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Review

Effect of resistance training on inflammatory markers of older adults: A meta-analysis

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ABSTRACT

Introduction: Low-grade inflammation is associated with several deleterious health outcomes and may aggravate sarcopenia and dynapenia during aging. A strategy to alleviate these conditions is resistance training (RT). Thus, the aim was to critically examine the effects of regular RT on inflammatory markers of older adults from previous studies.

Methods: The search was conducted on MEDLINE, July 2017. Only randomized controlled trials (RCTs) testing RT effects on C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and/or interleukin-6 (IL-6) of adults over 50 years-of-age were selected by two independent reviewers.

Results: The main meta-analyses showed RT reduced CRP in older adults (standard mean difference [SMD] = −0.61, 95%CI = −0.83; −0.31, $p < 0.001$), tended to reduce IL-6 (SMD = −0.19, 95%CI = −0.42; 0.02, $p = 0.07$) and did not change TNF-α. Further exploratory sub-group analyses showed a potential association of muscle mass for both CRP and TNF-α changes. Reductions in CRP and TNF-α only occurred in RCTs performing a higher number of exercises (> 8), higher weekly frequency (3 times/week) and longer durations than 12 weeks.

Conclusions: Anti-inflammatory effects of RT were significant only for CRP with a tendency for a decrease in IL-6 as well. The exploratory analyses suggested the reduction in inflammatory markers could be dependent on increases in muscle mass and higher volume of RT protocols. These potential mediators of RT anti-inflammatory effects should be addressed in future meta-analyses to clarify the effects of RT on inflammatory markers of older adults with very specific conditions and larger numbers of studies.

1. Introduction

The immune system homeostasis is negatively affected by advancing age. Chronic low-grade inflammation increases with aging (Franceschi and Campisi, 2014), which has been associated with several deleterious health outcomes and may aggravate the phenomena of sarcopenia and dynapenia (Argiles et al., 2015; Arnold et al., 2018). Moreover, chronic low-grade inflammation increases the risk of developing age associated diseases and is an independent risk factor for mortality in an apparently healthy adult population (Bonaccio et al., 2016).

Conversely, physical exercise is recommended as an important non-pharmacological strategy to attenuate these age-related health impairments (ACSM et al., 2011; Chodzko-Zajko et al., 2009). Several narrative reviews have addressed the benefits of exercise training on inflammatory parameters, proving beneficial effects of moderate intensity aerobic exercise training (Calle and Fernandez, 2010; Gleeson et al., 2011; Pedersen and Bruunsgaard, 2003; Petersen and Pedersen, 2005; Walsh et al., 2011; Woods et al., 2012). Resistance training (RT) has well been established with positive effects on muscular strength and muscle growth, contributing to the maintenance of functional independence and reductions in the risk of falling (Chodzko-Zajko et al., 2009; Csapo and Alegre, 2016; Ishigaki et al., 2014; Reid et al., 2008).

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However, the effects of RT on inflammatory biomarkers, especially in elderly people, remain controversial.

For example, some studies found beneficial effects of RT on inflammatory biomarkers (Lera Orsatti et al., 2014; Nunes et al., 2016; Tomeleri et al., 2016) while others failed to note such effects (Azizbeigi et al., 2015; Calle and Fernandez, 2010). These disparate findings might be due to different study samples (e.g.: age, sex, diseases, and baseline inflammation profile), type of RT protocols (e.g.: intensity, volume, and duration of intervention) which deserves a pooled effect analysis considering all these different conditions. In addition, the effect of RT on body composition (increase in muscle mass and decrease in body fat) might influence the anti-inflammatory effects of exercise (Mavros et al., 2014; Tomeleri et al., 2016) and might contribute to the understanding of the anti-inflammatory RT effects.

Therefore, the present study has aimed to critically examine the effects of RT on inflammatory parameters of older individuals through a systematic review and meta-analysis of randomized controlled trials (RCTs). The most prevalent markers among studies were selected: C-reactive protein (CRP), interleukine-6 (IL-6) and tumor necrosis factor-α (TNF-α). These markers have been associated with the aging process and frailty, and reduction of their concentration through lifestyle modifications is associated with lower disease and mortality risks (Alley et al., 2007; Gleeson et al., 2011; Singh and Newman, 2011; Soysal et al., 2016). However, although IL-6 is often classified as a pro-inflammatory cytokine, when it is produced and released by skeletal muscles, it has also very important anti-inflammatory properties (Pedersen and Fischer, 2007).

2. Methods

2.1. Search strategy

A systematic search was conducted on MEDLINE with the last update on July 13, 2017. The search included combined terms to match inflammatory markers ("biological markers" or "inflammation" or "inflammatory" or "immune response" or "cytokines" or "interleukin" or "myokines" or "tumor necrosis factor alpha" or "C-reactive protein") with RT ("weight training" or "weight lifting" or "strength training" or "resistance exercise" or "strength exercise" or "resistance program" or "strength program") and aging ("age" or "elderly" or "older adults" or "postmenopausal").

The flowchart of study selection is detailed in Fig. 1. We included RCTs testing effects of RT isolated therapies on blood concentration of CRP, IL-6 and/or TNF-α in adults with > 50 years-of-age. After the overall screening, three RCTs were not included in the meta-analysis due to the lack of quantifiable results. Moreover, one RCT including kidney transplanted patients was excluded since the baseline inflammatory state of this population was very different of our overall sample, and the immunosuppressant medication could be an important confounding factor for RT effects.

Two independent reviewers selected studies and extracted data. Among the 13 studies selected, 11 assessed CRP, 11 IL-6 and 7 TNF-α (Chupel et al., 2017; Deibert et al., 2011; Hagstrom et al., 2016; Hsieh et al., 2016; Karabulut et al., 2013; Martins et al., 2010; Nunes et al., 2016; Perreault et al., 2016; Rodriguez-Miguelez et al., 2014; Strandberg et al., 2015; Theodorou et al., 2016; Tomeleri et al., 2016; Tomeleri et al., 2018; Wanderley et al., 2013). Mean, standard deviation (SD) and sample number (n) were used for analysis. Standard error (SE) was converted to SD by the equation $SD = SE * (\sqrt{n})$, if SD was not provided in the original study. Furthermore, median and interquartile range (IQR) was replaced by median and SD ($SD = (IQR / 1.35)$) (Hozo et al., 2005).

The features of study populations, RT interventions and secondary adaptations analyzed in the original studies were clustered for further sub-group analysis. The baseline levels of CRP between "high risk" and "moderate risk" for incident coronary heart disease were dichotomized according to the cut-off point proposed by Buckley et al. (2009). Protocols prescribing 70% of one maximum repetition (1RM) or less were classified as moderate intensity, while the ones prescribing over 70% of 1RM were classified as vigorous intensity. When a specific disease was not used as inclusion criteria, individuals were considered healthy, even though among the overall sample a few diseased individuals could have been included. When the original studies did not report specific features, the study was removed from the specific sub-group comparisons.

The PEDro scale assessed quality of the studies and the two questions regarding blinded patient and care providers were nulled as it is not possible in exercise interventions RCTs (Maher et al., 2003). Thus, scores on PEDro scale ranged from 0 (very low methodological quality) to 9 (high methodological quality). The quality of the studies was used for qualitative assessment, and it was not an exclusion criteria. Egger's tests were performed to check the risk of publication bias in each of the meta-analyses.

2.2. Statistical analyses

The three meta-analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3.3.070. The effect size was calculated based on standard mean difference (SMD: difference between the changes within training and control groups). Since there was no statistical significance for heterogeneity, fixed effect models were selected for all analyses. The independent RT groups within a study were treated as a separate RCT for meta-analysis (both interventions compared to the same control group) (Karabulut et al., 2013; Nunes et al., 2016). Conservative pre-post correlations of 0.5 were assumed (Boreinstein et al., 2009).

Sub-group analyses were performed for effects of RT on CRP and TNF-α considering their inconsistency between studies (CRP: $I^2 = 43.97\%$ and TNF-α: $I^2 = 47.51\%$). Sub-group analysis considered the effects of features for the study population, training protocols and body composition adaptations over the main effects. Among sub-group analyses, mixed effects were applied when there was significant heterogeneity between studies within one of the sub-groups compared, while fixed effects were applied when there was no heterogeneity between the studies within both sub-groups. For all the analyses, the p-value < 0.05 was considered significant. Unfortunately, sub-group analyses were not possible for IL-6 due to its homogeneity between studies ($I^2 = 0.00\%$).

3. Results

3.1. Evidence synthesis

The characteristics of the studies are described in Table 1. The quality of the studies ranged from 4 to 8 in PEDro scale, and details of their classification can be assessed in Table 2. Egger tests suggested there were no significant effects for publication bias in the three meta-analyses performed herein ($p > 0.05$ for all).

The forest plots (Fig. 2) showed RT significantly reduced CRP in older adults ($SMD = -0.61$, 95%CI = −0.83; −0.31, $p < 0.001$), tended to reduce IL-6 ($SMD = -0.19$, 95%CI = −0.42; 0.02, $p = 0.07$) and did not change TNF-α.

RCTs that increased muscle mass showed significantly larger CRP reductions than interventions maintaining unaltered muscle mass (Table 3). RCTs reducing fat mass showed significant reduction in TNF-α, while studies maintaining body fat showed no significant effects, however no significant difference between groups was found (Table 4).

Regarding RT features, only RCTs with a higher number of muscle group exercises (> 8), higher weekly frequency (3 times/week) and longer durations than 12 weeks intervention, significantly reduced CRP and TNF-α (Tables 3 and 4). Moreover, RCTs applying moderate intensity RT tended to reduce CRP ($p = 0.059$) and TNF-α ($p = 0.054$) to a higher extent than RCTs prescribing vigorous intensity RT (Tables 3