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The effect of exercise on inflammaging: A systematic review

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Abstract

The health benefits of exercise have been extensively explored in the literature and are widespread, exerting a positive effect in various organ-systems in the body and in all age groups.

The beneficial impact of exercise has been explored in both healthy individuals and those presenting different diseases. Exercise has even been “prescribed” for health conditions that initially would appear to contraindicate exercise.

Meanwhile, there are also numerous studies on the link between aging and disease, with attempts to identify the different factors associated with alterations in the immune system that occur with age. Indeed, it appears that many age-related diseases are associated with chronic, low-level inflammation, or inflammaging. Exercise appears to exert a beneficial impact on aging through pathophysiological mechanisms that result in reduced inflammation. We aimed to explore the beneficial impact of exercise on inflammaging by performing a systematic review of the literature in this field. More specifically, we aimed to identify and analyze studies on the impact of exercise in age-related diseases associated with inflammation. Our method included conducting searches in 3 databases: PubMed, Web of Science, and EMBASE. Additionally, hand searches of the reference lists of all included studies and previously published systematic reviews on the effects of exercise on inflammaging were conducted to ensure completeness of the search. Only articles in English were included; however, no geographical restriction was applied. The search in each database was performed from 10 years to the current time (2021/03/31). All levels of screening were conducted by two independent reviewers with unanimous agreement, followed by a full-text review to assess papers regarding their eligibility. Data from included papers was extracted using standardized forms. A narrative synthesis was conducted considering the strength, consistency of results, and the methodological quality of the studies. Despite some conflicting evidence, there is a consensus in this field that exercise has a positive impact in the elderly population, including improved physical functioning, and may have a beneficial impact on the inflammatory profile of subjects. The evidence in this field is promising and may be clinically relevant, particularly in patients with specific conditions and diseases.

Resumo

Os benefícios ao nível da saúde associados ao exercício têm sido extensamente explorados na literatura e são abrangentes, exercendo um efeito positivo em vários órgãos e sistemas no corpo humano.

O impacto positivo do exercício tem sido investigado tanto em grupos de indivíduos saudáveis como naqueles que apresentam diferentes tipos de doença. De facto, o exercício tem sido "prescrito" para estados de saúde que inicialmente podiam parecer serem condições em que o exercício estaria contraindicado.

Entretanto, existem numerosos estudos sobre a associação entre envelhecimento e doença que procuraram identificar diferentes fatores associados às alterações no sistema imunitário que se verificam em idades mais avançadas. De facto, existem múltiplas doenças associadas a idades mais avançadas em que se observa uma inflamação crónica de baixo grau. O exercício parece exercer um impacto benéfico no envelhecimento através de mecanismos fisiopatológicos que resultam numa redução da inflamação. O nosso objetivo na realização desta revisão sistemática consistiu em explorar a literatura nesta área sobre os efeitos benéficos do exercício no inflammaging, um conceito criado para descrever inflamação crónica de baixo grau associada ao envelhecimento. Mais especificamente, o nosso objetivo era identificar e analisar estudos sobre o impacto do exercício em doenças associadas à inflamação. O nosso método consistiu em pesquisar 3 bases de dados: PubMed, Web of Science and EMBASE. Também procuramos listas de referências de todos os estudos incluídos no nosso estudo e outras revisões sistemáticas sobre os efeitos do exercício no inflammaging para assegurar que a nossa pesquisa era o mais abrangente possível. Apenas artigos publicados em inglês foram incluídos; no entanto, não aplicamos nenhuma restrição geográfica. A pesquisa em cada base de dados foi realizada para incluir artigos publicados desde há 10 anos até 2021/03/31. Dois revisores independentes reveram os títulos e resumos e subsequentemente realizaram uma revisão de todo o texto para assegurar que os artigos que eram relevantes fossem incluídos na análise. Os dados relevantes dos artigos foram extraídos utilizando formulários estandardizados. Uma síntese narrativa foi realizada considerando a força de evidência, consistência dos resultados, e a qualidade metodológica dos estudos. Apesar de existir alguma evidência contraditória, existe um consenso nesta área de que o exercício tem um impacto positivo na população idosa, incluindo melhoria ao nível do funcionamento físico, e poderá ser benéfico ao nível do perfil inflamatório dos sujeitos. A evidência nesta área é promissora e poderá ser clinicamente relevante, particularmente em doentes com condições e doenças específicas.

Keywords: Exercise, Inflammaging, Aging, Elderly, Inflammation, Inflammatory markers

Introduction

Rationale

Inflammation is a critical aspect of our host defense system. However, poorly regulated innate immunity and inflammation can cause chronic disease. In fact, there are biomarkers of low-level chronic inflammation that may predict disease. A few diseases associated with poorly regulated innate immunity include cardiovascular disease, osteoporosis, and type 2 diabetes mellitus (1).

Inflammaging was a term introduced by Franceschi *et al* in 2000 to describe older individuals with chronic inflammation and associated comorbidities (2). Inflammaging is associated with a two to four-fold increase in the levels of cytokines, and proinflammatory mediators in the plasma (3). Altered production and release of cytokines are associated with chronic diseases and increased mortality in the elderly (3). Additionally, increased levels of cytokines have a negative impact on physical performance and muscle function (3).

Although it may seem counterintuitive, exercise is linked to an anti-inflammatory effect in both young and older individuals (1). Despite the fact that there are some studies with contradictory results in the literature, there is increasing evidence for the beneficial impact of exercise on inflammation (1). Indeed, performing exercise regularly may result in decreased inflammatory cytokine levels, thereby reducing the impact of chronic inflammation associated with aging and chronic disease (4). Also, reduced inflammatory mediators and improved physical performance in the elderly may also be achieved through exercise interventions (5,6).

Based on the review by Gleeson *et al* (2011), there are 3 main mechanisms that have been reported by which exercise exerts an anti-inflammatory effect: production and release of anti-inflammatory cytokines from muscle; reduction in visceral fat mass; and reduced expression of toll-like receptors on macrophages and monocytes (7). However, there are other mechanisms for the anti-inflammatory effect of exercise, including phenotypic switching of macrophages in adipose tissue, increased levels of circulating cortisol and adrenaline, and inhibition of macrophage infiltration into adipose tissue, among others (7).

Regarding cytokines linked with chronic inflammation, interleukin- 6 (IL-6) is associated with a substantial pro-inflammatory effect. Indeed, in a study by Peterson and Pederson (2005), increased levels of IL-6 were linked to the following diseases: type 2 diabetes, Alzheimer's disease, cardiovascular disease, osteoporosis, etc. Additionally, high levels of IL-6 may also have an impact on muscle strength and functional capacity in older individuals (8).

IL-6 also inhibits the pro-inflammatory cytokine tumor necrosis factor (TNF-α). Meanwhile, exercise is associated with lower levels of pro-inflammatory cytokines, including IL-6 and TNF-α. In older individuals, increased levels of TNF-α are associated with negative diseases and conditions. For example, based on a study by Phillips *et al* (2010), increased levels of TNF-α may be associated with loss of muscle mass in older individuals with sarcopenia. Additionally, increased levels of TNF-α are seen in obesity and in individuals with increased visceral fat, conditions which are accompanied by an increased prevalence of other related conditions, including type 2 diabetes mellitus (T2DM) (7).

Sources of IL-6 include adipocytes, leukocytes, brain, and liver (7). Transient marked increases in IL-6 levels are associated with prolonged exercise; however, modest increases have been reported for exercise of shorter duration. The transient rise in IL-6 results in an increase in anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1R), as well as stimulating the release of cortisol from the adrenal gland (7). IL-10 is responsible for modeling the adaptive immune responses and the expression of several pro-inflammatory cytokines (7).

Excess body fat is associated with increased all cause-mortality and is linked to several diseases, including T2DM, CVD and dementia (7). Excess adipose tissue is associated with an increase in pro-inflammatory adipokines, including TNF, IL-6, IL-19, monocyte chemotactic protein (MCP1), and leptin, among others; meanwhile, anti-inflammatory cytokines are reduced, leading to a state of chronic low-grade systemic inflammation (7).

Consistent exercise can result in a substantial decrease in abdominal and visceral fat, independent of any loss of body weight in both females and males and at any age. Based on the literature, exercise is associated with higher levels of adiponectin and lower levels of circulating proinflammatory adipokines, namely IL-6, TNF, and leptin, among others. Consequently, a reduction in systemic inflammation through decreased secretion in pro-inflammatory adipokines can be achieved by reducing the amount of visceral fat (7).

Overall, there is substantial evidence in the literature that supports the beneficial impact of exercise on low-grade systemic inflammation. Therefore, we aimed to perform a systematic review of the literature in this field, specifically focusing on reports that provide evidence of the beneficial impact of exercise on inflammaging in populations of individuals aged ≥65 years.

There have been previous attempts to review the literature in this field. Indeed, there is a systematic review that was published last year on this topic, a study by Bautmans *et al* (2021) (9). However, our analysis of this systematic review revealed some inconsistencies that justified our attempt to perform a new systematic review in this field. Some inaccuracies that were noted in the review by Bautmans *et al* (2021) include the fact that there was no mention of a protocol or registration number for their study. Also, the methods do not adhere to the criteria that is required for a systematic review, namely the use of google scholar as a reference and the use of only two databases for the literature review. Additionally, Bautmans *et al* (2021) chose not to search the Embase database, which is a database known for its rigorous criteria and is more encompassing regarding the available literature (9). Additionally, the results that they report are vague.

Objective

The aim of our review was to identify, assess and synthesize the available evidence on the impact of exercise on chronic systemic inflammation in the elderly population (subjects aged ≥65 years).

Methods

Study registration

Our study is registered in PROSPERO (Study ID CRD42021255460).

Eligibility criteria

A systematic review was conducted on studies that investigated an association between exercise and inflammaging in populations of individuals aged ≥65 years with at least one follow-up time point.

More specifically, studies were included if the reported outcomes were improvement in the form of a decrease in the level of one or more inflammatory markers or improvement of symptoms associated with inflammaging, specifically age-related diseases with an associated pathophysiological mechanism of inflammation.

Regarding the type of studies that were included, only prospective and retrospective cohort studies or randomized controlled trials (RCT) published in peer-reviewed journals were selected. Also, only articles in the English language were included; however, no geographical restriction was applied. Exclusion criteria included the following: studies in languages other than English, as well as case series, case reports, case-control studies, systematic reviews, reviews, conferences proceedings, and Master or PhD theses.

Search strategy

The results are presented in accordance with the PRISMA statement recommendations.

Terms related to key subject areas of the review question such as (inflammaging OR inflammageing) OR (inflammation AND aging) AND exercise. Keywords or database-specific subject headings (e.g., MeSH) and the Boolean operators 'OR' and 'AND' were used to combine the search terms. The search terms were adjusted to the specificities of the different databases. The following databases were systematically searched from 10 years to 3/31/2021: PubMed, Embase, and Web of Science. The search strategy was in PubMed: PubMed [("Inflammation"[Mesh]) AND "Aging"[Mesh]) AND "Exercise"[Mesh]] OR (inflammaging OR inflammageing) OR (inflammation AND aging) AND exercise. In Embase: 'inflammaging'/exp AND 'exercise'/exp OR [(inflammaging OR inflammation

OR inflammageing) AND aging AND exercise], and Web of Science [(inflammaging OR inflammageing) AND (exercise) OR TITLE: (inflammaging OR inflammation OR inflammageing) AND TOPIC: (aging OR aged OR elder OR eldest OR oldest) AND TOPIC: (exercise)]. The last search was conducted on March 31st, 2021.

Additionally, hand searches of the reference lists of all included studies and previously published systematic reviews were conducted to ensure completeness of the search.

Titles and abstracts of the articles were screened for eligibility, followed by a full-text review, by three reviewers (C.M, A.P., H.D.). The quality of the relevant studies was assessed using the Cochrane risk of bias tool for randomized controlled trials and the Newcastle Ottawa scale for non-randomized studies.

Data was extracted from the articles using standardized forms. Data collected included the following: article citation, type of study, country of origin, purpose, inclusion criteria, exclusion criteria, recruitment methods, type of inflammatory markers, frequency of measurement of inflammatory markers, type of exercise, duration of exercise, age of participants, number of participants, results, and conclusion.

Results

In all, 1156 articles were retrieved from the 3 databases (PubMed, Embase and Web of science). A total of 955 articles remained after removing 201 articles from the three databases that were duplicates. Additionally, regarding hand searches, we identified and included two studies from a systematic review.

Then, we analyzed the titles and abstracts of the articles to determine eligibility for inclusion, and subsequently, we performed a full-text analysis of the remaining articles (Fig. 1).

Our screening process identified the following articles that were removed due to ineligibility based on the following criteria, with some studies presenting an overlap in the reason for ineligibility status: 645 articles were removed due to study outcome, 683 articles due to intervention, 858 articles due to population, 292 due to study type, and 7 articles were protocols.

Ultimately, 16 articles were identified that adhered to the inclusion criteria.

Methodological quality

Regarding study type, 7 in 16 studies were RCTs, while 5 studies were retrospective studies, one was a randomized observer blind design, and the remaining 3 studies did not specify the type or study design; however, they had a prospective-type study design. We used the

CONSORT checklist for randomized controlled trials to aid in the assessment of the methods and results of the selected studies. Based on our assessment of the studies using this checklist, the overall score for most studies was 18 in 25. Regarding our assessment based on the specific items on the checklist, only 3 studies included “randomized controlled trial” in the title. Also, some studies were missing some information. Specifically, in the Methods section, some studies were missing a description of the trial design, eligibility criteria for participants, and sample size. In the Results section, many studies were missing details regarding recruitment of participants. For the Discussion section, many studies were missing information regarding generalizability of the results.

Types of Exercise

Based on type of exercise, the 16 studies could be categorized as follows: 7 studies that evaluated resistance exercise, 2 studies on aerobic exercise, and 7 studies on a combination of both aerobic and resistance exercise. Details regarding the exercise intervention are provided in Table 1.

In all, 11 studies had a prospective study design, in which an exercise intervention was applied and subsequently changes were analyzed in inflammatory biomarkers; meanwhile, 5 studies had a retrospective study design and used a survey, interview, test, or instrument to evaluate the level of physical fitness of the participants

Five in 16 studies assessed the history of exercise in the following ways. Balan *et al* (2020) investigated the impact of exercise on inflammation and senescence in 4 groups of individuals: young sedentary subjects, young, trained cyclists, older sedentary subjects, and older trained cyclists (10). These 4 groups were compared, with cardiorespiratory fitness assessed via a maximal incremental fitness test on a cycle ergometer (10). Colbert *et al* (2004) used a survey to assess level of physical fitness by evaluating the physical activities performed in the previous week that ranged from light physical activity of daily living to moderate or high intensity exercise and/or weight training (11). Meanwhile, de Gonzalo-Calvo *et al* (2012) used a questionnaire to compare two groups of subjects: trained and sedentary subjects, with and without a history of regular physical activity, respectively (12). Lavin *et al* (2019) used a questionnaire and interview to compare 3 groups of subjects: old lifelong exercisers, old healthy non-exercisers, and young exercisers (13). Finally, Nilsson *et al* (2018) performed an accelerometer-based assessment of physical activity for one week to determine total sedentary time, as well as time spent in light physical activity and moderate to vigorous physical activity (14).

All 5 studies except one (Balan *et al* (2020)) assessed the history of the two general types of exercise: aerobic and resistance exercises.

The remaining 11 studies in 16 were prospective in that some form of exercise was applied as an intervention. Only 2 studies applied an aerobic type of exercise intervention. Santos *et al* (2012) assessed the impact of running exercise in a group of 22 sedentary older subjects for a duration of 24 weeks (15). In the study by Nishida *et al* (2015), 62 postmenopausal females were randomized to a bench step exercise group or to a control group (16). The bench-step exercise program consisted of 3 daily sessions performed for a total of 12 weeks. Each session had a duration of approximately 10 minutes and was home-based, and therefore, unsupervised. However, weekly sessions were held at a community center to maintain the participants' motivation for exercise (16).

Three studies applied an exercise intervention that used both the aerobic and resistance modalities. Andersson *et al* (2020) compared an exercise intervention group with an active control group of older adults with rheumatoid arthritis (RA), in which the intervention group was guided by a physiotherapist to perform gym based aerobic and resistance exercises at moderate to high intensity three times a week for 20 weeks (17). Both the intervention and control groups were instructed to perform twice weekly low-intensity daily physical activities, as well as home-based exercises without the use of weights or equipment for increased mobility and strength (17).

Beavers *et al* (2010) performed a study on 424 older subjects who were randomized to one of two groups: a 12-month exercise intervention of moderate to vigorous physical activity or a health education group (4). The exercise intervention included aerobic and resistance type exercises and was divided into 3 phases: adoption, transition, and maintenance phases. The first phase had a duration of two months, with three supervised center-based sessions per week lasting 40-60 minutes. The second phase (transition) had a duration of 4 months, in which the center-based sessions were reduced to two weekly sessions, and a home-based exercise program was performed at a minimum of three times per week. The third and final phase (maintenance) lasted the remaining 6 months and consisted of the home-based intervention, optional center-based sessions once or twice weekly, and monthly telephone contacts (4).

Kim *et al* (2018) compared two types of exercise training programs lasting 6 weeks with a control group (18). More specifically, 47 healthy older adults were randomized into 3 groups: control group, resistance exercise group, and combination group that performed both aerobic and resistance exercises. The exercises were performed using 6 pieces of outdoor exercise equipment, specifically leg extension, pull weight, chair pull, sky walk, and cross country. Regarding exercise intensity and frequency, the resistance group performed exercises for 70 minutes three times per week, while the combination exercise group performed 90 minutes three times weekly (18).

Finally, 6 studies applied an intervention that consisted solely of resistance exercises. In the study by Chen *et al* (2018), the population consisted of a group of 33 elderly women diagnosed with sarcopenia that were randomly assigned to a kettle ball weight training group or a control group (19). The kettle ball training group were enrolled in a twice weekly program for 8 weeks that consisted of progressive resistance training and included 11 different movements that targeted full-body major muscle groups. These movements included the following: biceps curl, triceps extension, squat lunge, kettlebell swing, kettlebell deadlift, kettlebell goblet squat, kettlebell row, single arm kettlebell row, two-arm kettlebell military press, Turkish get up, and comprehensive dynamic workout. Meanwhile, the control group was instructed to maintain their daily living activities and diet. After the 8-week period, there was a detraining period lasting 4 weeks, in which both groups were instructed to maintain their daily living activities and diet (19).

Hsieh *et al* (2018) studied 30 older subjects with type 2 diabetes mellitus who were randomized to a resistance training group or a control group for a duration of 12 weeks (20). The resistance exercise group performed 3 sets with 8-12 repetitions of 8 different types of resistance exercises in a fitness facility under the supervision of a licensed physical therapist, in which exercise intensity was progressively increased. The exercises included the following: biceps curl, shoulder press, hip abduction, chest press, standing calf raise, standing hip flexion, leg press, and abdominal crunch (20).

Jiménez-Jiménez *et al* (2008) investigated the effect of a session of muscle-damaging eccentric exercise, followed by a twice weekly 8-week training period of submaximal eccentric exercise and, subsequently, a second session of muscle-damaging eccentric exercise (21). The population consisted of a group of 11 healthy elderly men between 66-75 years of age. The two muscle damaging sessions performed before and after the 8-week training period consisted of 10 sets of 10 repetitions that involved eccentric movements using a device with a load at a specific velocity and angle to induce muscle damage. The submaximal eccentric training used the same device and eccentric movements as in the muscle damaging session, but with only 4 sets with 12-12 repetitions and with a progressively increasing load (21).

Mejías-Peña *et al* (2017) assessed the effect of resistance training on a group of 26 healthy men and women who were randomly assigned to either a training group or a control group (22). The training group consisted of an 8-week resistance exercise program, with two weekly sessions. Each session consisted of a 10-min warm up on a cycle ergometer, followed by three exercises (leg press, peck deck and bicep curl), in which the load for each exercise was progressively increased (22).

Ogawa *et al* (2010) assessed the impact of a low-intensity exercise program on a group of 21 elderly women that did not perform exercise regularly (23). The exercise program consisted of at least one weekly session for 12 weeks, in which each exercise session had a duration of approximately 40 minutes, with a progressive increase in intensity for 4 types of exercise: foot press, front traction, vertical traction, and shoulder press (23).

Schober-Halper *et al* (2016) evaluated a group of 88 institutionalized older adults that were randomized to one of 3 groups: control group, resistance training group, and resistance training plus nutrition supplementation group. The resistance training intervention had a duration of 6 months, with twice weekly supervised progressive resistance training using only elastic bands. The sessions lasted approximately 40 minutes, in which one or two exercises were performed for each of the 6 main muscle groups (legs, arms, abdomen, back, chest and shoulders), with progressive increase in exercise intensity following a 4-week adaptation phase. In addition to this training, subjects in the group with nutrition supplementation drank a supplement with vitamins, minerals, and essential amino acids that was taken before and after each training session (24).

Effect of intervention on inflammatory markers

Some cytokines that are commonly associated with systemic inflammation and are frequently found in this field in the literature include the following: C-reactive protein (CRP), IL-6, and tumor necrosis factor alpha (TNF-α). Indeed, these 3 cytokines were the most common inflammatory markers evaluated among the 16 studies included in our review, with CRP and IL-6 investigated in 9 studies and TNF-α in 8 studies. We provide more details regarding the specific inflammatory markers evaluated in each study in Table 2. Below we provide an overview of the most significant findings of the studies included in our review.

In the study by Andersson *et al* (2020), there was a reduction in CRP levels after 20 weeks of a combination of aerobic and resistance exercises in patients with rheumatoid arthritis; however, this result was not significant (17).

Balan *et al* (2020), observed that exercise appears to be associated with decreased inflammation by reduced macrophage infiltration, specifically CD68 macrophages, in older adults. Furthermore, reduced IL-8 and TNF-α levels in older trained individuals indicated a reduced inflammatory profile associated with exercise (10).

In the study by Beavers *et al* (2010), a 12-month intervention that includes a combination of aerobic and resistance exercises resulted in lower systemic concentrations of IL-8 and IL-15 in individuals with an increased level at baseline in a population of elderly individuals; however, these results were not significant (18).

In their study on the impact of kettle ball weight training in elderly women with sarcopenia, Chen *et al* (2018) observed a significant reduction in hs-CRP after training, as well as 4 weeks later after a detraining period (19). Meanwhile, in the control group, hs-CRP increased when measured 8 weeks after the baseline measurement and four weeks after the 8-week measurement. However, IL-6 and TNF-α levels were not significantly altered at the 8-week measurement and after the detraining period (19).

Colbert *et al* (2004) observed that higher levels of exercise were associated with lower levels of inflammatory markers (CRP, IL-6, and TNF-α) (11). Also, in the exercise group, BMI, and levels of TNF-α, IL-6, and CRP were lower, and there was a lower incidence of diseases in this group, including hypertension, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, and respiratory disease. There was a slight attenuation of the association between lower inflammatory biomarkers when adjustments for body fat were made. In the non-exercise group, increased physical activity was linked to lower levels of both CRP and IL-6, but not TNF-α. Additionally, individuals taking antioxidant supplements had lower levels of CRP and IL-6, independent of exercise level (11).

de Gonzalo-Calvo *et al* (2011) observed that long-term training was associated with reduced levels of the following inflammatory biomarkers: IL-10, IL-1ra, IL-6, and sTNF-RI (12). Meanwhile, no statistical difference was observed between the sedentary and trained groups of men for the following inflammatory biomarkers: IL-1β, sIL-6R, TNF-α, and sgp130. Lastly, increased MCP-1 levels were observed in the group with a history of training (12).

In the randomized controlled trial by Hsieh *et al* (2016), a resistance exercise intervention was implemented in 30 older adults with T2DM to assess the impact on QoL, physical function, muscle function, and cardiometabolic risks (20). Prior to enrollment in the study, none of the participants had previously engaged in structured resistance training. Although there were no significant between-group differences between the intervention and control groups, Hsieh *et al* (2016) observed a decrease in hs-CRP in the exercise intervention group and an increase in this biomarker in the control group (20). Also, these authors noted a decrease in body weight and percentage body fat after the 12-week intervention (20).

Jiménez-Jiménez *et al* (2008) implemented an intervention that included 2 eccentric exercise sessions that were performed before and after an 8-week submaximal eccentric training in 11 subjects 66-75 years of age. They assessed levels of IL-6 in peripheral blood mononuclear cells and observed an overexpression of this biomarker following the first session of eccentric training and subsequently observed a significant decrease in IL-6 levels after the 8-week submaximal eccentric training (21).

Kim *et al* (2018) compared the impact on fitness, insulin resistance, IL-6, and chemerin of a 6-week resistance exercise intervention and a combination of resistance and aerobic exercise in a population of elderly Korean subjects (18). They observed a reduction in IL-6 and chemerin, but only in the combined resistance and aerobic exercise group (18).

Lavin *et al* (2019) assessed the effects of acute resistance exercise in 3 groups of men: older lifelong exercisers (LLE), older sedentary men (OH), and young exercisers (YE) (13). Additionally, two subgroups were created within the LLE group: LLE-Fitness (LLE-F) for subjects who participated in low intensity exercise for physical fitness and LLE-Performance (LLE-P) for subjects that trained more vigorously to participate in competitive events. Inflammatory biomarkers were assessed in circulation and in skeletal muscle and included the following: serum CRP, IL-6, TNF-α, and IGF-1. Regarding basal levels of circulating inflammatory markers, IL-6 was reduced in LLE and YE compared to OH. The 3 main groups were similar regarding levels of serum TNF-α and CRP. For IGF-1, it was lower by 43% in both LLE and OH than in YE; however, when comparing the two LLE subgroups (LLE-F and LLE-P), the LLE-P subgroup had a 23% increase in IGF-1 levels compared to LLE-F. Meanwhile, CRP, TNF-α, and IL-6 levels were similar between the LLE-P and LLE-F subgroups. Regarding the effects of acute resistance exercise, only the OH group had a significantly higher level of TNF-α. The level of IL-6 was higher in the 2 groups of older individuals (OH and LLE) than the YE group, particularly the LLE group (13).

Mejías *et al* (2017) implemented a resistance training intervention in 26 healthy older adults to study autophagy, NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, and apoptosis in peripheral blood mononuclear cells (PBMCs). The authors observed that following the 8-week resistance exercise intervention, autophagy was increased in PBMCs, while NLRP3 inflammasome activity and apoptosis was decreased (22).

Nilsson *et al* (2018) assessed physical activity using an accelerometer in a population of 111 healthy older women with different levels of metabolic risk for metabolic syndrome to determine the effect of objectively measured physical activity behaviors of different intensities (light physical activities (LPA) and moderate to vigorous physical activities (MVPA), and sedentary behaviors) on CRP, fibrinogen, and adiponectin (14). The study population of older women were classified into one of two groups: high (57%) or low (43%) metabolic risk. Based on the results, women in the high metabolic risk group had higher levels of CRP and fibrinogen and lower levels of adiponectin than the women in the low metabolic risk group. Also, women in the high metabolic risk group were less likely to engage in MVPA. Fibrinogen was significantly associated with all 3 types of physical activities, while CRP was only significantly associated with MVPA. Subsequently, the authors performed isotemporal displacement of physical activity behaviors by substituting sedentary behaviors with LPA or MVPA. They observed that replacing sedentary behaviors with either LPA or MVPA had a significant effect on the levels of fibrinogen. However, this effect was not observed when substituting an activity from the LPA category for an activity in the MVPA category. Regarding CRP, a significant effect was only observed when substituting an activity from either the category of sedentary activities or from the LPA category for an activity of the MVPA category. Meanwhile, no association was found between adiponectin and the three types of physical activities (sedentary, LPA, and MVPA). These results were independent of the level of metabolic risk of the subjects (14).

Nishida et al. (2015) implemented a 12-week home-based bench step exercise intervention in a population of 62 older Japanese women to study the impact of the intervention on interferon (IFN)-ϒ (16). A decreasing trend was observed in IFN-ϒ levels in the intervention group; however, this result was not significant (16).

Ogawa *et al* (2010) implemented a 12-week low-intensity resistance exercise intervention in elderly women to study the impact on low grade inflammation by assessing the following markers: serum CRP serum amyloid A (SAA), heat shock protein (HSP) 70, TNF-α, IL-1, IL-6, monocyte chemotactic protein (MCP-1), insulin, insulin-like growth factor (IGF)-I, and vascular endothelial growth factor (VEGF) (23). The resistance exercise intervention was associated with reduced levels of CRP, SAA, HSP70, IGF-I, and insulin. However, these results were not significant after applying a Bonferroni correction (23).

Santos *et al* (2012) implemented an aerobic exercise intervention in a population of healthy older sedentary males to determine the impact on cytokine levels (15). They assessed the following biomarkers: IL-1, IL-6, IL-10, TNF-α, and plasminogen activator inhibitor type-1 (PAI-1). Based on the results of this study, both IL-6 and TNF-α levels were significantly decreased after the exercise intervention; meanwhile, levels of IL-10 were significantly increased following the intervention. Also, the TNF-α/IL-10 ratio was significantly decreased after the exercise intervention (15).

Schober-Halper *et al* (2016) implemented a 6-month progressive resistance intervention with elastic bands in older adults to determine the impact of the intervention on CRP and TGF-β levels in PBMCs (24). In this study, a reduction in TGF-β receptor I mRNA expression in PBMCs was observed. However, no changes were observed in circulating inflammatory markers after training (24).

Discussion

Overall, the 16 studies included in our systematic review had some essential differences. For example, regarding the populations of the included studies, most of the studies were performed on populations of healthy older individuals (13 in 16 studies). However, 3 studies were performed on populations with disease, specifically rheumatoid arthritis (RA), sarcopenia, and T2DM in the studies by Andersson *et al* (2020), Chen *et al* (2018), and Hsieh *et al* (2018), respectively. It is worth noting that these 3 studies obtained non-significant results for all or some of the biomarkers that were selected to measure the inflammatory profile of the participants.

Another important difference among the studies was whether an intervention was applied to the participants versus assessment of the history of exercise training in the population. Also, the types of exercise that were assessed varied among the 16 studies. This is important considering that there are reports in the literature that specific types and intensities of exercise performed in specific populations can be beneficial, whereas differences in intensity may result in lack of significant results (7). Indeed, there are other variables associated with the intervention that can influence the results, including duration and frequency of exercise.

Regarding the significance of the results obtained for the 16 studies in our review, there were 4 studies (17, 18, 21, 24) in which significant results were not obtained for the inflammatory biomarkers that were measured. These 4 studies in which non-significant results were obtained share some common characteristics. For example, all 4 studies are randomized controlled trials (RCTs). These 4 studies are among a total of 7 RCTs that were included in our review. It may be that RCTs have more rigorous criteria that increases the likelihood of a lack of significant results compared to other types of studies or study designs. This may be particularly relevant in RCT with smaller sized populations, which was the case for all 4 studies, in which each study included less than 50 subjects.

Another factor that all 4 studies had in common was that an intervention was used (prospective study design) versus assessment of history of exercise in older populations (retrospective study design). Additionally, 2 in 5 studies had a duration of ≤12 weeks. For the other 2 studies, one had a duration of 20 weeks (17) and the other a duration of 12 months (4); however, this last study with a 12-month duration had 6 months of unsupervised exercise training in which it would be more difficult to control proper performance of the exercises and adherence to the training program.

Also, as previously mentioned, 3 in 4 studies without significant results included a population that presented a specific condition, namely RA and T2DM. It may be that a specific type, frequency, or duration is necessary to achieve a reduction in inflammation for a specific disease or condition. Additionally, 2 in 4 studies used resistance exercise, while 2 studies used a combination of resistance and aerobic exercise. Indeed there is a report in the literature that intense exercise associated with resistance training may be less beneficial for reducing systemic inflammation in older populations compared to moderate or vigorous exercise (45).

Although Andersson *et al* (2020) did not obtain significant results regarding the impact of an exercise intervention in their population of older subjects with RA, there are reports in the literature of the beneficial impact of exercise interventions in patients with this disease (17). According to these authors, the lack of significant results may be due to several limitations of their study, namely the fact that many of the patients in their study had low disease activity or were in remission (17). However, most subjects in the intervention group had improved global impression of health compared to the control group (17).

In the study by Balan *et al* (2020), IL-8, TNF-α, and macrophage infiltration (CD68 macrophages) were decreased in older experienced cyclists (10). Endurance training status was not associated with a decrease in markers of senescence (p16/p21 mRNA); however, inflammatory markers were decreased. Based on the literature, senescent cells recruit macrophages and secrete pro-inflammatory cytokines, thereby inducing a pro-inflammatory environment (10). Endurance training is linked with the release of IL-6 from muscle, which inhibits TNF-α, a pro-inflammatory cytokine (10). Meanwhile, regarding IL-8, although it is a pro-inflammatory cytokine, its role is still unclear. Indeed, based on the literature, IL-8 levels appear to vary depending on the type of exercise and the training level of the population (10). The authors concluded that if macrophage infiltration associated with aging is linked to senescence, then it may be masked by the effect of endurance training in muscle tissue (10).

In the study by Beavers *et al* (2010), exercise lowered systemic concentrations of IL-8 and IL-15 in older individuals with an increased level at baseline; however, these results were not significant (4). According to the authors, this may be due to the fact that weight loss was not achieved in their study population after the exercise intervention compared to other studies that obtained significant decreases in these inflammatory markers associated with exercise. Additionally, low adherence rates in the intervention group may be associated with the non-significant results (4).

In the study by Chen *et al* (2018) on the effect of kettle-ball training in elderly women with sarcopenia, the level of hs-CRP, a chronic pro-inflammatory cytokine, was reduced in the intervention group (19). Meanwhile, no changes were observed in the levels of IL-6 and TNF-α. It has been reported that CRP plays an important role in innate immunity, and hs-CRP is an important biomarker for chronic inflammation and cardiovascular disease (25). Regarding TNF-α, increased levels of this inflammatory marker may be associated with loss of muscle mass in older individuals with sarcopenia (5). The results of this study are in line with previous studies in which participation in resistance training reduces CRP, but not IL-6 or TNF- α, in elderly populations (19).

In the study by Colbert *et al* (2004), a positive association was observed between exercise and non-exercise physical activities and lower levels of inflammatory markers (CRP, IL-6, and TNF-α) (11). This finding is important since elderly individuals are more likely to want to engage in increased physical activities that may not include exercise training. The authors state that the modest association between TNF-α and exercise may be due to the fact that this inflammatory marker may be less sensitive to changes induced by physical activity compared to IL-6 and CRP (11).

In the study by de Gonzalo-Calvo *et al* (2011), TNF- α and IL-1β were unchanged in both the sedentary and trained groups; meanwhile, the chemokine MCP-1 was increased (12). These results are in line with those obtained by Pederson et al. (2009), in which the cytokine cascade associated with exercise was independent of TNF-α and IL-1β (26). Regarding MCP-1, although it has been linked to atherosclerosis and myocardial infarction, de Gonzalo-Calvo et al. (2011) hypothesized that the increase in this chemokine may be explained by the fact that both exercise and MCP-1 are linked to angiogenesis (12). The authors concluded that cytokines, chemokines, and immune cells work in network; therefore, attempts to assess individual "intervenients" may not "reflect the complexity of the inflammatory processes in vivo" (12). Therefore, they hypothesized that it would be better to analyze an increased number of inflammatory biomarkers in future studies to gain a better perspective of the clinical status of the study population (12).

In the study by Hsieh *et al* (2018) on patients with T2DM, the increase in hs-CRP levels in the control group and decrease in the intervention group were associated with maximal leg press strength (20). Therefore, the results observed in this study appear to be related to exercise rather than to reduced body weight or fat control; however, there were no significant differences between the intervention and control group (20). The authors believe that the lack of differences between groups regarding impact of the intervention on inflammation may be due to increased patient variability and decreased baseline hs-CRP in the study population (20). Also, it may be that high intensity exercise is the type of exercise needed to achieve a positive effect in individuals with metabolic diseases such as T2DM. Indeed, a significant anti-inflammatory effect was achieved in patients with T2DM using a combination of high intensity aerobic exercise plus resistance training (27).

In the study by Jiménez-Jiménez *et al* (2008), decreased IL-6 levels in PBMCs after the 8-week eccentric training intervention is in line with previous studies that show a beneficial effect of exercise on IL-6 levels (21). For example, these authors referred a study by Jankord and Jemiolo (2004) who observed that older males who participated in regular aerobic exercise had significantly lower levels of IL-6 compared to a non-exercising control group (11). Also, in a study by Colbert *et al* (2004), higher levels of physical activity had significantly lower levels of IL-6 (11).

In the study by Kim *et al* (2018), circulating chemerin levels and IL-6 were reduced after the combination intervention that included both aerobic and resistance exercise. Meanwhile, this result was not observed in the resistance exercise intervention group. These results are in line with previous studies that report reduced chemerin levels after exercise or other lifestyle changes in different populations, including obese subjects and patients with T2DM.

Additionally, the authors noted that changes in circulating chemerin levels after exercise was a strong predictor for change in insulin resistance in patients with diabetes (19).

Based on the results of the study by Lavin *et al* (2019), exercise increased the expression of TNF-α (13). Furthermore, the proteolytic effects of TNF-α appeared to be attenuated by the anti-inflammatory profile in individuals with a history of exercise training. Indeed, increased expression of anti-inflammatory IL-10 and TGF-β observed in lifelong exercisers (LLE) may be associated with suppression of pro-inflammatory factors. Meanwhile, the LLE-P group with a history of higher intensity training had lower levels of TNF-α and transforming growth factor (TGF-β), which suggests that these cytokines may modulate each other's activity. Also, no effects of different training intensities were seen regarding IL-6 levels. Also, there was a modest elevation in IL-6 after exercise in the LLE group compared to the other 2 groups. Regarding acute session of resistance training, LLE and YE appeared better able to tolerate the stress induced by the exercise session, while OH group demonstrated an exaggerated response in the form of elevated levels of both TNF-α and TGF-β. Indeed, based on the literature, TNF-α may stimulate proteolytic pathways within the muscle (e.g., NF-κB, MAPK) (28). Meanwhile TGF-β may contribute to chemotaxis of inflammatory cells or help with tissue repair resulting from mechanical stress (29, 30).

The results of the study by Mejías *et al* (2017) include increased NOD-like receptor family, pyrin domain containing 3 (NLRP3) activity and decreased autophagy (22). Based on the literature, inflammaging is associated with increased apoptosis and NLRP3 activity, and a decrease in autophagy. Autophagy is an important catabolic process responsible for the natural degradation of the cell, in which damaged cellular components are present in lysosomes. Meanwhile, cell aging is associated with the accumulation of damaged cellular proteins and organelles. Therefore, autophagy has been implicated as a key aspect in senescence (31). Regular physical exercise has been linked to increased autophagy, thereby helping to delay the onset of aging and age-related comorbidities (32). Meanwhile, NLRP3 inflammasome is linked to age-related inflammation. More specifically, it appears that exercise inhibits NLRP3 inflammasome (33). Additionally, increased apoptosis is also linked to the aging process and apoptosis is negatively associated with autophagy (22).

In the study by Nilsson *et al* (2018), reduced fibrinogen was observed by reallocating 30 minutes of sedentary time with either time in LPA or MVPA. Meanwhile, a significant reduction in CRP was observed by reallocating a 30-minute period in sedentary activities or LPA with MVPA. These results suggest that there is an intensity threshold that may exist that determines whether a physical activity will have a beneficial effect on systemic inflammation. However, further studies are needed to confirm this result.

In the study by Nishida *et al* (2015), exercise was associated with decreased IFN-ϒ, which is considered an atherogenic factor (16). Indeed, in a representative rodent model, administration of exogenous IFN was linked to atherosclerosis. Meanwhile, IFN-ϒ deficient mice appeared to be protected from this disease (34). Based on the literature, IFN-ϒ appears to act directly on vascular smooth muscle cells (35). Nishida *et al* (2015) concluded that bench step exercise leads to improvements not only in the classical risk factors of atherosclerosis, but also arterial stiffness in elderly women (16).

Based on the results of Ogawa *et al* (2010), exercise training is beneficial in elderly women to reduce the levels of inflammatory cytokines, namely CRP, SAA, and heat shock protein (HSP)70 (23). Both SAA and CRP are formed in the liver by hepatocytes and released into the serum (36). Meanwhile, both CRP and SAA have been independently associated with future cardiovascular events (37, 38, 39). Regarding serum HSP70, there are reports that high levels are associated with the following diseases: peripheral and renal vascular disease (40), hypertension (41), and cerebral ischemia (42), among others. Also, Shin *et al* (2006) observed a decrease in serum HSP70 after a 14-week cardiac rehabilitation intervention in patients with coronary artery disease (43). Meanwhile, Ogawa *et al* (2010) reported that the reduced serum HSP70 levels after the resistance exercise were associated with reduced inflammation (23). HSP70 is released from the cell due to necrotic cell death; it may be that other stressful conditions, including strenuous exercise, may also cause the release of HSP70 into the extracellular compartment (23). However, further studies are needed, since the role of circulating, extracellular HSP70 in reducing systemic inflammation is still unclear (23).

The results of the study by Santos *et al* (2012) are in line with previous studies in which exercise training is associated with a decrease in levels of IL-6 and TNF-α , while CRP and IL-1β levels remained unchanged (15). These results, as well as the decreased TNF-a/IL-10 ratio support the premise that moderate exercise has a beneficial impact on inflammation in the elderly population (15).

Regarding age-related pathology, prolonged elevation of TGF-β signaling has been linked to the following diseases: obesity, muscle atrophy, and Alzheimer's disease. In the study by Schober-Halper *et al* (2016), although the progressive resistance training intervention with elastic bands did not have an impact on chronic low-grade inflammation, TGF-β signaling appeared to be affected in PBMCs through changes in TGF-βRI mRNA expression (24). Therefore, the authors concluded that the results suggest an association between physical activity and TGF-β expression in PBMCs of older subjects (24).

Conclusions

As previously mentioned, there were 3 studies performed on subjects with disease (RA, T2DM and sarcopenia), in which 1 study was specifically performed on women with sarcopenia (19). Regarding gender of the study populations, among the 16 studies, 4 studies were exclusively performed on men (10, 12, 22, 13), while 4 studies were exclusively performed on women (20, 14, 16, 24). Among the 4 studies exclusively performed with a population of women, 3 in 4 studies were prospective studies; meanwhile 3 in 4 studies that were conducted exclusively on populations of men were retrospective in nature. Interestingly, in our review, studies with non-significant results were more commonly prospective studies compared to retrospective studies.

Prospective studies that used resistance exercise intervention

There was a total of 6 prospective studies that used a resistance exercise intervention (20, 21, 22, 23, 24, 25). Two prospective studies that used a resistance exercise intervention did not achieve significant results (21, 24). In Ogawa *et al* (2010), the population consisted of elderly women, the duration of the intervention was 12 weeks, and the frequency of the exercise training was once weekly (23). It may be that the duration and frequency of the exercise was inadequate, and/or the population (women) and type of exercise (resistance exercise) may have influenced the results. In Hsieh *et al* (2018), the population included individuals with T2DM (20). As previously mentioned, T2DM is associated with comorbidities, including metabolic disease and obesity. Therefore, baseline levels of inflammatory markers may be elevated compared to a population of healthy individuals, and therefore, a more intense type of intervention may be needed to achieve significant results (20). Furthermore, the duration for this study was only 12 weeks, which may be an inadequate amount of time to achieve significant results in this specific population.

Meanwhile, the remaining 4 studies (20, 22, 23, 25) among this group of 6 prospective studies did achieve significant results. It is important to note that 2 studies among these 4 studies investigated other biomarkers in contrast to the more frequently assessed interleukin cytokines (IL-6, CRP, and TNF-α), namely NLRP3 in Mejías *et al* (2017) and TGF-β in Schober *et al* (2016). Furthermore, the study by Jiménez-Jiménez *et al* (2008) assessed IL-6 levels; however the intervention that was used differed from all other interventions in this group of 4 studies, as well as in the overall group of 16 studies (21). Indeed, an acute intense muscle damaging eccentric exercise preceded an eccentric training intervention lasting 12 weeks, followed by another acute eccentric exercise session (21). Jiménez-Jiménez *et al* (2008) compared a group of older and younger individuals and found that results were comparable among these groups, in which a marked increase in levels of IL-6 after the acute exercise session was attenuated by the training program (21).

Notably, regarding the 3 most frequent inflammatory markers assessed in all 16 studies in this review (TNF-α, IL-6, and CRP), CRP levels were assessed in a total of 9 in 16 studies, in which 6 in 9 studies had a prospective study design. However, among these 6 intervention studies, significant results in CRP levels were only observed in one intervention study (19) performed on patients with sarcopenia. This is in line with the results of other studies in the literature, in which resistance exercise is associated with decreased CRP, compared to IL-6 and TNF-α, which remained unchanged (19). Meanwhile, in the remaining 5 studies (17, 18, 21, 24, 25) in which CRP was assessed in prospective studies, the results were not significant. Among these 5 studies (17, 18, 21,24, 25), 3 studies used resistance exercise and were of relatively short duration, while 2 used combination exercises for longer duration. However, in the 2 studies using a combination of aerobic and resistance exercises, one study applied the intervention to a group with a medical condition (RA) (17), while the other study noted attenuated adherence of the study subjects to the exercise intervention (4).

Prospective studies that used a combination of aerobic and resistance exercise interventions

There were 3 prospective studies using a combination of aerobic and resistance exercise interventions. In Andersson *et al* (2020), the authors hypothesized that the non-significant results were due to the fact that the cohort consisted of 48 patients with RA, in which the disease was in remission (17). Despite the non-significant results regarding levels of measured biomarkers in this study, patients did report an improvement in overall health based on results of global impression of health, supporting prior studies that show that exercise training in individuals with RA is associated with improved immune function (17). Additionally, these authors refer the fact that timing of measurement is important to achieve valid results, since there are well known transient responses to acute exercise (17).

In contrast, Beavers *et al* (2010) applied a 12-month moderate intensity exercise intervention in 424 elderly men and women (4). Significant results were only obtained for one biomarker, IL-8; also, diabetes was more prevalent in the intervention group (18). The authors hypothesized that the lack of significant results in all but one biomarker may be due to the fact that weight loss was not achieved in this study (4). Also, the attenuated adherence rates to the exercise intervention throughout more than half of the duration of the study may have contributed to the lack of results in most biomarkers measured in this study (4). Additionally, the authors refer inconsistencies in the literature between lack of significant results in RCTs and significant results in epidemiologic studies (4). More specifically, small population with high baseline levels of inflammatory markers and short intervention duration may be related to the significance of the results in epidemiologic studies (4). Finally, the authors reported that local anti-inflammatory effects may be present but may not be evident in systemic inflammation;

however, these local anti-inflammatory effects may have clinical implications in patients with diseases such as sarcopenia (4).

Meanwhile, Kim *et al* (2018) investigated a 6-week exercise intervention that compared results of combination exercise versus resistance exercise in 47 Korean elderly subjects (19). They observed that only the combination exercise group obtained a significant reduction in levels of chemerin. However, the authors reported that limitations of their study include a small sample size and differences in the total amount of exercise between the combination and resistance exercise intervention groups.

Prospective studies that applied aerobic exercise intervention

Two studies had a prospective design and applied an aerobic exercise intervention (15, 16). The study by Nishida *et al* (2015) was the first RCT at the time that it was published that had obtained significant results regarding lower IFN-ϒ levels associated with exercise training in a group of postmenopausal females (16). It was also the first study to report an inverse relationship between IFN-ϒ and high-density lipoprotein cholesterol (HDL-C) levels (16).

Meanwhile, in the study by Santos *et al* (2012), reduced levels of IL-6 and TNF-α were observed, while CRP levels were unchanged (15). It may be that aerobic exercise has a greater impact on these two inflammatory biomarkers (IL-6 and TNF-α) than CRP (15).

Retrospective studies

In a group of 5 retrospective studies (10, 11, 12, 13, 14) among the 16 studies in this review, 4 studies applied a combination exercise and 1 applied an aerobic exercise intervention. The duration of the exercise varied significantly, ranging from 53 years in one study to 7 days in another. Regarding the common inflammatory biomarkers, TNF-α was assessed in 4 among the 5 studies, CRP was assessed in 3 studies, and IL-6 in 3 studies. All studies had significant results for some or all the inflammatory markers that were assessed. Also, 2 studies were performed only in men and 1 study only in women.

Although many of the included studies did not obtain significant results for some or all the measured inflammatory biomarkers, it is important to note that all 16 studies in this review reported some beneficial results in the form of improved physical functioning or overall physical performance in the older populations that were studied. However, further studies are needed to determine the optimal type, frequency, and duration to reduce systemic inflammation in healthy elderly populations, as well as populations of patients with specific conditions or diseases to properly “prescribe” exercise whenever it is appropriate.

Strengths and limitations

This review has some noteworthy strengths. First, based on the literature, there is interest in this topic and an increasing number of articles published in this field. Indeed, we found a systematic review published in this field (9). However, this review had some limitations, particularly the fact that there was no mention of a protocol or registration number and only two databases were searched.

A strength of our study is the narrow focus of the question, especially regarding the age criteria for the elderly population (>65 years) and the selection of studies that include results that provide evidence for the beneficial impact of exercise. Additionally, we performed a comprehensive search for evidence and a criterion-based selection of related evidence. Also, we proceeded to perform an appraisal of validity, as well as an objective summarized analysis of the data and evidence-based inferences.

A significant limitation of this systematic review is the fact that few studies were included and each one measured a set of specific biomarkers, with only some overlap among the studies regarding these biomarkers. Also, it is possible that our electronic database search may have resulted in the omission of some relevant studies. Also, in a few studies, basal inflammatory biomarkers were not the primary outcome measure, and these studies may not have been designed to properly assess a secondary outcome measure. Additionally, it is noteworthy that none of the studies mentioned any adverse effects of the exercise or training intervention.

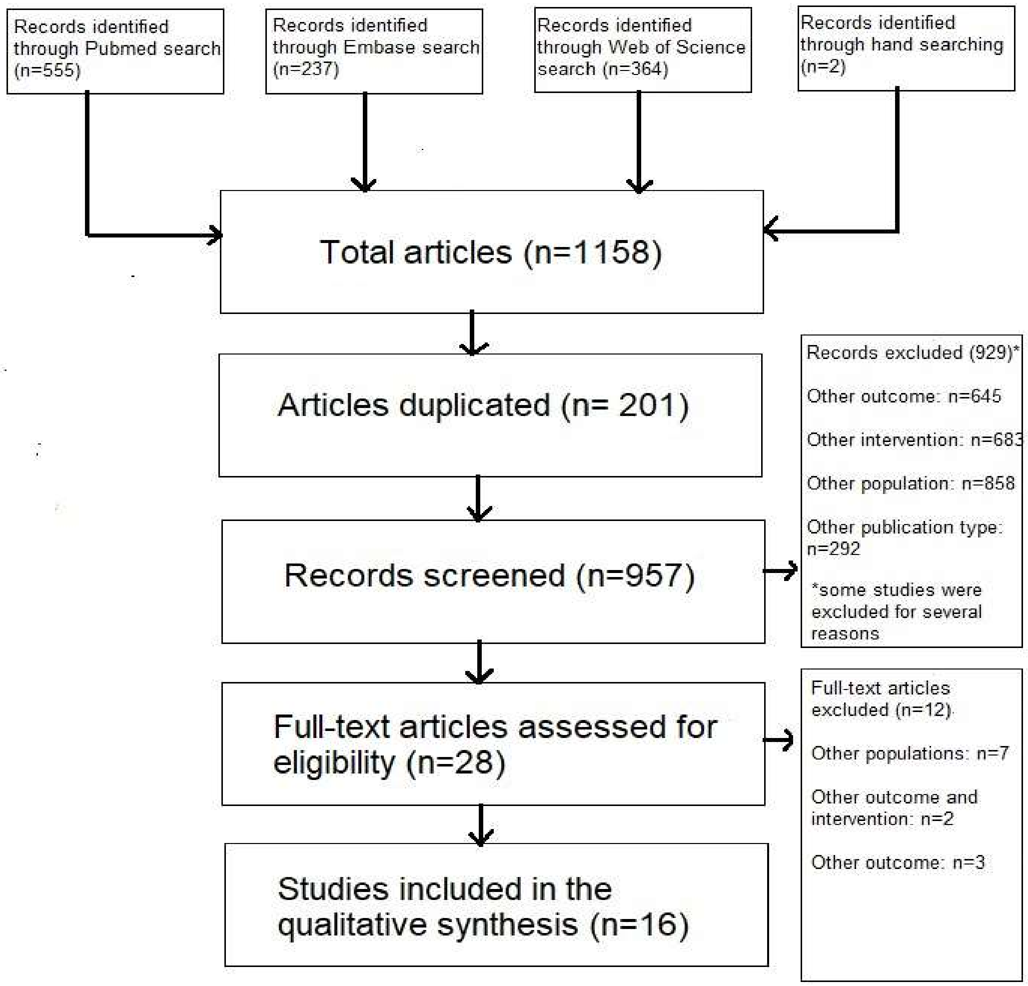

Figure 1- Flow chart diagram presenting the selection process for the studies

Table 1- Exercise interventions

Study	Study design	Type of exercise	Duration of exercise
Andersson *et al* (2020)	Prospective	Gym-based resistance and aerobic exercise performed at moderate- to high intensity (70%–89% Max. heart rate and 70%–80% of 1 repetition)	Three times a week for 20 weeks
Balan et al. (2020)	Retrospective	Cycle ergometer and survey to compare young and old sedentary individuals and trained cyclists	A total of ≥6 h training a week for at least 5 years
Beavers *et al* (2010)	Prospective	Combination of aerobic, strength, balance, and flexibility exercises	Twelve months divided into three phases: Adoption phase- 3 times per week, 40–60 min each session for 2 months; Transition phase- 2 center-based sessions per week for 4 months, and home-based exercises 3 times per week; Maintenance phase- home-based intervention, with optional one to two times per week center-based sessions for 12 months
Chen *et al* (2018)	Prospective	Kettle ball weight training, featured 11 movements performed for three sets, each with 8–12 repetitions. Each session lasted for 60 min and was separated by a 48-h interval	Twice a week for 8 weeks
Colbert *et al* (2004)	Retrospective	Survey of physical activities performed in the previous week	Survey used to determine the frequency and duration spent performing physical activities in the previous 7 days, as well as the intensity

			level or pace for the exercise and walking questions for activities for the last 12 months
de Gonzalo-Calvo *et al* (2012)	Retrospective	Comparison of trained individuals versus sedentary subjects regarding self-directed and combined endurance and resistance activities	Trained subjects had performed at least 60 min per session, with 3 sessions per week, for the previous 40 years
Hsieh *et al* (2018)	Prospective	Eight resistance training exercises—the chest press, shoulder press, biceps curl, hip abduction, standing hip flexion, leg press, standing calf raise, and abdominal crunch	Three sets of 8 to 12 repetitions, 3 times per week for 12 weeks
Jiménez-Jiménez *et al* (2008)	Prospective	Eccentric training in which eccentric movement consists of eccentric phase of the inclined leg-press); load was progressively increased from 40% to 50% of the Max. MVIC	Two times weekly during 8 weeks- 4 sets per session with 10-12 repetitions per set
Kim *et al* (2018)	Prospective	Resistance exercise and combined aerobic and resistance exercise using 6 pieces of equipment	Resistance exercise: 70 min, 3 times per week; Combined aerobic and resistance: 90 min, 3 times per week
Lavin *et al* (1985)	Retrospective	Survey and interview to assess exercise history; included lifelong exercisers with a history of 53 +/-	Acute intervention: 3 sets of 10 repetitions

		1 year of aerobic training	
Mejías-Peña *et al* (2017)	Prospective	Resistance exercise	16 sessions throughout 8 weeks (2 sessions per week)
Nilsson *et al* (2018)	Retrospective	Accelerometer-based assessment of physical activity for one week, specifically time spent in light physical activity and moderate to vigorous physical activity	Approximately 1.5 hours for 5 days
Nishida *et al* (2015)	Prospective	A sub-maximal graded bench stepping exercise to be performed at home after providing subjects with instructions	A total of 12 weeks, 3 times daily
Ogawa *et al* (2010)	Prospective	Low-intensity resistance exercise	At least once a week for 12 weeks, with a duration per session of 40 minutes
Santos *et al* (2012)	Prospective	Running	A total of 60 min per day, 3 days per week for 24 weeks
Schober-Halper *et al* (2016)	Prospective	Progressive resistance training with elastic bands	One-hour sessions, 2 times per week for 6 months

MVIC, maximal voluntary isometric contraction

Table 2- Inflammatory markers and Results

Study	Type of Inflammatory markers	Results
Andersson et al. (2020)	CRP	No significant changes in Disease Activity Score 28 (DAS28) or CRP
Balan *et al* (2020)	CD68, IL-8, TNF-α	Endurance training status associated with reduced levels of IL-8, TNF-α and reduced CD68 macrophages in skeletal muscle
Beavers *et al* (2010)	CRP, IL-6, IL-6sR, IL-1sRII, sTNFRI, sTNFRII, IL-8, IL-15, Adiponectin, IL-1ra, IL-2sRα, TNF-α	IL-8 was the only inflammatory biomarker affected by the PA intervention
Chen *et al* (2018)	hs-CRP, IL-6 , TNF-α	A significant reduction in hs-CRP, but no significant change in the levels of IL-6 and TNF-α after training
Colbert *et al* (2004)	CRP, IL-6, TNF-α	Higher levels of exercise were associated with lower levels of CRP ($p < 0.01$), IL-6 ($p < 0.001$), and TNF- α ($p = 0.02$)
de Gonzalo-Calvo *et al* (2012)	TNF-α, sTNF-RI, IL-1β , IL-1ra, IL-10 , IL-6 , sIL-6R, sgp130, MCP-1	Long-term training was associated with lower levels of white blood cell counts, neutrophil counts, IL-6, IL-10, IL-1 receptor antagonist, and soluble TNF receptor-I, as well as an increase in the concentrations of IGF-1 and dehydroepiandrosterone in the long-term training group
Hsieh *et al* (2018)	CRP	Non-significant decrease in hs-CRP levels in the exercise group
Jiménez-Jiménez *et al* (2008)	IL-6 and chemerin	IL-6 was significantly elevated after the acute bout of eccentric exercise; however, the overexpression of IL-6 disappeared after the program of eccentric training
Kim *et al* (2018)	IL-6 and chemerin	Participants in the combined exercise group exhibited significant reduction in insulin, HOMA-IR and chemerin levels, while significant reduction was observed in HOMA-IR only in the resistance exercise group compared with the control group
Lavin *et al* (1985)	CRP, IL-6 and TNF-α, IGF-1	Increased ($p \leq 0.05$) circulating IL-6 and skeletal muscle COX-1, mPGES-1, and CD163 expression. However, LLE had significantly lower serum IL-6 ($P \leq 0.05$ vs. OH) and a predominantly anti-inflammatory

		muscle profile [higher IL-10 (p ≤0.05 vs. YE), TNF-α, TGF-β, and EP4 (P≤0.05 vs. OH)]. In OH only, acute exercise increased expression of pro-inflammatory factors TNF-α, TGF-β, and IL-8 (p ≤0.05). LLE had postexercise gene expression similar to YE, except lower IL-10 (p ≤0.10), mPGES-1, and EP3 (p ≤0.05).
Mejías-Peña *et al* (2017)	NLRP3, Pro-caspase-1 and Caspase-1, and Caspase-1/procaspase-1 ratio.	Resistance exercise induced a decrease in NLRP3 expression and in the caspase-1/procaspase-1 ratio.
Nilsson *et al* (2018)	CRP, Fibrinogen, Adiponectin	Fibrinogen- Reallocating 30 minutes of sedentary time with either time in LPA (β -0.47; p <0.05) or MVPA (β = -0.42; p<0.05) was related to reduced fibrinogen level; CRP- Reallocating a 30-minute period in sedentary (β =-0.70; p <0.01) or LPA (β =-0.71; p <0.01) with MVPA was associated with a significant reduction in CRP level
Nishida *et al* (2015)	IFN-Ɣ	IFN-Ɣ was reduced in the exercise group
Ogawa *et al* (2010)	CRP, SAA, HSP-70, TNF-α, IL-1, IL-6, MCP-1, Insulin, IGF-I, and VEGF	Training reduced the circulating levels of CRP, SAA (p <0.05), HSP70, IGF-I, and insulin (p <0.01). The reductions in CRP and TNF-α associated with training were significantly (p <0.01; p <0.05) associated with increased muscle thickness (r =−0.61, r =−0.54), respectively. However, none of the results were significant after applying a Bonferroni correction
Santos *et al* (2012)	IL-1, IL-6, IL-10, TNF-α, PAI-1	After training, the levels of IL-6 (p <0.0001) and TNF-a (p <0.0001) and the ratio of TNF-a/IL-10 (p <0.0001) were decreased, while IL-10 levels were increased after training (p <0.001).
Schober-Halper *et al* (2016)	TGF-β and hs-CRP	Reduction in TGF-β receptor I (TGF-βRI) mRNA expression in PBMCs (p = 0.006), while circulating inflammatory markers were unaffected

CRP, C-reactive protein; DAS28, Disease Activity Score 28; IL, interleukin; TNF-α, tumor necrosis factor α; sgp130, soluble gp130; MCP-1, monocyte chemoattractant protein 1; NLRP3, NOD-like receptor family pyrin domain containing 3; interferon (IFN)-Ɣ, SAA, serum amyloid A; heat shock protein (HSP)-70, IGF-I, insulin-like growth factor I; VEGF, vascular endothelial growth factor; PAI-1, plasminogen activator inhibitor type-1; TGF-β, tumor growth factor.

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