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The Anti-Inflammatory Actions of Exercise Training

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Abstract

The list of diseases with a known inflammatory etiology is growing. Cardiovascular disease, osteoporosis, diabetes, geriatric cachexia, and Alzheimer's disease have all been shown to be linked to or exacerbated by aberrantly regulated inflammatory processes. Nevertheless, there is mounting evidence that those who are physically active, or who become physically active, have a reduction in biomarkers associated with chronic inflammation. There was strong early consensus that exercise-induced reductions in inflammation were explained by body mass index or body fatness, but recent studies provide support for the contention that exercise has body fat–independent anti-inflammatory effects. With few exceptions, the anti-inflammatory effects of exercise appear to occur regardless of age or the presence of chronic diseases. What remains unclear are the mechanisms by which exercise training induces these anti-inflammatory effects, but there are several intriguing possibilities, including release of endogenous products, such as heat shock proteins; selective reduction of visceral adipose tissue mass or reducing infiltration of adipocytes by macrophages; shift in immune cell phenotype; cross-tolerizing effects; or exercise-induced shifts in accessory proteins of toll-like receptor signaling. However, future research endeavors are likely to uncover additional potential mechanisms, and it could be some time before functional mechanisms are made clear. In summary, the potential anti-inflammatory influences of exercise training may provide a low-cost, readily available, and effective treatment for low-grade systemic inflammation and could contribute significantly to the positive effects of exercise training on chronic disease.

Keywords

anti-inflammatory; exercise training; chronic disease

Cardiovascular disease, diabetes, osteoporosis, and several other chronic diseases are now known to be strongly linked to inflammatory processes.[1–4] Chronic diseases linked to inflammation are known to occur in greater frequency in older and sedentary individuals,[5] but evidence is emerging that exercise has anti-inflammatory effects.[6–9] For example, there is a substantial reduction in biomarkers of low-grade systemic inflammation in physically active adults or adults who undertake exercise training.[10–14]

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Chronic low-grade inflammation, "persistent but more subtle than the acute phase response,"[15] is frequently assessed by measurement of circulating C-reactive protein (CRP) and, somewhat less frequently, serum amyloid A. C-reactive protein concentration is higher in those with high body mass index,[16,17] metabolic syndrome and/or diabetes,[1,18] below-normal high-density lipoprotein cholesterol,[19] chronic infection,[20] and in cigarette smokers.[21] Therefore, the inflammation/ damage is diffuse in low-grade inflammation and is apparently associated with several organs and tissues such as endothelial cells and adipocytes. Conversely, light to moderate alcohol intake,[22] weight loss,[23] medications such as glitazones[24] and statins,[25] and the focus of this review—increased physical activity—are associated with lower CRP concentration and reduction in other markers of inflammation.

It has been argued that CRP is a better predictor of cardiovascular disease risk than serum cholesterol,[26,27] but this contention is quite controversial.[28–31] Although CRP has gained acceptance as an independent marker of cardiovascular risk,[4] recent research suggests that it is more than an "innocent bystander."[32] There is evidence that CRP may contribute to damage during myocardial infarct[33,34] and contribute directly to atherogenesis.[32]

Serum or plasma pro-/anti-inflammatory cytokines are frequently used as biomarkers of inflammation. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are most commonly measured and are known to stimulate CRP release from the liver.[20] TNF-α and IL-6 are also frequently linked to increased incidence of disease,[2,3,35–37] physical frailty or muscle wasting,[38–40] and early death.[41] The anti-inflammatory cytokine IL-10 and the adipocytokine adiponectin are also being measured with increased frequency.[42–47] Adiponectin appears to be released in inverse proportion to fat mass[23] and has anti-inflammatory effects such as negating the influence of TNF-α on endothelial cell adhesion,[48] decreasing NF B activation,[49] and slowing macrophage foam-cell development.[50]

The mechanisms for the apparent systemic and tissue-specific anti-inflammatory effects of exercise training or increased physical activity have not been elucidated. There are several intriguing possibilities, such as exercise-induced release of heat shock proteins, shifts in immune cell phenotype, training-induced reductions in visceral adipose tissue, or reduced tissue hypoxia. These are discussed in detail later in this review.

Our recent research has been focused on finding the mechanism for our observation that resistance exercise training lowered lipopolysaccharide (LPS)–stimulated inflammatory cytokine production in women aged 65 to 85.[7] Our research efforts have been focused on the pattern recognition receptor toll-like receptor 4 (TLR4)—the primary signaling receptor for LPS. We found that TLR4 was substantially lower in individuals with high levels of physical activity, and TLR4 expression was reduced by exercise interventions.[7,9,10,51] However, we are uncertain to what extent these changes contribute to the overall anti-inflammatory effect of exercise training.

It appears that exercise exerts anti-inflammatory effects, independent of losses in body fat, that are available to subjects of any age and to subjects with chronic diseases such as heart failure, type 2 diabetes, and osteoporosis. Exercise is known to exert positive influences on

chronic diseases, but the extent to which the anti-inflammatory influence contributes to these positive effects is, as yet, unknown. Nevertheless, this is an exciting and intriguing new area of research that holds considerable promise for future researchers.

Inflammation and Chronic Disease

Recent research highlights the role that low-level systemic inflammation plays in initiating or exacerbating chronic disease.[1–3] For example, cardiovascular disease was once believed to be primarily a disease of lipid deposition, but inflammation is now known to play a role in all stages of atherosclerotic plaque development.[52] Further evidence of the emerging role of inflammation in chronic disease is provided by recent findings on the cholesterol-lowering (statin) drugs. Statins are now known to possess potent anti-inflammatory properties[53]—making it difficult to determine what proportion of cardiovascular risk reduction can be attributed to statin's low-density lipoprotein (LDL) lowering or inflammation-lowering properties.[54]

There are several other interesting examples to illustrate the role of inflammation in chronic disease. Inflammatory markers effectively predicted the future development of diabetes,[55–57] and elevated levels of inflammatory biomarkers were positively correlated with both insulin resistance and diabetes risk.[58–61] Another example of the inflammatory influence on chronic disease is obesity, which exerts some of its comorbid influence through inflammatory processes.[62] Adipocytes, or the resident macrophages in adipose tissue, are now known to produce a range of inflammatory products that contribute to insulin receptor dysfunction and related insulin insensitivity.[1,8,57,63] Obese and overweight individuals have higher concentrations of inflammatory markers than normal-weight individuals;[64,65] however, as will be discussed later, there is some disagreement in the literature whether it is the exercise training per se or body fat loss that elicits the decrease in inflammatory markers in studies that employ exercise, caloric restriction, or exercise and caloric restriction in combination to induce weight loss.[57,64,66,67]

Inflammation has been linked to several other chronic diseases, such as osteoporosis[3,68–70] and muscle/lean tissue loss in geriatric cachexia,[11,71] that are associated with disuse and inactivity. Furthermore, inflammation may suppress protein synthesis,[12,72] and inflammatory biomarkers such as IL-6, TNF-α, and CRP are often used to predict subsequent mobility limitations or physical frailty.[38–40,73] As will be discussed below, there is evidence that adaptations to exercise are preceded by an exercise training-induced blunting of inflammation.[13] Therefore, exercise training has the potential to ameliorate inflammation and permit adaptations that can enhance strength and other aspects of physical function.

Collectively, as the detrimental effects of low-grade systemic inflammation become evident, our ability to control these inflammatory processes is growing in importance. A newfound emphasis on inflammation and chronic disease has led to the search for interventions that could lessen the impact of low-level systemic inflammation on health. Increased physical activity potentially provides a low-cost, readily available, positive side effect treatment for reducing inflammation.

Anti-Inflammatory Influences of Exercise

Acute Exercise

The focus of this review is to examine and discuss the potential anti-inflammatory influences of exercise training, but acute exercise can also stimulate an increase in anti-inflammatory agents.[74–78] This topic was the focus of a recent review[79] and will only be dealt with briefly herein.

Acute exercise stimulates an increase in plasma pro-inflammatory cyto-kines.[75,77,78,80,81] For example, cycling exercise (80% $VO_{2\ max}$; 30 minutes) increased serum TNF-α and IL-1α,[77] whereas plasma TNF-α and IL-1β increased modestly, yet significantly, following a marathon.[81] Acute exercise also increases anti-inflammatory cytokines, such as IL-10, IL-1ra, and IL-4.[74–78,81] Several researchers reported that acute exercise did not increase plasma concentration of TNF-α or IL-1β.[75,82–85] Therefore, it appears that the pro-/anti-inflammatory balance during and immediately following exercise is dependant on several factors. These include subject health status,[80,86] intensity or duration of exercise,[76,77,82,87,88] glucose availability,[87–90] and sampling time.[74,75,91] For example, TNF-α was increased during moderate exercise in patients with chronic obstructive pulmonary disease but not in age-matched healthy controls.[80] Intensity also plays a role, such that high-intensity cycling at ~80% $VO_{2\ max}$ increased serum TNF-α, IL-1α, and IL-6, as well as intracellular (monocyte) interferon-gamma (IFN-β) and IL-4.[77] Long-duration, lower intensity, 2-legged exercise (120 minutes, 55% $VO_{2\ max}$) did not increase plasma TNF-α, but IL-6 increased progressively throughout exercise.[82] Furthermore, IL-1ra and IL-10 were inversely correlated with plasma glucose levels at the end of a competitive marathon.[88] In addition, IL-1ra and IL-10 levels were higher in marathon runners who consumed an artificially sweetened placebo beverage compared to those consuming a sports drink.[88] Finally, sampling time is important when interpreting the current literature because IL-10 is typically not elevated until the postexercise period.[74,75]

The traditional view of IL-6 is pro-inflammatory, with IL-6 linked to fever,[92,93] induction of acute phase proteins such as CRP,[20,93] and increased monocyte and macrophage production of inflammatory cytokines.[94,95] Recent research has shown IL-6 release from skeletal muscle during exercise,[82,83,96,97] with IL-6 exerting endocrine-like effects, such as the ability to alter carbohydrate (CHO) and lipid metabolism.[98] IL-6 infusion increased production of IL-10 and IL-1ra and blunted the inflammatory response to subsequent endotoxin.[99,100] Specifically, Starkie et al[100] showed that either low-intensity exercise (180 minutes) or recombinant human IL-6 infusion equally dampened TNF-α production in response to endotoxin infusion.[100] These authors suggested that IL-6 release during exercise modulated the subsequent response to endotoxin in the same fashion as the infused IL-6.[100] Further evidence for the potential anti-inflammatory influence of IL-6 was shown by Steensberg et al,[99] such that IL-6 infusion elicited the appearance of plasma IL-1ra and IL-10.[99] Therefore, IL-6 is garnering support as an anti-inflammatory cytokine[79,99,100] or as the first myokine.[101] IL-6 is shown to have acute anti-inflammatory properties, and the cyclic increases in IL-6 that would occur during exercise training may help explain some of the mechanisms for the anti-inflammatory effect of exercise.

Confusion is created by the fact that IL-6 has been linked to cardiovascular disease,[35–37] morbidity and mortality,[102,103] sarcopenia, and physical frailty.[38–40] Ridker et al[37] found the highest rate of myocardial infarction in subjects who were in the highest quartile of plasma IL-6 concentrations. IL-6 was also linked to muscle atrophy and may be a cause of muscle wasting.[38–40,71] One possible explanation for this apparent paradoxical role of IL-6 is that IL-6 merely reflects or reacts to the presence of TNF-α.[104–106] That is, the IL-6 response to TNF-α is an attempt to initiate an anti-inflammatory response. Plasma TNF-α is correlated with plasma IL-6[104] and has been found to increase IL-6 in vitro.[106,107] Because TNF-α is apparently not required for exercise-induced IL-6 release,[74,78] it may be that the stimulus for IL-6 release helps to explain the apparent paradox.[35–37,99,100] Simply put, contraction-induced IL-6 may exert positive, anti-inflammatory actions, whereas IL-6 release in response to TNF-α may reflect disease, injury, or chronic infection.

Increased Physical Activity or Exercise Training

A rather impressive array of research is available to show that high levels of physical activity or exercise training elicit anti-inflammatory effects. Although there are dissenters,[45,47,67,107–109] several reports show the potential anti-inflammatory influence of increased physical activity or formal exercise training. Researchers employing cross-sectional designs regularly observe lower plasma IL-6,[42,110–114] TNF-α,[110,112,114] CRP;[6,14,18,112–119] increased IL-10;[42,43] and increased adiponectin levels[43] in physically active/physically fit individuals compared to physically inactive/low-fit individuals. Exercise interventions have also been shown to reduce in vitro inflammatory cytokine production[7,120] and other markers of systemic inflammation,[43,66,114,121–126] along with documented tissue-specific effects.[11,12,127,128] As an example of the latter, exercise training lowered skeletal muscle TNF-α,[11,12] IL-6,[11] and IL-1β[11] expression in older adults. It is of interest to note that periods of intensive training or overreaching did not elevate[123] and even decreased[14,129] biomarkers of inflammation.

In some studies, exercise combined with dietary restriction more effectively reduced visceral fat,[128] abdominal adipocyte size,[127] and markers of inflammation[66] than dietary restriction alone. Nevertheless, it appears that both surgical/dietary restriction-induced fat loss and exercise training, without fat losses, have positive influences on markers of inflammation.[23,43,64,66,67,109,121,130] It is not known to what extent the anti-inflammatory effects of exercise training contribute to the positive influence that exercise has on chronic disease, but promising new findings lead us to speculate that the anti-inflammatory influence of exercise could explain a significant portion of the therapeutic influence of exercise on chronic disease states.[13,131]

An attempt to find a consistent pattern among those studies showing no anti-inflammatory effects of exercise training[45–47,67,107,108,132] was unsuccessful. These researchers studied a range of age groups,[45,47,108] included overweight subjects and subjects with disease,[46,67,107,108] imposed long-term interventions[46,67] and short-term interventions,[107,108] and conducted population studies assessing the amount of leisure time physical activity.[47] One consistent finding among this group of studies was the lack of an adiponectin response to exercise training.[44–46,107,108] This is not particularly surprising

because adiponectin is strongly linked to fat mass[23] and may not change when weight loss is small.[46] However, short-term exercise training (4 weeks) has been shown to increase plasma adiponectin levels.[43] In addition, exercise training increased adiponectin mRNA expression in diabetic rats[133] and increased adiponectin receptor expression in mice.[134]

Anti-Inflammatory Influence of Exercise Training: Link to Body Fat?

There is evidence to suggest that exercise training-induced lowering of inflammatory biomarkers and relationships between physical activity and inflammatory biomarkers are linked to body fat or body mass index (BMI).[16,17,67,111,134] Hammett et al,[134] for example, reported that baseline associations between $VO_{2\ max}$ and inflammatory markers in female smokers were largely explained by differences in BMI. Furthermore, there were no additional reductions in inflammatory markers when these women completed a 12-week (3 days per week, 45 minutes per session) low-intensity (60%–70% estimated maximal heart rate) endurance exercise program. Additional evidence for the lack of an exercise-only anti-inflammatory effect was provided by a randomized control trial employing a large number of patients with documented osteoarthritis ($n > 200$).[67] Nicklas et al[67] found that exercise had neither an independent anti-inflammatory effect nor an additive effect when exercise was combined with dietary restriction-induced weight loss. These findings were surprising in light of the fact that these subjects completed an 18-month diet, exercise, or diet and exercise intervention period. Exercise has been shown to be effective as a combined therapy in other research, such that exercise had an additive anti-inflammatory effect when combined with statin treatment[135]—a cholesterol-lowering drug with potential anti-inflammatory properties.[25]

There is a growing body of evidence that exercise training interventions have anti-inflammatory effects independent of changes in body fat.[43,51,66,121,125,129] In contrast to the Nicklas et al[67] study described above, Giannopoulou et al[121] found that 14 weeks of moderate endurance exercise training (walking 3–4 days per week; 65%–70% $VO_{2\ peak}$) led to only slight weight/fat losses but lowered CRP levels to a similar extent (~15%) as diet alone or diet and exercise combined (–4.5-kg change in body weight). However, other inflammatory markers and adipokines were not substantially altered by any of the 3 interventions. Substantial anti-inflammatory effects have also been observed when short, intensive exercise interventions were employed. Oberbach et al[43] found that only 4 weeks of exercise training (60 minutes per day; 4 days per week) significantly reduced high-sensitivity CRP (hsCRP) and increased adiponectin in type 2 diabetics, subjects with impaired glucose tolerance, and subjects with normal glucose tolerance. There were slight, but significant, changes in BMI and body fat, but these authors argued that the changes in adiponectin and CRP were “disproportionally higher than expected from the improvement in percent body fat, $VO_{2\ max}$, and insulin sensitivity, suggesting additional beneficial effects of exercise on plasma concentrations of these parameters.”[43] **[*PAGE NUMBER?*]**

There are a number of cross-sectional studies showing the disconnect between body fat and the anti-inflammatory effects of high levels of physical activity.[14,115,116] For example, Tomaszewski et al[14] reported that both lean (BMI < 25 kg/m^2) and non-lean (BMI > 25 kg/m^2) ultra-distance runners had lower hsCRP levels than lean and nonlean untrained

subjects. Aronson et al[115] suggested that physical fitness has an important independent impact, such that hsCRP levels (n = 892) were decreased with increasing levels of fitness (quartiles) after adjusting for age, gender, tobacco use, BMI, diabetes and hypertension, lipid levels, and hormone replacement, anti-inflammatory drug, and statin use.

Greater weight could be given to the Nicklas et al[67] study described above because of high subject number and sound research design, but there are several interesting points of comparison that may help to explain the differences between conflicting studies. First, subjects in the Nicklas et al[67] study were allowed to opt for home-based exercise after the first 4 months. Roughly 36% of the subjects opted for some or all home-based exercise. Home-based exercise may not provide the same stimulus for physiological adaptation as supervised or group exercise,[136–138] but home-based exercise reduced inflammatory markers in other studies.[13] Second, baseline CRP levels were quite high (~6.5 mg/L) in the osteoarthritis patients in the Nicklas et al[67] study, and the relative change in CRP—even in the diet-only or diet and exercise treatment groups that lost large amounts of body weight—was relatively small (~3%). It is possible that patients with osteoarthritis do not respond in the same fashion as a healthy group of older patients. For example, CRP was reduced by roughly 35% in a small group of obese (BMI 35 kg/m^2) but otherwise healthy women who underwent a 2-year diet and exercise intervention.[139] In another study, an aggressive 2-week low-fat/high-fiber ad libitum diet and exercise program was shown to reduce CRP levels by 45% in postmenopausal women.[140] Declines in CRP concentration in short-term focused exercise training studies generally range from 15% to 50%.[43,121,140] Thus, although the Nicklas et al[67] study may provide an example of what can be expected when large groups of diseased patients are encouraged to exercise, focused exercise training frequently provides a significant anti-inflammatory effect.[7,12,13,43,66,121,122,129]

Tissue-Specific Responses

Fewer studies have been conducted to examine the tissue-specific anti-inflammatory response to exercise training. Greiwe et al[12] found that 12 weeks of resistance exercise training significantly reduced skeletal muscle TNF-α mRNA expression and TNF-α protein content in frail older subjects (mean age 81 years). In fact, training reduced these variables to the same level as the healthy young controls (mean age 23 years) and increased protein synthesis in inverse proportion to the change in TNF-α protein content. Exercise training-induced reductions in skeletal muscle inflammatory protein content were also reported by Gielen et al,[11] who found that 1 year of training, leading to a 30% increase in $VO_{2\ peak}$, significantly reduced skeletal muscle TNF-α, IL-6, and IL-1α content in men with coronary heart failure. It is of interest that these effects occurred without substantial corresponding changes in serum inflammatory markers.[11]

Greiwe and coworkers' contention[12] that training may blunt inflammation, enhance protein synthesis, and fight wasting disease in older subjects is supported by findings from several studies.[71,72,141,142] Lang et al[72] found that TNF-α blunted protein synthesis in both skeletal and heart muscle—largely by an impaired translational initiation. TNF-α is known to lower circulating insulin-like growth factor-1 (IGF-1),[141] reduce appetite,[143] and increase insulin resistance[144]—all of which could negatively affect muscle growth.

Bruun et al[65] recently found that a combination of diet and exercise training reduced macrophage infiltration into adipose tissue. Morbidly obese subjects (mean BMI 45.8 kg/m^2) were placed on a hypocaloric diet, designed to reduce body weight by 1% per week, and an aggressive exercise program (2–3 hours of moderate physical activity 5 days per week) for 15 weeks. Adipose tissue expression of macrophage markers CD68 and CD14 declined significantly compared to baseline measures (Figure 1), as did plasma CRP (~28%), IL-6 (~26%), and monocyte chemoattractant protein (~16%). Plasma adiponectin levels were significantly increased (~33%), but TNF-α was unchanged. Unfortunately, the study design does not allow us to distinguish between the influence of substantial fat loss and the influence of the aggressive exercise program. To our knowledge, there are no other published exercise intervention studies in which the macrophage infiltration of adipose tissue has been examined.

It has been suggested that macrophages residing in adipose tissue are responsible for the majority of adipokine production and that visceral adipose tissue is a more aggressive producer of inflammatory cytokines than other fat depots.[63,145–148] A potential mechanism for exercise training-induced anti-inflammatory effects that occur in the absence of whole body fat loss is a selective reduction in visceral adipose tissue.[128,149,150] Indeed, Giannopoulou et al[128] found that exercise and diet combined and exercise alone significantly reduced visceral adipose tissue mass; however, inducing significant total body fat losses with diet alone did not change visceral adipose tissue mass. There are researchers who reported that exercise did not augment visceral fat losses when combined with diet.[151,152] Nevertheless, the ability of exercise to reduce visceral fat, without influencing total body fat, could help explain exercise's anti-inflammatory effect. Weight loss by diet alone can be problematic, such that a significant amount of skeletal muscle mass can be lost when diet is not combined with exercise.[152]

Exercise and diet combined was also reported to significantly reduce abdominal adipocyte size, but this did not occur with diet alone.[127] It is generally accepted that reductions in abdominal fat significantly reduce disease risk.[62,151,153,154]

Inflammation and Training Adaptations

Inflammation appears to blunt protein synthesis,[12,72] which leads to the speculation that exercise training must first blunt inflammation before skeletal muscle hypertrophy can occur. This speculation is supported by novel research from Gielen's group,[13] but with a twist—Gielen et al[13] suggested that the anti-inflammatory responses were required before their subjects could make adaptations to endurance training. These authors found negative correlations between inducible nitric oxide synthase (iNOS) and cytochrome-c oxidase activity in coronary heart failure (CHF) patients who improved their $VO_{2\ peak}$ by 29% after 6 months of training. Their interpretation was that anti-inflammation must precede metabolic adaptation. That is, because the change in cytochrome-c oxidase was strongly correlated to $VO_{2\ peak}$, the reductions in iNOS, putatively reducing mitochondrial suppression, allowed aerobic adaptations in their patients. Adamopoulos et al[155] reported similar findings after training by CHF patients but did not observe an effect in normal controls, leaving open the possibility that these mechanisms may be active only in persons

with chronic disease. Finally, Sriwijitkamol et al[131] showed that 8 weeks of endurance training reversed the diabetes-induced suppression of "NF B inhibitors," which was concomitant with a 37% increase in insulin sensitivity and a significant decline in TNF-α. These novel and intriguing "which comes first" scenarios may further our understanding of the benefits of exercise's anti-inflammatory effects and underscore the importance of elucidating mechanisms to determine the role that these adaptations may play in chronic disease.

Inflammation and Aging: Effects of Exercise

Inflammatory markers are often increased with advancing age,[12,41,156] but the anti-inflammatory effects of exercise training do not appear to have an upper age limit. Samples taken from subjects with high physical activity levels or following exercise interventions show lower serum IL-6 concentration,[21,42,113] serum CRP,[112,113,157] LPS-stimulated inflammatory cytokine production,[7,9,10] and skeletal muscle TNF-α protein content and mRNA[11,12] in persons older than age 65. In fact, exercise has been shown to have anti-inflammatory effects in healthy older subjects,[7,122] subjects with coronary heart failure and coronary artery disease,[11,155,158] breast cancer survivors,[126] subjects taking beta-blockers,[114] and those with metabolic syndrome.[135] Therefore, the findings from several studies lead to the conclusion that neither age nor health status appear to limit the ability of exercise training to reduce inflammation.

Beharka et al[159] argued that age-associated differences in inflammation disappear when those with acute infections or other diseases are removed from the data set. Similarly, when we compared healthy physically active and healthy inactive younger and old subjects, we found that activity level was more important than age. Specifically, we found that physical activity level (physically active vs physically inactive) had a significant influence on CRP, LPS-stimulated cytokine production (Figure 2), and TLR4 expression, whereas age group (65–80 vs 18–35) had no effect on TLR4 or cytokine production and only a modest effect on CRP[10] (Figure 3). Older subjects who were physically inactive had somewhat higher CRP levels than physically inactive younger subjects, but obligate activity could help to explain these differences. Our younger subjects were students who walked a considerable distance during the school week to attend classes. That type/amount of physical activity would have significantly increased the activity levels of our inactive older population. Thus, the apparent age-related difference in CRP could be due, in part, to higher physical activity levels in the young group. With respect to the ability of exercise training to exert body fat–independent anti-inflammatory effects, the older physically active individuals with relatively high body fat had similar CRP and TLR4 levels as young inactive subjects with substantially lower body fat[10] (Figure 3). In a subsequent study, inactive younger and older subjects trained for 12 weeks. After training, CRP was reduced to the same level as groups of age-matched physically active subjects (unpublished data: Figure 4).

Potential Mechanisms for the Anti-Inflammatory Effect of Exercise

Physically active individuals have lower indexes of chronic inflammation, which reflects a reduced risk of developing metabolic syndrome, cardiovascular disease, and other related

disorders.[7,10,120,122,160] The anti-inflammatory actions of regular exercise have been well documented; however, the mechanism underlying these effects has not been elucidated.[7,161] Nevertheless, based on the current literature, several viable mechanisms exist. These potential mechanisms could directly or indirectly alter whole-body inflammation. The remainder of this section is devoted to further exploring the specifics of mechanisms for the anti-inflammatory influence of exercise training.

Anti-Inflammatory Effects of Exercise: Does It Take a Toll?

In work from our laboratory,[7,9,10,121,162] higher levels of physical activity or exercise intervention resulted in blunted inflammation and lower monocyte toll-like receptor 4 expression. Toll-like receptors (TLRs) are pattern recognition receptors, with TLR4 recognized as the primary signaling molecule for lipo-polysaccharide.[163,164] The TLR4 signaling activates innate immunity and other inflammatory processes.[164]

Our interest in TLR4 stemmed from the finding that 10 weeks of resistance exercise training blunted LPS-stimulated inflammatory cytokine production in whole-blood cultures from older women.[7] The details of our TLR work can be found in a recent review.[162] We found that TLR4 was lower in physically active young and old subjects compared to age-matched inactive subjects,[10] and TLR4 was lower after 12 weeks of exercise training in previously inactive younger and older subjects.[122] In fact, the training reduced TLR4 to levels similar to subjects who had been physically active for several months to years (Figure 5). We also found that TLR4 expression was related to LPS-stimulated production of inflammatory cytokines.[7,10] Although it appears that training-induced declines in TLR4 may help to explain the training-associated blunting of mitogen-stimulated cytokine production, it is not, at present, known to what extent TLR4 downregulation contributes to the anti-inflammatory actions of exercise training.

Inflammatory Monocytes

Blood monocytes have the capacity to influence whole-body inflammation by producing and releasing pro- and anti-inflammatory cytokines in response to a variety of endogenous and exogenous ligands.[91,120,164,165] Recent evidence suggests that a subset of monocytes, referred to as inflammatory monocytes (CD14+CD16+), is responsible for the majority of monocyte-derived pro-inflammatory cytokines.[91,166] Inflammatory monocytes also express higher levels of TLR2 than classical (CD14+CD16–) monocytes,[167] are higher in patients with rheumatoid arthritis,[167] and are expanded in sepsis.[168]

Acute exercise (cycling at 400 W for 60 seconds) was reported by Steppich et al[166] to induce a several-fold increase in the circulating inflammatory monocyte number. Because some of the increase can be blocked by propanolol, the authors attributed the changes to an epinephrine-induced release of inflammatory monocytes from the marginal pool.[166] To our knowledge, no published studies have examined the effect of exercise training on inflammatory monocytes, nor are we aware of reduced inflammatory monocyte concentration or activity being used as a means of explaining the anti-inflammatory effects of exercise. However, in a recent study from our lab, we found that older physically active individuals had a lower number of circulating inflammatory monocytes than physically

inactive subjects of the same age (unpublished data). We are in the process of determining whether exercise training can lower inflammatory monocyte concentration in previously sedentary older subjects. The underlying stimulus by which chronic exercise training could alter monocyte phenotype is not known, but it has been reported that the inflammatory monocyte population is nearly depleted by high-dose glucocorticoid treatment.[169] Therefore, it is possible that pulsatile changes in glucocorticoids associated with daily exercise sessions have a similar effect on inflammatory monocytes.

Th1/Th2 Balance

Type 1 helper T cells (Th1) play an important role in mediating the actions of the innate immune system. The local and systemic actions of blood monocytes and adipose tissue macrophages are controlled by cytokines, released from helper T cells (Th). Type 1 helper T cells activate components of the innate immune system by releasing type 1 cytokines: IFN-γ and IL-2.[93,161,170] Type 2 helper T cells (Th2) activate selective components of the adaptive immune system by releasing type 2 cytokines: IL-4 and IL-10.[9,93,170,171] Activation of Th1-mediated immunity (blood monocytes, peripheral tissue macrophages, and other phagocytes) enhances the leukocyte inflammatory capacity; however, activation of Th2 suppresses inflammation by activating the adaptive immune system.

Both acute exercise and a short period of intensified training have been reported to induce Th2 dominance and decrease the circulating concentration of Th1 cells, thus decreasing inflammatory capacity.[161,170,171] Steensberg et al,[171] for example, reported a significant decline in Th1 cells after 2.5 hours of treadmill running (75% $VO_{2\ max}$). The shift in Th1:Th2 was largely due to changes in Th1 because the Th2 cells were unchanged with exercise.[171] We believe it is possible that the inflammatory capacity of blood monocytes and peripheral tissue macrophages is decreased following a period of exercise training due to alterations in the relative balance of Th1 and Th2 cells, such that anti-inflammatory processes are favored.

Adipocytes

Exercising individuals tend to experience a redistribution of body composition, such that their adipose tissue atrophies.[61,95,172] Adipocyte atrophy has been linked to a reduction in the inflammatory capacity of adipose tissue.[172] Adipose tissue is a rich, metabolically active organ that has far-reaching physiological influences.[94] Obesity and physical inactivity are believed to negatively alter the coordinated regulation of energy balance and other processes.[67,93,94] For instance, IL-6 release from the adipose tissue of obese patients increased monocyte and macrophage production of inflammatory cytokines (IL-6, TNF-α, IL-1β, and IL-8).[94,95]

It was originally believed that adipocytes were the primary source of inflammatory cytokines released from adipose tissue; however, recent evidence suggested that adipose tissue macrophages produce all of the TNF-α and roughly one third of the IL-6 from adipose tissue.[95,173,174] Accumulation of adiposity is associated with an increased migration of monocytes from the blood to adipose tissue, which further exacerbates inflammatory cytokine release.[95,173,174] Monocyte infiltration of adipose tissue is minimized in nonobese

individuals by the hormone ghrelin, suggesting that ghrelin could have anti-inflammatory effects.[95,174,175] It is not known whether ghrelin interacts with the TLR4 pathway or an alternate pathway to induce its anti-inflammatory action. Obese individuals have low plasma ghrelin and elevated plasma leptin, a combination that stimulates a rapid transmigration of monocytes from the blood to adipose tissue.[95,175,176] Given the regulatory influence of leptin and ghrelin on monocytes, it is possible that these proteins are responsible for the anti-inflammatory effects of exercise-induced weight loss. Adipocyte production and release of leptin can alter inflammation at both the local (ie, adipose tissue and recruitment of monocytes) and systemic levels (alteration of blood monocytes).[177] Excessive release of TNF-α from adipose tissue macrophages during weight gain is believed to be partially responsible for the development of insulin resistance, which, incidentally, may be a response to prevent additional weight gain.[95,177,178] Exercise training is associated with a redistribution of body composition, such that adipocyte atrophy occurs. Adipocyte atrophy has been reported to decrease monocyte accumulation in adipose tissue and subsequent release of TNF-α.[95,177,178] Reduction in TNF-α release would be consistent with an anti-inflammatory effect localized to adipose tissue.

Heat Shock Proteins

The anti-inflammatory effects of exercise training may be linked to the production and release of heat shock proteins (HSP) during a period of exercise training.[165,179] Repeated bouts of eccentric exercise have been shown to increase intramuscular stores of heat shock proteins, which may be responsible for skeletal muscle-specific anti-inflammatory effects following a period of chronic resistance exercise training.[180,181] Acute bouts of eccentric exercise damage skeletal muscle, which results in a release of HSP60 and HSP70 into the circulation.[182,183] During repeated bouts of eccentric exercise, separated by 2 weeks, skeletal muscle inflammatory cytokine release decreases,[180,181] which is consistent with an anti-inflammatory adaptation. Heat shock proteins have been implicated as a possible cross-tolerance signal, which influence blood monocyte/peripheral macrophage LPS-stimulated inflammatory cytokine production and hepatic acute phase protein production.[165] Pretreatment of monocytic cell lines in vitro with HSP60 significantly decreased cellular responses to LPS and cell surface expression of TLR4, HLA-DR, and CD86[184]—suggesting that HSP can induce cross-tolerance against LPS at the systemic level. Therefore, an increase in intramuscular HSP may provide protection against future eccentric insults and tolerize monocytes, which may explain local and systemic anti-inflammatory effects. Heat shock protein may exert its effects through TLR or another yet to be identified pathway. Evidence of exercise-induced tolerance to endotoxin (LPS) exists, such that Starkie et al[100] found that both 3 hours of cycling exercise (75% $VO_{2\ max}$) and IL-6 infusion blunted subsequent TNF-α responses to endotoxin infusion.

Reduction of Local Hypoxia/ Cross-Tolerance

Exercise training has been reported to decrease local hypoxia and ischemia, which may reduce inflammation.[185,186] Hypoxia and ischemia cause the release of intracellular substances (ie, organelles, heat shock proteins, ATPγ **[*PLS. SPELL OUT*]**, etc) that may play a role in promoting inflammation.[185,186] Ischemia and hypoxia are physiological responses associated with both exercise-induced damage to skeletal muscle and adipocytes.

Kariko et al[186] speculated that ischemic products have the capacity to induce a cross-tolerance with TLR that is similar to endotoxin tolerance (induced by LPS or another ligand). Ischemia is associated with tissue damage, release of intracellular proteins, and exposure of circulating blood monocytes and tissue macrophages to endogenous ligands.[185] Ischemia also occurs following damage to skeletal muscle as blood supply is disrupted, and thus the effect may be similar to ischemic stroke.

Kaufmann et al[185] reported that tissue damage resulted in the release of ATPγs from damaged cells, which stimulated monocyte transmigration from the blood and decreased the ability of TLR2 and TLR4 to respond to lipoteichoic acid and LPS, respectively. Thus, ATPγ has been shown to induce cross-tolerance of TLR2 and TLR4 against other endogenous and exogenous ligands.[187]

Accessory Proteins

In our previous work, we found that the TLR4 signaling pathway may play an important role in mediating exercise training-induced changes in LPS-stimulated inflammatory cytokine production.[7,10] The TLR accessory proteins play a critical role in mediating TLR responsiveness to LPS and other ligands, both endogenous and exogenous. Soluble CD14 (sCD14) has a similar molecular structure as membrane-bound CD14; however, it allows cells that lack CD14 (ie, vascular endothelial, smooth muscle cells, adipocytes, skeletal muscle cells, etc) to use TLR4 pathways to respond to the challenge from various ligands.[187] Soluble CD14 has been shown to increase cellular responses to LPS both in vivo and in vitro.[188] Inflammatory atherosclerotic disease has been reported to significantly elevate plasma sCD14 concentration and markers of chronic inflammation compared to normal individuals.[189–191] Plasma sCD14 concentration has also been linked to the pathophysiology of other inflammatory disease states.[192–195] To our knowledge, only 1 group has examined the effect of exercise training on sCD14.[192] Exercise training did not alter sCD14; however, these researchers employed a modest subject number (n = 18) and only 8 weeks of exercise.[192]

Lipopolysaccharide binding protein (LBP), an accessory protein required for LPS binding to CD14 or sCD14,[196] has a similar link to inflammatory disease as sCD14.[187] However, there is no research to document the LBP response to exercise or exercise training. The lipopolysaccharide binding protein is also an acute phase protein,[187] and circulating levels could decrease with training, in a similar fashion to CRP. LBP:sCD14 may also play a role, such that Stoll et al[197] found that lower LBP:sCD14 increased LPS-stimulated cellular activation.

Summary and Future Directions

Previous research provides evidence that a physically active lifestyle is associated with lower whole-body inflammatory biomarkers.[42,110–114] The anti-inflammatory actions of chronic exercise training are evident after as little as 2 to 12 weeks of supervised exercise training.[7,43,122,140] Anti-inflammatory effects of exercise training have been reported by our group and several others,[7,43,66,114,120–122,124–126] but a number of researchers, conducting exercise intervention studies, report minimal or no anti-inflammatory effect of

exercise.[45,67,107,108,132] The interpretations are complicated by results from cross-sectional studies showing that when covariates (eg, BMI, body fat, etc) are included in the analysis, the inverse relationship between physical activity and inflammatory biomarkers disappears.[16,17,111,132] Although the weight of evidence appears to be in favor of a body fat–independent influence of increased physical activity, more research is needed to settle this debate. Unique designs that can separate the influence of diet and exercise—such as those that institute dietary restriction-induced weight loss after an extended period of exercise training without weight loss—are required to solve this problem. Also, use of animal models may be an effective way to control key independent variables that may influence the degree of reduction in whole-body inflammation following a period of exercise training. These study designs may also be useful in identifying the mechanism(s) by which chronic exercise training exerts its effects.

In this review, we presented a number of mechanisms that may underlie the anti-inflammatory effects of chronic exercise training. Among these, our group has published descriptive findings showing that subjects with high physical activity level had significantly lower TLR4 expression.[9,10] We also found that exercise training reduced TLR4 expression in previously sedentary subjects.[7,122] The next logical step is to complete a detailed mechanistic study of the toll-like receptor pathway and attempt to identify how its intermediates are changed following exercise training. It is possible that release of endogenous ligands (ie, heat shock protein, ATPγ, etc) from contracting skeletal muscle or atrophied adipose tissue may mediate changes in TLR pathway intermediates. Other possible mechanisms of the anti-inflammatory influence of exercise that we are presently exploring include the influence of exercise training on Th1:Th2 and inflammatory monocytes. To our knowledge, none of the above mechanisms has been scrutinized as possible explanations for the anti-inflammatory actions of exercise training. We proposed several potential mechanisms in this review but acknowledge that the anti-inflammatory influences of exercise training are likely mediated by a complex interaction among multiple pathways.

Identification of the mechanism(s) underlying the anti-inflammatory effects of exercise training is important because these pathways may serve as targets for future pharmaceutical treatments. It is also possible that a better understanding of the mechanisms that are responsible for exercise-induced lowering of whole-body inflammation may allow physicians and scientists to develop more effective exercise countermeasures. Nevertheless, a number of important research questions need to be addressed to develop a comprehensive understanding of the link between low-grade chronic inflammation and physical activity.

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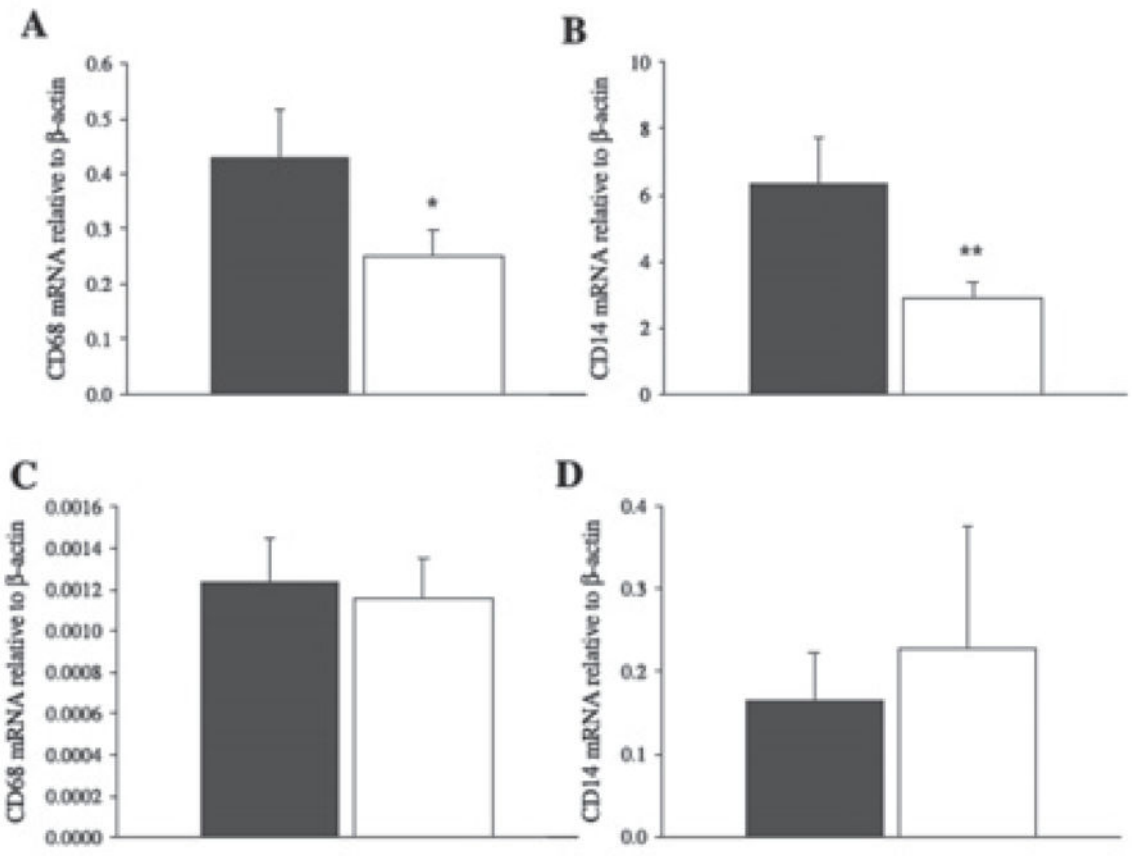

Figure 1.

CD68 and CD14 expression changes in adipose tissue (n = 19; panels A and B, respectively) and skeletal muscle (n = 14; panels C and D, respectively) biopsies obtained from obese patients before (dark bars) and after (open bars) a 15-week diet and exercise intervention leading to significant fat losses in body fat. Mean ± SE; *P < .05 and **P < .001 compared to baseline.[65]

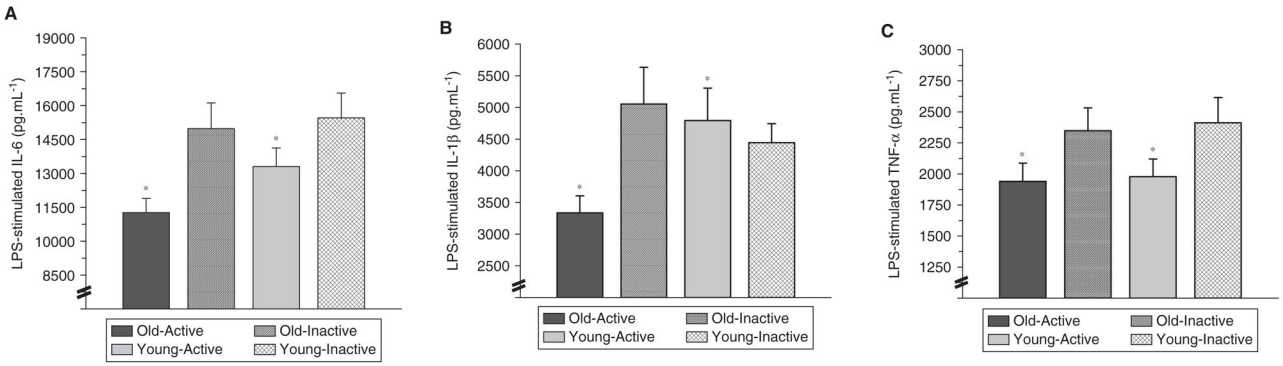

Figure 2.

Lipopolysaccharide (LPS)–stimulated (A) interleukin-6 (IL-6), (B) IL-1β, and (C) tumor necrosis factor-alpha (TNF-α) production from whole-blood cultures that were obtained from young inactive (18–35 years; n = 19), young physically active (n = 21), old inactive (65–80 years; n = 21), and old physically active subjects (n = 23).

*P < .05 for group (physically active vs inactive).[10]

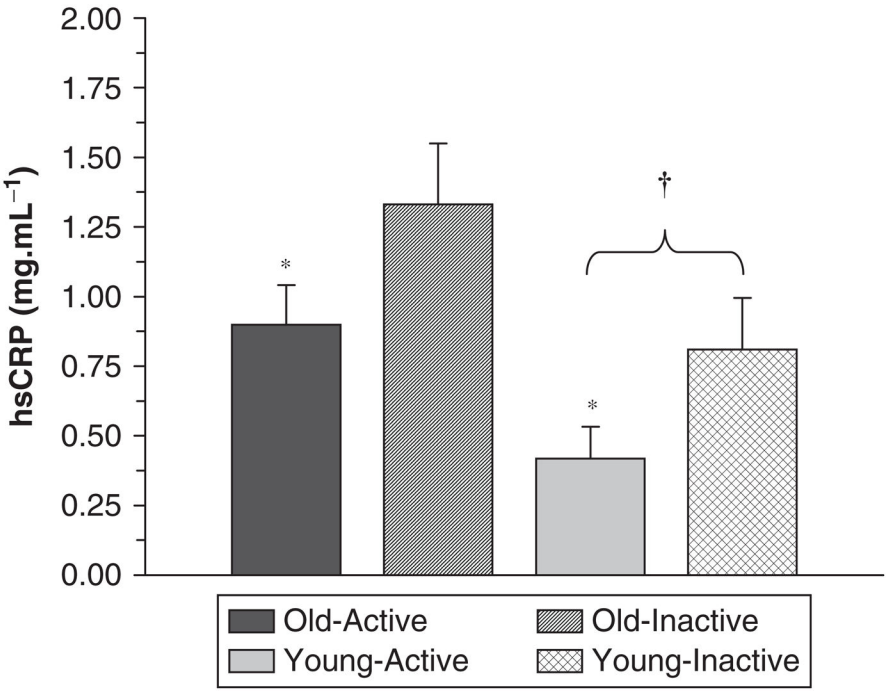

Figure 3.

High-sensitivity C-reactive protein (hsCRP) levels (mg/dL) from young inactive (18–35 years; n = 19), young physically active (n = 21), old inactive (65–80 years; n = 21), and old physically active subjects (n = 23). *P < .05 for group (physically active vs inactive). †P < .05 (age effect; young lower than old).[10]

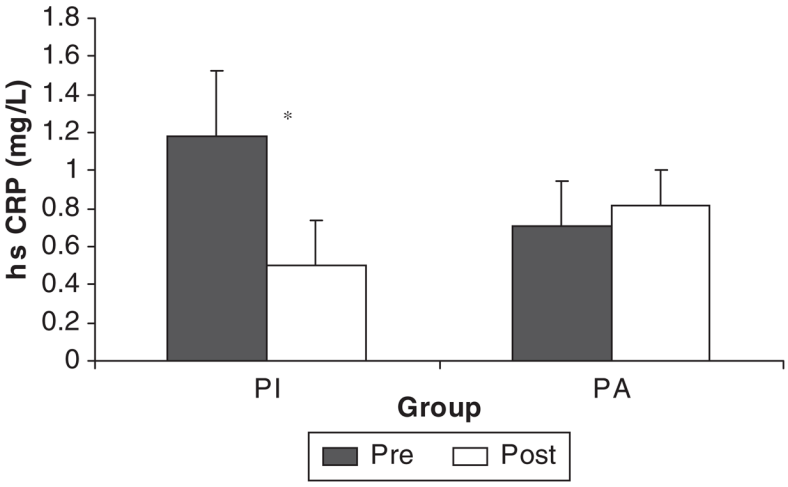

Figure 4.

High-sensitivity C-reactive protein (hsCRP) before and after 12 weeks of endurance (20 minutes of treadmill walking, 3 days per week) and resistance exercise (2 sets of 8 exercises, 3 days per week) training in previously inactive subjects (PI) and a control group of physically active (PA) subjects who maintained normal activity. Data collapsed across age groups (PI, young physically active and old physically inactive combined; PA, young physically active and old physically active) (unpublished data). *Significant difference after training for PI ($P < .05$).

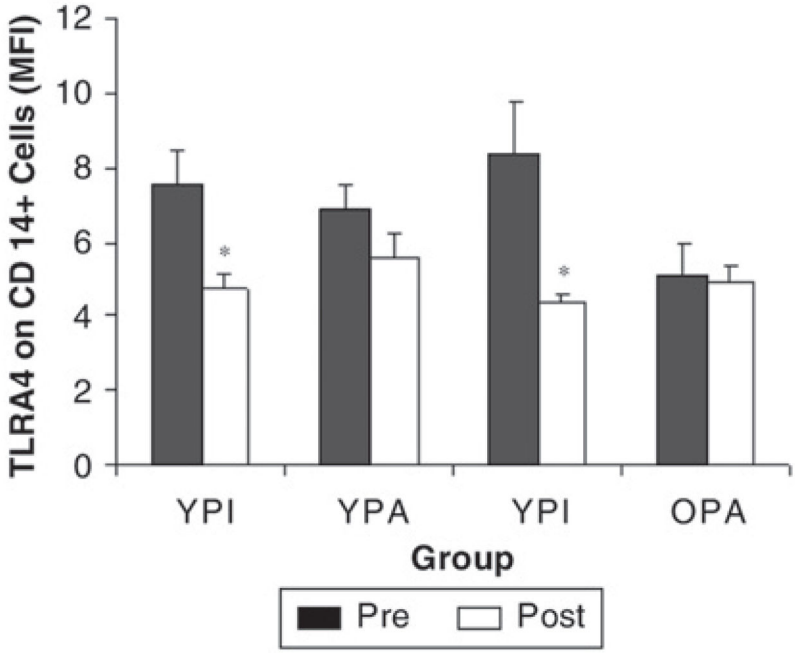

Figure 5.

$CD14^+$ cell surface expression of TLR4 from young (18–35 years) and old (65–80 years) physically inactive (YPI and OPI) and young and old active (YPA and OPA) subjects. Measurements were made before (PRE) and after (POST) 12 weeks of endurance and resistance training for physically inactive (YPI and OPI) or before and after 12 weeks of maintaining a physically active lifestyle for physically active subjects (YPA and OPA). That is, the physically inactive subjects trained for 12 weeks, and the physically active subjects maintained their activity levels as an active control group.[122] *$P < .05$ for training effect.[122] MFI, mean fluorescence intensity.