TNF- α , IL6, and IL10 polymorphisms and the effect of physical exercise on inflammatory parameters and physical performance in elderly women

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Abstract High levels of inflammatory mediators are associated with reduced physical capabilities and muscle function in the elderly. Single nucleotide polymorphisms (SNPs) may affect the expression and synthesis of these molecules, thus influencing the intensity of the inflammatory response and susceptibility to certain diseases. Physical exercise may attenuate age-related chronic inflammation and improve physical performance. This study evaluated the interaction between the SNP rs1800629 in TNF- α , rs1800795 in IL6, and rs1800896 in IL10 and the effect of physical exercise on physical performance and inflammation in elderly women. There was a significant interaction

between rs1800629 and the effect of exercise on physical performance and between the combined 3-SNP genotype and changes in physical performance in response to exercise. These SNPs did not influence the effect of exercise on inflammatory parameters. Elderly women with a combination of genotypes associated with an anti-inflammatory profile (low TNF- α and IL-6 production, high IL-10 production) showed better physical performance independent of exercise modality, evidence of an interactive influence of genetic and environmental factors on improving physical performance in elderly women.

Keywords Polymorphism · Cytokines · Physical exercise · Elderly

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Introduction

Aging is associated with chronic, sub-threshold inflammation, characterized by a two- to fourfold systemic increase in the plasma levels of inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor alpha (TNF- α), and IL-6 (Krabbe et al. 2004). An imbalance in the production and release of these cytokines has been associated with the appearance or worsening of age-related chronic conditions and increased mortality in the elderly (Gallucci et al. 2007; Krabbe et al. 2004). High levels of cytokines are

associated with reduced physical performance and muscle function (Oliveira et al. 2008; Schaap et al. 2009; Tiainen et al. 2010).

Interindividual variability in the expression of inflammatory mediators may occur because of functional genetic variations in the promoters region of genes encoding these molecules (Bidwell et al. 1999; Maat et al. 2004), the most common are the single nucleotide polymorphisms (SNPs). SNPs may affect genetic transcription and cytokine synthesis (Bidwell et al. 1999; Maat et al. 2004), altering the intensity of the inflammatory response and individual susceptibility to certain diseases (Lio et al. 2003; Maat et al. 2004; Stephens et al. 2007).

The TNF- α -308G/A (rs1800629), IL6 -174G/C (rs1800795), and IL10 -1082G/A (rs1800896) SNPs are associated with age-related diseases such as Alzheimer's (Vural et al. 2009), type-2 diabetes (Stephens et al. 2007), and cardiovascular disease (Maat et al. 2004), as well as with longevity (Khabour and Barnawi 2010; Lio et al. 2003). These SNPs are also associated with a predisposal toward a pro-inflammatory cytokine profile. Therefore, the presence of the -308A allele of TNF- α and -174GG IL6 homozygosity are associated with higher plasma levels of TNF- α (Karimi et al. 2009) and IL6 (Olivieri et al. 2002; Pereira et al. 2011). The presence of the -1082A allele of IL10 is associated with lower production of this mediator (Turner et al. 1997).

Regular physical activity may reduce the levels of inflammatory cytokines, thus reducing the effects of the chronic inflammatory process related to aging and chronic disease (Beavers et al. 2010; Petersen and Pedersen 2005). Physical exercise is also considered one of the most effective strategies for improving physical performance in the elderly (Gu and Conn 2008; Latham et al. 2004) and reducing plasma levels of inflammatory mediators (Kohut et al. 2006; Phillips et al. 2010). In this context, the genes involved in regulation of chronic inflammation may contribute not only to individual variation in cytokine production but also to the response of these variables to physical exercise.

Cytokines act in a complex and coordinated network in which their functions may be modified, replaced, or modulated by other cytokines (Bidwell et al. 1999). Therefore, investigating a polymorphism in a single cytokine without considering its interaction with the genotypes of other cytokines may lead to misinterpretation since their combined activity may lead to different effects.

Since genetic variations may influence cytokine production, we hypothesize that genetic polymorphisms in modulators of the inflammatory process may interact with the effects of physical exercise on inflammatory and physical parameters in elderly individuals. This clinical trial, registered in the Brazilian Registry of Clinical Trials [Registro Brasileiro de Ensaios Clínicos (ReBEC: RBR9v9cwf)], investigated the interaction between -308G/A of TNF- α (rs1800629), -174G/C of IL6 (rs1800795), and -1082G/A of IL10 (rs1800896) and the effect of physical exercise on inflammatory and physical parameters in elderly women.

Methods

The study protocol and methods have been previously described in detail (Pereira et al. 2012). The study population included 451 community-dweller elderly women aged 65 or older, all of whom led a sedentary lifestyle. Individuals who did not perform regular physical activity (three times per week for at least 40 min during the 3 months prior to recruitment) were considered to lead a sedentary lifestyle. The exclusion criteria included cognitive alterations detectable by the Mini Mental State Examination (Bertolucci et al. 1994; Folstein et al. 1975), considering cut-off points of 13 for illiterate individuals, 18 for those with 1 to 7 years of schooling, and 26 for those with eight or more years of schooling; acute inflammatory or infectious disease; neoplasia in the last 5 years; immunosuppressant drug use; lower limb amputation; surgeries on or fractures in the lower limbs in the last 6 months; presence of neurologic illnesses or sequelae; and previous participation in other physical activity programs.

The study was approved by the Ethics and Research Committee of the Universidade Federal de Minas Gerais/UFMG (ETIC 038/2010), and all the volunteers signed a free and informed consent form agreeing to participate in the study, according to the principles of the declaration of Helsinki (1969).

Plasma levels of sTNFR1, sTNFR2, IL-6, and IL-10

Peripheral blood (5 mL) was collected in citrate vacutainers. Blood collection took place between 8 and 10 a.m. to minimize circadian effects. The vacutainer tubes were centrifuged at 1,500 rpm for 15 min; plasma was removed in a sterile environment and stored in

Eppendorf tubes at -80°C . Cytokine plasma concentrations were quantified by ELISA (enzyme-linked immunosorbent assay), using the DuoSet ELISA kit (R&D Systems, Minnesota, MN, USA) for sTNFR1 and sTNFR2 and high-sensitivity kits (Quantikine®HS, R&D Systems Minneapolis) for IL-6 and IL-10, according to manufacturer protocols. Blood collection was performed in the resting state before beginning the training program (48 h after performing the physical tests) and after (at least 72 h after the last exercise session). The assay detection limits for sTNFRs, IL-6, and IL-10 were 5, 0.15, and 0.75 pg/mL, respectively.

Physical performance

Physical performance was evaluated using the Timed Up and Go (TUG) (Podsiadlo and Richardson 1991) and 10-m walking speed (10MWT) tests (VanSwearingen and Brach 2001). TUG measures the time (seconds) required for an individual to stand up from a standardized chair (seat height 47 cm, no arm rests), walk 3 m, turn 180° , return, and sit back down in the chair. The test provides high intra- and interobserver reliability ($\text{ICC}=0.99$ and $\text{ICC}=0.99$; Podsiadlo and Richardson 1991).

To evaluate walking speed, participants were instructed to walk a 10-m path at their usual walking speed (self-selected). A verbal command was given to initiate the procedure, and time (seconds) was registered for the six central meters, laterally identified by marking tape, to avoid the acceleration/deceleration bias of the first and last 2 m. The 10MWT provides good intra- and interobserver reliability ($\text{ICC}=0.78$ and $\text{ICC}=0.93$; VanSwearingen and Brach 2001).

Other measurements

Social and demographic data and information regarding clinical status were obtained via a structured questionnaire, administered during an interview by trained researchers. The body mass index (BMI; kilograms per square meter), expressed by the relationship between body weight in kilograms and height in meters, was used as an anthropometric measure. For the evaluation of body mass, portable digital scale (G-Tech/BALGLA3C) was used, and for height, an inelastic tape measure was used.

Genotyping

Peripheral blood samples were collected in EDTA vacutainers. The blood was extracted in a sterile environment and stored in a freezer at -80°C . Genomic DNA was isolated from 500 μL peripheral blood by phenol-chloroform extraction. DNA quality and integrity were evaluated by spectrophotometry (Nanodrop, Thermo Scientific-GE) at 260 and 280 nm (A_{260} and A_{280}). Samples were stored at -20°C until analysis.

Genotyping was performed with validated TaqMan genotyping assays (Applied Biosystems, Inc., Foster City, CA, USA) for TNF (rs1800629; assay ID: C__7514879_10) and IL10 (rs1800896; assay IDs: C__1747360_10). The IL6 genotype (rs1800795) was performed with the following primers and probes: forward (GAGGACCTAAGCTGCACTTTTC) and reverse (GGGCTGATTGGAAACCTTATTAAGATTG); probe A (*VIC*-CCTTTAGCATCGCAAGAC-*MGB-NFQ*) and probe B (*FAM*-CTTTAGCATGGCAAGAC-*MGB-NFQ*).

DNA amplification and genotyping were performed in 384-well plates on a GeneAmp PCR system 9700HT (Applied Biosystems, Inc., Foster City, CA, USA). Reactions contained 0.25 μL TaqMan SNP Genotyping Assay (20 $\times$), 2.5 μL Master Mix (2 $\times$), and 15 ng DNA in 2.25 μL DNase-free H_2O , in a total volume of 5 μL . At least two negative controls and one positive control were included in each run. Genotype discrimination and plotting were performed in Sequence Detection System (SDS; Applied Biosystems) software.

Intervention

Subjects were allocated to muscle strengthening exercise (SE) and aerobic exercise (AE) groups. Both protocols lasted 10 weeks and included 30 sessions performed three times per week under direct supervision by physiotherapists. During the training period, the volunteers were instructed to maintain their usual activities and not to initiate other physical exercise programs.

SE Protocol The exercise session included 10 min of walking, followed by stretching exercises for the rectus femoris and the psoatic, ischiosural, and triceps surae muscles. The resistance exercise was conducted in therapeutic gym. Muscle strengthening exercises included flexion, abduction, adduction, and extension

of the hip (two sets, ten reps; after 2 weeks: three sets, eight reps), flexion and extension of the knee (two sets, ten reps; after 4 weeks: three sets, eight reps), and mini squats (two sets, ten reps; after 2 weeks: three sets, eight reps). The load, individualized for each participant, was defined by calculating a maximal resistance (RM). The participants initiated exercise at 50 % RM and increased to 75 % after 2 weeks (seventh session). In the 13th and 22nd sessions, the RM was recalculated, with the exercises carried out at 75 % of the new RM (Lustosa et al. 2010). Blood pressure and heart rate were measured at the beginning and end of each session. The program consisted of a total of 30 1-h sessions.

AE Protocol The aerobic exercise protocol consisted of 5 min of warm up; 40 min of aerobic activity, including walking and free exercises (calisthenics exercises) for the upper and lower limbs; and 5 min cool-down as suggested by the American College of Sports Medicine (Chodzko-Zajko et al. 2009). During the warm-up and recovery periods, heart rate was maintained at 60 % of the age-predicted maximum heart rate (HRmax); during exercise, it was maintained between 65 % and 80 % of HRmax. To ensure heart rate was maintained within appropriate training limits, participants were monitored with heart rate monitors. The work overload (movement speed and walking speed) was progressively increased so that the HR was maintained within training range. Blood pressure and heart rate measurements were performed at the beginning and end of each training session. The aerobic exercise was conducted in a sport hall, outside.

Statistical analysis

Descriptive statistical analysis using central trend measurements (mean and median) and variability (amplitude and standard deviation) was performed for sample characterization. Normal data distribution was verified by the Kolmogorov–Smirnov test. Hardy–Weinberg equilibrium was assessed by using the chi-square test for each SNP.

Genotypes were grouped according to allelic variants related to modulation of plasma levels of inflammatory mediators, i.e., high vs. low production of cytokines: IL-6 (rs1800795): GG versus CC+GC; TNF- α (rs1800629): AA+AG versus GG; and IL-10 (rs1800896): GG versus AA+AG.

Interaction between polymorphisms and the effects of exercise on inflammatory parameters and physical performance (determined by the TUG and 10MWT) was investigated using a covariance analysis (ANCOVA). The difference between post-intervention and baseline (delta) values was considered a dependent variable, while polymorphisms and intervention constituted independent variables (fixed factors). Analyses were adjusted for BMI, stress levels, and depressive symptoms. Bonferroni correction was used to adjust the level of significance due to multiple comparisons. We considered alpha equal to 5 % for statistical significance. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 17.0.

Results

Four hundred and fifty-one elderly female community residents met the inclusion criteria; 229 were allocated to the SE group and 222 were allocated to the AE group, with a loss rate of 21.3 % for the SE group and 25 % for the AE group. During the study, two individuals were excluded from the AE group because they were diagnosed with cancer.

Sample characteristics are shown in Table 1. Genotypes were consistent with Hardy–Weinberg ($p > 0.05$). Genotype frequencies for each polymorphism are shown in Table 2. There was no significant difference in genotype distribution between exercise programs.

At baseline, there was no significant difference between genotypes of IL6 (rs1800795): GG versus CC+GC; TNF- α (rs1800629): AA+AG versus GG;

Table 1 Social, demographic, and clinical characteristics of subjects in the muscle strengthening exercise (SE) and aerobic exercise (AE) groups before intervention

Variables	SE ($n=229$)		AE ($n=222$)		p value
	Mean	SD	Mean	SD	
Age (years)	71.03	4.8	70.33	4.5	0.123
School (years)	6.12	4.17	6.71	4.42	0.144
MMSE	26.03	2.97	25.9	2.71	0.436
No. of comorbidities	2.63	1.57	2.65	1.70	0.775
BMI (kg/m^2)	29.12	4.8	28.97	4.79	0.874

Mann–Whitney test, $\alpha=5\%$

MMSE mini mental state examination, BMI body mass index

Table 2 Genotype frequencies of –308A/G TNF- α , –174G/C IL6, and –1082A/G IL10 in the muscle strengthening exercise (SE) and aerobic exercise (AE) groups

Genotypes	SE (n=229)	AE (n=222)	Total sample	p value
TNF-α (−308G/A)				
GG	170 (74.2 %)	155 (70.5 %)	325 (72.4 %)	0.795
AA	4 (1.7 %)	7 (3.2 %)	11 (2.4 %)	
AG	55 (24.0 %)	58 (26.4 %)	113 (25.2 %)	
IL6 (−174G/C)				
GG	140 (61.1 %)	117 (53.2 %)	257 (57.2 %)	0.096
CC	12 (5.2 %)	14 (6.4 %)	26 (5.8 %)	
GC	77 (33.6 %)	89 (40.5 %)	166 (37.0 %)	
IL10 (−1082G/C)				
GG	32 (14.0 %)	27 (12.3 %)	59 (13.1 %)	0.413
AA	81 (35.4 %)	87 (39.5 %)	168 (37.4 %)	
AG	116 (50.7 %)	186 (84.2 %)	222 (49.4 %)	

Mann–Whitney test, $\alpha=5\%$ TNF- α tumor necrosis factor alpha, IL6 interleukin-6, IL10 interleukin-10

and IL10 (rs1800896): GG versus AA+AG for any inflammatory or functional parameter. There was no significant interaction between genotype and variables at baseline ($p>0.05$).

There was a significant interaction between the –308 polymorphism of TNF- α and the effect of exercise on TUG test performance ($F=10.5$; $p=0.001$), independent of the exercise type ($F=0.001$; $p=0.996$). Individuals homozygous for the G allele presented a higher percentage of change with exercise, with better functional performance in comparison to individuals with genotypes AA+AG (Fig. 1). There was no interaction between IL6 and IL10 polymorphisms and the effects of exercise on

TUG test performance ($p>0.05$). Once the interaction between polymorphisms and the effect of exercise on outcomes was analyzed independent of the type of exercise performed, the combined results of SE and AE groups are presented in Table 3.

Significant interaction was observed between the three polymorphisms and improvement in TUG performance after exercise ($F=13.9$; $p=0.001$). Individuals with combined genotypes TNF- α GG, IL6 CC+CG, and IL10 GG (low production of TNF- α and IL-6 and high IL-10 production) showed greater improvement in TUG in comparison to other genotypes ($p=0.001$). This interaction was significant, regardless of the exercise program ($F=0.001$; $p=1.0$). There was no significant interaction between the investigated polymorphisms and the effects of exercise on 10MWT ($p>0.05$).

There was no interaction between TNF- α , IL-6, and IL-10 and the effects of exercise on any of the analyzed cytokines ($p>0.05$). There were also no observed interactions between polymorphisms for these variables.

Discussion

We observed a significant interaction between the TNF- α –308A/G polymorphism and the effect of exercise on physical performance in elderly women, as evaluated by the TUG test. Likewise, three polymorphisms, that is, TNF- α –308A/G, IL6 –174G/C, and IL10 –1082A/G, in combination influenced changes in physical performance, independent of the exercise type. Individuals with genotypes related to low TNF- α

Fig. 1 Changes in Timed Up and Go test (delta) performance according to the TNF- α –308G/A genotype. TNF- α tumor necrosis factor alpha; Timed Up and Go (time in seconds)

Table 3 Inflammatory and functional parameters at baseline and after exercise according to the TNF- α , IL6, and IL10 genotypes

Variables		TNF- α (-308G/A) ^a		IL6 (-174G/C) ^a		IL10 (-1082G/C) ^a	
		GG	AA+AG	GG	CC+CG	GG	AA+AG
sTNFR1	Baseline	1,104.17 $\pm$ 485.7	1,186.03 $\pm$ 668.6	1,114.7 $\pm$ 582.5	1,142.8 $\pm$ 486.4	1,244.7 $\pm$ 576.0	1,108.9 $\pm$ 536.2
	Delta	-42.4 $\pm$ 292.9	-38.8 $\pm$ 439.5	-17.6 $\pm$ 350.7	-73.6 $\pm$ 329.8	-18.8 $\pm$ 327.0	-44.4 $\pm$ 345.2
sTNFR2	Baseline	3,362.5 $\pm$ 1,403.9	3,360.1 $\pm$ 1,411.6	3,340.1 $\pm$ 1,426.5	3,390.9 $\pm$ 1,377.6	3,869.6 $\pm$ 1,263.6	3,285.0 $\pm$ 1,410.2
	Delta	-116.4 $\pm$ 978.7	-19.4 $\pm$ -117.7	-173.2 $\pm$ 1,032.8	29.5 $\pm$ 1,287.7	-275.5 $\pm$ 1,078.0	-61.3 $\pm$ 1,159.1
IL-6	Baseline	2.2 $\pm$ 3.5	1.8 $\pm$ 3.1	2.1 $\pm$ 3.5	2.2 $\pm$ 3.3	2.2 $\pm$ 3.5	2.1 $\pm$ 3.4
	Delta	0.13 $\pm$ 2.5	0.09 $\pm$ 1.8	0.2 $\pm$ 2.3	0.03 $\pm$ 2.3	-0.2 $\pm$ 2.4	0.2 $\pm$ 2.3
IL-10	Baseline	7.7 $\pm$ 13.7	6.9 $\pm$ 11.8	7.1 $\pm$ 11.7	8.2 $\pm$ 14.9	6.9 $\pm$ 10.9	7.7 $\pm$ 13.5
	Delta	-1.6 $\pm$ 13.2	-0.1 $\pm$ 5.4	-1.1 $\pm$ 8.9	-1.3 $\pm$ 14.2	-0.8 $\pm$ 6.1	-1.2 $\pm$ 11.9
TUG ^a (seconds)	Baseline	10.4 $\pm$ 1.8	10.3 $\pm$ 1.8	10.4 $\pm$ 1.8	10.3 $\pm$ 1.7	10.6 $\pm$ 1.8	10.3 $\pm$ 1.7
	Delta	-1.5 $\pm$ 5.4	-0.93 $\pm$ 1.7	-1.1 $\pm$ 1.9	1.7 $\pm$ 6.8	-2.9 $\pm$ 1.2	-1.1 $\pm$ 1.7
Walking (seconds)	Baseline	5.0 $\pm$ 0.95	4.9 $\pm$ 1.1	10.3 $\pm$ 0.9	5.1 $\pm$ 1.0	5.2 $\pm$ 0.7	5.0 $\pm$ 1.0
	Delta	-0.37 $\pm$ 0.81	-0.29 $\pm$ 0.87	-0.2 $\pm$ 0.8	-0.5 $\pm$ 0.8	-0.36 $\pm$ 0.8	-0.34 $\pm$ 0.83

Data presented as mean $\pm$ SD; ANCOVA, $\alpha=5\%$

sTNFR1, *sTNFR2* soluble receptors of TNF- α 1 and 2; *IL6* interleukin-6; *IL10* interleukin-10; *TUG* Timed Up and Go test (seconds)

^a Interaction between polymorphisms and the effects of physical exercise on the Timed Up and Go test

(-308AA+AG) and IL6 (-174GG) and high IL-10 (-1082GG), an “anti-inflammatory” profile (Lio et al. 2003), showed better improvement in post-intervention physical performance.

Cytokine levels and physical performance at baseline did not significantly differ between genotypes, and we did not observe any interactions between the polymorphisms for any of the variables. Some research has shown the effect of TNF- α -308A/G, IL6 -174G/C, and IL10 -1082A/G on cytokine production (Karimi et al. 2009; Olivieri et al. 2002; Pereira et al. 2011; Turner et al. 1997) and in different health conditions (Khabour and Barnawi 2010; Stephens et al. 2007), while other studies have produced conflicting results (Cederholm et al. 2007; Kubaszek et al. 2003; Liu et al. 2008). These inconsistencies may be related to several factors, from study population heterogeneity, including characteristics such as age, gender, and specific health conditions, to small sample sizes. In addition, aging and age-related health conditions are complex phenotypes influenced by interactions between polymorphisms and environmental factors, all of which may yield differential modulation of gene expression.

Elevation of inflammatory cytokine levels in plasma is associated with reduced physical performance and independence in the elderly (Tiainen et al. 2010).

TNF- α is a pro-inflammatory cytokine with a potent catabolic effect on muscle (Reid and Li 2001). Considering the short half-life and low circulating levels of TNF- α , its soluble receptors represent more reliable markers of activity and, therefore, of inflammatory response (Aderka et al. 1992; Coelho et al. 2008). Increased levels of TNF- α and its soluble receptors are associated with sarcopenia, a predictive factor for incapacity and mortality in the elderly (Schaap et al. 2009; Visser et al. 2005). Studies have shown that the -308G/A polymorphism of TNF- α may influence circulating levels of this cytokine (Karimi et al. 2009) and longevity (Khabour and Barnawi 2010; Lio et al. 2003). TNF- α -308 A is a strong activator of TNF- α transcription, associated with high plasma TNF- α levels and higher expression of this cytokine in muscles (Karimi et al. 2009).

Although it did not influence the changes in inflammatory parameters, the -308G/A polymorphism of TNF- α showed significant interaction with the effect of physical exercise on physical performance. Individuals with genotype -308GG, associated with lower TNF- α production, showed a better percent improvement in TUG test results than A allele carriers, regardless of the exercise modality. In contrast, Nicklas et al. (2005) observed that individuals with the A allele had better functional performance after

exercise. This contrast may be related to the sample characteristics of the Nicklas et al. (2005), which included patients who were overweight or obese, with osteoarthritis of the knee. Body adiposity and osteoarthritis are potential confounding factors, as both conditions are characterized by increased production of inflammatory cytokines (Mohamed-Ali et al. 1999; Webb et al. 1998). Therefore, the effect of polymorphisms in these conditions may differ, particularly as adipose tissue a major source of circulating TNF- α (Mohamed-Ali et al. 1999).

The IL6 -174G/C and IL10 -1082A/G polymorphisms had no individual influence on the effect of exercise on any of the variables of physical performance. Our results for IL6 -174G/C were similar to those described previously (Nicklas et al. 2005). This is the first report to describe the influence of IL10 -1082A/G on the effects of exercise in the elderly.

Since cytokines act as a complex and coordinated network (Bidwell et al. 1999), investigating a single cytokine may be too simplistic, since the combined action of several genotypes may produce different results. We identified an interaction between TNF- α -308G/A, IL6 -174G/C, and IL10 -1082G/A and changes in functional capacity in the elderly after exercise. The combination of genotypes associated with low TNF- α (-308AA+AG) and IL-6 (-174GG) production and high IL-10 (-1082GG) production, the “anti-inflammatory” profile, was associated with a better percent improvement in TUG test performance in elderly women. However, no significant interaction was observed between any of the studied polymorphisms and the effect of exercise on 10MWT. The 10MWT and TUG tests are widely used to evaluate physical performance in the elderly, in research and clinical practice (Podsiadlo and Richardson 1991; VanSwearingen and Brach 2001). Although considered a predictor of adverse events in the elderly population, walking speed is a simple test to assess individual performance on a straight 10-m walk at normal walking speed (VanSwearingen and Brach 2001). The TUG test, on the other hand, involves a series of motor tasks requiring integration of the motor, sensory, and cognitive systems required for daily activities and essential for independent mobility (Podsiadlo and Richardson 1991). Thus, differences in the components and domains of physical performance involved in each test may provide a higher sensitivity when evaluating the influence of genetic factors.

High plasma levels of TNF- α and IL-6 are associated with reduced physical performance and the ability to perform everyday tasks (Tiainen et al. 2010; Visser et al. 2005), and are predictors of disability in the elderly population (Gallucci et al. 2007). On the other hand, anti-inflammatory cytokines such as IL-10 have been associated with successful aging and longevity (Lio et al. 2003). Therefore, variations in these cytokines influence the inflammatory response in the elderly, such that a balance between pro- and anti-inflammatory responses may be critical to the maintenance of functional ability. Thus, the results of this study suggest that a genotype related to low-intensity inflammatory response yields a better response to physical intervention, which may contribute to better physical performance in the elderly. This hypothesis is supported by findings from other studies in which the combination of genotypes related to an anti-inflammatory profile were associated with longevity (Lio et al. 2003) and constituted a protective factor against cognitive decline in nonagenarians (Dato et al. 2010) and in Alzheimer's disease (Vural et al. 2009).

There was no significant interaction between the effect of physical exercise on cytokine production and the studied polymorphisms, considered separately or in combination. Few studies have evaluated the interaction of polymorphisms and the effects of physical exercise on cytokine production (Kilpelainen et al. 2010; Oberbach et al. 2008). For example, Oberbach et al. (2008) observed that the polymorphism IL-6 -174G/C was predictive of changes in plasma IL-6 levels in pre-diabetic individuals who underwent an aerobic exercise program; Kilpelainen et al. (2010), with a similar sample, found that IL-6 plasma concentrations were not affected by the polymorphism. No published research has focused on this topic in the elderly population.

Some limitations must be addressed. The fact that the sample comprised only women restricts the generalization to the elderly population as a whole, since gender differences may influence gene expression (Roth et al. 2003). It is also important to consider that other polymorphisms not evaluated may influence the effects of exercise in the elderly population. However, the strengths of this study include the fact that it covers polymorphisms in cytokine genes relevant to the inflammatory process. In addition, the analysis of genetic, inflammatory, and functional parameters integrates experimental and clinical data, broadening our understanding of the association between these factors in preventive and therapeutic approaches in the elderly.

The results of this study demonstrated that promoter polymorphisms in TNF- α , IL6, and IL10 interact with each other and the effect of exercise on physical performance. Elderly women with a genotype combination associated with an anti-inflammatory profile showed a better percent improvement in functional physical performance, independent of training modality. These findings suggest that genetic and environmental factors, like the practice of physical exercise, interact and contribute to the improvement of functional ability in elderly women.

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