Physical activity and modulation of systemic low-level inflammation

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Abstract: It has been recognized for some time that cardiovascular disease and type 2 diabetes are, to a major extent, inflammatory disorders associated with an environment characterized by a sedentary lifestyle together with abundant intakes of calories. Systemic low-level inflammation is suggested to be a cause as well as consequence of pathological processes with local tumor necrosis factor α production as an important biological driver. It is hypothesized that physical inactivity contributes to an enhanced proinflammatory burden independently of obesity, as regular muscle contractions mediate signals with myokines/cytokines as important messengers, which suppress proinflammatory activity at distant sites as well as within skeletal muscle. Muscle-derived interleukin (IL)-6 is considered to possess a central role in anti-inflammatory activities and health beneficial effects in relation to physical exercise. It is discussed how this fits the consistent observation that enhanced plasma levels of IL-6 represent a strong risk marker in chronic disorders associated with systemic low-level inflammation and all-cause mortality. *J. Leukoc. Biol.* 78: 819–835; 2005.

Key Words: *myokines · TNF-α · IL-6 · proinflammatory · anti-inflammatory · exercise*

INTRODUCTION

During the last decade, it has become clear that inflammatory mechanisms are key players in pathological processes of several chronic diseases such as ischemic cardiovascular disease (CVD) [1], colorectal cancer [2], stroke [3], type 2 diabetes (T2D) [4], chronic obstructive pulmonary disease (COPD) [5], and Alzheimer's disease [6], which are among the most common causes of mortality in the Western world. At the same time, it has been recognized that pleiotropic cytokines are not only important signals in immune function, as they also represent important regulators of endocrine systems, the metabolism, the coagulation system, and the brain function [7]. In addition, it has been discovered recently that circulating levels of cytokines in vivo are affected significantly by contributions of cells outside the immune system such as adipose tissue, skeletal muscle, and endothelial cells in healthy humans; e.g., 30% of interleukin (IL)-6 in plasma is derived from fat tissue [8] (**Fig. 1**). The concept of regulatory adipokines has developed together with the discovery of fat tissue as an important endocrine organ, producing and secreting classical cytokines including tumor necrosis factor (TNF)-α, IL-6, IL-18, as well as a wide range of other new peptides [9, 10]. Moreover, at the millennium, it was demonstrated that working skeletal muscles produce and also release cytokines to the circulation [7]. Considering that skeletal muscle is the largest organ in the body, the perspective of this finding is revolutionary, and it provides a molecular explanation about a molecular level by which we may understand how exercise mediates some of the health beneficial effects in relation to chronic disorders associated with systemic low-level inflammation.

The purpose of the present review is to discuss how physical exercise is able to modulate cytokine production. The hypothesis is discussed that muscle contractions reduce systemic low-level inflammation in several chronic diseases, as skeletal muscle acts as an endocrine organ, which is able to influence the metabolism and modify cytokine production in other tissues and organs through signals mediated by "myokines." Mainly, activities of TNF-α and IL-6 are reviewed as models of links amongst physical activity, the metabolism, endocrine systems, and the immune system. However, it would be naïve not to recognize that other cytokines are relevant in this context as well.

SYSTEMIC LOW-LEVEL INFLAMMATION, LIFESTYLE FACTORS, AND CHRONIC INFLAMMATORY DISORDERS

New and more sensitive assays for proinflammatory products have demonstrated an increased risk of all-cause mortality among persons who were previously thought to have circulating (plasma/serum) values within the normal range. Systemic low-level inflammation is defined as two- to fourfold elevations in circulating levels of proinflammatory and anti-inflammatory cytokines, natural occurring cytokine antagonists, and acute-

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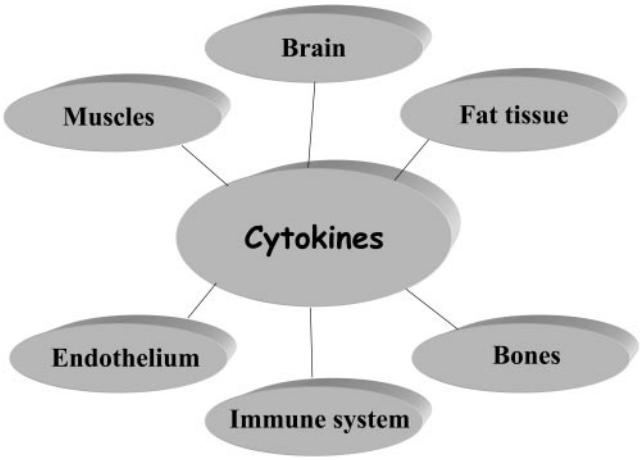


Fig. 1. Sources of cytokines. A wide range of organs and different cell types contribute to the production of cytokines, which possess local as well as endocrine activities, and act as important regulators of the metabolism and immune functions.

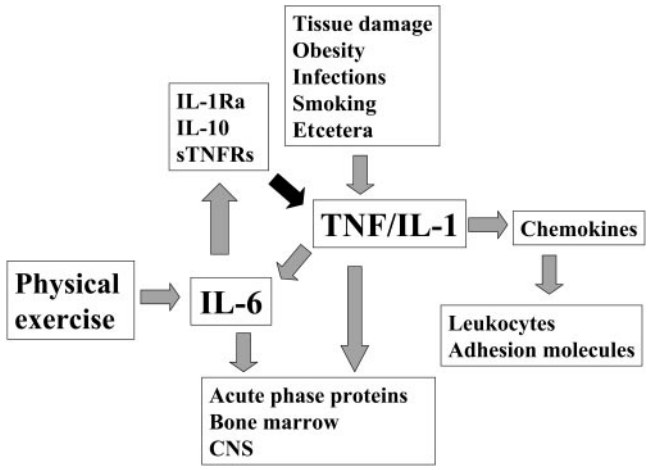


Fig. 2. The acute-phase response and the cytokine response in exercise. Shaded arrows mark positive stimulation. Solid arrow marks inhibition. IL-1Ra, IL-1 receptor antagonist; sTNFRs, soluble TNF receptors; CNS, central nervous system.

phase proteins, as well as minor increases in counts of neutrophils and natural killer cells [11]. Although these increases are far from levels observed during acute, severe infections, systemic low-level inflammation is strongly associated with increasing age, lifestyle factors such as smoking, obesity, and dietary patterns, together with increased risk of CVD, T2D, COPD, cognitive decline, and wasting/cachexia (loss of skeletal muscle cells) [4, 12–21]. Moreover, systemic low-level inflammation is a strong, consistent, and independent predictor of all-cause mortality and CVD-cause mortality in elderly populations [22–32].

These observations lead to the speculation whether individual mediators in the cytokine network are causal related to specific pathology or if systemic low-level inflammation represents a spillover from pathological processes. It has been suggested that insufficient proinflammatory responses can lead to increased susceptibility to infections and cancer, whereas excessive responses cause morbidity and mortality in diseases such as atherosclerosis, diabetes, Alzheimer's disease, autoimmune disease, and shock during acute infections [33]. Circulating levels of inflammatory mediators are often strongly correlated with each other as a result of their tight, regulated production (**Fig. 2**). Moreover, levels of inflammatory mediators are correlated with other risk factors in chronic morbidity, including levels of fibrinogen, albumin, cholesterol, arterial blood pressure, and body mass index (BMI), among others (**Fig. 3**). This considerable covariance makes it difficult to separate effects from each other and to make causal analyses in epidemiological designs and in some experimental studies. Nevertheless, in my opinion, TNF-α deserves attention as a key player in systemic low-level inflammation and associated chronic diseases, as it promotes a proathersclerotic, procoagualant, and procachectic profile.

ACTIVITIES OF TNF-α IN CHRONIC, INFLAMMATORY DISEASE

TNF-α is an early mediator of local inflammatory processes as well as an initiator of the systemic acute-phase response (Fig. 2). It has been demonstrated recently that acute infections such as respiratory tract infections and urinary tract infections are associated with a transient increase in the risk of vascular events including stroke and myocardial infarction [34], indicating a connection amongst infections, immune activity, and thromboembolic complications. Consistent with this, TNF-α increases independently of IL-6 systemic levels of plasminogen activator inhibitor 1, which is an inhibitor of fibrinolysis and a risk factor in the metabolic syndrome and CVD [35], and TNF-α stimulates via IL-6 the production of fibrinogen [36]. In addition, low-grade activation of the TNF system and systemic low-level inflammation are observed in relation to chronic, asymptomatic infections such as chlamydia pneumoniae [37], bacteriuria [38], and dental infections [39], which are risk factors in atherosclerosis, probably through their contribution to the systemic inflammatory burden [40]. However, TNF-α production is not restricted to the context of infections.

Obesity is strongly associated with enhanced circulating TNF-α levels, whereas weight loss reduces systemic levels

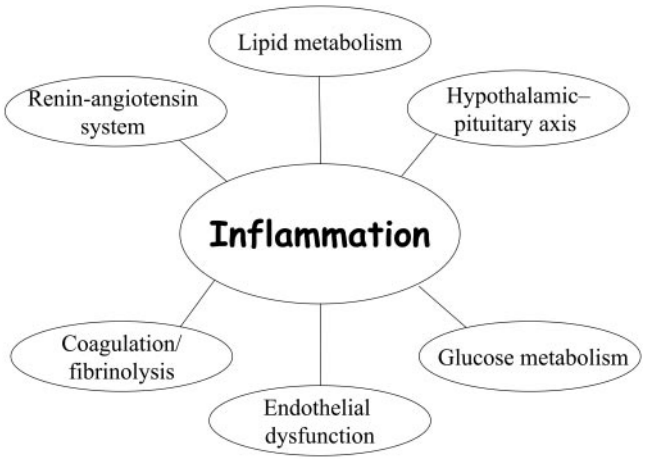


Fig. 3. Inflammatory mediators interact with the metabolism and several endocrine systems. See text for further details.

[41]. Adipose tissue from obese individuals shows accumulation of macrophages, which provide the major cellular source of a concomitant, enhanced, local expression of the TNF-α protein [42, 43]. TNF-α induces insulin resistance in experimental animal models [44, 45] by mechanisms that involve serine phosphorylation of the insulin receptor substrate 1 (IRS-1) [46, 47]. This phosphorylation reduces insulin receptor tyrosine kinase activity in response to insulin and the ability of IRS-1 to associate with the insulin receptor and thereby, is downstream signaling- and insulin action-inhibited (see refs. [48, 49] for recent reviews). The responsible intracellular pathways involve activation of c-Jun N-terminal kinases [50] and the inhibitor of κB kinase (IKK) [51, 52], whereas activation of members in the suppressor of cytokine signaling (SOCS) family represents alternative intracellular stress pathways in cytokine-mediated inhibition of insulin signaling [53, 54]. In addition, TNF-α causes insulin resistance indirectly, as it induces lipolysis in adipocytes [55, 56] with an increased release of free fatty acids (FFA), which has also been implicated as a causative factor in phosphorylation of IRS-1 [48, 49]. Enhanced levels of FFA are accompanied by hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and elevated, small, dense low-density lipoprotein in the circulation (reviewed in refs. [49, 57]). Finally, increased TNF-α production is associated with hypertension through activation of the renin-angiotensin system, but the precise interaction remains to be described [58]. Accordingly, TNF-α is a potential biological driver in the metabolic syndrome characterized by abdominal obesity, hypertension, a reduced level of HDL, elevated triglycerides, and high-fasting glucose [16] and constitutes an important risk factor in atherosclerosis and T2D (**Fig. 4**).

Vascular inflammation is central in the pathology of atherosclerosis [59]. TNF-α is a likely contributor, as it stimulates the expression of adhesion molecules by endothelial cells [60], and it induces endothelial dysfunction [61]. This provides a likely mechanism by which smoking is a risk factor in atherosclerosis: Smoking causes endothelial dysfunction accompanied by increased plasma levels of TNF-α, inflammatory mediators downstream in the inflammatory cascade [62], and enhanced circulating levels of soluble intercellular adhesion molecules [13], indicating vascular inflammation with spillover to the circulation. TNF-α-mediated local inflammatory processes are also considered to be central in the relation between smoking and COPD [63].

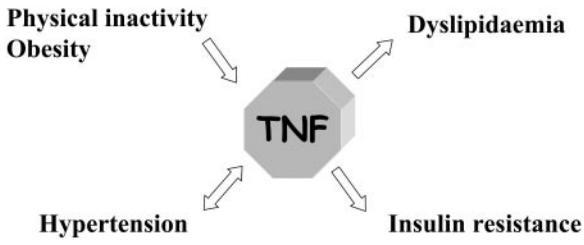


Fig. 4. TNF-α is a potential driver in the metabolic syndrome. Fat tissue produces TNF-α, and circulating levels of TNF-α are correlated with the fat mass. Muscle contractions inhibit TNF-α production in vivo, and physical inactivity is associated with high circulating levels of TNF-α. Hypertension may induce increased production of TNF-α and vice versa. TNF-α induces insulin resistance and dyslipidaemia. See text for further details.

End stages of CVD, COPD, cancer, human immunodeficiency virus infections, and rheumatoid arthritis are often associated with wasting [17, 20, 21, 64–66]. TNF-α is again a possible, common basis, as TNF-α is also named cachectin, as it increases the basal energy expenditure, and it leads to the erosion of lean body mass and a pronounced impairment in muscle protein balance [21, 67, 68]. Consistent with this, systemic low-level inflammation is correlated inversely with muscle mass, muscle strength, and functional capacity in elderly populations [14, 18, 69, 70]. Moreover, muscle protein synthesis rate is related inversely to levels of TNF-α protein in skeletal muscle in elderly, frail humans [71].

Finally, studies of TNF-α polymorphisms have demonstrated that enhanced promoter activity is associated with unstable angina [72], insulin resistance [73–76], and increased risk of coronary heart disease in patients with T2D [77], supporting the hypothesis of TNF-α as an important driver in the metabolic syndrome and an active parameter in the elevated risk of CVD, which is associated with T2D and hypertension.

TNF-α works mainly locally, and TNF-α has a short half-life [78]. As a result, I suggest that an elevated level of TNF-α protein is not always detected in the circulation, despite enhanced gene transcription during systemic low-level inflammation. Rather, local TNF-α may stimulate production of IL-6 and subsequent mediators in the inflammatory cascade. In my opinion, it is likely that systemic low-level increases in IL-6, IL-8, C reactive protein (CRP), IL-1Ra, sTNFRs, IL-10, and inflammatory cells, among others, reflect on-going TNF-α production. For instance, plasma levels of TNF-α and sTNFRs are strongly correlated but sTNFRs are more stable in the circulation, and it has been suggested that they act as long-term markers of TNF-α [79, 80]. Although low-grade increases in circulating levels of IL-6 and CRP are, in particular, strong predictors of inflammatory morbidity, I postulate that they reflect, to a large extent, a response to local TNF-α activities rather than TNF-α-independent pathological processes. In support of this view, polymorphisms in the CRP gene are not a risk factor in arterial thrombosis [81], although polymorphisms affect levels of CRP protein in the blood [82]. However, it would be naïve to point to TNF-α as the agent solely responsible in inflammatory disorders. Harmful activities can indeed be isolated for most inflammatory mediators, and considering the strong interactions, their activities should probably be considered together as parallel pathways (pathological effects in relation to sustained low-grade elevations in IL-6 is discussed in a later section). Furthermore, it is possible that attention should, to a higher degree, be directed toward the balance between proinflammatory activities and counteracting responses, as a strong anti-inflammatory response has turned out to be important for the course of chronic, inflammatory diseases; e.g., a polymorphism in the IL-10 promoter is associated with enhanced transcription activity and decreased mortality from CVD [83].

Accordingly, cytokines serve as a model on a molecular level, by which we can explain some of the interconnection amongst markers of inflammation, coagulation/fibrinolysis, glu-

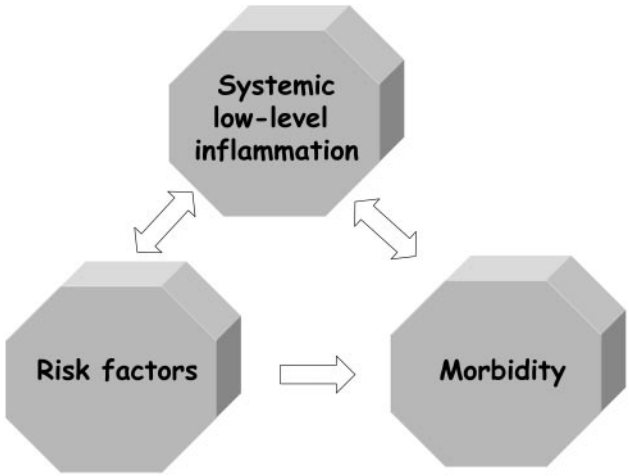


Fig. 5. Systemic low-level inflammation, age-related risk factors, and morbidity. Systemic low-level inflammation is probably a cause and a consequence of age-related morbidity and associated risk factors, providing a self-enhancing cascade (see text).

cose metabolism, lipid metabolism, the renin-angiotensin system, the hypothalamic-pituitary axis, and others in chronic disease associated with systemic low-level inflammation (Fig. 3). It is possible that chronic disease and aging result from the constant use of these interfacial responses, as the organism trades short-term benefit for long-term damage. Systemic low-level inflammation may, to some extent, represent a spillover from local proinflammatory processes, which second-affect the function in other organs and tissues, providing a self-enhancing cascade (**Fig. 5**). This leads me to the hypothesis that systemic low-grade inflammation is a cause as well as a consequence of pathological processes, and local TNF-α production is an important biological driver. Then the question arises whether this negative circle can be interrupted.

PHYSICAL ACTIVITY AND SYSTEMIC LOW-LEVEL INFLAMMATION

Physical activity offers protection against CVD [84, 85], T2D [86], colorectal cancer [87], breast cancer [88], age-related cognitive decline [89–91], and all-cause mortality [92]. Furthermore, physical training is effective in the treatment of coronary heart disease [93], chronic heart failure [94], T2D [95], and COPD [96].

A recent number of papers have documented that self-reported physical activity or physical performance is correlated inversely with systemic low-level inflammation [32, 70, 97–106], although the lack of an association has also been reported [107], especially when adjusting for other factors in multivariate analyses [108, 109] (**Table 1**). Positive associations between inflammatory markers and physical activity do not necessarily reflect a direct causal relationship; e.g., inflammatory mediators could simply act as markers of the health status and/or disease states. Weight and smoking are other important cofactors. It is probable that different degrees of contributions from these factors explain inconsistencies between studies. However, a high self-reported degree of physical activity is associated with attenuated circulating levels of TNF-α, IL-6, CRP, and SAA compared with those devoted to a sedentary lifestyle, independently of gender, age, smoking habits, BMI, total cholesterol, blood glucose, and blood pressure in the Greek ATTICA study [97]. Additionally, a similar association is observed within a subgroup with the metabolic syndrome and within a subgroup without [98]. Thus, a high level of physical activity is apparently associated with reduced levels of peripheral inflammatory mediators in the range of 20–60% compared with a sedentary lifestyle.

Several studies have reported that exercise intervention programs reduce systemic low-level inflammation in patients with coronary heart disease [110], claudicants [111], and chronic heart failure [112–115] and in healthy, young adults [116]. A failure of a positive effect has been reported in old nursing home patients [117] and in obese elderly [118]. Markers of systemic low-level inflammation were not reduced in patients with chronic heart failure in one study, although decreased inflammation was detected locally within skeletal muscle [119] (**Table 2**). Different modes of training interventions are obvious reasons for discrepancies, e.g., endurance training versus resistance training; differences in the intensity of exercise; and the time duration of the single bout of exercise, as well as the full intervention program. In addition, a large interpersonal variability in peripheral inflammatory markers together with a considerable coefficient of variability in high-sensitivity cytokine assays make power problems common. Finally, the effect of physical activity is likely differentiated in disorders associated with systemic low-level inflammation. It is probably easier to revert endothelial dysfunction, insulin resistance, and dyslipidaemia in CVD than cachexia in a terminal state. In this regard, it is possible that there is a threshold beyond which systemic low-level inflammation represents an irreversible state; e.g., among patients with chronic heart failure, exercise training reduces plasma levels of TNF-α significantly among survivors but not among nonsurvivors [114]. Furthermore, the degree of activity in the TNF system at baseline was correlated inversely with the muscle strength after 12 weeks of resistance training in frail, old nursing home residents with multi-morbidity [119]. Nevertheless, it is a bit surprising that so many rather small studies actually are able to detect a reduction in systemic low-level inflammation by simply modulating the level of physical activity. This makes me conclude that cross-sectional studies, adjusted for several confounders together with interventional studies, suggest the existence of an independent relation between the level of physical activity and the degree of systemic low-level inflammation.

AN ACUTE BOUT OF EXERCISE AND SYSTEMIC CHANGES IN LEVELS OF INFLAMMATORY MEDIATORS

A large number of studies have demonstrated that in relation to an acute bout of exercise, plasma levels of IL-6 increase exponentially up to 100-fold, with a total decline in the post-exercise period (see ref. [7] for a review). The IL-6 response is followed by elevations in circulating levels of inflammatory

TABLE 1. Self-Reported Physical Activity and Physical Performance in Relation to Systemic Low-Level Inflammation in Epidemiological Studies

Refs.	Subjects	Circulating inflammatory parameters	High physical activity versus sedentary lifestyle
[97]	3042 adults (>18 years) without CVD	TNF, IL-6, CRP, SAA, WBC, fibrinogen	Lower levels of all parameters
[98]	Same population as in ref. [97] divided into 701 adults with the metabolic syndrome and 2341 without	TNF, IL-6, CRP, SAA, WBC, fibrinogen	High physical activity in both groups were associated with a lower degree of inflammation
[99]	3075 well-functioning humans aged 70–79 years	TNF-α, IL-6, and CRP	Lower levels of TNF-α and IL-6
[108]	892 male subjects, free from clinical CVD aged 35–59 years	CRP, SAA, fibrinogen	CRP and fibrinogen reduced in univariate analyses but not in multivariate analyses adjusting for BMI, smoking, education, diabetes, lipids, alcohol
[70]	1020 humans aged >65 years living in the area of Chianti	CRP, IL-6, TNF-α, IL-10, IL-1β, IL-6sR, and IL-1Ra	CRP, IL-6, and IL-1Ra were correlated inversely with physical performance and hand-grip strength, independently of demographics, chronic conditions, medication use, and other biological variables
[107]	760 humans aged 49–70 years with plaque in carotid artery without symptoms	CRP	No difference
[100]	114 postmenopausal women	CRP	Reduced CRP
[106]	67 male ultramarathon runners and 63 controls matched by sex, age, and BMI	IL-6, CRP	Reduced CRP but not IL-6 independently of leptin and BMI
[109]	109 men and women aged 20–70 years	CRP	No association. CRP was associated with BMI
[32]	333 relatively healthy 80-year-old humans	TNF-α and IL-6	Lower levels of TNF-α and IL-6
[101]	4072 adults >17 years	CRP, fibrinogen, WBC	Reduced levels of at least one parameter
[102]	133 postmenopausal women aged 50–73 years without CVD or diabetes	CRP	Reduced CRP independent of oral HRT use, age, smoking, alcohol consumption, aspirin, and statin but not when body fat and age were included in the multivariate analysis
[103]	870 healthy persons aged 70–79 years	IL-6 and CRP	High levels of recreational activity associated with reduced levels of IL-6 and CRP
[104]	12 healthy men aged 65–75 years; 6 active and 6 less active	MIP-1α, IL-1Ra, IL-1β, IL-6, IL-10, and CRP	Reduced IL-6 and increased IL-10
[105]	356 male and 103 female athletes, 45 male and 40 female untrained controls, and 35 elderly coronary patients	CRP	Reduced CRP in swimmers and rowers compared with untrained controls

SAA, Serumamyloid A; WBC, white blood cell count; HRT, hormone replacement therapy; MIP-1α, macrophage-inflammatory protein-1α; circulating levels, concentration in serum or plasma.

markers downstream in the acute-phase response, including IL-1Ra, IL-10, sTNFRs, and CRP [121–123] (Fig. 2). The size of the response depends on the intensity, duration, and the mode of the exercise [7].

An initial study suggested that increased systemic levels of inflammatory parameters were related to muscle damage, as increased IL-6 levels were first detected in eccentric exercise models in which a positive correlation was also demonstrated to considerable creatine kinase (CK) increases [124]. However, later studies have not confirmed an association between peak IL-6 and peak CK levels [122, 123, 125]. Moreover, the IL-6 response is also observed during concentric exercise without any signs of muscle damage [126]. It has been suggested in a review of this literature that the marked and immediate increase in plasma IL-6 in response to exercise is independent of muscle damage, whereas muscle damage per se is followed by repair mechanisms, including invasion of macrophages into the muscle leading to IL-6 production, which occurs later and is of smaller magnitude than the IL-6 production related to muscle contractions [7].

Thus, physical exercise is associated with a systemic cytokine response comparable with the levels observed during severe infections, except the important difference is that increases in TNF-α and IL-1β are minute if present at all when concentric exercise without muscle damage is performed (Fig. 2). This indicates that in nontraumatic exercise models, the cytokine cascade differs importantly from the classical acute-phase response studied in infectious systems.

TABLE 2. Inflammatory Parameters Following Interventions in the Level of Physical Activity

Refs.	Subjects	Intervention	Training protocol	Inflammatory mediators in plasma/serum	Effects on systemic low-level inflammation
[116]	14 marathon runners		9 months of preparation for a marathon run	CRP	Reduced
[118]	316 obese (BMI > 28), elderly (>60 years) humans with knee osteoarthritis	Randomized to control group; diet; physical exercise; diet + physical exercise	Combined weight training and walking for 1 h 3/week for 18 months	IL-6, sTNFR-I, CRP	No effect on inflammation. Weight loss reduced parameters without an interaction with exercise
[120]	20 obese adults with BMI > 28	Randomized to diet; physical exercise	Bicycle exercise 3/week for 8 weeks	TNF-α mRNA in skeletal muscle	No change in the exercise group but small reduction in the diet group
[110]	28 patients with coronary artery disease aged 64 ± 7.1 years		45 min of aerobic exercise training program at 70–80% of max-HR 3/week for 12 weeks	IL-1, IL-6, IL-10, IFN-γ, CRP	Reduced IL-1, IL-6, IFN-γ, CRP, increased IL-10
[111]	67 claudicants	39 patients were randomized: training group N = 22; observed N = 17	Supervised exercise for 12 months	CRP, SAA, fibrinogen	Reduced CRP (3 months) and SAA (6 months)
[112]	12 patients with stable CHF; ischaemic heart failure N = 6; dilated cardiomyopathy N = 6	A randomized cross-over design	Bicycle exercise at 70–80% of max-HR 30 min 5/week for 12 weeks	GM-CSF, MCP-1, sICAM-1, sVCAM-1	Reduced levels of all parameters
[113]	20 patients with stable CHF	Training group N = 10; control group N = 10	Bicycle exercise at 70% of max-HR 20 min/day and 60 min of callisthenics 1/ week for 6 months	TNF-α, IL-1β, IL-6	Parameters unaffected in the circulation but reduced in skeletal muscles
[114]	28 patients with ischemic CHF		Bicycle exercise at 80% of max-HR heart 3/week for 30 min + 45 min of callisthenics 3/week	TNF-α, IL-6, IL-8	Reduced TNF-α
[115]	23 patients with stable CHF; ischemic CHF N = 12; dilated cardiomyopathy (N = 11)		30 min of resistance training (50% of 1-RM) and 20 min of bicycle exercise (90% of max-HR) 3/week for 4 months	TNF-α, IL-6, sTNFR-I, and sTNFR-II	Reduced levels of sTNFR for the whole group and in the ischaemic group
[71]	8 elderly adults aged >75 years. Frail based on physical performance tests but without co-morbidity	Randomized to resistance training or observation	Resistance training (50–100% of 1-RM) 50–90 min 3/week for 12 weeks	TNF-α mRNA and protein in skeletal muscle	Reduced in skeletal muscle. Systemic levels were not evaluated
[119]	21 nursing home residents aged 86–95 years with multi-morbidity	Randomized to resistance training N = 10 or social activities N = 11	Resistance training (50–80% of 1-RM) of knee extensors and flexors 45 min 3/ week for 12 weeks	TNF-α, IL-6, sTNFR-I	No changes

HR, Heart rate; IFN-γ, interferon-γ; CHF, chronic heart failure; GM-CSF, granulocyte macrophage-colony stimulatory factor; MCP-1, monocyte chemoattractant protein-1; sICAM-I, soluble intercellular adhesion molecule I; sVCAM, soluble vascular cell adhesion molecule I; I-RM, one repetitive maximum.

PHYSICAL ACTIVITY AND MYOKINES

Monocytes are major producers of IL-6 in relation to infections. Accordingly, investigators turned first toward these cells to find the cellular source of IL-6 during physical exercise. Nevertheless, IL-6 mRNA or protein is not increased in circulating monocytes during or following concentric exercise without muscle damage [127].

Skeletal muscle cell cultures express several cytokines such as TNF-α, IL-6, IL-8, IL-15, and IFN-γ [128–130]. A large number of studies have demonstrated enhanced IL-6 mRNA and increased transcription rate of the IL-6 gene in muscle

biopsies during exercise with a rapid decrease in the post-exercise period [121, 126, 131, 132]. IL-6 mRNA is not increased as a result of a systemic effect: In rats subjected to electrically stimulated contractions of the one hind leg while the other leg rests, IL-6 mRNA is elevated only in the muscle from the exercising leg [133]. In young men who perform a one-leg knee extensor exercise, IL-6 production in working muscles can account for the increase in plasma IL-6 during exercise when arterial-femoral venous differences are measured over the exercising and the resting leg and adjusted for the blood flow [134]. Immunohistochemical studies of skeletal muscle have demonstrated that type 1 and type 2 muscle fibers show marked and homogenous staining of IL-6 protein following exercise with a different, predominant accumulation, depending on the mode, intensity, and duration of the performance [135–137].

In summary, there is strong evidence in support of the hypothesis that skeletal muscle is a major source of IL-6 during nontraumatic exercise, as transcription levels, mRNA levels, and protein levels increase largely within muscle fibers, and the IL-6 release from working muscles can largely account for systemic increases during physical activity. In addition, small amounts of IL-6 are produced from adipose tissue [138], the brain [139], and peritendon tissue [140].

Several studies have reported that carbohydrate ingestion attenuates elevations in plasma IL-6 during running and cycling [131, 141–143], whereas low muscle glycogen concentration further enhances IL-6 mRNA and the transcription rate for IL-6 [126, 132, 144].

The IL-6 release from working muscles is preserved in healthy, 70-year-old men [145] and in patients with T2D [146] when a two-leg knee extensor exercise is performed without muscle damage. In contrast, IL-6 mRNA is decreased in elderly men who perform downhill running [147], and the increase in systemic IL-6 levels is modest in elderly men who perform eccentric leg exercise [148] compared with young controls. The latter two models involve a major component of muscle damage, suggesting an age-associated impairment in leukocyte activation related to repair mechanisms rather than a blunted, muscle cell-derived IL-6 response induced by muscle contractions.

TNF-α mRNA is detectable in resting muscles, and it is increased in the elderly [71], in obesity [120], and in patients with T2D [128]. When young, healthy men perform 180 min of a knee extensor exercise, TNF-α mRNA increases only slightly (approximately fourfold, $P=0.08$) during the first 30 min of exercise, and after this time, it does not increase any further, whereas IL-6 increases ~100-fold in the same model [146, 149]. Consistent with this, there is no measurable increase in systemic levels, and there is not detectable TNF-α net release from the working legs [146, 149].

IL-8 mRNA increases pronouncedly in skeletal muscles in response to exercise [150, 151], and IL-8 protein is expressed within the cytoplasma of muscle fibers [150]. Systemic IL-8 levels increase only in relation to exhaustive exercise with an eccentric component [141, 152, 153] but not in relation to concentric exercise without muscle damage [150, 151]. The latter studies suggest that muscle-derived IL-8 has important autocrine or paracrine effects, which are yet unknown but could involve angiogenesis [150].

IL-15 is highly expressed in skeletal muscles [154], and it is believed to affect muscle anabolism [155]. Systemic IL-15 levels [122] or IL-15 mRNA in skeletal muscle [151] do not seem to be enhanced in response to concentric exercise without muscle damage, whereas increased circulating levels have been reported following eccentric modes of exercise [156].

Adiponectin is an adipocytokine, which exerts insulin-sensitizing effects on the liver and skeletal muscle and inhibits TNF-α production and endothelial activation induced by TNF-α. It has recently been reported that mRNA and protein are also expressed in skeletal muscle in response to in vivo lipopolysaccharide (LPS) administration in mice and following in vitro incubation with TNF-α and IFN-γ in combination, but not IL-6 or IL-1β in human myotubes [157].

Accordingly, skeletal muscles produce a wide range of different myokines/cytokines in vitro and in vivo. There is only evidence so far that IL-6 is released to the circulation during physical activity in models without muscle damage. It is, however, expected that new myokines will be identified with the increasing interests in physical activity and skeletal muscles in health and disease.

IL-6 AND THE METABOLISM DURING EXERCISE

During exercise, skeletal muscles need to increase the uptake of glucose and FFA to generate adenosine 5′-triphosphate (ATP) and to quickly refill glycogen pools. Several metabolic genes are transcriptionally activated in the recovery phase from exercise, presumably with the purpose to rebuild energy stores [158]. If IL-6 is an energy sensor in the muscle, and IL-6 is released when the local glycogen content is low, it is possible that the large amounts of muscle-derived IL-6 in the circulation act as a hormone with the purpose to mobilize extracellular substrates and/or to augment substrate delivery during exercise [159].

IL-6 induces lipolysis and increased fat oxidation without causing triacylglycerolemia when it is administrated in doses mimicking systemic levels during exercise [160, 161] as well as higher doses [162]. Consistent with this, IL-6 induces lipolysis in 3T3-LI adipocytes and increases fat oxidation in myotubes [160] and in isolated rat soleus muscle [163]. In addition, it has been suggested that IL-6 influences glucose homeostasis during exercise [164]. In the latter study, young men performed a bicycle exercise at three separate occasions, at a relative high intensity or at a low intensity, with or without an infusion of recombinant (r)IL-6, which matched the circulating concentration of IL-6 in the high-intensity trial. It was demonstrated by the use of stable isotopes that the endogenous glucose production, whole-body glucose disposal, and the metabolic clearance rate of glucose were higher during the rIL-6 infusion + low-intensity exercise than low-intensity exercise alone, despite identical exercise intensities and the same levels of insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone [165]. This finding implicates an entirely novel un-

derstanding of the role for IL-6 in glucose production and clearance.

Adenosine monophosphate-activated protein kinase (AMPK) is a fuel-sensing enzyme, which is activated by changes in the energy state of a cell, as well as by exposure to such hormones as adiponectin, leptin, and catecholamines [166]. Once activated, AMPK stimulates a variety of processes, which increase ATP generation, including fatty acid oxidation, glucose transport in cardiac and skeletal muscle, and glycolysis in heart and WBC. AMPK is activated in skeletal muscle during contractions, and it is thought to contribute to many of the changes in muscle fuel metabolism in relation to physical activity. IL-6 can activate AMPK in muscle and adipose tissue, and this contributes to the increase in AMPK activity in these tissues in response to exercise [167].

Infusion of rIL-6 exerts a positive feedback on IL-6 mRNA expression in skeletal muscle and in fat tissue in human volunteers when it is administrated in doses corresponding to levels observed during exercise [168]. Similar effects are observed in cell cultures of adipocytes [169] and liver cells [170], whereas a negative autoregulation is observed in monocytes [170]. IL-6 binds to the IL-6sR and the complex associates with two gp130 molecules for the initiation of intracellular signaling [171]. The gp130 receptor is expressed ubiquitously, whereas the IL-6R expression is restricted [172]. It has been demonstrated recently that muscle contraction induces post-exercise expression of IL-6R mRNA and protein in human skeletal muscle in vivo with the possible purpose to sensitize the muscle to the decreasing systemic IL-6 levels [173].

The exercise-induced expression of IL-6 mRNA in fat tissue is most pronounced in the recovery period, but it does not show the same relative increase as observed in skeletal muscle during physical activity, and the response is blunted by carbohydrate ingestion [138]. It is likely that muscle-derived IL-6 induces IL-6 production by adipose tissue, considering that the enhanced IL-6 production in adipose tissue is concomitant with an augmented need of FFA, as metabolism goes toward fat oxidation when glycogen stores are low [138]. Epinephrine infusion also induces a rapid, marked, but brief increase in IL-6 mRNA in subcutaneous adipose tissue of lean, healthy men with a concomitant increase in plasma IL-6, but this does not explain the prolonged expression of IL-6 mRNA following exercise [174].

Accordingly, there is evidence in support of the hypothesis that during physical exercise, IL-6 has the capacity to act in a "hormone-like" manner to direct the metabolism toward enhanced energy supply to working skeletal muscles, exerting especially strong effects on adipose tissue.

PHYSICAL ACTIVITY AND MODULATION OF PROINFLAMMATORY ACTIVITY

Considering that nontraumatic muscle contractions induce a systemic cytokine response independently of TNF-α and IL-1β (Fig. 2), together with the health beneficial effect of physical activity in chronic inflammatory disorders in which local TNF-α and/or IL-1β activities may act as initiators of pathological processes, it has recently been speculated whether regular exercise directly reduces the inflammatory burden by anti-inflammatory mechanisms [175].

IL-1Ra is a selective IL-1 antagonist, whereas IL-10 is a strong, anti-inflammatory cytokine, as it attenuates the cell-surface expression of TNFRs, and it inhibits the production of cytokines by monocytes and type 1 T cells (reviewed in ref. [176]). IL-10 and IL-1Ra arise in the circulation subsequently to IL-6 in relation to exercise [121–123]. In addition, cortisol levels and neutrophil counts are enhanced following exercise [177, 178]. Neutrophils also exert, beside their antimicrobial properties, anti-inflammatory effects such as the production of sTNFRs, which bind circulating TNF-α [176]. It has previously been reviewed that although IL-6 is often classified as a proinflammatory cytokine, it also has many anti-inflammatory and immunosuppressive effects, as it stimulates the pituitary-adrenal axis, inhibits the synthesis of TNF-α, stimulates the production of IL-10 and IL-1Ra, and induces the shedding of TNFRs by neutrophils [179]. In accordance with this, the anti-inflammatory response, including elevated levels of IL-10, IL-1Ra, sTNFRs, and activation of the pituitary-adrenal axis, could likely be elicited by muscle-derived, systemic IL-6 during exercise, as rIL-6 infusions in similar doses also induce enhanced, systemic levels of these parameters, whereas levels of adrenaline and noradrenaline are not affected [180]. In addition, it is likely that other mediators also contribute to anti-inflammatory effects during exercise; e.g., adrenaline attenuates TNF-α production and enhances IL-10 production following LPS stimulation [181]. However, adrenaline only induces small increases in circulating levels of IL-6, which cannot account for the systemic IL-6 response observed during exercise [182].

With the aim to test the hypothesis that exercise-induced, anti-inflammatory activities have the potential to inhibit low-grade elevations in systemic TNF-α, Starkie et al. [183] performed three experiments in which healthy young men rested for 3 h (control), rode a bicycle for 3 h, and were infused with rIL-6 for 3 h. After 21/2 h, subjects received a bolus of *Escherichia coli* endotoxin in all experiments. This resulted in a twofold increase in circulating TNF-α in the control experiment, whereas the response was totally attenuated in relation to exercise or rIL-6 administration. This experiment supports the hypothesis that physical activity mediates strong anti-inflammatory effects by mechanisms that involve IL-6. Consistently, the TNF response was blunted in rats exercised before LPS administration, and the TNF response remained attenuated when LPS was administered up to 6 h after completion of exercise [184]. TNF-α overexpression returned to normal levels in TNFR knockout (KO) mice after only 1 h of exercise [185]. A modest decrease in TNF-α was also observed in IL-6 KO mice, suggesting the existence of anti-inflammatory exercise effects mediated via IL-6 and an IL-6-independent mechanism [185].

In accordance with experimental observations, TNF-α mRNA was increased in frail, old humans compared with young controls, but this overexpression declined after the performance of a training program for only 12 weeks [71]. Similarly, TNF-α mRNA in skeletal muscle declined in relation to a training intervention in patients with chronic heart failure, whereas a decline in systemic low-level inflammation was not detected [113].

However, TNF-α mRNA was not reduced in skeletal muscle after 8 weeks of bicycle exercise in obese adults [120].

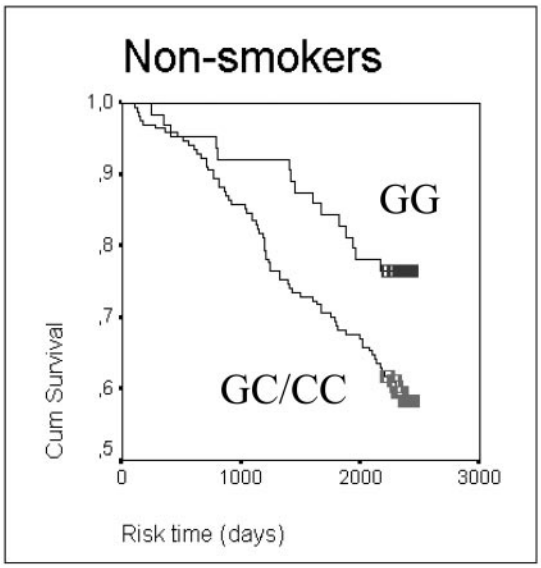
In summary, there is good evidence that physical activity mediates anti-inflammatory effects in skeletal muscle and fat tissue. The underlying mechanisms appear to involve IL-6-dependent and -independent pathways. Even moderate physical activity is probably sufficient to induce the anti-inflammatory effects of exercise, as an increased transcription rate of the IL-6 gene is already detected after 30 min of two-leg extensor exercise at 60% of the individual maximal power output [132]. A two-legged knee extensor exercise at 50% of the maximal power output induces a 20-fold increase in plasma IL-6 but only a moderate increase in heart rate (113–122 beats/min), which is equivalent to a brisk walk [137]. When the same model is applied to elderly people, the IL-6 response is even more pronounced [145]. Thus, only 30 min of moderate exercise on a regular basis probably has the power to facilitate an anti-inflammatory environment characterized by enhanced levels of IL-10, IL-1Ra, and sTNFRs between bouts of physical activity. In theory, a reduced, local TNF-α production could explain a part of the decline in systemic low-level inflammation together with the improvement in symptoms and risk factors associated with the metabolic syndrome, CVD, T2D, and COPD in relation to regular exercise. In support of this, health beneficial effects of physical exercise have been ascribed to enhanced insulin sensitivity [186], an improved lipid profile [187], and decreased arterial blood pressure [188], representing factors that are all modulated by TNF-α as already discussed. Diet seems, however, to be more effective than physical activity in severe obesity.

THE PARADOX OF IL-6 IN PHYSICAL ACTIVITY AND SYSTEMIC LOW-LEVEL INFLAMMATION

Considering that low-grade increases in circulating IL-6 constitute a strong prognostic risk factor in T2D, CVD, cognitive decline, functional disability, and all-cause mortality, it seems to represent a paradox that large amounts of IL-6 are released during an acute bout of exercise, which is, in general, considered to be health beneficial.

IL-6 is often postulated to cause insulin resistance, but at the same time, insulin sensitivity is increased during and following exercise when IL-6 is elevated pronouncedly in the circulation. Data in relation to IL-6 and insulin sensitivity are highly controversial (see ref. [189] for a recent review). In humans, neither splanchnic glucose output measured by the arterial-venous balance across the hepatosplanchnic tissue [190] nor isotopic tracer-determined endogenous glucose production is increased by human rIL-6 administration in physiological doses in healthy men [191] or in patients with T2D [160]. IL-6 KO mice develop late-onset obesity and glucose intolerance, which is reversed by IL-6 administration [192]. Consistent with this, mice with IL-6-secreting tumors reduce their fat mass and have low blood glucose levels, whereas the lean body mass is preserved [193, 194]. Conversely, transgenic mice expressing constitutively active IKK-β in hepatocytes have low-level activation of nuclear factor-κB and increased expression of IL-6 protein, but not TNF-α, in liver tissue, concomitant with insulin resistance in liver and systemically, which is improved by neutralizing IL-6 antibodies [195]. It is most consistent that IL-6 has been shown to suppress insulin sensitivity in the mouse liver [195–201], probably with the involvement of SOCS-3 as a mediator. With regard to adipose cells, it has been demonstrated that acute IL-6 treatment increases basal and insulin-stimulated glucose uptake in 3T3-LI adipocytes with an additive effect of insulin [202], but it has also been reported that IL-6 suppresses insulin-stimulated glucose transport in the same cell line [203]. Although skeletal muscle contributes to >90% of the glucose disposal in the body, only a few studies have investigated the relation between IL-6 and insulin sensitivity in this tissue in details. IL-6 enhances glycogen synthesis in skeletal muscle in the presence of insulin by a mechanism that involves increased Ser-473 phosphorylation of Act [204]. Conversely, it has been reported that acute IL-6 treatment in supraphysiological doses reduces insulin-stimulated glucose uptake in skeletal muscle, and this is associated with defects in insulin-stimulated IRS-1-associated phosphatidylinositol-3 kinase activity and increases in fatty acyl-coenzyme A levels during hyperinsulinemic-euglycemic clamps in mice [196]. Reverse effects of IL-6 in liver and skeletal muscle [197, 204] may explain a part of the controversies. However, based on the present review, the role of IL-6 in insulin sensitivity appears to be inconclusive with contrasting findings in studies of mice versus humans, acute versus chronic elevations in IL-6 levels, and reverse effects in different tissues. In contrast, there is convincing evidence that IL-6 is a strong lipolytic factor, and considering that IL-6 also increases fat oxidation [161], it is unlikely that IL-6 causes serious dyslipidaemia.

IL-6 production is mainly regulated on the transcriptional level [205]. The IL-6 –174G/C promoter polymorphism is common [206]. The –174C variant is associated with low promoter activity in LPS or IL-1-stimulated HeLA cells and decreased plasma levels of IL-6 in healthy subjects aged 40–75 years [207]. The C variant is a risk factor in CVD [208–211], T2D [73], colorectal cancer [2], and all-cause mortality in old populations [210, 212]. In accord, the C variant is associated with risk factors such as endothelial dysfunction [213], a high systolic blood pressure [208], elevated levels of fibrinogen [214], and high WBC counts [215]. The clinical effect interacts, moreover, with lifestyle factors such as smoking [210] and physical fitness [215]. Considering the experimental investigations of promoter activity [207], the association amongst the C variant, CVD, T2D, and colorectal cancer points toward a protective role of IL-6 in these disorders. However, the interpretation in the literature has widely been the opposite, as the C variant is associated with high plasma levels of IL-6 in several cohorts of elderly adults [210, 214, 216] and in patients with small abdominal aortic aneurisms [209], and moreover, the C variant is associated with increased levels of CRP [208, 214, 217]. Nonetheless, the opposite relation amongst plasma IL-6 and the –174C variant [207, 218, 219], no association [220, 221], or an association in newborns but not in adults [222] has also been reported. It is likely that associations amongst cytokine polymorphisms, low-level inflammation, and morbidity are blurred by the accumulation of a wide



Cox regression:

	HR	P
C variant	2.04	0.02
IL-6 pg/ml	1.07	0.02

GG is reference for the C-variant (GC and CC). Adjusted for the effect of gender, BMI, CVD, and cancer.

Fig. 6. The IL6 –174G>C promoter polymorphism and mortality in 234 nonsmoking 80-year-olds. Follow-up time is 5–6 years. HR, Hazard ratio; GG is reference for the C allele; IL-6, serum levels (continuous variable; from ref. [210]).

range of other contributing factors in elderly populations and patients. Moreover, high plasma levels of IL-6 probably have a poor correlation with the capacity of IL-6 production in populations characterized by systemic low-level inflammation. A weak counteracting IL-6 response to local TNF-α activities could result in higher chronic circulating IL-6 levels as a result of an increased inflammatory burden, contrasting the intuitive thought of a direct association between low promoter activity and low plasma levels. In support of this hypothesis, low-grade increases in systemic IL-6 and the –174C polymorphism (low IL-6 transcription) were independent of each other, strongly associated with high mortality risk in nonsmoking octogenarians [210] (**Fig. 6**). Accordingly, polymorphism studies support that IL-6 plays an active part in disorders associated with systemic low-level inflammation, but the understanding of the effect is highly controversial in the literature. In my opinion, polymorphism studies indicate a protective role of IL-6 in CVD, T2D, and colorectal cancer based on the present review and discussion.

IL-6 has been implicated in anemia in chronic disease [223]. Studies in human liver cell cultures, mice, and human volunteers indicate that IL-6 induces the iron regulatory peptide hormone hepcidin during inflammation, and the IL-6-hepcidin axis is responsible for the hypoferremia of inflammation [224]. Furthermore, IL-6 has been implicated in anorexia and increased energy expenditure [162, 192, 193]. To my knowledge, these activities have only been evaluated in models with high circulating levels of IL-6, whereas the impact has not been explored in experimental models of systemic low-level inflammation.

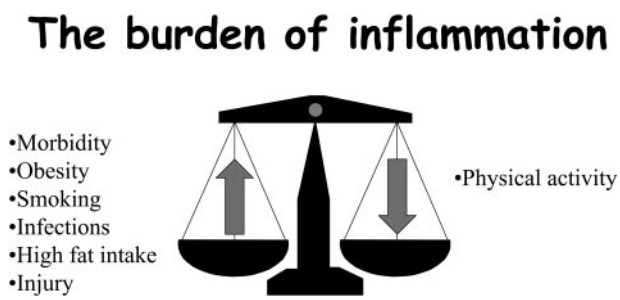


Fig. 7. The inflammatory burden in elderly populations. A wide range of factors contributes to systemic low-level inflammation in epidemiological studies. Physical activity is a counteracting factor.

IL-6 production appears on a turning point between dominance of proinflammatory and anti-inflammatory activity in the classical acute-phase response (Fig. 2). Assuming that IL-6 mainly reflects local proinflammatory activities in the context of systemic low-level inflammation, it remains to be determined if IL-6 per se is counteracting the effect of TNF and/or IL-1β. Considering that IL-6 induces an anti-inflammatory response and suppresses the production of TNF-α, it is possible that a critical balance between TNF-α and IL-6 is important in chronic, inflammatory morbidity. Consistent with this hypothesis, the TNF-308A promoter polymorphism (high TNF-α transcription) in combination with IL-6 –174C (low IL-6 transcription) is a risk factor in the development of T2D [73]. When IL-6 is produced independently of TNF-α/IL-1β during physical activity, I suggest it exerts mainly anti-inflammatory activities. In addition, it is possible that large, short-lasting elevations in systemic IL-6 promote health beneficial activities contrasting chronic, low-grade increases, which promote procoagulant changes [225, 226], the development of lymphoma [227, 228], and perhaps insulin resistance [195]. This suggests that IL-6 may act as a double-edged sword in health and disease.

CONCLUSION

It has been argued in the present review that systemic low-level inflammation is a cause and consequence of local pathological processes in chronic disorders with local TNF-α production as an important biological driver, as TNF-α promotes a proin-

flammatory, proatherosclerotic, a procoagulant, and a cachectic profile. I have suggested that subsequent mediators in the inflammatory cascade (IL-6, CRP, and others) are enhanced in systemic low-level inflammation as a response to local TNF-α production rather than independently of TNF-α.

Muscle contractions without trauma induce a myokine response, which is characterized by a large release of IL-6 from working muscles, independently of TNF-α and IL-1β. It has been suggested that the contraction-induced IL-6 expression in skeletal muscle is a specific biochemical phenomenon with the purpose to mobilize substrate from fuel depots within the body to facilitate energy metabolism [159]. The IL-6 response is followed by a systemic anti-inflammatory response. This could provide a common underlying pathway by which TNF-α activity is attenuated after a single bout of exercise following rIL-6 administration and in response to training interventions, as discussed in this review. An exercise-induced reduction in the proinflammatory burden is a plausible way to explain a part of the relation amongst regular physical activity, prevention, and improved symptoms in chronic disorders associated with systemic low-level inflammation (Fig. 7).

It represents a new paradigm that skeletal muscle acts as an endocrine organ, which by contractions, stimulates the production and release of myokines, which can influence the metabolism and modify cytokine production in other tissues and organs. Based on the present review, I suggest a fine balance between proinflammatory and anti-inflammatory activity across different tissues and organs to keep the body optimally tuned. It has been recognized for the last decade that obesity disturbs such a balance by enhanced proinflammatory activities. Obviously, physical inactivity contributes indirectly to a proinflammatory burden through the tight relation to obesity. In addition, I speculate that physical inactivity causes a proinflammatory profile independently of obesity, as regular muscle contractions mediate signals with myokines as messengers that suppress proinflammatory activities at distant sites as well as within skeletal muscle. It has been suggested that high proinflammatory activity protects us against infections, but the price may be increased risk of chronic, inflammatory disorders such as CVD [83]. This risk is probably accentuated when it is combined with a lifestyle that evolves physical inactivity, smoking, and obesity.

We have probably only seen the top of the iceberg in the understanding of inflammatory processes in relation to physical activity, as new cytokines/myokines/adipokines are discovered all the time. In the future, it will be a major challenge to investigate pathways and to determine the interaction and regulatory role for the presently known myokines as well as the new myokines, which we will likely discover in the future. We also need to identify tissue-specific biomarkers of inflammation in the circulation. We need to discuss whom we will recommend to perform physical exercise in the future and how this activity should be carried out to optimize the myokine response. This will take large studies, which should address the necessary duration of the training program, intensities of the exercise, how many and which muscle groups should be involved, and if long-term indurance training is more effective with regard to anti-inflammatory activities than short-term, high-intensity resistance training. So far, physical activity appears to be an effective way to modulate proinflammatory activity in relation to disorders associated with atherosclerosis. This is likely a result of a reversal of endothelial dysfunction/activation, increased insulin sensitivity, a reduced arterial blood pressure, an improved lipid profile, and weight loss. We need to explore if there is a point when systemic low-level inflammation becomes irreversible; e.g., sarcopenia is to a major extent caused by physical inactivity, but we do not know if cachexia is reversible by physical exercise in chronic, inflammatory disorders. We also need to look for biomarkers to determine when we should motivate frail patients to exercise and when we should limit our efforts.

In conclusion, physiological experiments, molecular analyses, and epidemiological studies suggest together that physical activity per se mediates strong anti-inflammatory mechanisms with sufficient power to reduce proinflammatory activity in vitro and in vivo.

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