

Effects of 8 weeks of moderate-intensity resistance training on muscle changes in postmenopausal women with different angiotensin-converting enzyme insertion/deletion polymorphisms of interest

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Abstract

Objective: The aim of the study was to explore the association between angiotensin-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism and muscle adaptations to moderate-intensity resistance training in postmenopausal women.

Methods: Forty healthy postmenopausal Chinese women (aged 53–66 years) were recruited and grouped by *ACE* I/D polymorphism (the homozygous deletion genotype [DD], n = 12; the I allele carriers [II/ID], n = 28). All participants performed an 8-week full-body resistance training program at moderate intensity with 15-repetition maximum. Upper- and lower-limb muscle mass, grip and back strength, anatomical cross-sectional area of the rectus femoris ($ACSA_{RF}$), isokinetic knee extension strength (MVC_{KE}) and knee flexion strength were measured before and after training.

Results: Our results showed significant genotype \times time interaction in $ACSA_{RF}$ and MVC_{KE} ($P = 0.007$ and $P = 0.03$, respectively) with the DD group having greater changes in corresponding parameters than the I-allele carriers ($P = 0.012$ and $P = 0.018$, respectively). Multivariate linear regression results showed that the *ACE* DD genotype was positively related to the grip strength adaptation ($r = 0.48$, $P = 0.05$).

Conclusions: This study improves our understanding of the association between the *ACE* I/D polymorphism and muscular responses to moderate intensity resistance training among postmenopausal women and revealed that the DD genotype has predominant adaptations in grip strength, rectus femoris size, and knee extensor strength.

Key Words: *ACE* I/D polymorphism – Muscle changes – Postmenopausal women – Resistance training.

Decreased physical performance, muscle mass, and muscle strength are typical characteristics of aging. The muscle function and strength of women decline significantly after menopause.¹ Many studies have reported the positive effect of resistance training on ameliorating muscle degeneration in postmenopausal women by improving muscle strength and muscle quality (the ratio of maximum isometric strength to lean tissue mass),² increasing muscle volume,³ and preserving bone mineral density.^{4,5}

Notably, the training response differs among individuals. Ahtainen et al⁶ reported adaptation differences in muscle size and strength after a 6-month resistance training program with

a wide range of variance from –11% to 60%. Genetic composition is a factor that related to this individual variance. Many gene polymorphisms are associated with athletic performance and physical capability,⁷ among which is the polymorphism of the angiotensin-converting enzyme (*ACE*) gene that encodes ACE, which plays an important role in blood pressure regulation through the renin-angiotensin system and the kallikrein-kinin system. The insertion (I) or deletion (D) polymorphism of *ACE* is determined by the presence or absence of a 287-bp Alu repeat sequence within intron 16. Studies have reported a connection between *ACE* I/D polymorphism and exercise events with a dominant percentage of I allele among top athletes in endurance-oriented activities such as marathon running,⁸ long-distance swimming,⁹ and mountain climbing.¹⁰ Meanwhile, the D allele is more frequently found in strength and speed-oriented activities such as sprinting and short-distance swimming.¹¹

Although the relationship between *ACE* I/D polymorphism and physical performance in athletes has been well-reported, the possible connection between *ACE* I/D alleles and resistance training adaptations in postmenopausal women remains poorly understood. Related studies will improve our understanding of the association between gene polymorphisms and individual variances in muscular changes induced by resistance training. Previous studies reported that 8-week resistance training programs can significantly increase muscle

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strength in postmenopausal women¹² and older adults.¹³ Therefore, this research was conducted to explore muscle adaptations after 8 weeks of moderate-intensity resistance training in Chinese postmenopausal women with different *ACE* I/D polymorphism. Considering the close relationship between the D allele and muscle strength, we hypothesized that women with the homozygous deletion (DD) genotype had greater improvements in muscular parameters than the I-allele carriers after resistance training.

METHODS

Participants

A total of 163 independently living postmenopausal women were recruited from local communities around Beijing Sport University. Through screening questionnaires, 40 postmenopausal women (aged 53-66 years) were selected for our intervention study. These participants shared the following characteristics: (1) no muscular issues such as osteoporosis or arthritis or nervous system diseases such as Alzheimer disease or Parkinson disease; (2) similar physical activity levels (evaluated by the International Physical Activity Questionnaire¹⁴); (3) ability to exercise without a doctor's guidance (evaluated by the Physical Activity Readiness Questionnaire); (4) no history of hormone therapy or dietary supplements; and (5) no menstrual periods within the previous 12 months. All participants were notified of the training program and provided written informed consent. This study was approved by the Human Ethics Committee of Beijing Sport University (2016010H).

DNA extraction and angiotensin-converting enzyme insertion/deletion polymorphism analysis

DNA samples were extracted using a Chelex-100 (Sigma-Aldrich, St. Louis, MI) and proteinase K (Bio Basic Inc, Markham, Canada) protocol¹⁵ from buccal cells collected by cotton swabs. Polymerase chain reaction (PCR) was used to amplify the DNA with the forward primer 5'-CTG GAG ACC ACT CCC ATC CTT TCT-3' and the reverse primer 5'-GAT GTG GCC ATC ACA TTC GTC AGA T-3'.¹⁶ DNA samples were amplified by GeneAmp 9600 PCR System (Applied Biosystems, Kenilworth, NJ) at 94°C for 5 minutes, followed by 35 cycles of 30 seconds each at 94°C, 60°C, and 72°C. The amplification was ended with a final elongation of 10 minutes at 72°C and was held at 15°C. The reaction system (15 µL) consisted of 1.5 µL of 10× PCR buffer, 0.2 µL of 10 µM of each primer (Sangon Biotech, Shanghai, China), 0.1 µL of 5 U/µL Hot Start Taq polymerase (Takara Bio Inc, Kusatsu, Japan), 1.2 µL of 2.5 mM deoxynucleoside triphosphate Mixture, 1.0 µL of DNA sample, and 11 µL of double-distilled water. To identify the *ACE* I/D genotype, a 3 µL PCR amplicon was electrophoresed on a 2.5% agarose gel with the presence of a 182-bp fragment indicating a D allele and a 469-bp fragment indicating an I allele.

Training protocol

Resistance training was performed nonconsecutively three times per week for 8 weeks at the Tennis Complex Training

Hall of Beijing Sport University. The training protocol consisted of three sets of the following eight exercises: shoulder press, shoulder pull down, chest press, arm curl, knee extension/flexion, and hip extension/flexion. Each set included 1 minute of exercise and 1 minute of rest. The participants performed the exercise on muscle workout equipment (Technogym, Cesena, Italy) at a moderate intensity with a 15-repetition maximum (RM). The load for each participant for each exercise was evaluated and adjusted every 2 weeks by certified trainers. Each participant performed a 10-minute warm-up on a cycle ergometer before the training and 20 minutes of stretching after the training. All participants were trained under the guidance of certified trainers and advised to maintain their regular lifestyle during the study.

Parameter measurements

Body composition was analyzed using an Inbody 720 (BioSpace, Seoul, South Korea), which has good consistency with magnetic resonance imaging estimates of body composition (intra-class correlation coefficient [ICC] = 0.73-0.97) in middle-aged women.¹⁷ The measurements were taken according to the manufacturer's instructions. Before the test, the participants were asked to remove any metal attachments and stand barefoot on the electrodes. During the test, they were asked to stand still and look straight forward with their upper limbs slightly abducted from the trunk. The waist-hip ratio (WHR) and skeletal muscle masses of the upper (SMM_{UPPER}) and lower (SMM_{LOWER}) limbs were recorded for further analyses.

Grip strength of the dominant hand was measured using a WCS-II grip strength dynamometer (Jianmin, Beijing, China). The participants were tested in a standing position with their arms straight down. Back strength was measured using a BLJ-II back strength dynamometer (Jianmin) according to the manufacturer's instructions. Three trials were completed of both strength tests and the highest values were analyzed.

The anatomical cross-sectional area of rectus femoris (ACSA_{RF}) on the dominant side was measured using B-mode ultrasonography with a 10-MHz probe of a Vivid 7 system (GE Healthcare, Chicago, IL). The participants were tested in a supine position. A pillow was placed beside the dominant leg to keep the toes in an upright pointed position during the scan. The probe was placed at the point at four-fifths of the length from the anterior superior iliac spine to the superior patellar border. The ACSA_{RF} of each participant was measured three times and the mean value was analyzed. The ultrasound scans were made by the same technician with good test consistency (ICC = 0.81).

A Biodex System 3 (Biodex Medical Systems, Shirley, NY) was used to measure isokinetic knee strength. Before the measurement, the participants were asked to perform two warm-up sessions. The first section was a general warm-up. The participants were asked to ride on a free-loaded cycle ergometer for 5 minutes. The second section consisted of familiarization to the testing process. The participants were

TABLE 1. Descriptive data of participants in different angiotensin-converting enzyme insertion/deletion subgroups at baseline level

Characteristics	ACE I/D genotype		P	Power
	DD	II/ID		
N	12	28		
Age, y	57.5 ± 4.6	59.6 ± 4.1	0.330	—
Body mass, kg	67.3 ± 4.6	59.0 ± 5.9	—	—
Height, m	1.62 ± 0.04	1.58 ± 0.04	0.048 ^a	0.806
BMI, kg/m ²	25.7 ± 1.8	23.6 ± 2.0	0.046 ^a	0.877
WHR	0.87 ± 0.05	0.85 ± 0.03	—	—
Light activity (MET-min/wk)	2,398.0 ± 399.1	2,350.1 ± 316.0	—	—
Moderate activity (MET-min/wk)	4,195.0 ± 358.2	4,026.4 ± 494.7	0.463	—
Vigorous activity (MET-min/wk)	1,026.7 ± 130.6	1,062.9 ± 256.2	0.749	—

ACE I/D, angiotensin-converting enzyme insertion/deletion; BMI, body mass index; DD, homozygous deletion; II/ID, I allele carriers; WHR, waist-hip ratio. ^aSignificantly different between DD and II/ID groups, $P < 0.05$.

asked to complete three repetitions of knee extension and flexion under a 180°/s model and one repetition under a 60°/s model. Gravity effect torque was adjusted at 30° of knee flexion (0° representing full extension). The formal test consisted of eight repetitions of full-range isokinetic knee extension and flexion at 60°/s. The peak torques of the knee extensors (MVC_{KE}) and flexors (MVC_{KF}) were analyzed.

Statistical analysis

Each measurement was made by the same blinded assessor before and after the resistance training. Descriptive data are reported as mean ± standard deviation and were analyzed using SAS 9.4 (SAS Institute, Cary, NC). Considering that the ACE DD genotype is predominant in power performance,¹⁸ the participants were separated into the II/ID group (n = 28) and the DD group (n = 12). Muscular phenotypes were normalized for body mass. The Shapiro-Wilk normality test was used to check the normality of each parameter. Intergroup comparisons were made by the Student *t* test at baseline and post-training levels. To compare genotype-related adaptations after the resistance training, repeated-measures analysis of variance (ANOVA) was used in normally distributed parameters with genotype and time as two factors. To study the association between ACE I/D polymorphism and muscular changes, multivariate linear regression analysis was used with percentage changes of

muscular phenotypes as dependent variables and ACE I/D polymorphism, age, height, and baseline body mass as independent variables. Statistical significance was set at a level of 0.05.

RESULTS

Anthropometric and physiological characteristics

A normality test showed that most of the parameters were normally distributed except for light activity, WHR, and body mass (Supplementary Table S1, <http://links.lww.com/MENO/A417>). The participants' baseline descriptive characteristics are presented in Table 1. There was no significant difference in daily physical activity levels among the two genotype groups. Although overweight participants were found in both genotype groups as indicated by body mass index ([BMI]: >23.9 kg/m²) and WHR (>0.8), participants with the DD genotype had a significantly higher mean BMI than the I-allele carriers ($P = 0.046$, power = 88%).

Effects of resistance training on anthropometric and muscular changes

Values of anthropometric and muscular parameters before and after the intervention are shown in Table 2. Before the intervention, the ACE DD participants showed lower grip strength ($P = 0.01$) and SMM_{LOWER} ($P = 0.006$) values than the II/ID group. After the resistance training, mean ACSA_{RF}

TABLE 2. Comparisons of anthropometric parameters between angiotensin-converting enzyme insertion/deletion subgroups at baseline and post-training levels

Parameter	Baseline		Post-training		P values from repeated measures ANOVA		
	DD	II/ID	DD	II/ID	Genotype	Time	Genotype × time
N	12	28	12	28			
BMI, kg/m ²	25.7 ± 1.8 ^a	23.6 ± 2.0	25.7 ± 1.6 ^a	23.5 ± 2.0	0.034	0.560	0.422
ACSA _{RF} , mm ²	90.77 ± 7.51	85.04 ± 8.20	181.69 ± 19.93 ^a	153.98 ± 20.51	0.022	<0.001	0.007
SMM _{UPPER} , kg/kg	0.06 ± .003	0.07 ± .006	0.06 ± .003	0.07 ± .006	0.452	<0.001	0.942
SMM _{LOWER} , kg/kg	0.09 ± .003 ^b	0.10 ± .010	0.20 ± .019	0.20 ± .019	0.349	<0.001	0.362
MVC _{KE} , N · m/kg	1.25 ± 0.15	1.35 ± 0.16	1.53 ± 0.19	1.56 ± 0.17	0.440	<0.001	0.030
MVC _{KF} , N · m/kg	0.61 ± 0.13	0.65 ± 0.14	0.79 ± 0.20	0.82 ± 0.16	0.634	<0.001	0.735
Grip strength, kg/kg	0.33 ± 0.03 ^a	0.40 ± 0.05	0.41 ± 0.04	0.46 ± 0.07	0.032	<0.001	0.284
Back strength, kg/kg	0.79 ± 0.17	0.90 ± 0.21	0.89 ± 0.20	1.02 ± 0.26	0.272	<0.001	0.726

ACSA_{RF}, anatomical cross-sectional area of rectus femoris; ANOVA, analysis of variance; BMI, body mass index; DD, homozygous deletion; II/ID, I allele carriers; MVC_{KE}, isokinetic knee extension strength; MVC_{KF}, isokinetic knee flexion strength; SMM_{LOWER}, skeletal muscle mass of lower limbs; SMM_{UPPER}, skeletal muscle mass of upper limbs.

^aSignificantly different between DD and II/ID groups at the same testing time point, $P < 0.05$.

^bSignificantly different between DD and II/ID groups at the same testing time point, $P < 0.01$.

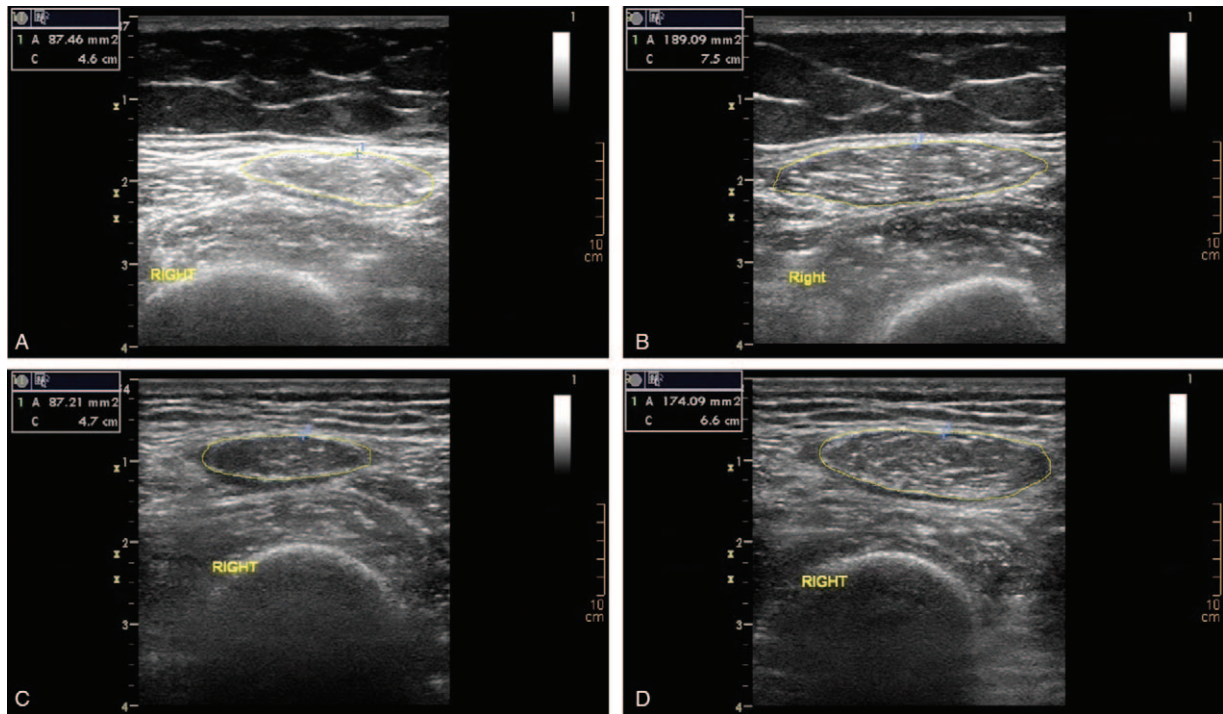


FIG. 1. Ultrasound images of rectus femoris measured before and after resistance training. Anatomical cross-sectional areas of rectus femoris are outlined with yellow circles. **A**, Before training (DD group). **B**, After training (DD group). **C**, Before training (II/ID group). **D**, After training (II/ID group).

level (Fig. 1) was significantly larger in the DD group ($P=0.012$). Results of repeated-measures ANOVA showed significant genotype and time interactions in $ACSA_{RF}$ and MVC_{KE} ($P=0.007$ and $P=0.03$, respectively) with high statistical powers (Supplementary Table S2, <http://links.lww.com/MENO/A417>).

As presented in Table 3, percentage changes of SMM_{UPPER} , MVC_{KF} , and back strength did not differ between the two genotype groups. The increase in mean SMM_{LOWER} value in the DD group was significantly higher than that in the II/ID group ($P=0.05$). MVC_{KE} and grip strength in the DD group increased by 22.5% and 21.4%, respectively. Both parameters were significantly higher than that in the II/ID group ($P=0.018$ and $P=0.001$, respectively).

Associations between percentage changes of muscular phenotypes and *ACE* I/D polymorphism

As shown in the linear regression results (Table 4), participants with the DD genotype had greater increases in muscular parameters except for back strength. Age was not significantly associated with changes in muscular phenotypes. This might be related to the relatively narrow age range of our participants. Based on the linear regression results, the *ACE* DD genotype was positively associated with the percentage change in grip strength ($r=0.48$, $P=0.05$).

DISCUSSION

The main findings of this study regarding healthy post-menopausal women included: (1) *ACE* I/D polymorphism is

TABLE 3. Percentage changes of muscular parameters after training

Parameter	$\Delta_{\text{post-baseline}}$ (%)		<i>P</i> values from <i>t</i> test	Power
	DD	II/ID		
Body mass, kg	0.14 ± 1.47	-0.60 ± 1.90	0.409	—
$ACSA_{RF}$, mm ²	100.01 ± 11.17	80.85 ± 15.11	0.012 ^a	0.990
SMM_{UPPER} , kg/kg	2.94 ± 1.79	2.83 ± 2.06	0.916	—
SMM_{LOWER} , kg/kg	128.36 ± 15.86	109.89 ± 19.17	0.050 ^a	0.859
MVC_{KE} , N · m/kg	22.54 ± 6.05	16.00 ± 4.77	0.018 ^a	0.879
MVC_{KF} , N · m/kg	27.41 ± 6.21	25.67 ± 5.53	0.542	—
Grip strength, kg/kg	21.44 ± 1.80	14.73 ± 5.56	0.001 ^b	>0.999
Back strength, kg/kg	12.98 ± 7.51	12.79 ± 6.85	0.957	—

$ACSA_{RF}$, anatomical cross-sectional area of rectus femoris; DD, homozygous deletion; II/ID, I allele carriers; MVC_{KE} , isokinetic knee extension strength; MVC_{KF} , isokinetic knee flexion strength; SMM_{LOWER} , skeletal muscle mass of lower limbs; SMM_{UPPER} , skeletal muscle mass of upper limbs.

^aSignificantly different between DD and II/ID groups, $P < 0.05$.

^bSignificantly different between DD and II/ID groups, $P < 0.01$.

TABLE 4. Multivariate linear regression results of angiotensin-converting enzyme insertion/deletion polymorphism and percentage changes in muscular parameters

	$\Delta\text{ACSA}_{\text{RF}}$	$\Delta\text{SMM}_{\text{UPPER}}$	$\Delta\text{SMM}_{\text{LOWER}}$	$\Delta\text{MVC}_{\text{KE}}$	$\Delta\text{MVC}_{\text{KF}}$	$\Delta\text{Grip strength}$	$\Delta\text{Back strength}$
<i>ACE</i> I/D polymorphism (DD = 0, II/ID = 1)							
Parameter	-15.56	-0.13	-9.57	-5.82	-2.17	-6.65	2.06
<i>P</i>	0.08	0.92	0.42	0.11	0.55	0.05	0.64
β	-0.44	-0.03	-0.23	-0.46	-0.18	-0.55	0.14
r^2	0.18	<0.01	0.04	0.16	0.02	0.23	0.01
Age							
Parameter	-1.34	-0.12	-0.55	-0.05	0.02	-0.31	-0.53
<i>P</i>	0.15	0.36	0.66	0.90	0.96	0.35	0.26
β	-0.35	-0.27	-0.12	-0.04	0.01	-0.23	-0.33
r^2	0.13	0.06	0.01	0.001	<0.01	0.06	0.08
Baseline body mass							
Parameter	0.76	0.08	0.92	0.11	0.22	0.09	0.04
<i>P</i>	0.26	0.43	0.32	0.69	0.44	0.72	0.91
β	0.31	0.26	0.31	0.12	0.26	0.10	0.04
r^2	0.08	0.04	0.07	0.01	0.04	0.01	<0.01
Height							
Parameter	-138.78	-23.23	4.2	-6.57	-56.28	-33.30	20.98
<i>P</i>	0.21	0.16	0.98	0.88	0.24	0.41	0.71
β	-0.35	-0.50	0.01	-0.05	-0.41	-0.24	0.13
r^2	0.10	0.13	<0.01	<0.01	0.09	0.05	0.01
<i>P</i>	0.06	0.66	0.26	0.26	0.67	0.13	0.60
r^2	0.44	0.14	0.28	0.28	0.14	0.36	0.16

ACE I/D, angiotensin-converting enzyme insertion/deletion; ACSA_{RF} , anatomical cross-sectional area of rectus femoris; MVC_{KE} , isokinetic knee extension strength; MVC_{KF} , isokinetic knee flexion strength; $\text{SMM}_{\text{LOWER}}$, skeletal muscle mass of lower limbs; $\text{SMM}_{\text{UPPER}}$, skeletal muscle mass of upper limbs.

associated with body composition, whereby the *ACE* DD genotype is related to a significantly higher BMI and (2) *ACE* I/D polymorphism responses were different in rectus femoris size, knee extensor strength, and grip strength after moderate-intensity resistance training with the *ACE* DD homozygote having greater improvement than the I-allele carriers.

Obesity and overweight are related to an increased risk of falls among older people.¹⁹ The increased abdominal fat deposition caused by low estrogen in postmenopausal women implies that hormonal changes contribute more to changes in body fat distribution than general obesity.²⁰ Our study found that postmenopausal women with the *ACE* DD genotype had a significantly higher mean BMI than I-allele carriers, which might contribute to the increased risk of cardiovascular diseases among the *ACE* DD carriers.²¹

It is well established that resistance training can help ameliorate musculoskeletal degeneration during the aging process.²² Correa et al²³ found that knee extensor strength and rectus femoris volume were improved by 40% and 38%, respectively, in older women after a 12-week resistance training program with a 15 to 20 RM load. Similarly, we found increases of >16% in normalized MVC_{KE} and >80% in ACSA_{RF} after moderate-intensity resistance training. However, the adaptive change of ACSA_{RF} in our study contradicted the finding of Sattler et al,³ who reported no significant change in mean ACSA_{RF} value after a 12-week resistance training with an 8 to 12 RM load among perimenopausal women. One possible explanation might be that our participants had smaller muscle sizes (0.85-0.91 cm²) than that in Sattler study (2.2 cm²). Therefore, the muscle sizes of our participants were much easier to improve after resistance training. Moreover, we scanned ACSA_{RF} at the point of

four-fifths of the length from the anterior superior iliac spine to the superior patellar border, whereas Sattler measured ACSA_{RF} at 31% of the total femoral length from the distal to proximal end. According to the findings of Ema et al,²⁴ the mean ACSA_{RF} value of the distal part demonstrated significantly greater improvement than that of the proximal part after resistance training. Therefore, the inconsistency of the ACSA_{RF} change between the study of Sattler et al³ and our study could have also resulted from different scan positions.

Our study showed differences in adaptive changes of muscle mass between the upper and lower limbs as well as varied increasing rates between muscle mass and muscle strength induced by resistance training. In our study, muscle hypertrophy occurred after training and the improvement in muscle mass in the upper limbs was smaller than that in lower limbs. A possible mechanism of this adaptation difference between the upper and lower limbs might be the different composition of muscle fibers considering that there is a higher portion of type II fibers in the thigh muscles and lower legs than in the upper arms,²⁵ whereas resistance training mainly induces hypertrophy in type IIA fibers.²⁶ Such a mechanism is supported by the finding of more decreased muscle power, which is closely related to the type II fibers, in the lower versus upper limbs during aging.²⁷ In addition to the regional difference in exercise-induced muscle mass changes, incremental rates of muscle mass and muscle strength changes also varied during training. Our results demonstrate that muscle mass increased more than muscle strength, implying the presence of different adaptive mechanisms of muscle mass and muscle strength in resistance training. Both muscle mass and muscle strength can improve with sufficient nutrition during exercise,²⁸ whereas muscle mass can also be increased through elevated growth hormone and testosterone levels,

both of which play important roles in protein synthesis²⁹ and can be induced by resistance training.³⁰ Regarding changes in muscle strength, nervous system alterations are an important factor. Spinal motor neuron loss occurs with aging, a process that results in reduced muscle strength and muscle power regardless of an athlete's training level.³¹ The improvement in neural factors occurs at the beginning of muscle adaptation in resistance training, whereas intramuscular factors become more important as training continues over several months.³² Therefore, considering the short-term intervention in our study, the adaptation of muscle strength might have resulted from ameliorations in neuromuscular aspects such as increased motor unit recruitment, firing rate, and synchronization.³³

Several studies on the relationship between *ACE* I/D polymorphism and muscular changes induced by exercise training were previously reported, but the conclusions remain debatable. Pescatello et al³⁴ reported that young participants with the DD genotype had greater increases in elbow flexor strength than their II/ID counterparts after a 12-week upper arm resistance training. In contrast, Charbonneau et al³⁵ found no association between the *ACE* genotype and muscle hypertrophy after a 10-week knee extensor resistance training program in older participants. Our results showed that an 8-week resistance training program helped increase the ACSA_{RF}, muscle strength, and muscle mass of postmenopausal women, with the DD genotype having a predominant response. The greater increase in muscle mass in the DD genotype can be attributed to its association with a high *ACE* level,³⁶ which facilitates the conversion from Ang I to Ang II.¹¹ As a hypertrophic factor, Ang II induces muscle fiber growth,³⁷ enhancing muscle mass and strength.³⁸ Meanwhile, our linear regression results showed that *ACE* I/D polymorphism was significantly related to the adaptive change in grip strength, in which the *ACE* DD participants had greater improvement than the I-allele carriers. Since the increase in grip strength is considered a robust factor of reduced falling risk and improved quality of life,³⁹ our findings imply that postmenopausal women with the DD genotype might benefit more from resistance training than women with the I allele.

Limitations

Our study has a limited sample size and only explored the association between *ACE* I/D polymorphism and muscular changes induced by resistance training. In addition to the *ACE* I/D polymorphism, previous studies found that polymorphisms of other genes such as interleukin-15 receptor subunit alpha, insulin-like growth factor-1, and vitamin D receptor, are related to physical performance.⁷ Moreover, a 12-week power training program in older women demonstrated a significant combined effect of *ACE* I/D and alpha-actinin 3 (*ACTN3*) R/X polymorphisms with the "power (*ACTN3* RR+RX and *ACE* DD) group" showing greater increases in walking speed, vertical jump, and leg extension strength than the "non-power (*ACTN3* XX and *ACE* II+ID) group."^{40,41} Considering that muscular phenotypes are

overall results of multifactorial and polygenic effects, studies on the combined effect of multiple exercise-related genes can be more informative.

Moreover, in this study, years since menopause and glucose tolerance were not involved in the impact of muscle changes. Wu et al⁴² found that women whose age at menopause were greater than 49 years had a 6% increased risk of impaired glucose tolerance (OR = 1.06) for each year after menopause. Based on this finding, the risk of developing glucose intolerance in our oldest participant (66 years old) was twice that of our youngest participant (53 years old). Since glucose intolerance is negatively related to thigh muscle mass⁴³ and muscle strength,^{44,45} the difference in glucose intolerance risk among our participants might also be connected with variances in muscular phenotypes.

CONCLUSIONS

In conclusion, this study improves our understanding of the association between *ACE* I/D polymorphism and muscle adaptations to moderate-intensity resistance training in postmenopausal women. The *ACE* DD genotype has predominant adaptations in grip strength, cross-sectional area of the rectus femoris and knee extensor strength.

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