

Original Article (short paper)

## Twice-weekly exercise training reduces oxidative stress and proinflammatory cytokine levels in elder women

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**Abstract** — **Aim:** Reactive oxygen species and high concentrations of proinflammatory cytokines are related to diseases that are often triggered during the aging process. This study aimed to investigate the effect of moderate-intensity physical exercise, twice a week, on oxidative stress and inflammation biomarkers. **Methods:** Participants were older women aged 60-70 years, engaged in a moderate-intensity exercise program carried out in 60 minutes sessions, twice a week, for 24 weeks. Exercise sessions consisted of step, resistance and stretch exercises. Thiobarbituric acid reactive substances (TBARS), serum iron and cytokines IL-6, IL-1 $\beta$  and IL-1ra were determined using specific kits. Physical fitness was assessed using tests provided by AAPERD. A paired t test was performed. **Results:** Moderate-intensity exercise program provided a reduction in lipid peroxidation (27%) and in the serum release of prooxidant iron ions (40%). Cytokine levels were reduced by 37% for IL-6, 16% for IL-1 $\beta$  and 32% for IL-1ra. Improvements in cardiorespiratory fitness (13%), muscular endurance (11%) and flexibility (12%) were also observed. **Conclusion:** Diminished redox state and inflammation were obtained using a twice-weekly exercise program. These results have important implications for older adults who are unable or unwilling to attend exercise programs more than twice a week. Moreover, these results could re-establish the minimum exercise activity necessary for obtaining health benefits in the elderly population.

**Keywords:** community-based, aging, antioxidant, inflammation, reactive oxygen species, iron.

### Introduction

The older population is rising around the world as well as aging-related metabolic and cardiovascular diseases. Increased oxidative stress seen in the elderly might contribute to the development of different senior diseases. Impairment of the mitochondrial electron transport during aging increases superoxide anion generation, leading to higher susceptibility to muscle injury and exacerbated inflammatory responses<sup>1,2</sup>. Therefore, suppression of the immune system activity<sup>3</sup> and systemic chronic inflammation have been considered, in the aged population, as a strong risk factor to atherosclerosis, sarcopenia and Alzheimer's disease<sup>4,5</sup>.

Regular and moderate exercise is largely recommended as an efficient nonpharmacological intervention to prevent or minimize some cardiovascular and metabolic diseases, including those in elderly people. The major benefits promoted by regular exercise are based on several cellular and molecular adaptations including up-regulation of endothelial nitric oxide synthase (eNOS), induced angiogenesis, improvements in insulin sensitivity, and adequate antioxidant/prooxidant enzyme expression and/or activity<sup>6,7</sup>.

However, some older people have social and economic barriers to engage in regular exercise programs carried out

under proper professional supervision. They attend groups in their local communities in which different activities are offered, like aqua-based exercises, dance classes, and low-to-moderate intensity gym classes. Therefore, this study aimed to investigate the effectiveness of moderate-intensity exercise sessions, twice a week, on oxidative stress and inflammation biomarkers in elderly women.

### Methods

#### Participants Screening

Informed consent was obtained from all individual participants after a full explanation about the study and its procedures. Experimental protocol was approved by Institutional Ethics Committee (Certificate N°124/2008). Inclusion criteria were: volunteers aged 60 to 70 years, nonsmoking, non-diabetic (fasting glucose level < 126 mg/dL). Exclusion criteria were: alcohol consumption > 3 drinks per day, hormone replacement therapy, antioxidant supplementation, and anti-inflammatory medication use. Medical history and medication use were assessed by a brief interview.

Thirty-two elderly women were eligible according to inclusion/exclusion criteria and had been engaged in a physical activities program. After 24 weeks, only eleven women had reached 70% of exercise session adherence and had their blood collected for analysis. The lower adherence to exercise program could be due to several factors including public transport problems, grandchildren sitting and health problems.

### *Moderate-intensity exercise program and functional fitness assessment*

An exercise program was offered in a public community centre and exercise sessions were carried out for sixty minutes, twice a week, for twenty-four weeks. Exercise intensity was monitored using the Borg Scale (range 6 to 20) and women were encouraged to maintain the effort at 12-13. Physical exercise sessions were conducted as circuit training with aerobic (step) and upper and lower limb resistance exercises. All sessions included warm-up and cool-down activities using dynamic or static stretching exercises, respectively.

Physical fitness was assessed using standard tests proposed by the American Alliance for Health, Physical Education, Recreation and Dance (AAPHERD). Each volunteer performed a bout of tests to determine cardiorespiratory fitness, muscular endurance, flexibility, coordination, and agility. Scores obtained before and after exercise program were compared intra-individually.

### *Body mass index and arterial blood pressure measurements*

Body mass index (BMI) was calculated dividing weight (kg) by the square of height (m<sup>2</sup>). Measurements of height were made using a clinical stadiometer in bare and body weight was measured with a digital calibrated precision scale (Plenna, Brazil). Measurements were carried out at initial time and after 24 weeks of exercise program.

Participants were instructed to not exercise outside laboratory before blood pressure measurement. Systolic and diastolic blood pressures were measured after 15 minutes of seated quiet rest using aneroid sphygmomanometer (Tycos, USA) with an appropriately sized cuff. Three blood pressure measurements were done, and the average was recorded. This procedure was done initially and after 24 weeks of physical exercise.

### *Assessment of oxidative stress biomarkers and cytokines*

Twenty-four hours after the last exercise session, blood samples were collected after 13 hours overnight fasting, serum or plasma was used to determine oxidative stress and inflammation biomarkers levels. Oxidative stress was estimated by measuring plasma concentration of thiobarbituric acid reactive substances (TBARS) formed from lipid-derived aldehydes as an index of the lipid peroxidation using a commercial kit with a detection range

from 0 to 50 µM (TBARS, Cayman Chemical, USA). Serum iron was determined by Goodwin method using a colorimetric assay kit (Bioclin, Brazil). Inflammatory cytokines IL-1β (detection range: 3.9 to 250 pg/mL), IL-1ra (detection range: 31.2 - 2,000 pg/mL), and IL-6 (detection range: 3.12 to 300 pg/mL) were determined by using enzyme immunoassay kits (DuoSet R&D System, USA). Creatine kinase activity was also determined in plasma, as an index of volunteers training status, using a colorimetric assay kit (Bioclin, Brazil).

### *Statistics*

Data are presented as mean ± Standard Error Mean (S.E.M). All data were analyzed using GraphPad InStat software and paired *t*-test was done to compare results obtained initially and after twenty-four weeks of exercise program. The level of significance was *p*<0.05.

## **Results**

After twenty-four weeks, no changes were observed in BMI and blood pressure. On the other hand, plasma creatine kinase activity was augmented by 33% after the exercise program. Improvements in cardiorespiratory fitness (13%), muscular endurance (11%) and flexibility (12%) were also observed (Table 1).

Table 1. Characteristics of the participants at Baseline (Pre) and after 24 weeks (Post Ex) of Moderate-intensity Exercise.

	Pre	Post Ex	<i>p</i> Value
Age (years)	66 ± 2	66 ± 2	<i>ns</i>
BMI (kg/m <sup>2</sup> )	27.6 ± 1.4	27.7 ± 1.2	<i>ns</i>
SBP (mm Hg)	131 ± 3	128 ± 2	<i>ns</i>
DBP (mm Hg)	89 ± 2	87 ± 2	<i>ns</i>
CRF (s)	671 ± 83	586 ± 72	.0008
ME (repetitions)	17 ± 1	19 ± 2	.0182
FLEX (cm)	52 ± 3	58 ± 3	.0108
COO (s)	14 ± 1	15 ± 2	<i>ns</i>
AGIL (s)	30 ± 1	29 ± 1	<i>ns</i>
Creatine Kinase (U/L)	81 ± 11	121 ± 20	.022

Notes: Data are mean ± S.E.M, *n* = 11. BMI= body mass index, SBP= systolic blood pressure, DBP= diastolic blood pressure, CRF= cardiorespiratory fitness, ME= muscular endurance, FLEX= flexibility, COO= coordination, AGIL= agility. *ns*: non-significant.

The moderate-intensity exercise program was effective in decreasing both plasma TBARS (-27%; *P*=0.02) and serum iron concentrations (-40%; *P*=0.01), as shown in Figure 1. Regarding inflammation biomarkers, plasma concentrations of IL-6 (16.1±1.3 vs 10.1± 0.5 pg/mL, *P*=0.001), IL-1β (3.3±0.2 vs 2.8±0.2 pg/mL, *P*=0.006), and IL-1ra (0.043±0.007 vs 0.029± 0.001 pg/mL, *P*=0.048) were decreased by 37, 16 and 32%, respectively (Figure 2).

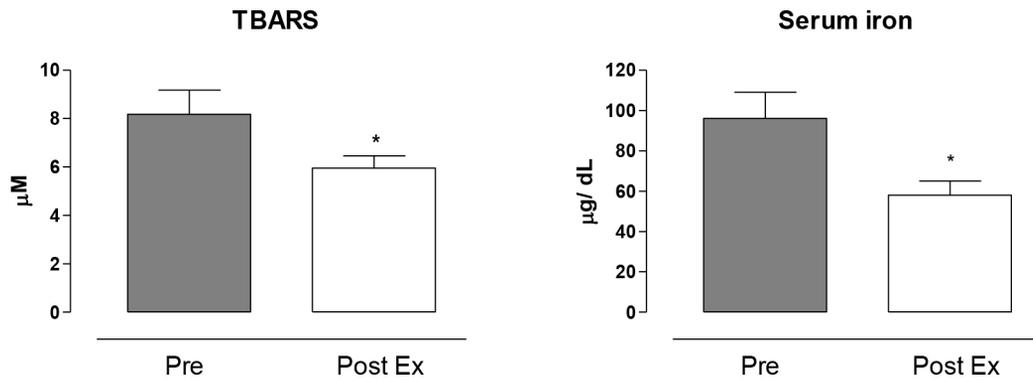


Figure 1. Plasma MDA concentration and serum iron level at baseline (filled columns) and after twenty-four weeks of moderate-intensity physical exercise (open columns) in older women. Paired *t*-test, data are mean  $\pm$  S.E.M,  $n = 11$ . \* Different from Pre.

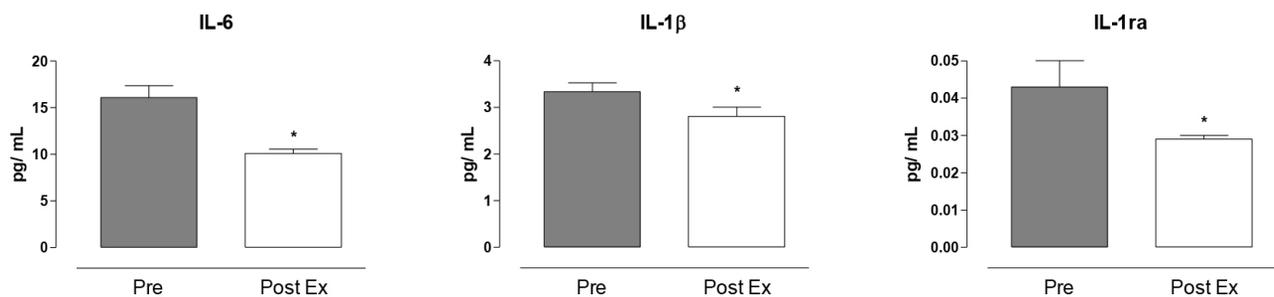


Figure 2. Cytokine concentration at baseline (filled columns) and after twenty-four weeks of moderate-intensity physical exercise (open columns) in older women. Paired *t*-test, data are mean  $\pm$  S.E.M,  $n = 11$ . \* Different from Pre.

## Discussion

The moderate-intensity exercise program, twice a week, was an efficient approach in reducing oxidative stress and inflammatory cytokines in older women.

The American College of Sports Medicine truthfully recommends regular exercise programs containing moderate-vigorous intensity endurance, resistance and flexibility exercises for that purpose<sup>8</sup>. Frequencies are 150-300 min $\cdot$ wk<sup>-1</sup> to endurance exercises and at least 2 d $\cdot$ wk<sup>-1</sup> to resistance and flexibility exercises. These recommendations are either to maintain or improve cardiorespiratory fitness and strength, minimizing risk for chronic diseases, premature death, and functional fitness decline<sup>8</sup>. It is noteworthy that many studies have already shown significant enhancement in muscle strength and functional fitness using twice-weekly resistance training<sup>9,10</sup>.

Improvement in cardiorespiratory fitness, muscular strength and flexibility were seen in our study using a twice-weekly exercise program containing different types of physical activities. The CK activity is increased after the training period indicating that the exercise program was effective to stimulate functional and physiological adaptations, such as protein turnover and muscle metabolism. This result has important implication for older adults who are unable or unwilling to attend exercise programs more than twice a week. On the other hand, this exercise program was not sufficient to lower blood pressure or affect body weight. A combined nutrition-exercise program is necessary for that purpose<sup>11,12</sup>.

An association between the metabolism of reactive oxygen species (ROS) and the aging process had been firmly reported by Harman<sup>13</sup>. The “free-radical theory of aging” highlights the knowledge about ROS toxicity and its linkage with degenerative processes. Indeed, age-related diseases as Parkinson’s, Alzheimer’s and cataract have a molecular basis on ROS metabolism<sup>5,14</sup>. Arterial relaxation is also reduced by ROS due to superoxide anion reaction with nitric oxide, a potent vasodilator, which is thereby removed from the endothelial locus<sup>15</sup>. In addition to the impaired vasodilatation, the reduction in nitric oxide availability mediates proinflammatory and prothrombotic processes in arterial wall increasing the risk to develop the peripheral vascular disease during aging<sup>16</sup>.

During aerobic exercises, the main source of ROS production is derived from the mitochondrial electron transport chain<sup>17</sup>. A physiological concentration of iron is essential for cell metabolism and aerobic respiration by acting as a cofactor of several proteins. However, excessive iron concentrations promote pro-oxidant effects, associated with cell toxicity and oxidative damage to cellular structures due to its relation to the formation of ROS<sup>18</sup>. Not surprisingly, iron homeostasis is meticulously controlled within aerobic organisms, as iron ions (Fe<sup>2+/3+</sup>) are efficiently bound to specific proteins such as transferrin and ferritin, to avoid or minimize iron-catalyzed oxidation reactions. The iron-copper redox cycle promotes the Fenton reaction which leads the aggressive hydroxyl radical from H<sub>2</sub>O<sub>2</sub><sup>19</sup>.

Excessive ROS production during exercise (usually, at a high-intensity mode) can be considered harmful unless

proportional antioxidant defenses could sustain an adequate redox balance within exposed cell/tissues. On the other hand, mild increases on ROS levels from moderate exercise are beneficial due to the adequate up-regulation (increased activity) of responsive antioxidant defense systems<sup>2</sup>. The protective effect of regular moderate exercise against oxidative stress is based on the increased expression of antioxidant enzymes such as SOD-1 and SOD-3, and reduced expression of prooxidant enzymes such as NADPH oxidase and its subunits gp91<sup>phox</sup>, gp67<sup>phox</sup> and p22<sup>phox</sup><sup>6,15</sup>. Interestingly, recent studies have shown that exercise adaptations in response to increased ROS could be blunted by high consumption of antioxidant supplements due to the removal of essential redox signals in this adaptive process<sup>20,21,22</sup>. In agreement with the exercise/antioxidant adaptation concept, lower levels of lipoperoxidation (TBARS in figure 1) were observed in the plasma of the moderate-intensity exercising aged women here, even done twice a week.

In addition to its beneficial role in the redox status, moderate-intensity exercise training was also related to improvements in inflammatory conditions. Accordingly, the anti-inflammatory role of exercise training has been seen in different studies that showed reductions in proinflammatory cytokines and C-reactive protein<sup>23,24</sup>.

During the aging process, IL-6 concentration is slightly high even in older persons without illness diagnoses<sup>25</sup>. High levels of IL-6 are associated with chronic degenerative diseases, functional decline, sarcopenia, and mortality<sup>26-28</sup>. However, a negative correlation has been seen between IL-6 levels and physical fitness in elder persons<sup>29,30</sup>. In our study, IL-6 concentration was lowered by moderate-intensity exercise training. The IL-6 response to physical exercise session was reported to be biphasic, showing a higher concentration after the exercise session and a decrease in its concentration during the recovery period<sup>31</sup>.

Another pro-inflammatory cytokine investigated was IL-1 $\beta$ . This cytokine is associated with apoptosis and muscle catabolism<sup>32,33</sup>. Lower IL-1 $\beta$  muscular expression after exercise training in heart failure patients and improvement in muscle catabolism – feature related to this illness – might be observed<sup>34</sup>. Muscular catabolism also occurs during the aging process. On this issue, exercise training could ameliorate muscle catabolism while after moderate-intensity exercise training a reduction of about 16% in IL-1 $\beta$  concentration was observed. Additionally, IL-1 $\alpha$  production was reported to be up-regulated in response to acute or chronic inflammation<sup>35</sup>. In our study, IL-1 $\alpha$  concentration was diminished by about 32% after moderate-intensity exercise. It might be relevant since previous studies have evidenced an association between high levels of IL-1 $\alpha$  as mortality predictive in elder persons<sup>27,35</sup>.

## Conclusion

Moderate-intensity exercise program provided a reduction in lipid peroxidation as well as in the serum release of pro-oxidant iron ions. Although the anti-inflammatory role of exercise has

already been reported in other studies, the novelty here is that diminished redox state and inflammation were obtained after a twice-weekly exercise program. Since oxidative stress and high levels of proinflammatory cytokines are recognized as risk factors to the development of chronic degenerative diseases, our exercise protocol might be considered an efficient approach to minimize risks and improve women's health. These results have important implications for elder people who are unable or unwilling to attend exercise programs more than twice a week. Moreover, these results could re-establish the minimum exercise amount necessary for obtaining health benefits in the elderly population.

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