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ORIGINAL ARTICLE

Strength training enhances endothelial and muscular function in postmenopausal women

La musculation améliore la fonction endothéliale et musculaire chez les femmes ménopausées

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Summary
Objectives. — The aim of this study was to evaluate the effect of sixteen weeks of strength training on forearm blood flow (FBF) and nitric oxide (NO) production at rest induced by exercise in postmenopausal women.
Equipment and methods. — Twenty postmenopausal sedentary women 60 ± 5 years participated in this study. The volunteers were randomly assigned into two groups: The trained group (TG, $n = 10$), performed 3 sessions of approximately 1 hour of strength exercise per week during 16 weeks, and the control group (CG, $n = 10$), did not perform the systematic physical activity. Forearm blood flow was measured by venous plethysmography and the measurements of nitric oxide production by Griess assay. The measurements were performed before and after training with subjects at rest and undergoing a protocol of handgrip.
Results. — After strength training TG increased significantly FBF values after exercise (3.98 ± 1.81 vs. 2.37 ± 1.03 ml.100 ml^{-1}.min^{-1}; $P < 0.05$), and the post-exercise values were greater than post-exercise values observed before training (3.98 ± 1.81 vs. 2.74 ± 0.61 ml.100 ml^{-1}.min^{-1}; $P < 0.05$) and there was a significant decrease in plasma

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concentration of $NO_2^- + NO_3^-$ at rest and after exercise compared to pre-training values for TG, furthermore, TG increased significantly muscle strength in all exercises assessed. The present study demonstrates that sixteen weeks of strength training performed at moderate intensity, enhanced endothelial and muscular function in healthy postmenopausal women.

MOTS CLÉS
Entraînement en résistance ;
Endothélium ;
Vasodilatation et postménopause

Résumé
Objectifs. — Cette étude vise à évaluer l'effet de seize semaines de musculation sur la circulation sanguine dans l'avant-bras (FBF) et la production d'oxyde nitrique (NO) au repos induit par l'exercice chez les femmes ménopausées.
Matériels et méthodes. — Vingt femmes sédentaires ménopausées de 60 ± 5 ans ont participé à cette étude. Les volontaires ont été répartis au hasard en deux groupes: le groupe formé (TG, $n = 10$), a effectué 3 séances d'environ 1 heure d'exercice physique par semaine pendant 16 semaines, et le groupe témoin (CG, $n = 10$), n'a pas effectué l'activité physique systématique. Le débit sanguin de l'avant-bras a été mesuré par pléthysmographie veineuse et les résultats de la production d'oxyde nitrique ont été mesuré par le test de Griess. Les mesures ont été réalisées avant et après l'entraînement avec des sujets au repos et sous protocole de prise en main.
Résultats. — Après l'entraînement en force, le TG a augmenté significativement les valeurs de FBF après l'exercice (3,98 ± 1,81 contre 2,37 ± 1,03 ml.100 ml-1.min -1; $p < 0,05$), et les valeurs post-exercice étaient supérieures aux valeurs post-exercice observées avant entraînement (3,98 ± 1,81 contre 2,74 ± 0,61 ml.100 ml-1.min-1; $p < 0,05$) et il y avait une diminution significative de la concentration plasmatique de $NO_2^- + NO_3^-$ au repos et après l'exercice par rapport à la pré-formation. De plus, TG a augmenté significativement la force musculaire dans tous les exercices évalués. La présente étude démontre que seize semaines de musculation qui ont été effectuées à l'intensité modérée, la fonction endothéliale et musculaire améliorée chez les femmes ménopausées en bonne santé.

1. Introduction

The increase in the elderly women population raises health concerns related to menopause, since it has been associated with increased risk of developing type 2 diabetes, sarcopenia, changes in body composition, lipid profile and cardiovascular diseases [1]. The exact mechanisms underlying the increased risk of developing cardiovascular disease in postmenopausal women remain poorly understood. Postmenopausal women commonly present higher total cholesterol, LDL cholesterol, triglycerides, and lower HDL levels as well as increases in body weight, arterial hypertension and increased endothelial dysfunction [2]. Deprivation of endogenous atheroprotective estrogen can be assumed as another important cause for the increased risk for cardiovascular disease in this population. On the other hand, evidence shows that chronic exercise reduces the risk and progression of cardiovascular disease in women [3]. During exercise, the endothelium is stimulated by increased blood flow and this stimulus has clinical implications, providing benefits on vascular reactivity [4,5]. Furthermore, vascular endothelium secretes important hemostatic factors besides several substances with different roles in the control of vascular function, acting on the smooth muscle cells (modulating vascular tone) and on leukocytes (at the beginning and progression of inflammatory processes). The endothelium-dependent regulation of vascular tone is achieved mainly through the release of nitric oxide (NO). The NO release may be caused by shear stress due to increased blood flow, inducing vasodilation [6], besides inhibition of platelet adhesion and aggregation [6—8].

Strength training induces improvements on lipid profile, insulin resistance and diastolic blood pressure, which positively affects endothelial function and, therefore, decreases risk of cardiovascular events in aging individuals [9,10]. However, the impact of moderate-intensity strength training on the endothelial function of postmenopausal women is poorly investigated. To the best of our knowledge, only two studies have analyzed the effects of strength training on endothelial function in postmenopause. Nevertheless, both studies were performed using experimental models in rats [11,12]. Therefore, the effects of strength training on FMD in postmenopausal women should be further investigated. Thus, the aim of this study is to evaluate the effect of sixteen weeks of strength training on forearm blood flow (FBF) and NO production at rest induced by exercise in postmenopausal women. Our hypothesis is that moderate strength training will positively affect the endothelium function in postmenopausal women.

2. Materials and Methods

2.1. Subjects

Twenty sedentary postmenopausal women (60 ± 5 years), not engaged in any regular and systematic exercise training in the last year, were invited to participate in the study. They had at least one year since their last menstrual period, and had no cardiovascular, pulmonary, metabolic or neuromuscular disease that prevented their participation in the study. Volunteers attended a lecture about the project and responded to an interview and to the ''physical activity readiness questionnaire'' (PAR-Q). All participants signed a consent form and the study was approved by the research ethics committee of the University (No. 19322) according to Helsinki Declaration.

2.2. Proceedings

Participants were randomly assigned into two groups with 10 participants in each group: The trained group (TG), performed strength training three times a week for 16 weeks, and the control group (CG), did not conduct systematic physical activity over the course of the study. During the intervention period, volunteers were instructed to maintain their dietary routine.

2.3. Physical characteristics

Body density (BD) was determined using prediction equation previously described in accordance to Pollock et al. [13].

$BD = 1.099492 - 0.0009929\ (\Sigma 3SKF) + 0.0000023\ (\Sigma 3SKF)^2 - 0.0001392\ (age)$

Body fat percentage (%BF) was calculated using Siri equation [14].

$\%BF = (4.95 \div BD - 4.50) \times 100$

Body composition was divided in three components: bone mass (BM), residual mass (RM), and muscle mass (MM) using the following prediction equations:

$BM = 3.02\ (H^2 + R + F \times 400)^{0.712}$

$RM = TBM \times (20.9 \div 100)$

$MM = TBM - (BF + BM + RM)$

Where H^2 represents the stature (cm), F and R represent femur and radio length (cm), respectively.

2.4. Maximal dynamic strength

Maximal strength was assessed using the one-repetition maximum test (1-RM) in all exercises. The bilateral elbow flexion 1 RM was performed with free-weights and using a bar and the bilateral knee extension in an exercise machine (World-Esculptor, Porto Alegre, Brazil). One week prior to the test day, subjects were familiarized with all procedures in two sessions. On the test day, the subjects warmed up for five minutes on a cycle ergometer, stretched all major muscle groups, and performed specific movements for the exercise test. Each subject's maximal load was determined with no more than five attempts with a four-minute recovery between attempts. Performance time for each contraction (concentric and eccentric) was two seconds, controlled by an electronic metronome (Quartz, CA, USA). The test-retest reliability coefficient (ICC) was 0.99 for the knee extension and 0.95 for the elbow flexion.

Maximum grip strength was measured through handgrip dynamometer (Jamar hydraulic hand dynamometer, Sammons Preston, Rolyon, Bolingbrook, IL). Non-dominant arm grip strength was assessed three times, with 15 seconds rest between measurements. The participants were instructed to apply maximal effort for 3 seconds in every trial. These results were used to determine the exercise intensity to the blood flow evaluation.

2.5. Strength training

The TG performed three sessions of approximately 1 hour of strength exercise per week during 16 weeks. The strength training sessions involved exercise for all major muscle groups: bench press (horizontal adduction), lat pull-down (horizontal abduction), biceps curl, triceps extension, hip adduction and abduction, knee extension and flexion. During the first week of training, TG performed a familiarization session with the exercises of training program. One maximum repetition (1RM) test was performed to determine the training load. During the first, second and third weeks the subjects performed two sets with maximum repetitions with loads of 30%, 40% and 50% of 1RM, respectively, progressing to 60 to 75% of 1 RM from the fourth to fifteenth week. In order to correct the training load, 1 RM tests were conducted in the fourth, eighth, and twelfth weeks.

2.6. Blood Flow

Blood flow was evaluated using a venous occlusion plethysmography technique according to methods previously described by Copeland et al. (1996) (Copeland, Mills et al., 1996). All the tests were performed in the morning and the volunteers were instructed not to consume caffeine 24 hours before testing and fasted for 8 h. The room temperature was kept between 24° and 27 °C. The tests began with volunteers resting in a supine position for 20 minutes, with his non-dominant arm extended and raised to a height above the chest with the aid of a support. To perform plethysmography at rest, the automatic pneumatic cuff (Hokanson TL-400, USA) was positioned on the arm (measurement cuff), the manual cuff was placed on the wrist (exclusion cuff) and a mercury strain gauge was placed on the point of the greatest circumference of forearm. An exclusion cuff was inflated to 200 mmHg to prevent blood flow and venous return of the hand and the measurement cuff was inflated to 60 mmHg only preventing venous return from the forearm to the arm. As the arterial inflow continued to the forearm, the member swelled, distending the strain gauge, increasing the resistance to electric current passing through the mercury, showing a curve in the data acquisition system. This procedure was repeated three times for ten seconds each, obtaining three curves [15,16]. The procedure was performed at rest and after exercise.

Immediately after the measurement of rest blood flow, the subject performed a set of 5 seconds isometric contractions with 5-second intervals at 30% of maximum grip strength with the handgrip dynamometer, during 2 minutes.

Table 1 Body composition before and after training for Training Group and Control Group.

	CG Pré	CG Post	TG Pré	TG Post
Age (years)	55.8 ± 3.9	–	56 ± 4.5	–
Height (cm)	158 ± 0.07	159 ± 0.09	157 ± 0.07	157 ± 0.07
Body Mass (kg)	72.5 ± 8.5	71.9 ± 8.8	66.2 ± 8.2	67.3 ± 9.7
Muscle Mass (kg)	21.2 ± 1.7	20.6 ± 1.8*	20.4 ± 2.5	21.0 ± 2.6*
Body Fat (%)	35.1 ± 4.4	36.3 ± 5.3	32.7 ± 4.3	32.5 ± 5.8

Control group (CG), Trained group (TG).
* Significant difference within groups before and after training, $P < 0.05$.

In order to get the blood flow after exercise, the procedure was the same used at rest. After the 16 weeks of strength training, we conducted a maximum handgrip strength retest of the non-dominant arm and a 30% of maximum strength recalculation for exercise tests [17].

2.7. NO Production (NO_2^- e NO_3^-)

Blood samples (8 ml) were collected by an experienced nurse before resting plethysmography and pre and post-training. A colorimetric assay was used for the measurement of total nitrites and nitrate simultaneously (tNOx) in a 96 well plate. [18]. The plasma samples were analyzed in duplicate after reduction of NO_3^- to NO_2^- using nitrate reductase (Aspergillus species) based on the Griess reaction. NO_2^- was measured by observation of the also magenta pigment formed by the reaction of NO_2^- with Griess reagent (0.1% N-[1-Naftil] ethylenediamine dihydrochloride, (NED) be 1% sulfanilamide in 5% phosphoric acid). The absorbance was registered at 543 nm in comparison with the blanks containing only the Griess reagent. The concentrations of NO_2^- were determined using a standard curve generated with known concentrations of sodium nitrate ($NaNO_2$). Biochemical analyzes were also performed by a blinded evaluator, who was unaware of the group which the samples belonged [19].

2.8. Statistics

All data are presented as mean ± standard deviation. Shapiro-Wilk test was used to verify the normal distribution of data, and Levene test to assess the homogeneity of variances. The effects of interventions were compared using two-way analysis of variance (Anova) with Bonferroni's post hoc test. When appropriate, Student's *t* test for paired samples was used to identify significant differences. When significant time vs. group interaction was observed, relative changes were compared using Student's *t* test for independent samples. The significance level was set at $P < 0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows.

3. Results

The strength training program induced an increase in the muscle mass. At the same time the control group suffered a deterioration in muscle mass (Table 1).

Fig. 1 shows pre- and post-training FBF at rest and after exercise for TG (A) and CG (B).

As shown in Fig. 1, before training, there were no significant changes in the FBF induced by exercise in both groups. After strength training period, although no changes were observed at rest, TG increased significantly FBF values after exercise (2.37 ± 1.03 vs. 3.98 ± 1.81 ml.100 ml^{-1}.min^{-1}; $P < 0.05$), and the post-exercise values were greater than observed before training (2.74 ± 0.61 vs. 3.98 ± 1.81 ml.100 ml^{-1}.min^{-1}; $P < 0.05$). As expected, in the CG, there were no significant changes in the FBF at rest and induced by exercise after 16 weeks (1.90 ± 0.44 vs. 2.68 ± 1.10 ml.100 ml^{-1} .min^{-1}; $P > 0.05$)

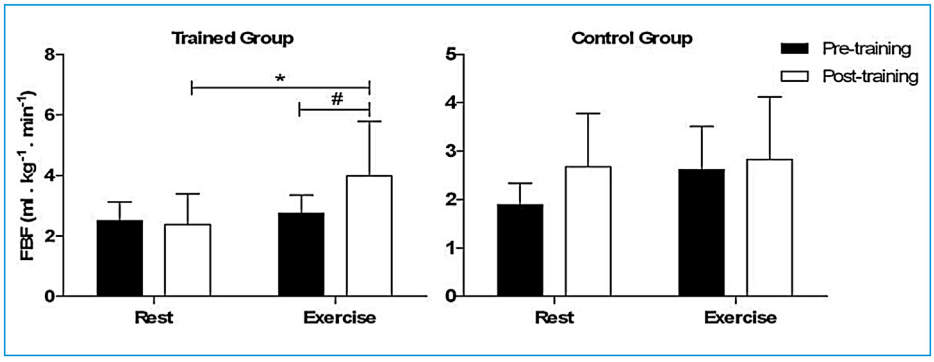

Figure 1 Forearm blood flow for the Control and Trained Group at rest and after exercise: pre- and post-training period. Values are mean ± SD; * $P < 0.05$ post-training rest vs after exercise; # $P < 0.05$ after exercise pre- vs post-training.

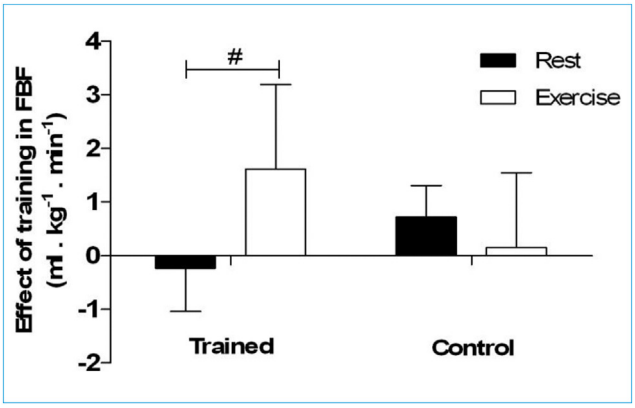

Figure 2 Effects of training on forearm blood flow: at rest and after exercise for both groups (absolute Δ). Values are mean $\pm$ SD # $P < 0.05$. Effect of training rest vs after exercise for the trained group.

Fig. 2 shows the effects of strength training on forearm blood flow. There was an increase in FBF after exercise in TG and no differences were observed in CG.

Before training, there was a significant increase in plasma levels of nitrites and nitrates after exercise for both groups (Fig. 3). After 16 weeks of training, there was a significant decrease in plasma concentration of $NO_2^- + NO_3^-$ at rest and after exercise compared to pre-training values for TG, whereas no significant differences were observed in CG.

The results for 1RM are shown in Table 2. As expected, TG increased significantly muscle strength in all exercises assessed, while no changes were observed in CG. After training, TG presented significant greater muscle strength values than CG. Regarding body composition, TG showed a significant increase in fat free mass while the CG showed a significant decrease in fat free mass (Table 1). Nevertheless, there were no significant differences between groups.

4. Discussion

To the best of our knowledge, this is the first study conducted to analyze the effects of strength training on endothelial function in postmenopausal women. The main finding of this study was that 16 weeks of strength training induced beneficial changes in endothelial function induced by exercise in sedentary postmenopausal women, besides marked improvements in neuromuscular function. These results show that strength training is an effective intervention to improve endothelial function in postmenopausal women, which may reduce the risk of cardiovascular disease in this population.

FBF results are consistent with other studies that applied strength training with moderate intensity in young healthy individuals [16,20]. There are few data on the effects

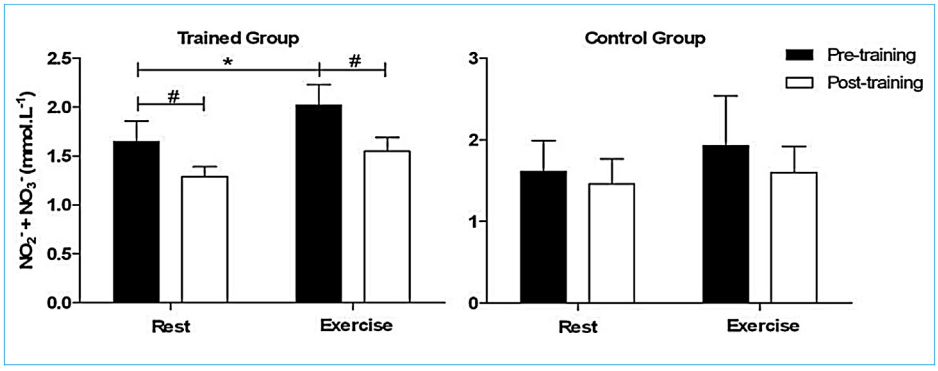

Figure 3 Plasma levels of Nitrites and Nitrates—Control Group and Trained group: before and after exercise in the pre- and post-training periods. * $P < 0.05$ rest vs after exercise pre-training; # $P < 0.05$ post-training vs pre-training at rest and after exercise.

Table 2 Results of 1RM testing for both groups, before and after the training period.

	GC Pré	GC Post	GT Pré	GT Post
Bench Press (kg)	18.0 ± 2.2	19.0 ± 3.3	19.3 ± 5.4	33.8 ± 6.2*,a
Lat Pulldown (kg)	27.1 ± 2.4	27.1 ± 3.3	29.5 ± 6.2	36.3 ± 5.6*,a
Bíceps Curl (kg)	5.5 ± 1.2	5.8 ± 1.3	5.6 ± 1.2	10.0 ± 2.6*,a
Tríceps Extension (kg)	21.6 ± 2.6	20.0 ± 2.2	19.5 ± 4.3	24.8 ± 4.2*,a
Hip Adduction (kg)	23.3 ± 5.1	22.5 ± 5.2	25.9 ± 5.8	32.7 ± 6.3*,a
Hip Abduction (kg)	33.7 ± 8.9	30.4 ± 8.1	35.0 ± 6.9	41.2 ± 7.9*,a
Knee Extension (kg)	20.0 ± 7.1	19.1 ± 6.2	23.2 ± 6.4	34.8 ± 9.3*,a
Knee Flexion (kg)	11.2 ± 2.1	8.7 ± 2.6	11.0 ± 2.4	15.7 ± 2.8*,a

Control group (GC), Trained group (GT).
* Significant difference within groups before and after training, $P < 0.05$.
[a] Significant difference between groups after training, $P < 0.01$.

strength training in FBF in postmenopausal women. In the study of Rossow et al. (2014) no improvements of FBF were shown after 12 weeks of strength training performed at 80% of 1RM [21]. In contrast, another study demonstrated improvements in post-exercise vasodilatation capacity within 5 min after maximal treadmill exercise during resistance and endurance trained men [22]. In addition, Copeland et al. found a greater increase in FBF immediately following an acute isometric handgrip exercise after 3 weeks of resistance training compared with endurance training [16]. Improvements in FBF post-exercise could be due to a reduction in the local sympathetic reflex response and/or increased shear stress in response to increase in blood flow, improving vessel reactivity by the stimuli given to the vascular musculature [20,21]. Possible discrepancies between the study by Rossow et al. (2014) reporting no improvement in FBF in postmenopausal women and our study could be explained by different exercise volume used during both studies. While our study employed 16 weeks of training, participants in the Rossow et al. study trained for eight weeks. It is possible that our moderate to high intensity strength training protocol represented a sufficient stimulus to provide increases in FBF.

Regarding the basal FBF, some studies have shown increased after training interventions, [2,23,24], whereas others did not show significant changes. In the present study, no changes were observed in FBF at rest. A possible explanation for these different results could be due to different training protocols used and different subjects investigated. In addition, because of the scarce number of studies conducted in postmenopausal women, the effect of strength training in the FBF at rest remains to be elucidated.

In addition endothelial function impairments are systematically attributed to the increase in the formation of reactive oxygen species (ROS) (48), mainly due to the formation of peroxynitrite (ONOO-) and consequent increase in lipid peroxidation [25]. In this sense, there appears to be an increase in ROS production to an acute exercise session in sedentary individuals, followed by a compensatory increase in the activity of antioxidant enzymes in response to the systematic exercise [25,26].

Plasma concentration of nitrites and nitrates increased in both groups after exercise in pre-training. Nonetheless, the trained group showed a decrease in the concentration of nitrites and nitrates at rest and after exercise comparing pre-and post-training values. This result can be explained through a decrease in the sympathetic-induced vasoconstriction, at the beginning of exercise, allowing an increase in blood flow with a lower bioavailability of NO [27]. In fact, the role of NO in the control of sympathetic vasoconstriction has been previously demonstrated [28]. In studies with healthy men, after the inhibition of this local factor, there were no changes in the sympathetic vasoconstrictor response during the exercise. It was suggested that NO is not required for blocking sympathetic vasoconstriction [29,30]. Similarly, our data support the evidence that NO is not required for vasoconstriction by sympathetic blockade. This indicates that other mechanisms such as adenosine, potassium, prostaglandins (PG) and Endothelium-derived hyperpolarizing factor (EDHF) may be regulating blood flow [31,32]. Moreover, some data suggest that the assessment of blood NO concentration does not reflect its bioactivity [33], and it is possible that even with a reduction of NO concentration, there is an increase in its bioactivity, which could increase the FBF induced by exercise [34].

In many tissues, including skeletal muscle, EDHF have been identified as factors that independent of NO and PG, can hyperpolarize smooth muscles causing vasodilation in response to substances that accentuate endothelial calcium levels (as acetylcholine and bradykinin). Many different EDHFs seem to exist in different tissues and vessels. In human skeletal muscle, bradykinin has been described as hyperemia inducing agent independent of NO and PG, suggesting a mechanism mediated by EDHF. The bradykinin could respond to the increase of the EDHF activating endothelial G-protein causing improvements in intracellular calcium in cell [35]. Furthermore, the exercise training could decrease the Endothelin-1 (ET-1), another potent vasoconstrictor that could be also related to decreased blood flow. A study on older women undergoing 3 months of aerobic exercise, 5 days per week for 30 minutes at 80% of the second ventilatory threshold showed a significant decrease in plasma concentration of ET-1, accompanied by a reduction in blood pressure and improvement in vascular function independent of NO [36]. Thus, both the increase of vasodilators factors such as reduction of vasoconstrictor agents may have influenced our results, where there was increased FBF simultaneously with the reduction of NO production.

In addition, it has been demonstrated that high intensity exercises are capable of modulating the NO production in red blood cells (RBC) of young individuals (1,2), it is important to note that in the present study the NO bioavailability was measured by the NO2 and NO3 plasma levels. In this way the synthesis of NO by RBC may represent an alternative mechanism of vasodilation [37,38]. However, there are no records of studies conducted with postmenopausal women for possible comparisons.

The article is unique and is one of the few to compare NO responses in postmenopausal women after strength training.

The TG obtained a significant increase in strength in all exercises, along with beneficial changes in body composition. Previous studies have shown that these strength gains are related to neuromuscular adaptations, increased voluntary neural activation of the agonist muscles and lower activation of antagonistic muscles [10,39,40].

5. Conclusion

The present study suggests that sixteen weeks of strength training performed at moderate intensity enhance endothelial and muscular function in healthy postmenopausal women. These results are relevant given that vascular health and physical fitness are associated with lower cardiometabolic risk factors in this population. Future studies could investigate the effects of different types of exercise on the responses of substances involved in vasodilation and vasoconstriction to elucidate the mechanisms involved and adaptations to resistance and endurance training.

Disclosure of interest

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The authors declare that they have no conflicts of interest concerning this article.

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