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Persistent low-grade inflammation and regular exercise

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1. ABSTRACT

Persistent low-grade systemic inflammation is a feature of chronic diseases such as cardiovascular disease (CVD), type 2 diabetes and dementia and evidence exists that inflammation is a causal factor in the development of insulin resistance and atherosclerosis. Regular exercise offers protection against all of these diseases and recent evidence suggests that the protective effect of exercise may to some extent be ascribed to an anti-inflammatory effect of regular exercise. Visceral adiposity contributes to systemic inflammation and is independently associated with the occurrence of CVD, type 2 diabetes and dementia. We suggest that the anti-inflammatory effects of exercise may be mediated via a long-term effect of exercise leading to a reduction in visceral fat mass and/or by induction of anti-inflammatory cytokines with each bout of exercise.

2. INTRODUCTION

Over the past decade, there has been an increasing focus on the role of persistent low-grade inflammation in the pathogenesis of atherosclerosis (1-3). Further, inflammation has been suggested to be a key factor in insulin resistance (4, 5) and neurodegeneration (6, 7).

Persistent low-grade systemic inflammation is reflected by increased systemic levels of some cytokines (8), as well as C-reactive protein (CRP). Numerous reports investigating various markers of inflammation have confirmed an association between low-grade systemic inflammation on one hand and several chronic diseases on the other (9, 10).

Infiltration of immune cells into white adipose tissue, and subsequently local inflammation in fat tissue, is

correlated with the development of insulin resistance and type 2 diabetes (11). Similarly, activated immune cells and inflammation have an important role in cardiovascular diseases (12, 13) and local inflammation in the brain is a feature of Alzheimer's disease. In addition, it appears that systemic inflammation may further stimulate the progression of these neurological disorders (14).

3. EXERCISE AND CHRONIC DISEASES

Over the past several decades, numerous large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all-cause mortality. A recent meta-analysis included a total of 33 studies with 883,372 participants with a follow-up time of up to more than 20 years. Concerning cardiovascular mortality, physical activity was associated with a risk reduction of 35%, whereas all-cause mortality was reduced by 33% (15). The risk reduction is, at least in part, attributed to the favourable effect of physical activity on the cardiovascular risk factors. Increased physical activity lowers blood pressure in hypertensive individuals, increases high-density lipoprotein cholesterol in a dose-response fashion, and reduces the incidence of diabetes (16). Taken together, there is no doubt that physical activity is independently associated with a marked decrease in risk of cardiovascular disease (CVD) as well as CVD mortality in both men and women.

Randomised controlled trials including people with impaired glucose tolerance have found that lifestyle modification (diet and moderate physical activity) protects against the development of type 2 diabetes. A Finnish trial randomised 522 overweight middle-aged people with impaired glucose tolerance to physical training combined with diet or to control and followed them for 3.2 years (17). The risk of type 2 diabetes was reduced by 58% in the intervention group. The effect was greatest in the patients who made the greatest lifestyle modification. An American trial randomised 3,234 people with impaired glucose tolerance to either treatment with metformin, lifestyle modification entailing dietary change and at least 150 minutes of physical exercise weekly, or placebo, and followed them for 2.8 years (18). The lifestyle modification reduced the risk of type 2 diabetes by 58%. The reduction was thus the same as in the Finnish trial (17), whereas treatment with metformin only reduced the risk of diabetes by 31%. After a median of 4 years of active intervention period, participants in the Finish study who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. During the total follow-up, the incidence of type 2 diabetes was 4.3 and 7.4 per 100 person-years in the intervention and control group, respectively, indicating 43% reduction in relative risk. The risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat and increased intake of dietary fibre, and increased physical activity (19).

Also, the beneficial effect of training in patients, who have been diagnosed with type 2 diabetes, is well documented (20). Post-intervention HbA1c was lower in the exercise groups than in the control groups (7.65% versus 8.31%). In comparison, intensive glycaemic control with metformin reduced HbA1c by 0.6% (21). A meta-analysis encompassing 95,783 non-diabetic individuals showed that cardiovascular morbidity is strongly correlated to fasting blood glucose (22). The effect of physical training on HbA1c is thus highly clinically relevant.

In humans, type 2 diabetes is associated with impaired cognitive function, including learning, memory, and processing speed (23). Large longitudinal population-based studies show that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes (24). A recent review (25) showed that the incidence of 'any dementia' was higher in individuals with type 2 diabetes than in those without. This high risk included both Alzheimer's disease and vascular dementia.

Interestingly, a couple of studies suggest that regular exercise also protects against dementia (26-28).

Chronic inflammation accompanies CVD, type 2 diabetes and dementia, potentially explaining the clustering of these conditions in epidemiological studies. The fact that regular exercise offers protection against these diseases further suggest that the beneficial effects of exercise may at least in part be mediated by anti-inflammatory mechanisms.

4. THE EFFECTS OF EXERCISE ON SYSTEMIC AND LOCAL INFLAMMATION

Regular exercise appears to induce anti-inflammatory effects. An association between physical inactivity and low-grade systemic inflammation has been demonstrated in cross-sectional studies, including healthy younger individuals (29-34), elderly people (35), as well as in patients with intermittent claudication (36). However, also longitudinal studies show that regular training induces a reduction in CRP level (37, 38), suggesting that physical activity *per se* may suppress systemic low-grade inflammation. Several studies have shown that markers of inflammation are reduced following longer-term behavioural changes involving both reduced energy intake and increased physical activity (39-46).

In the Finish diabetes prevention study, lifestyle interventions reduced circulating levels of CRP and IL-6. Increases in fibre intake and moderate to vigorous leisure time physical activity but not total leisure time physical activity, predicted decreases in CRP and/or IL-6 and remained associated even after adjustment for baseline BMI or changes in BMI during the first year of the study. Changes in carbohydrate or fat intake were either weakly or not linked to reductions in CRP and IL-6 (47).

It appears that exercise may have anti-inflammatory effects, which are independent of weight-loss. However, the mediators of this effect are unclear. A number of mechanisms have been identified. Exercise increases the release of epinephrine, cortisol, growth hormone, prolactin and other factors that have immunomodulatory effects (48).

Furthermore, exercise results in decreased expression of Toll-like receptor on monocytes suggested being involved in mediating whole body inflammation (49).

A recent study demonstrates that exercise training decreases expression of inflammation-related adipokines through reduction of oxidative stress in rat white adipose tissue (50).

In the latter study, it was shown that the levels of inflammation-related adipokines, such as tumor necrosis factor-alpha and monocytes chemo attractant protein-1, in white adipose tissue of trained rats were lower than those in sedentary rats. Interestingly, the effects of exercise training were more remarkable in visceral fat than in subcutaneous fat. Another experimental study showed that training increased the IL-10/TNF-alpha ratio in rat adipose tissue (51). They furthermore showed that the mesenteric depot was more responsive to moderate intensity exercise training than the retroperitoneal pad, and that such heterogeneity of response was present also in healthy animals.

Furthermore, it was demonstrated that the expression of TNF-, MCP-1, PAI-1 and IKKβ was increased in adipose tissue from mice on high fat/high sucrose diet compared with chow mice, whereas exercise training reversed the increased expression of these inflammatory cytokines (52).

A study evaluated the effect of 12 wk of exercise (aerobic and resistance) or 12 wk of weight loss (7% reduction) in obese individuals. They found that exercise resulted in a 37% decrease in TLR-4 mRNA while weight loss had no significant effect. Additionally, exercise led to a 50% decrease in IL-6 and TNF- mRNA in muscle, while weight loss had no effect (53). The latter study confirmed that exercise but not weight loss had a beneficial effect on markers of muscle inflammation in frail obese elderly individuals.

5. EXERCISE AND ABDOMINAL ADIPOSITY

Abdominal adiposity is associated with cardiovascular disease (54), type 2 diabetes (55), and dementia (56). Moreover, abdominal adiposity is directly associated with all-cause and cardiovascular disease mortality independently of body mass index, even in people with a normal body weight (57). Abdominal adiposity reflects most often accumulation of visceral fat, which is more inflamed than subcutaneous fat tissue (58, 59). Moreover, the inflammation of the visceral fat is thought to be a major cause of the systemic low-grade inflammation (60). It is therefore obvious that regular exercise may mediate anti-inflammatory effects simply by reducing visceral adipose tissue mass.

A number of studies suggest that physical activity reduces abdominal and particularly visceral fat in healthy overweight and obese men and women, independently of changes in dietary energy intake (61). In accordance, a recent longitudinal study showed that when women go through the menopausal transition, they have deleterious changes in inflammatory markers and adipokines that correlate with increased visceral adiposity (62).

Importantly, however, another study concluded that in early postmenopausal women, the level of physical activity accounts for the variability in abdominal fat distribution observed, while menopausal status and age do not play a significant role (63).

Our group recently conducted a longitudinal study, in which a group of young healthy men decreased their daily stepping for 2 weeks to 1500 steps from the range recommended for US adults of around 10 000 steps. In this time, they experienced a 7% increase in intra-abdominal fat mass without a change in total fat mass and while total fat-free mass decreased. Moreover, they developed metabolic changes suggestive of decreased insulin sensitivity and attenuation of postprandial lipid metabolism. Accordingly, the anti-inflammatory effects of regular exercise may be mediated, at least in part, by an effect of exercise on visceral fat.

6. ACUTE EXERCISE AND ANTI-INFLAMMATION

To study whether acute exercise induces a true anti-inflammatory response, a model of “low grade inflammation” was established in which a low dose of E. Coli endotoxin to healthy volunteers, who had been randomised to either rest or exercise prior to endotoxin administration. In resting subjects, endotoxin induced a 2 to 3 fold increase in circulating levels of TNF-α. In contrast, when the subjects performed 3 h of ergo meter cycling and received the endotoxin bolus at 2.5 h, the TNF-α response was totally blunted (64). This study provides some evidence that acute exercise may inhibit TNF production.

The cytokine response to exercise differs from that elicited by severe infections (65, 66). The fact that the classical pro-inflammatory cytokines, TNF-α and IL-1β, in general do not increase with exercise indicates that the cytokine cascade induced by exercise markedly differs from the cytokine cascade induced by infections. Typically, IL-6 is the first cytokine released into the circulation during exercise. The level of circulating IL-6 increases in an exponential fashion (up to 100 fold) in response to exercise, and declines in the post-exercise period (67, 68).

The circulating levels of well-known anti-inflammatory cytokines such as IL-1ra and IL-10 also increase after exercise. Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10. The appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines and a number of studies have demonstrated that contracting skeletal muscle fibers per se produce and release IL-6. Moreover, it appears that muscle-derived IL-6 can account for most of the systemic IL-6 response to exercise (67-69). Recent work has shown that both up-stream and down-stream signalling pathways for IL-6 differ markedly between myocytes and macrophages.

It appears that unlike IL-6 signalling in macrophages, which are dependent upon activation of the NFκB signalling pathway, intramuscular IL-6 expression is regulated by a network of signalling cascades that among other pathways are likely to involve cross talk between the Ca2+/NFAT and glycogen/p38 MAPK pathways (70).

The possibility exists that with regular exercise, the anti-inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation, but such a direct link between the acute effects of exercise and the long-term benefits has not yet been proven.

7. THE LINK BETWEEN INFLAMMATION, INSULIN RESISTANCE AND ATHEROSCLEROSIS

Mounting evidence suggests that TNF-α plays a direct role in the metabolic syndrome. Patients with diabetes demonstrate high protein expression of TNF-α in skeletal muscle (71) and increased TNF-α levels in plasma (72-74), and it is likely that adipose tissue, which produces TNF-α, is the main source of the circulating TNF-α (75, 76). Mounting evidence points to an effect of TNF-α on insulin signaling. TNF-α impairs insulin-stimulated rates of glucose storage in cultured human muscle cells (77) and impairs insulin mediated glucose uptake in rats (78). Obese mice with a gene knockout of TNF-α are protected from insulin resistance (79) and inhibition of TNF-α with an anti-TNF-α antibody treatment improves the insulin sensitivity in the insulin resistance rat model (80). *In vitro* studies demonstrate that TNF-α has direct inhibitory effects on insulin signalling (81-83). Recently, it was demonstrated that TNF-α infusion in healthy humans induces insulin resistance in skeletal muscle, without an effect on endogenous glucose production. TNF-α directly impaired glucose uptake and metabolism by altering insulin signal transduction. These data provide a *direct* molecular link between low-grade systemic inflammation and insulin resistance (84).

It has also been proposed that TNF-α indirectly causes insulin resistance *in vivo* by increasing the release of free fatty acids (FFA) from adipose tissue (85-90). TNF-α increases lipolysis in human (90, 91), rat (87, 92) and 3T3-L1 adipocytes (93-95). Recently, it was found that TNF-α had no effect on muscle fatty acid oxidation, but increased fatty acid incorporation into diacylglycerol, which may be involved in the development of TNF-α-induced insulin resistance in skeletal muscle (96).

Recent evidence suggests that TNF-α plays a key role in linking insulin resistance to vascular disease (97, 98). Several downstream mediators and signalling pathways seem to provide the crosstalk between inflammatory and metabolic signalling. These include the discovery of c-Jun N-terminal kinase (JNK) and I kappa beta kinase (IκK) as critical regulators of insulin action activated by TNF-α (99). In human TNF-α infusion studies, TNF-α increases phosphorylation of p70 S6 kinase, extra cellular signal-regulated kinase-1/2, and c-Jun NH (2)-terminal kinase, concomitant with increased serine and reduced tyrosine phosphorylation of insulin receptor substrate-1. These signalling effects are associated with impaired phosphorylation of Akt substrate 160, the most proximal step identified in the insulin signalling cascade regulating GLUT4 translocation and glucose uptake (84).

With regard to IL-6, its role in insulin resistance is highly controversial. In humans, circulating IL-6 levels may (100) or may not (101, 102) be associated with insulin resistance. Infusion of rhIL-6 into resting healthy humans does not impair whole body, lower limb or subcutaneous adipose tissue glucose uptake or endogenous glucose production (EGP) (103), although IL-6 contributes to the contraction-induced increase in endogenous glucose production (104, 105). When diabetes patients were given recombinant human (rh) IL6-infusion, plasma concentrations of insulin declined to levels comparable with that in age and BMI-matched healthy controls, indicating that the IL-6 enhanced insulin sensitivity (106). *In vitro* studies demonstrate that IL-6 can induce insulin resistance in isolated 3T3-L1 adipocytes (107) and in mice (108). Interestingly, IL-6 knockout mice develop impaired glucose tolerance, which is reverted by IL-6 (109). Thus, accumulating data suggest that IL-6 enhances glucose uptake in myocytes.

AMP-activated protein kinase (AMPK) activity stimulates a variety of processes that increases ATP generation including fatty acid oxidation and glucose transport in skeletal muscle (110). Incubation with IL-6 increases the phosphorylation of AMPK (an indicator of its activation) and that of its target molecule, acetyl CoA carboxylase (ACC) in skeletal muscles. In addition, AMPK activity and ACC levels are very low in IL-6 knockout mice, suggesting a role of IL-6 in the regulation of AMPK activity. These data suggest that IL-6 activation of AMPK is dependent on the presence of IL-6 (111).

A number of studies indicate that IL-6 enhances lipolysis (112-115), as well as fat oxidation (115). Consistent with this idea, Wallenius *et al* (109) demonstrated that IL-6 deficient mice developed mature-onset obesity and insulin resistance. In addition, when the mice were treated with IL-6, there was a significant decrease in body fat mass in the IL-6 knockout, but not in the wild-type mice. To determine whether physiological concentrations of IL-6 affected lipid metabolism, our group administered physiological concentrations of rhIL-6 to healthy young and elderly humans as well as patients with type 2 diabetes (103, 106). The latter studies identified IL-6 as a potent modulator of fat metabolism in humans, increasing lipolysis as well as fat oxidation without causing hypertriacylglycerolemia.

Of note, whereas it is known that both TNF-α and IL-6 induce lipolysis, only IL-6 appears to induce fat oxidation. High levels of IL-6 and TNF-α in patients with the metabolic syndrome is associated with truncal fat mass (116) and both TNF-α and IL-6 are produced in adipose tissue (117-120). Given the different biological profiles of TNF-α and IL-6 and given that TNF-α can trigger IL-6

release, one theory holds that it is TNF-α derived from adipose tissue that actually is the "driver" behind insulin resistance and cardiovascular diseases and that locally produced TNF-α cause's increased systemic levels of IL-6.

8. CONCLUSION

Several chronic diseases are associated with chronic low-grade inflammation and evidence exists that inflammation is a causal factor in the development of insulin resistance and atherosclerosis.

Visceral fat is inflamed and appears to contribute to systemic inflammation. On the other hand, evidence suggests that regular exercise protects against systemic inflammation and induces anti-inflammatory effects. We suggest that anti-inflammatory effects of exercise may be mediated via a long-term effect on abdominal adiposity and/or by elevation of anti-inflammatory cytokines following acute bouts of exercise.

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