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Effects of Aerobic Exercise on Bone-Specific Alkaline Phosphatase and Urinary CTX Levels in Premenopausal Women

Premenopozal Kadınlarda Aerobik Egzersizin Kemik Spesifik Alkalen Fosfataz ve Üriner CTX Üzerindeki Etkileri

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Summary

Objective: This study aimed to investigate the effects of moderate-intensity aerobic exercise on bone turnover by urinary cross-linked C-telopeptide of type I collagen (CTX) and serum bone-spesific alkaline phosphatase (BAP) in comparison with a control group.
Materials and Methods: 100 premenopausal volunteers from our outpatient unit were randomized into 2 equal groups. The exercise group (n=50) performed the exercise sessions supervised by a physiotherapist for 40 min a day, 5 times a week for a duration of 2 months. The control group (n=50) maintained their sedentary lifestyle for the duration. Urinary CTX and BAP levels in the subjects were measured before and at the end of the intervention.
Results: The changes in CTX and BAP from baseline were statistically significant in the exercise group for but not in the control group. When the groups were compared with each other, the exercise group was found to be superior to the control group for the change in CTX.
Conclusion: Two months of regular submaximal aerobic exercise decreased bone resorption rate in premenopausal sedentary women.
Key Words: Aerobic exercise, bone-spesific alkaline phosphatase, cross linked c telopeptide of type 1 collagen.

Özet

Amaç: Orta şiddette aerobik egzersizin üriner tip I kollajen karboksi terminal çapraz bağ telopeptid (Ctx) ve serum kemik spesifik alkalen fosfataz (BAP) üzerindeki etkileri araştırıldı.
Gereç ve Yöntem: Polikliniğimize başvuran 100 gönüllü sedanter premenopozal kadın iki eşit gruba randomize edildi. Egzersiz grubu (n=50) günde 40 dk, haftada 5 kez ve 2 ay boyunca fizyoterapist eşliğinde toplu egzersiz yaptı. Kontrol grubu (n=50), sedanter yaşam şeklini devam ettirdi. Üriner Ctx ve serum BAP, çalışmanın başında ve sonunda olmak üzere iki kez değerlendirildi.
Bulgular: Ctx ve BAP da başlangıçtan bu yana olan değişimler, sadece egzersiz grubunda istatistiksel olarak anlamlı bulundu. Kontrol grubuyla karşılaştırıldığında, egzersiz grubu sadece Ctx seviyelerindeki değişim bakımından kontrol grubuna üstün bulundu.
Sonuç: İki ay düzenli yapılan submaksimal aerobik egzersizin, premenopozal sedanter kadınlarda kemik rezorpsiyonunu azalttığı gözlendi.
Anahtar Sözcükler: Aerobik egzersiz, kemik spesifik alkalen fosfataz, tip ı kollajen karboksi terminal çapraz bağ telopeptid

Introduction

Bone is a dynamic tissue that is able to adapt its structure and strength to mechanical loading environment and it has been suggested that weight-bearing exercise increases bone density and prevents or reduces postmenopausal or age-related bone loss (1,2). Based on current understanding of the pathology of osteoporosis and its modification by physical activity, generally accepted strategies to improve bone health and to reduce the incidence of osteoporotic fractures in women aim to: maximize peak bone mass during growth (childhood and adolescence), minimize age-related bone loss (middle-aged adults/premenopausal women) and prevent falls and fractures (in older adults/postmenopausal women) (3). The efficacy of mechanical loading as a potent osteogenic influence on bone is a well-known issue in bone health research, but there is still a wide gap between research and practice in terms of using physical activity as an effective and inexpensive means of preventing osteoporosis (3,4). Given that 15% to 25% of bone mineral density (BMD) can be lost during the premenopausal years alone, if prevention of osteoporosis is not properly addressed in this at-risk population, considerable social and health care costs will continually be directed towards treatment and this will be an economically undesirable outcome (5,6).

Different findings have emerged from previous systematic reviews and meta-analyses evaluating the optimal type and

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amount of exercise intervention that can significantly alter bone turnover and remodeling in premenopausal women and impact exercises (aerobic and weight-bearing exercises) have put forth consistent positive results (7-9). High-impact activities are most effective in improving femoral neck BMD at the hip, a common site of osteoporotic fracture (10). However, the dose response, the optimal amount, intensity, frequency, and duration of exercise are less known, because of difficulties in long-term evaluation of the effects of exercise in population-based studies (11).

Weight-bearing stimulus can be produced by both resistance exercises and aerobic exercises. It has been reported that forces greater than those experienced in daily living activities are required for improving bone mass (12).

Dual energy x-ray absorptiometry (DEXA) is used to quantify BMD and to diagnose osteoporosis or osteopenia, however, it has little value for monitoring the efficacy of a medical or exercise therapy in a few months. For this purpose, bone turnover markers are helpful in clinical practice. Biochemical markers of bone remodeling, a dynamic process of breakdown and renewal of bone in order to maintain mechanical integrity of skeleton, provide a dynamic measurement of skeletal status (13). Resorption markers fall in 2-12 weeks while formation markers act a little bit slower (3-6 months). When there is a change in the remodeling process, formation markers such as alkaline phosphatase or resorption markers like collagen cross-links can be measured in blood or urine as a reflection of the bone turnover. Serum cross-linked C-telopeptide of type I collagen (CTX) is a marker of osteoclast activity and is used to assess the level of bone resorption (14). Bone specific alkaline phosphatase (BAP) levels reflect the osteoblastic activity and the bone mineralization process. This study aimed to investigate the effects of moderate-intensity aerobic exercise on bone turnover by urinary CTX and serum BAP in comparison with a control group and to determine whether additive weight-bearing physical activity would cause observable changes in bone metabolism.

Materials and Methods

Patients

The study population consisted of 100 sedentary premenopausal women who volunteered to participate in the study from the outpatient unit of our department. Data collected from the subjects included age, body weight and height (BMI), detailed medical history for systemic illness or medication, menopause and physical activity levels. Physical activity level for each subject was determined to be 'sedentary' according to her lifestyle as 'office worker or housewife getting little or no exercise' or functionally as 'walking less than 1.5 km/day or standing 4 hrs/day (16-18).

We excluded subjects with metabolic bone-related diseases (e.g., primary hyperparathyroidism, kidney dysfunction requiring chronic hemodialysis, thyroid dysfunction, osteomalacia, etc.), other systemic diseases (e.g., infectious diseases, rheumatic disorders or malignancy) or those who were participating in an exercise group. Before starting the intervention, the hospital ethics committee approval and the patients' written informed consent were obtained.

Randomization

100 subjects were randomized into 2 equal groups. Simple randomization was performed using a computer-generated table of random numbers. No stratification or blocking was done during the randomization procedure.

Intervention

The exercise group (n=50) performed the exercise sessions under the supervision of a physiotherapist for 40 min a day, 5 times a week for a duration of 2 months. The aerobic exercise program consisted of warming (5 minutes), stretching (5 minutes), step aerobics (20 minutes), cooling (5 minutes) and stretching (5 minutes) sections. Blood pressures and radial pulses of the subjects were checked before and after the therapy. Intensity of aerobic exercise in this study was defined in terms of the Borg Scale (17,18) and in the intervention group was adjusted to a submaximal level 12-14, matching the targeted heart rate for submaximal aerobic exercise as 60–85% of Heart Rate Maximum (220-age) (2,18,19). Borg's rating of perceived exertion (RPE) is a widely used psycho-physical tool to assess subjective perception of effort during exercise. RPE between 12-14 at the Borg Scale suggests physical activity is being performed at a Borg Scale level of 'somewhat hard' or 'moderate level of intensity' matching the submaximal level of aerobic exercise. The patients were warned of the cardiac symptoms; chest pain, dizziness and dyspnea as well as abnormal lumbar pain during the exercise program and were advised to stop and notify the supervisor. The subjects in the control group (n=50) were instructed to maintain their sedentary lifestyle for the duration.

Blood and urinary samples were taken once from each patient before and at the end of the intervention between 8:00 and 10:00 a.m. after a 12-hr fast.

Biochemical Analysis

Urinary CTX was measured by Osteosal kit and expressed as T-scores. CrossLaps measured by Osteosal is a bone resorption marker found on the C-telopeptide of type 1 collagen. Serum alkaline phosphatase (IU/L) and BAP levels (range: 0-20%l) were measured by C16000 Abbott Architect System. BAP rate (%) was changed to IU/L manually according to total alkaline phosphatase levels.

Statistical Analysis

Statistical analysis was done by SPSS version 11.5 for Windows. The groups were evaluated by the Kolmogorov-Smirnov test if they were or were not normally distributed for all of the variables. Since the variables in both groups were normally distributed, student-t test was used to determine whether any differences existed among the initial mean values in the groups for the variables; age and body mass index (BMI) (Table 1). Changes from baseline values for each group (within comparisons) were evaluated using a paired samples t-test for normally distributed variables (Table 2).

Comparison of the groups as change scores were done by student's t-test (Table 3). Statistical analysis was done according to the intention to treat principle.

Results

100 voluntary female subjects were enrolled in this study and randomized into exercise (n=50) and control (n=50)

Table 1. Baseline patient characteristics in the exercise and control groups showed that the groups were homogenous for age and BMI.

	Exercise Group (mean ±SD)	Control Group (mean ±SD)	p-value
Age	47±7	49±5	0.54
BMI (kg/m^2)	24.08±3.45	25.01±5.33	0.15

BMI: Body Mass Index

Table 2. Changes in CTX and BAP from baseline.

		Baseline (mean ±SD)	2nd month (mean ±SD)	p-value
CTX (T-score)	Exercise Group	1.02±0.97	0.64±0.57	0.008
	Control Group	0.97±0.65	1.13±0.81	0.421
BAP (IU/L)	Exercise Group	5.41±0.92	6.85±2.36	0.025
	Control Group	7.44±2.09	7.18±1.04	0.173

CTX: Urinary Cross-linked C-telopeptide of Type I Collagen, BAP: Serum Bone-specific Alkaline Phosphatase

Table 3. Comparison of the groups by laboratory variables as percent changes at the end of the 2nd month.

	Exercise Group (mean ±SD)	Control Group (mean ±SD)	p-value
CTX (T-score)	-0.37±0.02	0.16±0.12	0.03
BAP (IU/L)	0.26±0.19	-0.03±0.01	0.51

CTX: Urinary Cross-linked C-telopeptide of Type I Collagen, BAP: Serum Bone-Specific Alkaline Phosphatase

groups with the mean age of 47±7 and 49±5, respectively. In addition, at baseline evaluation, groups were determined to be homogeneous for patient characteristics (p>0.05) (Table 1)

All patients completed the program and none of the patients had cardiovascular or other systemic problems. Four subjects in the exercise group missed some (1 to 3) of the exercise sessions, but all of the participants were included in the statistical analysis regardless of attendance irregularities.

Changes from baseline were statistically significant in the exercise group for CTX (p=0.008) and BAP (p=0.025). There was no significant change in the control group from baseline (Table 2). When the groups were compared with each other, the exercise group was found to be superior to the control group for the change in CTX (p=0.03) (Table 3).

Discussion

The strength of aging bone depends on the balance between the resorption and formation phases of the remodeling process. The purpose of this study was to examine the interaction of aerobic exercise training with the potential to exert positive influences on bone turnover. Therefore, this study revealed that 2 months of regular submaximal aerobic exercise decreased bone resorption marker, CTX, in premenopausal sedentary women. CTX concentrations decrease steeply between birth and 25 years but persist in significant amounts throughout adult-life until menopause. Body weight is associated with bone age as an independent variable for CTX and osteocalcin (20). Because both groups in our study were homogeneous for baseline physical characteristics such as age and weight, CTX can be assumed to be unaffected from physical parameters.

Bone resorption markers can decrease or increase daily and CTX has a diurnal rhythm and for its stabilization, 2 months time is needed. BAP is not influenced by the diurnal rhythm and treatment changes become stable at 3-6 months. Nevertheless, unstable changes may occur daily. In our study, when the groups were compared with each other at the end of the 2nd month, the difference in BAP was not statistically significant, probably because of the short follow-up period.

Disparate findings have emerged from previous systematic reviews and meta-analyses evaluating the optimal type and amount of exercise intervention that can significantly alter bone turnover and remodeling in premenopausal women (10, 21,22). In a systematic review of randomized trials by Wallace and Cumming (21), it has been shown that both impact and non-impact exercises have a positive effect at the lumbar spine in pre- and postmenopausal women. Impact exercise probably has a positive effect at the femoral neck. The most important narrative reviews on exercise and bone mass concluded that intervention studies show a positive effect of exercise on bone mass or that intervention studies provide conflicting results (23-28). Gutin and Kasper (29) concluded that in general, bone mass can be enhanced by both strenuous aerobic exercise and strength training. All agree that cross-sectional studies show larger positive effects.

It seems that mild general exercise such as walking is not effective in preventing postmenopausal bone loss or enhancing bone mass in younger age. The way in which exercise is thought to act on the skeleton is through gravitational forces or muscle pull producing strains within the skeleton which are perceived by bone cells as osteogenic. If a strain is detected as greater than the optimum strain, then bone formation will occur (30). Nevertheless, another study revealed that 12 weeks of high-intensity resistance training did not appear to enhance bone formation or inhibit bone resorption in young adult women, as assessed by biochemical markers (CTX, BAP, deoxypridinolin) of bone metabolism (31).

Based on a recent meta-analysis, brief high-impact exercise improves BMD at the hip but not at the lumbar spine (32). The individual studies in this review also showed no consistent benefit of this type of exercise on spinal BMD. It has been suggested that the loads engendered during high-impact exercise are hinged upon the interaction between the targeted bone morphology and the amount and orientation of mechanical load applied to it (33). It appears that the mechanical load generated during jumping exercises could have been attenuated before being translated to the spine and it does not generate sufficient osteogenic stimulus for bone formation (34). Moreover, different bone regions may respond differently to mechanical loads due to similar movements (33).

In the Japanese population-based osteoporosis (JPOS) cohort study which revealed the association between biochemical markers of bone turnover and bone loss (determined by BMD measurement . Premenopausal women with elevated levels of resorption and formation markers showed significantly greater bone loss during the follow-up than those with lower levels, after adjustment for the effects of age, body mass index, diet, regular exercise and smoking. The greatest coefficient of determination during the first 3 years of follow-up was observed between CTX levels and bone loss at the hip (35). The inverse relationship between the quintile of CTX and mean bone density is consistent in other different and various references (36).

With the foregoing evidence that biochemical markers of bone turnover may predict bone loss, this exercise intervention was planned to reveal the biochemical effect of increase in physical activity by means of moderate-intensity aerobic training in sedentary premenopausal women. In conclusion, our study provides clear evidence that bone resorption rate measured by CTX can be altered by aerobic exercise in a 2 months period. Our limitation is the inadequate follow-up period to determine the change in the bone formation marker; BAP, because of the reason that formation can take three to six months until the new bone structural unit is fully formed. Therefore, further studies on the physiologic effects of exercise training on bone metabolism and bone quality to prevent or treat bone loss are needed with a longer follow-up period.

Conflict of Interest

Authors reported no conflicts of interest.

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