Effects of Different Intensity Resistance Exercise Programs on Bone Turnover Markers, Osteoprotegerin and Receptor Activator of Nuclear Factor Kappa B Ligand in Post-Menopausal Women

Farklı Şiddetteki Direnç Egzersiz Programlarının Postmenopozal Kadınların Kemik Turn-Over Markerleri, Osteoprotegerin ve Nükleer Faktör Kappa B Reseptör Aktivatör Ligandı Üzerine Etkileri

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ABSTRACT Objective: To investigate the effects of 12-week two-different intensity resistance training programs on bone turnover markers, bone mineral density (BMD), osteoprotogerin (OPG), and soluble receptor activator of nuclear factor kappa β ligand (sRANKL) in postmenopausal women. **Material and Methods:** Forty healthy women (aged 45-60 years) participated in the study. High-intensity group (HIG; n=14) worked 4 days a week and performed two sets of 8-10 repetitions at ~70-80% of 1 repeat maximum (RM). Low-intensity group (LIG; n= 13) worked in the same duration, with 13-17 repetitions, at ~40-50% of 1RM. Control group (CG; n = 13) did not perform any exercises. Body composition, 1RM value for 10 exercises, repetitions of sit-ups for 30 seconds, bone formation and resorption markers, serum osteocalcine (OC), bone alkaline phosphatase (BAP), βCrossLabs, OPG, and sRANKL levels were measured before and after the training program. BMD was measured via dual energy X-ray absorptiometry. **Results:** Resistance training caused increases in spine BMD in HIG and LIG ($p< 0.05$), and OC levels increased in the HIG ($p< 0.05$). We observed a significant difference between the percent change in HIG versus the percent change in CG in the spine BMD values ($p< 0.01$). sRANKL levels decreased significantly in all three groups. Strength measures increased in both exercise groups ($p< 0.001$), favoring the HIG. **Conclusion:** High-intensity resistance training may be more effective for increasing muscle strength and protecting against osteoporosis and fractures. Due to insignificant changes in OPG levels and significant reductions in sRANKL in all groups, measures of circulating OPG and sRANKL levels seem not to be so useful to predict BMD or bone turnover status after resistance training programs. Therefore, these parameters remain to be determined directly in the bone microenvironments together with BMD measures and bone turnover markers.

Key Words: Osteoporosis, postmenopausal; RANK ligand; osteoprotegerin

ÖZET Amaç: İki farklı yüklenme şiddetinde yapılan 12 haftalık direnç antrenman programlarının postmenepozal dönemdeki kadınların, kemik turnover markerleri, kemik mineral yoğunluğu (KMY), osteoprogerin (OPG) ve soluble nükleer faktör kappa B reseptör aktivatör ligandı (sRANKL) üzerine olan etkisini belirlemek. **Gereç ve Yöntemler:** Post-menopoz dönemdeki 40 sağlıklı kadın (45-60 yaş) çalışmaya katıldı. Yüksek şiddet grubu (YŞG; n= 14) haftada 4 gün, 1 tekrar maksimumun (TM) ~%70-80'i şiddetinde, iki set, 8-10 tekrarla çalışırken, düşük şiddet grubu (DŞG; n= 13) aynı sürede, 1 TM'nin ~%40-50'si şiddetinde, 13-17 tekrarlık bir direnç antrenman programı uyguladılar. Kontrol grubu (KG; n= 13) ise herhangi bir egzersiz programı uygulamadı. Antrenman programından önce ve sonra, tüm katılımcıların vücut kompozisyonu, 10 hareket için 1 TM değerleri, mekik hareketi için 30 sn'deki tekrar sayısı, kemik yapım ve yıkım markerleri, serum osteokalsin, kemik alkalen fosfataz beta croslabs değerleri, OPG ve sRANKL seviyeleri ölçüldü. Kemik mineral yoğunluğu ise dual energy X-ray absorbsiyometre yöntemi kullanılarak ölçüldü. **Bulgular:** Direnç antrenmanı YŞG ve DŞG'nin omurga KMY'sinde ($p< 0.05$); YŞG'nin ise OC düzeylerinde ($p< 0.05$) artışlara neden oldu. YŞG ve KG'nin omurga KMY'lerinin % değişimleri arasında anlamlı bir farklılık saptandı ($p< 0.01$). sRANKL seviyeleri her üç grup için istatistiksel olarak anlamlı derecede azaldı. Kuvvet parametreleri, her iki egzersiz grubunda $p<0.001$ düzeyinde, YŞG lehine anlamlı olarak arttı. **Sonuç:** Yüksek şiddette direnç antrenmanları kas gücünü arttırmada, fraktürlerden ve osteoporozdan korunmada daha etkili olabilir. Tüm gruplarda OPG'de anlamlı değişiklik olmaması ve sRANKL düzeylerinin anlamlı azalmasına bağlı olarak dolaşımdaki OPG ve sRANKL düzeylerinin ölçümü direnç antrenmanlarından sonra KMY ve kemik döngüsünü belirlemede çok yararlı değil gibi görünmektedir. Bu nedenle, bu parametreler, KMY ölçümleri ve kemik döngüsü markerleri ile birlikte özellikle kemik mikro çevrelerinde direkt olarak belirlenmelidir.

Anahtar Kelimeler: Osteoporoz, postmenopozal; RANK ligandı; osteoprotegerin

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Osteoporosis is a serious problem characterized by a reduction in the amount of bone mass. There are studies reporting that resistance training both increases bone mass[1-3] and prevents age-related declines in bone mineral density (BMD) in nonestrogen replaced postmenopausal women.[4] Although optimum training strategies are still being discussed, people think that training should be population specific. Understanding the interaction between exercise and bone turnover and bone formation is important to develop an effective exercise program for population-specific groups such as postmenopasual women.

Markers of bone turnover are useful indices of metabolic changes in bone. Osteocalcin (OC) is generally considered to cause osteoblastic activity,[5] while β-CrossLaps (CTx), is an important bone resorption marker. Alkaline phosphatase (ALP) is essential for mineralization.[6] Thus, biochemical markers of bone metabolism have been used for some time now, particularly in clinical studies to evaluate bone metabolism in skeletal diseases.[7-11] Studies of the physiological response of these markers in healthy subjects during exercise have been limited, and the existing studies have contradictory results. Hatori et al determined that BMD increases without a change in OC levels with high-intensity walking programs;[12] Milliken et al found a trend towards increment in OC with exercise;[13] and Etherington et al determined reductions in OC and ALP with weight-bearing exercise.[14] CTx levels were found to be related to increased osteoporosis and accepted as determinants of future fracture risks.[15,16] The recent discovery of the osteoprotegerin (OPG)-TNF-α-receptor antagonist ligand (RANKL) system provides further insight into the regulation of the equilibrium between osteablasts and osteoclasts.[17-21] Receptor activator of nuclear factor kappa β (RANK) induces the differentiation of osteoclasts, enhances the activity of mature osteoclasts, and inhibits osteoclast apoptosis by binding to its functional receptor, RANK, which is expressed on osteoclasts or their progenitors. OPG acts as a decoy receptor for RANK and blocks the interaction between RANKL and RANK, and thus inhibits the osteoclastogenic action of RANKL. Several studies have been designed to assess the importance of OPG to the skeleton in human populations. However, the results of these epidemiology studies have been conflicting. In one study, women having osteoporosis were shown to have higher circulating levels of OPG than controls;[22] in another study, no difference was detected.[23] When OPG is administered as a therapeutic agent, it results in reduction in the bone turnover state, but not enough is known about its long-term effect on the bone density.[24] The relative expression of OPG and RANKL is a critical factor in the regulation of osteoclast activity and in the perpetuation of the remodeling cycle in the bone. Thus, to determine the net effect of this OPG-RANKL system on bone, the sRANKL/OPG ratio should be evaluated. However, the existing studies are generally on OPG, and the study authors tried to determine the correlations between serum OPG levels and BMD as well as bone turnover markers.[22,25-28] Kim et al reported that the decrease in the sRANKL/OPG ratio observed after estrogen placement therapy (EPT) was not related to changes in bone mass and bone turnover markers.[29] Similarly, Liu et al demonstrated no association between BMD and serum sRANKL or sRANKL/OPG ratios, but they found an inverse correlation between serum OC and serum sRANKL and sRANKL/OPG ratios.[30]

The latest scientific advances have enabled us to detect circulating OPG and RANKL in peripheral blood; however, it is still not certain whether circulating OPG and RANKL reflect changes in bone metabolism as a result of physical activity since there are very few studies with conflicting results indicating the correlation between the physical activity and the OPG/sRANKL system,[16,31] however there are no studies examining the effects of resistance training for 12 weeks on OPG/sRANKL system, with the other bone turnover markers and BMD of some certain sites in postmenopausal women. Therefore, the aim of the present study was to illuminate the changes in sRANKL and OPG-serum levels, as well as the other bone turnover markers and BMD of some certain sites in postmenopausal women following a 12-week high- versus low-intensity resistance training.

MATERIAL AND METHODS

SUBJECT SELECTION

Forty postmenopausal women between the ages of 45 and 60 years, not having menses for at least one year, participated in this study. The women who were recruited through mass mailings of recruitment flyers were not randomized. To maintain compliance, subjects were allowed to choose either exercise or control groups to join. Exercise groups were assigned as the high-intensity group [HIG; n= 14; age (median (25%-75% percentiles)= 49.00 (46.75-52.25 years)] and the low-intensity group [LIG; n= 13; age (median (25%-75% percentiles)= 49.00 (49.00-52.50 years)]. The control group (CG) consisted of 13 women who did not follow any exercise regimen [age (median (25%-75% percentiles)= 50.00 (48.50-52.50 years)]. Baseline physical characteristics [median (25%-75% percentiles)] of the exercise and control groups are given in Table 1. Baseline variables did not differ statistically among the three groups.

All information about the subjects was collected via questionnaires. The subjects were examined thoroughly before the initiation of the study. Subjects were excluded if they had diabetes mellitus, hyperthyroidism, pituitary disease, chronic liver disease or chronic renal disease; had a history of a musculoskeletal condition such as muscular dystrophy or rheumatoid arthritis, a history of bone fractures, or conditions that contraindicated exercise training; were taking pills known to affect bone mineral metabolism such as bisphosphonate, calcitonin, diuretics, vitamin D, or calcium supplements. Participants were expected not to have been engaged in any resistance training program during the past 12 months. None of the participants were osteoporotic considering World Health Organization criteria.[32] Because of these strict conditions, only a limited number of participants were enrolled in the study. After being informed of the purpose and the risks associated with the study, consent was given by all subjects. If a potential participant met the above-mentioned criteria, they were scheduled for a laboratory screening. In the laboratory, the electrocardiography and body compositions of the participants were measured and their blood pressures were taken.

Before starting the program, all participants were required to fill out the section related to the eating habits of "The Health-Profile Lifestyle Profile," developed by Wakler et al. [33] It was statistically analyzed and no significant differences among the groups in terms of their eating habits were found. They were told not to change their dietary habits throughout the study period. However, in order to equalize their calcium intake, a calcium intake of 1350 mg per day was assigned to all par-

TABLE 1: Baseline physical characteristics of the subjects.

Variable	HIG (n= 14)	LIG (n= 13)	CG (n= 13)	P
Age (year)	49.00 (46.75-52.25)	49.00 (49.00-52.50)	50.00 (48.50-52.50)	NS
Height (cm)	160.50 (155.00-166.75)	164.00 (159.50-167.00)	160.00 (158.50-164.00)	NS
Weight (kg)	77.35 (67.00-87.65)	78.40 (69.75-84.80)	81.20 (71.25-85.55)	NS
BMI (kg/m^2)	29.95 (25.97-32.67)	28.30 (26.45-30.50)	31.40 (29.15-33.35)	NS
Body fat (%)	39.76 (33.86-43.91)	39.10 (34.30-42.05)	42.85 (38.49-45.60)	NS
Lean body weight (kg)	45.70 (42.92-49.42)	48.00 (44.15-49.30)	45.60 (42.95-48.50)	NS

HIG= High intensity group; LIG= Low intensity group; CG= Control group; BMI= Body Mass Index; Group comparisons were made using Kruskall-Wallis test; NS= No significant.

ticipants. Celal Bayar University Ethical Council of the Faculty of Medicine approved this study. This study was conducted in accordance with the principles of Helsinki Declaration.

EXPERIMENTAL DESIGN

Before the experiment, all subjects were familiarized with the laboratory environment and the experimental procedures. The one repetition maximum (1-RM) was assessed at baseline, at the end of the sixth week to adjust the exercise intensity for strength gains throughout the training program, and at the end of the training program to measure the strength outcomes due to the training program. Exercise groups performed resistance training for 12 weeks, four days per week. Control group members maintained their daily routine throughout the study period, but they did not perform any type of exercise. Subjects had no alcohol or caffeine for 24 hours before the tests, which were performed at least three hours after a meal. In addition, the subjects were not tested within 48 hours of the previous training session. All testing and training took place at the same time of the day to control the circadian variation in performance. Subjects showed 90% compliance with exercise training. Bone mineral metabolism and body composition were assessed at baseline and at week 12 of the study.

RESISTANCE TRAINING PROTOCOL

Appropriate periodization is essential to supply appropriate muscular development and to prevent injuries, thus, there should be resistance (amount of weight used) variations and the loads should gradually be increased. Subjects performed each of the following exercises: Chest press, lat-pull-down, shoulder press, triceps press down, leg extension-right/left, leg curl, calf raise, abduction, adduction, and squat. They performed two sets of these exercises throughout the program. Calf raise was replaced by squat exercise in the second six weeks. Rest between sets was 1.5-2 minutes for low intensity group (LIG); 3 minutes for high intensity group (HIG). For the first six weeks, each set consisted of 10 repetitions for the HIG and 17 repetitions for the LIG. For the second six weeks, HIG performed eight repetitions; LIG performed 13 repetitions. Each session lasted approximately 50 minutes. Training logs were kept for each session to monitor the progress of each participant and to adjust the resistance loads. To examine the effects of training intensity on the outcome variables and criterion measures, the LIG trained at 40% for the first six weeks and at 50% of their 1RM for the second six weeks, whereas the HIG used loads corresponding to 70% for the first six weeks and 80% of their 1RM for the second six weeks. This regimen was chosen because 80% of 1RM for eight repetitions is commonly used in studies performed in older adults and corresponds to the lower repetition limit of the American College of Sports Medicine (ACSM) recommendations.[34] The intensity of 50% of 1RM for 13 repetitions was chosen for two reasons: one, because it represents the upper repetition limit of the ACSM recommendations, and two, it approximates the training volume of the regimen of 80% of 1RM for eight repetitions. This allowed the groups to perform at different training intensities (defined by percentage of 1RM) while completing comparable volumes of work. Exercise specialists monitored the participants in pairs. Each subject received appropriate instruction concerning warm-up and cool-down techniques as well as how to monitor the intensity of the exercise.

BONE MINERAL TURN-OVER MARKERS AND BMD MEASUREMENTS

Venous blood samples were collected from an antecubital vein (20 mL) from each subject in the sitting position after a 20-minute rest at baseline and at the end of week 12, between 8.00-9.00 a.m. Serum was separated by centrifugation, and samples were stored at -80C° until assays were determined (within one month) in all samples.

Serum OC and β- CrossLaps were assessed by an electrochemiluminescence immunoassay on Roche E170 immunoassay analyzer (Roche Diagnostics GmbH., Mannheim, Germany). The inter-assay and intra-assay coefficient of variation (CV) for OC at level 4.0 ng/ml were 7.0% and 4.8% respectively. Intra-assay CV for β- CrossLaps at level 390 pg/ml was 1.8%. Serum bone alkaline phosphatase (BAP) levels were measured using ELISA met-

hod (QUIDEL Corporation, San Diago, USA). The intra-assay and inter-assay CV at level 35 U/L were 3.9% and 7.6%, respectively. The lower limit of detection for bone alkaline phosphatase was 0.7 U/L.

Serum concentrations of OPG were measured using ELISA method (BioVendor Research and Diagnostic Products, Modrice, Czech Republic). The intra-assay CV at level 5.41 pmol/L and inter-assay CV at level 5.59 pmol/L for OPG assay were 2.4% and 4.2%, respectively. The lower limit of detection for OPG was 0.4 pmol/L. Serum concentrations of sRANKL were measured using ELISA method (BioVendor Research and Diagnostic Products, Modrice, Czech Republic). The intra-assay CV at level 96 pmol/L and inter-assay CV at level 88 pmol/L for sRANKL assay were 7.9% and 8.3%, respectively. The lower limit of detection for sRANKL was 10 pmol/L.

Body composition was measured using bioelectrical impedance analyzer (Model TBF-300, Tanita Corp., Tokyo, Japan). Body fat was expressed as percentage of body weight. Total and regional BMD were assessed non-invasively using dual-energy x-ray absorptiometry (model DPX-L, Lunar Radiation Corp., Madison, WI).

STATISTICAL ANALYSES

Since a one-sample Kolomogorov-Smirnov test indicated that the variables were not normally distributed, nonparametric tests were used and the descriptive statistics were given as median (25%-75% percentiles) values. Kruskall-Wallis test was used to compare percentage changes among the study groups. The Post-hoc Dunn's test was used to determine the difference between the two groups. The differences between pre-training and post-training values were determined by using Wilcoxon Signed Ranks test. Bivariate Spearman Correlation coefficient was applied between the percent changes in OPG-RANKL system and BMD; between OPG-RANKL and bone turnover markers; between bone turnover markers and BMD; and between the percent changes in strength measures and OPG-RANKL, BMD, and bone turnover markers. All comparisons were considered statistically significant at $p< 0.05$.

RESULTS

No significant differences were observed in any of the physical characteristics in exercise groups after 12-week resistance training (Table 2).

We detected a significant increase in OC in HIG ($p< 0.05$) and significant reductions in sRANKL in HIG ($p< 0.05$), LIG, and CG ($p< 0.001$). The changes determined in sRANKL/OPG ratio were significantly different in LIG and CG ($p< 0.01$); however, there was not a significant difference in this ratio in the HIG. No other changes in the other measured parameters were detected for any group (Table 3).

TABLE 2: Changes in physical characteristics for the HIG, LIG and CG following 12 weeks of resistance training period.

	HIG (n= 14)			LIG (n= 13)			CG (n= 13)		
Variable	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
Weight (kg)	77.35 (67.00-87.65)	79.30 (67.47-89.15)	NS	78.40 (69.75-84.80)	80.30 (68.30-83.55)	NS	81.20 (71.25-85.55)	81.10 (72.00-86.05)	NS
Body fat (kg)	31.65 (22.32-38.95)	31.50 (23.87-41.12)	NS	28.70 (24.20-35.40)	31.60 (24.85-34.70)	NS	35.40 (29.75-39.50)	35.20 (30.05-40.05)	NS
Lean body weight (kg)	45.70 (42.92-49.42)	47.55 (42.85-50.45)	NS	48.00 (44.15-49.30)	47.00 (42.75-49.40)	NS	45.60 (42.95-48.50)	44.50 (42.35-47.50)	NS
Percent body fat (%)	39.76 (33.86-43.91)	40.85 (36.15-45.17)	NS	39.10 (34.30-42.05)	37.40 (35.40-42.35)	NS	42.85 (38.49-45.60)	44.00 (41.39-45.69)	NS
BMI ($kg.m^{-2}$)	29.95 (25.97-32.67)	29.50 (26.77-32.42)	NS	28.30 (26.45-30.50)	28.20 (26.45-31.00)	NS	31.40 (29.15-33.35)	31.80 (29.85-33.95)	NS

HIG= High intensity group; LIG= Low intensity group; CG= Control group; BMI= Body Mass Index; Within-group comparisons were made using Wilcoxon Signed Ranks test; NS= No significant; Kruskall-Wallis test revealed no significant differences in the percent changes of the variables among three groups.

TABLE 3: Changes in bone turn-over markers for the HIG, LIG, and CG following 12 weeks of resistance training period.

	HIG (n= 14)			LIG (n= 13)			CG (n= 13)		
Variable	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
OC (ng/ml)	4.01 (2.65-5.12)	4.54 (3.57-7.08)	<.05	5.83 (3.55-6.91)	5.76 (5.06-8.58)	NS	5.95 (4.59-7.10)	5.81 (3.89-7.75)	NS
BAP (U/l)	26.06 (20.31-29.21)	25.41 (21.65-29.76)	NS	27.08 (21.48-33.24)	28.38 (21.11-36.11)	NS	29.63 (22.67-40.35)	28.62 (21.00-38.54)	NS
CTx (pg/ml)	352.40 (244.72-423.07)	325.70 (244.05-473.77)	NS	489.30 (411.50-567.35)	449.40 (366.45-531.90)	NS	461.80 (370.40-605.15)	400.00 (308.40-537.60)	NS
OPG (pmol/l)	6.31 (5.31-7.37)	6.90 (5.58-7.43)	NS	6.27 (5.01-8.21)	6.45 (5.36-7.76)	NS	5.31 (4.48-7.12)	5.31 (4.41-7.22)	NS
sRANKL (pmol/l)	403.50 (224.75-467.75)	303.50 (205.25-444.00)	<.05	311.00 (203.00-570.50)	251.00 (145.50-424.00)	<.01	384.00 (291.00-489.50)	285.00 (239.00-396.00)	<.01
sRANKL/OPG	0.06 (0.03-0.08)	0.04 (0.03-0.06)	<.05	0.05 (0.03-0.10)	0.04 (0.02-0.07)	<.05	0.08 (0.05-0.11)	0.05 (0.04-0.09)	<.05

HIG= High intensity group; LIG= Low intensity group; CG= Control group; Within-group comparisons were made using Wilcoxon Signed Rank test; NS= No significant; Kruskall-Wallis test revealed no significant differences in the percent changes of the variables among three groups.

BMD data are presented in Table 4. Twelve-week of resistance training resulted in significant increases at the spine region in exercise groups ($p< 0.05$). In addition, the percent change observed at the spine region in the HIG was significantly different from the one observed in CG ($p< 0.01$). We found no other significant BMD changes in any of the sites measured in any of the groups (Table 4).

As Table 5 indicates, 12-week resistance training resulted in favorable strength gains in exercise groups because significant increases were determined in all strength measures ($p< 0.001$). In addition, the percent changes determined in the HIG in seated row and adduction ($p< 0.05$); leg extension, calf rise, squat, and total strength ($p< 0.01$) were different from those of the LIG. The percent changes found in the HIG in all strength measures were significantly different from those of the CG ($p< 0.001$; Table 6). The percent changes observed in the LIG in chest press, shoulder press, triceps

TABLE 4: Changes in BMD for the HIG, LIG, and CG following 12 weeks of resistance training period.

	HIG (n= 14)			LIG (n= 13)			CG (n= 13)		
Region BMD ($g.cm^{-2}$)	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
Arm	0.81 (0.78-0.85)	0.81 (0.78-0.83)	NS	0.81 (0.75-0.85)	0.81 (0.75-0.84)	NS	0.79 (0.76-0.87)	0.81 (0.75-0.86)	NS
Spine	1.09 (1.02-1.20)	1.14 (1.04-1.23)	<.05	1.12 (1.06-1.20)	1.19 (1.04-1.24)	<.05	1.16 (1.04-1.20)	1.13 (1.01-1.23)	NS
Femoral Neck	0.97 (0.89-1.10)	0.95 (0.89-1.08)	NS	0.94 (0.83-1.03)	0.94 (0.82-1.00)	NS	0.91 (0.85-1.00)	0.89 (0.85-1.01)	NS
Ward's triangle	0.76 (0.71-0.92)	0.79 (0.70-0.89)	NS	0.80 (0.69-0.87)	0.77 (0.70-0.88)	NS	0.73 (0.69-0.85)	0.74 (0.70-0.88)	NS
Trochanter	0.79 (0.69-0.90)	0.79 (0.69-0.91)	NS	0.73 (0.68-0.85)	0.75 (0.66-0.84)	NS	0.76 (0.69-0.82)	0.76 (0.70-0.82)	NS
Total hip	1.02 (0.89-1.13)	1.02 (0.91-1.14)	NS	0.95 (0.87-1.04)	0.95 (0.87-1.04)	NS	0.97 (0.93-1.02)	0.97 (0.94-1.03)	NS

HIG= High intensity group; LIG= Low intensity group; CG= Control group; Within-group comparisons were made using Wilcoxon Signed Ranks test; Kruskall-Wallis and Dunn's tests revealed a significant difference between the percent change in HIG [6.59(-8.3-12.9)] versus the percent change in CG [-0.19(-6.5-9.2)] in the spine values ($p< .01$); NS= No significant.

TABLE 5: Changes in the strength for the HIG, LIG, and CG following 12 weeks of resistance training period.

	HIG (n= 14)			LIG (n= 13)			CG (n= 13)		
Variable (kg)	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
Chest press	26.25 (25.00-33.00)	39.55 (33.55-47.63)	<.001	27.50 (25.00-31.50)	38.00 (34.50-40.99)	<.001	27.50 (25.00-33.00)	28.00 (24.50-35.00)	NS
Seated row	43.50 (38.75-51.25)	59.00 (53.20-67.62)	<.001	46.00 (45.00-50.00)	55.10 (51.10-59.00)	<.001	45.00 (39.00-53.00)	45.00 (38.75-52.50)	NS
Shoulder press	20.00 (17.00-25.00)	30.87 (25.94-35.40)	<.001	24.00 (17.75-25.00)	28.50 (27.35-30.75)	<.001	22.00 (17.75-25.00)	21.00 (18.25-26.00)	NS
Triceps press down	17.00 (17.00-17.62)	23.75 (21.19-25.93)	<.001	17.50 (16.60-18.88)	21.50 (21.00-25.00)	<.001	17.00 (17.00-17.75)	18.00 (15.00-19.50)	NS
Leg extension	42.00 (34.50-42.00)	57.50 (48.00-64.38)	<.001	42.50 (36.25-48.75)	51.20 (46.00-58.75)	<.001	42.00 (34.00-42.00)	40.00 (32.50-43.00)	NS
Leg curl	27.50 (25.00-31.38)	36.00 (32.88-43.88)	<.001	30.00 (27.75-31.25)	35.00 (33.00-38.00)	<.001	27.50 (25.00-31.75)	28.00 (25.50-30.50)	NS
Calf rise (first 6 wk)	64.00 (57.25-69.00)	107.50 (101.20-132.25)	<.001	70.00 (66.00-87.50)	95.00 (88.45-119.00)	<.001	65.00 (60.50-76.50)	65.00 (60.50-76.00)	NS
Abduction	36.50 (34.38-40.00)	55.00 (47.88-60.63)	<.001	38.00 (35.00-45.00)	50.00 (45.00-57.50)	<.001	38.00 (35.00-40.00)	37.00 (35.00-42.50)	NS
Adduction	45.00 (40.00-50.00)	63.00 (55.00-68.00)	<.001	45.00 (43.25-53.75)	57.50 (48.25-60.00)	<.001	45.00 (40.00-50.00)	47.00 (41.00-51.50)	NS
Squat (second 6 wk)	70.00 (65.00-82.25)	101.50 (88.00-123.25)	<.001	75.00 (74.50-76.50)	88.00 (80.00-95.00)	<.001	70.00 (65.00-84.50)	72.00 (66.50-85.50)	NS
Total strength	415.00 (350.00-460.00)	600.00 (517.50-660.00)	<.001	440.00 (389.00-450.00)	530.00 (500.00-545.00)	<.001	420.00 (370.00-450.00)	420.00 (375.00-445.00)	NS

HIG= High intensity group; LIG= Low intensity group; CG= Control group; within-group comparisons were made using Wilcoxon Signed Ranks test; NS= No significant.

press down, leg curl and abduction ($p< 0.001$); seated row, leg extension, calf rise, adduction, squat, and total strength ($p< 0.01$) were significantly different from those of the CG.

Bivariate Spearman Correlation coefficient analysis did not reveal any significant correlations among parameters mentioned before (data are not shown).

DISCUSSION

The results of this study indicate that high-intensity resistance training may be able to offset the age-related decline in bone mass and muscle strength in postmenopausal women. Perhaps, the most important finding is the improvement in spine BMD. HIG demonstrated an increase of approximately 5.5% BMD at the spine after 12 weeks of high-intensity resistance training, which was significantly greater than those of LIG and CG. The other important finding is the improvement in OC, a bone formation marker, in HIG. The reduction observed in all groups in sRANKL is also significant. Muscle strength, an important factor to maximize balance and minimize the falls that may result in bone fractures, has been significantly improved in exercising women in all measured sites.

BMD AND MUSCLE STRENGTH

Wolff's law states that stress or mechanical loading applied to the bone via the muscle and tendons has a direct effect on bone formation and remodeling.[35] According to Karlsson et al, this effect is site-specific, based on the higher total body BMD and higher BMD in all sites measured.[36] The studies of other researchers also support the theory that the effects of resistance training on bone are site-specific.[36-38] It has been shown that athletes engaging in impact sports like volleyball and gymnastics have a greater BMD at a majority of skeletal sites[39] when compared with athletes performing nonweight bearing

TABLE 4: Changes in BMD for the HIG, LIG, and CG following 12 weeks of resistance training period.

Variable (kg)	HIG (n= 14)	LIG (n= 13)	CG (n= 13)	P
Chest press %Δ	36.75 (30.00-47.19)[d]	33.23 (20.71-45.80)[d]	2.22 (-3.03-6.06)	<.001
Seated row %Δ	32.64 (19.09-46.00)[a,d]	17.14 (10.66-25.00)[c]	0.00 (-1.58-1.13)	<.001
Shoulder press %Δ	36.18 (29.78-60.86)[d]	26.32 (13.41-47.82)[d]	0.00 (0.00-6.11)	<.001
Triceps press down %Δ	30.46 (21.08-48.49)[d]	23.46 (20.28-41.43)[d]	2.86 (-8.68-7.94)	<.001
Leg extension %Δ	51.25 (36.67-66.67)[b,d]	20.00 (13.71-22.61)[c]	-3.16 (-5.71-2.38)	<.001
Leg curl %Δ	22.94 (19.84-42.61)[d]	17.86 (16.67-25.83)[d]	0.00 (-2.72-2.92)	<.001
Calf rise (first 6 wk) %Δ	65.57 (56.11-96.28)[b,d]	32.97 (20.81-48.46)[c]	0.00 (-2.74-2.87)	<.001
Abduction %Δ	48.86 (36.56-65.77)[d]	35.56 (20.32-44.29)[d]	2.50 (0.00-5.71)	<.001
Adduction %Δ	41.42 (23.28-53.66)[a,d]	19.05 (6.55-31.54)[c]	2.00 (0.00-4.22)	<.001
Squat (second 6 wk) %Δ	42.26 (35.63-53.46)[b,d]	17.33 (6.67-22.92)[c]	1.12 (0.00-2.20)	<.001
Total strength %Δ	47.00 (42.39-52.17)[b,d]	24.71 (18.87-29.68)[c]	0.00 (0.00-2.40)	<.001

HIG= High intensity group; LIG= Low intensity group; CG= Control group; Group comparisons were made using Kruskall-Wallis and Dunn's tests; NS= No significant; [a]p< 0.05 vs. LIG ; [b]p< 0.01 vs LIG.; [c] p< 0.01 vs CG; [d] p< 0.001 vs CG.

activities such as swimming.[40] A study by Nelson et al revealed that women in a two day per week resistance training program gained an average of 1% in BMD of the femoral neck and lumbar spine, whereas the control group lost 2.5% and 1.8% at these sites, respectively.[1] They also showed that the resistance trained women had a 35-70% increase in strength, a 14% improvement in dynamic balance, and a 1.2-kg increase in total body muscle mass, but the control group showed declines in all these parameters. In another study, Vincent and Braith determined significant increases in femoral neck BMD in high-intensity resistance training group of elderly people.[41] Pruitt et al examined the effects of 12 months of high- versus low-intensity resistance exercises on lumbar spine, femoral neck, and ward's triangle BMD of elderly women.[4] They found significant increases in strength measures, but not in BMD.[4] Similarly, Nichols et al found no significant changes in BMD as a result of high-intensity resistance training.[42] Wallace and Cummings indicated in their review article that randomized trials clearly show that exercise slows the rate of bone loss at the spine in postmenopausal women.[43] Randomized studies also provide strong evidence that exercise programs have a positive effect on bone mass at the lumbar spine in premenopausal women. Their review revealed that the results for the femoral neck are less clear cut. They found out that the results are less robust than those for the lumbar spine and the existing ones have inconsistency. Another meta-analysis by Bérard et al also indicated that exercise was effective at the lumbar spine, but not at the femoral neck or forearm.[44] Our findings support the benefits of resistance training on the spine BMD. Our results favor high-intensity resistance training due to the 1.76% greater increase determined in HIG than LIG. The greater increases in the spine BMD of exercise groups can be attributable to the squat, seated row, and partly rever-

se sit-up exercises. To keep the inclination of the trunk segment constant, a force necessitating backward rotation of the trunk segment should be applied. This force must be supplied by muscle contraction of the erector spinal muscle group and abdominal muscles, and the contraction may cause a larger compressive stress in the trunk region during squat exercises. In addition, of the exercises performed, seated row may have created a similar effect as in squat since a great contraction of muscles are necessary to keep the trunk segment stable during the performance of the exercises. When the muscles in that area are mechanically loaded, a response occurs in the bones attached to the muscles contracted during these exercises. The combination of high magnitude compressive stress and site-specifity play a vital role in increasing the BMD.[12] Causing some improvements in the spine BMD is of great importance since this body part is more influenced by the osteoporosis due to menopause.

Some authors reported an increase of BMD in the trochanter region,[45,46] because the muscle pull is mediated through the force of the muscle contraction at the site of attachment of tendon to bone; thus, bone may respond locally to reallocate the forces generated from the muscle at the site loading.[47] They stated that the reason of not finding any increases in femoral neck BMD may be the same mechanism since no muscles are attached to that region. Tsuzuku et al found significant increases in the BMD of lumbar spine, pelvis, leg, and whole body of the power lifters.[48] Granhed et al also found that BMC of the lumbar vertebrae in power lifters was significantly higher than the controls.[49] These studies support the idea that large mechanical loading on bone is useful for increasing BMD, however the response of bone to mechanical load is site specific, and cannot be generalized throughout the skeleton. Our study could not find any increases in the BMD of the measured sites apart from the spine, which may have resulted from the exercise programs conducted by our participants. The duration of the training program (12 weeks) may not be long enough to obtain significant increases in the majority of the sites measured. Therefore, our findings are in accordance with Davey et al who also suggested the need of programs with longer duration to increase BMD.[50]

There is little evidence regarding what intensity is necessary to achieve significant improvements in muscular strength in older adults. One recent study examined the effects of high-intensity (80% of 1RM for seven repetitions) or low-intensity (40% of 1RM for 14 repetitions) resistance training on strength, thigh cross-sectional area, and BMD.[51] After training three days per week for 52 weeks at one of the two intensities, the women showed a mean increase in strength of 59% and 41% for the high and the low groups, respectively. Similarly, the results of this study indicate that both training regimens used were effective in increasing muscular strength. Our data are in accordance with Brown et al., Frontera et al, and Hagberg et al, who all reported increased strength after resistance training in older adults.[52-54] Therefore, the results of our study are important since they indicate that resistance training in postmenopausal women, whether conducted via 40-50% or 70-80% 1RM, can decrease the risk of osteoporosis by simultaneously influencing multiple risk factors for osteoporotic fractures.

BONE TURNOVER MARKERS

Biochemical markers of bone metabolism have recently been used, particularly in clinical studies, to evaluate bone metabolism in skeletal diseases.[7,8] OC and ALP are the markers for bone formation and osteoblastic activity.[55] However, attempts to evaluate the effect of exercise on skeleton using these markers have revealed conflicting results. Etherington et al found significant decreases in OC and ALP with 10-week weight-bearing exercise.[14] Brooke-Wavell et al found no significant changes in OC as a result of 12-month brisk walking in post-menopausal women.[56] Similarly, Rudberg et al found no obvious exercise-induced changes of OC as a result of neither cycle ergometer until exhaustion nor 30-40 minute jogging.[57] On the other hand, Milliken et al found that exercisers, who performed both weight-bea-

ring aerobic training and resistance training, showed a trend toward larger positive changes in both bone formation and resorption over 12 months vs controls.[13] In our study, the significant increase in OC in HIG can be accepted as a sign of positive effects of high-intensity resistance training on bone formation. Our finding is in parallel with other studies that found increases in OC levels as a result of strength training.[13,41,58,59] Vincent et al, Fujimura et al, and Menkes et al found increases in ALP activities of the athletes.[41,58,59] However, we could not observe any changes in BAP activities in any of our groups.

CTx, one of the most specific markers of bone resorption, has not been measured in many studies. The EPIDOS study has shown the relevance of elevated CTx levels in predicting severe clinical events, such as hip fractures.[15] Hermann and Hermann hypothesized that elevated CTx concentrations could be used to identify athletes at risk of osteoporosis and future fractures.[16] Despite being not significant, a 4% and 8% decreases determined in HIG and LIG, respectively, in this present study might be the positive effect of resistance training when compared to the 2% increase in CG.

OPG-RANKL

The OPG-RANKL system has recently been considered to play an important role in bone remodeling. Several studies has tried to reveal its relationship between bone turnover markers and BMD. Previous research have indicated that BMD is positively[60] or negatively[22] related or not related[25-27,30,61] to serum OPG levels. Patients with low BMD at some certain sites have demonstrated higher OPG[62] and sRANKL levels;[63-65] or negative correlations between serum OPG and RANKL levels with BMD.[66] These negative correlations enabled the researchers to propose a hypothesis that sRANKL is in inverse relationship with BMD, reflecting the extent of osteoclastogenesis and OPG might be increased as the compensatory mechanism against the activity of RANKL, to reduce bone resorption.

In recent years, researchers have given considerable attention to the effect of physical activity on OPG and sRANKL levels. Herrmann and Herrmann found out no change in OPG and sRANKL levels of athletes (cross-country skiers and biathlon athletes) and controls.[16] There were no significant changes in sRANKL in postmenopausal women who underwent six weeks of energy restriction and aerobic exercise (walking or jogging at 60% VO_{2max}).[31] The exercise-bound changes in our study are controversial with the aforementioned research results since we detected significant reductions in sRANKL, but no significant changes in OPG levels in our exercise groups. RANKL is an essential factor for osteoclasts' activities;[17] therefore, the significant reduction observed in sRANKL levels in HIG and LIG may be explained with the positive effects of resistance training on bone formation. Therefore, considering the high levels of sRANKL being related to some diseases,[63-65] doing exercises effective in reducing sRANKL levels may be protective against these diseases, and indirectly against bone loss or osteoporosis. However, the reduction observed in our CG is somewhat difficult to explain.

To determine the net effect of OPG-RANKL system on bone, evaluating the sRANKL/OPG ratio is vitally important. There are controversial results related to the effect of this ratio on BMD. Hofbauer et al demonstrated lower sRANKL/OPG ratios in women taking oral contraceptives.[61] Kim et al found no relationship between the reduction in the sRANKL/OPG ratio and bone mass and bone turnover markers.[29] However, Liu et al found an inverse correlation between serum OC and serum sRANKL and sRANKL/OPG ratios.[30] In this present study, despite a significant reduction in the percentage of sRANKL/OPG ratios in LIG and CG, we found that neither BMD at any skeletal site measured nor bone turn-over markers correlated with sRANKL/OPG ratio. Since we observed a significant reduction in sRANKL in all groups and significant reductions in sRANKL/OPG ratios in LIG and CG without any significant change in HIG, we can infer that this reduction might not have been affected by the resistance training protocol. The cause of this reduction lies unanswered. Further studies with larger study cohorts are necessitated to find a clear answer to that question.

CONCLUSION

This study reveals that a 12-week high-intensity resistance training program is more useful than a low-intensity program since it resulted in more favorable improvements in the spine BMD and OC together with higher strength gains. Therefore, such a program is advisable to postmenopausal women due to these aforementioned benefits. A 12-week resistance training of high or low intensity is unlikely to have effects on OPG. Because of no significant change in OPG levels and significant reductions in sRANKL levels in all groups, measures of circulating OPG and sRANKL levels do not seem to be clinically useful for predicting BMD or bone turnover status following resistance training programs. Therefore, it would be beneficial to assess the levels of OPG and RANKL directly in the bone microenvironments together with the BMD measures, bone turnover markers, and circulating OPG-sRANKL levels in postmenopausal women following different intensity resistance training programs.

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