Possible beneficial role of exercise in modulating low-grade inflammation in the elderly

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Aging is associated with increased levels of tumor necrosis factor-α (TNF) and interleukin (IL)-6. These two cytokines are tightly linked in that TNF induces production of IL-6, which again inhibits TNF gene expression. In epidemiological studies, both cytokines have been associated with obesity, insulin resistance and atherosclerosis. However, based on basal studies, we suggest that TNF (and not IL-6) is the driver behind insulin resistance. Thus, it is possible that selective enhancement of the IL-6 level may inhibit TNF—induced insulin resistance. Muscle contractions induce production and release of IL-6, but not TNF, into the circulation, in both young and elderly humans. We suggest that muscle-derived IL-6 contributes to mediate the beneficial metabolic effects of exercise and may contribute to inhibit TNF-production and thereby insulin resistance.

Recent studies have demonstrated that circulating levels of plasma cytokines are highly influenced by age and that chronic elevated levels of some cytokines are associated with chronic disease. It is also known that muscular exercise enhances plasma levels of several cytokines. Thus, the purpose of this review is to discuss the possible biological effects of age-associated chronic low-grade inflammation and to discuss the possible role of exercise in modulating the cytokine response in the elderly.

Pro- and anti-inflammatory cytokines

The present review focuses on the biological role of chronic minute elevations in circulating cytokines in the elderly and the possible role of exercise in modulating this phenomenon. However, most information about cytokines comes from studies on acute infections and tissue injury. Pro- and anti-inflammatory cytokines are considered as a highly dynamic part of the inflammatory response to acute infections or tissue injury. Thus, cytokines are released at the site of inflammation (caused by an infectious pathogen or traumatic injury) and facilitate an influx of lymphocytes, neutrophils, monocytes and other cells, that participate in the clearance of the antigen and healing. The local inflammatory response is accompanied by a systemic response known as the acute phase response. This response includes the production of a large number of hepatocyte-derived acute phase proteins, e.g., C-reactive protein (CRP).

The first two cytokines in the cytokine cascade are tumor necrosis factor (TNF)-α and interleukin (IL)-1β, which are produced locally. Injection of TNF or IL-1 into laboratory animals or humans will induce most, if not all, mediators of the acute phase response (Dinarello, 1992). These cytokines are therefore usually referred to as pro-inflammatory cytokines. Tumor necrosis factor and IL-1 stimulate the production of IL-6, which has been classified as both a pro- and an anti-inflammatory cytokine. However, the present view is that IL-6 has primarily anti-inflammatory effects (Tilg, Dinarello, Mier, 1997).

Infusion of IL-6 into humans will result in fever but does not cause shock or capillary-leakage-like syndrome as observed with the prototypical pro-inflammatory cytokines, IL-1 and TNF (Rehman, Mills, Carter, Chou, Thomas, Maisel, 1997). Unlike IL-1 and TNF, IL-6 does not up-regulate major inflammatory mediators such as nitric oxide or matrix metalloproteinase. Previous studies provide evidence for the notion that IL-6 inhibits the production of TNF and IL-1. Thus, IL-6 inhibits LPS-induced TNF production both in cultured human monocytes and in the human monocytic line U937 (Schindler, Mancilla, Endres, Ghorbani, Clark, Dinarello, 1990). The suppressive effect occurs at the level of transcription in human peripheral blood mononuclear cells (Schindler et al.,
The elderly demonstrated larger initial increases in TNF and sTNFR, and more prolonged levels of TNF, sTNFR and CRP (Krabbe, 2001). Furthermore, the elderly had a slower normalization of the fever response. In accordance with the latter study, aging was associated with a prolonged inflammatory response (TNF and sTNFR) to severe pneumococcal infection (Bruunsgaard, Skinhoj, Qvist, Pedersen, 1999). Thus, these studies indicate that aging is associated with defect termination of inflammatory activity that may result in pre-activation of cytokine producing cells.

**Chronic elevation of circulating cytokines in the elderly**

During aging circulating levels of a number of cytokines increase. Thus, increased plasma levels of TNF (Paolillo et al., 1998; Bruunsgaard, Andersen-Ranberg, Jeune, Pedersen, Skinhj, Pedersen, 1999; Dobbs, Charlett, Purkiss, Dobbs, Weller, Peterson, 1999; Bruunsgaard, Skinhoj, Pedersen, Schroll, Pedersen, 2000), IL-6, IL-1ra (Dobbs et al., 1999) and sTNFR (Catania et al., 1997; Bruunsgaard et al., 1999; Hasegawa, Sawada, Ozaki, Inagaki, Suzumura, 2000) have been demonstrated. In addition aging is also associated with increased levels of acute phase proteins such as CRP and Serum Amyloid A (SSA) (Ballou et al., 1996) as well as high neutrophil counts (Bruunsgaard, Pedersen, Schroll, Skinhoj, Pedersen, 1999). Although increases in circulating cytokines and acute phase proteins are only two-four fold compared to levels in young subjects, low-grade inflammation is clearly associated with disease in the elderly (Bruunsgaard, Pedersen, Pedersen, 2001). Given the close interaction between these cytokines in the inflammatory response, fig. 1, it is not unexpected that the levels of these cytokines in general are found to intercorrelate, e.g., plasma levels of TNF were positively correlated with IL-6, sTNFR-II, and CRP in 126 centenarians (Bruunsgaard et al., 1999).

Although, a linear relationship was found for TNF and IL-6, high levels of TNF, but not IL-6, was associated with dementia and atherosclerosis (Bruunsgaard et al., 1999) in centenarians (n = 126). The finding of a relationship between TNF and atherosclerosis was confirmed in a study including 81-year-old humans (n = 130). Also, elevated levels of circulating IL-6 have been associated with several disorders. Thus, increased levels of TNF and IL-6 have been observed in obese individuals, in smokers and in non-insulin dependent diabetes mellitus (Vgontzas, Papanicolaou, Bixler, Hopper, Lottsikas, Lin, 2000). In two population-based studies, plasma concentrations of IL-6 have been shown to predict all-cause mortality as well as cardiovascular mortality (Harris, Savage, Tell, Haan, Kumanyika, Lynch, 1997; Volpato et al., 2001). Furthermore, plasma concentrations of IL-6 and

**The acute cytokine response in the elderly**

The acute cytokine response to an infection can be studied by the classical sepsis model in which *E. Coli* endotoxin is injected intravenously. Using this human endotoxin challenge model, nine very healthy, elderly volunteers aged 61–69 years and eight young controls were given a bolus of endotoxin. Plasma levels of TNF, IL-6, IL-8, IL-10, sTNFR and IL-1ra increased markedly after endotoxin administration in both groups.

**The cytokine balance**

[Fig. 1. The cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 are tightly related. Thus, TNF induces the production of IL-6, which again inhibits the production of IL-6.]
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TNF have been shown to predict the risk of myocardial infarction in several studies (Ridker, Hennekens, Buring, Rifai, 2000; Ridker, Rifai, Stampfer, Hennekens, 2000; Toft et al., 2002).

It has been proposed that IL-6 is the mediator that links the acute phase response to visceral obesity, insulin resistance and atherosclerosis (Yudkin, Kumari, Humphries, Mohammed-Ali, 2000). High levels of IL-6 in patients with metabolic syndrome may be explained by the fact that IL-6 is produced in adipose tissue (Mohammed-Ali, 1997; Fried, Bunkin, Greenberg, 1998). Omental adipose tissue produces more IL-6 than subcutaneous tissue (Fried et al., 1998). Adipose tissue also produces and releases TNF (Tsigos, Kyrou, Chala, Tsapogas, Stavridis, Raptis, 1999). However, in contrast to IL-6, the available data suggest that TNF plays a mechanistic role in insulin resistance. Thus, TNF-α down-regulates GLUT-4 and inhibits insulin receptor activity (Hotamisligil, 1999). Unpublished data from our group clearly demonstrates that IL-6 infusion to healthy elderly and young humans as well as patients with diabetes type II, does not inhibit glucose uptake or GLUT-4 expression (Steensberg et al., unpublished data).

Since TNF-α can trigger IL-6 release, one theory holds that it is adipose tissue derived TNF-α that actually is the “driver” behind the metabolic syndrome. In support of this theory is the finding that in elderly people serum-levels of leptin and TNF-α were correlated also when adjusting for the effect of gender and body mass index (Bruunsgaard, Pedersen, Schroll, Skinhøj, Pedersen, 2000). Furthermore, it was also demonstrated that blood levels of sTNFR (an indicator of TNF-activation) correlate with blood leptin levels in both controls and diabetic subjects (Muniztoros, Moschos, Avramopoulos, Kaklamani, Liliios, Doulgerakis, 1997). Given the fact that TNF is the prototype of a pro-inflammatory cytokine, whereas IL-6 is now placed as an anti-inflammatory cytokine, it is possible that TNF-α rather than IL-6 should be placed in the center as the cytokine that induces insulin resistance and thereby initiates diabetes type 2 and atherosclerosis.

The cytokine response to concentric exercise

It has been well demonstrated that the plasma concentration of IL-6 increases up to more than 100-fold during muscular exercise (Pedersen & Hoffman-Goetz, 2000; Pedersen, Steensberg, Schjerling, 2001). This increase is followed by the appearance of cytokine inhibitors such as IL-1ra and sTNFR and the anti-inflammatory cytokine IL-10 (Ostrowski, Rohde, Zacho, Asp, Pedersen, 1998; Ostrowski, Hermann, Bangash, Schjerling, Nielsen, Pedersen, 1998; Ostrowski, Rohde, Asp, Schjerling, Pedersen, 1999). In addition, the concentrations of the chemokines, IL-8, MIP-1α and MIP-1β, are elevated after strenuous exercise (Ostrowski, Rohde, Asp, Schjerling, Pedersen, 2001), fig. 2. Whereas most exercise studies show no effect of exercise on the production of TNF and IL-1, strenuous, prolonged exercise, such as marathon running, may cause a very small increase in the plasma concentration of TNF-α (Pedersen, Ostrowski, Rohde, Bruunsgaard, 1998; Suzuki et al., 2000; Toft et al., 2000; Starkie, 2001). Even though there is a moderate increase in the systemic concentration of these cytokines, the underpinning fact is that the appearance of IL-6 in the circulation is by far the most marked and that it’s appearance precedes that of the other cytokines. Thus, following a marathon race IL-6 increases up to 100-fold compared to rest (Ostrowski et al., 1999), comparable with the increases observed in patients with severe infections (Hack, Aarden, Thijs, 1997; Bruunsgaard et al., 1999). The augmented plasma IL-6 following exercise was associated with muscle damage in an earlier study (Bruunsgaard, Galbo, Halkjaer-Kristensen, Johansen, MacLean, Pedersen, 1997), but today it is very clear that pure concentric exercise without any muscle damage also induces marked production of IL-6 and that IL-6 is produced as a direct consequence of contraction per se (Pedersen et al., 2001). Plasma IL-6 during exercise increases with intensity and duration of exercise (Ostrowski, Schjerling, Pedersen, 2000). Interestingly, IL-6 mRNA is up-regulated in exercising human muscles (Ostrowski et al., 1998; Steensberg, van Hall, Osada, Sacchetti, Saltin, Pedersen, 2000; Keller et al., 2001; Starkie, Arkinstall, Koukoulas, Hawley, Febbraio, 2001) as well as in electrically stimulated rat hind limb (Jonsdottir, Schjerling, Ostrowski, Asp, Richter, Pedersen, 2000). Epinephrine has been suggested to trigger the IL-6 response during exercise (Papanicolaou et al., 1996). However, infusion of epinephrine comparable to the levels observed during exercise, induce only a six-fold increase in

![IL-6 is increased during exercise](image-url)

**Fig. 2.** The figure demonstrates the cytokine cascade in relation to exercise. Tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, IL-1-receptor antagonist (IL-1ra) and macrophage inflammatory protein (MIP)-1. Relative increases in plasma concentrations are shown (y-axis) in response to 3 h of exercise (x-axis). Plasma concentrations of IL-6 increases more than any other cytokine, whereas TNF does not increase.
plasma IL-6 compared to a 30-fold during exercise (Steenberg, Toft, Halkjaer-Kristensen, Pedersen, 2001). Furthermore, in another study both an exercising and a resting leg were subjected to the same hormones, but only the exercising leg released IL-6 (Steenberg et al., 2000). It has been demonstrated that monocytes in the blood are not the source of the elevated plasma IL-6 during exercise (Starkie, 2001). Furthermore, it was recently demonstrated that IL-6 was released from a contracting limb and from the resting limb of the same subjects. It was further calculated that this release could account for the augmented plasma IL-6 levels (Steenberg et al., 2000). More recently, two studies have found that both the IL-6 release and mRNA (Steenberg et al., 2001) as well as the IL-6 transcription rates and mRNA (Keller et al., 2001) are further augmented when exercising with low intramuscular glycogen levels compared to control. Thus, the recent research regarding IL-6 during exercise suggests that working muscles produce and release IL-6 as a consequence of contraction per se and low intramuscular glycogen or altered energy turnover (Steenberg et al., 2000; Keller et al., 2001; Steensberg et al., 2001).

The fact that IL-6 is produced locally in working muscles and released into the circulation in large amounts during exercise suggests that it has important biological roles. Thus, it is tempting to suggest that IL-6 works in a hormone-like fashion, exerting its effect on the liver and adipose tissue, thereby contributing to maintain glucose homeostasis during exercise and mediating exercise-induced lipolysis. Muscle-derived IL-6 may also work to inhibit the effects of pro-inflammatory cytokines such as TNF-α and thereby protect against insulin resistance and atherogenesis (Pedersen et al., 2001).

Effect of aging

There are no published studies on the effect of aging on muscle-derived IL-6. However, elderly people may in theory benefit from exercise-induced IL-6 production, which according to our theory, may work to lower the TNF production and to enhance lipolysis, thereby contributing to protect against insulin resistance and atherosclerosis. Due to a lower training degree, elderly individuals may be relatively more dependent on glycogen as energy source. We have unpublished data from a study testing the hypothesis that aging was associated with a higher IL-6 response due to a higher glycogen oxidation during concentric exercise (Pedersen et al., unpublished data). The IL-6 release from working skeletal muscles, muscle IL-6 mRNA and muscle glycogen content were estimated before, during and after 3 h of dynamic knee-extensor exercise at 50% of $W_{\text{max}}$ in healthy elderly and young males. The absolute net-IL-6 release and the decline in muscle glycogen concentration during exercise did not differ between age groups. However, when corrected for workload, the glycogen utilization and the change in net-IL-6 release were higher in the old subjects. The study suggests that an enhanced release of muscle-derived IL-6 relative to workload in elderly subjects is related to a higher utilization of glycogen during exercise.

The cytokine response to eccentric exercise

The type of muscle contraction also appears to have a large effect on the time-course of the systemic appearance of IL-6. During prolonged (Hellsten, Frandsen, Orthenblad, Sjödin, Richter, 1997; Rohde, MacLean, Richter, Kiens, Pedersen, 1997) eccentric, one-legged knee extensor exercise or two-legged eccentric knee extensor exercise lasting 30 min (Bruunsgaard et al., 1997) the IL-6 level does not peak until well after the cessation of exercise. In contrast, during running, cycling or concentric knee-extensor exercise the IL-6 level peaks at the cessation of exercise before progressively declining into recovery (Pedersen, Steensberg, Schjerling, 2001). It is clear therefore that the kinetics of IL-6 differ between that induced by concentric muscle contractions and that induced by eccentric exercise associated with muscle damage. In fact, Bruunsgaard et al. (1997) observed that using an eccentric exercise model, peak IL-6 was associated not with exercise intensity or duration but with creatine kinase (CK) levels, a traditional marker of muscle damage. Due to these observations, it was commonly thought that the IL-6 response to exercise represented a reaction to exercise-induced muscle injury in that the exercise-induced increase in IL-6 was a consequence of an immune response, due to local damage in the working muscles (Nieman et al., 1998).

Although an earlier study provided some evidence that the increase in plasma IL-6 was a consequence of an immune response, due to local damage in the working muscles (Bruunsgaard et al., 1997) more recent studies from our group (Ostrowski et al., 1998; Ostrowski et al., 1999) and others (Croisier et al., 1999) did not show an association between peak IL-6 and peak CK levels. Recently we examined plasma IL-6, CK and myoglobin (another indicator of muscle membrane damage) during and for 5 days after eccentric exercise in healthy young and elderly subjects. Despite marked increases in both CK and myoglobin, the plasma IL-6 increased only a few-fold, reaching peak levels 4h after exercise (Toft et al., 2002). These findings suggest that the large increase in plasma levels of IL-6 in exercise models where the CK level does not change or is enhanced only a few-fold, is related to mechanisms other than muscle damage. During the 30 min of eccentric exercise, there was a three-fold increase in plasma-IL-6 in the young subjects (Toft et al., 2002). This increase is comparable to that seen after
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30 min of concentric exercise (30). Thus, it seems that concentric and eccentric exercise induces the same increase in plasma IL-6 during the exercise. However, we are not aware of any studies where subjects have performed eccentric exercise for 2–3 h and thus it is not known whether eccentric exercise of long duration will provoke a 30–100-fold increase in plasma IL-6 as is seen in long duration concentric exercise (Ostrowski et al., 1998, 1999). In concentric exercise, the plasma IL-6 concentration declines rapidly immediately after the exercise. Therefore, the finding of a peak-IL-6 (two–eight-fold) 4 h after 30 min of eccentric exercise (Toft et al., 2002) should probably be ascribed to muscle damage.

To summarize, it is most likely that the marked and immediate increase in plasma IL-6 in response to long-duration 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. The IL-6 production in relation to muscle damage occurs later and is of less magnitude compared with the IL-6 production related to muscle contractions.

The effect of aging on plasma cytokines in eccentric exercise

We recently hypothesized that old subjects have an impaired ability to produce IL-6 and other cytokines in response to muscle damage (Toft et al., 2002). Elderly and young humans completed 60 min of eccentric lower limb exercise at the same relative oxygen uptake. Plasma cytokines were measured before, immediately after and 5 days into recovery from exercise, as were the biochemical markers of muscle damage, CK and myoglobin. In both groups, IL-6 increased (P < 0.05) immediately following exercise and peaked 4 h after exercise. However, the increase in IL-6 in both groups was modest relative to the increases in CK peaking at 539 ± 413 vs. 10301 ± 5863 UL−1 for elderly and young, respectively. In addition, the increase in IL-6 was less pronounced (P < 0.05) in elderly compared with young subjects. These results suggest that IL-6 increases progressively following eccentric exercise, suggesting that this increase is related to muscle damage. However, the modest increase in IL-6, despite large increases in CK, supports that the IL-6 response to muscle damage does not make an important contribution to the large increase in IL-6 observed during concentric exercise of long duration. The available data, however, also indicate that aging may be associated with impaired repair mechanisms to exercise-induced muscle damage.

Conclusion and perspectives

Aging is associated with low-grade inflammation. Early mediators of this inflammatory activity are TNF and IL-6. These two cytokines are tightly linked in that TNF induces production of IL-6, which again inhibits TNF gene expression. In epidemiological studies, both cytokines have been associated with obesity, insulin resistance and atherosclerosis. However, based on basal studies, we suggest that TNF (and not IL-6) is the driver behind insulin resistancy. Thus, it is possible that selective enhancement of the IL-6 level may inhibit TNF – induced insulin resistancy. Muscle contractions induce production and release of IL-6, but not TNF, into the circulation, in both young and elderly humans. We suggest that muscle-derived IL-6 contributes to mediate the beneficial metabolic effects of exercise and may contribute to inhibit TNF production and thereby insulin resistancy.

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