting in LV hypertrophy.[31] However, because the training bouts last for only brief periods per day, it is possible that other more chronic factors may be responsible for LV hypertrophy. Previous studies conducted on hypertensive individuals have indicated that arterial stiffness may be causally linked with LV hypertrophy index via its influence on afterload.[32] Consistent with these observations, changes in LV mass and LV hypertrophy index with resistance training were significantly associated with changes in arterial compliance in the present study. These results raise the possibility that central arterial stiffening induced by resistance training may contribute, at least in part, to the concentric LV hypertrophy.

It may be feared that our present findings may discourage the practice of resistance training. We should emphasize, however, the important difference between the training protocol used in the present study and those recommended by the major health organizations.[9,10] The intensity, volume, and frequency of the resistance training used in the present study were much greater than those recommended for the comprehensive health programs.[9,10] In light of the role of resistance training on the maintenance of functional ability and the prevention of osteoporosis, the "properly prescribed" resistance training should still be highly encouraged, particularly for older adults. Our present study raises a caution when heavy and strenuous weight training is to be prescribed especially to high-risk populations.

In summary, in marked contrast to the beneficial effect of aerobic training, several months of resistance training reduces the central arterial compliance in healthy men. The reduction in arterial compliance returned to baseline levels during the subsequent detraining period, confirming that the change in central arterial compliance was because of the effect of resistance training per se. In addition, structural changes in the LV induced by the resistance training and detraining were associated with corresponding changes in central arterial compliance. The underlying physiological mechanisms and clinical implications of these findings warrant further investigation.

Acknowledgments

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Effects of treadmill exercise on bone mass, bone metabolism, and calciotropic hormones in young growing rats

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Abstract The aim of the present study was to examine the effects of exercise on bone mass, bone metabolism, and calciotropic hormones in young growing rats. Twenty 6-week-old female Wistar rats were randomized into the following four groups with 5 animals each: 7 weeks of exercise, 7 weeks of sedentary control, 11 weeks of exercise, and 11 weeks of sedentary control. The exercise regimen consisted of running on a treadmill at 25 m/min for 1 h each day on 5 days a week. After each period of exercise, the bone mineral content (BMC) of the tibia and fifth lumbar spine was measured by dual-energy X-ray absorptiometry, using a Lunar DPX-L instrument. The femoral length and levels of bone markers and calciotropic hormones were also assessed. Seven and 11 weeks of exercise increased the serum osteocalcin and 1,25-dihydroxyvitamin D_3 levels, and decreased the serum parathyroid level. Seven weeks of exercise decreased the urinary deoxypyridinoline level, and 11 weeks of exercise increased the serum alkaline phosphatase level and decreased the serum tartrate-resistant acid phosphatase level. As a result, 7 and 11 weeks of exercise increased the femoral length and tibial BMC, but did not alter the lumbar BMC. The present study demonstrates that treadmill exercise stimulates bone formation and suppresses bone resorption, increases the serum 1,25-dihydroxyvitamin D_3 level, and decreases the serum parathyroid hormone level, resulting in an increase in bone mass with stimulation of longitudinal bone growth, especially at weight-bearing sites, in young growing rats. Further studies with long-term exercise may be needed to obtain a positive effect on the lumbar BMC.

Key words exercise · bone mineral content (BMC) · bone formation · parathyroid hormone · vitamin D_3

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Introduction

Current strategies for the prevention of osteoporosis focus on maximizing bone mass early in life during growth and maturation and minimizing bone loss later in life [1,2]; maximal bone mass at skeletal maturity, in particular, is considered to be the best protection against osteoporotic fractures [3]. Because physical activity during childhood and adolescence may be one of the most important determinants of peak bone mass, exercise during this period should be emphasized to maximize peak bone mass.

Several experimental studies have shown the effect of exercise on bone mass during the growth period [4–7], and it has been confirmed that exercise increases bone mass in young rats. However, a few studies have reported the effect of exercise on both bone markers and calciotropic hormones in young growing rats [6–8]. It is accepted that exercise promotes a positive calcium balance and increases skeletal mass largely as a result of an increase in 1,25-dihydroxyvitamin D_3 and enhancement of intestinal calcium absorption in rats [8]. However, the response of parathyroid hormone (PTH) to exercise is not consistent [9–15]. Thus, the mechanism by which exercise increases bone mass during the growth period is not fully understood. In the present study, in young growing rats, we examined the effects of treadmill exercise on bone mass, bone markers, and calciotropic hormones to clarify the mechanism by which exercise increases bone mass.

Materials and methods

Animal care and exercise program

Twenty female Wistar rats, aged 3 weeks, were purchased from Clea Japan (Tokyo, Japan), and housed in individual cages (25 × 18 × 34 cm^3) in a specific

pathogen-free room with a temperature of 23 ± 2°C, humidity of 55 ± 5%, and a 12-h on/off light cycle. They were allowed free access to water and a pelleted chow diet (CE-2; Funabashi Farm, Chiba, Japan). After 3 weeks of adaptation to this diet and the new environment, the 6-week-old rats were randomized, using the stratified weight method, into the following four groups with 5 animals each; 7 weeks of exercise (7EX), 7 weeks of sedentary control (7CON), 11 weeks of exercise (11EX), and 11 weeks of sedentary control (11CON). The exercise regimen consisted of daily running on a flat-bed treadmill (Shinano Instrument, Tokyo, Japan). During the first 2 weeks, the speed of the treadmill and duration of each running session were gradually increased from 8 m/min for 5 min to 14 m/min for 45 min. The running speed and duration were gradually increased to 25 m/min for 60 min each day in the third week, and this speed and duration were maintained for 5 days a week for the remaining period. The experiment was performed at Kitasato Institute Hospital, and the protocols were approved by the Research Animal Resource Committee of Kitasato Institute Hospital.

Measurement of bone markers and calciotropic hormones

After the exercise regimen had been completed, 24-h urine was collected, using a metabolic cage. A blood sample was taken from the vena cava with the animals under pentobarbital sodium anesthesia (100 mg/100 g body weight, intraperitoneal injection). The urinary deoxypyridinoline (DPD) level was measured by enzyme immunoassay. The serum osteocalcin (OC) level was measured by radioimmunoassay. The serum tartrate-resistant acid phosphatase (TRAP) level was measured by colorimetric assay, using the substrate naphthyl-phosphatase. The serum PTH and 1,25-dihydroxyvitamin D_3 levels were also measured by radioimmunoassay.

Measurement of gastrocnemius muscle weight, length of femur, and bone mineral content (BMC) and bone mineral density (BMD) of tibia and lumbar spine

After the urine and blood samples had been collected, the animals were killed by exsanguination from the vena cava. The right gastrocnemius muscle was dissected, and weighed immediately. The right femur and tibia and fifth lumbar (L5) spine were dissected free of soft tissue. The total length of the femur was measured three times, using a dial caliper, and the mean value was taken as the length of the femur. With regard to the right tibia and L5 spine, each bone was put on an acryl plate (20-mm-thick) in air and scanned three times by dual-energy X-ray absorptiometry (DXA), using a regular Lunar DPX-L instrument (Madison, WI, USA) adapted for measurement in small animals. A high-resolution mode (voltage of 76.0 kVp; current of 150 μA, collimation of fine, sample size of 0.15 × 0.3, sample interval of 1/64) was used with scan width of 15 mm and scan length of 50 mm for the tibia and 20 mm for the L5 spine. The BMC and BMD of the whole tibia, and the proximal, middle, and distal thirds of the tibia, as well as the L5 spine were analyzed in each scan, and the mean values of three analyses were taken. The reproducibility of the data was evaluated by measuring the coefficient of variation (CV = 100 × SD/mean) of measurements, performed within 24 h using specimens from five animals. The CV of these measurements was less than 2.0%.

Statistical analysis

All data values were expressed as means ± SD. Analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD) test was used to compare data among the groups. All statistical analyses were performed using the Stat View J-5.0 program (SAS Institute, Cary, NC, USA) on a Macintosh computer. A significance level of $P < 0.05$ was used for all comparisons.

Results

Body weight, gastrocnemius weight, femoral length, and tibial and lumbar BMC and BMD

Table 1 and Figs. 1 and 2 show the body weight, gastrocnemius weight, femoral length, and tibial and lumbar BMC and BMD. There were no significant differences in the initial body weight among the four groups. Maturation-related increases in the final body weight, and in tibial and lumbar BMC and BMD were observed. Seven and 11 weeks of exercise increased the femoral length and tibial BMC, but did not alter the body weight, tibial BMD, and lumbar BMC and BMD. With more detailed data for tibial BMC, although 7 and 11 weeks of exercise did not increase the proximal, middle, or distal tibial BMD, 7 weeks of exercise increased the middle and distal tibial BMC, and 11 weeks of exercise increased the proximal, middle, and distal tibial BMC. The mean percent increase in the proximal, middle, and distal tibial BMC obtained through 11 weeks of exercise was 12.2%, 25.6%, and 30.8%, respectively. The response of BMC to exercise was greatest in the distal tibia and least in the proximal tibia, when the mean percent increase in BMC obtained through 11 weeks of exercise was compared among the proximal, middle, and distal tibiae.

Table 1. Body weight, gastrocnemius weight, femoral length, and tibial and lumbar BMC and BMD

	7 Weeks			11 Weeks		
	7EX	7CON	*P* value	11EX	11CON	*P* value
Initial body weight (g)	149.0 ± 6.8	154.0 ± 3.7	NS	150.8 ± 5.4	152.0 ± 5.8	NS
Final body weight (g)	231.6 ± 18.9	236.0 ± 8.5	NS	248.0 ± 13.6	258.0 ± 14.4*	NS
Gastrocnemius weight (g)	5.87 ± 0.79	5.85 ± 0.44	NS	6.39 ± 0.44	6.36 ± 0.47	NS
Femoral length (cm)	3.22 ± 0.08	3.14 ± 0.03	<0.05	3.26 ± 0.10	3.16 ± 0.02	<0.05
Tibial BMC (g)						
Whole	0.176 ± 0.012	0.142 ± 0.007	<0.05	0.218 ± 0.009	0.182 ± 0.010**	<0.05
Proximal	0.084 ± 0.004	0.076 ± 0.002	NS	0.101 ± 0.002	0.090 ± 0.001**	<0.05
Middle	0.035 ± 0.002	0.024 ± 0.003	<0.05	0.049 ± 0.006	0.039 ± 0.001*	<0.05
Distal	0.056 ± 0.007	0.042 ± 0.007	<0.05	0.068 ± 0.003	0.052 ± 0.003*	<0.05
Tibial BMD (g/cm²)						
Whole	0.175 ± 0.006	0.177 ± 0.008	NS	0.194 ± 0.003	0.193 ± 0.004**	NS
Proximal	0.190 ± 0.006	0.187 ± 0.004	NS	0.216 ± 0.009	0.219 ± 0.004**	NS
Middle	0.145 ± 0.006	0.142 ± 0.004	NS	0.155 ± 0.003	0.160 ± 0.008**	NS
Distal	0.171 ± 0.008	0.167 ± 0.009	NS	0.194 ± 0.015	0.182 ± 0.020	NS
Lumbar BMC (g)	0.059 ± 0.005	0.053 ± 0.012	NS	0.073 ± 0.009	0.076 ± 0.007**	NS
Lumbar BMD (g/cm²)	0.204 ± 0.007	0.201 ± 0.008	NS	0.226 ± 0.018	0.224 ± 0.012**	NS

* $P < 0.05$; ** $P < 0.01$ vs 7CON group
Data values are expressed as means ± SD. Data comparison was performed by unpaired *t*-test
NS, not significant; BMC, bone mineral content; BMD, bone mineral density; EX, exercise; CON, control

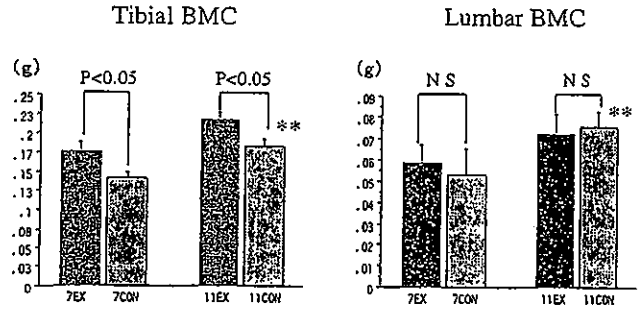

Fig. 1. Tibial and lumbar bone mineral content (*BMC*). All data values are expressed as means ± SD. Analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD) test was used to compare data among the groups. Maturation-related increases in the tibial and lumbar BMC were observed. Seven and 11 weeks of exercise increased the tibial BMC, but did not alter the lumbar BMC. *$P < 0.05$; **$P < 0.01$ vs 7CON group. *NS*, not significant; *7EX*, 7 weeks of exercise; *7CON*, 7 weeks of sedentary control; *11EX*, 11 weeks of exercise; *11CON*, 11 weeks of sedentary control

Bone markers and calciotropic hormones

Table 2 and Fig. 3 show the levels of bone markers and calciotropic hormones. Maturation-related decreases in serum OC, ALP, and TRAP levels, and in urinary DPD levels, were observed, without any alterations shown in the serum PTH and 1,25-dihydroxyvitain D_3 levels. Seven and 11 weeks of exercise increased the serum OC and 1,25-dihydroxyvitamin D_3 levels, and decreased the serum PTH level. Seven weeks of exercise decreased the urinary DPD level, and 11 weeks of exercise increased the serum ALP level and decreased the serum TRAP level.

Discussion

It is generally accepted that, although bone formation and bone resorption take place actively in young bone, they decline with maturation. In the present study, maturation-related increases in the final body weight, and in tibial and lumbar BMC and BMD, were observed, with decreases in the serum OC, ALP, and TRAP levels and in urinary DPD levels. These findings suggest that the animals experienced maturation-related bone gain with a decline in bone turnover.

Treadmill exercise increased the tibial BMC and length of the femur, but did not increase the lumbar vertebral BMC. The tibia and femur are likely to receive much more mechanical loading than the lumbar spine during treadmill running in rats, as they are tetrapedal animals [16,17]. Our findings suggest that treadmill exercise increases bone mass and stimulates longitudinal bone growth, especially at weight-bearing sites, in young growing rats. It is well documented that weight-bearing bones like the tibia and femur may have a higher sensitivity to treadmill exercise than less weight-bearing bone like the lumbar spine in rats [7,16–18]. Our findings are consistent with the results of these previous studies, and also support the generally accepted concept that weight-bearing activity has a positive influence on bone health [19].

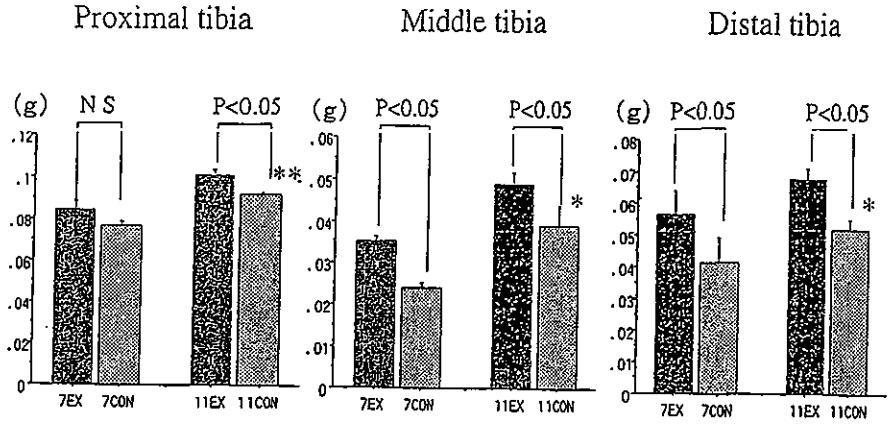

Fig. 2. Proximal, middle, and distal tibial BMC. All data values are expressed as means ± SD. ANOVA with Fisher's PLSD test was used to compare data among the groups. Seven weeks of exercise increased the middle and distal tibial BMC, and 11 weeks of exercise increased the proximal, middle, and distal tibial BMC. The mean percent increases in the proximal, middle, and distal tibial BMC obtained through 11 weeks of exercise were 12.2%, 25.6%, and 30.8%, respectively. $*P < 0.05$; $**P < 0.01$ vs 7CON group

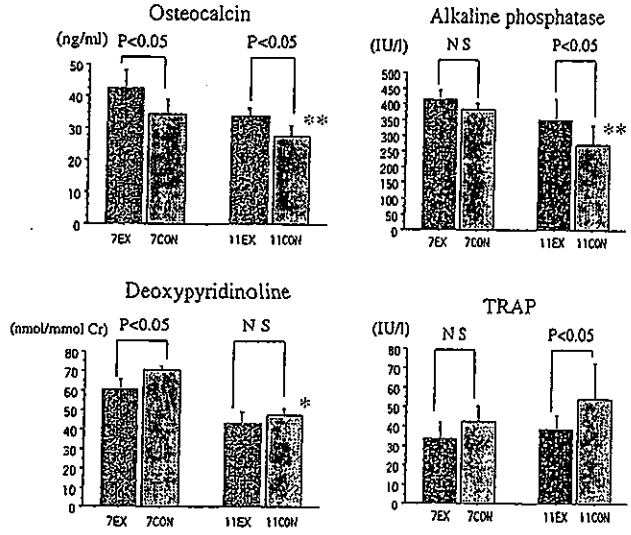

Fig. 3. Bone markers. All data values are expressed as means ± SD. ANOVA with Fisher's PLSD test was used to compare data among the groups. Maturation-related decreases in the serum osteocalcin, alkaline phosphatase, and tartrate-resistant acid phosphatase (*TRAP*), and urinary deoxypyridinoline levels were observed. Seven and 11 weeks of exercise increased the serum osteocalcin level. Seven weeks of exercise decreased the urinary deoxypyridinoline level and 11 weeks of exercise increased the serum alkaline phosphatase level and decreased the serum TRAP level. $*P < 0.05$; $**P < 0.01$ vs 7CON group. *Cr*, creatinine

The response of BMC to exercise was greatest in the distal tibia and least in the proximal tibia. Iwamoto et al. [5] also clearly demonstrated that treadmill exercise increased the proximal and distal cancellous bone mass in young growing rats, but did not alter the lumbar cancellous bone mass, and that the response of cancellous bone to treadmill exercise was greater in the distal tibia than in the proximal tibia. The mechanism for this greater response of cancellous bone mass or BMC in the distal tibia than in the proximal tibia remains uncertain; however, the location and diameter of the bone tissue area may contribute to this result to some extent. The distal tibia is likely to receive more mechanical loading than the proximal tibia during treadmill exercise because the distal tibia is situated farther away from the body mass of the rat. This distal location increases the total load on the distal tibia as compared with the proximal tibia. Additionally, the total diameter of the distal tibia is smaller than that of the proximal tibia, and therefore the distal tibia supports greater weight per surface area during treadmill exercise. These findings are supported by the concept that high strain magnitude may be more effective than low strain magnitude in exerting a positive effect on bone mass [19,20].

In our study, treadmill exercise stimulated longitudinal bone growth and increased BMC at weight-bearing sites, but did not alter BMD. These findings suggest that treadmill exercise during the growth period increased bone size in the longitudinal direction, maintaining bone density. In contrast, in mature or aged rats, treadmill exercise increases BMD at weight-bearing sites without stimulation of longitudinal bone growth [16,21]. Thus, in young growing rats, longitudinal bone growth is sensitive to gravitational mechanical loading; treadmill exercise stimulates longitudinal bone growth. However, because of the lack of bone histomorphometric and peripheral quantitative computed tomography (pQCT) analyses of cortical bone, it remains uncertain whether treadmill exercise stimulated radial bone growth. Recently, Yeh et al. [22] developed a noninvasive animal model of circular motion exercise to evaluate the effect of isometric exercise on bone in rats. They demonstrated that circular motion exercise (isometric exercise) under force without additional weight-loading caused bone-modeling drift in the radial direction, with an increase in bone turnover to reconstruct the bone shape as an adaptation to the demand for strength, and they showed that circular motion exercise did not enhance longitudinal bone growth. Gravitational force caused by treadmill exercise can at least enhance longitudinal bone growth, while horizontal

Table 2. Bone markers and calciotropic hormones

	7 Weeks			11 Weeks		
	7EX	7CON	*P* value	11EX	11CON	*P* value
Serum						
Calcium (mg/dl)	10.1 ± 0.1	10.0 ± 0.4	NS	10.2 ± 0.3	9.8 ± 0.4	NS
Phosphorus (mg/dl)	7.5 ± 0.5	7.6 ± 0.2	NS	7.1 ± 0.4	7.5 ± 0.9	NS
ALP (IU/l)	417.0 ± 28.3	382.6 ± 22.3	NS	351.8 ± 68.6	270.4 ± 62.0**	<0.05
Osteocalcin (ng/ml)	42.8 ± 5.5	34.4 ± 4.6	<0.05	34.0 ± 2.3	27.6 ± 3.4**	<0.05
TRAP (IU/l)	34.0 ± 8.0	42.6 ± 7.9	NS	38.9 ± 7.0	54.2 ± 18.2	<0.05
PTH (pg/ml)	29.8 ± 2.7	51.0 ± 24.1	<0.05	40.0 ± 3.7	58.0 ± 6.0	<0.05
1,25 $(OH)_2$ D_3 (pg/ml)	37.6 ± 1.4	22.0 ± 7.0	<0.001	25.8 ± 4.1	18.9 ± 4.2	<0.05
Urine						
DPD (nmol/mmol Cr)	61.0 ± 4.7	70.4 ± 1.9	<0.05	43.2 ± 5.9	47.5 ± 3.4*	NS

* $P < 0.01$; ** $P < 0.001$ vs 7CON group
Data values are expressed as means ± SD. Data comparison was performed by unpaired *t*-test
NS, not significant; ALP, alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase; PTH, parathyroid hormone; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; DPD, deoxypyridinoline; Cr, creatinine

force caused by circular motion exercise can enhance radial bone growth.

The mechanism by which treadmill exercise increases bone mass, especially at weight-bearing sites, remains uncertain. There are a few studies that have focused on the effects of exercise on bone formation and bone resorption in young rats by assessing cellular activities [4–7]. Exercise increases cancellous bone mass through increased bone formation and/or decreased bone resorption, and increases cortical bone mass as a result of increased periosteal bone formation [4–7]. In particular, exercise in young growing rats is associated with an initial increase and then a decrease in bone resorption, while active bone formation is sustained [6]. Exercise increases bone formation and prolonged exercise decreases bone resorption. In the present study, bone gain through exercise in young rats was suggested to be attributable to increased bone formation and decreased bone resorption in response to increased mechanical loading. We detected a decrease in bone resorption, probably following an initial increase, and sustained active bone formation.

With regard to the effect of exercise on calciotropic hormones, it is accepted that exercise promotes a positive calcium balance and increases skeletal mass, largely as a result of an increase in 1,25-dihydroxyvitamin D_3 and enhancement of intestinal calcium absorption in rats [8]. However, reports concerning the response of PTH to exercise are conflicting; it has been shown to be unchanged, decreased, or increased [9–15]. In the present study, treadmill exercise increased the serum 1,25-dihydroxyvitamin D_3 level and decreased the serum PTH level. It is speculated that treadmill exercise stimulated bone formation and suppressed bone resorption, resulting in an increased demand for minerals that was satisfied by an increase in serum 1.25-dihydroxyvitamin D_3 level and increased intestinal absorption of calcium; it is also speculated that the increase in calcium absorption suppressed the serum PTH level.

Despite the changes in the levels of calciotropic hormones, treadmill exercise altered the tibial BMC but not the lumbar BMC. These findings suggest that an increase in bone mass through short-term exercise appears to be achieved by the combined actions of local mechanical loading and general calciotropic hormones, and that weight-bearing activity appears to be important in the promotion of longitudinal bone growth and bone gain. However, it is possible that long-term exercise could increase the lumbar BMC through the actions of general calciotropic hormones. Thus, further studies with long-term exercise are needed to clarify whether treadmill exercise can alter the mass of less weight-bearing bones through the actions of calciotropic hormones.

The limitation of the present study is the lack of bone histomorphometric analysis. Therefore, the alterations in local bone formation and bone resorption, cellular activities, and bone architecture in the tibia and lumbar spine remain uncertain. Further studies will be needed to clarify the effects of treadmill exercise on these parameters in the tibia and lumbar spine.

In conclusion, the present study demonstrates that treadmill exercise stimulates bone formation and suppresses bone resorption, increases the serum 1,25-dihydroxyvitamin D_3 level, and decreases the serum PTH level, resulting in an increase in bone mass with stimulation of longitudinal bone growth, especially at weight-bearing sites, in young growing rats. Further studies with long-term exercise may be needed to obtain a positive effect on the lumbar BMC.

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Effect of walking exercise on bone metabolism in postmenopausal women with osteopenia/osteoporosis

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Abstract The purpose of this prospective study was to determine whether moderate walking exercise in postmenopausal women with osteopenia/osteoporosis would affect bone metabolism. Fifty postmenopausal women, aged 49–75 years, with osteopenia/osteoporosis were recruited: 32 women entered the exercise program (the exercise group) and 18 served as controls (the control group). The exercise consisted of daily outdoor walking, the intensity of which was 50% of maximum oxygen consumption, with a duration of at least 1 h with more than 8000 steps, at a frequency of 4 days a week, over a 12-month period. Lumbar (L2–L4) bone mineral density (BMD) was measured at the baseline and every 6 months with dual-energy X-ray absorptiometry (DXA) in both groups. Serum bone-specific alkaline phosphatase (BAP) and urinary cross-linked N-terminal telopeptides of type I collagen (NTX) levels were measured at baseline and at months 1, 3, 6, 9, and 12 by EIA and ELISA, respectively, in the exercise group, and urinary NTX level was measured at the baseline and every 6 months in the control group. There were no significant differences in baseline characteristics including age, height, body weight, bone mass index, years since menopause, lumbar BMD, and urinary NTX level between the two groups. Although no significant changes were observed in lumbar BMD and the urinary NTX level in the control group, lumbar BMD in the exercise group was increased as compared with the control group, but was sustained from the baseline. In the exercise group, the urinary NTX level rapidly responded to walking exercise from month 3, and this reduction was sustained until month 12, followed by reduction in the serum BAP level. A moderately negative correlation was found between the percent change in the urinary NTX level at month 3 and that in lumbar BMD at month 12 in the exercise group. This study clearly demonstrates that the mechanism for the positive response of lumbar BMD to moderate walking exercise in postmenopausal women with osteopenia/osteoporosis appears to be the suppression of bone turnover, and that an early change in the urinary NTX level may be useful to predict the long-term response of increasing lumbar BMD to exercise, although its efficacy for lumbar BMD may be quite modest.

Key words walking exercise · bone metabolism · bone mineral density · postmenopausal women · osteoporosis

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Introduction

Osteoporosis primarily affects postmenopausal women, because estrogen deficiency caused by menopause induces marked bone loss. Physical activity plays an important role in the prevention of osteoporosis [1]: increased physical activity increases bone mass [2–4], while decreased physical activity such as bed rest causes bone loss [5]. Although a number of studies have reported the effect of exercise on bone mass in postmenopausal women with or without osteopenia/osteoporosis [3,6–15], the results were not always consistent, probably because the age of the subjects, skeletal sites assessed, and the mode, intensity, duration, and frequency of exercise varied from study to study. However, it may be accepted that high-intensity aerobics and weight-bearing exercise as well as resistance exercise seem to be more effective to increase bone mass than low- to moderate-intensity walking exercise.

In regard to the mechanism by which exercise brings about the positive effect on bone mass in postmenopausal women with or without osteopenia/osteoporosis, several well-controlled studies have reported the effect of physical activity on bone markers [16–19]: some studies showed that walking at an anaerobic threshold level or weight-bearing exercise decreased serum osteocalcin (OC) level or urinary calcium excretion [16,17], while other studies showed that combined aerobic and anaerobic exercise increased serum OC level, and brisk walking did not significantly affect bone

markers [18,19]. Thus, the effect of exercise on bone metabolism in postmenopausal women is not yet established.

An exercise program for the elderly should be safe and easy to perform and continue. Although high-intensity exercise is suitable for young athletes, moderate aerobic exercise, i.e., walking, may be safe and effective to maintain general health in elderly women with osteoporosis. Recently, bone marker measurements have been developed, and a bone resorption marker, the urinary cross-linked N-terminal telopeptides of type I collagen (NTX), which is more specific for bone than urinary deoxypyridinoline (DPD), has become available. In particular, the usefulness of urinary NTX measurement in the treatment with bisphosphonates for osteoporosis has been established; an early dynamic decrease in the urinary NTX level can be used to monitor and predict the long-term response to bisphosphonate therapy in elderly women [20]. The purposes of this prospective study were to determine whether moderate walking exercise in postmenopausal women with osteopenia/osteoporosis would affect bone metabolism as measured by bone markers including urinary NTX and to confirm the usefulness of urinary NTX measurement in intervention with exercise for osteopenia/osteoporosis.

Subjects and methods

Subjects

Fifty postmenopausal women, aged 49–75 years, with osteopenia/osteoporosis [21,22] were recruited in our outpatient clinic during a 1-year period between July 1999 and June 2000. Thirty-two women entered the exercise program (the exercise group) and 18 served as controls (the control group), according to the wish of the participants. Because exercise training requires effort on the part of the patients, the subjects who hoped to perform walking exercise were placed into the exercise group and those who did not so wish were placed into the control group.

Preliminary screening included medical history, physical examination, blood and urine examination, plain X-ray examination of the thoracic and lumbar spine, and measurement of lumbar bone mineral density (BMD). Serum calcium, phosphorus, and alkaline phosphatase (ALP) levels were measured by standard automated laboratory techniques. Bone markers and lumbar BMD were measured as described below. Vertebral fractures were determined by the Japanese criteria [21,22]. None of the subjects had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism, such as glucocorticoid, warfarin, methotrexate, bisphosphonate, vitamin D, vitamin K, and calcitonin, before this trial. None of them were past or current smokers. None of the women suffered from cardiopulmonary disease or severe osteoarthritis and osteopathy that might have affected physical activity. In addition, none of the subjects had participated in a sporting activity with a frequency of one or more times a week for at least the previous 5 years and none of them participated in such activity during this trial. All subjects were strictly encouraged to consume 800 mg calcium daily in their food, according to the instruction of dietitians.

The exercise program consisted of daily outdoor walking. After the target heart rate (THR) of each subject was calculated with Karvonen's formula [23], corresponding to 50% of maximal oxygen consumption, which was determined with Blackburn's formula [24], each subject learned a walking speed that corresponded to their corresponding THR by using an exercise treadmill at the beginning of the exercise program, and was instructed to walk for at least 1 h with more than 8000 steps a day for at least 4 days a week for 12 months at the determined walking speed. During walking exercise, they checked their heart rate with a handheld heart rate meter every 10 min to sustain the THR. The daily step count and heart rate were monitored every month in the exercise group. All data of daily step count and heart rate were recorded in a notebook by each subject in the exercise group. Informed consent was obtained from all subjects, and this protocol was approved by the Ethical Committee of Keio University School of Medicine. Five subjects in the exercise group and three in the control group discontinued this trial without any specific reason.

Bone marker measurements

Blood samples were collected after an overnight fast and serum samples were obtained by centrifugation at baseline and months 1, 3, 6, 9, and 12 in the exercise group. Urine samples were collected from the second voiding at baseline and months 1, 3, 6, 9, and 12 in the exercise group and at baseline and every 6 months in the control group. Both serum and urine samples were stored at −80°C until the measurement of serum bone-specific alkaline phosphatase (BAP) and OC and urinary NTX levels.

Serum BAP and OC were measured using an enzyme immunoassay (EIA) [25] and a two-site immunoradiometric assay (IRMA) [26], respectively. The former was measured with monoclonal antibody anti-BAP (Metra Biosystems, Mountain View, CA, USA), and the latter was specific for intact human OC and was measured with a BGP-IRMA kit (Mitsubishi Chemical, Tokyo, Japan) [27]. These assays were carried out by Mitsubishi

Kagaku Bio-Clinical Laboratories (Tokyo, Japan). The urinary NTX level was quantified by an enzyme-linked immonosorbent assay (ELISA) (MOS-19; Mochida Pharmaceutical, Tokyo, Japan) using a specific monoclonal antibody [28].

Measurement of lumbar BMD

Lumbar (L2–L4) BMD was measured at the baseline and every 6 months by dual-energy X-ray absorptiometry (DXA) using a Norland XR-36 (Atkinson, WI, USA) in the exercise and control groups. The coefficient of variation (CV) value of five measurements each time with repositioning within 72h was less than 1.1% in three persons.

Statistical analysis

Data are expressed as the mean ± standard error (SE). Data comparisons were performed by the Mann–Whitney U test. The correlation between percent changes in bone markers and lumbar BMD was examined by single regression analysis. A significance level of $P < 0.05$ was used for all comparisons. All statistical analyses were performed using BMDP statistical software on an NEC computer.

Results

Characteristics of study subjects

Table 1 shows the baseline characteristics of the study subjects who completed this trial, 27 subjects in the exercise group and 15 in the control group. There were no significant differences in mean age, height, body weight, body mass index, years since menopause, serum calcium, phosphorus, ALP, BAP, OC, and estradiol levels, urinary NTX level, and lumbar BMD between the two groups. All subjects showed normal ranges of serum calcium, phosphorus, and ALP levels, but a low (≦20 pg/ml) serum estradiol level. None of the subjects revealed any evidence of thoracic or lumbar vertebral fractures.

The baseline characteristics of the 8 subjects who discontinued this trial did not significantly differ from those of the 42 subjects who completed the trial.

Daily step count and heart rate

Table 2 shows the daily step count and heart rate in the exercise or control group. In the exercise group, the mean baseline THR was 108 beats/min, and the mean baseline daily step count was 4256. In the control group,

Table 1. Characteristics of study subjects

Characteristic	Exercise (n = 27)	Control (n = 15)
Number of subjects		
Osteopenia	11	6
Osteoporosis	16	9
Age (years)	64.2 ± 2.9	65.7 ± 2.7
Height (cm)	155.4 ± 1.3	155.7 ± 1.2
Weight (kg)	51.2 ± 1.4	50.1 ± 1.6
Body mass index (kg/m²)	21.2 ± 0.7	21.1 ± 1.1
Years since menopause (years)	16.6 ± 1.7	14.6 ± 1.6
Serum values		
Calcium (mg/dl)	9.2 ± 0.3	9.5 ± 0.3
Phosphorus (mg/dl)	3.4 ± 0.4	3.6 ± 0.4
ALP (U/l)	236 ± 18	212 ± 12
BAP (U/l)	28.9 ± 1.8	ND
OC (ng/μl)	6.6 ± 0.5	ND
Estradiol (pg/ml)	≦20	≦20
Urine		
NTX (nmol BCE/mmol Cr)	49.5 ± 4.5	49.0 ± 5.6
Lumbar BMD (g/cm²)	0.699 ± 0.082	0.728 ± 0.078
T score (%)	67.2 ± 7.25	69.9 ± 6.71

Data are expressed as mean ± SE
Mann–Whitney U test was used to compare the data between the two groups; there were no significant differences in all parameters between the two groups
BMI, body mass index; ALP, alkaline phosphatase; BAP, bone-specific alkaline phosphatase; OC, osteocalcin; NTX, cross-linked N-terminal telopeptides of type I collagen; BCE, bone collagen equivalent; BMD, bone mineral density; ND, no data

Table 2. Daily step count and heart rate

	Exercise (n = 27)	Control (n = 15)
Heart rate (beats/min)		
Baseline (THR)	108 ± 7.5	ND
Month 6	107 ± 6.3	ND
Month 12	102 ± 5.6*	ND
Walking speed at baseline (km/h)	4.2 ± 0.4	ND
Daily step count (steps/day)		
Baseline	4256 ± 348	4025 ± 315
Month 6	8053 ± 352**	ND
Month 12	8185 ± 315**	ND
Frequency of exercise (days/week)	4.2 ± 0.3	ND

Data are expressed as mean ± SE
Data comparisons were performed by Mann–Whitney U test
In the exercise group, the mean THR decreased by 0.82% at month 6 and 5.52% at month 12, with a significant decrease at month 12, and the mean daily step count increased by 89.2% at month 6 and 92.3% at month 12, with a significant increase at months 6 and 12
* $P < 0.05$ vs baseline THR, ** $P < 0.05$ vs baseline

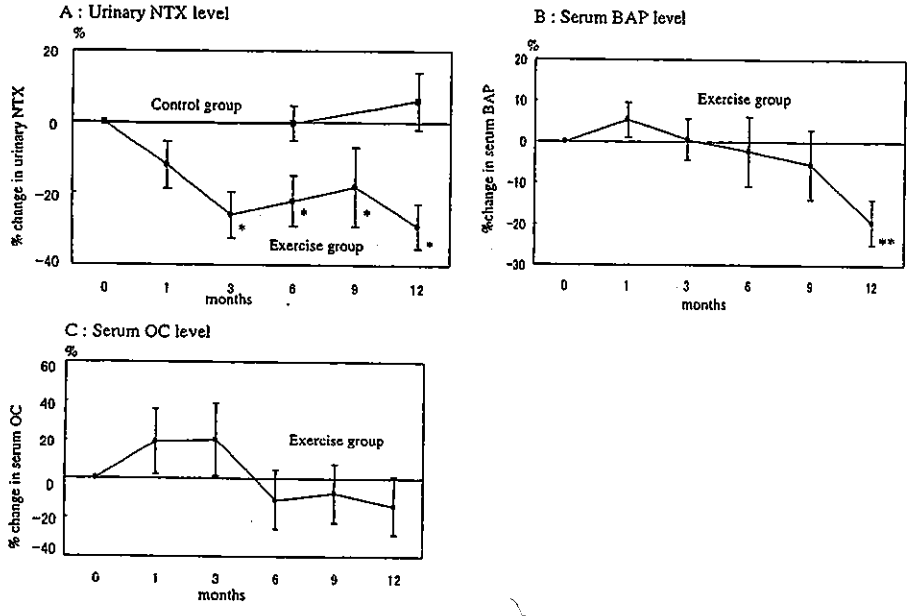

Fig. 1. Percent changes in bone markers. Data are expressed as means and SE. Data comparisons were performed by Mann–Whitney U test. In the control group, the urinary NTX level (**A**) did not significantly alter from the baseline. In the exercise group, the urinary NTX level rapidly responded to walking exercise from month 3 (25% reduction), and this reduction was sustained until month 12, followed by reduction in the serum BAP level (**B**). The serum OC level (**C**) did not significantly alter in the exercise group. * $P < 0.05$ vs baseline, ** $P < 0.05$ vs baseline. *NTX*, cross-linked N-terminal telopeptides of type I collagen; *BAP*, bone-specific alkaline phosphatase; *OC*, osteocalcin

the mean daily step count was 4025 with no significant difference. In the exercise group, the mean heart rate decreased by 0.82% at month 6 and 5.52% at month 12, with a significant decrease at month 12, and the mean daily step count increased by 89.2% at month 6 and 92.3% at month 12, with a significant increase at months 6 and 12. Finally, the mean frequency of exercise was 4.2 days a week.

Changes in bone markers

Figure 1 shows the changes in bone markers in the exercise and control groups. In the control group, the urinary NTX level did not significantly alter from the baseline. In the exercise group, the urinary NTX level rapidly responded to walking exercise from month 3 (25% reduction), and this reduction was sustained until month 12, followed by reduction in the serum BAP level. The serum OC level did not significantly alter in the exercise group.

Changes in lumbar BMD

Table 3 shows the change in lumbar BMD in the exercise and control groups. The mean percent change in lumbar BMD from the baseline at months 6 and 12 was