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ORIGINAL ARTICLE

Effects of Exercise on Low Density Lipoprotein Receptor Related Protein 5 Gene Expression in Patients With Postmenopausal Osteoporosis

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ABSTRACT

Objectives: This study aims to investigate the effects of aerobic exercise on low density lipoprotein receptor related protein 5 (LRP5) gene messenger ribonucleic acid expression and evaluate the relationship between the clinical parameters and gene expression in patients with postmenopausal osteoporosis (OP).

Patients and methods: Seven patients with postmenopausal OP (mean age 60.0±5.3 years; range 51 to 66 years) were included in the study. An exercise protocol/program consisting of treadmill exercising for 30 minutes three days a week for six weeks was performed at a moderate intensity. LRP5 gene expression levels were evaluated before the onset of the exercise program and then four hours after the end of the first session and 12th (fourth week) and 18th (sixth week) sessions of exercise.

Results: Our results demonstrated variable changes in the LRP5 gene expression after the aerobic exercise sessions. Excluding one patient, the LRP5 gene expression levels showed a slight tendency to increase. In spite of this tendency, gene expression differences during the exercise sessions were not significant.

Conclusion: Our results suggest that interindividual variations of LRP5 gene expression exist after moderate intensity aerobic exercises in patients with postmenopausal OP. Despite of this variability, LRP5 gene expression levels increased slightly, except in peripheral blood in one patient. Future studies with larger sample sizes and different sampling time/tissues are required to shed more light on the impact of exercise at molecular level in OP.

Keywords: Exercise; lipoprotein receptor related protein 5; messenger ribonucleic acid expression; osteoporosis.

Osteoporosis (OP) is a common metabolic bone disease which is characterized by decreased bone mass and deterioration in the microarchitecture of the bone tissue, leading to an increased fracture risk. The etiology of OP includes both genetic and environmental factors. Genetic factors have an important role in the regulation of the bone mineral density (BMD) and contribute to 80% of the variation in BMD among individuals.[1,2] Many determinants of the osteoporotic fracture risk are heritable, such as body mass index, hip axis length, femoral neck geometry, biochemical markers of bone turnover, muscle strength, peak bone mass, menarche, and menopause status.[3-11]

Environmental factors, under the influence of the genetic variations, play a significant role in the pathogenesis of OP; yet the contribution of this interaction remains poorly understood. Among the environmental factors, physical exercise is a well-known determinant in attaining and keeping the peak bone mass. Exercise has generally been considered to have a positive effect on the bones and thus to be useful in the treatment of OP. Likewise, physical activity as a way of preventing

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OP is based on the evidence that it helps bone maintenance and stimulation of bone formation including mineralization; strengthens muscles, improves balance and postural control. Exercise also increases fitness and quality of life, decreases pain intensity, fracture risk, and prevents age-related decline in the levels of vitamin D.[12-15]

Several studies suggested that genetic variations may modify the effects of intensive physical training on the musculoskeletal system.[16-18] Among these genetic variations, lipoprotein receptor related protein 5 (LRP5) variants have been found to influence the effects of physical activity on spine bone density in males and Wnt signaling *in vitro*.[16]

The Wnt signaling pathway including LRP5 and Wnt proteins regulate osteoblastic activity and bones mass.[19] This pathway promotes proliferation and mineralization in osteoblasts and inhibits osteoclastogenesis by increasing the osteoprotegerin/receptor activator of receptor activator of NFκB ligand (RANKL) ratio.

The LRP5 gene harbors naturally occurring coding polymorphisms which have been proposed to contribute to the normal population variance in bone metabolism.[20-22] Also, mutations in the LRP5 gene have been shown to result in various single gene disorders with either a high or low BMD phenotype.[20,23] Polymorphisms and mutations in the LRP5 gene have been studied in several populations and countries.[16,20,24,25] Some of those studies have showed a modulatory effect of different LRP5 alleles on the Wnt signaling as well as on the association between BMD and physical activity. However, to the best of our knowledge, the effects of exercise on LRP5 gene expression have not been reported in the literature. Therefore, in this study, we aimed to investigate the effects of aerobic exercise on LRP5 gene messenger ribonucleic acid expression and evaluate the relationship between the clinical parameters and gene expression in patients with postmenopausal OP.

PATIENTS AND METHODS

A total of seven untrained patients with postmenopausal OP (mean age 60.0±5.3 years; range 51 to 66 years) were included from outpatient clinic of department of physical medicine and rehabilitation, Hacettepe University. Patients who had cardiac, neurological or orthopedic disorders which may cause difficulty in walking or those using any medication known to affect the bone metabolism were excluded. Demographic characteristics of the patients and their risk factors for OP including body mass index, alcohol and cigarette usage, daily activity level and exercise habits, immobilization and fracture history, family history of bone disease, style of clothing, daily length of stay in the sun light, calcium intake, medications, and concomitant diseases were also recorded. The study protocol was approved by the local Ethics Committee of Hacettepe University and written informed consents were obtained from all subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Serum levels of calcium, phosphate, osteocalcin, bone specific alkaline phosphatase, carboxyterminal telopeptide of type I collagen, parathyroid hormone, 25-hydroxy vitamin D_3 ($25(OH)D_3$), complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver/renal function tests, thyroid-stimulating hormone, and free T_4 were measured.

Radiographies of the pelvis, thoracic and lumbar spine were taken. Bone mineral content and BMD of the spine (L2-L4) and the hip were measured by dual energy X-ray absorptiometry using Hologic QDR 4500 densitometer (Hologic, Inc., Bedford, MA).

The exercise protocol consisted of treadmill training at a moderate intensity for 30 minutes three days a week for six weeks under direct supervision. Exercises started after a warm-up period and ended with stretching exercises lasting five to 10 minutes. Exercises were performed at a moderate intensity as followed by the target heart rate which has been determined according to the Karvonen method.[26]

Blood samples were collected into PAXgene Blood RNA Tube (QIAGEN GmbH, Hilden, Germany) for LRP5 gene expression evaluations. The first sample was taken after an eight-hour overnight fasting period. The follow-up samples were drawn four hours following the end of the first, 12th and 18th sessions of exercise. Twenty-four hours prior to the test sessions, subjects

consumed a standard diet and abstained from alcohol and caffeine consumption as well as strenuous exercise.

Total ribonucleic acid was isolated using PAXgene Blood RNA Kit (QIAGEN GmbH, Hilden, Germany) protocol and reagents.[27,28] Complementary deoxyribonucleic acid was synthesized using Quantitect Reverse Transcription Kit (QIAGEN GmbH, Hilden, Germany) as described by the manufacturer. After reverse transcription, the SYBR Green based quantitative real-time polymerase chain reaction was performed using the BioradiCycler IQ5 real-time Detection System (Applied Biosystems). LRP5 complementary deoxyribonucleic acids were run simultaneously and in triplicate. LRP5 gene expression was normalized to beta-actin and TATA-binding protein housekeeping genes. Fluorescent emission data were captured and messenger ribonucleic acid levels were quantified by comparative Ct method.[29]

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 16.0 software (SPSS Inc., Chicago, IL, USA). Friedman test was used for the analysis of gene expression level measurements. Pearson correlation analysis was used for the assessment of relationship between parameters. Data are expressed as median ± standard deviation. Statistical significance was set at $p<0.05$.

RESULTS

Patients 5 and 7 were smokers, but none of them were using alcohol. Laboratory test results are given in Table 1. Patients 5, 6 and 7 had 25(OH)D_3 levels below 20 µg/L while five patients' serum bone specific alkaline phosphatase levels were above the reference values (12.5-22.4 ug/L) for our center. Otherwise, all patients' test results were normal. BMD of the patients are given in Table 2.

Total ribonucleic acid concentration was determined spectrophotometrically at 143-149 ng/uL. Individual changes in LRP5 gene expression levels after the aerobic exercise sessions are shown in Figure 1. Excluding patient 4, LRP5 gene expressions showed a slight tendency to increase. However, this increase was not statistically significant. The differences between LRP5 gene expression levels in seven patients after each aerobic exercise session are given in Figure 2.

Table 1. Laboratory test results of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
White blood cell (/µL)	4900	5900	5400	3700	6200	3700	6000
Hemoglobin (g/dL)	13.6	13.6	13.9	12.8	12.4	13.4	13
Hematocrit (%)	39.7	41.2	41.5	36.9	36.8	39.4	38.9
Platelet (/µL)	324000	219000	256000	149000	303000	197000	222000
Erythrocyte sedimentation rate (mm/h)	10	5	11	11	38	13	11
C-reactive protein (mg/dL)	0.21	0.37	0.19	0.27	0.8	0.17	0.17
Blood urea nitrogen (mg/dL)	19.9	13	18	17	16	12	21
Creatinin (mg/dL)	0.74	0.8	0.58	0.8	0.7	0.91	0.86
Calsium (mg/dL)	9.27	9.2	9.4	8.9	8.8	9.5	8.9
Phosphate (mg/dL)	3.43	4.2	3.49	4.32	3.2	3.93	4.92
Albumin (g/dL)	4.58	4.4	4.61	3.9	4.3	4.27	4
Aspartate aminotransferase (U/L)	23	16	14	18	16	20	22
Alanine aminotransferase (U/L)	19	11	22	15	15	15	23
Alkaline phosphatase (U/L)	72	77	69	75	78	75	38
sT_3 (pmol/L)	3.92	4.74	4.62	6.2	4.9	4.44	6.03
sT_4 (pmol/L)	14.23	14.99	15.97	19.8	13.7	13.37	14.92
Thyroid-stimulating hormone (uIU/mL)	0.76	2.15	1.76	2.44	1.8	2.35	2.22
Parathyroid hormone (pg/mL)	41.4	36.2	30.6	18.1	106	50.1	101
25-hydroxy vitamin D3 (µg/L)	20.2	23.2	42.2	44.7	7.4	13.8	16.6
Osteocalsin (ng/mL)	30.12	25.55	29.86	19.31	15.7	29.02	14.37
Bone specific alkaline phosphatase (ug/L)	32	28.4	41.8	29.6	20.1	33.5	13.2
Carboxyterminal telopeptide of type I collagen (ng/mL)	0.55	0.24	0.68	0.56	0.39	0.45	0.15

Table 2. Bone mineral density results of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
T score							
L_{1-4}	-2.8	-2.4	-2.9	-2.5	-3.3	-2.3	-3.4
Femoral neck	-2.0	-2.2	-1.9	-1.9	-1.5	-1.1	-2.0
Total hip	-1.8	-2.8	-1.8	-1.2	-1	-0.4	-1.4
Bone mineral density (g/cm^2)							
L_{1-4}	0.89	0.9	0.84	0.89	0.78	0.91	0.78
Femoral neck	0.81	0.73	0.77	0.78	0.83	0.88	0.76
Total hip	0.85	0.66	0.78	0.86	0.89	0.96	0.83

DISCUSSION

To the best of our knowledge, this is the first study assessing the effects of exercise on LRP5 gene expression in patients with postmenopausal OP. Our results suggest that interindividual variations of LRP5 gene expression occur after moderate intensity aerobic exercises in this group of patients. Nonetheless, LRP5 gene expression levels showed a slight increase, except for one patient.

Low BMD comprises the major risk for fractures that cause significant morbidity and mortality in patients with OP. Longitudinal studies on families and twins suggest that variation in BMD is strongly influenced by genes;[1] however, the exact nature of the genes governing BMD variation remains poorly understood. To date, the effects of different genes (vitamin D, aromatase, sex hormone receptors etc.) and their variations have been widely studied.[5,30] Lately, the Wnt signaling pathway including the LRP5 and Wnt proteins has been discovered as an important pathway regulating the osteoblastic activity and thereby bone mass. Moreover, mutations in the LRP5 gene have been demonstrated to cause different single gene disorders resulting in either increased or decreased BMD.[20] Besides these mutations, coding polymorphisms in the LRP5 gene have been suggested to contribute to the normal population variance in bone metabolism. The association between various polymorphisms in LRP5 gene and peak bone mass has been investigated in different populations.[20,21,31] A significant association between physical activity and polymorphisms in the LRP5 gene has been discovered through these studies.[16,32] LRP5 gene seems to affect the adaptive response of bone to mechanical loading and may also play role in the regulation of bone metabolism.[33]

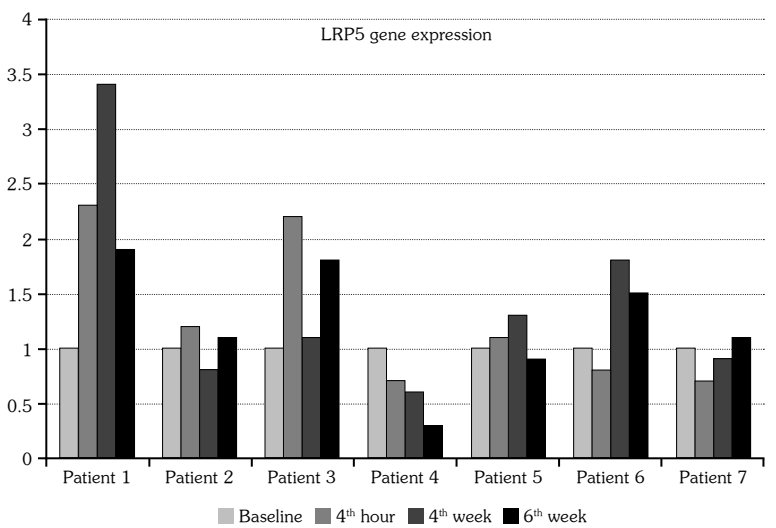

Figure 1. Individual changes in low density lipoprotein receptor related protein 5 (LRP5) gene expression levels after aerobic exercise sessions.

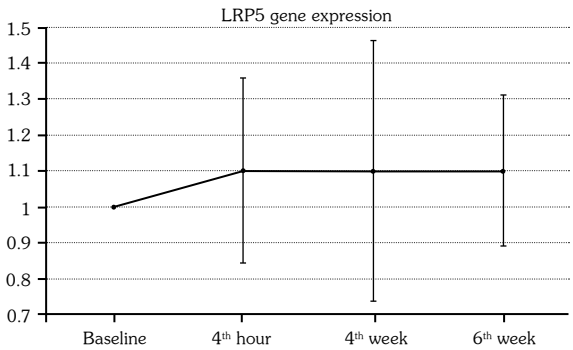

Figure 2. Differences between low density lipoprotein receptor related protein 5 (LRP5) gene expression levels after each aerobic exercise session.

The regulation of human LRP5 gene expression is still not known. Li et al.[34] cloned the human LRP5 promoter and analyzed its transcriptional regulation and demonstrated that both specificity protein 1 and Krüppel-like factor 15 motifs were essential for human LRP5 promoter activity. It has been demonstrated that the expression of LRP5 in osteoblast was increased by bone morphogenetic protein 2.[35] Fretz et al.[36] discovered that $1,25(OH)_2D_3$ may induce binding of the vitamin D receptor to sites within the LRP5 gene locus. This interaction is thought to cause a modification in chromatin structure within the LRP5 locus and induce LRP5 messenger ribonucleic acid transcription in osteoblasts. They also suggested that the contributory effect of this up-regulation of LRP5 by $1,25(OH)_2D_3$ to the overall actions of $1,25(OH)_2D_3$ on bone remained to be determined.[35] Actually, if there is such an interaction between vitamin D and LRP5 gene expression, this might have at least partially played some part in the variation of our patients' LRP5 expression patterns.

Whether exercise has an influence on LRP5 gene expression is still unclear. There are several studies about the regulatory effect of exercise on various myogenic and metabolic gene expressions.[37,38] Mode of exercise, timing of sampling, type of the gene studied, host factors like feeding status, age, sex, and activity level are all important variables that might influence the gene induction response to exercise in humans. Yang et al.[38] studied the time course of myogenic and metabolic gene expression in response to acute exercise in human skeletal muscle and suggested that timing of the gene induction was variable and that it showed a peak four to eight hours after exercise. Likewise, we took our samples four hours following the exercise sessions. Although the effect of exercise on gene expression has usually been investigated on muscle biopsy sections, Buttner et al.[39] showed that white blood cells are a useful source to analyze gene expression after exercise. So, in this study, we decided that peripheral blood sampling would be efficient and acceptable.

In conclusion, our study provides preliminary clues about the effects of exercise on LRP5 gene expression levels. The results of our study demonstrated a slight increase in LRP5 gene expressions after exercise sessions in all patients, except one patient. The reason for this discrepancy may be due to genetic background among individuals. Therefore, analyzing LRP5 gene polymorphisms may help to establish a correlation between LRP5 genotypes and LRP5 expression levels. Future studies with larger sample sizes and different sampling time/tissues are required to shed more light on the impact of exercise (at molecular level) in OP.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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