

Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions

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Abstract

Since the 19th century, many studies have enlightened the role of inflammation in atherosclerosis, changing our perception of “vessel plaque due to oxidized lipoproteins”, similar to a “rusted pipe”, towards a disease with involvement of many cell types and cytokines with more complex mechanisms. Although “physical activity” and “physical exercise” are two terms with some differences in meaning, compared to sedentary lifestyle, active people have lower cardiovascular risk and lower inflammatory markers. Activities of skeletal muscle reveal “myokines” which have roles in both the immune system and adipose tissue metabolism. *In vitro* and *ex-vivo* studies have shown beneficial effects of exercise on inflammation markers. Meanwhile in clinical studies, some conflicting results suggested that type of activity, exercise duration, body composition, gender, race and age may modulate anti-inflammatory effects of physical exercise. Medical data on patients with inflammatory diseases have shown beneficial effects of exercise on disease activity scores, patient well-being and inflammatory markers. Although the most beneficial type of activity and the most relevant patient group for anti-inflammatory benefits are still not clear, studies in elderly and adult people generally support anti-inflammatory effects of physical activity and moderate exercise could be advised to patients with cardiovascular risk such as patients with metabolic syndrome.

Key words: inflammation, physical activity, atherosclerosis, obesity, myokines, adipokines, insulin resistance, metabolic syndrome.

Introduction

The inflammatory hypothesis of atherosclerosis emerged in the 19th century as inflammation-based arterial changes for atherogenesis [1]. As it became clear within the century, the process starts with injury to the endothelium, orchestrated by endothelial cells, smooth muscle cells, platelets, lymphocytes, monocytes and macrophages, and all of these cells generate many molecules such as cytokines, growth factors, eicosanoids, proteases and reactive oxygen species, and provoke acute and eventually chronic inflammation within the vessel wall, not only as just “plaque within the lumen”, within a complex process involving many humoral and hormonal factors [2-5]. The role of chronic inflammation in propagation

from atherogenesis to thrombotic events described in the medical literature led clinicians to use inflammatory markers to evaluate disease activity, in particular leukocyte count, high sensitivity C-reactive protein (hsCRP), interleukins (IL-6, IL-18), and soluble CD40 ligand [6].

Inflammation is also revealed in conditions increasing cardiovascular disease risk such as insulin resistance, visceral obesity, metabolic syndrome and type 2 diabetes, with higher proinflammatory cytokines secreted by macrophages infiltrating visceral fat [7-12]. A similar increase in cardiovascular risk has been associated with physical inactivity [13-15], even independently from body mass index [16]. In this era of increasing inactivity with age even among children [17], medical data show that besides the potential to raise mood and the effect on endorphin and coupled nitric oxide pathways [18], physical activity causes more complex interactions between organ systems, including anti-inflammatory pathways. Both "physical exercise" and "physical activity" (PA) refer to voluntary movements expending more calories than a resting position, but physical exercise is a form of PA that is specifically planned, structured, repetitive and regular, to improve cardiovascular-respiratory fitness, muscle power and endurance, flexibility, agility, balance and/or body composition [19]. Compared with a sedentary lifestyle, insufficiently active lifestyle and "week-end warrior"-style high activity pursuits, regular physical exercise (spending ≥ 1000 kcal/week) provides the best decreases in mortality risk [20]. Meanwhile, meta-analytic results revealed that PA formulated on the basis of fitness activities provides significant cardiovascular benefit [21]. Since in the medical literature these two terms are used interchangeably, our review involves effects of both PA and exercise.

Hence the aim of our review is to evaluate the relationship between PA and inflammation, in relationship to cardiovascular disease risk and other inflammatory diseases. Therefore a PubMed/Embase search was performed up to June 2012 using combinations of "Physical activity, exercise, physical exercise" and "inflammation, inflammatory disease, cytokines, CRP" with each of the following key words: cardiovascular disease, coronary disease, atherosclerosis, obesity, metabolic syndrome, diabetes, prediabetes, impaired glucose tolerance (IGT), hypertension, cancer, asthma, chronic obstructive pulmonary disease (COPD), renal disease, renal failure, and rheumatologic diseases. Preclinical studies, randomised controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

Physical activity, myokines and inflammation

As adipose tissue, muscle tissue was also suggested to be an "endocrine organ" with myokines providing cross-talk between adipose tissue, the immune system, hypothalamus and muscle cells [16]. Fischer *et al.* reported a 100-fold increase in IL-6 after acute exercise [22] which was not preceded by an increase in tumour necrosis factor α (TNF- α) as in sepsis [23]. Meanwhile the exercise duration and involved muscle mass was directly related to the degree of this post-exercise IL-6 amplitude [22-24].

Interleukin-6 increases hepatic glucose production during exercise and lipolysis in adipose tissue [23]. Increase in IL-6 also enhances insulin action and sensitivity [25] unlike TNF- α -induced insulin resistance [26]. Absence of classical proinflammatory cytokines (TNF- α and IL-1 β) in the exercise-induced cytokine cascade causes an increase of IL-6, IL-1ra, IL-19 and sTNF-R [27], creating an anti-inflammatory environment. It appears that exercise inhibits TNF- α directly by IL-6 [28] and indirectly via epinephrine [29]. The down-regulation of TNF- α induced by skeletal-muscle-derived IL-6 may also participate in mediating the atheroprotective effect of PA [30].

Other myokines that increase after exercise are IL-8 and IL-15 [31]. IL-15 was suggested to have an anabolic role and decrease adipose tissue mass [32], and IL-8 may play a role in angiogenesis [33].

Besides actions of myokines, physical exercise causes laminar shear stress activation and down-regulates endothelial angiotensin II type 1 receptor (AT1R) expression, causing decreased reactive oxygen species (ROS) generation, preserving NO availability and, consequently, having anti-atherogenic effects [30].

Habitual PA and exercise training decreases TNF- α and resistin levels and increase adiponectin levels [34]. In fact, high adiponectin and low hsCRP levels may have a relationship with resolution of metabolic syndrome [35].

On the other hand, impaired PA causes insulin resistance via genes involved in inflammation and endoplasmic reticulum stress, and impaired expression of peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α) [36]. PPAR- β/δ activation blocks inflammation in myocytes [37]. As one of the key regulatory factors in active skeletal muscle, PGC-1 α may also be a link between metabolism, inflammation and skeletal muscle activity [38].

Another link between PA and insulin resistance may be its association with satiety hormones. In a small study carried out on children, increased PA caused increased obestatin, a decreased ghrelin to obestatin ratio, and increased leptin and soluble leptin receptor [39]. Meanwhile, in premenopausal women, exercise with a diet programme decreased

ghrelin and ICAM-1 levels, and increased plasma adiponectin [40].

Thus, there are many different pathways in the mechanism of anti-inflammatory action of PA, and although some systemic effects are known, mediators of these effects are not clearly demonstrated yet (Figure 1).

Effects of physical activity on inflammation in cardiovascular and non-cardiovascular diseases

In vitro and *ex-vivo* studies

In diet-induced obese rats, both acute and chronic exercise blunt Toll-like receptor-4 (TLR-4) signalling and cause improved post-receptor insulin action [41]. Exercise reduces protein tyrosine kinase phosphatase 1B activity and insulin receptor substrate 1 serine phosphorylation, with concomitant reduction in c-jun N-terminal kinase activities in the muscle of diet-induced obese rats [42].

Studies in Zucker diabetic fatty rats, a rodent model of type 2 diabetes, show that 10 weeks of exercise as 5 km/day running significantly decreased IL-6, haptoglobin, malondialdehyde levels and JNK phosphorylation, and also decreased hepatic phosphoenolpyruvate carboxykinase levels and Ser(307)-phosphorylated insulin receptor substrate-1. All these changes indicate decreased JNK activity and decreased hyperglycemia [43]. This model of rats also showed increased adiponectin and decreased CRP levels after regular exercise [44]. Treadmill exercise may also decrease CRP in renal proximal tubules and increase IL-10. It also restores renal dopamine D1 receptor functions in rats [45],

suggesting interaction of exercise with inflammatory cytokines and kidneys.

Exhaustive exercise and endurance exercise training differently modify the physiological status of the body, and therefore may have different anti-inflammatory results. Studies on rats revealed that endurance training increased the rate of tricarboxylic acid cycle and antioxidant activity whereas exhaustive exercise increased urea markers and inflammation in rat liver tissue [46].

In diet-induced obese mice, physical exercise decreases expression of TNF- α , MCP-1, PAI-1 and IKK- β in adipose tissue but not in liver [47]; therefore there may be cross-talk between muscle and adipose tissue just after muscle activity, causing changes directly in adipose tissue.

In contrast, overtraining may activate pro-inflammatory cytokines. In fact, overtrained groups of rats showed elevated levels of IL-10 and IL-6 in adipose tissue, accompanied by increased TLR-4 and NFkBp65 compared to control and trained groups [48]. Training may provide necessary changes to adapt to exercise and to trigger mechanisms against inflammation that will occur after muscle activity. Acute exercise causes endoplasmic reticulum stress (detected as increased mRNA levels and x-box binding proteins), and increases inflammatory markers (e.g. IL-6, TNF- α) and oxidative stress (detected as increased metallothionein 1F, metallothionein 1H, and NADPH oxidase) [49]. That means the effects of acute exercise are extremely different from those of chronic training [50].

In mice with a high fat diet exercise ameliorates the progression of endothelial dysfunction and decreases atherosclerotic areas. Meanwhile it has

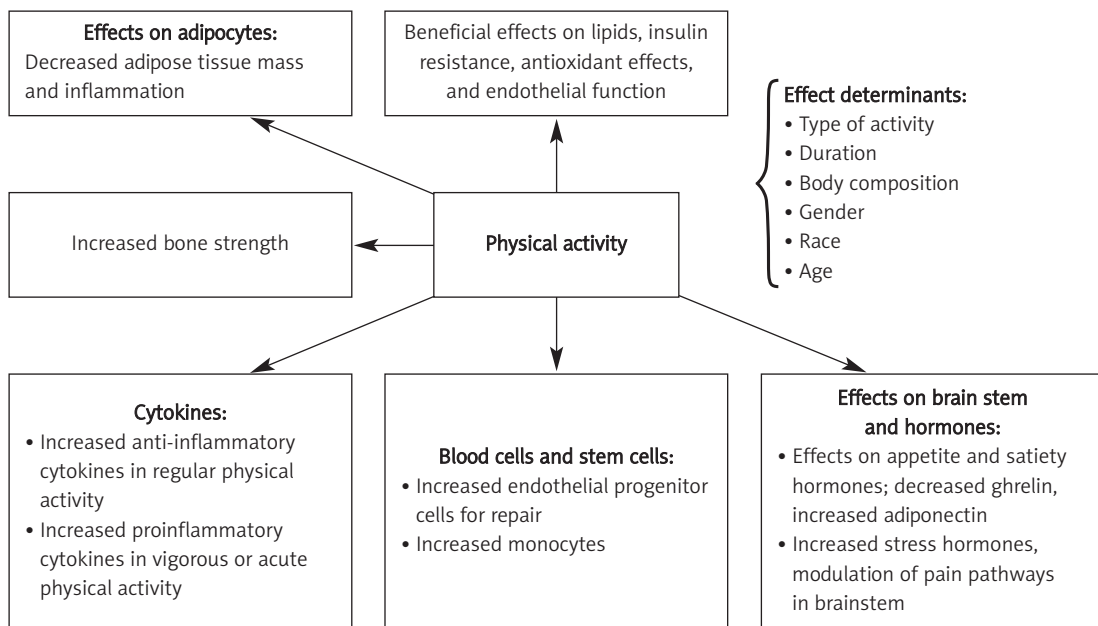


Figure 1. Systemic effects of physical activity and main determinants

anti-inflammatory effects such as decreased IL-6 and macrophage chemoattractant protein-1 and higher adiponectin levels [51]. Thus, exercise may be beneficial by mechanisms other than anti-inflammatory effects against atherosclerosis and obesity.

Besides adipocytes, satiety hormones, markers of atherosclerosis, endothelial cells, bone tissue and kidneys, PA even may affect blood cells. Endurance exercise may also affect behaviour of blood cells, increasing tissue factor activity of lipopolysaccharide-stimulated monocytes, IL-8 increase and increased lipopolysaccharide-induced thromboxane B2, these increases being more prominent after a second bout of exercise [52]. Vigorous exercises such as marathon running increase neutrophilia, and also anti-inflammatory and antioxidant defences were activated to prevent exercise-induced oxidative stress [53], together with hormonal responses, e.g. acute growth hormone release accompanying IL-6 increase and later catecholamines possibly suppressing neutrophil responses [54, 55].

Clinical evidence

Studies on general population

Physical activity and cardiorespiratory fitness are consistently associated with 6-35% lower CRP levels, and longitudinal training studies have demonstrated reductions in CRP concentrations of 16% to 41%, an effect that may be independent of baseline levels of CRP, body composition or weight loss, indicating that the PA and CRP relationship is dose-dependent [56]. In a review evaluating 19 articles on the acute inflammatory response to exercise, 18 on cross-sectional comparisons of subjects by PA levels, and 5 examining prospectively the effects of exercise training on the inflammatory process, it was concluded that short-term exercise produces an inflammatory response but long-term training has anti-inflammatory effects [57].

In a study involving 13,748 participants, leisure time PA was associated with lower fibrinogen and white blood cell counts and higher albumin concentrations [58]. Besides beneficial effects on inflammatory markers, PA causes better haemostasis [59].

In a Finnish study, 3803 adults were evaluated for effects of physical exercise on CRP levels [60]. After adjustment for age, PA and CRP levels were inversely associated for both men and women, and after adjustment for all other factors, this relationship was present only for women. In the EPIC-Norfolk Prospective study, people with an active lifestyle had significantly lower CRP levels than inactive ones [61]. In a further study carried out on 796 healthy subjects, fibrinogen and IL-6 were related to PA, and CRP levels were inversely related to activity after adjustments for body mass

index, waist-to-hip ratio, smoking, hypertension, diabetes and lipids [62].

In elderly subjects, high-volume regular PA was found to be associated with lower levels of IL-6 and higher levels of IL-10 [63]. Similar results were also seen in the study of Reuben *et al.*, with 870 elderly people [64]. In a further cohort of 5888 elderly people lower concentrations of CRP, white blood cells, fibrinogen, and factor VIII activity were associated with higher PA quartiles [65]. Therefore probably elderly people may particularly benefit from PA.

Race and gender may also be important in anti-inflammatory effects of PA; in the study of Majka *et al.*, there was a tendency to have lower hsCRP levels by PA tertiles only in black and white men, but not in any female groups [66]. In the PLAY study conducted in South Africa, 193 black children were evaluated for their CRP levels in different activity categories. "Fit" children had lower CRP, and especially in girls higher PA groups showed lower CRP levels [67]. In a cross-sectional study of more than 3000 Chinese urban men, CRP was tested and obesity, smoking and alcohol intake were associated with high CRP levels whereas high PA was inversely associated [68].

Studies on populations with high cardiovascular risk

In the ATTICA study conducted in the Attica region of Greece, 1514 men and 1528 women with metabolic syndrome were evaluated for their self-reported PA status and inflammatory and coagulation markers [69]. Serum CRP, white blood cells, serum amyloid A protein, and fibrinogen were significantly lower in physically active patients than in inactive ones.

Four weeks of physical exercise training in impaired glucose tolerance and type 2 diabetic patients improved plasma adipokine concentrations and CRP concentrations but the effect on IL-6 was not significant [70].

Moreover, 152 sedentary, obese or overweight postmenopausal women who were free of chronic inflammatory diseases were tested for PA energy expenditure (PAEE), total energy expenditure (TEE) and resting energy expenditure (REE), and the relationships between these PA markers and serum hsCRP, haptoglobin, soluble tumor necrosis factor- α receptor 1 (sTNFR1), interleukin-6, orosomucoid and white blood cells were evaluated [71]. While TNF-1 was positively correlated with TEE and REE, PAEE was found to be an independent predictor of hsCRP and haptoglobin.

In a study carried out on hypertensive patients, sequential physical training decreased body mass index, waist circumference and blood pressure, and improved glycemia and lipemia, but a significant reduction in hsCRP levels was only significant in metabolic syndrome patients [72], suggesting a link

between hsCRP and metabolic parameters, rather than PA itself. But probably the type of exercise and patient group may cause differences in anti-inflammatory results of physical exercise; in a small group of type 2 diabetics, leptin, resistin and IL-6 decreased after 12 months of aerobic and aerobic + resistance exercise, and IL-1 β , TNF- α and IFN- γ decreased whereas IL-4 and IL-10 increased in aerobic and resistance exercise groups, independent of weight loss [73]. Also angiographically documented coronary disease patients benefit from leisure time PA regarding its beneficial effects on inflammatory markers [74].

Similar to patients with coronary artery disease, patients with peripheral arterial disease also benefit from anti-inflammatory effects of PA. A higher level of activity was found to be associated with lower sVCAM, D-dimer, homocysteine, CRP and sICAM levels in these patients [75].

In a further small sample size study in obese people practising exercise together with diet, anti-inflammatory effects were only observed in adipose tissue, and not in skeletal muscle [76]. Therefore body fat distribution may also affect anti-inflammatory effects of exercise.

In most clinical studies PA was evaluated by self-reported questionnaire or pedometers. There are few interventional studies performed in healthy people or different groups of patients with selected types of regular exercise showing beneficial effects on inflammatory markers (Table I).

Effects of excessive physical activity

Although it was known that vigorous PA may trigger an inflammatory response in muscle tissue, in a study carried out on 520 adolescents, vigorous PA was associated with decreased CRP levels in boys [77]. High endurance physical exercise in non-athlete adults increases CRP and TNF- α and IL-6 changes may not be significant [78]. Different levels of bench press exercise intensity were not associated with changes in IL-6, IL-1 β and TNF- α levels, although maximal creatinine kinase levels were reached [79].

Prolonged vigorous exercise such as the spartathlon (246 km continuous running) causes an acute inflammatory response in muscle tissue, marked increases in plasma levels of CRP, IL-6, SAA, MCP-1, IL-8, sVCAM-1, sICAM-1, thrombomodulin (sTM) and NT-pro-BNP, and increased endothelial progenitor cells as a repair mechanism [80]. Similar results of increased inflammatory markers were also observed in marathon and ultra-marathon (200 km) runners and triathlon racers [81-83].

Conflicting results of clinical studies

Apart from this large body of evidence supporting the positive effect of PA on inflammation, oth-

er studies have reported neutral, partial or opposite effects. For instance, the PREPARE (Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement) programme randomized trial did not reveal anti-inflammatory effects of ambulation [84]. In another recent study, physical exercise per se did not have any benefit regarding sVCAM, sICAM or IL-6, but when combined with diet, exercise caused significant reductions in sICAM and sE-selectin [85]. In elderly patients, 12-month moderate intensity PA significantly lowered IF-8 levels, but no effect was observed on other inflammatory markers such as TNF- α or soluble receptors of IL-1 or 6 [86].

The "Physical Activity as a preventive agent of the Development of Overweight, Obesity, Allergies, Infections, and Cardiovascular Risk Factors in adolescents" study (La Actividad Física como Agente Preventivo del Desarrollo de Sobrepeso, Obesidad, Alergias, Infecciones y Factores de Riesgo Cardiovascular en Adolescentes, AFINOS) evaluated 192 adolescents [87] and controlled effects of 7 days' PA measured by accelerometer on CRP, IL-6 and complement factors C3 and C4. Independent from HOMA-IR, only body fat was related to CRP, and PA measures were not independently associated with inflammatory markers. Similarly, in the European Young Heart Study, CRP and C3 were negatively correlated with cardiovascular fitness but inversely related to body fat mass [88].

The Inflammation and Exercise (INFLAME) study was conducted to test whether diet or PA can reduce CRP in individuals with increased CRP levels. A 4-month period of physical training was started for sedentary people and there was no significant difference between exercising and sedentary groups regarding CRP when adjusted for gender and body weight [89]. Also data from 950 people evaluated in the National Health and Nutrition Survey (1999-2002) showed no beneficial association between reported PA rates and CRP [90].

In another study carried out on 892 male subjects, a questionnaire was used to detect levels of PA and after adjustments for personal characteristics there was no relationship between PA status and CRP or serum amyloid A or fibrinogen levels [91]. In a study with elderly subjects, interestingly, PA was correlated with lower levels of inflammatory markers (e.g. CRP, IL-6 and TNF- α) but this association was also observed in people who do not exercise but take antioxidants [92].

In a study involving 109 healthy men and women, body mass index was related to hsCRP levels, but PA was not [93].

Meanwhile, in the "DNA Polymorphism and Carotid Atherosclerosis" (DNASCO) study investigating whether PA slows progression of atherosclerosis and effects of genetic factors, hsCRP lev-

Table I. Types of physical activity in prospective clinical studies on inflammation-related parameters

Activity	Patients	Reference	Result
Treadmill exercise for 3 months	Patients with intermittent claudication ($n = 82$). Sixty-seven claudicants and 15 controls	Tisi, <i>et al.</i> 1997 [122]	Beneficial
Individually trained treadmill exercise programmes, mean 2.5 h/week	High cardiovascular risk people ($n = 43$)	Smith, <i>et al.</i> 1999 [123]	Beneficial
Long distance running – 9 months of training, mean distance increased from 31 ± 9 km to 53 ± 15 km	Healthy subjects ($n = 14$)	Mattusch, <i>et al.</i> 2000 [124]	Beneficial
Jogging and aerobic dancing	Adults over 17 years ($n = 4072$)	King, <i>et al.</i> 2003 (NHANES III study, after adjustments) [97]	Beneficial
Individually tailored moderate intensity resistance training for upper and lower extremity large muscles, group walking and hiking	Middle-aged overweight subjects ($n = 522$)	Lindström, <i>et al.</i> 2003 (Finnish Diabetes Prevention Study) [125]	Beneficial
Low- to moderate-intensity aerobic exercise	Healthy men ($n = 140$)	Rauramaa, <i>et al.</i> 2004 (DNASCO study) [94]	Beneficial
Four weeks of aerobic exercise training	Normal, impaired glucose tolerance and type 2 diabetic patients ($n = 60$)	Oberbach, <i>et al.</i> 2006 [70]	Beneficial
Individually tailored aerobic exercise	Post-acute myocardial infarction patients ($n = 60$)	Balen, <i>et al.</i> 2008 [126]	Beneficial
Sequential training from 3 METs/week to 6 METs/week	Overweight patients ($n = 80$)	Cicero, <i>et al.</i> 2009 [72]	Beneficial
Submaximal single-leg ergometer test for 20 min/day	Chronic obstructive lung disease patients ($n = 25$). Fifteen lung disease patients and 10 controls	Mercken, <i>et al.</i> 2009 [104]	Beneficial
Gradually increasing walking by 3000 steps/day on 5 days of the week, for 12 weeks	Healthy males ($n = 48$), 24 exercising subjects and 24 controls	Gray, <i>et al.</i> 2009 [127]	Not beneficial
10-30 min stationary cycling at an intensity of 12-16 out of 20 at the rate of perceived exertion (RPE) on Borg scale in aerobic group and using ankle weights for knee extension, hip abduction and flexions at an intensity of 15-17 out of 20 at the RPE on Borg scale in resistance group	Haemodialysis patients ($n = 21$). Seven patients in aerobic resistance, 7 in interdialytic exercise and 7 in control groups	Afshar, <i>et al.</i> 2010 [118]	Beneficial
Twice-a-week supervised aerobic and resistance training plus structured exercise counselling	Sedentary type 2 diabetics and metabolic syndrome patients ($n = 606$)	Balducci, <i>et al.</i> 2010 (IDES study) [128]	Beneficial
Minimum 30 min of aerobic exercise, 5-6 times/month	Hypercholesterolaemic men ($n = 157$)	Sjögren, <i>et al.</i> 2010 [85]	Beneficial
Bicycle home ergometer, home-based exercise plan	Patients who underwent percutaneous coronary intervention ($n = 62$), 33 patients taking exercise and 29 sedentary	Astengo, <i>et al.</i> 2010 [129]	Not beneficial
Moderate intensity aerobic activity for 12 months	Elderly nondisabled men and women ($n = 368$)	Beavers, <i>et al.</i> 2010 [130]	Not beneficial
40-minute walking for 5 days per week	Coronary heart failure patients ($n = 28$). Eighteen patients in exercise and 10 patients in non-exercise group	Tsarouhas, <i>et al.</i> 2011 [121]	Beneficial

els were not significantly lower in the exercising group [94]. In another study carried out on obese people, PA was only inversely related to C-peptide and insulin levels, whereas other inflammatory markers such as CRP, IL-6, and soluble TNF receptors 1 and 2 were not affected [95].

Therefore although large, population-based cohort studies support anti-inflammatory effects of PA, data from large, randomized, controlled trials have conflicting results [96]. Besides age, gender and duration, type of PA (for example aerobic dancing vs weight lifting or gardening) is probably important [97].

Studies on non-cardiovascular inflammatory diseases

In a systematic review, 19 studies in children and adults with chronic inflammatory diseases were collected and acute and chronic effects of physical exercise on inflammatory markers were tested [98]. Acute exercise increases inflammatory markers but training decreases them, but the results depend on the nature of the PA.

Rheumatological diseases – Anti-inflammatory effects of physical exercise were first noticed in chronic inflammatory diseases such as autoimmune arthritis or chronic obstructive lung disease [99]. It was found that physical exercise decreases IL-6 and CRP levels in these patients [99].

In studies carried out on rheumatoid arthritis patients, the number of CD4(+) cells in synovial fluid decreases after moderate physical exercise [100]. The role of exercise in synovial inflammation was also similar in vascular inflammation in these patients [101].

Respiratory diseases – together with pharmacological treatment, exercise reduces oxidative stress and airway inflammation and increases antioxidant enzyme activities in asthmatic children [102, 103], whereas tests in COPD patients showed increased oxidative stress without an increase in inflammatory markers after acute exercise (e.g. continuous single leg exercise) [104]. The degree of PA is also associated with lower hs-CRP and IL-6 levels in COPD patients [105]. Similarly, physical training in asthmatic patients leads to decreased serum hs-CRP levels and better pulmonary function [106]. In the recent prospective cohort study of Waschki *et al.*, PA was shown to be the strongest predictor of all-cause mortality in COPD patients [107].

Exercise training may be protective in lung ischaemia, protecting against ischaemia-reperfusion injury by improving pulmonary vascular permeability, as shown in rats [108].

Cancers – Metabolic syndrome and related parameters are clearly associated with colon cancer [109] and breast cancer incidence [110].

Since PA decreases insulin resistance, obesity, CRP and estrone levels, its effects in breast cancer were hypothesized and studied at the beginning of this century [111]. Physical exercise was found to have slight to moderate effects on improving some biomarkers in breast and colon cancer patients including insulin, leptin, estrogens, inflammation, immune function and apoptosis regulation [112]. In fact, both acute and chronic exercise alter the number of circulating cells of the innate immune system; for example, it is agreed that lymphocytosis occurs during and after acute exercise, and mobilization of T and B cells is largely influenced by catecholamines [113]. Among nearly 73 studies examining the effects of exercise on breast cancer risk, there is a 25% average risk reduction among physically active women compared to the least active ones [114]. Besides breast cancer, lung cancer also has a strong correlation with decreased PA; PA reduces lung cancer by 20-30% in women and 20-50% in men, possibly via improved pulmonary function, reduced concentrations of carcinogenic agents in the lungs, enhanced immune function, reduced inflammation, enhanced DNA repair capacity, changes in growth factor levels and possible gene-PA interactions [115]. Similar mechanisms may also be involved in the preventive effect of physical exercise against colon cancer [116].

Chronic renal failure – In chronic renal failure patients, especially those under haemodialysis treatment, who usually have a low PA, the available studies are low in number, and the effects of malnutrition generally prevent evaluation of the effects of PA [117, 118]. However, in a recent study, self-reported PA levels were inversely related to the hsCRP serum level [119].

Chronic heart failure – In New York Heart Association grade II-II heart failure patients evaluated by peak before and after a 12-week physical training programme in a cross-over design, a significant correlation between training-induced oxygen consumption and reduction in soluble intercellular adhesion molecule-1 (sICAM) and soluble vascular cell adhesion molecule-1 (VCAM-1) levels was found, reflecting beneficial monocyte-endothelial cell-macrophage interaction in these patients [120]. Better asymmetric dimethyl arginine (ADMA) and homocysteine levels were also observed in the same group of patients after a standardized exercise programme [121].

Conclusions

Despite increasing evidence of an inflammation modulatory effect of PA, much research is needed to better understand which kind of activity or exercise is associated with the largest anti-inflammatory effect, which kind of patients could benefit most from this approach, and whether the PA-relat-

ed decrease of systemic inflammation is associated with an improvement in cardiovascular prognosis. The current data suggest that moderate PA could have some anti-inflammatory effects in both adult and elderly healthy subjects as well as in patients with cardiovascular risk factors such as metabolic syndrome. The mechanisms involved in its anti-inflammatory action and knowledge about determinants of physical exercise are not clearly elucidated yet. Meanwhile, prospective clinical studies with PA interventions to study anti-inflammatory effects are still too low in number to decide about the type of activity for specific groups of patients.

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