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ORIGINAL ARTICLE

Impact of an Exercise Program on Muscular and Functional Performance and Plasma Levels of Interleukin 6 and Soluble Receptor Tumor Necrosis Factor in Prefrail Community-Dwelling Older Women: A Randomized Controlled Trial

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Abstract

Objective: To examine the impact of a muscle resistance program (MRP) on muscular and functional performance and on interleukin 6 (IL-6) and soluble tumor necrosis factor receptor-1 (sTNFr1) plasma levels in prefrail community-dwelling women.

Design: Randomized controlled trial crossover design with a postintervention and short-term follow-up.

Setting: University hospital.

Participants: Prefrail community-dwelling women (N=32; ≥65y).

Intervention: The MRP was designed based on the exercise at 75% of each participant's maximum load (10wk, 3 times/wk).

Main Outcome Measures: Plasma concentrations of IL-6 and sTNFr1 (high-sensitivity enzyme-linked immunosorbent assay kits), muscle strength of the knee extensors (isokinetic), and functional performance (Timed Up & Go [TUG] test and 10-meter walk test [10MWT]).

Results: There were significant differences in functional and muscular performance between the pre-MRP, post-MRP, and 10-week follow-up period. After the MRP, both functional (TUG, pre-MRP=11.1s vs post-MRP=10.4s, $P=.00$; 10MWT, pre-MRP=4.9s vs post-MRP, 4.4s, $P=.00$) and muscular performances (pre-MRP=77.8% and post-MRP=83.1%, $P=.02$) improved. After cessation of the MRP (follow-up period), sTNFr1 plasma levels increased by 21.4% at 10-week follow-up (post-MRP, 406.4pg/mL; 10-week follow-up, 517.0pg/mL; $P=.03$). There were significant differences in sTNFr1 ($P=.01$).

Conclusions: The MRP was effective in improving functional and muscular performances, although alterations in plasma levels of IL-6 and sTNFr1 could not be identified after the MRP. Cessation of the MRP after 10 weeks resulted in increased plasma levels of sTNFr1.

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The risk of frailty syndrome increases with age and occurs in 10% to 25% of people over 60 years of age and in 46% of those over 85 years of age.[1] This is a clinical, multifactorial syndrome characterized by reduced energy reserves and decreased resistance to stressors resulting in a cumulative decline of physiological systems.[1,2] Three factors may potentially influence this syndrome: (1) dysfunction in the neuroendocrine system, (2) dysfunction in the immune system, and (3) sarcopenia.[1-4] The observed alterations in the neuroendocrine and immune systems have been shown to influence muscular and functional changes in older adults.[4,5] There is evidence that high plasma levels of interleukin 6

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(IL-6) and tumor necrosis factor-alpha (TNF-α) are associated with the development of frailty, sarcopenia, functional incapacity, Alzheimer disease, as well as an increase in obesity, metabolic dysfunction, and increased mortality rates.[5-12] Several authors have reported a positive correlation between sarcopenia and elevated plasma levels of proinflammatory cytokines including IL-6, C-reactive protein, and TNF-α.[5,6,9,10,13]

Some authors have shown that muscle contractions result in the production of IL-6[11-13] depending on the type of contraction (concentric vs eccentric), as well as the intensity and duration of the exercise program.[11-13] During a muscle contraction, IL-6 is released by a TNF-α-independent pathway and stimulates the production of other anti-inflammatory cytokines, such as interleukin 1 receptor antagonist and interleukin 10. This cascade inhibits the deleterious effects of TNF-α on muscle.[11,12] The literature suggests that regular physical activity may be associated with a reduction in plasma concentrations of IL-6 and TNF-α, which are released simultaneously.[11-13] As a result, the deleterious effects of these cytokines on muscles are reduced. In this case, some authors have reported an independent-pathway release, which results in an increase of IL-6 (myokine) and a decrease of TNF-α after exhausting exercise.[11-15] Greiwe et al[16] reported that concentric resistive exercises could reduce plasma expression of TNF-α in their older adult participants. A recent study by Brandt and Pedersen[13] further supports that muscle contraction releases IL-6. They showed that IL-6 induces lipolysis and fat oxidation and is involved in glucose homeostasis during exercise. Thus, interventions that promote the strengthening of large muscle groups may modify plasma levels of IL-6 and TNF-α.[11] In spite of the correlation between frailty syndrome and increased levels of IL-6 and TNF-α, and the growing evidence supporting a beneficial effect of physical exercise on plasma levels of these inflammatory markers, the impact of an exercise program in a prefrail-aged population has not yet been well established. Thus, to verify the effects of resistive exercise on older adults may bring fresh knowledge in this field.

Therefore, the objectives of this study were as follows: (1) to verify the impact of a muscle resistance program (MRP) at 75% of each participant's maximum load on functional capacity, muscle strength, and plasma levels of IL-6 and soluble tumor necrosis factor receptor-1 (sTNFr1) in prefrail community-dwelling older women and (2) to assess these variables after a 10-week follow-up period after cessation of the MRP. We hypothesized that the changes achieved with the MRP would return to baseline levels within 10 weeks of exercise cessation, and would be directly related to the lack of muscle stimulation during that time frame.

Methods

This study was a randomized, blinded, crossover controlled trial approved by the Research Ethics Committee of Universidade Federal de Minas Gerais (decree ETIC 321/2007). The protocol for this study was registered in BioMed Central under number ISRCTN62824599 (http://www.controlled-trials.com/ISRCTN62824599) and was previously published.[17] Participants were recruited from 2 universities through both advertisement and verbal invitation, and all participants signed an informed consent prior to enrollment in the study. After initial evaluation, they were randomly assigned into either group: the MRP group or the control group (CG). The MRP group participants started the training that was scheduled for 3 times a week for 10 weeks. The CG participants were asked to continue their daily routine activities, and they were instructed to not start any new physical activities. At the end of 10 weeks, all participants were reevaluated to assess the immediate effects of the MRP (MRP group) and their daily routine activities (CG). Reevaluation was carried out over 7 days, which was also considered a wash out period, after which the MRP group participants were instructed to discontinue the MRP. CG participants were then entered in the same MRP previously administered to the MRP group subjects. At the end of the CG's 10-week muscle exercise program, outcomes were measured in both groups in order to assess the immediate effects of the MRP in the CG as well as an equal period of relative inactivity in the original MRP group (follow-up period) (fig 1). In this way, the effects specifically caused by the MRP could be assessed independent of the influence of time and/or changes related to inactivity. In addition, any changes occurring after completion of the MRP could be identified. Finally, this approach addressed ethical concerns by guaranteeing that the participants all received the same treatment. The physiotherapist responsible for the intervention had no knowledge of the evaluations being performed, and the evaluators were blinded to the subject group.

List of abbreviations:

ANOVA	**analysis of variance**
CG	**control group**
IL-6	**interleukin 6**
MRP	**muscle resistance program**
sTNFr1	**soluble tumor necrosis factor receptor-1**
10MWT	**10-meter walk test**
TNF-α	**tumor necrosis factor-alpha**
TUG	**Timed Up & Go**

Sample

Thirty-two community-dwelling women (aged ≥65y) were selected; the prefrail criteria used was in accordance with the phenotype proposed by Fried et al[2] (hand grip strength, low caloric expenditure, gait speed, exhaustion, and loss of corporal weight). Those who presented 1 or 2 criteria were selected to participate in the study. All participants answered a questionnaire designed to assess the clinical and sociodemographic characteristics of the sample.

Exclusion criteria included the presence of cognitive impairment,[18] orthopedic and neurologic diseases that limited physical activity, acute inflammatory disease, cancer, and the use of medications with known immunologic effects.

Plasma levels of IL-6 and sTNFr1

Plasma levels of IL-6 and sTNFr1 were measured by enzyme-linked immunosorbent assay using high-sensitivity kits.[a] Samples were read by a microplate reader set to 490Nm and corrected to a wavelength of 650Nm. The analyses were performed on different days than the exercise training, with at least a 48-hour interval and always in the morning between 8 and 10 AM, without fasting, to guarantee that the circadian rhythm does not influence the measurements.[17] Blood was collected 2 days prior to the intervention and 48 to 72 hours after completion of the exercise-training program. In the follow-up group, blood was collected at the end of the 10-week period of inactivity. Blood samples were collected by a qualified professional who