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Session 6: Role of physical activity on immune function Physical activity, exercise and low-grade systemic inflammation

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Prospective studies have shown that chronic low-grade inflammation may contribute to the pathogenesis of the most common chronic diseases and in particular CVD. Obesity has repeatedly been associated with moderately raised levels of inflammation, and this observation has led to the view that obesity is characterised by a state of chronic low-grade inflammation. There is now great interest in elucidating how physical activity and exercise modulate inflammation. This review summarises the current research addressing the influence of physical activity and exercise in mitigating the risks of obesity and diseases such as type-II diabetes and CVD, through its action on the low-grade inflammatory state. Most research on this topic hypothesised that the association between physical activity and inflammatory markers is independent of fatness, but very few studies have proven this. Given that physical activity and obesity are often inversely related, it is not clear as to whether the anti-inflammatory health benefits of a physically active lifestyle are due to exercise *per se* or result from favourable changes in the body composition.

Physical activity: Exercise: Low-grade inflammation: Obesity

Low-grade inflammation

Inflammation is a key function in the process by which the body responds to an injury or an infection, and the acute phase of inflammation normally leads to recovery from infection to healing, and a return to normal values within a few days. However, if the response is not properly phased, the process can develop into a chronic low-grade inflammatory state which may trigger different diseases under pathological conditions^(1,2). Prospective studies in adults have shown that chronic low-grade inflammation may contribute to the pathogenesis of diseases such as atherosclerosis^(3,4), type I- and type-II diabetes^(1,2), cancer⁽⁵⁾, several types of neurodegenerative disorders⁽⁶⁾ and autoimmune diseases⁽⁷⁾.

Several parameters of the inflammatory reaction can be measured in plasma. The inflammatory markers that have

been shown to be associated with obesity or the metabolic syndrome include acute phase proteins, pro-inflammatory cytokines, adhesion molecules and adipokines (proteins secreted by adipose tissue). C-reactive protein (CRP) concentrations are easily, accurately and fairly inexpensively measured in blood. It is an acute phase reactant and a very sensitive marker of inflammation. High-CRP levels have no specificity in differentiating disease entities from one another, but despite its lack of specificity, CRP has now emerged as one of the most powerful predictors of cardiovascular risk^(4,8,9). In a direct comparison of a panel of inflammatory and lipid markers in their ability to predict cardiovascular events in adults, CRP surpassed other classical risk markers, including LDL-cholesterol^(10,11). The American Heart Association and the Centres for Disease Control and Prevention in the USA issued a joint statement confirming that CRP is the best and most clinically useful

Abbreviation: CRP, C-reactive protein.

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of the markers of inflammation currently available, with the following cut-off points for assessing CVD risk: low risk (CRP < 1.0 mg/l), average risk (1.0–3.0 mg/l) and high risk (> 3.0 mg/l)⁽⁸⁾. Most studies use CRP as the only marker of inflammation, however, choosing a wider spectrum of inflammatory markers can give us a better picture of the specific mechanisms involved. Other commonly used acute-phase reactants include complement factors C3 and C4, serum amyloid A and ceruloplasmin. Pro-inflammatory cytokines, such as IL-6, IL-1 β and TNF α , are often included in the panel of inflammatory markers and have been associated with obesity and components of the metabolic syndrome. The endothelial expression of vascular adhesion molecules VCAM-1 and intracellular adhesion molecule ICAM-1 and E-selectin are used as markers of the filtration of inflammatory cells in the arterial wall. Of the adipokines, the most studied is adiponectin^(1,12).

Obesity-induced chronic low-grade inflammation

Obesity has repeatedly been associated with moderately raised levels of inflammation, and this observation has led to the view that obesity is characterised by a state of chronic low-grade inflammation⁽¹³⁾. Adipose tissue is now widely recognised as having endocrine functions⁽¹³⁾. Adipokines are locally produced in the adipose tissue seem to increase the hepatic synthesis of acute phase inflammatory proteins (e.g. CRP, complement factors and serum amyloid A). The continued identification of bioactive proteins secreted by adipokines supports the theory that an excess of adiposity plays a central role in the metabolic syndrome and in insulin resistance^(1,2,12).

In the metabolic syndrome, obesity is the main determinant of inflammation, and the relative implication of each component may be difficult to disaggregate when they cluster together in a metabolic disorder.

Insulin: an anti-inflammatory hormone?

Recent observations in *in vitro* studies have proposed a pro-inflammatory effect of glucose and an anti-inflammatory action of insulin^(1,2,12). These observations have led to a working hypothesis explaining how the pro-inflammatory state that accompanies the metabolic syndrome associates with both insulin resistance and endothelial dysfunction, via the connection between inflammation and metabolic processes. This hypothesis would also explain why insulin-resistant states (like obesity and type-II diabetes) are associated with oxidative stress, inflammation and atherosclerosis.

Physical activity counteracting obesity-induced low-grade inflammation

Body fat seems to be the main determinant of inflammation. However, physical activity is a major modifiable risk factor of obesity and therefore offers a potential therapeutic approach to modulate low-grade inflammation.

The health benefits of a physically active lifestyle are well recognised. Physical inactivity and obesity are also increasingly recognised as modifiable behavioural risk factors for a wide range of chronic diseases, and in particular for CVD⁽¹⁴⁾. It could therefore be reasonable to hypothesise that health benefits attributed to physical activity may be mediated by reducing or preventing inflammation.

Physical fitness, physical exercise and physical activity are used as interchangeable concepts in most reviews on this topic, but it is important to point out the differences to highlight the potential differences in outcomes. Physical activity is any body movement that increases energy expenditure⁽¹⁵⁾. Self-reported data of physical activity is easy and feasible to ask in a questionnaire or interview in large populations, but is a measurement subject to recall and reporting biases. Exercise is planned, structured and repetitive physical activity, while physical fitness is the capacity to perform physical activity, and makes reference to a full range of physiological and psychological qualities. Physical fitness has been also defined as 'a set of attributes that people have or achieve that relates to the ability to perform physical activity'⁽¹⁵⁾. To eliminate reporting bias that could be present in self-reported physical activity measurement, several studies have examined the relationship between cardiorespiratory fitness and inflammatory markers.

V_{O₂}max attained during a graded maximal exercise to voluntary exhaustion has long been considered by WHO as the single best indicator of cardiorespiratory fitness⁽¹⁶⁾. Nevertheless, one should bear in mind that the measurements are different and that different metabolic pathways for any possible anti-inflammatory effect could be present, and therefore clearly differentiate the methodologies used.

Excellent reviews of the evidence addressing the influence of physical activity and fitness on low-grade inflammation from epidemiological studies as well as clinical trials on the general adult population have been published^(17,18), also in athletes^(19,20), and to a lesser extent in children and adolescents⁽²¹⁾. A wide range of inflammatory markers have been measured and assessed against physical activity; these include fibrinogen, cytokines, leucocytes, although CRP is by far the most commonly used.

Acute v. regular exercise

IL-6 and other cytokines which are produced and released by skeletal muscles have been suggested to be involved in mediating the health-beneficial effects of exercise and play important roles in the protection against diseases associated with low-grade inflammation. The following hypothesis is based on years of observation by Pedersen and co-workers^(22–24): plasma IL-6 increases in an exponential fashion with exercise and is related to exercise intensity, duration, the mass of muscle recruited and one's endurance capacity. Consequently, the contracting skeletal muscle is a major source of circulating IL-6 in response to acute exercise. During heavy exercise, such as a marathon, there is up to a 60-fold increase in the IL-6 plasma levels⁽²⁵⁾ with the duration of the event explaining more than 50% of the variation⁽²⁶⁾. The mentioned plasma IL-6 increase

supports the hypothesis that the post-exercise cytokine production is related to skeletal muscle damage with an acute inflammatory response⁽²⁷⁾.

Interestingly, IL-6 shows a markedly lower response to acute exercise in trained subjects. The health benefits of long-term regular exercise are ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6. Physiological concentrations of IL-6 stimulate the appearance in the circulation of the anti-inflammatory cytokines IL-1ra and IL-10, and inhibit the production of the pro-inflammatory cytokine TNF α . The anti-inflammatory effects of exercise may therefore offer protection against TNF-induced insulin resistance. Moreover, IL-6 stimulates lipolysis as well as fat oxidation. The increase of IL-6 at the end of acute exercise is responsible for the increased CRP levels during late recovery. In response to regular physical activity, basal as well as post-exercise plasma levels of IL-6 decreases by mechanisms that might include increased glycogen content, improved anti-oxidative capacity and improved insulin sensitivity. The lower levels of IL-6 in circulation will subsequently result in lower CRP levels. When untrained, basal plasma IL-6 and CRP levels are elevated via mechanisms that may involve impaired insulin sensitivity and/or increased oxidative stress^(22,23).

Few studies have prospectively examined the effect of exercise training on low-grade inflammatory status, and the data obtained from intervention studies are less consistent when compared with cross-sectional population studies or with clinical experiments. A lower number of subjects or a good physical condition at the start of some intervention studies may explain a part of this inconsistency. Nevertheless, two longitudinal studies in athletes show that regular training induces a reduction in the CRP level^(28,29).

Physical activity-based lifestyle change appears to be the most variable component of energy expenditure and therefore has been the target of behavioural interventions to modify body weight. However, combined dietary and exercise interventions do not provide consistent evidence that exercise *per se* and not weight loss is more important for reducing inflammatory factors, and it is beyond this summary and can be reviewed elsewhere⁽³⁰⁾.

Conflicting findings exist in clinical trials that have involved exercise only. Several training interventions have not produced changes in the basal IL-6 or CRP^(31–34), while significant reductions in inflammatory markers have been observed following training without changes in BMI or body fat in elderly participants^(35,36). The biggest trial with exercise training on inflammation was performed in 652 sedentary healthy, young and middle-aged, white and black women and men in the HERITAGE Family Study after a 20-week training intervention⁽³⁷⁾. There was no control group to compare with, and every subject served as his/her own control. A non-significant reduction was consistent across all population groups and varied between 1.2 and 2.2 mg/l. Considering that the variation over time in CRP in healthy individuals with stable lifestyles is small⁽⁸⁾, the reduction, although non-significant, could nevertheless reflect the true effect of exercise training. Further stratification according to basal CRP levels showed a reduction by about 1.3 mg/l in subjects with initial CRP levels above

3.0 mg/l. This observation is potentially important from a public health and clinical point of view by decreasing the risk of CVD in individuals with high CRP. Thus, baseline levels may be an important factor.

Elderly people and disease states

Elderly people have higher basal levels of inflammation independent of disease status, and a considerable number of studies have been carried out in this population to assess the associations between physical activity and inflammatory markers^(38–43). Rather consistent inverse BMI independent associations are found and the associations are suggested to be dose-dependent; the more physically active the person, the lower the inflammatory markers^(24,44). Also, subjects over 80 years show consistent inverse associations between inflammation and physical activity⁽⁴⁵⁾. A mean score of functional fitness was associated with IL-6, and IL-1RA (but not CRP, TNF α , IL-10 or IL-1 β) in a prospective population-based study of 1020 participants aged 65 years and above^(38,46). Muscle strength was also evaluated in this study and low hand-grip strength was associated with high levels of CRP ($P < 0.001$) and IL-6 ($P < 0.001$)⁽⁴⁶⁾. A few more studies have shown a negative association of CRP, IL-6 and TNF α with muscle strength^(41,47).

Exercise intervention in elderly people or patients with CVD shows more consistent results of an anti-inflammatory effect. After a 6-month individualised, supervised exercise programme for 43 subjects at a high risk of IHD, a trend towards reduced CRP levels (35%) was observed. The subjects exercised for a mean of 2.5 (range, 0.3–7.4) h per week⁽⁴⁸⁾. Another study has reported a decrease of basal plasma IL-6 after aerobic training in patients with coronary artery disease⁽⁴⁹⁾. A randomised trial of 39 patients with intermittent claudication demonstrated that both serum CRP and amyloid-A levels were significantly reduced after 3 and 6 months of supervised exercise compared with controls⁽⁵⁰⁾. In a relatively large intervention study of exercise training on cardiac rehabilitation patients, the median CRP concentrations were significantly reduced by 41% (mean change from 5.9 (SD 7.7) mg/l to 3.8 (SD 5.8) mg/l; median change from 3.4 to 2.0 mg/l) in 235 patients with coronary artery disease, while CRP concentration did not change in 42 subjects who did not exercise⁽⁵¹⁾. Again, the exercise training seemed to be more effective in those with the highest CRP concentration, independent of changes in body weight or percentage of body fat⁽⁵¹⁾ indicating that baseline levels of low-grade inflammation may be an important factor.

In disease states such as symptomatic CVD or in patients with the metabolic syndrome, as well as in elderly people, levels of inflammatory markers are generally higher than in healthy young adults. Evidence points out that higher basal low-grade inflammation may be a factor in determining the relative contribution of fitness. Studies in patients with diabetes⁽⁵²⁾ and metabolic syndrome^(53,54) have consistently demonstrated inverse associations between fitness and inflammation independent of fatness. In one study, the independent associations of fitness were

in fact more prominent among metabolic syndrome patients compared with healthy participants^(53,54).

Middle-aged, younger adults and children

Several studies of large population cohorts, such as the British Regional Heart Study⁽⁴⁰⁾, the ATTICA study⁽⁵⁵⁾, the Third National Health and Nutrition Examination Survey^(56,57), the men's Health Professionals Follow-up Study⁽⁵⁸⁾, the Nurses' Health Study II⁽⁵⁸⁾ and the Women's Health Study⁽⁵⁹⁾, provide evidence for an inverse, independent dose–response relationship between plasma CRP concentration and level of physical activity in both men and women, but the consistency is less than in elderly subjects, or in disease states.

On the contrary, the associations found between self-reported physical activity, and soluble receptor of TNF-R1 and TNF-R2, serum IL-6 and CRP in a study including healthy men from The Men's Health Professionals Follow-up Study and healthy women from the Nurses' Health Study II⁽⁵⁸⁾ were no longer significant when adjusting for BMI and leptin, suggesting that inflammation does not directly account for the beneficial effects of physical activity. The effects in healthy men and women of BMI, CRP and physical activity were measured longitudinally over 1 year and retrospectively for physical activity the previous year, concluding that BMI, but not previous year or current physical activity, predicts CRP⁽⁶⁰⁾. A univariate analysis of CRP levels in 2120 Finns showed that CRP was associated with obesity indices and physical activity among both sexes⁽⁶¹⁾. In multivariate correlates, however, the determinants of CRP levels include obesity and smoking in men and obesity, oral contraceptives use and physical activity in women. The study showed that about one in three healthy women who used oral contraceptives had CRP concentration exceeding 3 mg/l, which should be taken into account when studying younger females. In a longitudinal study⁽⁶⁰⁾ of healthy men and women, BMI, but not current- or previous-year physical activity, was significantly related to CRP. Similarly, a cross-sectional study⁽⁶²⁾ in men found no relationship between leisure time, physical activity and CRP, fibrinogen and serum amyloid A, after correction for BMI and current smoking status.

Cross-sectional studies in men from the Aerobics Center Longitudinal Study have demonstrated that cardiorespiratory fitness levels are inversely associated with CRP values and also the prevalence of elevated CRP values⁽⁶³⁾. Analyses with fibrinogen and leucocyte count showed similar results⁽⁶⁴⁾. The competing effect of weight and fitness (assessed by submaximal graded exercise treadmill testing) on cardiorespiratory fitness levels was studied in the NHANES (1999–2002) which included 2112 US adults without previously diagnosed CVD⁽⁶⁵⁾. Both fitness and BMI were independently associated with increased fasting insulin and CRP. However, when patients with low, moderate and high fitness were further stratified as normal, overweight, or obese, weight remained significantly associated with CRP, but fitness did not.

Disease-free young population studies have assessed the interaction between inflammatory markers (CRP, IL-6 and TNF α), physical activity or cardiorespiratory fitness and

fatness^(66–74). Organised leisure time exercise (assessed by questionnaire) in children has shown negative correlations with serum IL-6 concentrations, independent of adiposity and fat localisation⁽⁶⁸⁾, and in 10-year-old children, a borderline significant negative association was observed between CRP and self-reported physical activity, independent of ponderal index⁽⁶⁶⁾. US children and young adults (aged 6 to 24 years) from the Columbia University Bio-Markers Study showed an inverse correlation between cardiovascular fitness level and CRP, but only in boys, which remained after adjustment of confounders including BMI⁽⁶⁹⁾. Only one study has used accelerometry (an objective measure of total physical activity compared with leisure time physical activity or exercise) instead of questionnaires as well as cardiovascular fitness⁽⁷⁴⁾. In this study of 9-year-old Swedish children, total physical activity was unrelated to CRP, fibrinogen, C3 or C4, but exercise was. Nevertheless, once body fat was entered in the regression models, no associations with cardiovascular fitness or physical activity and either of the inflammatory markers measured were observed⁽⁷⁴⁾. Similarly, no associations were found between cardiorespiratory fitness or self-reported physical activity and CRP in 12-year-old healthy Welsh children⁽⁷⁵⁾.

CRP, C3 and ceruloplasmin (but not C4) were negatively associated with muscle strength after controlling for sex, age, pubertal status, weight, height, socioeconomic status and cardiorespiratory fitness, but did not remain when adjusting body fat. Nevertheless, when stratifying according to overweight status, CRP (but not C3, C4 or ceruloplasmin) was associated with muscle strength in overweight adolescents (but not normal weights) after controlling for potential confounders, including body fat and fat-free mass⁽⁷⁶⁾.

Gender effects

It has been suggested that the role of fatness in relation to fitness and inflammatory pathways may be especially prominent in women⁽¹⁷⁾. In three studies^(38,42,69) an inverse relationship between fitness and CRP was demonstrated for males, but not females after adjusting for fatness. The reason for this gender-related discrepancy is unclear, but may be related to less physical activity in women. Nevertheless, there is a close link between sex steroids, sub-clinical inflammation, insulin resistance and body fat distribution in regularly menstruating women, and serum concentrations of CRP significantly change during the menstrual cycle⁽⁷⁷⁾. Furthermore, CRP levels are more strongly related to insulin resistance and the individual components of the metabolic syndrome in women than in men⁽⁷⁸⁾.

Summary

Most research on this topic hypothesised that the association between fitness and inflammatory factors is independent of fatness. Given that physical activity and obesity are often inversely related, it is not clear as to whether the anti-inflammatory health benefits of a physically active

lifestyle are due to exercise *per se* or result from favourable changes in body composition. Related anti-inflammatory effects could be mediated by increased insulin sensitivity and/or improved concentrations of HDL-cholesterol, reactive oxygen species or endothelial function, which all demonstrate anti-inflammatory actions⁽⁷⁹⁾, and are related to both body fat and exercise. A systematic review by Hamer addresses whether fitness or fatness has the greatest impact on inflammatory factors⁽¹⁷⁾. The review concluded that both fitness and fatness are associated with systemic inflammatory status, although the relative contributions of both may be dependent on age, disease status and gender. For example, the association between adiposity and low-grade systemic inflammation has been shown to be considerably stronger in women than in men⁽⁸⁰⁾.

Most apparent is the comparison between consistency in studies between elderly population and children or adolescents, or obese *v.* lean subjects.

Although increasing physical activity may be an effective therapy for weight loss and may also emerge as a promising treatment for reducing overall inflammation, the magnitude of the effect to produce clinically meaningful results in the general population requires further research. Nevertheless, exercise is uniquely positioned to reduce inflammation and even small non significant reductions in CRP levels may contribute to clinical benefits by reducing cardiovascular and metabolic risk.

Conclusions

Few studies have proven that the association between physical activity and inflammatory markers is independent of fatness. Given that physical activity and obesity are often inversely related, it is not clear as to whether the anti-inflammatory health benefits of a physically active lifestyle are due to exercise *per se* or result from favourable changes in body composition. Nevertheless, we consider that there is enough evidence to suggest that regular physical activity induces favourable changes on the metabolic profile including the inflammatory status, contributing as such to clinical benefits by reducing cardiovascular and metabolic risk.

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