Evidence-based effects of multicomponent exercise training on biomarkers related to frailty in older persons: a systematic review

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Abstract:

Introduction: Frailty is a complex syndrome that can be characterized by the loss of physical functional capacity. The effects of multicomponent exercise training on frailty and correlated biomarkers are not yet fully explored in the scientific literature. **Objective:** Based on the available literature data, our first endpoint in this systematic review was to present the current knowledge on the influence of multicomponent exercise training in older persons diagnosed with the frailty syndrome. In addition, a second endpoint was to identify not only the most evaluated and responsive biochemical markers in this population, but also how they responded to multicomponent exercise training. **Methods:** The electronic databases PubMed, SciELO, LILACS, and Science Direct, were accessed. The search was conducted in the English language using MeSH keywords in order to verify which biochemical markers were investigated in the studies that associated frail older persons and multicomponent physical exercise. This systematic review was registered under the reference CRD42018089912. **Results:** Six randomized controlled trial studies met our inclusion criteria and were used to perform this review. In response to our endpoints, these studies reported that multicomponent exercise training was able to decrease or reverse frailty by improving functional fitness, muscle strength, speed and agility. In addition, this type of exercise training was associated with alteration in several biomarkers, namely C-reactive protein (CRP), interleukin (IL-6), Tumour Necrosis Factor (TNF- α), insulin-like growth factor (IGF-1), haemoglobin (HbA), albumin, oxidation products, antioxidants, Vitamin D, and serum/plasma/saliva hormone levels of dehydroepiandrosterone (DHEA), testosterone and parathyroid hormone (PTH). **Conclusion:** Multicomponent exercise training is a powerful tool to prevent or even revert frailty development in older persons, namely through its mediating action in several metabolic, hormone and pro-inflammatory markers.

Keywords: Physical function, RCT, Muscle Strength, Inflammatory markers, Hormones.

Introduction

The Frailty Syndrome (FS) can be defined as a loss of physical and functional capacity with multifactorial traits in which the loss of muscle mass is highlighted (Marzetti et al., 2019). The physical frailty syndrome (PFS) is defined as an ageing-related multifactorial clinical condition marked by a progressive decline of multiple physiological domains that compromise the individual capacity to withstand stress (Fried et al., 2001) and can be assessed by evaluating 5 factors: lean mass loss, diminished handgrip strength, reported fatigue/exhaustion, reduction of walking speed, and low physical activity levels. It has been proposed that these losses could be closely associated with a sedentary lifestyle and the lack of previous beneficial interventions, such as physical exercise programs (Milanović et al., 2013; Booth et al., 2012). In fact, these factors are also associated with the increasing number (and risk) of falls in frail older persons (Leitão et al., 2015). There are a handful of studies that aimed to investigate whether exercise training could putatively reverse frailty (frail to pre-frail or pre-frail to robust), or, at least, achieve a lower degree of frailty in older persons (Manãs et al., 2019). A systematic review concluded that structured physical training has positive impacts on frailty and should be used for management of the syndrome (Theou et al., 2011). Therefore, it can be said that the beginning of a physical

activity program in an older person (which usually does not perform supervised body movements), tends to induce biological/physiological adaptations that will definitely affect the final score of the Fried scale.

It is paramount to mention that, among several exercise training protocols, multicomponent exercise training programs that focus on at least 3 different physical modalities in the same exercise session (Chodzko-Zajko et al., 2009; Baker et al., 2007) including aerobic, strength, balance and flexibility exercises, could promote healthy ageing (Leitão et al., 2015). The results of a meta-analysis showed that training interventions involving multidirectional movements, weight transfers, and elements of functional strength training, improved functional capacity, and also decreased falls by 52% in older persons (Sherrington et al., 2017). Multicomponent exercise programs have also resulted in major improvements in functional capacity, which is strategic for maintaining the skills and independence to perform the basic tasks of daily living (Casas-Herrero et al., 2019). There is growing evidence that the older persons engaged in a multicomponent exercise training program present, in a general way, a better health status as a long-term result (Cadore et al., 2019; Arrieta et al., 2019; Silva et al., 2017; Makizako et al., 2012; Hopps et al., 2011; Theou et al., 2011). Multicomponent programs are considered, by some authors, as the most beneficial type of training to optimize functional capacity of frail older persons and to prevent functional and physical incapacity (Cadore et al., 2014; Villareal et al., 2011), but to our knowledge there are no systematic reviews to clarify the impact of this kind of exercise program in frail older persons.

A main inflammatory profile consisting of greater concentrations of C-reactive protein and lower concentrations Interleukin 8 (IL- 8) with gender-specific signatures has been recognised in the background of physical frailty, together with decreased systemic levels of interleukin-10 (IL-10), a typical anti-inflammatory cytokine, and increases in Tumor Necrosis Factor-alpha (TNF- α) levels are linked with ageing (Marzetti et al., 2019). For many authors, physical exercise training has the potential to provide protection against frailty in advanced aged persons, and that most of these benefits, at least in part, are related to the cognitive, anti-inflammatory and metabolic effects of exercise (Aguirre & Villareal, 2015; Gleeson et al., 2011; Petersen & Pedersen, 2005). Physical exercise stimulates the release of cytokines, such as IL-6, IL-10 and IL-1ra, in response to contracting skeletal muscles, which are responsible not only for tissue restoration and energy metabolism, but also for the adjustment of the systemic inflammatory status (Pedersen & Febbraio, 2012). However, the benefits of physical exercise programs in reducing frailty by improving functional capacity, muscle strength, speed, and agility, did not seem to elicit significant alterations in several systemic biomarkers in some studies (Ferreira et al., 2018). A review on the effect of multicomponent exercise on biochemical markers related to health in frail older persons is needed to better clarify the role of these biomarkers and help understand on how to detect, prevent and manage frailty.

Materials & methods

This study followed a pre-determined Systematic Review (SR) protocol redistricted in the PROSPERO database, under the number CRD42018089912, carried out by taking into account different guidelines, utilized to stratify, evaluate and select the scientific reports included in this SR.

In order to guarantee the rigor, accuracy, and replicability in this SR, the following steps were followed: (i) definition of systematic search terms through operationalization and concepts description; and (ii) pilot systematic search of articles in order to verify the search accuracy in each previously selected database.

Search Strategy

To formulate our research question and choose our MeSH search Terms we used the PICO (population, intervention, comparison, outcomes) methodology (Doig et al., 2003). We performed a systematic search for studies published in English on the following databases: PubMed, SciELO, LILACS and Science Direct. Scientific reports were accessed between July 2018 and January 2020 in order to identify original studies, published between 2001 and 2020, presenting multicomponent exercise training, volunteers over 60 years of age, of both sexes, who were living or not, in residential care homes. The following MeSH (Medical Subject Headings) terms were used: “multicomponent exercise”, or “physical exercise”, or “multi-modal exercise training”, or “exercise therapy”, or “combined exercise training”, or “circuit-based exercises”, or “circuit training”, or “muscle strength exercises”, or “muscle strength training”, or “resistance training”, or “physical fitness programs”, or “concurrent training”, or “home-based exercise” AND “elderly” or “older subjects”, or “older populations” AND “biomarkers” or “biochemicals”, or “immune system”, or “hallmarks” AND “Fried frailty criteria”.

Quality of assessment:

Selection of the article’s strategies followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Panic et al., 2013). In addition, the CONSORT checklist was used, since it provides guidelines for evaluating the quality of the selected studies (Begg et al., 1996), allowing to identify possible errors or methodological weaknesses. In order to avoid the risk of bias, the evaluation of the articles was carried out by 2 different researchers (blinded), with help of a third researcher if no consensus on the scores of the articles was reached (Donato et al., 2019).

The following eligibility criteria were adopted: (i) regarding the population: individuals over 60 years of age presenting frailty (defined as frail or pre-frail, by the Fried criteria (Fried et al., 2001)); and (ii) randomized controlled trials or clinical trials investigating the effect of multicomponent exercise training protocols on physical frailty and biomarkers. The exclusion criteria used were: non-original studies, reviews or meta-analysis, non-randomized controlled trials (nRCT).

Results

A total of 130 articles were identified through database searching (PubMed=25, SciELO=15, and Science Direct=90). The screening of database LILACS did not render any record.

By applying the first study selection criteria, 45 studies were excluded, and 85 studies proceeded to the screening phase. At this stage, after reading the abstracts, 43 studies were further excluded. From the 42 remaining articles, 10 studies were included after the eligibility phase. After that, 4 were excluded because they did not use Fried's frailty criteria or due to incompatibilities on study protocols. A total of 6 articles met the inclusion criteria and were used to perform this SR (see Flowchart of figure 1).

Figure- 1 Prisma Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

Sample Study Characteristics

The six studies included in this SR, represent a total of 336 frail men and women, aged ≥ 70 years and living in residential care homes. Supervised exercise interventions were used, with in some cases addition of non-supervised exercises. Tarazona-Santabalbina, 2016, used a 24 weeks combined program of endurance, strength, coordination, balance, and flexibility exercises; Arrieta et al., 2018, a 6 months multicomponent exercise protocol. Furtado et al 2019; 2020, a 28 weeks multi-modal exercise; Sadjapong et al., 2020, a 12 weeks

multicomponent exercises; Ferreira et al., 2018, a 12-weeks physical exercise program strength, coordination, balance, and flexibility.

Main Results of the Selected Studies

Regarding multicomponent exercise training programs in frail older persons, the study performed by Tarazona-Santabalbina and collaborators (2016), demonstrated that their program was able to revert frailty, improving physical function, anthropometric parameters, cognitive and emotional domains. Sadjapong and collaborators (2020) showed the reverse of frailty to pre-frailty status, with improved physical performance, especially balance. Furtado and colleagues (2019, 2020) observed decreased frailty, with benefits in physical activity levels (gait speed and muscle strength) and diminished functional disability. Ferreira and colleagues (2018) also found reduced frailty through improvements in functional capacity, muscle strength, speed, and agility. Arrieta and collaborators (2018), evidenced improvement in physical fitness. Full descriptions of these studies are presented in table 1.

Concerning biomarkers (Table 2), Tarazona-Santabalbina and collaborators (2016), monitored an increase in the levels of brain-derived neurotrophic factor (BDNF). Arrieta and collaborators (2018), found an increase in myostatin levels. Ferreira and colleagues (2018) monitored glucose, insulin, total cholesterol, triglycerides, vitamin D3, and C-reactive protein (CRP; pro-inflammatory marker) and found improvements in biochemical variables but no effects in inflammatory parameters. Furtado and colleagues (2019, 2020), focused on cortisol, testosterone, dehydroepiandrosterone, testosterone/cortisol ratio, salivary immunoglobulin-A (IgA), salivary lysozyme levels (Lys), pro-inflammatory interleukines-1 beta and 6 (respectively, IL-1 β , IL-6) and Tumour Necrosis Factor-alpha (TNF- α), anti-inflammatory interleukine-10 (IL-10), interferon-gamma (IFN- γ), and CRP, with improvement in hormonal response and better balance between pro- and anti-inflammatory environments. Sadjapong and collaborators (2020), measured IL-6 and CRP and obtained decreases in these inflammation markers.

Table 1- Summary of Study and Participant Characteristics

Author (year)	Main Goals	Characteristics of participants	Biomarkers	Comparison	Results on Biomarkers	Results on frailty outcomes
Arrieta et al (2018) SPAIN	to determine the association of serum myostatin concentration with body composition, physical fitness, physical activity level, frailty.	Women 86.2 $\pm$ 6.8 years men 82.0 $\pm$ 6.3 years n=88	Myostatin	6-months exercise, twice a week, involving strength, balance, stretching exercises, and walking recommendations	higher serum levels of myostatin were found to be associated with better physical fitness. however, the use of this protein as a biomarker for physical fitness, rather than frailty, merits further study.	Decrease frailty
Tarazona-Santabalbina et al (2016) SPAIN	to multicomponent exercise program (mep) performed by frail older and improve functionality, cognitive, emotional, and social networking, biomarkers	Men and women 79.5 years n= 100	BDNF	24 weeks a combined program of endurance, strength, coordination, balance, and flexibility exercises. 65 min session, 5 days/week	Improved functional measurements, cognitive, emotional, and social networking determinations. it also leads to a decrease significant improvement in frailty biomarkers	The men group reversed frailty
Ferreira et al (2018) BRAZIL	To verify the effects of exercise training on biochemical, inflammatory, and anthropometric indices and functional performance in institutionalized frail elderly	Men and women 73.3 $\pm$ 6.4 years n=71	Glycaemia, Insulin TC, TR HDL, LDL Vitamin D3, CRP IL6, IL10 IL1a, IL1RAcP	12-weeks physical exercise program strength, coordination, balance, and flexibility	Improving muscle strength, speed, agility, and biochemical variables, with but, no effects in anthropometric and inflammatory parameters were noted.	Reversal of the frailty condition
Furtado et al (2019)	To analyse the effect of two different 28-weeks chair exercise programs	Institutionalized dwelling women n=60 81 $\pm$ 7.84 years	Cortisol Testosterone Dehydroepiandrosterone Testosterone/Cortisol	28-weeks chair exercise programs multimodal and muscles	Both exercise interventions used in this study produced significant benefits	Diminish the physical frail condition

PORTUGAL	(multimodal and muscles strengthening with elastic bands on physical frailty, functional disabilities and steroid hormones in institutionalized pre-frail and frail women	ratio	strengthening with elastic bands	in order, decreased functional disability and also, stimulated satisfactory hormonal responses.
Furtado et al (2020)	to analyse the effects of 28-weeks of two different exercise protocols on the functional fitness and immune profiles of institutionalized pre-frail and frail women with mild cognitive impairment.	Institutionalized pre-frail and frail women with mild cognitive impairment 81±7.84 years n=60	sIgA, sLys, IL-1β, and IL-6; TNF-α, IFN-γ IL-10 CRP	28-weeks chair exercise programs multimodal and muscles strengthening with elastic bands
PORTUGAL				The evidence regarding the use of systematic and moderate long-term exercise as therapy for promoting a better balance between pro- and anti-inflammatory environments and a decrease in the inflammatory index for the cme group were the most promising results from this study..
				Reduces levels frailty

Table 2- Identification of the biological systems involved.

Author	Biochemical/molecular mechanisms studied	Confirmation of hypothesis
Arrieta et al (2018)	Muscle Tissue	Increases in myostatin concentration (muscle activity)
Tarazona-Santabalbina et al (2016)	Nervous System	Increase in the BDNF serum levels group multicomponent
Ferreira et al (2018)	Lipid profile and cytokines pro inflammatory	Improvements in biochemical variable but no effect in inflammatory parameters
Furtado et al (2019)	Neuroendocrine Cortisol, Testosterone, Dehydroepiandrosterone, Testosterone/ Cortisol Ratio	Stimulated satisfactory hormonal responses.
Furtado et al (2020)	Immune system, pro/anti inflammatory	Decreased inflammation in frail older adults.
Sadjapong et al (2020)	Immune system pro/anti inflammatory	Decreases inflammation in frail older adults

Discussion

Unfortunately, we could only find 6 studies that reached our eligibility criteria, evidencing a lack of studies targeting biomarkers as the mediators of multicomponent exercise training in frail older persons. Those biomarkers are crucial to better understand frailty prevention, development and progression, and its consequences on ageing well being.

Among the 42 articles selected in the first evaluation phase, 10 (24%) studies used multicomponent exercise training programs, which confirms their increasing use in frail older persons. Multicomponent exercise training programs (ME) seem to be predominantly used in frail older persons (Silva et al., 2017), and may be

considered an ideal intervention for this specific population (Pillatt et al., 2019). The combination of multicomponent strength, aerobic, and balance exercises demonstrated remarkable positive effects on health outcomes as compared to their isolated prescription (Baker et al., 2007). Furthermore, multicomponent exercise training has also been shown to be advantageous and most attractive for older persons as they are similar to their daily activities (Angulo et al., 2020). Our SR confirms the potential of ME in preventing or revert frailty in older persons: three (3) studies showed reverted frailty, two (2) diminished frailty and one (1) improved physical fitness. Moreover, these studies are also in accordance with other robust studies using ME in frail older persons (Cadore et al., 2019; Arrieta et al., 2019; Silva et al., 2017; Makizako et al., 2012; Hopps et al., 2011; Theou et al., 2011).

Regarding the frequency of the multicomponent exercise programs described in this SR, a variation of 2-5 times per week with a total duration between 3 to 8 months was found, with the ability to attenuate frailty and positive impact on biomarkers. Moreover, there seems to be a consensus that the inclusion of resistance, gait, and balance training in the multicomponent exercise training programs is the corollary strategy for improving frailty hallmarks, as well as for reducing falls risk in frail older persons. In addition to maintain functional capacity during ageing, ME combines several actions, such as cognitive training that also enhances cognitive performance and, thus, prevents cognitive impairment (Tarazona-Santabalbina et al. 2016). Results from other studies using different exercise protocols also confirm this (Cadore et al., 2019; Theou et al., 2011; Arrieta et al., 2019; Makizako et al., 2012; Justine et al., 2010).

This SR showed that the preferential and the most responsive biomarkers assessed in the selected studies were IL-6, CRP and TNF- α (see Table 2), as those biomarkers were evaluated in 3 of the 6 studies. In this respect, it is noteworthy to point out that multicomponent exercise training showed the capacity to induce significant alterations in these biomarkers, especially in the studies of Furtado and collaborators (2020) and Sadjapong and collaborators (2020), which indicated that ME contributed to lower inflammation levels in frail older persons. Taking other studies with young and older persons into account, there is solid evidence that the regular practice of physical exercise decreases systemic levels of CRP, IL-6, and TNF- α , reinforcing the findings discussed above (Hopps et al., 2011; Nicklas et al., 2008; Petersen & Pedersen, 2005; Petersen et al., 2007).

Recently Petrella and collaborators (2021) reported that the multicomponent exercise training program is an inexpensive intervention that could be replicated in care centers, for the avoidance and treatment of frailty, mainly acting in the pro and anti-inflammatory pathways, but also optimizing anabolic processes (based biomarkers). Among the studied biomarkers of frailty, it is worth mentioning: Glycaemia, Insulin, Total Cholesterol, Triglycerides, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), CRP, Vitamin D3, cytokines IL-6, IL-10, IL-1 α , IL-1RAcP, Myostatin, Cortisol, Testosterone, Dehydroepiandrosterone, and Testosterone/Cortisol ratio [Tarazona-Santabalbina and collaborators (2016); Arrieta and collaborators (2018); Ferreira and colleagues (2018); Furtado and colleagues (2019, 2020); and Sadjapong and collaborators (2020)]. In agreement with the literature, immune/inflammatory dysfunction is considered to be at the core of frailty, due to its direct crosstalk with neuroendocrine and neuromuscular impairments (Ng et al., 2018).

Thus, among the well-accepted benefits of physical exercise training – such as maintaining the health and functionality in older people by increasing muscle strength, improving balance, and avoiding falls – this nonpharmacological intervention has also demonstrated the capacity to decrease the levels of pro-inflammatory biomarkers (Seguin & Nelson, 2003; Furtado et al., 2020), which can cause a positive impact in older persons by preventing and/or reversing frailty development.

Despite the precise mechanisms by which physical exercise promotes healthier ageing are still not fully understood (Sadjapong et al., 2020), a relevant contribution for that, could be associated to the favourable improvement in muscle mass and reduction in adipose tissue, which has been linked to lower pro-inflammatory levels and, thus, a better inflammatory balance (Cartee et al., 2016; Gonzalez-Gil et al., 2020).

Moreover, most of the subjects studied here were institutionalized-dwelling older, who usually are at higher risk of frailty compared to those not living in residential home care centers (Soriano, DeCherrie, & Thomas, 2007). Although in apparent disadvantage, the impacts of ME were still significant for this specific population, highlighting the usefulness of this practice in maintaining the quality of life, especially in residential care homes.

Although there are convincing signs that multicomponent exercise training in frail older persons is an effective intervention for controlling frailty, further studies are necessary to increase our understanding of the mediating effects of exercise on immune and hormonal pathways involved in frailty.

Study limitations, Suggestion for Future Studies

The fact that only 6 studies matched our inclusion criteria could be considered a limitation of this SR, but it is important to clarify that the criteria used here were designed to identify those studies with a consistent frailty phenotype evaluation, allowing a better comparison between studies. Nevertheless, some other limitations should be taken into account, like different follow-up times, differences in physical exercise programs (sequence, duration, progression, intensity), and differences in previous levels of physical fitness, which could lead to some potential bias. Future research should focus on a better definition of the physical activity “dose” capable of

improving the biochemical profile in older persons and its association with frailty, in order to promote healthier ageing with more years and better quality of life. In addition, the study of the impact of nutritional supplementation in combination with multicomponent exercise training could also be important in the context of frailty.

Practical applications

Since a progressive rise in the number of older persons in Europe is still predicted for the next decades, accurate studies associating the triad frailty-inflammaging-physical exercise training (especially multicomponent exercise programs) are reasonably necessary to increase our knowledge on how to improve functional fitness, health and quality of life of older people, assuring their autonomy and independence for longer years.

Conclusion

This SR showed that multicomponent exercise training, designed to address frailty in older persons, was able not only to improve several parameters associated with physical function and metabolic balance, but also benefited cognitive, emotional, and social functions. Our SR confirms the potential of ME programs of 2-5 times per week with a total duration between 3 to 8 months, in preventing or reverting frailty in older persons, associated with positive impacts on biomarkers, especially those associated with decreased pro-inflammatory parameters, mainly CRP, IL-6, TNF- α , and with better regulation of metabolic and hormone pathways. The number of studies is still scarce and more looking at the mediating effect multicomponent exercise training programs on biomarkers are needed, in order to better understand the aetiology of the frailty syndrome and improve the prevention and management of frailty in older populations.

Conflicts of interest – No conflicts of interest to declare.

Contributors

Adriana Caldo organized acquisition of data and writing of the paper, Guilherme Furtado helped in the acquisition of data. Nelo Zanchi, Alain Massart and Guilherme Furtado supported the interpretation of data and reviewed the paper critically. Marcelo P. Barros and André L.L. Bachi helped in the discussion as well as reviewed the paper critically. Alain Massart and Ana Maria Teixeira reviewed the paper critically and coordinated the research study protocol.

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