

MUSCLE AGING AND INFLAMMATION

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Human ageing is associated with a significant decline in neuromuscular function and performance (Doherty et al, 1993a, Ross et al, 1997 and Vandervoort, 2002). The term sarcopenia was first used by Rosenberg (Rosenberg, 1989), to describe age associated loss of skeletal muscle mass. Sarcopenia is now generally used to describe age-associated changes that occur within skeletal muscle and thus include the effects of altered central and peripheral nervous system innervation, altered hormonal status, altered caloric and protein intake and inflammatory effects. All these contribute to sarcopenia and to the characteristic skeletal muscle atrophy and weakness, which are considered major contributing factors to the loss of functional mobility, independence and frailty present in many elderly (Roubenoff and Hughes, 2000; Roubenoff et al. 2001). Because our society is an ageing one, understanding the underlying mechanisms of sarcopenia is essential for the development of effective interventions to prevent disability and optimize quality of life in older people. This review will focus on the potential role of inflammatory factors in sarcopenia and on the effects of exercise interventions.

1. Age related loss of skeletal muscle mass

Several studies have reported total muscle cross sectional area (CSA) decreases around 40% between the ages of 20 and 60 years (Doherty et al. 1993a, Porter et al, 1995 and Vandervoort, 2002). Increases in non-muscle tissues (fat and connective tissue) have also been reported (Rice et al, 1989). Increases of 59% of non-muscle tissue for the quadriceps and 127% for the hamstrings have been reported by Overend et al. (Overend et al., 1992a). CSA measurements from whole muscle obtained post-mortem showed reductions of 40% for subjects between 20 and 80 years old with

an average reduction of 10% at 50 years accelerating thereafter (Lexell et al 1988). In a study measuring total appendicular skeletal muscle mass (TASM) using dual –energy X-ray absorptiometry (DEXA) the authors (Gallagher et al, 1997) found, after adjusting for factors like height, body weight and age, that men had larger TASM than women and showed larger age-related decreases in TASM (14,8 vs 10,8%) when compared to women. A study using whole body magnetic resonance imaging (MRI) to determine skeletal mass in a sample of 268 men and 200 women aged between 18 and 88 years old (Janssen et al, 2000), showed significantly more muscle mass in men in both absolute terms (33,0 vs. 21kg) and relative to body mass (38,4 vs. 30,6%) after controlling for height and body mass, with greater losses of muscle mass with ageing when compared to women. The reduction in skeletal muscle mass with age was greater in the lower body for both men and women with a noticeable decrease in skeletal muscle mass beginning at 45 years of age in both men and women.

2. Age related loss of strength

Not only age-related loss of muscle mass but also age-related loss of strength has been well established with cross sectional studies of limb muscles tested under isometric and dynamic conditions, usually comparing groups of healthy young, middle-aged and older men and women (Doherty et al, 1993a; Porter et al, 1995; Vandervoort, 2002). Studies comparing knee extensor strength (Larsson et al, 1979; Young et al, 1984; Young et al, 1985; Overend et al, 1992b; Ivey et al, 2000) in groups of young and healthy older subjects (70-80 years of age) have on average reported age-related decreases in strength on the order of 20 to 40% with greater losses (50% or more) being reported for subjects in their ninth decade and beyond (Murray et al, 1980; Murray et al, 1985).

In general similar losses in strength have been reported for proximal and distal limb muscles (reviewed by Doherty, 2003a) with relative losses similar for men and women. Longitudinal studies have provided important information concerning the rate of strength decline with age (Basseby and Harries, 1993; Kallman et al, 1990). In the study by Basseby and Harries (Basseby and Harries, 1993) a 3% loss of grip strength per year for men and 5% for women over 4 years was reported while in a study with a large cohort (3680) of Japanese –American men (Rantanen et al, 1998) with a 27 year follow up a 1% per year decline in grip strength was reported. It also showed a more significant rate of decline for those older at baseline or with chronic diseases like diabetes and arthritis.

In general it appears that healthy men and women in their seventh and eight decades show, on average, 20-40% less strength compared with their younger counterparts. These losses are even greater (50% or more) for the very old.

3. Mechanisms underlying sarcopenia

Age-associated loss of muscle mass appears to be the most significant factor for age-associated loss of muscle strength (reviewed by Doherty, 2003c) and associated disability in older men and women. Histological data has provided some insight into the cause of age-related atrophy, mostly from needle biopsy sampling of the vastus lateralis muscle. Most studies report reductions in type II fiber size, the type I fiber size being a lot less affected with age (Lexell et al, 1988; Ross et al, 1997; Vandervoot, 2002). Reductions in type II fiber area range from 20 to 50%, type I fiber area losses range from 1 to 25%. There is also histochemical evidence of fiber type grouping, fiber atrophy and increase coexpression of myosin heavy chain isoforms in the same fiber consistent with a progressive denervation and reinnervation process (Andersen et al, 1999; Oertel, 1986). Taken together, these findings suggest that α -motoneuron loss may play an important role in age-related loss of muscle mass. Electrophysiological studies using either macro electromyographic techniques or motor unit number estimation techniques have found losses of whole functioning motor units in proximal and distal muscles in the upper and lower extremities (De Koning, 1988; Doherty and Brown, 2002; Stalberg et al 1989). These studies are consistent with anatomic data that has demonstrated losses of anterior horn cells and ventral root fibers with aging (Doherty et al, 1993; Kawamura et al, 1977a; Kawamura et al, 1977b; Mittal et al, 1987). Cross sectional studies suggest that motoneuron or motor unit numbers are well maintained until the seventh decade and then begin to decline rapidly (McComas, 1991; McComas 1998).

Loss of muscle mass secondary to muscle fiber loss and secondarily to fiber atrophy appear largely responsible for sarcopenia. Hormonal, metabolic, nutritional and immunologic factors also contribute to sarcopenia (reviewed by Roubenoff and Hughes, 2000). It has been postulated that with aging there may be a withdrawal of, or resistance to anabolic factors and a shift towards catabolic processes in the muscle.

4. Systemic low grade inflammation

Ageing is associated with systemic low-grade inflammation and the elevation of basal circulating levels several cytokines (Reviewed by Krabbe et al, 2004). Systemic low grade inflammation has also been associated with decreased muscle mass (Ferrucci et al, 2002; Pedersen et al, 2003; Visser et al, 2002) as well as the development of functional disability in the elderly (Ferrucci et al, 1999).

The local response to infections or tissue injury involves the production of cytokines that are released at the site of inflammation. Cytokines are small polypeptides, that have immunoregulatory roles. They facilitate the influx of lymphocytes, neutrophils, monocytes and other cells to the site of inflammation. The local inflammatory response is accompanied by a systemic response called the acute-phase response. This includes the production of a large number of acute phase proteins, such as C-Reactive Protein (CRP) and can be mimicked by the injection of the cytokines TNF- α , IL-1 β and IL-6 into laboratory animals or humans (Akira et al, 1992; Akira et al, 1993; Dinarello, 1992). The first cytokines to appear in the cytokine cascade are TnF- α , IL-1 β , IL-6, IL-1 receptor antagonist (IL-1ra), and soluble TNF- α receptors (sTNF-R). IL-1ra inhibits IL-1 signal transduction and sTNF-R are the naturally occurring TNF- α inhibitors (Akira et al, 1992; Akira et al, 1993; Dinarello, 1992). In response to acute infection or trauma, the cytokines and their inhibitors may increase several fold and decrease when the infection or trauma is resolved.

Chronic low-grade systemic inflammation is used to describe conditions in which a two to threefold increase in the circulating concentrations of TNF- α , IL-1, IL-6, IL-1ra, sTNF-R and CRP occurs. In this case the stimuli for the cytokine production are not known, but it is assumed that the origin of TNF on chronic low-grade systemic inflammation is mainly the adipose tissue (Coppack, 2001; Hotamisligil, 1993).

4. Age-associated Increased levels of circulating cytokines

With ageing, increased plasma levels of IL-6 (Wei et al, 1992; Ershler et al, 1993; Bruunsgaard et al 1999a; Hagger et al 1994), TNF- α (Bruunsgaard et al, 1999a; Bruunsgaard et al, 2000; Paolisso et al, 1998) , IL-1ra (Dobbs et al, 1999), sTNF-R (Bruunsgaard et al, 1999; Catania et al, 1997) and CRP (Ballou et al, 1996) have been reported. These cytokines work in a network and their levels are found to intercorrelate,

for example, plasma levels of TNF- α were positively correlated with IL-6, sTNF-R and CRP in centenarians with high levels of TNF- α but not IL-6 being associated with dementia and atherosclerosis (Bruunsgaard et al, 1999a). Although some authors have reported no changes in IL-6 and TNF- α plasma levels with age (Fagiolo et al, 1993; Peterson et al 1994) it is possible that these discrepancies relate to the health status of the participants and to differences in their age. For example IL-6 but not TNF- α was increased in middle aged people whereas both cytokines were elevated in octogenarians (Bruunsgaard et al, 1999a). Inflammatory mediators also act as disease markers and levels were higher in randomly selected subjects (Bruunsgaard et al, 1999a; Di Iorio et al, 2003, Ferrucci et al, 1999) compared to very healthy elderly individuals (Baggio et al, 1998) selected in accordance with the SENIEUR protocol. A larger consensus seems to exist regarding the anti-inflammatory mediators (IL-1ra and sTNF-R) acute phase proteins (CRP), sIL-2R and neutrophils with circulating levels and numbers increased in elderly populations (Ballou et al, 1996; Cakman et al, 1997; Catania et al, 1997; Gerli et al 2000; Rea et al, 1996). Increases in inflammatory markers are in the order of 2-4 fold and thus far from the increases observed during acute infection.

5. Effects of inflammatory mediators in age-associated chronic diseases.

Elevated levels of inflammatory mediators have been associated with several disorders namely the metabolic syndrome, Type 2 diabetes, atherosclerosis, cardiovascular disease and dementia (Alvarez et al, 1996; Barzilay et al, 2001; Duncan et al, 2003; Festa et al, 2002; Ford, 2002; Han et al, 2002; Hofman et al, 1997; Pradhan et al, 2001). Atherosclerotic plaques contain smooth muscle cells, macrophages and activated T lymphocytes and it is widely accepted that this pathology results from an inflammatory response to injuries in the vessel walls and endothelial dysfunction caused by factors like oxidised low-density lipoprotein (LDL), diabetes mellitus, hypertension, free radicals induced by smoking, infectious agents and a combination of these and other factors. The activated endothelial cells are targets as well as sources of inflammatory cytokines and chemokines that induce upregulation of adhesion molecules and promote leucocyte migration across the endothelial wall. Several studies have linked systemic low grade inflammation in elderly population to the prevalence and prognosis of cardiovascular disease. For example, plasma levels of TNF- α have been correlated with dyslipidemia and a high prevalence of cardiovascular disease in 80 year old subjects (Bruunsgaard et

al, 2000). TNF- α was also correlated with the blood pressure, insulin resistance, levels of cellular adhesion proteins and common carotid intima-media thickness in healthy middle-aged men (Sloog et al, 2002). IL-1 β serum levels were associated with congestive heart failure, angina and a history of dyslipidemia in 1292 subjects (Di Iorio et al, 2003). Circulating IL-6 levels acted as a marker of subclinical cardiovascular disease in a case control study of elderly people (Jenny et al, 2002) and was a predictor of mortality related to cardiovascular disease in a group of 65+ years old (Harris et al, 1999). IL-6 was also shown to be a predictor of myocardial infarcts in healthy middle-aged men (Ridker et al, 2000). IL-1 β , TNF- α and IL-6 induce the production of CRP, which as been shown to be a strong predictor of coronary events in several studies (reviewed in Pepys and Hirschfield, 2003).

It has been widely assumed that systemic low grade inflammation in cardiovascular disease is caused by the inflammation within the atheromatous lesions but now scientists are wondering if atherosclerosis could be a consequence of systemic low-grade inflammation. Chronic systemic non-vascular inflammation is known to be proatherogenic in general and acute systemic inflammatory episodes are strongly associated with atherothrombotic events (Jones et al, 2001). Also some studies have shown that systemic low-grade inflammation has the potential to induce several risk factors for cardiovascular disease: TNF- α induces insulin resistance and impairs the endothelium upregulation of adhesion molecules (Bruunsgaard and Pedersen, 2003). Both TNF- α and IL-6 affect the coagulation system and lipid metabolism, causing a procoagulant state and dyslipidemia (Bruunsgaard and Pedersen, 2003).

Inflammatory mechanisms have also been linked to age-associated cognitive decline, including Alzheimer's Disease and vascular dementia (Hofman et al, 1997) and to depression in aged subjects (Penninx et al 2003). In a study with centenarians, plasma TNF- α was shown to be associated with dementia (Bruunsgaard et al, 1999a). Increased plasma levels of IL-1 β have also been reported in patients with Alzheimer's disease (Licastro et al, 2000; Alvarez et al, 1996). Studies on autopsy specimens have found a marked over expression of IL-1 (Griffin et al, 1989) and IL-6 (Bauer et al, 1991) in the brains of Alzheimer's disease patients. Elevated levels of TNF (increases in 25-fold) have also been found in cerebrospinal fluid (Tarkowski et al, 2003) of patients with Alzheimer's disease. Patients with vascular dementia also had significant higher levels of TNF- α in their cerebrospinal fluid when compared to control individuals. However their plasma levels of TNF- α were similar to the control groups (Tarkowski et al, 2003). These results point to the CNS has a major site of TNF- α production in overt dementia. An efflux of IL-6

from the CNS in healthy young subjects has also been reported (Nybo et al, 2002). It appears that the CNS not only is able to produce cytokines, but can also contribute to the pool of circulating cytokines. Whether the cytokine elevations found in patients with Alzheimer's disease and vascular dementia are actually causing damage or indicate the presence of reparatory processes is unanswered. A few studies have shown that peripheral administered cytokines do affect human brain functions with negative effects on sleep (reviewed by Pollmacher et al, 2002), memory and depression (Reichenberg et al, 2001). However, at the moment, there are no experimental data available on whether small chronic increases in cytokines, like the one seen with ageing, affect human brain function. Acute and chronic cytokine increases may have different effects on cognition, as small amounts of cytokines seem to be necessary for normal neurological function.

6. Inflammatory mediators and sarcopenia

Sarcopenia has been associated with the development of functional disability in the elderly (Ferruci et al, 1999) and plays a central role in the frailty syndrome. It has been suggested that this syndrome reflects a metabolic imbalance caused by the overproduction of catabolic cytokines and the diminished availability of anabolic hormones, resulting from ageing itself and the presence of associated chronic conditions (Hamerman, 1999). The loss of muscle mass has been associated with systemic low-grade inflammation. It is also known that TNF- α has effects that may contribute directly to sarcopenia: TNF- α can disrupt the differentiation process in cultured muscle cells and promotes catabolism in mature muscle cells. It also induces apoptosis through the triggering of death domain receptors that are upregulated in the aged muscle cells (Roubenoff, 2003). TNF- α also causes increased basal energy expenditure, anorexia and loss of muscle and bone mass *in vivo* (Goodman, 1991). Since skeletal muscle is the primary site for glucose and triglyceride disposal (Dinneen et al, 1992; Lithell et al, 1981) and the predominant determinant of metabolic rate (Zurlo et al, 1994), age-associated muscle loss may also contribute to peripheral insulin resistance, dyslipidemia and increased adiposity. There is no simple mechanism to explain age-associated muscle loss. Skeletal muscle mitochondrial and contractile protein synthetic rates decline with age (Rooyackers et al, 1996; Yarasheski et al, 1993), accounting for some of the muscle loss and decrease of functional capacity. Plasma levels of TNF- α and other cytokines (as previously mentioned) also increase with ageing. An increase in TNF- α , especially if it were to occur in skeletal muscle could play a role in the progressive muscle loss of

advancing age. In a study with frail very elderly subjects (Greiwe et al, 2001), higher levels of TNF- α mRNA and protein were observed in muscle tissue from elderly compared to young adults and muscle protein synthesis was inversely related to the local levels of TNF- α in skeletal muscles. In a recent study by Plomgaard et al, (Plomgaard et al, 2005), immunohistochemistry analysis of biopsies from the triceps, vastus and soleus muscles, demonstrated that TNF- α and IL-18 were solely expressed by type II fibers, whereas the expression of IL-6 was more prominent in type I fibers. With age, TNF- α expression is increased predominantly in the vastus lateralis muscle (predominantly type II) when compared to the soleus muscle (Philips and Leeuwenburgh, 2005). These findings support the idea that TNF- α levels are important in the circulation but also within the muscle tissue. Furthermore, it has also been demonstrated that IL-18 also plays a role in apoptosis and tissue destruction (Finotto et al, 2004).

The role of IL-6 in sarcopenia is controversial. Although studies have reported that IL-6 is strongly associated with functional disability and loss of muscle mass (Ferrucci et al, 1999; Ferrucci et al, 2002; Visser et al, 2002), experimental studies have not been able to link IL-6 to sarcopenia. It is possible that IL-6 acts as a surrogate marker of TNF- α because the production of both cytokines is closely related: TNF- α stimulates the production of IL-6 and in return IL-6 inhibits the transcription of TNF- α and stimulates the production of anti-inflammatory cytokines and the shedding of TNF-R. Age-related sarcopenia has also been shown to be partly reversed by exercise. Resistance training of frail very elderly people resulted in decreased levels of TNF- α in skeletal muscles (Greiwe et al, 2001) and muscle strength after resistance training was inversely correlated with baseline levels of sTNF-R indicating that the gain of muscle strength was negatively influenced by activities in the TNF system (Bruunsgaard et al, 2004). sTNF-R bind TNF- α with high affinity and may act as inhibitors or carriers of TNF- α , prolonging its biological effects (Richards et al, 1995). sTNF-R are more stable in the plasma than TNF- α and are often a more consistent marker of activity in the TNF system than the plasma levels of TNF- α (Richards et al, 1995).

7. Cytokine responses to sepsis and exercise

In view of the previously discussed it is important to understand how the inflammatory system reacts to injury and to exercise. In sepsis and experimental models of sepsis, the

cytokine cascade consists of (named in order) TNF- α , IL-1 β , IL-6, IL-1ra, sTNF-R and IL-10 (Akira et al, 1993). The first two are produced locally and are usually referred as proinflammatory cytokines (Dinarello, 1992). TNF- α and IL-1 β stimulate the production of IL-6, which has been classified both as a pro and an anti-inflammatory cytokine (Tilg et al, 1997). The cytokine response to exercise is different from that elicited by infections, TNF- α and IL-1 β , usually do not increase with exercise (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Suzuki et al, 2002). Typically, IL-6 is the first cytokine present in the circulation during exercise, its levels increasing exponentially (up to 100-fold) in response to exercise and declining in the postexercise period (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Suzuki et al, 2002). Increased circulating levels of anti-inflammatory cytokines and cytokine inhibitors such as IL-1ra and sTNF-R in response to exercise are also found (Ostrowski et al, 1999; Ostrowski et al, 2000). In summary exercise provokes initially an increase in IL-6, followed by an increase in IL-1ra and IL-10. The appearance of IL-6 in the circulation is the most marked and it precedes that of the other cytokines.

8. IL-6 response to exercise

A marked increase in circulating levels of IL-6 after exercise without muscle damage has been a most consistent finding in exercise literature (reviewed by Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2003; Pedersen et al, 2003; Pedersen et al, 2001). Plasma IL-6 increases are related to exercise intensity, duration, the mass of muscle recruited and individual endurance capacity (reviewed by Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2003; Pedersen et al, 2003; Pedersen et al, 2001). IL-6 mRNA is upregulated by the contracting skeletal muscle (Febbraio et al, 2003; Nieman et al, 2003; Steensberg et al, 2001) and its transcriptional rate is markedly enhanced by exercise (Keller et al, 2001). It has also been demonstrated that the IL-6 protein is expressed in contracting muscle fibers (Penkowa et al, 2003; Hiscock et al, 2004) and released (Steensberg et al, 2002) from skeletal muscle during exercise whereas this is not the case for TNF- α (Steensberg et al, 2002; Steensberg et al, 2000). Even moderate exercise seems to have major effects on muscle derived IL-6. When a group of young healthy subjects performed 3h of dynamic two-legged knee-extensor exercise at 50% of their individual maximal power output a 16-fold increase in IL-6 mRNA and a 20-fold increase in plasma IL-6 was observed (Fischer et al, 2004). When

the same model was applied in healthy elderly subjects, even higher amounts of IL-6 were released from the working muscle (Pedersen et al, 2001).

Carbohydrate ingestion has been shown to attenuate the elevation of plasma IL-6 during both running and cycling (Nehlsen-Canarella et al, 1997; Nieman et al, 1998) whereas low muscle glycogen concentration enhances IL-6 mRNA and transcription rate (Keller et al, 2001; Steensberg et al, 2001). Preexercise intramuscular glycogen content appears to be an important stimulus for the IL-6 gene transcription with muscle derived IL-6 acting as an energy sensor. Muscle-derived IL-6 is regulated by an autocrine mechanism (Keller et al, 2003) as shown by the increase in the IL-6 gene expression after infusion of rhIL-6 in humans.

Small amounts of IL-6 are also produced and released by the adipose tissue (Lyngso et al, 2002), and some studies indicate that the brain (Nybo et al, 2002) and the peritendon tissue (Landberg et al, 2002) may also release IL-6 in response to exercise. Monocytes do not seem to be major contributors to the IL-6 response to exercise (Moldoveanu et al, 2000; Starkie et al, 2001). Although the precise biological action of muscle-derived IL-6 is not known yet, current data suggests that IL-6 released from the contracting muscle during exercise acts in a hormone-like manner to mobilize extracellular substrates and augment substrate delivery during exercise.

9. Anti-inflammatory effects of exercise induced cytokines.

IL-6 seems to have some anti-inflammatory effects. It inhibits TNF- α and IL-1 production, stimulates the production of IL-1ra and IL-10 (Steensberg et al, 2003a). It also stimulates the release of soluble TNF- α receptors (Tilg et al, 1997) and induces the production of the hepatocyte-derived acute phase proteins, many of which have anti-inflammatory properties (Akira and Kishimoto, 1992). IL-6 has been shown to inhibit lipopolysaccharide (LPS)-induced TNF- α production in cultured human monocytes and in the human U937 cell line (Schindler et al, 1990). IL-6 knockout mice show markedly elevated levels of TNF- α (Matthys et al, 1995) indicating that IL-6 has a regulatory effect on TNF- α levels. In addition, rhIL-6 infusion in healthy young adults inhibits the endotoxin-induced increase in circulating levels of TNF- α (Starkie et al, 2003b).

IL-10 has been shown to inhibit the production of IL-1 α , IL-1 β , TNF- α and IL-8 (Moore et al, 1993). These cytokines are involved in the activation and recruitment of granulocytes, monocytes/macrophages, T, B and NK cells to the sites of inflammation. IL-10 is also able to suppress cytokine synthesis in LPS stimulated human mononuclear cells by

inhibiting the transcription of the cytokines genes (Wang et al, 1994). IL-10 is also able to prevent cytokine protein synthesis by posttranscriptional mechanisms (mRNA degradation) as shown in LPS stimulated human macrophages where the release of IL-1a, IL-6 and TNF- α release was inhibited when IL-10 was added to the cells (Bogdan et al, 1992). Thus, IL-10 seems to play an important role in orchestrating the inflammatory reaction, mainly in what concerns the activation of the monocytes/macrophage cells.

The IL-1ra molecule acts by inhibiting signal transduction into the cells by binding to the IL-1 receptors. IL-1ra binds to the IL-1 receptor complex does not induce any intracellular response (Dinarello, 2000). IL-1ra is also an acute phase protein because both cultured human hepatocytes and human hepatoma cell line HepG2 produce IL-1ra after IL-6 stimulation (Gabay et al, 1997).

CRP levels also increase after long duration exercise and it has been shown to induce the release of anti-inflammatory cytokines by circulating monocytes and to suppress the synthesis of proinflammatory cytokines in tissue macrophages (Pedersen and Hoffman-Goetz, 2000; Pue et al, 1996).

10. Anti-inflammatory effects of exercise

Cross-sectional studies have demonstrated an association between physical inactivity and low-grade systemic inflammation in healthy elderly people (Abramson and Vaccarino, 2002; Geffken et al, 2001; Mattusch et al, 2000; Wannamethee et al, 2002).

In order to assess if acute exercise induced a true anti-inflammatory response, Starkie et al (Starkie et al, 2003) developed a model for "low-grade inflammation" in which they injected a low dose of *Escherichia coli* endotoxin in healthy volunteers, who had either been resting, rode a bicycle for 3h or were infused with rhIL-6 for 3h. In the control group the TNF- α plasma levels increased significantly in response to the endotoxin while in the other two groups the TNF- α response was totally attenuated. Both exercise and rhIL-6 infusion, at physiological concentrations, were able to inhibit endotoxin-induced TNF- α production in humans. This paper provided the first experimental evidence of exercise mediated anti-inflammatory activity and suggests that the mechanism include IL-6, which is produced and released from exercising muscles. This was further supported by a study in TNF-R knockout mice (Keller et al, 2004) that demonstrated that exercise normalised the overexpression of TNF- α in these mice. Another study demonstrated that IL-6 deficient mice developed mature-onset obesity and insulin resistance, which was reversed by the administration of IL-6 (Wallenius et al, 2002). So lack of IL-6 caused

insulin resistance. Given the fact that TNF- α induces insulin resistance, exercise may enhance insulin sensitivity through suppression of TNF- α production. Another important finding was the fact that after a progressive resistance exercise training program of 3days/week for 3 months, with healthy young and frail elderly subjects, muscle TNF- α mRNA and protein levels decreased in the exercising group but did not change in the control group (Greiwe et al, 2001). Thus exercise seems to suppress skeletal muscle TNF- α expression.

It is possible, that with regular exercise, the anti-inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation. This long term effect of exercise may be ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6. IL-6 also stimulates lipolysis as well as fat oxidation. In general the plasma cytokines found following exercise induce a strong anti-inflammatory effect and may offer protection against TNF-induced insulin resistance.

It appears that the anti-inflammatory cytokines produced and released by the skeletal muscle may be involved in mediating the health beneficial effects of exercise and play important roles in the protection against the diseases associated with low-grade inflammation.

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