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HEALTH SCIENCES

Association between ACE and ACTN3 genetic polymorphisms and the effects of different physical training models on physically active women aged 50 to 75

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Abstract: The aim of this study was to analyze the association between ACE (DD + ID versus II) and ACTN3 (TT + TC versus CC) polymorphisms in the response of multicomponent physical training programs and combined in the health parameters of physically active women aged 50 to 75 years. Participants were randomly divided into two groups: multi-component training and combined training. Intervention lasted 14 weeks, 180 minutes a week. Genomic DNA was extracted from blood samples and genotyping analyzes were performed by conventional and real-time PCR. Associations were observed between polymorphisms in anthropometric measurements, blood pressure, physical capacity and quality of life in both models physical training, with improvement in group II - (ACE-multicomponent training in terms of abdominal circumference and sit-to - Combined training in terms of waist circumference) and TT + TC group (ACTN3 - multicomponent training in tests of muscle strength and mental quality of life domain, and combined training in body mass index, waist circumference, diastolic blood pressure, upper limb strength and cardiorespiratory capacity). Fourteen weeks of multicomponent and combined physical training in physically active women aged 50 to 75 years resulted in greater health benefits for genotypes II (ACE) and TT + TC (ACTN3).

Key words: Alpha-actinin, angiotensin-converting enzyme, elderly women, combined training, multicomponent training.

INTRODUCTION

The ageing process leads to morphological, biochemical, and functional alterations, causing a reduction in the functionality of various systems of the human body, such as the osseous, muscular, and cardiovascular systems (Franceschi et al. 2018).

Such declines, combined with physical inactivity, can cause falls and more serious problems among the elderly, so it is essential for that age group to practice regular physical exercises (Angulo et al. 2020). Evidence suggests that multicomponent and combined training are promising strategies that can improve different health parameters, including physical aptitude and increased muscle mass (Cadore et al. 2018, Leitão et al. 2021).

Although many of these benefits can be found in the literature, the studies present different, somewhat variable results with regard to the benefits that physical exercise can provide (Caldo-Silva et al. 2021). Thus, genetics is a component that can collaborate in understanding the response of health variables to physical training (Mota et al. 2013).

Studies indicates that genetic polymorphisms can be defined as different natural variations within the nucleic acid of a particular chromosomal location that express a unique trait and affect more than 1% of the population (Coffey & Hawley 2007). The genes that codify the angiotensin-converting enzyme (ACE) and the alpha-actinin 3 protein (ACTN3) can potentially influence physical aptitude and the magnitude of response to training programs in adults and seniors (Pereira et al. 2013).

ACE converts angiotensin I into angiotensin II, which form part of the renin-angiotensin-aldosterone system and are responsible for controlling bodily fluids and especially blood pressure (Guth & Roth 2013, Durmic et al. 2017). The variants associated with an ACE polymorphism (rs1799752) have an influence in terms of reducing and increasing enzymatic activity, alleles I (insertion) and D (deletion) of a 287-base pair (bp) Alu element fragment at intron 16, whit the genotypes (II, ID and DD), respectively (Lima et al. 2011, Costa et al. 2021). The literature reveals that genotype II is associated with a higher percentage of type I fibers than in individuals with genotype DD, and also appears to be associated with greater muscle resistance performance. Genotype DD has been associated with sprint, power, and short-duration activities (Broos et al. 2012, Chen et al. 2015).

The ACTN3 is located within muscle cells in a Z-line, aiding in the actin filament, this gene is specifically expressed in the fast-twitch muscle fibers and codifies α-actinin-3, an actin-binding protein in numerous structural, metabolic, and signaling proteins (Ma et al. 2018). C>T ACTN3 polymorphism (rs1815739) promotes a premature change from arginine (C, cytosine) to stop codon (T, thymine) at amino acid 577 in exon 16 (Wagle et al. 2021), resulting in the absence of the α-actinin-3 protein in type II muscle fibers in individuals with the TT genotype - this is because the truncated protein is rapidly degraded. It has been demonstrated that the absence of α-actinin-3 induces metabolic alterations in the oxidative metabolism, resulting in greater oxidative enzyme activity and lower glycolytic enzyme activity (Costa et al. 2012). It has also been verified that the presence of α-actinin-3 in individuals with the CC genotype leads to an increase in strength generation, an increase in rapid fiber diameter growth, and greater muscular resistance capacity (Chodzko-Zajko et al. 2009). These results indicate that the T and C alleles of ACTN3 polymorphism can lead to opposing phenotypes, resulting in specific advantages in activities that present distinct characteristics.

There are studies in the literature that associate physical and functional capacities with the ACE and ACTN3 genes, however there are few that seek to understand the influence of the genetic characteristics of physically active women within the context of ageing and none of them have investigated the response to different physical training models (Zago et al. 2010).

Thus, the aim of this study is to evaluate the association between genetic polymorphisms (ACE and ACTN3) and the response to multicomponent and combined physical training programs in terms of physical and functional capacities and other health parameters in physically active women aged between 50 and 75.

MATERIALS AND METHODS

Samples collection

70 women took part in the research, who had been practicing regular physical exercise for at least six months, for at least 150 minutes per week, according to the guidelines of the American College of Sports Medicine (ACSM 2011). The participants were recruited from

the Physical Education for Seniors Program, a university extension project of the School of Physical Education and Sport of Ribeirao Preto of the University of São Paulo (EEFERP-USP), and randomly distributed into two groups, multicomponent (n=35) and combined (n=35) training, for a period of 14 weeks.

Participants' medical histories were reviewed at their first visit. The inclusion criteria were being female and aged between 50 and 75 years. The exclusion criteria were the presence of any medical, mental or musculoskeletal conditions which could impede the performance of engine tests and physical training programs; body mass index> 35 kg / m2, maximum systolic BP> 160mmHg and maximum diastolic PA> 100 mmHg; participation in any other physical exercise program in the previous six months or during the intervention proposed by this study; and presence <75% in the activities proposed by the intervention. The participants were subjected to physical and functional capacity evaluations, anthropometric and blood pressure measures, blood collection, and they answered pre and post-intervention questionnaires (Fig. 1).

Ethical aspects

The study was approved by the Research Ethics Committee of the EEFERP-USP (CAAE 45889915.0.0000.5659). Trial registration: RBR-3g38dx Date of registration: May 15, 2018. Before starting this research and signing the free and informed consent form, the participants attended a workshop, in which all the details of the project were presented and all questions answered.

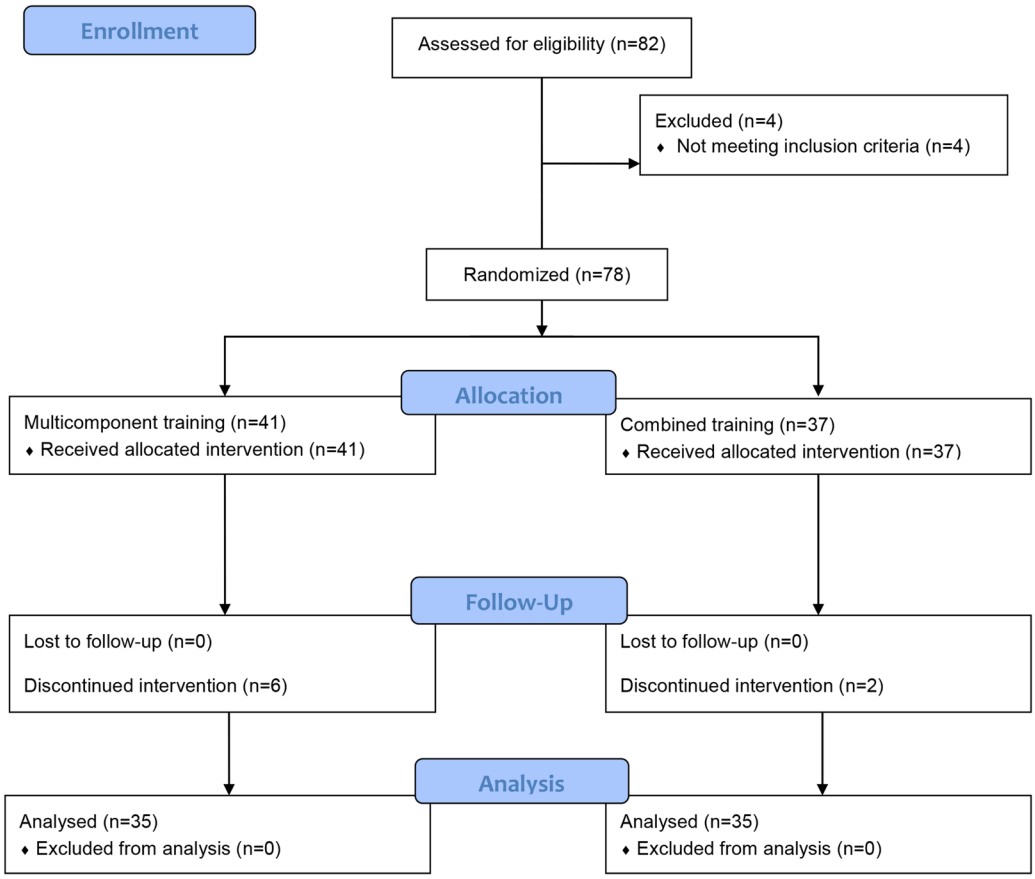

Figure 1. Study Flow Diagram.

Availability of data and materials

The datasets generated during the current study are not publicly available, as the participant consent forms did not address open public access to the data and due to limitations of the research ethics approval. Data are available upon request from the corresponding author on reasonable request and subject to Research Ethics Committee review.

Physical activity level, nutritional evaluation, and quality of life

To evaluate the physical activity level, the short version of the International Physical Activity Questionnaire (IPAQ) (Matsudo et al. 2001) was used. The food habits assessment was carried out using the Food Consumption Markers Form of the Health Ministry, from the Food and Nutritional Monitoring System, which aims to identify how often the interviewee has consumed a number of foods or drinks in the seven days prior to the interview (Ministério da Saúde 2008). Quality of life was assessed by the Short Form 36 (SF-36) questionnaire, translated into Portuguese and validated (Ciconelli 1999).

Anthropometric and blood pressure measures

The following parameters were assessed according to the literature: height, body mass, and body mass index (BMI) (Rattan 2014). Waist circumference was measured at the midpoint between the last costal margin and the iliac crest, with the individual standing and at the maximum point of normal expiration. The tape precision was 1 mm (Rattan 2014). Blood pressure was evaluated using an OMRON® automatic digital arm pressure measuring device, model HEM-7113. The measurement was taken on first contact, with the participant having rested for at least five minutes, according to the 7ª Brazilian Guideline on Arterial Hypertension (Sociedade Brasileira de Cardiologia 2016).

Physical capacities

The upper and lower limb assessments were carried out using the elbow flexion and extension test, in which the participants made elbow flexion and extension movements with their dominant arm in a seated position with a 2.27kg halter, carrying out the maximum repetitions in 30 seconds, and sit-to-stand, which consists of sitting down on and standing up from a chair 45cm in height, as many times as possible in 30 seconds. The shoulder stretch flexibility test was also carried out, in which the distance between the ends of the middle fingers is measured with a ruler; the sit-and-reach test, which uses a chair and consists of measuring the distance between the distal end of the middle finger and the distal end of the toe; and a cardiorespiratory assessment using the six minute walk test (distance traveled on a rectangular track measuring 4.57m × 18.28m - the participants were asked to walk as fast as possible without running) proposed by Rikli & Jones (1999), as well as an agility test in which each participant stood up from a chair and walked around a cone located 1.5m to the right and 1.8m behind, returning as fast as possible to sit on the chair. Immediately, each participant raised their legs from the floor, thus guaranteeing the conclusion of the movement. Then the same movement was begun to the opposite side, completing one cycle. One attempt is equal to two cycles (Osness et al. 1990).

Training load

To control the training load, the TRIMP (training impulse) was calculated as the product between the subjective perception of the physical strength using the Borg scale from 0 to 10 at the end of each training session and the total duration of the session expressed in minutes (Foster 1998). Monotony was calculated by the mean of the

training loads of the sessions (TRIMP) divided by their standard deviation.

Blood analyses

The blood was analyzed at the Clinical Analyses Laboratory of the Ribeirão Preto Faculty of Pharmaceutical Sciences (FCFRP), evaluated by a biochemist and BT 3000 plus auto analyzing device from the Wiener Lab brand. The reagents used for the analysis were from the same batch (LABORLAB) and the methods used were the enzymatic method for uric acid, glycaemia, total cholesterol, and triglycerides. The colorimetric method was used for HDL-cholesterol and LDL-cholesterol was calculated using the Friedewald equation (Warnick et al. 1990).

Genotyping

A peripheral blood sample was collected in EDTA tubes and stored at -80°C. The DNA was extracted from 500 µl of peripheral blood using the salting out method, and the concentration was tested using spectrophotometry (Nanodrop, ThermoScientific - GE). DNA integrity was analyzed by electrophoresis after loading 50 ng of DNA on a 0.8% agarose gel. The ACE I/D (rs1799752) polymorphisms were amplified by the chain reaction of the polymerase (PCR) and the products of the amplification were genotyped using electrophoresis in agarose gel. The primers used were F-5'-CTGGAGACCACTCCCATCCTTTCT-3' and R-5'- GATGTGGCCATCACATTCGTCAGAT -3'. The PCR conditions were: initial denaturation at 95°C for 3 min, 35 cycles at 95°C for 30 s, 58°C for 30 s, 72°C for 30 s, and final extension at 72°C for 10 min. The fragments with insertion (allele I) result in a 490pb amplicon and the fragments without insertion (allele D) result in a 190pb amplicon. Fragments were detected in 1.5% agarose gel containing ethidium bromide. The ACTN3 c.1747 C>T (rs 1815739) polymorphism was determined by PCR in real time (qPCR). The reaction was carried out using the customized Taqman allelic discrimination assay (resynthesis reference number AH51790, Thermo Fisher, USA) and the TaqMan genotyping master mix (Applied Biosystems, USA). The reactions were prepared according to the manufacturer's specifications for each sample: 1x master mix, 1x Taqman genotyping assay, and 50ng of DNA mold in a final volume of 10µl. The real time PCR was carried out in the StepOnePlus equipment (Applied Biosystems, USA) and analyzed using the manufacturer's software (Guth & Roth 2013, Matsudo et al. 2001).

Multicomponent and combined training protocols

The multicomponent training protocol consisted of a session with different types of physical activities and exercises to develop the conditioning motor capacities (cardiorespiratory resistance, strength, flexibility, and speed) and coordinating motor capacities (motor coordination, motor control, motor reaction, and rhythm) (Bompa & Buzzichelli 2015). The sessions lasted 90 minutes, were carried out twice a week, and were divided into three stages: an initial 15 minutes of warm-up, balance, motor coordination, and games, 35 minutes of muscle strength, 35 minutes of aerobic activities, and five minutes relaxing at the end. The training intensity was controlled using a Polar Team heart rate monitoring system and the Borg scale and the goal was to obtain, at the end of each session, values between 6 and 7 on a scale of zero to 10, representing a moderate to difficult intensity (Trapé et al. 2017).

The combined training intervention was carried out three times a week, on alternate days (7:30 in the morning), with a total duration of one hour - approximately 30 minutes of strength exercise and 30 minutes of aerobic exercise. The strength exercises chosen were

the incline chest press, leg curl, leg extension, 180° leg press, neutral-grip triceps extension, pull, bar press, and triceps extension. During the aerobic exercise, the heart rate was continuously monitored using the Polar Team[2] (Polar, Finland). All the participants used the flexible non-linear periodization (Silva Neves et al. 2018). In relation to the resistance training, in the first training session each week, the participants could choose the number of maximum repetitions (MR) that would be carried out on the day, depending on their physical and psychological readiness. The options offered were two series with five to seven MR, 10 to 12 MR, or 15 to 17 MR. During the aerobic training, the participants could choose the heart-rate reserve for carrying out 30 minutes of exercise (70, 60, or 50%). In the second training session each week, the participants chose between the two remaining options in the resistance and aerobic exercises. In the third training session each week, the participants chose the one that had not been chosen in the previous two sessions. The training intensity was also controlled by the Borg scale, with a goal of 6 to 7 at the end of each session.

Statistical analysis

The data analysis was carried out using the STATISTICA statistical program version 7.0. A descriptive analysis was carried out using position and dispersion measures. For the intra and inter-group comparisons, three-way ANOVA was used for repeated measures followed by the Tukey post-hoc test. The genotype distribution was calculated based on the observed genotype distribution and expected genotype distribution according to the Hardy-Weinberg equilibrium using the X^2 test. The significance level adopted was 5%.

RESULTS

The distribution of the ACE DD, ID, and II genotypes was n=21 (30%), n=30 (42.8%), and n=19 (27.2%), respectively. No statistical significance was observed for the Hardy-Weinberg equilibrium (p=0.234). For the ACTN3 genotypes the distribution was TT n=10 (14.3%), TC n=38 (54.3%), and CC n=22 (31.4%). No statistical significance was found for the Hardy-Weinberg equilibrium (p=0.321) in this genotype either, demonstrating that the distributions are in equilibrium.

The age, anthropometric, and blood pressure data for the ACE polymorphism (DD+ID/II) are presented in Table I. In the multicomponent training group, no significant differences were observed for the anthropometric and blood pressure variables in women with the DD+ID genotype pre versus post-training; however, in women with genotype II, a decrease in waist circumference (p=0.029) was observed post versus pre-training. In the combined training group for women with the DD+ID genotype, a decrease in body mass (p=0.02) was observed, and for women with genotype II a decrease in waist circumference (p=0.023) and increase in systolic blood pressure (p=0.017) were observed. In relation to the physical capacities and quality of life data, comparing pre versus post-training, the multicomponent training group presented an increase in its score for the mental domain (p=0.048) of quality of life in women with the DD+ID genotype and an increase in lower limb muscle strength via the sit-to-stand test (p=0.007) in women with genotype II. In the combined training group, an improvement in agility (p=0.005) and cardiorespiratory capacity (p=0.004) was observed in women with genotype DD+ID, and a decrease in lower limb flexibility (p=0.027), improved agility (p=0.007), and increased cardiorespiratory capacity (p=0.003)

Table I. **Anthropometric variables, age, and blood pressure related to ACE polymorphism.**

	MT				CT			
	DD+ID (n=26)		II (n=9)		DD+ID (n=25)		II (n=10)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Age (y)	61.2±6.7		64±7.3		63.5±6.5		60.7±3.7	
Height (m)	1.58±0.4		1.54±0.6		1.59±0.5		1.58±0.6	
BM (kg)	70.4±9.3	70.1±9.3	71.5±9	71±9.5	69.4±15.2	68.5±15*	69.6±14	68.7±14
BMI (kg/m^2)	28.3±4	28.2±3.8	30±3.1	29.9±3.1	27.4±5	27±5.4	27.9±5.6	27.6±5.6
WC (cm)	93.3±8.9	91.2±10.1	97.4±9.8	93.4±9.9*	92.7±11.6	90.8±14.3	91.3±12.2	87.3±12.1*
SBP (mmHg)	123±20.7	123.8±23	132.1±16.4	135.8±20.1	127.8±12.7	130.8±17.8	120.9±9.8	133.4±15.2*
DBP (mmHg)	74±9	73±11.2	80.2±9	79.3±10.4	75.9±9.1	72.9±9.1	72.2±11.4	75.4±8.4

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). BM body mass, BMI body mass index, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, MT multicomponent training, CT combined training. *p <0.05 intragroup differences.

were observed in women with genotype II (Table II).

In relation to ACE polymorphism, no statistical significance was found for the levels of physical activity, food consumption, training impulse, monotony, and blood variables (Tables III and IV). Table V presents the age, anthropometric variables, and blood pressure data of women with genotypes TT+TC and CC for ACTN3 polymorphism. For the multicomponent training group no statistical significance was observed for the anthropometric and blood pressure variables in women with genotype TT+TC post versus pre-training. For the women with genotype CC, a significant reduction in waist circumference (p=0.003) was observed. In the combined training group, in women with genotype TT+TC, significant reductions were observed in the body mass (p=0.009), body mass index (p=0.01), waist circumference (p=0.003), and diastolic blood pressure (p=0.03) values. In the women with genotype CC, an increase in systolic blood pressure (p=0.013) was observed. In relation to the physical capacities and quality of life results for ACTN3 polymorphism, the multicomponent training group demonstrated a significant increase in upper limb strength in the elbow flexion and extension test (p=0.03), in lower limb strength via the sit-to-stand test (p=0.027), and an increase in score for the mental domain (p=0.008) of quality of life in women with genotype TT+TC. In women with genotype CC, no statistical significance was found (Table VI). In relation to the combined training group, an increase in upper limb muscle strength was found via the elbow flexion and extension test (p=0.038), improved agility (p=0.003), and an increase in cardiorespiratory capacity when walking for six minutes (p=0.003) in women with the TT+TC genotype. An improvement in agility (p=0.005) and increase in score in the physical domain (p=0.007) of quality of life were also observed in women with the CC genotype (Table VI).

Regarding to physical activity, food consumption, training impulse, and monotony levels, no significant differences were found in relation to the ACTN3 genotypes in both physical training groups post versus pre-training, with the exception of an increase in the volume of vigorous physical activities for the CC genotype with combined training (p=0.008) (Table VII).

Among the different physical training groups, no statistical significance could be observed in relation to the blood parameter analyses for ACTN3 polymorphism (Table VIII).

Table II. Physical capacities and quality of life of MT and CT groups related to ACE polymorphism.

	MT				CT			
	DD+ID (n=26)		II (n=9)		DD+ID (n=25)		II (n=10)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
SST (rep)	16.2±4.5	16.5±3.4	17.8±4.3	21±4.1*	18.2±5.9	19.8±6.1	18.9±3	21.4±3.5
EFE (rep)	17.2±3.8	18.4±3	21.3±1.5	19.7±4	20.6±5.3	21.7±5.3	19.3±2.4	20.3±3.6
SRT (cm)	0.9±8	-0.5±8.9	3.2±9.6	5.6±8.5	4.7±8.3	4.6±9.3	4.8±10.4	1±9.5*
SSFT (cm)	-6.9±9.4	-6.5±10.7	-2±9.5	-2.3±7.2	-1.1±6.3	-0.5±8.7	-2.6±9.4	-2.6±8.4
Agi (sec)	24.4±2.4	24.2±2.4	23.8±2.7	23.8±3.5	23.4±2.5	22.1±2.7*	23.2±3.6	21.5±3.1*
6MWT (m)	562±54	568±42	523±57	546±56	588±74[&]	625±50[$#]*	575±58	620±37*[#]
SF36 - PD (points)	62.4±8	61.9±9.5	66.1±7.2	69.1±7.6	63.2±7	62.7±7.1	61.8±7.7	65.7±3.7
SF36 - MD (points)	56.5±7.1	58.8±6.4*	60.6±11	63.4±7.5	58.9±6.8	60.6±7.2	57.7±4.5	58.6±5.5

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). SST sit-to-stand test, EFE elbow flexion and extension test, SRT sit-and-reach test, SSFT shoulder stretch flexibility test, Agi agility test; 6MWT six-minute walk test, SF36 quality of life questionnaire, PD physical domain, MD mental domain, MT multicomponent training, CT combined training. *p <0.05 intragroup differences. [$]p <0.05 versus DD+ID MT post. [&]p <0.05 versus II MT pre. [#]p <0.05 versus II MT post

Table III. Physical activity level, nutritional evaluation, and training load of MT and CT groups related to ACE polymorphism.

	MT				CT			
	DD+ID (n=9)		II (n=26)		DD+ID (n=12)		II (n=23)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
IPAQ - Walk (min/wk)	262±285	325±256	147±227	378±425	544±688	418±680	380±713	512±508
IPAQ - MIA (min/wk)	431±499	408±553	847±789	924±895	595±683	550±673	624±541	346±472
IPAQ - VIA (min/wk)	74.2±183.2	83.5±159.1	66.7±85.5	111.1±108.4	166.5±344	188.5±358	243±308	252.5±232
FCMF (points)	18.3±6.7	19.3±5.8	20.3±6.6	25.7±9.4	17.2±11	18.9±7.6	18.9±6.8	20.5±9.4
TRIMP (au)	814±217		925±143.4		928±193.5		796±166	
Monotony (au)	5.1±2		4.5±1.5		3.9±2		4.8±3.8	

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). IPAQ International Physical Activity Questionnaire, Walk walking, MIA moderate-intensity activity, VIA vigorous-intensity activity, FCMF Food Consumption Markers Form, TRIMP training impulse, au arbitrary unit, MT multicomponent training, CT combined training.

Table IV. Blood analyses of MT and CT groups related to ACE polymorphism.

	MT				CT			
	DD+ID (n=17)		II (n=8)		DD+ID (n=24)		II (n=10)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Uric acid (mg/dL)	3.8±1.0	4±1.0	3.5±0.6	3.5±0.8	4±0.8	3.6±0.7	4±1.6	4±1.5
Cholesterol (mg/dL)	174.6±38.2	199.7±30.9	209.4±28.9	216.1±37.9	203.5±38.3	200.3±41.9	205.9±29.9	209.1±52.4
Glucose (mg/dL)	94±13.8	92.8±9.0	91.3±18.2	95.8±26.4	96.1±16.0	92.8±11.9	92±10.2	94.2±11.4
HDL-C (mg/dL)	53.6±14.9	52.2±10.9	55.1±7.7	60.9±11.3	53.3±14.0	53.6±11.6	55.1±8.1	54±10.0
TRIGL (mg/dL)	116.8±65.7	123.7±49.7	129.3±47.4	110±44.5	134.5±75.6	134±74.5	131.1±68.4	114.1±43.5
LDL-C (mg/dL)	126.8±35.7	140.8±32.9	143.2±24.5	127.5±34	139.5±42.7	135.9±48.4	139.8±33.3	144.3±51.4

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). C cholesterol, TRIGL triglycerides, MT multicomponent training, CT combined training.

Table V. Anthropometric variables, age, and blood pressure related to ACTN3 polymorphism.

	MT				TC			
	TT+TC (n=21)		CC (n=14)		TT+TC (n=27)		CC (n=8)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Age (y)	63.3±6.9		59.8±6.3		62.6±6.5		63.3±4.7	
Height (m)	1.58±0.4		1.55±0.5		1.59±0.5		1.56±0.4	
BM (kg)	70.8±12.5	70.5±12.2	70.5±9.5	70±9.9	69.3±9.5	68±9.7*	70.1±14	70.3±14
BMI (kg/m^2)	28.3±4.8	28.4±4.9	29.4±3.4	29±3.4	27.2±3.7	26.8±3.6*	28.6±5.4	28.6±5.7
WC (cm)	92.2±10.9	91.3±13.3	97.7±9.3	92.4±9.6*	91.8±7.2	89.3±8.2$^{\#}$*	93.9±14	91.5±13.7
SBP (mmHg)	122.1±17.2	123.6±20.8	130.2±16.7	131.8±19	126.8±21.9	130±24.5	122.5±7.5	136.8±17.4*
DBP (mmHg)	75.5±10	74.9±10.9	75.8±9.4	74.2±8.8	75.6±8.8	72.2±11.6*	72.6±11	78.4±11.8

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). BM body mass, BMI body mass index, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, MT multicomponent training, CT combined training. *p <0.05 intragroup differences. $^{\#}$p <0.05 versus CC MT post.

Table VI. Physical capacities and quality of life of MT and CT groups related to ACE polymorphism.

	MT				CT			
	TT+TC (n=21)		CC (n=14)		TT+TC (n=27)		CC (n=8)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
SST (rep)	16.3±4.9	18.3±4.4*	17±5.7	16.9±5.6	18.3±3.9	19.9±3.7	18.6±3.5	21.4±4.8
EFE (rep)	17.8±4.3	19.9±4.9*	19.1±5.1	17.1±5.7	20.1±2.7	21.9±3.9$^{\#}$*	20.6±2.8	19.3±3.5
SRT (cm)	2±9.7	-0.7±9.2	0.7±9.5	2.8±10.6	4.7±6.7	3.5±9.3	4.9±7.3	3.6±3.4
SSFT (cm)	-5.9±10.8	-4±9.9	-5.6±6.7	-7.7±8.9	-0.5±8.3	-0.1±10.2	-4.7±8.5	-4.1±7.1
Agi (sec)	23.9±2.7	24.2±2.7	24.8±2.3	23.9±2.2	23.2±2.1	21.9±3*	23.9±4.2	21.9±4.2*
6MWT (m)	555±63.3	571±42.6	549±73.4	550±49	585±50.5	625±48.2*$^{\$\#}$	582±56.4	618±36.6$^{\#}$
SF36 - PD (points)	63.6±7.4	63.8±9.3	62.9±7.6	63.6±6.7	63.4±9	62.6±10.3	60.8±5	66.6±4.2*
SF36 - MD (points)	55.9±9.4	58.9±8.3*	60±6.4	61.6±7.2	58.4±6.6	59.9±4.1	59.2±5.8	60.5±5.4

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). SST sit-to-stand test, EFE elbow flexion and extension test, SRT sit-and-reach test, SSFT shoulder stretch flexibility test, Agi agility test; 6MWT six-minute walk test, SF36 quality of life questionnaire, PD physical domain, MD mental domain, MT multicomponent training, CT combined training. *p <0.05 intragroup differences. $^{\$}$p <0.05 versus TT+TC MT post. $^{\#}$p <0.05 versus CC MT post.

DISCUSSION

Studies of genetic variations have been used to answer questions related to physical training adaptations in the context of aging (Frederiksen et al. 2003). Therefore, it is imperative to analyze the influence of genetic polymorphisms in different intervention models to identify the association of responses to training in genotypes related to the increase or decrease in strength, muscle function, and health parameters in aging (Gomez-Gallego et al. 2009, Lima et al. 2009).

In both polymorphisms, associations with the analyzed physical training were evidenced. Regarding the ACE polymorphism, we can see that multicomponent training resulted in a decrease in waist circumference and improved lower limb strength in women with genotype II. There was also an increase in the score of the mental domain of quality of life in the DD

Table VII. Physical activity level, nutritional evaluation, and training load of MT and CT groups related to ACTN3 polymorphism.

	MT				CT			
	TT+TC (n=21)		CC (n=14)		TT+TC (n=27)		CC (n=8)	
	Pre	Post	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
IPAQ - Walk (min/wk)	251±284	458±454	204±157	159±118	581±766$^{@\&}$	415±542	191±200	549±684
IPAQ - MIA (min/wk)	551±701	610±796	517±786	436±858	679±635	491±595	320±233	506±275
IPAQ - VIA (min/wk)	91.9±138.2	101.4±132	42.9±68.3	74.3±104.4	210.6±356	151.2±162.3	118.8±119.4	390±474$^{*\$\#\%}$
FCMF (points)	17.8±7.3	20±8.1	20.5±7.3	22.4±9.4	18.6±7	18.8±9.7	14.8±11.9	21.4±5.4
TRIMP (au)	827±201		884±104.4		869±208		930±95.5	
Monotony (au)	4.7±2		5.1±1.5		4.5±2.8		3.8±0.8	

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). IPAQ International Physical Activity Questionnaire, Walk walking, MIA moderate-intensity activity, VIA vigorous-intensity activity, FCMF Food Consumption Markers Form, TRIMP training impulse, AU arbitrary unit, MT multicomponent training, CT combined training. *p <0.05 intragroup differences. $^{@}$p <0.05 versus TT+TC MT pre $^{\&}$p <0.05 versus CC MT pre. $^{\$}$p <0.05 versus TT+TC MT post. $^{\#}$p <0.05 versus CC MT post. $^{\%}$p <0.05 versus TT+TC CT post

+ ID genotype. These findings corroborate the research carried out by Moraes et al. (2018), who observed an association of ACE polymorphism with decreased waist circumference, however in ID genotype, and with improvement in lower limb strength in ID and II genotypes after 12 weeks of multicomponent training in women aged 50 to 70 years (Mores et al. 2018). Frederiksen et al. (2003), in their study of older Danish people aged 65 to 94, used multicomponent training for eight months in a 60-minute session per week and showed an increase in fat mass in the DD group. Foschini et al. (2010), in a study with 32 postpuberty obese Brazilian adolescents undergoing a 14-week dietary and exercise intervention, demonstrated equality in the decrease in body mass and the body mass index for the three groups of ECA genotypes. However, they have a limited size sample and a dietary intervention when compared to our study.

In the combined training group, there was a decrease in waist circumference, an increase in systolic blood pressure, worsening flexibility in the lower limbs, and an improvement in cardiorespiratory capacity in women with genotype II. Participants with the DD + ID genotype showed decreased body mass and improved cardiorespiratory fitness. In both genotypes, there was an improvement in agility. Keogh et al. (2015), in a study with physically inactive individuals (69.7 ± 5.3 years), pointed out that the association of the ECA polymorphism with the functional performance of the elderly after 12 weeks of combined training, with improvements in the sit and stand tests, elbow flexion and extension, and 6-minute walk in both DD + ID and II genotypes. However, Garatachea et al. (2012) studied Spanish octogenarians to assess the association between physical performance and ACE I/D polymorphism, and no association was found. The differences observed between the studies can be explained due to the distinction in the physical training protocols, level of physical activity, age, ethnicity, and sex of the participants.

Some studies have investigated ACE inhibitors as a tool to increase the physical capacity of the elderly (Lima et al. 2011), but it is a field that is still little explored and with indefinite results. In the study by Sumukadas et al. (2013), a randomized clinical trial was conducted with older people with functional impairment, coming from long-term institutions or hospitals. The mean age was 76 years for the group that took the medication (perindopril) and 75 years for the control group, in which

Table VIII. Blood analyses of MT and CT groups related to ACTN3 polymorphism.

	MT				CT			
	TT+TC (n=14)		CC (n=11)		TT+TC (n=26)		CC (n=8)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Acid uric (mg/dL)	3.8±0.9	3.7±0.8	3.8±0.8	4.1±1.1	3.8±0.9	3.5±0.7	4.6±1.6	4.3±1.6
Cholesterol (mg/dL)	200.8±36.6	204.8±36.6	195.1±33.6	205.2±31.1	198.1±39	193.8±49.7	221.1±23.5	228.1±22.4
Glucose (mg/dL)	95.3±12.7	95.3±10.4	89.9±18.3	91.5±22	94.8±16	92.1±11.7	95.3±9.3	96.1±11.4
HDL-C (mg/dL)	50.8±12.4	52.5±7.1	58.7±14.2	58.7±15	55.4±13.3	54.8±12.2	49.6±9.5	50.8±6.2
TRIGL (mg/dL)	139.2±65.5	132.9±37.7	95.4±57.9	99.8±56.1	114.1±73.7	118.6±69.5	187.9±72.9	154.4±61.7
LDL-C (mg/dL)	137±38	146±40.3	124.6±24.2	134.8±23.4	131.7±43.3	128±53.9	161.6±26.2	167.2±26.5

Data are presented as mean ± standard deviation (three-way repeated measured ANOVA followed by the post-hoc Tukey's test). C cholesterol, TRIGL triglycerides, MT multicomponent training, CT combined training.

placebo was administered. In both groups, the participants reported having multimorbidities. They underwent 20 weeks of progressive functional training - half of the training was conducted with guidance and supervision, and in the last ten weeks, the sessions were only guided. The main result was an improvement in the 6-minute walk, especially in the group that ingested the ACE inhibitor. In the other physical capacities evaluated and in the quality of life, there was no difference between the groups, although they have improved. The authors state that the intervention time was short and recommend the analysis of the phenotype of the older adults who use ACE inhibitors for long periods, in addition to analyzing the level of previous physical activity before each intervention (Sumukadas et al. 2013) Such results demonstrate the importance of genetic analysis of ACE before using a medication, which may not display positive outcomes for individuals with specific genetic characteristics (Guth & Roth 2013).

Regarding the ACTN3 polymorphism for the multicomponent training group, decreased waist circumference was found in women with CC genotype and improvement in the elbow flexion and extension test, sitting and standing, and mental domain of quality of life in women with TT + TC genotypes. As in the present study, Delmonico et al. (2007) found no difference in body mass index after ten weeks of strength training in older adults (men and women) physically inactive. For the ACTN3 polymorphism, we found no statistically significant differences in the flexibility values, which differs from the findings by Kikuchi et al. (2017), who researched the association of ACTN3 polymorphism with flexibility in women and men aged 23 to 87 years in two cohorts and demonstrated that the TT genotype was associated with lower values when compared to the TC and CC genotypes. Our study found no effect on cardiorespiratory fitness with multicomponent training. However, Silva et al. (2015), in a study with healthy adults, demonstrated that 18 weeks of cardiorespiratory resistance training had a positive association between the TT genotype and aerobic resistance - and after the intervention, there were no differences between groups.

Erskine et al. (2014) showed no differences in muscle strength and power in the genotype groups after nine weeks of strength training in the elderly. Gentil et al. (2011) investigated 141 participants over 18 years of age who performed resistance exercise for 11 weeks and underwent

strength tests, muscle biopsy, and genetic analysis. According to the results, there were also no differences in the gain of strength and muscle mass between the groups of ACTN3 genotypes. In our results, both in multicomponent and combined training, only the TT + TC group had higher strength values in the post-intervention moment when compared to the pre.

In the combined training group, we observed a decrease in body mass, body mass index, waist circumference, diastolic blood pressure, improvement in the elbow flexion and extension test, and six-minute walk in women with TT + CT genotypes. In contrast, for the CC genotype, an increase in systolic blood pressure and an improvement in the physical quality of life domain were observed - for agility, an improvement was observed in both TT + TC and CC genotypes. Potocka et al. (2019) studied the association of ACTN3 polymorphism with cardiorespiratory fitness in healthy young adults and observed that women with the CC genotype had lower maximum heart rate, which could indicate better functioning of the circulatory and respiratory system and better adaptation to physical exercise - no difference was noted in men. Evidence suggests that the CC genotype is associated with higher bone mineral density in older women, which may be favorable for the prevention of falls, impairment of functional capacity, decreased quality of life, and less likelihood of hospitalization and death (Min et al. 2016).

Clarkson et al. (2005) studied the association of ACTN3 polymorphism with increased muscle strength and the response of 12 weeks of strength training in men and women. They found that homozygous TT women had lower isometric muscle resistance and demonstrated more significant absolute and relative strength gains in the test of a maximum repetition after training compared with those with the homozygous wild type (TT) and the heterozygous genotype (TC). In our study, women with the TT + TC genotype were the only group to show improvement in the upper limb strength test.

In the present study, we did not observe the effect of physical training on the level of physical activity of the participants, as well as in another study that evaluated the association of ACE and ACTN3 polymorphisms during 12 weeks of multicomponent training in elderly women (Moraes et al. 2018). This result is related to the fact that the questionnaire was applied after the end of the intervention with physical training.

Regarding blood tests, our study did not observe positive effects in 14 weeks of training. However, the study by Motallebi et al. (2019) demonstrated a decrease in total cholesterol and an increase in HDL-cholesterol in physically inactive older women after 24 weeks of physical training associated with nutritional monitoring. Thus, we can emphasize that the characteristics of the sample, dietary intervention, and training time may have influenced the magnitude of the individuals' responses.

The fact that there are controversial results in the literature reinforces the importance of further studies in different populations. Such knowledge can identify individuals who are more likely to benefit from each type of physical exercise. In this way, the genetic characteristics would have numerous applications in professional practice, having the potential for, within a few years, to determine the best physical training program for each individual.

Strengths and limitations

We used the tests proposed by Rikli & Jones and AAHPERD due to the reliability, validity, ease of administration, viability for use in different locations, and especially because they are a good tool for accessing physical parameters

associated with functional mobility in seniors, taking into consideration the declines associated with the ageing process. We also used easily-applicable physical training protocols, with well-controlled and equal volumes and intensities, and which show health benefits in those who are ageing. Some limitations in this study can also be considered, such as the sample size, which was relatively small for genetics studies.

CONCLUSIONS

ACE (DD+ID vs II) and ACTN3 (TT+TC vs CC) polymorphisms are related to more benefits in physical/functional capacities and health parameters of physically active women aged 50 to 75 in both physical training groups.

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Karine P Rodrigues (KPR), Laís Souza Prado (LSP), and Carlos R Bueno Júnior (CRBJ) contributed to the conception and design of the study and to writing the manuscript. KPR, LSP, Atila Alexandre Trape (AAT), and Mariana Luciano de Almeida (MLA) carried out the data collection in physical and functional evaluations, DNA extraction, genotyping, and applying questionnaires. KPR and CRBJ conducted the data analysis and compiled the tables of study results. All the authors reviewed the manuscript and approved the final version.

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