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Original Article

Association of ACTN3 polymorphisms with BMD, and physical fitness of elderly women

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Abstract. [Purpose] Association of ACTN3 polymorphism with bone mineral density and the physical fitness of elderly women is still unclear. Therefore, this study investigated the association between ACTN3 genotype and bone mineral density, and the physical fitness of elderly women. [Subjects and Methods] Sixty-eight elderly women (67.38 ± 3.68 years) were recruited at a Seongbuk-Gu (Seoul, Korea) Medical Service Public Health Center. Measurements of physical fitness included muscle strength, muscle endurance, flexibility, agility, balance and VO_2max. Bone mineral density (BMD), upper limb muscle mass, lower limb muscle mass, percent body fat and body fat mass for the entire body were measured by dual-energy X-ray absorptiometry and an analyzer. Genotyping for the ACTN3 R577X (rs1815739) polymorphism was performed using the TaqMan approach. [Results] ACTN3 gene distribution of subjects were in the Hardy-Weinberg equilibrium (p=0.694). The relative bone mineral density trunk, pelvis and spine differed significantly among the ACTN3 genotypes. There were no significant differences among bone mineral densities of the head, arms, legs, ribs and total, but the RR genotype tended to be higher than other genotypes. Physical fitness was not significantly different among the ACTN3 genotypes. [Conclusion] These results suggest that ACTN3 gene polymorphisms could be used as one of the genetic determinants of bone mass in elderly women, and in particular, they indicate that individuals with the RR genotype have higher BMD and bone mineral composition.

Key words: ACTN3, Bone mineral density, Elderly women

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INTRODUCTION

Bone mass declines and the risk of fractures increases as people age, especially women undergoing menopause[1)]. After the age of 65, progressive decline in skeletal muscle mass is a serious change associated with which results in a downward spiral that may lead to decreased strength and osteoporosis[2)]. Skeletal muscle mass and bone mineral density are influenced by several hormonal and genetic factors[3)].

Several studies have reported the association of genetic factors with bone mineral density (BMD). Pouresmaeili et al.[4)] reported the association of a polymorphism in the vitamin D receptor BsmI (rs1544410) with bone mineral density in women. Additionally, the rs2275913 (−197G>A) polymorphism of the interleukin-17 (IL-17) gene stimulates osteoblasts to synthesize prostaglandin E2 and to express the receptor activator of nuclear factor κ-B ligand (RANKL), there by affecting osteoclastogenesis[5)]. Moreover, the low-density lipoprotein receptor-related protein 5 (LRP5)[6)] gene, Q233R of the leptin receptor gene[7)], and the Filamin B gene (FLNB)[8)] are also reported to be genetic factors associated with BMD.

The human ACTN3 gene encodes α-actinin-3, an actin-binding protein with a pivotal role in muscle structure. A common single nucleotide polymorphism (SNP) at codon 577 of ACTN3 R577X (rs1815739) results in the replacement of arginine

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(R) with a stop codon (X)[9]. Recent studies have shown that ACTN3 is associated with muscle power and sprint in athletes[10] and in ordinary people[11]. The ACTN3 genotype might promote the growth of muscle fiber components and the formation and structure of fast twitch fibers[12]. Women carrying the ACTN3 577XX genotype displayed lower peak torque values for knee extensor shortening and lengthening than groups of women with the genotypes, RR and RX[13]. Also, the XX genotype has been reported to be associated with greater decreased thigh muscle cross-sectional area in older women than the RR and RX genotype[14].

Using micro-CT, Yang et al.[15] showed that ACTN3$^{-/-}$ mice display significantly reduced bone mass, with reduced cortical bone volume and trabecular. This suggests a non-muscle α-actinin, α-actinin-3 is also expressed in osteoblasts. Thus, given the presence of α-actinins in bone cells, the loss of α-actinin-3 may contribute to various bone phenotypes. However, the association of ACTN3 polymorphism with BMD and the physical fitness of elderly women is still unclear. Therefore, this study investigated the association between ACTN3 genotype and the BMD and physical fitness of elderly women.

SUBJECTS AND METHODS

Sixty-eight elderly women (67.38 ± 3.68 years) were recruited at a Seongbuk-Gu (Seoul, Korea) Medical Service Public Health Center (Table 1). All the subjects who agreed to participate in this study had the study explained to them to ensure a complete understanding of its purpose and the methods, in accordance with the ethical principles of the Declaration of Helsinki. The subjects also signed an informed consent form before participation.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using an X-Scan Plus body composition analyzer (Jawon Medical, Gyeongsan, Korea). BMI was calculated as weight (kg) divided by height squared (m^2). BMD, upper limb muscle mass, lower limb muscle mass, percent body fat and body fat mass for the entire body were measured by dual-energy X-ray absorptiometry (GE Lunar DPX, GE Healthcare Technologies Lunar, USA) and an analyzer. Analysis was then performed on the BMD data of the arms, legs, trunk, ribs, pelvis, spine, and total.

Physical fitness items included muscle strength, muscle endurance, flexibility, agility, balance and VO_2max. For muscle strength, grip strength was used. Muscle endurance was evaluated with arm curl and 2 min walk tests, flexibility with chair sit and reach and a back scratch test, agility with the timed up-and-go test, and balance with the one-leg standing test. VO_2max was measured on a cycle ergometer.

Genomic DNA was extracted from buccal cells which were obtained using cotton swabs (Single Warpped, COPAN, CA, USA). After cell preparation, the samples were dissolved, and the cells were lysed in 400 µl of DNA lysis solution and incubated at 95 °C for 3 minutes. The samples were added to 400 µl of DNA stabilizing solution then stored at 4 °C until use in polymerase chain reactions (PCR). Genotyping for the R577X ACTN3 polymorphism was performed by real-time PCR using a TaqMan probe (rs1815739, Pre-Designed SNP Genotyping assays). The PCR was performed, using a thermal cycler (7500, Applied Biosystem, CA, USA) and the following conditions: 95 °C for 10 min, 40 cycles at 95 °C for 15 s, at 60 °C for 1 min.

The SPSS statistical package version 19.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical evaluations. Allele frequencies were determined by gene counting. The χ^2 test was used to confirm that the observed genotype frequencies exhibited a Hardy-Weinberg equilibrium distribution. For body composition, BMD and physical fitness, data were further analyzed for significant differences among the three genotypes using one-way ANOVA, and when appropriate the post hoc Bonferroni test. The relationships among variables were analyzed using Pearson correlation coefficients. Statistical significance was accepted at the 0.05 level. All variables are presented as the means ± standard deviations.

RESULTS

The distribution of the ACTN3 polymorphism and allele are presented in Table 2. The ACTN3 gene distribution of the subjects exhibited the Hardy-Weinberg equilibrium (p=0.694).

The body composition of the subjects according to each genotype are shown in Table 3. There were no significant differences in body composition among the genotypes.

The BMDs of the subjects of each genotype are shown in Table 4. The relative BMDs of the trunk, pelvis and spine differed significantly among the ACTN3 genotypes. There were no significant differences among BMDs of the head, arms, legs, ribs and total, but the RR genotype tended to be higher than those of the other genotypes (RX and XX). The bone mineral composition (BMC) of the subjects of each genotype are shown in Table 5. The relative BMC of the arms differed significantly among the ACTN3 genotypes.

The physical fitness items of the subjects of each genotype are shown in Table 6. There were no significant differences in physical fitness among the genotypes.

Table 7 shows the correlation coefficients of BMD and body composition. Positive correlations were found between weight and BMDs of the arms, legs, trunk, ribs, pelvis, spine and total. Positive correlations were also found between BMI (body mass index) and BMDs of the trunk, ribs, pelvis, spine and total, and a positive correlation was found between %BF and BMD of the spine. Moreover, a positive correlation was found between BMM (body muscle mass) and BMDs of the head, arms, legs, trunk, ribs, pelvis, spine and total.

Table 1. The characteristics of the subjects

Variable (n=68)	
Age (years)	67.4 ± 6.7
Height (cm)	153.3 ± 4.5
Weight (kg)	58.6 ± 6.3
BMI (kg/m^2)	25.0 ± 2.9
%BF (%)	30.1 ± 5.9
BMM (kg)	35.2 ± 2.6

Values are mean ± SD. BMI: body mass index; %BF: percent body fat; BMM: body muscle mass

Table 2. Distribution of ACTN3 genotypes among the subjects

	Genotype frequency, % (n)			Allele frequency, % (n)	
	RR	RX	XX	R	X
Subjects (n=68)	12 (17.65)	35 (51.47)	21 (30.88)	59 (43.38)	77 (56.62)
H-W	6 (8.82)	28 (41.18)	34 (50.00)		

H-W: Hardy-Weinberg equilibrium; Allele, R = (2RR) + RX; X = (2XX) + RX.
p=0.694

Table 3. Comparison of body composition among the ACTN3 genotypes

	ACTN3 polymorphism		
	RR (n=12)	RX (n=35)	XX (n=21)
Age (years)	68.3 ± 4.0	67.3 ± 3.7	66.9 ± 3.5
Height (cm)	154.9 ± 4.4	152.9 ± 4.4	153.1 ± 4.7
Weight (kg)	60.3 ± 7.1	57.6 ± 6.7	59.4 ± 5.2
BMI (kg/m^2)	25.1 ± 3.4	24.7 ± 3.1	25.3 ± 2.1
%BF (%)	30.1 ± 5.7	29.9 ± 6.8	30.6 ± 4.4
BMM (kg)	35.8 ± 2.8	34.8 ± 2.7	35.4 ± 2.3
AMM (g)	4,293.6 ± 765.0	4,094.1 ± 434.6	4,284.8 ± 378.8
LMM (g)	12,555.3 ± 1,573.3	11,962.3 ± 883.3	12,174.2 ± 1,089.1

Values are mean ± SD. BMI: body mass index; %BF: percent body fat; BMM: body muscle mass; AMM: arms muscle mass; LMM: legs muscle mass

Table 4. The BMDs of the subjects of each genotype

BMD (g/cm^2)	ACTN3 polymorphism			
	Total (n=68)	RR (n=12)	RX (n=35)	XX (n=21)
Head	1.847 ± 0.279	1.919 ± 0.187	1.827 ± 0.289	1.837 ± 0.309
Arms	0.773 ± 0.070	0.806 ± 0.084	0.755 ± 0.071	0.784 ± 0.049
Legs	1.068 ± 0.140	1.078 ± 1.076	1.066 ± 0.176	1.064 ± 0.083
Trunk	0.796 ± 0.059	0.834 ± 0.057*	0.778 ± 0.061$^+$	0.806 ± 0.047
Ribs	0.576 ± 0.043	0.588 ± 0.043	0.566 ± 0.047	0.585 ± 0.037
Pelvis	0.955 ± 0.081	1.007 ± 0.073*	0.933 ± 0.083$^+$	0.961 ± 0.067
Spine	0.917 ± 0.089	0.970 ± 0.077*	0.888 ± 0.090$^+$	0.934 ± 0.077
Total	1.001 ± 0.071	1.041 ± 0.075	0.993 ± 0.075	1.017 ± 0.057

Values are mean ± SD. BMD: bone mineral density.
*Analyzed by one-way ANOVA ($p<0.05$).
$^+p<0.05$ vs. RR genotype

Table 5. The BMCs of the subjects of each genotype

BMC (g)	ACTN3 polymorphism			
	Total (n=68)	RR (n=12)	RX (n=35)	XX (n=21)
Head	426.9 ± 71.1	439.6 ± 50.4	423.5 ± 85.2	425.3 ± 55.4
Arms	221.8 ± 29.2	235.2 ± 29.2*	213.6 ± 29.8	227.7 ± 24.8
Legs	685.6 ± 74.5	724.0 ± 93.0	669.4 ± 74.5	690.6 ± 55.2
Trunk	587.8 ± 113.2	620.9 ± 92.0	570.3 ± 134.3	598.1 ± 79.4
Ribs	170.9 ± 64.4	172.8 ± 28.82	169.2 ± 84.3	172.7 ± 36.3
Pelvis	228.5 ± 46.5	248.3 ± 46.7	218.9 ± 51.0	233.1 ± 35.0
Spine	188.4 ± 29.0	199.8 ± 23.2	182.2 ± 31.9	192.1 ± 25.3
Total	1,918.1 ± 228.6	2,019.8 ± 221.6	1,868.1 ± 251.9	1,943.1 ± 170.0

Values are mean ± SD. BMC: bone mineral content
*Analyzed by one-way ANOVA ($p<0.05$)

Table 6. The physical fitness items of the subjects of each genotype

	ACTN3 polymorphism			
	Total (n=68)	RR (n=12)	RX (n=35)	XX (n=21)
VO_2max (ml/kg/min)	24.6 ± 6.1	25.0 ± 4.6	25.1 ± 6.9	23.6 ± 5.6
Grip strength (kg)	22.5 ± 3.4	23.3 ± 4.6	21.9 ± 3.2	23.0 ± 2.9
2 minute walking (times)	112.1 ± 19.4	113.5 ± 14.6	113.2 ± 18.9	109.4 ± 22.8
Dumbbell curl (times)	21.3 ± 4.3	22.1 ± 4.4	20.8 ± 4.4	21.7 ± 4.2
Chair stand (times)	16.4 ± 4.6	16.5 ± 6.1	16.1 ± 4.2	16.7 ± 4.7
Back scratch test (cm)	−2.7 ± 8.2	0.5 ± 7.4	−3.3 ± 8.3	−3.6 ± 8.2
Chair sit and reach (cm)	14.2 ± 8.8	11.7 ± 11.4	16.6 ± 6.7	11.8 ± 9.6
Timed up and go (sec)	5.4 ± 0.8	5.4 ± 0.7	5.4 ± 0.9	5.4 ± 0.7
Balance test (sec)	36.3 ± 33.1	31.7 ± 31.0	34.2 ± 28.3	42.4 ± 41.5

Values are mean ± SD.

Table 7. Pearson's correlation coefficients for BMD and body composition

BMD	Age	Height	Weight	BMI	BMM
Head	−0.143	0.309*	0.196	0.019	0.345**
Arms	−0.210	0.179	0.336**	0.230	0.364**
Legs	−0.201	0.040	0.258*	0.217	0.283*
Trunk	−0.204	0.099	0.522**	0.445**	0.473**
Ribs	−0.104	−0.039	0.632**	0.618**	0.513**
Pelvis	−0.262*	0.171	0.439**	0.326**	0.431**
Spine	−0.118	−0.015	0.438**	0.422**	0.342**
Total	−0.219	0.152	0.420**	0.312**	0.439**

Pearson's correlation coefficient were calculated to determine the relationships among the parameters. BMI: body mass index; BMM: body muscle mass; BMD: bone mineral density.
*$p<0.05$, **$p<0.01$

Table 8 shows the correlation coefficients of BMDs and physical fitness items. A positive correlation was found between grip strength and BMD of the arms, and positive correlations were found between dumbbell curl and BMDs of the trunk, pelvis and spine.

DISCUSSION

The present study is the first of its kind to investigate the associations between ACTN3 genotypes and BMD, and the physical fitness of elderly women. The main finding of the study was the presence of associations of BMDs of the trunk pelvis and spine (Table 4), and BMC of the arms (Table 5), with the ACTN3 polymorphism.

Table 8. Pearson's correlation coefficients for BMD and physical fitness

BMD	VO_2max	GS	2MW	DC	CS	BST	CSR	TUG	BT
Head	−0.210	0.015	0.078	0.153	0.012	0.167	0.105	−0.078	0.078
Arms	0.007	0.444**	0.009	0.152	−0.061	0.037	−0.042	0.023	0.046
Legs	0.180	0.215	−0.008	0.088	−0.085	−0.009	0.165	0.022	0.047
Trunk	−0.011	0.113	0.083	0.268*	0.128	−0.099	−0.071	−0.079	−0.051
Ribs	−0.154	0.152	−0.045	0.109	−0.061	−0.037	−0.145	0.041	−0.145
Pelvis	0.034	0.208	0.135	0.309*	0.188	0.044	0.011	−0.132	−0.076
Spine	−0.051	−0.088	0.076	0.262*	0.162	−0.070	−0.122	−0.028	−0.059
Total	0.006	0.196	0.038	0.176	−0.006	0.059	0.038	−0.024	−0.002

Pearson's correlation coefficients were calculated to determine the relationships among the parameters. GS: grip strength; 2MW: 2-minute walking; DC: dumbbell curl; CS: chair stand; BST: back scratch test; CSR: chair sit & reach; TUG: Timed up-and-go; BT: balance test; BMD: bone mineral density.
*p<0.05, **p<0.01

Four known loci, encode alpha-actinins 1, 2, 3 and, 4[16]. Of these, ACTN3 is expressed in the skeletal muscle[17] and shows low levels of expression in the brain[9]. Moreover, a recent study reported that ACTN3 is also expressed in bone. These data suggest ACTN3 deficiency is significantly associated with lower bone mass in ACTN3$^{-/-}$ mice, which may be due to ACTN3 deficiency in bone cells. Furthermore, a 59% reduction in trabecular BV/TV (BV; bone volume, TV; total volume) and detailed histological analysis revealed a dual mechanism for this bone loss: a 20% reduction in mineral apposition rate, and a 24% increase in OscN/BS (osteoclast number per unit bone surface) in ACTN3$^{-/-}$ mice[15]. The finding of the present study, that BMD differed significantly among various ACTN3 genotypes, is similar to the results reported by Yang et al[15]. BMC of the arms also differed significantly among the ACTN3 genotypes, but BMC of the other regions and BMD of the head, arms, legs, ribs and total BMD showed no significant differences among the ACTN3 genotypes.

Decreased muscle mass and bone mineral density are significant changes that occur with aging, and these are often associated with an inability to adapt to the environment, which results in falls, functional disability, increased hospitalization, decreased quality of life, and increased mortality[18]. Several studies have reported a correlation between BMD and weight, and muscle mass in elderly women[19]. In this study, a positive correlation was found between body muscle mass (BMM) and BMD of the head, arms, legs, trunk, ribs, pelvis, spine, and total BMD, and a positive correlation was found between the weight and BMD of the arms, legs, trunk, ribs, pelvis, spine, and total BMD. The positive correlation between weight and BMD might be related to increased muscle mass, given that Kang et al.[20] demonstrated a negative correlation between BMD and % fat, and fat mass index. The positive correlation between BMD and grip strength, and dumbbell curl is supported by the results of the study by Lida et al.[21] which show there is an association between decreased BMD and decreased physical fitness in elderly women, indicating the importance of BMD for the improvement of the physical fitness of the elderly.

Physical fitness did not vary significantly among the different ACTN3 genotypes. In this study, measurements were mad of muscle strength (grip strength), muscle endurance (2-minute walking, dumbbell curl, and chair stand), flexibility (chair sit and reach, and back scratch test), agility (timed up-and-go), balance (one-leg standing), and VO_2max. Previous studies have reported an association between the RR genotype of the ACTN3 R577X polymorphism and muscle power in elite athletes[22] and ordinary people[23]. In particular, the XX genotype is lower among power/sprint-oriented athletes than the RR genotype[24], and this finding is supported by the observation that individuals with the XX genotype show lower thigh muscle cross-sectional area than those with the RR and RX genotypes[14]. However, considering the role of ACTN3 in skeletal muscle, and consequentially muscle strength and endurance, the present study surprisingly found no such relationship. This may perhaps be a result of the ages of the study subjects, which were more than 68 years. Physical activity is also widely known to be effective at reducing bone mass loss in the elderly[25]. In other words, genetic factors have little influence on the physical activity of elderly women. Therefore, it might be possible to maintain physical fitness through lifestyle or behavioral changes.

Further studies are required to review the relationship between ACTN3 polymorphisms and physical fitness in elderly women. Studies with larger sample sizes and different genders are also required to increase the statistical power of the analysis of genetic polymorphisms.

In conclusion, the ACTN3 genotypes showed the following distribution: 17.7% were RR genotype, 51.4% were RX genotype, and 30.9% were XX genotype. BMD of the trunk, pelvis and spine of the RR genotype was significantly higher than those of the other genotypes (RX and XX), and BMC of the arms of the RR genotype was also significantly higher than those of the other genotypes (RX and XX). However, no differences in physical fitness items were observed, even though positive correlations were observed between BMD and muscle mass, weight, grip strength, and dumbbell curl. These results suggest that ACTN3 gene polymorphisms might be a useful genetic determinant of bone mass in elderly women, and in particular, indicate that individuals with the RR genotype have higher BMD and BMC values.

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