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Effect of exercise training on chronic inflammation

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Abstract

Persistent, sub-clinical inflammation, as indicated by higher circulating levels of inflammatory mediators, is a prominent risk factor for several chronic diseases, as well as aging-related disability. As such, the inflammatory pathway is a potential therapeutic target for lifestyle interventions designed to reduce disease and disability. Physical exercise is well recognized as an important strategy for reducing the risk of chronic disease, and recent research has focused on its role in the improvement of the inflammatory profile. This review summarizes the evidence for and against the role of increasing physical activity in the reduction of chronic inflammation. Large population-based cohort studies consistently show an inverse association between markers of systemic inflammation and physical activity or fitness status, and data from several small-scale intervention studies support that exercise training diminishes inflammation. However, data from large, randomized, controlled trials designed to definitively test the effects of exercise training on inflammation are limited, and results are inconclusive. Future studies are needed to refine our understanding of the effects of exercise training on systemic low-grade inflammation, the magnitude of such an effect, and the amount of exercise necessary to elicit clinically meaningful changes in the deleterious association between inflammation and disease.

Keywords

inflammation; exercise; cytokines; acute phase proteins; physical activity

1. Introduction

Inflammation, the body's complex biological reaction to damaging stimuli, is a necessary response of the immune system to infection or trauma. This rapid and acute process results in major increases in circulating levels of inflammatory mediators [1; 2]. For example, in healthy, lean, younger persons, blood concentrations of the acute phase reactant C-reactive protein (CRP) are typically less than 2 mg/L in men [3] and less than 2.5 mg/L in women [4], yet can increase greater than 1000-fold in response to infection or trauma [2; 5; 6]. However, a prolonged inflammatory state has detrimental health effects and predisposes to a number of chronic diseases and health conditions as summarized below. Chronic inflammation is also a robust predictor of both disability and mortality even in the absence

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of clinical disease. Therefore, it is thought that the inflammatory pathway is a potential therapeutic target for interventions to reduce risk of disease and disability.

Although a few pharmacological interventions, such as statin and angiotensin converting enzyme inhibitor use, decrease inflammation—as evidenced by lowered CRP concentrations [7–9], presently none of the pharmaceutical agents with anti-inflammatory effects are approved for the on-going treatment of persistent inflammation. On the other hand, lifestyle behavioral interventions, including changes in food/dietary intake and physical activity, may have clinically significant benefits for improving inflammation over the long term [7]. This review summarizes both the observational and the clinical trial data regarding the effects of increasing physical activity on systemic inflammation. Since a single bout of exercise induces an inflammatory response that is similar to that brought about by infection or trauma, there is controversy surrounding whether or not increasing physical activity may truly be effective for reducing chronic inflammation and reducing its associated risk of disease and disability.

2. Health significance of elevated inflammatory mediators

The biological cascade of events comprising the body's natural defenses against injury or infection is a vital part of the immune system; yet, persistent, slight elevations in systemic biomarkers of inflammation are prospective risk factors for several chronic diseases. Empirical evidence now links low-grade inflammation with disorders of several body systems and tissues, including the circulatory (atherosclerosis, heart failure), endocrine (insulin resistance, metabolic syndrome), skeletal (sarcopenia, arthritis, osteoporosis), pulmonary (chronic obstructive pulmonary disease) and neurological (dementia, depression) systems, along with many other adverse health conditions now thought of as inflammatory disorders [8]. To date, CRP has been the most frequently studied circulating inflammatory biomarker with respect to disease risk prediction. Several prospective studies now provide convincing data indicating that CRP is a strong, independent predictor of incident cardiovascular disease (CVD) in both middle-aged [9–15] and older [16–21] individuals. The Centers for Disease Control and the American Heart Association provide clinical recommendations concluding that individuals with CRP values in the upper tertile of the adult population (>3.0 mg/L) have a 2-fold increase in CVD risk compared to those with a CRP concentration below 1.0 mg/L [22]. In addition to CVD, increased risk for several other diseases, including chronic heart failure [18; 23], diabetes [24–27], osteoarthritis [28; 29], cognitive decline/dementia [30; 31], and aging-related physical disability [32] is associated with elevated CRP levels.

In addition to CRP, there are several other acute phase reactants, as well as inflammatory cytokines and cytokine soluble receptors that are emerging as prospective risk factors for adverse health. In particular, elevations in interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), stimulators of CRP release from hepatocytes [33; 34], are strongly associated with increased risk for several diseases, including CVD [13; 18; 21; 35; 36], diabetes [24–26], cancer [37], and disability [32; 38]. More recently, IL-15 and IL-8 have been shown to be independent predictors of coronary heart disease [39–42], diabetes [43], and cancer [44]. Whether any one of these biomarkers is a more robust indicator of underlying inflammation than others, or whether there are additive effects for risk prediction is not known; although, recent evidence suggests that measuring levels of several inflammatory markers rather than a single marker may substantially improve risk assessment [35; 45].

The underlying mechanism by which elevated inflammatory biomarkers may predispose to chronic disease can be best understood by examining the metabolic effects of inflammation during acute illness. In a typical acute immune response, antigen-presenting cells

encountering a foreign peptide secrete pro-inflammatory cytokines, such as IL-1β and TNFα, which assist in the recruitment of T-cells and the development of an antigen-specific immune response. Additionally, these acute phase reactants have considerable effects on metabolism during acute illness leading to hyperglycemia, insulin resistance, and increased gluconeogenesis [46]. Elevations in these markers also increase proteolysis [47], bone resorption [48; 49], and dyslipidemia [50], in addition to up-regulating other members of the inflammatory cascade, each of which have their own downstream biologic effects. Although such alterations are more pronounced during inflammation due to acute infection or illness, it is thought that long-term exposure to low-grade inflammation may contribute to chronic disease progression.

Due to the ubiquitous nature of low-grade inflammation as an underlying risk factor for chronic disease, medical therapies or behavioral interventions that control or reduce inflammation may be effective in treating multiple adverse health conditions. In light of this review, the potential for regular physical exercise as an anti-inflammatory intervention is increasingly being recognized [51; 52]—even among inflammatory disorders in which exercise was previously contraindicated or not considered as a treatment, such as cancer cachexia [53], muscle myopathies [54; 55], COPD [56], rheumatic disease [57], periodontitis [58], lupus [59], and multiple sclerosis [60]. Yet, as pointed out below, the efficacy of exercise for reducing inflammation requires further research.

Role of increasing physical activity for the treatment of chronic inflammation

3.1 Evidence from observational studies

Observational data from large population cohort studies consistently show an association between physical activity and inflammation. Specifically, lower inflammatory biomarker concentrations are observed in individuals who report performing more frequent and more intense physical activity, including leisure and non-leisure time physical activity. This is true whether a single inflammatory biomarker is assessed, or whether inflammation is depicted as a summary factor derived from multiple biomarkers [61]. Tables 1a and 1b summarize the findings from 26 large observational studies examining the association between markers of systemic inflammation and self-reported physical activity [62–80] or directly measured aerobic fitness [75; 76; 81–87], respectively.

Several large population cohorts, including the British Regional Heart Study [64], the Third National Health and Nutrition Examination Survey (NHANES III) [66; 68], the Cardiovascular Health Study (CHS) [63], the Men's Health Professionals Follow-up Study, the Nurses' Health Study II [67], the MacArthur Studies of Aging [62; 69], the Multi-Ethnic Study of Atherosclerosis (MESA) [78], the In CHIANTI study [73], and the Health, Aging and Body Composition Study (Health ABC) [70], provide strong evidence for an inverse, independent, dose-response relationship between systemic CRP concentration and level of physical activity, although this finding is not unanimous [71; 77]. In NHANESIII, engaging in physical activity more than 22 times per month was associated with a 37% reduction in risk for an elevated CRP compared to engaging in activity less than three times per month [66]. In the British Regional Heart study, even occasional physical activity was associated with a 39% reduction in having a high CRP concentration (>4.27 mg/L) in middle-aged men, although interestingly, risk reduction did not improve with reportedly greater amounts of physical activity [64].

The inverse relationship between CRP and physical activity is seen across a wide age span, including the elderly [62; 63; 70; 73; 80]. However, the association is seen more consistently in men than in women. For example, an inverse, dose-response relationship between CRP

and physical activity was seen in men, but not in women, enrolled in the Pravastatin Inflammation/CRP Evaluation (PRINCE) clinical trial [72]. When stratified by gender and ethnicity, the strongest relationship between CRP and physical activity was seen in Hispanic men in the MESA study [78]; and, in the In CHIANTI study, relationships between level of physical activity and inflammation were independent of body mass index (BMI) in men only [73]. This sex discrepancy may be due to the fact that women have greater adiposity than men, a potential confounding factor in the association between physical activity and inflammation, as pointed out subsequently.

While CRP is the most frequently studied biomarker of chronic inflammation, there are data regarding the association of other inflammatory markers with physical activity as well. In Health ABC, there was a linear trend for lower IL-6 and TNFα, as well as CRP, with greater amounts of reported physical activity [70]. In elderly men, both IL-6 and CRP concentrations were negatively related to the number of reported hours per year of moderate and strenuous exercise [62]. In addition, the lowest concentrations of both CRP and IL-6 were found in elderly persons with the highest levels of recreational (but not household or work-related) activity [69]. Likewise, in a large study of metabolic syndrome in middle-aged and older Chinese, high levels of total physical activity were associated with lower levels of CRP and higher levels of adiponectin, while relatively higher levels of light-intensity activity and walking were associated with lower levels of soluble tumor necrosis factor receptor-2 (sTNFR2) [80]. In the Health Professionals Follow-up and Nurses' Health Studies, there was a significant dose-response relationship between absolute amount of physical activity reported and unadjusted inflammatory biomarker expression, such that individuals who ran more than four hours per week had 4% lower soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2, 6% lower IL-6, and 49% lower CRP than those running less than half an hour per week [67]. Finally, compared to sedentary persons in the ATTICA study, physically active individuals with metabolic syndrome had 30% lower IL-6, 15% lower TNFα, 19% lower serum amyloid-A (SAA), and 15% lower white blood cell (WBC) counts [74].

Despite recent evidence linking several inflammatory biomarkers to physical activity, it is not known whether any one of these alone—or in specific combinations—is a more robust indicator of the role of physical activity in the regulation of inflammation. To address this question, we recently used a factor analysis approach to identify multiple inflammatory factors from eight biomarkers measured in a subset (n=1269) of older (70–79 years) men and women enrolled in the Health ABC study [61]. Associations were then evaluated between identified factors and self-reported measures of physical activity. This analysis showed that five variables (TNFα, sTNFR1, sTNFR2, and IL-6 and IL-2 soluble receptors (IL-6sR, IL-2sR)) loaded highest on the first factor (TNFα-related), while three variables (CRP, IL-6, plasminogen activator inhibitor (PAI-1)) loaded highest on the second factor (CRP-related). After adjusting for age, gender, race, investigation site, and BMI, the CRP-related factor (OR=0.81, $p<0.01$), but not the TNFα-related factor, was associated with physical activity such that persons who had a higher CRP-related score were less likely to have high (≥1000 kcal/day) levels of physical activity. Thus, the use of statistical reduction techniques show that at least two inflammatory factors can be identified in an older population; of which, the CRP-related factor is more closely linked with physical activity. Future research is needed to clarify whether such an additive effect of inflammatory markers is seen in different disease states and populations.

A noteworthy limitation of the aforementioned studies is that all relied on self-report to assess physical activity status without directly measuring energy expenditure or activity. To our knowledge, there are no published data in non-diseased individuals that examined the association between inflammation and physical activity energy expenditure measured via

actigraphy or doubly-labeled water. However, several studies report that an inverse relationship exists between biomarkers of inflammation and direct measurement of cardiorespiratory fitness (VO_2max) assessed during an exercise test. In men from the Aerobics Center Longitudinal Study (ACLS), plasma CRP was inversely related, in a dose-response manner, to cardiorespiratory fitness [81]. The odds ratio of having a high CRP (> 1.84 mg/L) was 3.2 (95% CI: 1.8–5.8) for men in the lowest quintile of fitness compared to men in the higher quintiles of fitness. Additional adjustment for body fat percentage and/or waist girth did not alter the relationship between CRP and cardiorespiratory fitness [81]. Moreover, similar to the ATTICA findings, CRP levels were found to be lower in individuals with the metabolic syndrome who maintain a high fitness level than in those with a low fitness level [82]. In this study, adjusted mean CRP in those in the upper and lower fitness quartiles was 1.48 versus 0.93 mg/L in those without metabolic abnormalities, 2.40 versus 1.66 mg/L in those with one or two metabolic abnormalities, and 4.62 versus 2.20 mg/L in those with the metabolic syndrome—and these associations were independent of obesity. Importantly, it appears that differences in adiposity alone do not account for the strong association seen between higher cardiorespiratory fitness and lower chronic inflammation. As discussed below, there are training adaptations observed in skeletal muscle and immune cells that likely contribute to the lower levels of these systemic inflammatory biomarkers observed in physically fit and active individuals.

The reasons for the observed inverse association between physical activity and inflammation are not entirely understood, but this relationship is likely related, in part, to the effects of physical activity on adiposity. Amount of fat mass is undeniably one of the strongest correlates of circulating inflammatory biomarkers [7], and therefore needs to be accounted for when examining relationships between physical activity and inflammation. In most of the cohort studies, adjustment for adiposity (most often measured by BMI), attenuated, but did not negate, the strength of the relationship between inflammatory biomarkers and physical activity. For example, while adjustment for BMI reduced the effect of physical activity on CRP in the CHS study, the relationship was still significant [63]. Also, in NHANESIII, the association between elevated CRP, fibrinogen and physical activity was independent of both BMI and waist-to-hip ratio [66]. However, in men enrolled in the Health Professionals Follow-up Study and women enrolled in the Nurses' Health Study II, CRP was 25% and 68% lower in more physically active men and women, respectively; but, this association was reduced when BMI was included in the regression model, and was non-significant with the addition of plasma leptin, a surrogate measure of fat mass, to the model [67]. Because BMI is not a direct measure of fat mass, the strong associations observed between inflammation and physical activity/fitness may be confounded by variation in adiposity per se. Only one of these large cohort studies measured fat mass via dual energy x-ray absorptiometry, as well as abdominal visceral fat via computed tomography; and, additional adjustment for these confounders significantly reduced the association between IL-6 and physical activity and eliminated the association of CRP and TNFα with physical activity [70]. Consequently, it is feasible that inflammation is lower in physically active individuals primarily because of lower absolute amount of total and visceral body fat. However, more studies that account for this by using a direct measure of fat mass are needed before definitive conclusions can be drawn.

Overall, data from observational studies show that the greater the volume of reported physical activity, the lower the risk of elevated levels of inflammatory biomarkers. Furthermore, the relationship between inflammation and physical activity is often independent of total obesity as measured by BMI. However, as with all observational data, it is not possible to confirm whether inflammation and physical activity are causally related, nor to ascertain the direction of the relationship. Unanswered questions remain, including: 1) are individuals with less inflammation more likely to engage in physical activity?, 2) are a

physically active lifestyle and lower inflammatory biomarkers linked through some other related health behavior, such as nutrition, or through some other body parameter, such as abdominal adiposity or lean mass?, and 3) will increasing physical activity result in a decrease in chronic inflammation? As summarized next, there are some data from intervention studies conducted by us and others which begin to answer the latter question.

3.2 Evidence from intervention studies

Currently, data from intervention studies designed to examine the effects of exercise training on inflammation reflect less consistent findings than the data from observational studies. Reasons for this are numerous, but are likely related to: 1) publication of findings from studies that are underpowered, 2) differences between studies in the caloric expenditure of the exercise leading to differences in the intervention's effect on body fat, 3) differences in the type (e.g., aerobic vs. resistive), intensity and duration of the exercise, 4) differences between studies in the baseline inflammatory status of study participants, and 5) lack of studies with an appropriate control group. This section summarizes the published exercise intervention studies (limited to those studies with exercise only treatments), and points to the need for additional fully-powered and well-controlled studies to definitively assess the effects of exercise as a treatment for chronic inflammation.

Despite a large body of cross-sectional evidence showing that a higher volume of physical activity is associated with a lower systemic inflammation, not all intervention studies show an effect of increasing physical activity for reducing classical biomarkers of inflammation, especially CRP [88–95]. In fact, a recent meta-analysis which pooled five studies did not show an effect of aerobic exercise on CRP concentrations [96]. However, these studies (even the meta-analysis) were conducted with much smaller sample sizes than the observational studies. On the other hand, many of the studies that do show an effect of exercise training on CRP utilized an exercise intervention that resulted in slight to moderate decreases in body weight/fat [97–103]. However, in some studies, changes in CRP were independent of the magnitude of weight/fat lost [97; 98; 100]. Nevertheless, because of the strong association between inflammation and adiposity, it is important to delineate the separate effects of exercise in the absence of weight or fat loss on inflammation.

For the most part, intervention studies in participants with elevated inflammation due to chronic disease or obesity show a favorable exercise training effect (in the absence of weight loss) on specific inflammatory biomarkers. For instance, in 28 older coronary heart disease patients participating in cardiac rehabilitation, 12 weeks of aerobic exercise resulted in reductions in CRP, IL-6, interferon gamma (INF-γ), and IL-1, and increases in IL-10 [104], independent of changes in body weight or BMI. Similarly, in patients with chronic heart failure, 12 weeks of aerobic exercise reduced TNFα concentrations (but not IL-6 or IL-8) [105] and 16 weeks of combined aerobic and resistance exercise training decreased levels of both TNF receptors, but not TNFα itself, nor IL-6 [106]. In obese postmenopausal women with type 2 diabetes, 14 weeks of aerobic exercise decreased CRP by 15% and marginally decreased IL-6 ($p=0.07$), but did not change TNFα concentrations [101]. Likewise, 12 weeks of exercise reduced IL-18 levels by 17.5% in patients with metabolic syndrome [107]. In one of the largest, yet non-randomized, exercise studies conducted to date (HERITAGE Family study), plasma CRP was significantly reduced with 20 weeks of aerobic training only in the sub-group of persons with a high (>3.0 mg/L) baseline CRP. The approximate 29% CRP decrease in this study was not mediated by changes in body weight [108]. Collectively, these studies suggest that regular aerobic exercise has the potential to lower concentrations of inflammatory biomarkers in individuals with conditions associated with elevated inflammation. However, most of these studies did not compare individuals randomized to exercise versus a non-exercise control group. The large variability and transient nature of most biomarkers of inflammation within and among individuals,

necessitates the use of a control group and a randomized study design to definitely conclude that increasing physical activity through regular exercise reduces chronic systemic inflammation.

To date, there are relatively few adequately-powered, randomized, controlled trials (RCT) of an exercise intervention on inflammatory biomarkers. Table 2 summarizes the published RCT of aerobic exercise to date [90–93; 95; 102; 103; 109–113]. The included studies are limited to those with 20 or more subjects per primary treatment group, those that used supervised or center-based exercise interventions, and those where changes in body weight were not significantly related to changes in biomarkers of inflammation. One of the larger studies which did incorporate a control group (but did not randomize participants) demonstrated that a phase II cardiac rehabilitation and exercise training program reduced median CRP concentrations by 41% in CHD patients, but CRP did not change in CHD patients who did not undergo rehabilitation [97]. Again though, the effect of exercise training was more effective in patients with the highest CRP concentrations. In addition, patients with intermittent claudication randomized to exercise reduced CRP after 12 weeks, with no change observed in those randomized to the control group; however, this change did not persist at six or 12 months [109]. On the other hand, in older, overweight men and women with knee osteoarthritis, we did not observe an effect of 18-months of exercise training alone on IL-6, CRP, TNFα, or TNF receptors [93]. Similarly, randomization to a 12-month aerobic exercise intervention did not affect CRP levels in men and women with normal CRP baseline values [95]. Finally, in a small number of elderly (60–85 years) adults, six months of exercise training did not statistically alter serum CRP levels, even though the reduction in CRP was two times greater in the exercise versus the control group [92]. Thus, some, but not all, randomized studies show a trend toward lowering of inflammation with exercise, especially in those with higher inflammation at baseline.

We recently completed an ancillary study to The Lifestyle Interventions and Independence for Elders (LIFE) trial to determine the effects of a long-term exercise intervention (in the absence of weight loss) on several biomarkers of inflammation (CRP, IL-6, TNFα, IL-6sR, IL-1sRII, sTNFR1, sTNFR2, IL-8, IL-15, adiponectin, IL-1ra, and IL-2sRα) in elderly men and women [110],[114]. The LIFE study was a four-site, single-blind, randomized controlled trial comparing a 12-month Physical Activity (PA) intervention to a non-exercise "Successful Aging" (SA) intervention in 424 elderly (70–89 yrs), non-disabled, community-dwelling men and women at risk for physical disability. The PA intervention consisted of a combination of aerobic, strength, balance, and flexibility exercises and did not result in a change in body weight. Overall, the PA intervention resulted in a significant decrease in only two biomarkers—IL-6 and IL-8, compared to the SA intervention. There did appear to be an effect of baseline inflammatory status on intervention efficacy, as there was a greater effect of the PA intervention in participants with a higher baseline IL-6 and IL-15. Thus, a one-year physical activity intervention reduces some, but certainly not all, biomarkers of systemic inflammation in elderly individuals, and this benefit is most pronounced in those with more inflammation at baseline.

Although clearly more attention has been paid to the effects of aerobic exercise on inflammation, a handful of resistance exercise training studies have been conducted [115–119], with results largely negative. The first of such studies was conducted in 1996, and reported that 12 weeks of high-intensity progressive resistance strength training does not affect IL-1β, TNFα, IL-6, or IL-2 production [115]. Similarly, McFarlin and colleagues [117] did not observe an improvement in inflammatory cytokine expression (IL-6, TNFα) in resistance-trained older women (65–80 years), compared to untrained controls after an acute bout of resistance exercise. The small sample sizes in both of these studies (n=6–10 per treatment group) may have contributed to this null effect; however, in a larger trial of 56

middle-aged men and women, 10 weeks of resistance training did not significantly alter IL-6 or CRP expression [118]. In contrast to these findings, a 16-week resistance training intervention reduced CRP and increased adiponectin levels in Hispanic older adults (>55 years) with type 2 diabetes [116]. Lastly, and in agreement with the notion that obesity plays an integral role in inflammatory biomarker expression, a recent publication by Brochu et al. found that resistance training alone does not contribute to improving inflammatory markers, however when coupled with weight loss, significant improvements in inflammatory and metabolic variables were observed [119].

In conclusion, data from randomized, controlled trials indicate that aerobic exercise training interventions conducted in individuals with higher inflammation, or those that result in even a slight amount of weight reduction, are beneficial for reducing inflammatory biomarker levels, whereas it appears that increasing physical activity alone has a small, often undetectable, effect on inflammation in normal, healthy individuals.

3. Potential adaptations to exercise training contributing to improvement in inflammation

While the exact mechanisms by which physical activity may reduce inflammation are not entirely understood, there are some data pointing to factors that may contribute to an effect of repeated bouts of muscle contraction leading to improvements in inflammatory status over time. These factors include: 1) shifts in monocyte phenotype, specifically reductions in immune cell production of inflammatory mediators, with exercise training, 2) immune function adaptations that occur locally in exercised skeletal muscle, and 3) exercise-induced adaptations in intracellular generation of reactive oxygen species (ROS).

In one study, aerobic exercise training in adults at high risk for ischemic heart disease resulted in a 58% decrease in mononuclear cell production of atherogenic cytokines (INFγ, TNFα and IL-1α), while the production of atheroprotective cytokines (IL-10, IL-4, and transforming growth factor beta-1 (TGFβ1)) increased by 36% [120]. Exercise training also reduces CD14+CD16+ monocyte number, as well as TNFα production by monocytes, in healthy older men and women [121], and reduces monocyte cell-surface expression of toll-like receptor-4 (TLR4), a lipopolysaccharide (LPS) signaling receptor that likely contributes to attenuation of acute immune responses to infection or trauma [122–124]. Similarly, in healthy young adults, higher-intensity aerobic exercise training reduces stimulated production of TNFα by monocytes [125]. Thus, these data point to an adaptive down-regulation of cytokine release from innate immune cells in response to regularly performed muscular contraction.

The well-known activation of inflammatory pathways invoked by a single bout of exercise makes it almost counterintuitive that regular physical activity would serve to reduce chronic inflammation. However, it is now evident that an acute inflammatory response plays a major role in the training adaptations observed in exercised muscles. Contracting skeletal muscle produces and secretes several cytokines (myokines), most notably IL-6, which mediates metabolic changes during exercise [126]. IL-6 release from muscle increases up to 100-fold during contractile exercise and its production results in increased systemic anti-inflammatory cytokines (IL-1 receptor antagonist and IL-10), but decreased TNFα and IL-1β production [127]. There are also data to suggest that the exercise-induced increase in IL-6 inhibits TNFα production in the presence of low-grade inflammation [128]. Furthermore, skeletal muscle IL-8 expression also increases with acute exercise, and this increase may play a role in stimulating angiogenesis in response to physical activity [129]. Thus, acute exercise activates an immune response, but the effects are primarily anti-inflammatory and serve to enhance lipid and glucose metabolism. In turn, regular/chronic

exercise can lead to lower basal levels of circulating inflammatory markers, as well as reduce the inflammatory response to acute exercise.

Exercise training-induced improvements in inflammatory status may also result from the modulation of intracellular signaling pathways and cellular function that are mediated by nitric oxide (NO) and ROS. While ROS and NO are generated at low rates under resting conditions, the production of these molecules increases transiently during exercise and plays a role in inducing anti-inflammatory defense mechanisms [130]. ROS and NO have acute effects on contractile regulation and exert chronic effects on muscle gene expression. In particular, the adaptive process involves the up-regulation of genes encoding antioxidant enzymes and heat shock proteins. For example, treadmill training in rats reduced the release of ROS and NO from contracting muscles and increased skeletal muscle antioxidant content [131]. A significant reduction in skeletal muscle NO synthase expression has also been reported after exercise training [132]. These adaptive responses in redox-sensitive pathways with exercise training helps to protect skeletal muscle against subsequent exposure to exercise-induced increases in ROS generation. Given that ROS mediates some of the catabolic effects of TNFα on skeletal muscle, reductions in ROS generation may lead to attenuation of the inflammatory response. Thus, similar to the anti-inflammatory effects of acute cytokine production and release during muscular contraction, adaptive responses in redox-sensitive pathways may also serve to protect against chronic systemic low-grade inflammation.

4. Conclusions

Persistent, low-grade inflammation is an important contributor to the pathophysiology of several chronic health conditions. Given these widespread deleterious health effects of an augmented inflammatory state, identification of therapies that reduce inflammation is critical. Yet, to date, there is little definitive evidence for therapies that can effectively treat individuals with elevated markers of inflammation that are within the clinically normal range. However, consistent data from observational studies showing a link between self-reported levels of physical activity and inflammatory biomarkers, as well as some promising positive data from randomized, controlled trials, indicate that increasing aerobic physical activity could be effective for reducing chronic inflammation, especially in individuals with chronic diseases associated with a state of elevated inflammation. Additional trials targeting the magnitude of the effect of physical activity on inflammatory mediators, and the amount of exercise necessary to produce clinically meaningful reductions in inflammation are needed.

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Table 1a

a. Observational studies showing associations between systemic biomarkers of inflammation and self reported physical activity.

Author (year)	N (%M)	Age (yrs)	Self Report Physical Activity (PA) Measure	Association of Greater PA Measure to Inflammatory Biomarker(s)	Independent of Obesity?[b]
Taaffe (2000)	880 (47%)	70–79	PA frequency (hr/yr)	↓ CRP, ↓ IL-6	Yes
Geffken (2001)	5888 (42%)	≥ 65	PA (kcal/week)	↓ CRP, ↓ fibrinogen, ↓ Factor VIII activity, ↓ WBC, ↔ albumin	Yes
Abramson (2002)	3638 (51%)	>40	PA frequency (times/mo)	↓ CRP, ↓ fibrinogen, ↓ WBC count	Yes[c]; CRP, WBC count
Wannamethee (2002)	3810 (100%)	60–79	PA level	↓CRP, ↓ fibrinogen, ↓ WBC count	Yes
Ford (2003)	13,748 (47%)	≥ 20	PA (leisure-time) volume	↓ CRP, ↓ WBC, ↓ fibrinogen, ↑ albumin, ↔ UA	Yes[c]; albumin, CRP, fibrinogen
King (2003)	4072 (50%)	> 17	PA type[a] & frequency (times/mo)	↓ CRP, ↓ WBC, ↓ fibrinogen	Yes
Pischon (2003)	859 (47%)	M: 40–75 F: 25–42	MET-hrs/wk	↓ CRP, ↓ IL-6, ↓ sTNFR1, ↓ sTNFR2	Yes[f]; sTNFR2
Reuben (2003)	870 (47%)	70–79	PA level	↓ CRP, ↓ IL-6	Yes
Albert (2004)	2833 (61%)	60±12	PA frequency (times/week)	↓ CRP (men only)	Yes
Colbert (2004)	2964 (47%)	70–79	PA (leisure-time) frequency (min/week); PA (non leisure-time) (kcal/kg/wk)	Exercise: ↓ CRP, ↓ IL-6, ↓ TNFα Non-exercise: ↓ CRP, ↓ IL-6	Yes[d]; IL-6 Yes[d]; IL-6, CRP
Verdaet (2004)	892 (100%)	35–59	PA (leisure-time) volume	↓ CRP, ↓ fibrinogen, ↔ SAA	No
Elosua (2005)	1004 (44%)	≥ 65	PA frequency (times/week)	M: ↓ WBC, ↓ ESR, ↓ albumin, ↓ UA, ↓ fibrinogen, ↓ CRP, ↓ IL-6, ↔ sIL-6R, ↔ IL-10, ↔ IL1β, ↓ IL-1ra, ↓ IL18, ↓ TNFα W: ↓ WBC, ↓ ESR, ↓ albumin, ↓ UA, ↓ fibrinogen, ↓ CRP, ↓ IL-6, ↓ sIL-6R, ↔ IL-10, ↔ IL1β, ↓ IL-1ra, ↓ IL18, ↔ TNFα	Yes (men); fibrinogen, ESR, CRP, IL-6 Yes (women); UA, IL-6
Pitsavos (2005)	3042 (50%)	48±12	PA level	↓ CRP, ↓ WBC count, ↓ TNFα, ↓ IL-6, ↓ SAA	Yes[e]
Borodulin (2006)	3803 (45%)	25–74	MET-h/wk in PA domain	M: ↓ CRP (conditioning, non-conditioning) W: ↓ CRP (conditioning, non-conditioning, commuting)	Yes[e] (women only)
Hjelstuen (2006)	177 (100%)	40–47	PA level	↔ CRP, ↔ sVCAM-1, ↔ s-ICAM-1, ↓ E-selectin	Yes
Nazmi (2008)	3289 (58%)	22–24	PA level	↔ CRP	N/A
Autenrieth (2009)	796 (55%)	35–74	Volume of total and commuting PA	↓ CRP, ↓ IL-6, ↓ fibrinogen	Yes[c]
Majka (2009)	6142 (50%)	45–84	MET-mins/wk	↓ CRP	Yes (black women and Hispanic men only)
Yu (2009)	3289 (44%)	50–70	PA level (MET-hr/wk)	↓ CRP, ↑ adiponectin, ↔ TNFα, ↔ IL-6, ↔ RBP4	Yes

1b. Observational studies showing associations between systemic biomarkers of inflammation and aerobic fitness.

Author (year)	N (♂)	Age (yrs)	Aerobic Fitness (AF) Measure	Association of Greater PA Measure to Inflammatory Biomarker(s)	Independent of Obesity?[b]
Church (2002)	722 (100%)	51±10	Treadmill; VO_{2max}	↓ CRP	Yes[c]
Aronson (2004)	1640 (65%)	50±10	Treadmill; VO_{2max}	↓ CRP	Yes
Rahimi (2005)	209 (77%)	63±10	Treadmill/bicycle; MET-level	↓ CRP	Yes[c]
Borodulin (2006)	3803 (45%)	25–74	Polar Fitness Test; aerobic power (mL/kg*min)	↓ CRP	Yes[e]
Hjelstuen (2006)	177 (100%)	40–47	Cycle ergometer; time to exhaustion	↓ CRP, ↔ sVCAM-1, ↔ s-ICAM-1, ↔ E-selectin	Yes
Kullo (2007)	172 (100%)	51±9	Treadmill; VO_{2max}	↓ CRP, ↓ IL-6, ↓ fibrinogen, ↓ WBC count	Yes; CRP, IL-6, fibrinogen
Jae (2008)	425 (100%)	55±8	Treadmill; VO_{2max}	↓ CRP, ↓ fibrinogen, ↓ WBC count	Yes
Arsenault (2009)	272 (44%)	18–65	Cycle ergometer; physical working-capacity	M: ↔ CRP, ↔ IL-6, ↔ TNFα, ↓ adiponectin W: ↓ C ↓ IL-6, RP, ↔ TNFα, ↔ adiponectin	Yes[d] (men only)
Giallauria (2009)	124 (0%)	24±5	Cycle ergometer; VO_{2max}	↓ CRP, ↓ fibrinogen ↓ WBC count	Yes[d]

↑ = significantly higher; ↓ = significantly lower; ↔ = no difference; N = sample size; M = male; F = female; PA= physical activity; AF = aerobic fitness; CRP= C-reactive protein; WBC= white blood cell; SAA = serum amyloid A; IL = interleukin; TNFα = tumor necrosis factor alpha; ESR = erythrocyte sedimentation rate; sICAM-1 = soluble intercellular adhesion molecule 1; sVCAM-1 = soluble vascular adhesion molecule 1; RBP4 = retinol binding protein 4; sTNFR1 = soluble tumor necrosis factor receptor 1; sTNFR2 = soluble tumor necrosis factor receptor 2; UA = uric acid; VO_{2max} = maximal oxygen uptake; mL = milliliter; kg = kilogram; min = minute; hr = hour; MET = metabolic equivalent; wk = week; kcal = kilocalorie; mo = month; yr(s) = year(s).

[a] after adjustment significant reductions only seen for aerobic dancing and jogging;

[b] obesity quantified by BMI unless otherwise noted:

[c] BMI and WHR/waist girth,

[d] body fat (total and/or visceral),

[e] WHR/waist girth,

[f] BMI and leptin

Table 2

Randomized controlled trials examining the effect of aerobic exercise on markers of systemic inflammation

Author (year)	Duration	N(M:F)/age (years)	BMI (kg/m^2)	Health Status	Exercise Intervention	Biomarkers Assessed	Significance Reported
Tisi (1997)	12 mo	22[b] 17[b]	n/a[c] n/a[c]	Intermittent Claudication	Active and passive leg exercises 1 h 4 times/wk Control	SAA, CRP, Fibrinogen	Yes, ↓ SAA, ↓ CRP (at 6 and 3 mo only)
Nawaz (2001)	6 wk	26(22:4)/70(61–73) 26(21:5)/68(63–70) 15(9:6)/71(70–77)	n/a[c] n/a[c] n/a[c]	Intermittent Claudication	Lower body ergometer 2 times/wk for 20 min @ 75–80% HR_{max} Upper body ergometer 2 times/wk for 20 min @ 75–80% HR_{max} Control	vWF, E-selectin, CD11b, CD66b	None
Hammett (2004)	6 mo	30(13:17)/67±5 31(14:17)/66±4	25±3 26±4	Healthy	45 min exercise 4 times/wk @ 80% VO_{2max} Control	CRP	None
Nicklas (2004)	18 mo	67(17:50)/69±6 70(24:46)/69±6	34.6±5.8 34.5±5.3	Chronic Arthritis	15 min weight training & 30 walking @ 50–75% HR_{res} 3 times/wk Control	CRP, IL-6, IL-6sR, TNFα, sTNFR1, sTNFR2	None
Fairey (2005)	15 wk	24(0:24)/59±5 28(0:28)/58±6	29.4±7.4 29.1±6.1	Breast Cancer Survivors	15–35 min aerobic exercise 3 times/wk @ 70–75% VO_{2peak} Control	CRP	None
Marcell (2005)	16 wk	20[b]/44.4±9.5 17[b]/47.2±9.2 14[b]/44.1±9.5	32.5±5.3 33.9±4.9 35.3±3.7	Insulin Resistant	30 min aerobic exercise 5 times/wk @ 80–90% HR_{max} 30 min aerobic exercise 5 times/wk Control	CRP, adiponectin	None
Kohut (2006)	10 mo	48(19:29)/69.8±5.5 49(15:34)/70.3±4.6	28.2±0.8 29.3±0.8	Healthy	45 min aerobic exercise 3 times/wk@ 65–80% VO_{2max} 45 min flexibility/strength exercise 3 times/wk	CRP, IL-6, TNFα, IL-18	Yes, ↓ CRP, ↓ IL-6, ↓ IL-18 (TNFα ↓ in both groups)
Kadoglou (2007)	6 mo	30(13:17)/59.3±4.8 30(12:18)/63.8±7.0	32.1±3.2 32.0±3.4	Diabetes	30–45 min aerobic exercise 4 times/wk @ 50–75% VO_{2peak} Control	CRP, IL-10, IL-18, TNFα, adiponectin	Yes, ↓ CRP, ↓ IL-18, ↑ IL-10
Nicklas (2008)	12 mo	183(57:126)/76.4±4.1 186(45:141)/77.0±4.4	30.7±6.0 29.8±5.5	At risk for physical disability	150 min/wk walking Control	CRP, IL-6	Yes, ↓ IL-6

Author (year)	Duration	N(M:F)/age (years)	BMI (kg/m^2)	Health Status	Exercise Intervention	Biomarkers Assessed	Significance Reported
Campbell (2008)	12 mo	100(51:49)/40–75 102(51:51)/40–75	M: 29.7±3.7 F: 28.9±5.5 M: 29.7±6.0 F: 28.5±4.8	Healthy	60 min aerobic exercise 6 times/wk @ 60–85% HR_{max} Control	CRP	None
Walther (2008)	24 mo	51(51:0)/62±1 50(50:0)/60±1	27.2±0.4 28.0±0.5	Coronary Artery Disease	20 min daily aerobic exercise @ 70% HR_{max} rate + 1 d/wk 60-min group aerobic training session Percutaneous intervention	CRP, IL-6	Yes, ↓ in all
Campbell (2009)	12 mo	53(0:53)/60.5±7.0 62(0:62)/60.9±6.8	30.2±4.0 30.4±3.8	Healthy	45 min aerobic exercise 5 times/wk @ 60–75% HR_{max} Control	CRP, IL-6, SAA	Yes, ↓ CRP

[a] Compared to baseline and control;

[b] Baseline gender, age not provided;

[c] Baseline BMI not provided