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The effects of physical activity on chronic subclinical systemic inflammation

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Chronic subclinical systemic inflammation (CSSI) is a pathogenic event and a common risk factor for many non-communicable diseases like atherosclerosis, metabolic syndrome, cardiovascular disease, insulin resistance and type 2 diabetes, cancer, and obstructive lung disease. On the other hand, regular physical activity has been found to reduce this risk. Many studies of different design were conducted to assess the association between inflammatory mediators as markers of CSSI and regular physical activity. The aim of this review was to present the current level of evidence and understanding of potential mechanisms by which physical activity reduces inflammatory mediators involved in CSSI and the types of physical activity required for the expected effect. We have found that observational studies consistently report a positive association between regular physical activity and lower CSSI, but the design of these studies does not allow to infer a causal relationship. Interventional studies, in contrast, were not consistent about the causal relationship between regular physical activity and lower CSSI. The problem in interpreting these results lies in significant differences between these interventional studies in their design, sample size, study population, and intervention itself (intensity and extent, follow up, weight loss). We can conclude that the scientific community has to invest a significant effort into high-quality interventional trials focused on finding the type, intensity, and extent of physical activity that would produce the most favourable effect on CSSI.

KEY WORDS: *chronic diseases; inflammatory mediators; lifestyle*

Over the last two decades, we have learned that chronic subclinical systemic inflammation (CSSI) not only predicts chronic infection, as was believed in the past, but plays a significant role in the development of non-communicable diseases (NCDs), which account for 86 % of all deaths in Europe and as many as 93 % of deaths in Croatia (1). These include cardiovascular diseases, insulin resistance, osteoporosis, dementia, cachexia, and breast and colorectal cancer (2).

CSSI is defined as a two- to threefold increase in the circulating levels of pro-inflammatory and anti-inflammatory cytokines, cytokine antagonists, acute-phase proteins, neutrophils, and natural killer cells (3) and is strongly associated with older age, smoking, and obesity. Although these levels are lower than with the acute infection or trauma response, their persistence highly increases the risk of NCD morbidity and mortality, especially in the elderly (4).

Markers of CSSI

Inflammation plays a significant role in atherogenesis. A direct injury of the endothelium by hypertension or cigarette smoke activates the innate immune response: phagocytosis, complement system, and cytokine release. Cytokines are small immunoregulatory polypeptides that can both counter and boost inflammation. As atherogenesis advances, the immune system adapts by releasing T lymphocytes, antibodies, and more cytokines (5) in a cascade-like manner. These include tumour necrosis factor alpha (TNF-α), interleukin 1-beta (IL-1β), interleukin 6 (IL-6), interleukin 1 receptor antagonist (IL-1ra), soluble receptors of tumour necrosis factor (sTNFR), and C-reactive protein (CRP) (6).

CRP is an acute-phase reactant, a nonspecific mediator of systemic inflammation together with fibrinogen and serum amyloid A (SAA). Acute-phase reactants are released from the liver to respond to local stimuli, infection, or trauma following an increase in the circulating levels of IL-6, IL-1β, and TNF-α. CRP is a stronger predictor of cardiovascular diseases and sudden cardiac death than low-density cholesterol (LDL) (6, 7). The Centers for Disease Control and Prevention (CDC) categorise the risk of cardiovascular diseases as follows: people with CRP<1 mg L^{-1} are at low risk, those with 1-3 mg L^{-1} at average risk, and those with CRP>3 mg L^{-1} at high risk (8).

TNF-α is a pro-inflammatory, pro-atherosclerotic, pro-coagulant, and cachectic cytokine produced by the adipose tissue macrophages, vessel endothelial cells, and smooth

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muscle cells. It enhances lipolysis and thus increases the circulating levels of free fatty acids (FFA) (4). It also plays a role in the metabolism of glucose by enhancing insulin resistance and is a direct link between CSSI and the metabolic syndrome (3, 4). TNF-α and IL-6 enhance atherogenesis by increasing fibrinogen levels and stimulating the expression of adhesion molecules on endothelial cells. TNF-α is also called cachectin because it enhances energy and lean body mass consumption (4). It triggers a cascade of immune responses and the release of many inflammatory mediators. As TNF-α has a short half-life and acts locally, it is often undetectable and therefore a poor marker of CSSI.

Instead, recent research has proposed soluble TNF receptors (sTNFR) as markers of TNF-α activity. They are synthesised in the liver in response to IL-6 and have a stable and long half-life in the plasma (4).

IL-6 is both a pro-inflammatory and anti-inflammatory cytokine produced by the adipose tissue, mononuclear cells, and contracting skeletal muscles in response to TNF-α, but its role is controversial (4). Some studies established a correlation between IL-6 and the risk of NCDs because of the higher levels in the elderly, obese, and smokers (6). IL-6 released from the liver increases the circulating levels of CRP and fibrinogen and enhances lipolysis and FFA oxygenation (3, 7). IL-6 released from the contracting skeletal muscles plays an anti-inflammatory role. During physical activity, it soars 100-fold and precedes all other cytokines (6).

The cytokines IL-10 and IL-1ra are acute-phase reactants with anti-inflammatory properties, which lower pro-inflammatory TNF-α and IL-1 in the monocytes (6).

Physical activity

Physical activity is defined as any bodily movement produced by the skeletal muscles that results in energy expenditure (9). Its intensity and frequency can vary from low to high. Exercise is a physical activity consisting of repetitive and planed body movements with a goal to achieve or improve cardiorespiratory fitness (9). Cardiorespiratory fitness is an ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity (10) and correlates linearly with the intensity and frequency of physical activity (11).

Regular physical activity protects against diseases related to CSSI (6). Physical inactivity, in contrast, is a strong predictor of NCD morbidity, hypertension, hyperlipidaemia, diabetes, and obesity (3). Public health recommendations for adults (18-65 years) include moderate aerobic training for at least 30 minutes five days a week or vigorous aerobic training for at least 20 minutes three days a week (12).

Over the last two decades most of the studies investigating how physical activity affects the mediators of systemic inflammation concluded that it is almost as effective as pharmacological treatment (13).

The aim of this review was to update and summarise the existing evidence of the effects of regular physical activity on the mediators of CSSI obtained from observational and interventional studies in the general healthy population and populations at risk, such as the elderly and the overweight/obese. We also wanted to see whether different study design produces different evidence.

Evidence from observational studies

Evidence from large observational studies conducted in healthy participants is consistent in confirming the association between inflammatory mediators and physical activity. Table 1 summarises the data from 11 observational studies (2, 14-23) investigating the association between inflammatory mediators and physical activity or cardiorespiratory fitness as a surrogate measure of physical activity. These studies make part of large longitudinal prospective cohort studies pooling up data from nearly ten thousand participants aged between 12 and 102 years, such as the Third National Health and Nutrition Examination Survey (NHANES III), the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), the In CHIANTI Study, the Health, Aging and Body Composition Study (Health ABC Study), the MONICA Augsburg Survey, the Mac Arthur Studies of Successful Aging, and the Aerobics Center Longitudinal (ACL) Study. Although they somewhat differ in the methodology and variables, they have provided strong evidence that physical activity correlates inversely with pro-inflammatory and linearly with anti-inflammatory mediators. This correlation, however, has not been confirmed in children, probably because of the limited sample and invariably low (borderline detectable) level of CRP in healthy children (14).

The HPFS and NHS studies found that healthy workers who were training most intensively had lower CRP levels than the less active participants (29 % in men and 68 % in women). They also found that the participants who ran ≥4 h a week had 49 % lower CRP than those running 0.5 h a week. Less active participants running ≤0.5 h a week had a 4 % higher sTNFR1 and sTNFR2 and 6 % higher IL-6 than the participants running ≥4 h a week (15).

The large ACL Study that followed white, male, upper-class regulars to aerobic centres showed that those with the highest cardiorespiratory fitness level had 77 % lower CRPs than the participants with the lowest fitness level, as assessed by a treadmill test (16).

Comparable results were found in the Mac Arthur Studies of Successful Aging, conducted in a cohort of 880 seventy to seventy-nine-year-olds. Those exercising moderately to vigorously ≥46 h a year had 41 % lower CRP values than those exercising ≤21 hours a year (17).

In the MONICA Augsburg Survey, Autenrieth et al. (2) assessed the association between physical activity (at home,

Table 1 *Summary of observational study data on the relationship between physical activity and inflammatory mediators*

Reference, year of publication, study title (if available)	No. of participants (% men)	Age range (years)	Statistically significant relationships between physical activity and inflammatory mediators	Independent of BMI
Loprinzi et al. (14) 2013 (NHANES III)	Adults 2912 (49 %) Children 1643 (53 %)	29-48 12-16	**↓mean accelerometer counts per min→ ↑CRP** Mean accelerometer counts per min are not related to CRP in children	Yes Yes
Autenrieth et al. (2) 2009 (MONICA Augsburg Survey)	796 (55 %)	35-74	**↑MET mins per wk→↓fibrinogen, CRP, IL-6**	Yes
Hsu et al. (19) 2009 (Health, Aging and Body Composition study)	1088 (?)	70-79	↑kcal/wk of physical activity is not related to TNF-α, sTNFR 1 and 2, IL-6sR, IL-2sR **↑kcal/wk→↓CRP, IL-6, PAI 1**	Yes
Kullo et al. (22) 2007	172 (100 %)	26-84	**↑VO_2 max→↓ IL-6, CRP, fibrinogen**	Yes
McFarlin et al. (20) 2006	84 (?)	18-80	**↑VO_2 max→↓LPS stimulated IL-6, IL-1β, TNF-α, CRP**	Not assessed
Jankord & Jemiolo (18) 2004	12 (100 %)	60-74	**↑kcal/wk→↓IL-6, ↑IL-10,↑albumin,** Not related to CRP, MIP-1α, IL-1ra	Not assessed
Cesari et al. (21) 2004 (InCHIANTI Study)	660 (44 %)	65-102	**↓summary performance score→↑IL-6 and CRP**	Yes
Pischon et al. (15) 2003 (HPFS & NHSO)	859 (47 %)	40-75 men 25-42 women	**↑MET hrs per wk→↓sTNFR2, IL-6 and CRP** Not related to sTNFR1	No
Rawson et al. (23) 2003 (SEASON)	109 (57 %)	20-70	MET hrs per day, not related to CRP	No
Church et al. (16) 2002 (The Aerobics Center Longitudinal Study)	410 (100 %)	51±10	**↑MET in single testing→↓CRP**	Yes
Taaffee et al. (17) 2000 (MacArthur Studies of Successful Aging)	880 (47 %)	70-79	↑hrs per year of moderate-strenuous physical activity→**↓CRP and IL-6**	Yes

Legend: ↑=more; →=associated with;↓=less; CRP=C-reactive protein; IL=interleukin; TNF=tumour necrosis factor; PAI 1=plasminogen activator inhibitor 1; LPS=lipopolysaccharide; sR=soluble receptor; MET=metabolic equivalent; VO_2 max= maximal oxygen uptake; kcal=kilocalorie; min=minute; wk=week; yr=year; bold represents significant association

at work, travelling to work, and leisure time) and inflammatory mediators. Participants with high everyday physical activity (>6 MET) had a 42 % lower CRP than those with low physical activity (<3 MET). However, physical activity at home was not significantly associated with inflammatory markers. The same study also established a strong association between smoking and CRP. Physically less active smokers had 66 % higher CRP than very active non-smokers.

A study with 12 healthy men by Jankord and Jemiolo (18) established that aerobic exercise five times a week and high energy expenditure decreased pro-inflammatory IL-6 by 70 % and increased anti-inflammatory IL-10 by 36 %compared to aerobic exercise once a week.

In the Health ABC Study Hsu et al. (19) divided inflammatory mediators in two sets using component analysis. The CRP set with the related mediators IL-6 and plasminogen activator inhibitor 1 (PAI 1) inversely correlated with higher weekly energy expenditure. In contrast, the TNF-α set of mediators (sTNFR1, sTNFR2, IL-6sR, and IL-2sR) did not correlate with physical activity, when adjusted for the confounding factors of age, sex, race, and body mass index (BMI).

Even though the majority of the observational studies found a significant association between inflammatory mediators and physical activity, there are some limitations to these data, the most prominent being recall bias (as most of the studies relied on self-reported physical activity) and inability to establish a causal relationship. Some of the studies tried to avoid the recall bias by objectively assessing cardiorespiratory fitness. McFarlin et al. (20) established an inverse correlation between the fitness level (expressed

as VO_2max) and inflammatory markers. Participants having a below-average fitness level for their age had 24 % higher IL-6 and 21 % higher TNF-α than the participants fit above the average for their age. Inactive participants had 60 % higher CRP values than the active ones.

Church et al. (16) also found an inverse correlation between cardiorespiratory fitness and CRP. The odds ratio (OR) for CRP≥1.84 mg L^{-1} was 3.2 in favour of men with the lowest fitness (10.5 METs) *vs*. men with the highest fitness (12.4 METs) (measured by a modified Balke submaximal treadmill test).

Some studies have pointed out differences between men and women. One such study is the MONICA Augsburg Survey (2), in which the hand grip strength significantly correlated with CRP and IL-6 only in men. After adjustments for sex and BMI, the InCHIANTI Study (21) showed that BMI affected the association between physical activity and inflammatory mediators only in women. The association became statistically insignificant for CRP and IL-1ra after the results were adjusted for BMI in women, but it remained the same after the adjustment for BMI in men. This discrepancy was explained by a significant difference in body composition between the sexes; women have a much higher proportion of the adipose tissue, which is an important source of inflammatory cytokines.

This discrepancy also points to the role of the adipose tissue in inflammation mechanisms in relation to physical activity. The majority of the observational studies have established that the effect of physical activity on inflammatory mediators is independent of obesity (reflected by BMI). Beavers et al. (24) suggest that even though physical activity may reduce adipose tissue, study results have to be adjusted for BMI before making any conclusions. Several studies provide the opposing evidence that the association between physical activity and inflammatory mediators is partly weakened by BMI. Pischon et al. (15) found that it was significant for sTNFR2 ($p=0.01$) but borderline for CRP and IL-6 ($p=0.06$). Another yearlong longitudinal prospective cohort and nested cross-sectional study of Rawson et al. (23) did not find any effect of physical activity on CSSI. The 12 months of following 109 healthy men and women showed that CRP was significantly associated with BMI ($p<0.001$) but not with the changes in the frequency and intensity of physical activity ($p=0.84$). The association between CRP and BMI remained significant even after adjustments for physical activity, sex, age, and smoking. The authors conclude that when the BMI, weight, and waist-to-hip ratio remain stable, so does CRP, regardless of the frequency and intensity of physical activity. Judging by these findings, being overweight or obese seems to increase the risk of CSSI more than physical inactivity. However, the Rawson's study design may limit the interpretation of the results: the participants lived a sedentary lifestyle, their physical activity was self-reported (even though it matched the age averages), and, most importantly, did not vary much between the two years of the follow up, which made proper assessment of CRP alterations impractical. In fact, the evidence provided by this study is comparable to the evidence provided by interventional studies, to which we shall come later.

All things considered, even though much of the evidence corroborates the association between physical activity and inflammatory cytokines in the blood and excludes its dependence on BMI, observational studies are not designed to assess the cause-and-effect relationship between the measured variables. Furthermore, BMI is not a sensitive measure of the proportion of adipose tissue in the body (13). It is therefore valid to ask the following questions: 1) Is the relationship between inflammatory mediators and physical activity affected by the predictors of active lifestyle like nutrition, lean body mass, and visceral obesity? and 2) Can higher physical activity reduce CSSI?

These questions have been addressed by interventional studies summarised below.

Evidence from interventional studies

However, evidence from interventional studies designed to examine the effects of physical activity on inflammation is less consistent (13) for a number of reasons. Most of the interventional studies included in this review were designed as randomised control trials or as community-based clinical trials, and their sample sizes are smaller than in the observational studies. Most of the randomised trials recruited participants from specific groups, such as middle-aged men, pre- or postmenopausal women, adolescents, or the elderly, which prevents any generalisation beyond these groups. Some of the trials were not even randomised or controlled; their healthy participants differed in the baseline values, and interventions differed in duration, type, intensity, and frequency. These discrepancies affect the statistical power of their findings, which is already lower than in the observational (association) studies because of their design (comparison between groups). Furthermore, adding diet to physical activity may cause weight loss and reduce body fat, which also affects their findings (25).

This is why we have separated interventional trials focused on physical activity alone from those investigating the combined effects of physical activity and diet (caloric restriction). These two types of interventions provide two types of evidence. Table 2 summarises the evidence from 18 studies comparing moderate and high physical activity (26-43), while Table 3 summarises the trials with combined interventions.

Physical activity interventional studies

Steinberg et al. (26) found a 176 % increase in IL-6 and a 210 % increase in TNF-α from baseline in 15 healthy sedentary volunteers after a single bout of cycle-ergometer exercise performed to the time of exhaustion (but no longer than 12 min). The increase was short-term, 20 min, and the

Table 2 *Summary of interventional study data on the effect of physical activity alone on inflammatory mediators*

Reference, year of publication	No. of participants (% men)	Age (years)	Intervention	Training protocol and duration	Effect on inflammation mediators	Independent of BMI
Leggate et al. (33) 2012	12 (100 %)	18-34	Training	Cycling, 89.5 % of max HR 3x a week, 2 wks (HIIT)	**↓sIL-6R, MCP-1↓ adiponectin** No effect on IL-6, IL-10, TNF-α, sICAM-1	Not assessed
Nickel et al. (31) 2011	47 (100 %)	30-60	Training	Pre-marathon training, 4x a week, 10 wks	**↑adiponectin** No effect on IL-6 and TNF-α	No
Libardi et al. (34) 2011	47 (100 %)	49±5	Training/ observation	Resistance training, intensity of 8 RM, endurance training intensity of 55-85 % VO_2max, resistance training + endurance training, 60 min, 3x a wk, 16 wks	No effect on CRP, IL-6 and TNF-α	Not determined decrease of BMI
Beavers et al. (28) 2010 (LIFE-P Study)	368 (32 %)	70-89	Training/ health education	Resistance, aerobic, balance and flexibility training, Borg scale 12-13, 40-60 min, 3x a wk, 12 mo	No effect on CRP, IL-6, IL-6Sr, IL-1 sR2, IL-1ra, IL-2 sRα, TNF-α, sTNFR1&2, IL-8, IL-15, adiponectin	Not determined decrease of BMI
Thompson et al. (35) 2010	41 (100 %)	52±4 54±5	Training/ observation	Training int. of 50-70 % VO_2max, 30-60 min, 4x a wk, 6 mo	**↓IL-6** No effect on CRP, sICAM 1	Not assessed
Donges et al. (36) 2010	102 (44 %)	?	Res. training, aerobic training/ observation	Resistance training 70-75 % of 1RM, aerobic training 70-75 % of max HR, 30-50 min, 3x a wk, 10 wks	**↓CRP** No effect on IL-6	Yes
Campbell et al. (37) 2009	104 (0 %)	50-75	Training/ stretching 45 min per week	Aerobic training 60-75 % of max HR, 45 min, 5x a wk, 12 mo	**↓CRP** No effect on IL-6 and amiloid	Partly yes
Gray et al. (38) 2009	72 (23 %)	18-65	Training/ observation	30 min walks, 5x a week, 12 wks	No effect on CRP, IL6, sIL6R, TNF-α, sTNF-R1, sTNFR2	Not determined decrease of BMI
Nicklas et al. (29) 2008 (LIFE-P Study)	369 (32 %)	70-90	Training/ education	Aerobic, resistance, flexibility, and balance training, Borg scale 12-13, 5x a week, 12 mo	**↓IL-6** No effect on CRP	Yes

Reference, year of publication	No. of participants (% men)	Age (years)	Intervention	Training protocol and duration	Effect on inflammation mediators	Independent of BMI
Timmerman & Coen (39) 2008	30 (40 %)	65-80	Training/ observation	20 min walks, 60-70 % of max HR+ resistance training 30 min, 80 % of 1 RM, 3x a wk, 12 wks	**↓TNF-α** No effect on CRP	Not determined decrease of BMI
Markovitch et al. (40) 2008	12 (100 %)	54±4	Training	30 min walk, 75-85 % of max HR, single bout	No effect on CRP, IL-6, IL-10	Not assessed
Kim et al. (32) 2007	40 (100 %)	16-17	Training/ regular physical activity	Jumping rope exercise, 40 min, 5x a wk, 6 wks	**↑adiponectin** No effect on CRP, IL-6, TNF-α	Not assessed
Stewart et al. (30) 2007	60 (50 %)	18-85	Training/ observation	20 min cycling, 70-80 % of max HR + resistance training till exhaustion, 70-80 % of 1 RM, 3x a week, 12 wks	**↓CRP** No effect on IL-6, IL-1β, TNF-α	Not assessed
Olson et al. (41) 2007	28 (0 %)	22-44	Training/ education	Resistance training, 2x a wk, 12 mo	**↓CRP, ↑adiponectin** No effect on IL-6, sICAM-1, sVCAM-1	Not assessed
Steinberg et al. (26) 2007	15 (60 %)	42±4	Training	Cycle-ergometer, 20 W, single bout till exhaustion, max. 12 min	**↑IL-6, TNF-α**	Not assessed
Oberbach et al. (42) 2006	60 (48 %)	45.2±3.9	Training	Endurance + resistance training (HIIT), 60 min, 3x a week, 4 wks	**↓CRP, ↑adiponectin** No effect on IL-6 & IL-10	Yes
Zaldivar et al. (27) 2006	11 (100 %)	18-30	Training	Cycle-ergometer, 80 % of VO_2max, single bout, max 30 min	**↑IL-6, IL-1α, IL-10, TNF-α, ↓IL-4**	Not assessed
Nassis et al. (43) 2005	19 (0 %)	9-15	Training	Aerobic sports, HR>150 min^{-1}, 40 min. 3x a week, 12 wks	No effect on CRP, IL-6, sICAM-1, sVCAM-1, adiponectin	Yes

Legend: ↓=less; CRP=C-reactive protein; IL=interleukin; TNF=tumour necrotic factor; sR=soluble receptor; ra= receptor antagonist; sICAM=soluble intracellular adhesion molecule; sVCAM=soluble vascular adhesion molecule; MCP=monocyte chemotaxic protein; RM=repetition maximum; HR=heart rate; VO_2max=maximal oxygen uptake; HIIT=high intensity intermittent training; wk=week; mo=month; bold represents significant association

authors explained it with oxidative stress which preceded the increase in inflammatory mediators.

Using a similar design, Zaldivar et al. (27) established a parallel effect of a single 30-minute bout of intense physical activity on pro- and anti-inflammatory mediators in 11 healthy middle-aged men. Pro-inflammatory IL-1α, IL-6, TNF-α, and IL-10 rose, while anti-inflammatory IL-4 dropped. They explained this double effect as a way to prepare the organism for a variety of stressors, evidenced by an increase in T and B lymphocyte, NK cell, monocyte, and neutrophil counts. Of course, these studies are intentionally limited by design and do not reflect the effects of everyday physical activity on inflammatory markers.

Studies designed to assess longer-term effects of moderate regular exercise, however, are somewhat inconsistent. In 2010, Beavers et al. (28) conducted an intervention in a cohort of 368 elderly participants in a larger Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study, but found no effect of 12 months of regular, moderate, aerobic exercise on CRP, IL-6, IL-6sR, IL-1ra, IL-1sR2, IL-2sRα, TNF-α, sTNFR1, sTNFR2, and IL-15 after adjustment for confounding factors. The only

exception was the significant mean drop in IL-8 (p=0.03) and the drop in IL-6 in the participants with elevated baseline levels, but when these results were adjusted for multiple comparisons, the associations became insignificant. In contrast, the 2008 study by Nicklas et al. (29) on the same sample of LIFE-P study participants found a statistically significant drop in IL-6 (8.5 %) after adjustment for many confounding factors. The only difference between these two studies was the statistical analysis, which points to a possible methodological bias.

In the study of Stewart et al. (30) 60 participants aged 18-85 years went through a 12-week supervised, moderate, endurance training intervention on a treadmill combined with a resistance training intervention. Positive effects were established only for CRP (58 % decrease) but not for IL-6, IL-1β, or TNF-α.

In the study of Nickel et al. (31) 60 amateur marathon runners, divided in three groups (obese non-elite, lean non-elite, and lean elite), went through a 10-week personalised and supervised pre-marathon training programme. Only adiponectin (anti-inflammatory mediator) increased significantly (19 %) and only in the group of lean non-elite runners (who ran more than 38 km a week). Blood IL-6 and TNF-α dropped in all three groups, but the effect was not significant.

Kim et al. (32) published a rare randomised control trial in healthy but obese adolescents. According to the World Health Organization (WHO), 42 million children under the age of 5 were obese in 2014, with a high probability of becoming obese adults (44). Kim's study found a significant increase in adiponectin by 10 % after 6 weeks of moderate supervised training but no significant decrease in CRP, IL-6, or TNF-α (p>0.05 for all) compared to controls. These findings are similar to some interventional studies that found significantly lower circulating levels of adiponectin and higher CRP, IL-6, and TNF-α in obese children when compared to their lean peers (45).

Clearly, interventional studies with (moderate and long-term) physical activity alone show no or only a partial effect on inflammatory mediators.

Combined physical activity and diet interventional studies

In contrast, interventional studies combining physical activity with diet provide more robust evidence of positive effects on most inflammatory mediators. However, the participants of these studies were obese and had baseline circulating levels higher than population averages. Table 3 summarises the evidence from nine such studies (25, 46-53).

Imayama et al. (46) found that a yearlong, moderate training combined with a calorie-restrictive diet significantly reduced body weight, CRP, IL-6, and serum amyloid A (SAA). They divided 399 obese postmenopausal women in four groups: diet, diet and training, training, and control. In the diet group CRP dropped 36.1 %, IL-6 23.1 %, and SAA 17.5 % compared to control (p<0.05). In the combination group CRP, IL-6, and SAA dropped even further (41.7 %, 24.3 %, and 12 %, respectively). The training alone group, however, showed no significant changes. Weight loss in the intervention groups was 8.5 % in the diet alone group, 10.8 % in the combined group, and 2.4 % in the training alone group. These findings suggest that a weight loss above a certain threshold could have a significant clinical impact on inflammatory mediators and, consequently, reduce the risk of NCDs in obese postmenopausal women.

Similar findings in obese or overweight postmenopausal women were reported by You et al. (47) for a combined 6-month intervention with moderate physical activity and low-calorie diet, as CRP dropped 34 %, IL-6 27 %, IL-6sR 9 %, and sTNFR1 15 %. However, the diet alone group showed no significant changes, even though their weight loss and reduction of adipose tissue were also significant compared to baseline.

The study of Marfella et al. (48) has confirmed the hypothesis that physical activity (60-minute walks thrice a week) in combination with weight loss programmes (Mediterranean-style diet and counselling) works better in obese women with higher baseline levels of inflammatory mediators. After one year, their CRP decreased 44 %, IL-6 62 %, IL-18 30 %, and TNF-α 31 %.

Regardless of minor differences in design and outcomes, all these studies confirm that combined intervention is the most effective in reducing pro-inflammatory mediators, especially in individuals with higher baseline levels.

Possible mechanisms of action of physical activity on inflammation

Studies examining the effects of physical activity on immune cells suggest that physical activity inhibits the expression of leukocyte adhesion molecules and suppresses monocyte-endothelial cell interactions, inflammation, and release of pro-inflammatory cytokines from monocytes through its effects on oxidative stress in the cell. The last finding is based on the reports of increased cardiorespiratory capacity, reduced tissue hypoxia (47), and transient increase in cortisol level as a result of exercise (41, 54).

Physical activity also seems to suppress monocyte cell surface expression of the toll-like receptor 4 (TLR4), which triggers inflammatory response by activating antigen-presenting cells, which, in turn, induce the release of inflammatory mediators in the T cells (55). Findings from animal studies show that highly intensive exercises are more beneficial than moderate physical activity (56).

It was also found that Th1-type lymphocytes produce less cytokines after physical activity, more specifically IL-6, IL-1α, and interferon gamma (55).

In addition, recent studies have suggested a mechanism of IL-6 release independent of TNF-α, which makes the crucial difference in cytokine response between sepsis and

Table 3 *Summary of interventional study data on the effect of physical activity in combination with diet on inflammatory mediators*

Reference, year of publication	No. of participants (% men)	Age (years)	Intervention	Training protocol and duration	Effect on inflammation mediators	Independent of BMI
Imayama et al. (46) 2012 (NEW Study)	399 (0 %)	50-75	Diet, training, diet + training, observation	Aerobic training 60-75 % of max HR, 45 min, 5x a wk, 12 mo	**↓CRP, IL-6, SAA (TR, D+TR)** Without effect in the TR group	No
Fischer el al. (49) 2011	126 (0 %)	20-41	Diet, diet + aerobic training, diet + resistance training	Running, walking, 65-80 % of max HR, 60 min, resistance training, 60-80 % of 1 RM, 3x a wk, 8 wks	**↓CRP, IL-6, TNF-α, sTNFR1, sTNFR2**	No
Christiansen et al. (25) 2010	59 (49 %)	18-45	Diet, training, diet + training	Aerobic training, 60-75 min, 3x a wk, 12 mo	**↑adiponectin, ↓IL-15, IL-18, MIP-1α, MCP-1 (D, D+EX)** Without effect on all mediators in the TR group	Not for adiponectin, MIP1α and IL-15
Herder et al. (50) 2008 (DPS)	406 (?)	40-65	Diet + training/ information	Endurance training ± resistance training, ≥3.5 MET, 30 min, 12 mo	**↓CRP** Without the effect on IL-6	No
Bruun et al. (51) 2005	23 (48 %)	N/A	Diet + training	2-3 h of moderate to high intensive training, 5x a wk, 15 wks	**↓CRP, IL-6, IL-8, MCP1, ↑adiponectin** Without effect on TNF-α	Not done
You et al. (47) 2004	34 (0 %)	50-70	Diet, diet + training	Walking, 70 % of max HR, 3x a wk, 6 mo	**↓CRP, IL-6, sIL-6R, sTNFR1 (D+TR)** Without the effect on TNF-α and sTNFR2 D: without effect	Not for IL-6 and sTNFR1
Ryan et al. (52) 2004	37 (0 %)	50-70	Diet + training	Resistance or endurance training VO_2max >60 %, 45 min, 3x a wk, 6 mo	**↓CRP, IL6, sTNFR1** Without effect on TNF-α, sTNFR2, IL-6sR	No
Marfella et al. (48) 2004	107 (0 %)	24-44	Diet + training	60 min walks, 3x a wk, 12 mo	**Obese: ↓CRP, IL-6, IL-18, TNF-α** Without the effect in non-obese group	No
Esposito et al. (53) 2003	112 (0 %)	20-46	Diet + training/ information	Walking, swimming, sports, 175 min a wk, 24 mo	**↓CRP, IL-6, IL-18, ↑adiponectin**	No

Legend: ↑=more; ↓=less; D=diet; EX=exercise; TR=training; CRP=C-reactive protein; IL=interleukin; TNF=tumour necrotic factor; sR=soluble receptor; MCP=monocyte chemotactic protein; MIP=macrophage inflammatory protein; RM=repetition maximum; HR=heart rate; VO_2max=maximal oxygen uptake; MET=metabolic equivalent; wk=week; mo=month; bold represents significant effects

exercise. Namely, during exercise, blood IL-6 soars hundredfold without increasing TNF-α or IL-1β levels. The source of this IL-6 is the contracting skeletal muscle (6). This IL-6 release is unlike the one from the liver and mononuclear cells, which depends on TNF-α. The amount of secreted IL-6 is related to the intensity and duration of exercise and the muscle mass involved. The contracting muscle activates IL-6 mRNA, which transcribes the IL-6 gene (4, 6). The muscle-released IL-6 suppresses pro-inflammatory mediators TNF-α and IL-1β by stimulating their receptor antagonists and enhances the release of anti-inflammatory IL-1ra and IL-10 from the liver (55).

A number of studies propose how adipose tissue influences the effects of physical activity on inflammatory mediators. Macrophage-infiltrated adipose tissue can produce more than 70 inflammatory proteins (55). Most of them are released from the visceral, but some also from the subcutaneous adipose tissue. Chronic inflammation has

been established as a crucial link between the adipose tissue and metabolic disorders. Adipocyte hypertrophy leads to tissue hypoxia, oxidative stress, necrosis, and macrophage infiltration. Reducing adipocyte volume by calorie restriction and physical activity lowers endothelial cell and macrophage counts as well as the release of many cytokines (55). Some studies have evidenced increased mRNA expression for anti-inflammatory adiponectin and decreased expression for macrophage-specific markers CD14 and CD68 following sustained diet and exercise intervention (51). Physical activity combined with hypocaloric diet stimulates visceral and gluteal adipose tissue lipolysis through several mechanisms: it activates protein kinases, stimulates hormone-sensitive lipases and insulin-induced lipolysis, and enhances the β adrenergic pathway-stimulated lipolysis. The inverse relation of IL-6 and sTNFR1 with visceral lipolysis may explain one of the mechanisms connecting physical activity and inflammatory mediators (47).

CONCLUSIONS

Interventional studies designed to assess the effect of hypocaloric diet combined with physical activity on inflammatory mediators and large observational studies provide consistent evidence that moderate and highly intensive physical activity, higher cardiorespiratory fitness, lower caloric intake, and weight loss inversely correlate with the circulating levels of pro-inflammatory mediators. However, such evidence for physical activity alone is still inconsistent.

Combined interventions have been more effective in groups at risk of NCDs, such as the obese, the elders, and the smokers, whose baseline inflammatory marker levels are higher than average in the healthy population.

Further studies are needed to clearly determine the type, intensity, and frequency of exercise, with or without diet, that will achieve clinically significant reductions of CSSI.

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Učinci tjelesne aktivnosti na kroničnu subkliničku sustavnu upalu

Kronične nezarazne bolesti najznačajniji su javnozdravstveni problem. Kronična subklinička upala kao osnovni patološki supstrat zajednički je rizični čimbenik za većinu tih bolesti i stanja, kao što su arterioskleroza, metabolički sindrom, kardiovaskularne bolesti, rezistencija na inzulin i šećerna bolest tipa 2, novotvorine, opstruktivne plućne bolesti i mnoge druge. Nasuprot tomu, utvrđeno je da je redovita tjelesna aktivnost protektivni čimbenik u spomenutim bolestima. Provedene su mnoge studije različitoga dizajna s ciljem razotkrivanja povezanosti između kronične subkliničke upale i upalnih medijatora i redovite tjelesne aktivnosti. Cilj je ovog pregleda bio predočiti trenutačnu razinu dokaza te poimanja potencijalnih mehanizama u podlozi smanjenja kronične subkliničke upale kao posljedice redovite tjelesne aktivnosti, uključenih medijatora upale te oblika tjelesne aktivnosti potrebnih kako bi se postigao očekivani učinak. Utvrdili smo da su studije povezanosti predočile konzistentne dokaze u korist pozitivne povezanosti između redovite tjelesne aktivnosti i smanjenja kronične subkliničke upale. Dizajn tih studija ne dopušta zaključke o uzročno-posljedičnoj povezanosti ispitivanih fenomena. S druge strane, rezultati intervencijskih studija nisu konzistentni. Problem pri interpretaciji tih rezultata prouzročen je značajnom heterogenošću u dizajnu provedenih intervencijskih studija vezano uz veličinu uzorka, tip ispitanika te uz oblik intervencije (intenzitet i ekstenzitet tjelesne aktivnosti, trajanje intervencije, udruženost s gubitkom tjelesne mase). Na temelju trenutačne razine dokaza možemo zaključiti da je potrebno provesti više kvalitetnih intervencijskih studija radi definiranja tipa, intenziteta i ekstenziteta tjelesne aktivnosti koja će imati najznačajniji utjecaj na smanjenje kronične subkliničke upale.

KLJUČNE RIJEČI: *kronične bolesti; medijatori upale; stil života*