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Original Article

Physical activity as a non-pharmacological method for reducing systemic inflammation

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Abstract
Thepositive influence of physical activity on the human body is clear and irrefutable. Protection against cardiovascular, metabolic and autoimmune diseases, cancers,and psychiatric disorders are all among the advantages that can be mentioned. As low grade systemic chronic inflammation plays a crucial role in the pathogenesis of the abovementioned diseases, it is very possible that physical activity prevents their occurrence by reducing inflammation. In this article, we describe the influence of physical activity on systemic inflammation. We discuss aerobic and resistance training separately. We pay attention to circulating pro- and anti-inflammatory cytokinessuch as IL-1, TNF-α,IL-6, IL-8, and IL-10, the adhesion molecules, leukocytes, the levels of adipokine and leptin,the bioavailability of nitric oxide, and the Bacteroidetes to Firmicutes ratio in the gut. We also discuss the possible mechanisms responsible for reducing systemic inflammation, focusing on the positive influence of physical training on the adipose tissue, the muscles, the endothelium of the vessels, and the microbiome of the gut. We conclude that the influence of resistance training on the inflammatory status is not obvious and that aerobic activity reduces inflammation more clearly. However, the combination of both types of training appears to be the most advantageous.The long-term positive effects of physical activity outweigh the temporary increase of the pro-inflammatory influence. It is not obvious what is the main mechanism responsible for the reduction of inflammation. Probably the adipose tissue, the muscles, the endothelium of the vessels, and the microbiome cooperate and complement each other.We finish by presenting the recommendations of a number of organizations as to the length and frequency of physical activity.
Key words: **aerobic activity, resistance training, cytokines, C-reactive protein**

Introduction

There is indisputable evidence that regular physical activity (PA) reduces the risk of many diseases such as obesity, diabetes,metabolic syndrome, arterial hypertension, ischemic heart disease, depression, anxiety, dementia, some autoimmune disorders, and certain types of cancer (Ertek& Cicero, 2012; Ströhle, 2008; Potter et al. 2011). Studies confirm its positive influence on the lipid profile, insulin resistance, the function of the endothelium, and the increased number of epithelial progenitor cells. Regular physical activityincreases adipose tissue sensitivity to epinephrine-stimulated lipolysis, increases the density of bones, reduces appetite,and leads to the enhanced release of satiety hormones (Ertek& Cicero, 2012). As low grade systemic inflammation plays an important role in the pathogenesis of many diseases, one of the reasonsphysical activity brings so many benefits may beits positive effect on the inflammatory status of the organism. Physical inactivity leads to obesity, endothelial dysfunction, and negative changes in the microbiome which may eventually stimulate systemic low grade chronic inflammation and increase the risk of inflammation-related diseases.

The severity of inflammation may be assessed by measuring the plasma level of the main marker of inflammation – C-reactive protein (CRP).Circulating cytokines such as IL-1, IL-6, IL-10, TNF-α,receptors for the aforementioned cytokines, and T-lymphocytes with the CD3+, CD4+, or CD8+ phenotype may also be measured. IL-1 and TNF-α are the main pro-inflammatory cytokines, IL-10 is anti-inflammatory, and IL-6 secreted by myocytes appears to be anti-inflammatory, whereas IL-6 secreted chronically by adipose tissue appears to be pro-inflammatory.

In this article, we present the positive influence of PA on inflammation markers and discuss the possible mechanisms of this effect.

Effect of training on mediators of inflammation

The influence of PA on inflammation should be considered in two ways: the interim effects during and shortly after exercise, and the long-term effects of regular training. During physical exertion and immediately after stopping, a significant increase in the concentration of inflammation markers is observed(Nieman, 1997). The level of IL-6 increased up to 80 times and IL-8 up to 10 timesin the blood of well-trained participants after a

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marathon run (Suzuki et al., 2003).In the blood of the 308km ultramarathoners, a significant increase of CRP, IL-6, and also anti-inflammatory IL-10 was detected(Shin & Lee, 2013).Although an ad hoc increase in inflammation markers may be significant, its long-term impact clearly prevails over the ad hoc effects. Regular PA contributes to the improvement of the profile of inflammatory molecules inplasma. Pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, or CD3+ and CD8+ T-lymphocytes are decreased. The plasma level of anti inflammatory IL-10 is increased(Abd El-Kader & Al-Shreef, 2018; Abd El-Kader & Al-Jiffri, 2019). Also,the CRP levels in people who exercise regularlyis decreasedwhen compared with the CRP levels of people who do not (Fernandes, 2018).Plaisance &Grandjean(2006) reviewed 12 cross-sectional studies and found thatphysically active adults have CRP concentrations 19%–35% lower than those who are less active. These results are also supported by a systematic review by Kasapis&Thompson (2005).

Aerobic training

There are two types of physical activity: aerobic and resistance training. As their influence on inflammation differs, we discuss the two separately.

In the population of patients practising aerobic training, a significant reduction of systemic inflammation has been shown.In most of the studies,the patients performedthree trainings per week for about 40–60 minutes remaining in the range 60%–80% of the maximum heart rate (HRmax).In one of the studies, after six months of such regular activityon a treadmill, there was a significant decreasein the concentration of circulating cytokines and cells by: 32.7% TNF-α, 31.8% IL-6, 32.1% CD3+, 21.9% CD4+, 33.7% CD8+, and a 24.3% decrease of the CD4+/CD8+ ratio. The researchers also observed an increase of anti-inflammatory IL-10 by 28.4% (Abd El Kader & Al-Shreef, 2018).In another study, the group of participants consisted of the elderly with sleep disturbance. Six months of aerobic trainingin this population caused a decrease in theconcentration of TNF-α by 36.8% and IL-6 by 40.0%. IL-10 increased by 36.3%. Apart from the reduction of the inflammation,asignificantimprovementin the quality of sleep was observed (Abd El-Kader & Al-Jiffri, 2019).Another studywas conducted on people who were overweight or obesewho trainedon a treadmill three times a week for 60 minutes for four weeks. Although there was no change in body weight or fat mass, the level of TNF-α decreased, which indicates that PA may improve the inflammatory status of the organism independently of a change in fat mass. However, in this study,the CRP and adiponectin levels did not change significantly (Koh & Park, 2017).In the study conducted by Alhindawi CRP levels decreased significantly in healthy postmenopausal women after 14 weeks of aerobic training and the changein CRP levels was positively correlated with the reduction in body mass and body fat (2013).

Resistance training

The influence of resistance training on the inflammatory status is not so obvious. There are many studies concerning this topic and the results are inconsistent.In a study lasting 12 weeks,participantsperforming resistance training were divided into three groups depending on the training intensity. The participants lifted weights of a different mass and with a different number of repetitions.In each group,after 12 weeks of training, there was a significant increase of IL-8, sTNFR1 and IL-1Ra, but only in the male participants (Forti et al., 2016).In another study,young men (20–30 years old) performedtraining very similar to the training described above, but fornineweeks. Researchers observed a decrease in IL-6 and an overall increase incirculating IL-8. Other measured molecules,such as sTNFR1 and IL-1RA, indicated no significant changes (Forti et al., 2017).In the research cited in the aerobic training chapter (Abd El-Kader & Al-Shreef, 2018), the second group of participants performed resistance training three times per week for six months. Also, in this secondgroup, the concentration of circulating cytokines such as TNF-α and IL-6, the number of blood T-lymphocytes with CD3+, CD4+, CD8+ phenotype, and the CD4+/CD8+ ratio all increased.

Conflicting data about the impact of resistance training on the levels of different inflammation markers come from several meta-analyses (Calle & Fernandez, 2010; De Salles et al., 2010). This may be explained by the number of variables associated with the studiessuch as exercise protocol andtime intervals of blood sampling.Despite these differences,the positive influence of resistance training on the risk of low grade inflammation related diseases, such as cardiovascular disease and type 2 diabetes,appears to be conclusive(Calle & Fernandez, 2010).

Comparison of both types of training

Based on the citied studies and reviews, there is a clear advantage of aerobic training in the reduction of low grade chronic inflammation. In this form of training,a decrease in circulating CRP, IL-6, TNF-α, and the T lymphocytes count was clearly visible. In addition,an increase in anti-inflammatory IL-10 was observed in some studies.In long-term resistance training, a significant decrease inthe CRP level was observed, however, the influence of resistance training on other markable cytokines related to inflammation is equivocal. Nevertheless, there are other benefits of resistance training that are worth paying attention to, namely a reduced risk of low grade inflammation related diseases, such as atherosclerosis, obesity, and insulin resistance (Koh & Park, 2017).

Moreover, combining the two types of training may be beneficial, especially when performing bothtypes of training during one training session(Stewart et al., 2007; Ihalainen et al., 2017).

How physical activity affectslow grade chronic inflammation Most research focuses on adipose tissue as the organ that regulates systemic inflammation, however, PA also influences inflammation by affecting the muscles, the endothelium of the vessels, and the microbiome of the gut (Fig.1).

Microbiome of the gut

The human microbiome is defined as the unity of symbiotic microorganisms, mainly bacteria and fungi, which colonize the gut. The microbiome is involved in digestion, absorption, epithelial development, barrier function, and the activity of the immune system. Therefore,the microbiomeinfluences metabolism and trophism and is responsible for immunomodulation(Monda et al., 2017). Moreover,various metabolites and signalling molecules produced by gut microorganisms, such as SCFAs (short chain fatty acids), can activate the vagal afferent receptors of the enteric nervous system (Forsythe, Bienenstock& Kunze, 2014). These signals are propagated by the nucleus of the solitary tract to various projection regions, such as the limbic structures, which are important for mood and behaviour.

There are a variety of genera and species, both desirable and undesirable, that occur in different quantitative ratios and with different activities. Included among the desirable phyla are Bacteroidetes and the genera of Bifidobacterium, Lactobacillus,andAllobaculum. Included among the undesirable phyla is the phylum of Firmicutes including the genus of Clostridium. Many authors believe that the ratio of Bacteroidetes to Firmicutes is the most important.

The products and metabolites of the microbiome affect the activity of the immune system mainly by the induction of regulatory T cells, however, signalling molecules such as SCFAs can also influencethe activation of neutrophils and monocytes (Belkaid& Hand, 2014). There is a correlation between specific species of gut bacteria and the type of released cytokines, both pro- and anti-inflammatory such as IL-1β, IL-18, IL-6, TNF-α, IFN, IL-8, IL-10, IL-4, and TGF-β(Mendes, Galvão& Vieira, 2019). Therefore, the microbiome is importantin maintaining the balance between pro- and anti-inflammatory circulating cytokines.It is believed that the microbiome takes control of systemic inflammation. Each person has a unique, personalized microbiome,and evidence suggests that different factors can determine changes in the gut microbiota.The composition of the microbiome differs significantly between samples from individuals with different states of health and disease (Ursell et al., 2012). The study byRizzetto et al.(2018)proves a correlation between microbiome modifications and the frequency of some autoimmune diseases such as type 1 diabetes (Costa et al., 2016), systemic lupus erythematosus (Zhang et al., 2014),and multiple sclerosis (Chen et al., 2016).

Physical activityis one way to regulate the composition and activity of the microbiota. Intense and prolonged exercise can negatively influence the microbiome as it causes lower blood flow and increases body temperature, which both lead to intestinal barrier disturbances. This kind of activity induces secretion of pro-inflammatory cytokines (Feng et al., 2018; Clark & Mach, 2016). However, in the long term, the influence of PA is unequivocally beneficial. It has been shown that regular endurance training enhances the diversity of the gut flora and improves the Bacteroidetes to Firmicutes ratio (Monda et al., 2017).Similarly, in other studies, regular PA led to an increase in the number of species among the Firmicutes phylum, but also improved the relationshipbetween those species and Bacteroidetes (McFadzean, 2014; Sohail et al., 2019).Evans et al. (2014) found an inverse correlation between the distance run by mice and the Bacteroidetes to Firmicutes ratio. In the study by Heinzel et al. (2020),a group of physically inactive patients were examined and showed a Firmicutes-enriched enterotype. Ina population of obese children, adisadvantageous Bacteroidetes to Firmicutes ratio was observed(Riva et al., 2017). Interestingly, PA initiated in childhood is more effective in forming the correct microbiome (Mika et al., 2015). Apart from the direct impact on the microbiome, PA contributes to reducing body mass, which also improvesthe Bacteroidetes to Firmicutes ratio (Evans et al., 2014).A moderate level of PAappears to be the most beneficial for the microbiome (Galle et al., 2020).

Endothelium of the vessels

The endothelium performs many functions in the organism, such as blood tension control, haemostasis blood clotting, andthe secretion of many active molecules with the most important one being nitric oxide (NO). This molecule (NO), through its vasodilative effect, prevents platelets and leukocytes from adhering to the vascular wall (Li &Forstermann, 2000). Moreover, its anti-proliferative and anti-oxidant functionsplay an important role in coronary and pulmonary circulation (Lugnier, Keravis&Eckly-Michel, 1999; Gryglewski et al., 1998). In some diseases, the activated endothelial cellsstart to produce IL-1, IL-6, chemokines, and adhesion molecules, thereby inducing inflammation (Romano et al., 1997). Furthermore, previously induced systemic inflammation can stimulate the transcription factors in the endothelium such as AP 1 and NF-κB. Those proteins upregulate the expression of pro-inflammatory cytokines,such as IL-1 and TNF α(Blake &Ridker, 2002; Mizuno, Jacob & Mason, 2011; Kempe et al., 2005). Research shows that endothelial cells can also secrete pro-inflammatory IL-8, IL-25, and IL-33 (Opitz et al., 2005; Yang, Chang & Wei, 2016). Consequently, endothelial cells can have a persistent influence on inflammation.

Regular PA has been shown to reduce endothelial dysfunction markers such as adhesion molecules, E-selectin, TNF-α, and IL-6 (Abd El-Kader & Al-Shreef, 2019).This improved endothelial function is mainly due to the increased availabilityof NO (Taddei et al., 2000; Nyberg et al., 2012; Hambrecht et al., 2003). In one study, a significant increase inthe level of NO by 35.2% after 12 weeks of resistance training was observed (Tomeleri et al., 2017). PA contributes to the upregulation of the endothelial NO synthase by increasing the phosphorylation of this protein.Resistance training can induce the increase of NO synthases by up to 140 percent (Macedo et al., 2016). The most noticeable positive influence of PA on NO synthesis is observed in groups of people with endothelial dysfunction(Green et al., 2004).

As described above, PA significantly increases the plasma level and bioavailability of NO, which is the main factor contributing to the reduction of inflammation within the endothelium,thus protecting against diseases such as hypertension and atherosclerosis (Putnam et al., 2016; Yang, Chang & Wei, 2016).

Adipose tissue

The correct amount of adipose tissue (AT) in the human body is within the range of 8%–25% of body mass for men and 21%–36% for women. Naturally, such a large mass of tissue has a very large impact on the entire body. An excess of adipose tissue, especially abdominal, is associated with mortality and metabolic diseases (Pischon et al., 2008). AT performs many functions, such as thermoregulation, isolation, energy storage, detoxication, and secretion. Molecules secreted by this kind of tissue are named adipokines. Among them are TNF-α, IL-1, IL-6, IL-10,and growth hormone (Fantuzzi, 2005).

Studies have proven that obesity,and even being overweight, favoursthe secretion of pro-inflammatory cytokines, which leads to systemic inflammation and diseases connected with it (Bluher, 2009; Yudkin, 2003; Trayhurn& Wood, 2005).In addition, physical inactivity stimulatesthe secretion of pro-inflammatory adipokines. The plasma levels of IL-6 and sTNFR1 are significantly increased (Vendrell et al., 2004).Also TNF α (Tzanavari, Giannogonas&Karalis, 2010) and IL-1B secretion is positively corelated with an excess of adipose tissue (Trayhurn& Wood, 2005). In the study by Park et al.(2005),circulating CRP was almost 400 percent higher, TNF-α was 50 percent higher, and IL-6 was 30 percenthigher in the group of obese subjects when compared with the group of non-obese subjects. Obesity, mainly through secreted adipokines, is an important risk factor of diabetes, atherosclerosis, hypertension, insulin resistance, end-stage renal failure, and all after-effects of these diseases (Wisse, 2004). Moreover, cytokines secreted by the AT, mainly IL-1B, IL-6, and TNF-α compose a tumour microenvironment. Tumours caused by AT-related inflammation,such as breast, gastric, colorectal, or ovarian cancers, most often arise intissuesadjacent to AT or in common anatomical places(Deng et al., 2016; Grivennikov, Greten& Karin, 2010).Furthermore, inflammation promotes metastasis, which is the major causeof deathamong people with cancer (Hanahan & Weinberg, 2011).

The relationship between adipose tissue and physical activity is bidirectional. The blood flow in adipose tissue during PA is augmented by up to 300 percent(Karpe et al., 2002; Thompson et al., 2012).This is a merit of fatty acid mobilization (Horowitz, 2003; Al Mulla, Simonsen & Bulow, 2000)and increased metabolism of glucose and lactate(Thompson et al., 2012). In connection with increased energy demands,PAinitiatesan energy deficit,which contributes to the loss of body mass (Magkos et al., 2009).A reduction in mass of and the number of adipocytes(Mauriege et al., 1997; You et al., 2004)is accompanied by changes infat distribution, mainly a decrease invisceral adipose tissue (Schwartz et al., 1991; Ross& Bradshaw, 2009).A few studies have examined which type of intervention is the most advantageous in the context of visceral adipose tissue reduction and the conclusion was that at least 10 METs×hour per week of aerobic exercise was proven to be the most beneficial. This is explained by adrenergic activation and its influence on visceral AT(Chaston& Dixon, 2008; Kim et al., 2009; Ohkawara et al., 2007).PA directly suppresses the secretion of IL-6 by AT, there is no change in production of TNF-α, resistin, and leptin and the level of circulating adiponectin increases(Ertek& Cicero, 2012; Simpson & Singh, 2008). Most of the research, however, states that systematic exercise decreases the level of leptin in the blood thus causing the adiponectin/leptinratio to increase (Sirico et al., 2018).Convertingwhite AT into the brown phenotype has been suggested as being one of the mechanisms bywhich physical exercise improves body composition in overweight/obese individuals and improves the pro- to anti-inflammatory cytokine ratio (Brenmoehl et al., 2016).

Muscles

Cytokines secreted by muscles are named myokines. The most sensitive of them is IL-6, which is released proportionally to the intensity and duration of the exercise and muscle mass (Tir, Labor&Plavec, 2017). This cytokine enhances glucose production in the liver and lipolysis in adipose tissue. Together with an increasing level of IL-6, enhanced expression of IL-6R is also observed. Studies indicate that despite the pro-inflammatory effects of IL-6 and its receptor, this complex triggers anti-inflammatory cascades by inhibiting IL-1β and TNF-α andby increasing the release of IL-10 (Nimmo et al., 2013; Brandt & Pedersen, 2010; Mathur & Pedersen, 2008). It is also possible that IL-6 secreted by myocytes has anti-inflammatory properties, as opposed to IL-6 secreted chronically by the adipose tissue (Pedersen &Febbraio, 2005).An increase in IL-6 is not preceded by an increase in TNF-α, as occurs in sepsis (Ertek& Cicero, 2012). Researchers also observed elevated circulating levels of IL-15 and irisin, which are secreted from the muscles in response to exercise and have a positive influence on adipocytes, especially those located in the abdominal region (Nimmo et al., 2013).

Irisin triggers the transformation of white into brown adipocytes. IL-15 improves muscle glucose homeostasis and oxidative metabolism. Treatment with high doses of IL-15 results in an improvement of insulin sensitivity (Lee et al., 2016).

Recommendations

The WHO guidelines on physical activity and sedentary behaviour (2020), the latest guidelines of the ESC (2020) and The Physical Activity Guidelines for Americans (U.S. Department of Health and Human Services, 2018) all recommend at least 150 minutes (ideally spread over five trainings) of moderate-intensity or 75 minutes (spread over three trainings) of vigorous-intensity aerobic activity per week.For additional health benefits, 300 minutes and 150 minutes are recommended, respectively.Muscle-strengthening activities such as resistance training, performed at least twice a week are also recommended. The recommendations are the same for people 18–64 years of age and over 64 years of age, providingthere are no conditions that limit their mobility.

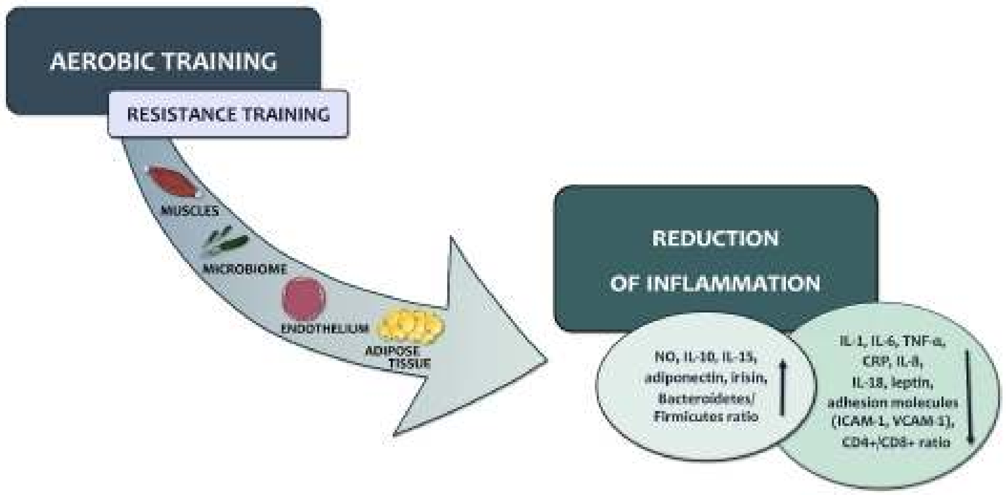

Figure 1. The mechanisms by which physical activity reduces low grade chronic inflammation

Conclusion

As mentioned above, PA unequivocally reduces the severity of low grade chronic inflammation. Long-term positive effects outweigh the temporary increase of pro-inflammatory influence. This occurs by changes inthe adipose tissue, the myocytes, the endothelium, andthe microbiome.It is still not obvious which of these structures fulfil this function in the most effective way. Most probably, they cooperate and complement each other. Based on the studies described above, there is a noticeable predominance of aerobic over resistance training in the reduction of inflammation. Nevertheless, the combination of aerobic and resistance activity seems to be the most advantageous. PA can be a good way to reduce systemic inflammation and the progression of diseases and disordersrelated to it,such as cardiovascular, metabolic, autoimmune,and cancers.

Conflicts of interest: none declared

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