Leucocytes, cytokines and satellite cells: what role do they play in muscle damage and regeneration following eccentric exercise?

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ABSTRACT

Exercise-induced muscle damage is an important topic in exercise physiology. However, several aspects of our understanding of how muscles respond to highly stressful exercise remain unclear. In the first section of this review we address the evidence that exercise can cause muscle damage and inflammation in otherwise healthy human skeletal muscles. We approach this concept by comparing changes in muscle function (i.e., the force-generating capacity) with the degree of leucocyte accumulation in muscle following exercise. In the second section, we explore the cytokine response to 'muscle-damaging exercise', primarily eccentric exercise. We review the evidence for the notion that the degree of muscle damage is related to the magnitude of the cytokine response. In the third and final section, we look at the satellite cell response to a single bout of eccentric exercise, as well as the role of the cyclooxygenase enzymes (COX1 and 2). In summary, we propose that muscle damage as evaluated by changes in muscle function is related to leucocyte accumulation in the exercised muscles. 'Extreme' exercise protocols, encompassing unaccustomed maximal eccentric exercise across a large range of motion, generally inflict severe muscle damage, inflammation and prolonged recovery (> 1 week). By contrast, exercise resembling regular athletic training (resistance exercise and downhill running) typically causes mild muscle damage (myofibrillar disruptions) and full recovery normally occurs within a few days. Large variation in individual responses to a given exercise should, however, be expected.

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The link between cytokine and satellite cell responses and exercise-induced muscle damage is not so clear. The systemic cytokine response may be linked more closely to the metabolic demands of exercise rather than muscle damage. With the exception of IL-6, the sources of systemic cytokines following exercise remain unclear. The satellite cell response to severe muscle damage is related to regeneration, whereas the biological significance of satellite cell proliferation after mild damage or non-damaging exercise remains uncertain. The COX enzymes regulate satellite cell activity, as demonstrated in animal models; however, the roles of the COX enzymes in human skeletal muscle need further investigation. We suggest using the term 'muscle damage' with care. Comparisons between studies and individuals must consider changes in and recovery of muscle force-generating capacity.

Keywords: Skeletal muscle, lengthening contractions, ultrastructural disruptions, necrosis, myokines, cyclooxygenase (COX1, COX2), non-steroidal anti-inflammatory drugs (NSAIDs)

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INTRODUCTION

Exercise-induced muscle damage has been a popular topic in exercise science for many years. In particular, the term 'delayed onset muscle soreness' (DOMS) has been a recurring theme since the early work of Hough (127) (e.g., (3,12,15,66,68,123,210)). Human studies investigating the physiological responses to eccentric exercise (i.e., lengthening muscle actions) were conducted as early as the end of the 19th century and the beginning of the 20th century (references in (16)). More controlled experiments on eccentric exercise (e.g., 'backwards' cycling) were conducted by Abbott *et al.* (1,2) and Asmussen (16) in the 1950's. Extending the pioneering work of Hill (21,122), Katz (144) carefully explored the basic physiology of muscle lengthening. Concerning the potential for eccentric muscle actions to cause muscle damage, Katz wrote: 'Rapid stretching of an active muscle, beyond its optimum length, is apt to break or weaken permanently parts of the contractile substance' (p. 64, (144)). Important research into muscle physiology and sarcomere and myofibrillar mechanics continued through the work of Gordon, Huxley and Julian (108,109,132,133), and later Julian and Morgan (140,141). Morgan (205) put forward the 'popping sarcomere hypothesis' to explain the observations of disruptions to the myofibrillar machinery of skeletal muscle fibres after eccentric actions (reviews: (5,206,207,245)). Many other investigators have contributed to the paradigm of exercise-induced muscle damage, but some worth mentioning for their significant contributions include Salminen and Vihko (258-260,306,307), Armstrong *et al.* (11,12,14,315), Faulkner *et al.* (37,88,89), McArdle and Jackson (134,186-188), and Fridén and Lieber (157-159). These investigators mainly worked with muscle preparations (*in vitro* studies) and animals models (e.g., rodents and rabbits). Work on humans at the myocellular level was initiated by Fridén *et al.* (96,97,101-103) and Newham et al (137,210,213) in the 1980's. These authors investigated the effects of downstairs running, eccentric (backwards) cycling, stepping exercise (one eccentric working leg), isolated eccentric work for the elbow flexors and backward walking on a treadmill (targeting the calf muscles). They reported disruptions at the ultrastructural level and more gross cellular damage, comprising leucocyte accumulation and regeneration. Thereby, they confirmed many of the findings from previous studies on muscle preparation and animals. During the last few decades researchers have, with ever more advanced techniques, attempted to understand the aetiology of exercise-induced muscle damage. This work has focused on mechanical tearing, metabolic stress, the local and systemic inflammatory response, as well as the recovery process involving satellite cell activation and muscle regeneration (64,86,170,232,247,275,292,296,298).

In the first part we review the evidence for muscle damage and local inflammation (i.e., accumulation of leucocytes in the muscle tissue) following various types of eccentric exercise. In general, the assessment of muscle damage requires reliable and valid markers. This is indeed a major challenge, because in human research there are currently no markers that are considered the 'gold standard'. Histological observations (light or electron microscopy) and changes in muscle function (force-generating capacity) seem to be the most valid markers of muscle damage, although both have some limitations. Histological examination of muscle biopsy samples (typically, sections cut from a 5–20 mg muscle sample) can

identify abnormalities such as myofibrillar disruptions and the presence of inflammatory cells. However, the question remains as to whether this small piece is representative of the whole muscle (12,26,316). Changes in force-generating capacity are an indirect measure of muscle damage. Nevertheless, with appropriate testing, changes in muscle function give a good indication of the status of the whole muscle (316). Muscle damage is therefore best assessed by measuring changes in force-generating capacity and performing histological observations. Other proxy markers of muscle damage, such as DOMS and circulating creatine kinase (CK), are generally not considered sufficiently valid (66,280,316), but do provide some additional or complementary information. In this section, we focus on the relationships between changes in muscle function and histological evidence for myofibrillar disruptions, inflammation and myofibre necrosis in human studies.

In the second part of this review, we look at the exercise-induced cytokine response. The systemic inflammatory response comprises a leucocytosis and an acute-phase response (86). Cytokines (e.g., IL-1 and IL-6) are part of the acute-phase response, and strenuous exercise generally seems to increase the circulating levels of a number of different cytokines. Cytokines are traditionally regarded as messenger molecules associated with leucocytes and inflammatory and immunological reactions. However, more recent research demonstrates that these cytokines are not only produced by leucocytes, but also by myofibres and peritendinous tissue (151,238). This had led to the term 'myokines', which refers to muscle-derived cytokines and chemokines. Uncertainty persists concerning the physiological actions and the precise source of production for cytokines found in the circulation during and after exercise. We have reviewed the literature for studies that have investigated the cytokine/myokine response in relation to eccentric exercise.

In the final part of this review, we describe the satellite cell response to single bouts of eccentric exercise. Satellite cells are undeniably required for regeneration of gross muscle damage where segments of myofibres are lost, for example, after a strain injury with torn myofibres (136). Surprisingly, satellite cells seem responsive to a variety of exercise protocols, both muscle damaging and non-damaging exercise. We review the satellite cell response to eccentric exercise. Non-steroidal inflammatory drugs that inhibit the activity of cyclooxygenase enzymes in skeletal muscle can also inhibit the satellite cell response. We discuss the evidence for this effect in humans.

1. DEFINING EXERCISE-INDUCED MUSCLE DAMAGE

Regular exercise generally makes our muscles stronger and/or more resistant to fatigue. However, during intense exercise our muscles fatigue and weaken temporarily. If the exercise is unaccustomed and/or very vigorous, we may even damage the working muscles, and it may take days for the muscles to recover. This type of muscle damage has been named 'exercise-induced muscle damage' (143,226). Various types of eccentric exercise (i.e., lengthening muscle actions) have been used to induce muscle damage experimentally (49,64,86,282). Exercise-induced muscle damage also occurs after long distance running (121,272,273,310) and to some degree after traditional resistance exercise (i.e.,

lifting weights; (94,251,281,308))—especially if the exercise is unaccustomed, very intense and/or too frequent (69,148,194). However, exercise-induced muscle damage does not have any established definition; it is merely characterised by a set of signs and symptoms (49,66,159,282). DOMS is the most common symptom of exercise-induced muscle damage, whereas histological evidence of disruptions of the myofibrillar structure and, especially, myofibre necrosis and inflammation are the ultimate signs of muscle damage (if we disregard methodological uncertainties; discussed below).

Necrotic cells go through several stages (304), but necrotic segments of myofibres may appear as swollen and rounded (on cross-sections). Immunohistochemical staining for cytoskeletal (e.g., desmin and dystrophin) and myofibrillar proteins (myosin) is diminished (or absent), which indicates degradation of these proteins (71,158,166). Disruption of the sarcolemmal membrane causes influx of extracellular proteins, such as fibronectin and albumin (72,283). Segmental myofibre necrosis[1] is manifested by inflammatory cells (particularly macrophages) that have invaded these myofibres and accumulation of myoblasts that originate primarily from satellite cells ((136,154,158,230,257,284); see also Figure 1). Because necrotic cells will attract immune-competent cells through receptors, such as toll-like receptors (50,78,184), accumulation of inflammatory cells within myofibres is a strong sign of segmental myofibre degradation and necrosis.

Some studies have reported signs of necrosis in voluntarily exercised muscles of seemingly healthy subjects (72,74,121,135,137,226,230,310). In rare cases, experimental subjects and patients have been diagnosed with rhabdomyolysis after exercise. Rhabdomyolysis is broadly defined by severe muscle pain/tenderness, swelling and muscle weakness, elevated blood activity of muscle proteins such as CK (> 10,000 IU/L), and dark urine, indicating myoglobinuria (65,146,264,271). Serious cases of rhabdomyolysis (including myoglobinuria) have been observed after various types of exercise, but rhabdomyolysis has been most frequently reported after extreme military training (135,262).

In experiments involving eccentric exercise, relatively little evidence of severe myofibre necrosis exists (Table 1; see addendum). A more common finding is accumulation of inflammatory cells, primarily monocytes/macrophages, in the endomysium and especially in the perimysium ((92,119,129,229,283); see also Table 1). However, in response to 'extreme' exercise massive leucocyte infiltration and cellular accumulation inside myofibres can be demonstrated (60,224,230,257). These observations suggest that the leucocytes are recruited to remove cellular debris and prepare for regeneration of necrotic segments of myofibres (56,85). Thus, necrotic myofibre segments seem to induce a strong chemotactic signal to recruit leucocytes; however, exercised muscle tissue may also summon leucocytes in the absence if necrosis (Figure 1—moderate damage versus severe damage).

Leucocytes may start to infiltrate the muscle tissue immediately after exercise, but are typically detected in the extracellular space 24–48 hours after exercise (25,92,119,229). They infiltrate the intracellular space ~4-7 days after exercise—if some myofibres become necrotic (60,229,230). Leucocyte accumulation therefore appears to be a gradual process regulated by the extent of damage. In response to severe damage, leucocyte accumulation peaks in time with the pres-

[1] 'Segmental myofibre necrosis' implies that there are segments or parts of the fibre that are necrotic, not necessarily the whole myofibre (99,136,158).

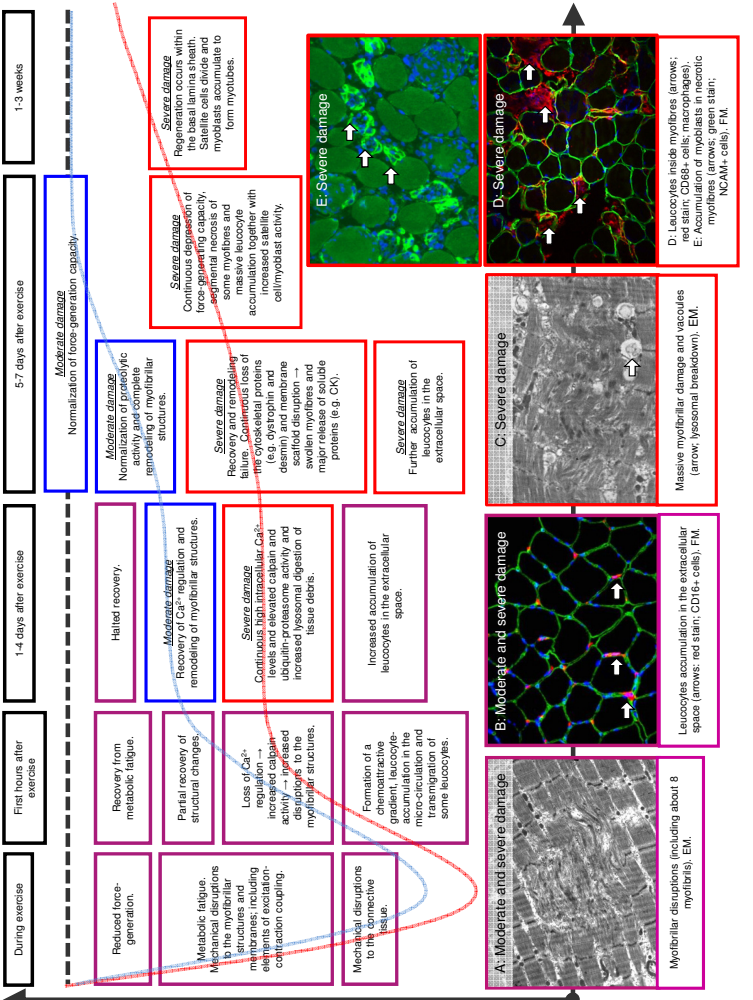

Figure 1. A model for central events in the recovery of the force-generating capacity after moderate (blue line) and severe (red line) exercise-induced muscle damage. Both moderate and severe exercise-induced muscle damage are accompanied by changes in the myofibrillar structure, together with an inflammatory response (purple boxes and images). The difference between moderate and severe damage becomes more prominent over time as the damage progresses in muscles with severe exercise-induced muscle damage. While the moderately damaged muscles enter the final phase of recovery (blue line and boxes), inflammation increases within the severely damaged muscles, probably in response to the presence of segments of necrotic myofibres (red line, boxes and images). Necrotic myofibres must be regenerated (by myoblasts), a process that may take several weeks and is manifested by a long-lasting reduction in the force-generating capacity. Note: large variation in individual responses has to be expected.
EM: Electron Microscopy (longitudinal sections).
FM: Fluorescence Microscope (cross-sections): Image B and D: Red stain: leucocytes; green stain: basal lamina (laminin); blue stain: nuclei (DAPI). Image E: Green stain: satellite cells/myoblasts (NCAM); blue stain: nuclei (DAPI).

ence of necrotic myofibres (60,137,229,230,257). In relation to muscle function, McCully and Faulkner (192) have reported a high correlation between gross muscle damage (apparent cellular infiltrate and myofibre necrosis) and reduction in the force-generating capacity.

Another histological characteristic of muscles following eccentric exercise is myofibrillar disruption. Fridén *et al.* (102,103) provided the first evidence of morphological changes in the 'contractile machinery' after eccentric exercise in humans (running down stairs and eccentric cycling). No gross damage or leucocytes were seen by light microscopy, but electron microscopy revealed subcellular disorganisation of the myofibrillar structure, especially that of the Z-bands (Z-band streaming and smearing (98)). Several subsequent studies have verified these findings (105,106,126,182,213,250), with (154,226,229) and without (71,223,324) simultaneous signs of inflammation and necrosis. Myofibrillar disruption is strongly associated with structural changes to the t-tubule system and the sarcolemma (245,289,315). Note that myofibrillar disruptions have been reported immediately after exercise, as well as one week after exercise, whereas the greatest disturbances are typically found after 1–4 days (103,121,213,250,325).

Whether myofibrillar disruptions indicate damage or remodelling and incorporation of new sarcomeres is debatable (71,97,126,154,213,324,325). Sarcomere disruption and myofibrillar disorganisation are linked to reduced force-generating capacity (106,154,162,176,250), and sarcomeres are disrupted following single eccentric muscle actions (39). These findings suggest that the myofibrillar disruption that occurs during or shortly after exercise represents damage. The changes in myofibrillar structures observed some days into recovery may, however, more appropriately be termed 'remodelling' (325). Minor myofibrillar disruptions can indeed occur without significant changes in the force-generating capacity (105,245). These findings raise the question of whether initial damage due to mechanical forces and activation of Ca^{2+}-dependent proteinases (e.g., calpain (161,250)) are required for remodelling. Nevertheless, disruption of intracellular Ca^{2+} regulation probably links myofibrillar damage with necrosis. Hence, if Ca^{2+} homeostasis is not re-established within a few days after exercise, the damage to the myofibrillar structure and the cytoskeleton may become irreparable, and segments of the myofibre become necrotic (Figure 1 and (5,98,107,245)).

Limited human research has examined changes to the extracellular matrix in response to eccentric exercise, but intracellular and extracellular events appear to occur simultaneously (40,73,173,250). Stauber *et al.* (283) reported that the extracellular matrix was separated from the myofibres after exercise. More recent studies have observed increased expression of tenascin C and PIIINP[2], which indicate remodelling of the extracellular matrix (73,250). Damage to the extracellular matrix may increase permeability of the sarcolemmal membrane, as indicated by increased efflux of CK and myoglobin, and influx of albumin and tetranectin (280,283,319).

Reports from various animal models show that exercise-induced muscle damage is linked to inflammation (88,200,274,275,296). Humans, however, can experience symptoms of exercise-induced muscle damage, such as DOMS and increased passive tension, without presenting classical signs of inflammation (i.e., leucocyte infiltration) in the muscle tissue (71,180,229,230,251). Based on

[2] N-terminal propeptide of Type III procollagen

well-controlled experiments, some researchers claim that voluntary eccentric exercise does not cause gross muscle damage (necrosis) or cellular infiltration in the exercised muscles (71,178,179,326). This concept challenges the validity of a series of human studies from the late 1980's and the 1990's (e.g., (60,92,119,137,226,257)). The main criticism of these classical 'muscle damage' studies is the risk of bias resulting from repeated biopsies from the same muscle (179). Malm *et al.* (180) reported no differences in leucocyte infiltration in muscle samples obtained from eccentrically-exercised muscle and resting muscle up to one week after exercise. Based on these observations they argued that the biopsy procedure itself, rather than exercise, increased inflammation in muscle. Electrical stimulation of human skeletal muscles causes significantly more damage than voluntary exercise (71,171). For these reasons, some researchers (71,179) also question the relevance of data from animal studies using rather 'non-physiological' muscle actions to inflict massive/gross muscle damage.

These problems arising from repeated biopsies, together with the results from electrical stimulation of human muscle, challenge the paradigm of exercise-induced muscle damage. Historically, this paradigm has been based on data from animal studies, and has muscle damage and inflammation as fundamental events (see introduction and (10,12,14,158,200)). Nevertheless, more recent studies that have collected samples from both exercised and resting muscle provide compelling evidence that eccentric exercise can lead to both accumulation of leucocytes and myofibre necrosis (154,229,230). Importantly, large variations in the individual responses to eccentric exercise were evident, and gross muscle damage did not occur in all individuals (229,230). The literature on exercise-induced muscle damage is therefore full of contradictory reports (e.g., see Table 1). Some of this variability is simply due to non-specific nomenclature used to identify and describe 'muscle damage' and inflammation.

Other confounding factors in this debate on exercise-induced muscle damage include variation in exercise protocols and inconsistent measurements of muscle function (i.e., the force-generating capacity) to assess muscle damage. Malm *et al.* (180,181) and Yu *et al.* (326) reported no signs of necrosis of inflammation after submaximal, eccentrically-biased exercise (i.e., backwards cycling, downhill running and running down stairs). Although they observed severe DOMS after these exercise protocols, changes in other markers of muscle damage were rather trivial compared with observations reported by others (e.g., (60,137,283)). Specifically, Malm *et al.* (181) reported that isometric strength (torque) decreased by only 15% in the first 24 hours after exercise. Isometric strength then returned to normal in the following 24 hours. Serum CK activity increased, but only about six times above pre-exercise values. By contrast, in other studies in which high-force eccentric exercise across large ranges of motion was used, isometric/concentric force-generating capacity decreased by about 50% after exercise. Recovery of muscle function in these other studies was also significantly slower, and plasma/serum CK activity reached more than 100 times pre-exercise values (see Table 1). These contrasting findings raise the question of whether it is appropriate to compare cellular responses from studies using quite different exercise protocols.

2. CHANGES IN MUSCLE FUNCTION REFLECT THE EXTENT OF MUSCLE DAMAGE

To assess muscle damage directly, histological analysis of muscle tissue is required (88). However, collecting tissue samples from humans can be unpleasant for the subjects and demanding on resources. Histological analysis of human muscle tissue can also be unreliable (26,115,156,316). For these reasons, proxy markers of muscle damage such as DOMS, range of motion, swelling, and serum CK activity are often used. But these markers do not always accurately reflect the extent of muscle damage, and do not always correlate with each other (100,128,210,218,219,255,280,316). By contrast, muscle function measured as force-generating capacity (e.g., maximal concentric or isometric strength) is relatively easy to measure, and is generally considered to be a reliable and valid marker for the degree of muscle damage (49,64,88,98,245).

Studies that have both obtained biopsies and measured changes in muscle function are summarised in Table 1 (see addendum). These studies point to an association between changes in force-generating capacity and histological observations such as myofibrillar disruptions, signs of necrosis and leucocyte accumulation. In those studies that report a minor reduction in the force-generating capacity (< 20% of pre-exercise values; Table 1A), few or no morphological/histological abnormalities are found. By contrast, those studies that report a large reduction in muscle function (> 50%; Table 1C) also report inflammation (leucocyte accumulation) and/or segmental myofibre degradation/necrosis. Eccentrically-biased exercise (e.g., downhill running) generally causes smaller changes in muscle function compared with isolated, eccentric muscle actions that involve a large range of motion (Table 1 and 2; see addendum).

Eccentrically-biased exercise and isolated eccentric exercise differ with regard to the mechanical characteristics of muscle-damaging exercise. The most critical factors for muscle damage are high force and large strain (i.e., muscle lengthening beyond the optimum length for force-generation (29,39,112,160,176,212,290,291)). Eccentric exercise that involves a large range of motion and high force-generation is very likely to cause substantial structural (myofibrillar) disruptions, and in turn, reduced muscle function. Other factors, such as joint angle velocity (51,52,192,227,312) and number of repetitions (41,162,219,221,291) may modify the degree of muscle damage. However, these factors seem secondary to the work (strain × force [J]) done to lengthen/stretch the muscles (38,88,167,321).

2.1 Mild exercised-induced muscle damage

Among those studies that report a relatively small reduction in the force-generating capacity (i.e., < 20%) and rapid recovery (33,71,90,181), only one study reported accumulation of leucocytes in the tissue ((71); Table 1A; see addendum). None of these studies observed any signs of necrosis, and plasma/serum CK activity did not surpass ~1,000 IU/L.

In the study by Bourgeois *et al.* (33), subjects exercised with a load equal to 80–85% of 1RM (i.e., traditional resistance exercise), whereas in the study of Feasson *et al.* (90) and Malm *et al.* (181), subjects ran downhill (on a treadmill). In the study of Crameri *et al.* (71), subjects completed a bout of unilateral, single joint (knee), maximal eccentric actions. Compared with studies that have used

similar protocols (24,25,201), the reduction of muscle function was surprisingly low in the study by Crameri *et al.* (71). Nevertheless, Crameri *et al.* (71) did observe both myofibrillar disruption and accumulation of macrophages (CD68+ cells). Interestingly, the contralateral leg completed the same number of eccentric actions, but was stimulated electrically (not shown in Table 1A). Compared with the voluntarily exercised muscle, the electrically-stimulated muscle was clearly damaged. Necrosis was indicated by accumulation of intracellular leucocytes (CD68+ cells) and myofibres that did not express desmin or dystrophin. The authors suggested that these variations may be due to differences in the pattern of muscle activation between voluntary and electrically-stimulated muscle actions (71).

Although increased numbers of leucocytes are not found (by immunohistochemistry) within muscle fibres after these exercise protocols, it does not exclude the possibility that there are interactions between the exercised myofibres and the immune system. Circulating leucocytes may indeed accumulate in the micro-vessels of the exercised muscles (229). Raastad *et al.* (251) used radionuclide imaging (which involves radiolabelling of autologous leucocytes—primarily neutrophils—and scintigraphy). They documented an early accumulation of leucocytes in muscle 1–24 hours after resistance exercise. The force-generating capacity decreased by 16% shortly after exercise and returned to normal between 28 and 47 hours after exercise, indicating only mild muscle damage. Based on this evidence, we propose that the immune system immediately responds to muscle damage resulting from the stress of high-force exercise. However, when muscle damage is mild, blood borne leucocytes do not leave the circulation in significant numbers (229). Although there is no accumulation of leucocytes in the muscle tissue after exercise, resident stromal cells, such as macrophages, may become activated, and thereby play a role in the recovery and adaptation to exercise (246). Evidence to support this notion awaits further experiments on human subjects.

Figure 2 (upper curve) demonstrates typical changes in the force-generating capacity of trained subjects that have performed a bout of a heavy traditional resistance exercise (3–8 repetition maximum) or subjects that are 'low responders' to eccentric exercise. Typically the reduction in the force-generating capacity after exercise is less than 20% and recovery is completed within 48 hours. We suggest using the term 'mild exercise-induced muscle damage' if the reduction in the force-generating capacity is less than 20% and/or recovery is completed within 48 hours after exercise.

2.2 Moderate exercise-induced muscle damage

Among those studies reporting a moderate reduction in the force-generating capacity (20–50%), only one study reported signs of necrosis (229), but five (24,25,129,229,287) of eight studies found accumulation of leucocytes in the exercised muscles (Table 1B; see addendum). Two of the three studies that did not report increased numbers of leucocytes also reported the smallest reduction in the force-generating capacity.

Paulsen *et al.* (229) reported very high serum CK activity in some subjects, and intracellular accumulation of leucocytes in four of eleven subjects. Although this histological observation was very infrequent (~1% of the counted fibres), it indicates that some degree of segmental necrosis did occur. Of note, tissue sam-

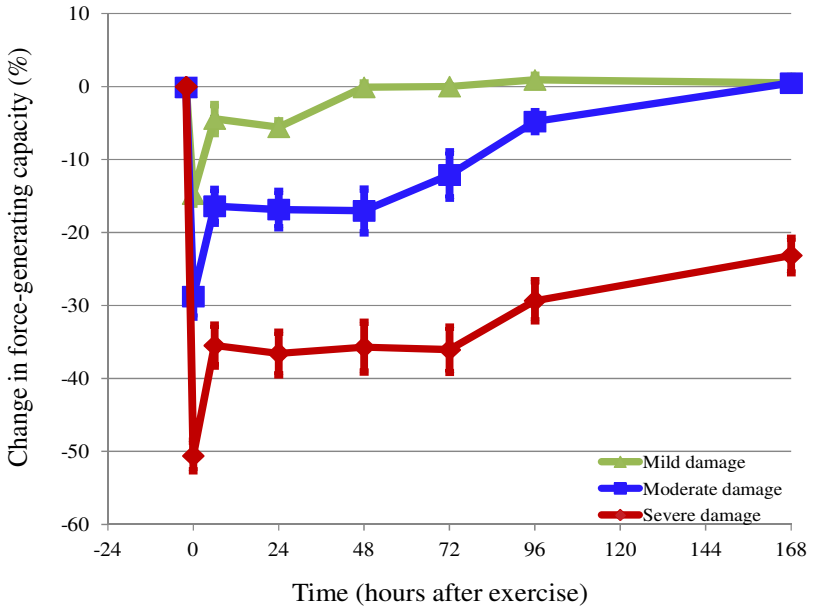

Figure 2. Recovery of the force-generating capacity of subjects that have performed heavy resistance exercise or maximal eccentric exercise (subjects from several studies are combined: (230,248-251), as well as unpublished data). The subjects are organized so that those who recover their force-generating capacity within 48 hours are represented as mild exercise-induced muscle damage (34 subjects). Those who recover between 2 and 7 days are presented as moderate exercise-induced muscle damage (17 subjects). Finally, subjects that do not recover within one week are presented as severe exercise-induced muscle damage (21 subjects). See further comments in the text. All data are gathered at the Norwegian School of Sport Sciences by Professor Truls Raastad. Data are presented as means ± standard error of the mean.

ples that exhibited intracellular leucocyte accumulation were typically collected from 'high responder' subjects who showed a substantial decline in muscle function (50–73% lower immediately after exercise, and 17–42% lower 1 week later), indicating they had suffered severe muscle damage.

Beaton *et al.* (25) did not observe necrotic myofibres, but did observe reduced immunohistochemical staining of both desmin and dystrophin, as well as increased numbers of macrophages between myofibres 4 and 24 hours after exercise. It is likely that necrosis was not evident at these early time points. The authors suggested that these findings were related to increased activity of the Ca^{2+}-dependent calpain system, as mentioned in Figure 1.

Figure 2 (middle curve) demonstrates the typical recovery of the force-generating capacity in subjects that have performed unaccustomed eccentric exercise and some subjects that have performed heavy traditional resistance exercise. We suggest using the term 'moderate exercise-induced muscle damage' if the largest reduction in the force-generating capacity is between 20–50%, and/or recovery is completed between 2 and 7 days after exercise.

2.2 Severe exercised-induced muscle damage

All studies reporting large loss of force-generating capacity (≥ 50% reduction) and long-lasting recovery (> 1 week) also reported accumulation of leucocytes in the exercised muscle tissue, and all but one found signs of segmental myofibre necrosis (Table 1C; see addendum). All studies that assessed serum/plasma CK activity also observed high CK activity (i.e., subjects with values > 10,000 IU/L). Although changes in CK activity have been reported to correlate poorly with other damage markers in some studies (100,182,280), very high CK activity does appear to accompany severe reductions in force-generating capacity (218,229) and evidence of severe muscle damage (137). Changes in CK activity in these cases follow a similar time course to histological observations of severe muscle damage (about 4 days after exercise; (60,137,230)). Thus, CK activity measurements may be used to separate subjects with mild muscle damage (< 1,000 IU/L) and severe muscle damage (> 10,000 IU/L; (66)). Considering the combination of reduced muscle function and increased CK activity with severe soreness and massive muscle swelling after exercise, many of the subjects in these studies would probably be diagnosed with rhabdomyolysis if they had attended an emergency room.

Muscle samples from subjects with very severe exercise-induced muscle damage may display a long-lasting regeneration process between 1 and 3 weeks after exercise (137,154,230,257). Increased numbers of macrophages (or other CD68 positive stromal cells) are present even after 3 weeks, but these cells are primarily located in the extracellular matrix around regenerated myofibres (230). The regeneration process therefore exceeds 3 weeks, and corresponds with incomplete recovery of muscle function at this time point. Sayers and Clarkson (263) have reported recovery times of 33–47 days for subjects with an immediate reduction in muscle function of > 70% after eccentric exercise with the elbow flexors. Foley *et al.* (93) observed that muscle volume of the elbow flexors decreased by about 10% for a period from 2–8 weeks after eccentric exercise. These two studies did not obtain muscle biopsies; but it seems very likely that necrosis of myofibres delayed muscle recovery and caused significant atrophy of the exercised muscles. The cross-sectional area of regenerating fibres is typically much smaller compared with undamaged adjacent myofibres 2–3 weeks after exercise (137,230,281).

Myofibrillar disruption was evident in several of the studies in Tables 1 (A–C) that also reported minor changes in muscle function. It appears that myofibrillar disruption is not directly—or at least not linearly—related to the accumulation of leucocytes. Some studies indicate that myofibrillar disruption can occur in the absence of leucocyte accumulation (90,103,326). Other studies, however, do show a significant correlation between myofibrillar disruption and leucocyte accumulation (92,229). Therefore, we suggest that when intracellular damage exceeds a certain level, leucocytes accumulate in the damaged tissue. The factors that regulate this degree of damage could include degradation and damage to the sarcolemma. As myofibrillar disruption worsens during the first days after exercise (probably due to failure to re-establish intracellular Ca^{2+}-homeostasis), the cytoskeletal framework eventually collapses, thereby leading to sarcolemmal damage (245). Significant leakage of intracellular proteins to the extracellular milieu stimulates inflammation (22,79,95,295). If the remodelling process fails to

restore the subcellular structure within a few days, further damage occurs and eventually segments of myofibers will become necrotic (Figure 1—severe damage).

Figure 2 (lower curve) displays the typical time course of changes in the force-generating capacity for subjects who do not recover within one week after exercise. Such changes are exclusively observed after unaccustomed eccentric exercise and are typically observed together with high circulating CK activity, histological signs of myofibrillar damage and leucocyte accumulation. We suggest using the term 'severe exercise-induced muscle damage' if the greatest reduction in the force-generating capacity is larger than 50%, and/or recovery is not completed within 7 days after exercise.

2.3 Muscle damage is dependent on the choice of exercise protocol

Unfortunately, relatively few studies investigating inflammation in muscle following exercise have examined changes in muscle function. However, it is possible to assess the degree of damage by considering the exercise protocols that were used in these studies (Table 2; see addendum). For the studies summarised in Tables 1A–C and Tables 2A and B, resistance exercise (with equal concentric and eccentric loads) and eccentrically-biased exercise, such as downhill running (~8°) and running down stairs (33,90,102,181,223,326), generally do not cause severe muscle damage or significant leucocyte accumulation in the exercised muscles. By contrast, tissue accumulation of leucocytes occurs consistently after single joint, maximal eccentric exercise across a large range of motion (24,25,60,137,177,283,320). Stepping exercise (i.e., isolated eccentric work for one leg (213,224)), very steep downhill running (e.g., 16° in Fielding *et al.* (92)) and very long distance running (74,121) appear to induce moderate or severe muscle damage and leucocyte accumulation (at least if the exercise is unaccustomed). Studies involving eccentric cycling have produced mixed findings (103,119,150,180,226).

Although single joint, maximal eccentric exercise across a large range of motion usually inflicts considerable muscle damage, responses to this form of exercise do vary. MacIntyre *et al.* (168,169) used an exercise protocol that consisted of 300 eccentric knee-extensions. Several other more recent studies have adopted this protocol (20,25,71,209,229). MacIntyre *et al.* (168) and Murphy *et al.* (209) observed that force-generating capacity decreased only moderately by 20–25% immediately after exercise. In the latter study, recovery was actually complete between 3 and 24 hours after exercise. By contrast, Paulsen *et al.* (229) and Beaton *et al.* (25) found that force-generating capacity decreased by about 50% shortly after exercise, and was about 30% below baseline at 48 hours after exercise. These measurements of muscle function point to differences between studies at the cellular level, despite the similarities in exercise protocol. The reasons for the rather large differences between studies are difficult to determine, but we provide some plausible explanations below.

2.4 Low and high responders make interpretations difficult

The differences between studies (Table 1 and 2; see addendum) are a challenge for understanding the physiology and/or pathology behind exercise-induced muscle damage. The inter-individual variation in each study is also problematic, especially in stud-

ies with low subject numbers. Large inter-individual variation in response to eccentric exercise is commonly reported (54,58,67,113,131,211,218,229,263,265,268). Individuals are sometimes characterised as 'low', 'medium/moderate' or 'high' responders, based on changes in muscle function (229,265), CK activity (58) and signs of necrosis and regeneration (230). The factors contributing to this interesting phenomenon are uncertain. One possibility is that so-called 'low-responders' show less impairment of muscle function because they have recently (i.e., within some months (220)) performed high-force eccentric work using the same muscle(s) (commonly referred to as the 'repeated-bout effect' (194)). Other contributing factors to the large variation in individual responses may include: age (53,138,155,183), gender (63,263,287), certain genetic factors (62,81,82,130,323) and training status (10,87,105,229,308), as well as flexibility (57,195), eccentric peak and end-range torque (265) and angle of peak torque (cf. the joint angle-torque relationship (207)). In combination with wide variation in exercise protocols and challenges with the biopsy analyses (26), this unpredictable inter-individual variability may explain much of the diverse findings and debate on the aetiology of exercise-induced muscle damage. Future studies on exercise-induced muscle damage should consider these factors. The most important action would probably be to carefully evaluate the number of subjects needed. Probably no more than one third of individuals are likely to be 'high' responders who display a clear local inflammatory reaction—even when using maximal voluntary eccentric exercise across a wide range of motion (72,229,230).

We would like to emphasise that using traditional statistics such as means and standard deviations to describe and illustrate the response to eccentric exercise can mask important and interesting observations, because of large inter-individual variations. We recommend to report individual data and classifying subjects as 'low', 'moderate' and 'high' responders, because this will allow for better presentation and interpretation of the data (229,265). Therefore, studies on exercised-induced muscle damage should be designed (with power estimations) for detecting different responders.

2.5 Inconsistencies between animal studies and human studies

The data summarised in Tables 1 and 2 (see addendum) suggest that a certain level of damage is required to initiate a detectable inflammatory reaction with leucocyte accumulation in exercised muscle tissue. This level of damage seems rather high, because it is mainly unaccustomed maximal eccentric exercise that induces extensive muscle damage and inflammation. By contrast, more applied modes of exercise, such as traditional resistance exercise, cause less or no gross muscle damage and inflammation.

Somewhat surprisingly, the relationship between the degree of muscle damage and inflammation (leucocyte accumulation) in animals seems even less clear. In experiments with rodents, leucocyte accumulation is evident after passive stretches and isometric actions that supposedly do not cause damage (147,164,243), and also after low mechanical impact exercises, such as swimming (208) and level running (252). Hence, there appears to be important differences between humans and (caged) mice with respect to exercise-induced muscle damage. Although the sequence of events is similar in humans and animals after muscle damaging exercise, the time course seems much faster in animals. For exam-

ple, in humans, plasma/serum CK activity and histological abnormalities seem to peak after 4–7 days (67,154,210,229,230), whereas in typical animal models, these events occur 1–3 days after exercise (13,37,100,153,192,193,204). These observations suggest that caution is advised when comparing data on inflammatory reactions to exercise-induced muscle damage between humans and animals.

Summary

Exercised-induced muscle damage is characterised by a set of symptoms and signs ('damage markers'). These markers typically include DOMS, increased passive tension, decreased range of motion, increased levels of circulating proteins such as CK and myoglobin, and decreased force-generating capacity (muscular strength), as well as histological evidence of myofibrillar disruption, cellular infiltration, and necrosis. The presence and severity of the different symptoms/signs varies widely between studies. A troubling fact is the relatively weak association between these damage markers (219,229,255,280,316). For example, DOMS does not reflect histological observations of myofibrillar disruptions or accumulation of inflammatory cells. However, as others have suggested (88,316), changes in muscle function appear to be the best marker for the degree of exercise-induced muscle damage. Although the capacity to activate the exercised muscles may change in the recovery phase (27,42,244), reduced force-generating capacity seems to reflect myofibrillar disruption, inflammation and necrosis better than any other markers of muscle damage. Based on our review of the literature, we suggest the following scheme for assessing the extent of muscle damage:

- 'mild exercise-induced muscle damage' corresponds with a decline in force-generating capacity of no more than 20% (during the first 24 hours), and/or full recovery within 48 hours;
- 'moderate exercise-induced muscle damage' corresponds with a 20–50% decline in force-generating capacity, and/or full recovery between 48 hours and 7 days;
- 'severe exercise-induced muscle damage' corresponds with a decline in force-generating capacity of more than 50%, and/or that recovery of force-generating capacity exceeds 1 week.

We further suggest that muscle function should be assessed as concentric actions at a slow velocity, e.g., 30–60°/s, and across a large range of motion. Peak torque, total work and angle of peak torque should be reported. Isometric contractions may also be used, but exercise-induced changes in the angle of peak torque can easily over- or underestimate the changes in peak torque when only one joint angle is tested (49,245). Baseline levels of force-generating capacity should be carefully established (≥ 1 familiarisation session), and muscle function should be monitored repeatedly (daily) until full recovery. Note, we advise caution about merely evaluating the immediate reductions in force-generating capacity (217), because this measurement may reflect muscle fatigue rather than muscle damage (88).

3. CYTOKINE RESPONSES TO EXERCISE-INDUCED MUSCLE DAMAGE

Researchers in exercise immunology have used various exercise protocols to investigate cytokine responses to muscle damage. These protocols include downhill running, eccentric actions of the leg or arm muscles, and traditional resistance exercise. Most studies have reported that these modes of exercise increase plasma

IL-6 concentration for several hours after exercise (see Table 3). Some studies have also reported that the plasma concentrations of interleukin-1 receptor antagonist (IL-1ra), monocyte chemotactic protein (MCP)-1 and granulocyte-colony stimulating factor (G-CSF) increase in the hours after exercise. Changes in the plasma concentrations of IL-8, IL-10, IL-12 and soluble tumor necrosis factor α receptor 1 (sTNF-αR1) are more variable. The plasma concentrations of IL-1β, IL-2, IL-5, IL-13, IL-15, IL-17, TNF-α, leukemia inhibitory factor (LIF) and interferon (IFN)-γ do not change at all following exercise. In skeletal muscle, following resistance exercise, mRNA expression of IL-1β, IL-6, IL-8 and TNF-α increases for up to 24 hours after exercise (see Table 4). IL-6, IL-8 and MCP-1 mRNA expression also increases for several hours after downhill running and eccentric actions of the quadriceps. Changes in IL-10 mRNA are more variable, while IL-2, IL-5 and IL-12 mRNA expression does not change after exercise. No research to date has investigated alterations in the anti-inflammatory cytokines IL-4 and IL-13 in skeletal muscle following acute exercise.

Table 3. Summary of systemic cytokine responses to eccentric and resistance exercise.

Reference	Exercise mode	Immediately post-exercise	1–4 h after exercise	4–24 h after exercise	≥ 24 h after exercise
(145,235,236, 239,277,294)	Downhill running	↑ IL-1ra, IL-6, IL-8, G-CSF, MCP-1	↑ IL-1ra, IL-6, IL-12p40, MCP-1	↑ IL-6, IL-7, IL-8, IL-10, MCP-1, MIP-1β	↑ IL-1ra
			↓ IL-8		↓ IL-8
		↔ IL-10, IL-12p40	↔ IL-10	↔ IL-2, IL-4, IL-5, IL-12p70, IL-13, IL-17, IFN-γ, IL-1β, TNF-α, G-CSF	↔ IL-6, G-CSF
(43,297)	Eccentric cycling	↑ IL-1ra, IL-6, sTNF-αR1	↑ IL-1ra, IL-6, sTNF-αR1		↑ IL-1ra, IL-6, sTNF-αR1
		↔ TNF-α	↔ TNF-α		↔ TNF-α
(77,228,256,322)	Eccentric exercise of the quadriceps	↑ IL-6, MCP-1, G-CSF, M-CSF	↑ IL-6, MCP-1, G-CSF	↑ G-CSF	
			↔ IL-1ra, IL-8, IL-10, TNF-α, G-SCF, M-CSF, sTNF-αR1	↔ IL-6, MCP-1, M-CSF	
(61,124,234,242)	Eccentric exercise of the elbow flexors	↑ IL-6	↑ IL-6, IL-10, G-CSF, sTNF-αR1	↑ G-CSF, IL-10	↑ IL-6, IL-10, G-CSF
		↓ IL-8, IL-10	↓ IL-8	↓ IL-8	↓ IL-8, TNF-α
		↔ TNF-α, IL-1ra, IL-8, IL-10, G-CSF	↔ TNF-α, IL-1ra, IL-8, IL-10	↔ IL-1ra, IL-6, IL-8, IL-10, TNF-α, sTNF-αR1	↔ IL-1ra, IL-6, IL-8, IL-10, TNF-α, sTNF-αR1
(35,36,214,215,276,305)	Resistance exercise	↑ IL-6, IL-8, IL-10	↑ IL-6, IL-8, IL-10		↑ IL-6, IL-10, M-CSF
				↓ IL-1β	↓ IL-1β
		↔ IL-6, IL-10, IL-15, TNF-α, LIF	↔ IL-6, IL-10, TNF-α	↔ IL-15	↔ IL-6, IL-10, IL-15, TNF-α

Table 4. Summary of intramuscular cytokine mRNA responses to eccentric and resistance exercise.

Reference	Exercise mode	Cytokine	1–4 h after exercise	4–24 h after exercise	≥ 24 h after exercise
(36,45,80,139,165,215,246,253,303)	Resistance exercise	IL-1β	↑	↑	↑
		IL-2	↔		
		IL-5	↔		
		IL-6	↑	↑	↔
		IL-8	↑	↑	
		IL-10	↔		↑
		IL-15		↑	↔
		TNF-α	↑, ↔	↑	↔
		LIF		↑	
(45,116)	Downhill running	IL-1β	↔	↔	↔
		IL-6	↑	↑	↑
		IL-8	↑	↔	
		TNF-α	↔	↔	↑
		TGF-β			↑
(59,129,177,203,256)	Eccentric exercise of the quadriceps	IL-1β	↑		↑
		IL-6	↑		↔
		IL-8	↑		
		MCP-1	↑		↑
		TNF-α	↔	↑	↔
(172)	Electrical stimulation of *gastrocnemius*	IL-1β			↔
		TNF-α			↔
		MCP-1			↑

3.1 Cytokines as mediators of exercise-induced muscle damage

As described previously, exercise induces systemic and local cytokine responses in skeletal muscle. Over the past decade or so, considerable attention has focused on the biological role of cytokines derived from muscle (so-called 'myokines') in regulating metabolism in skeletal muscle and adipose tissue (237). Less is known concerning the role of cytokines in regulating inflammatory responses and adaptation to exercise-induced muscle damage. To examine whether cytokines are a cause or a by-product of exercise-induced muscle damage, a small number of studies have investigated the relationship between cytokine responses and markers of muscle damage. Three studies report that plasma cytokine concentrations correlate with plasma CK activity and myoglobin concentration after exercise (43,124,216). Other research has investigated the relationship between cytokines and muscle damage more directly by comparing cytokine responses to concentric versus eccentric actions, submaximal versus maximal eccentric actions and single versus repeated bouts of eccentric exercise.

3.1.1 Eccentric versus concentric muscle actions

Several studies have examined cytokine responses to eccentric exercise, which causes greater muscle damage than concentric exercise. Bruunsgaard *et al.* (43) demonstrated that serum IL-6 concentration and CK activity are higher after eccentric cycling compared with concentric cycling (Table 5; see addendum). Clarkson *et al.* (59,129) have also reported greater strength loss and gene expression of both IL-1R and MCP-1 after eccentric actions compared with concentric actions of the quadriceps. However, others have reported no differences in the plasma cytokine responses to level running versus downhill running, despite higher plasma CK activity and myoblobin concentration after downhill running

(235,236). Variation in exercise protocols, training status of study participants, and sampling times may account for some of these inconsistent findings.

3.1.2 Submaximal versus maximal eccentric exercise

As a variation to research comparing eccentric and concentric exercise, other studies have compared muscle damage and cytokine responses to submaximal and maximal eccentric exercise, which cause differing degrees of muscle damage. Malm *et al.* (181) observed that loss of strength was greater 1 d after downhill running at a gradient of 8° versus 4°, but they detected no changes in serum or muscle cytokines after either exercise trials. In another study, muscle damage (as demonstrated by loss of muscle strength) was greater after maximal versus submaximal eccentric actions of the elbow flexors, but cytokine responses were similar between the two trials (234).

3.1.3 Repeated bouts of eccentric exercise

Several studies have investigated whether adaptations to repeated bouts of eccentric exercise are associated with alterations in cytokine responses. However, this research has also produced equivocal findings (Table 5; see addendum). The results of two studies indicate less muscle damage, smaller changes in circulating IL-6, IL-8 and MCP-1, and greater changes in circulating IL-10 and macrophage inflammatory factor (MIF)-1β in the days following two bouts of eccentric exercise (124,277). In contrast with these observations, other groups have found no difference in plasma IL-6 concentration following repeated bouts of eccentric actions of the knee extensors/flexors, despite evidence of less muscle damage (77,322). Once again, these discrepant findings may be due to differences in exercise protocols, training status of study participants, and sampling times. Two studies have reported that MCP-1 gene expression in *m. vastus lateralis* is higher following a repeated bout of eccentric actions (129), but lower after electrically-stimulated muscle actions (172) performed four weeks after an initial bout of the same exercise. As discussed previously, this discrepancy may reflect differences in the pattern of muscle fibre recruitment between voluntary and electrically-stimulated muscle actions.

3.2 Experimental considerations for examining the role of cytokines in muscle damage

Research to date has examined muscle cells and leucocytes as potential sources of cytokines during exercise; however, the dominant cellular source of circulating cytokines remains uncertain, for two main reasons. First, *in vitro* cell culture methods do not take into account the complex array of interactions between humoral factors produced by multiple organs during exercise. Although certain types of cells may generate large amounts of cytokines *in vitro*, cytokine synthesis i*n vivo* may depend on the presence of other inhibitory (or stimulatory) factors in the local or systemic environment. Second, molecular analysis of isolated RNA or protein extracts is often performed using homogenised muscle, which makes it difficult to identify specific cell sources of cytokines.

To clarify the role of cytokines in muscle damage and adaptation in greater detail, more complex experimental procedures are required. Analysis of the circulating concentrations of cytokines is arguably insufficient to examine the role of

cytokines in muscle damage for two reasons. First, most cytokines are produced locally within skeletal muscle during exercise. Second, with the exception of IL-6, these cytokines are not released into the circulation (285). Regular muscle sampling in the first few hours and days after exercise provides the most direct evidence as to whether cytokines regulate muscle damage and regeneration. However, due to the invasive nature of muscle biopsies, most studies to date have collected no more than four biopsy samples at various time points after exercise. Variation in the time points for muscle sampling, coupled with different exercise protocols, makes it difficult to obtain a clear understanding of the time course of inflammatory responses to exercise-induced muscle damage. As discussed previously, some researchers have also questioned whether the biopsy procedure itself causes more inflammation than exercise (180,181).

Another alternative approach is to modulate or block cytokine activity prior to muscle damage, and then examine subsequent muscle regeneration. These procedures are obviously difficult to implement in human studies. Several studies have examined muscle regeneration following freeze injury in mice lacking cytokine activity. Compared with wild-type mice, recovery of muscular isometric strength is lower between 7–28 days post-injury in $CCR2^{-/-}$ mice (314), at 12 days post-injury in mice depleted of TNF-α or its receptors (313), and at 14 days post-injury in $MCP^{-/-}$ mice (317). These findings indicate that rather than causing muscle damage, cytokines such as TNF-α and MCP-1 and their receptors are required for successful muscle regeneration to occur. Conversely, whether over-expression of these cytokines and their receptors increases muscle injury is currently unknown. MCP-1 deficiency causes more rapid recruitment and activation of neutrophils (through increased expression of neutrophil chemoattractants) and delays recruitment of macrophages in injured muscle tissue. These effects delay the formation of new muscle fibres and increase lipid accumulation and necrosis in regenerating muscle tissue (270,317). The mechanisms through which TNF-α deficiency impairs muscle regeneration are less clear, but may also involve a decline in infiltrating neutrophils and macrophages (240) and/or the expression of myogenic regulatory factors (313). In contrast with TNF-α and MCP-1, IL-6 deficiency does not appear to alter muscle regeneration, even though IL-6 expression in muscle increases following injury (313) and IL-6 regulates the proliferation and differentiation of myoblasts (17,267). Taken together, these findings do not necessarily exclude IL-6 as a regulatory factor in muscle regeneration, but suggest that other factors such TNF-α and MCP-1 and their receptors play more important roles. Few studies have reported any change in TNF-α mRNA expression in muscle after exercise, so its role in human skeletal muscle remains uncertain. IL-6 may be more active in regenerating tendon tissue (8). The research described above implicates TNF-α and MCP-1 and their receptors in muscle regeneration following acute muscle injury. They may play a different—and potentially negative—role in chronic diseases that involve muscle wasting.

Summary

In comparison with cellular inflammatory responses to exercise-induced muscle damage, much less is known about changes in local cytokine responses and their functional significance. Most studies have only collected muscle biopsies at one or two time points after exercise, which precludes any detailed assessment of the

role of cytokines during different phases of muscle inflammation and regeneration. Definitive evidence exists that muscle cells produce a variety of cytokines and chemokines *in vitro*, whereas it is more likely that various cell types synthesise cytokines in muscle following exercise. The results of studies that have used freeze or crush injury in animal muscle to investigate the role of cytokines are not necessarily applicable to humans, because this type of injury is generally more severe and localised than exercise-induced muscle damage. Although cytokines and chemokines regulate a variety of metabolic, endocrine and immunological functions, it remains unclear whether they are a cause or by-product of exercise-induced muscle damage. Until we gather more precise information about their functional role in exercise-induced muscle damage, there seems little rationale for athletes to attempt to attenuate cytokine responses to exercise through nutritional or pharmacological means.

4. SATELLITE CELL RESPONSE TO ECCENTRIC EXERCISE

Muscle cells are multi-nucleated, and can be five orders of magnitude larger than mononucleated cells (44,114). Because adult muscle nuclei (myonuclei) do not divide, new myonuclei must come from other sources when required. Satellite cells serve this role as so-called stem cells of skeletal muscle or myogenic precursor cells during both skeletal muscle adaptation and regeneration (55,118). During muscle hypertrophy, the growing myofibre may require additional myonuclei, because the area of the cytoplasm that each myonucleus can control is traditionally regarded as fairly constant (6,278). However, hypertrophy can proceed without satellite cell activity, probably because existing myonuclei are able to control larger areas of cytoplasm when stimulated (28,190,191).

Satellite cells are situated beneath the basal lamina, but in contrast to regular myonuclei, they are located outside the plasma membrane (sarcolemma). In response to an appropriate stimulus, satellite cells are activated, and then proliferate. Some activated satellite cells help to replenish the satellite cell pool. Other satellite cells migrate to areas where they differentiate and fuse with existing myofibres or produce new fibres. Exercise can stimulate satellite cells to re-enter the cell cycle and proliferate, as shown in several human training studies lasting 2–3 months (see summary in (174)). Interestingly, satellite cells may become activated and proliferate after a single bout of exercise that induces neither hypertrophy nor damage to myofibres (71,72,174,202). In this situation, although the satellite cells are activated, they do not necessarily fuse with myofibres to become myonuclei (no increase in number of myonuclei) or accumulate to generate new myofibres. This 'low threshold' activation of satellite cells may primarily serve to replenish the satellite cell pool, because a reduced satellite cell pool would diminish the regeneration potential of the muscle (261).

4.1 Satellite cell response to a single bout of eccentric exercise

Human studies investigating the skeletal muscle satellite cell responses to a single bout of eccentric exercise are summarised in Table 6. Figure 3 demonstrates the quantitative satellite cell responses in these studies. The proportion of satellite cells increases quickly within the first 24 hours after exercise and may remain elevated for 8 days or more.

Table 6: Human studies investigating the satellite cell (SC) response to a single bout of eccentric exercise in young, healthy subjects.

Reference	Exercise mode (thigh muscle if not indicated)	Subjects' training status	Sampling time points	Measure of SC given:	Context and comments
Crameri *et al.* (72)	Eccentric exercise: 50 one-leg 'drop down' jumps 8x10 reps at 30°/s 8x10 reps at 180°/s	Sedentary	2 d 4 d 8 d	NCAM % MN	First study to show increased SC number with single bout of exercise
Dreyer *et al.* (84)	Max eccentric: 6x16 reps at 60°/s	No resistance training	1 d	NCAM % MN /fibre	Larger SC response in younger than in older subjects
Crameri *et al.* (71)	Max eccentric: 10x10 reps at 30°/s 11x10 reps at 180°/s	No regular training	4 d 8 d	NCAM, Pax7 % MN	Larger response with electrical stimulation. No baseline data given
O'Reilly *et al.* (225)	Max eccentric: 30x10 reps 180°/s	No resistance training	4 h 1 d 3 d 5 d	NCAM % MN, /fibre	Association with HGF response
McKay *et al.* (196)	Max eccentric: 3.14 rad/s 30 x 10 reps	No resistance training	4 h 1 d 3 d 5 d	Pax7 % MN	Association with IL-6 signalling
Mikkelsen *et al.* (202)	Max eccentric: 10x10 reps at 30°/s 10x10 reps at 120°/s	Well trained	5 h 28 h 8 d	NCAM, Pax7 % MN, /fibre	SC response reduced by NSAID infusion
McKay *et al.* (197)	Max eccentric: 3.14 rad/s 30 x 10 reps	No resistance training	1 d	NCAM, Pax7 % MN, /fibre	Compared with FACS, similar results
Paulsen *et al.* (230)	Max eccentric (elbow flexors): 14x5 reps at 30°/s	Physically active	1 h – 7 d (combined)	NCAM % MN, /fibre	Biopsies from m. biceps brachii

NB: To quantify satellite cells, the number of positive cells is expressed relative to fibre number (per fibre) or as a proportion of the total number of myonuclei (MN), the latter calculated as (NCAM+ cells / [myonuclei + NCAM+ cells] × 100) or (Pax7+ cells / [myonuclei + Pax7+ cells] x 100).

In Figure 3, the relative satellite cell responses (normalised to pre-exercise values) observed in the studies from Table 6 are shown together. This figure shows that the observed responses are highly variable, even at similar time points and despite similarities between the exercise protocols. The satellite cell response does not appear to correlate with the stress and damage to the exercised muscle. For example, the study that reported the most damage after exercise (230) also reported the smallest increase in the number of satellite cells. When gross muscle damage does occur—as demonstrated in Paulsen *et al.* (230) and Crameri *et al.* (71)—the satellite cells leave their location and migrate as myoblasts to areas of need for regeneration (136,266). Note, however that in humans, the signs of severe damage and necrosis are first observed after about 4 days (71,137,230), while a strong satellite cell response is evident after only 24 hours (Figure 3). Further research is warranted to clarify the function and time course of changes in satellite cell activity in response to exercise-induced muscle damage.

4.1.1 Satellite cell identification

Satellite cells were first identified in 1961 using electron microscopy (185). Today, specific antibodies are generally used to identify and quantify satellite cells. Most human studies have used an antibody against NCAM (also known as CD56 and Leu19 (266)) to identify satellite cells (see Table 6). Because NCAM is a cell surface glycoprotein expressed on the membrane of satellite cells, this anti-

body marks the outer border of satellite cells. The transcription factor Pax7 is traditionally used to identify satellite cells in cell culture. Pax7 is a transcription factor that is expressed in the nuclei of satellite cells; thus, Pax7 antibodies only label the nucleus of the satellite cell. Lindström and Thornell (163) reported that 94% of all human satellite cells are both NCAM and Pax7 positive.

4.2 The role of the COX-pathway and NSAIDs in satellite cell activation signalling

Many factors are proposed to control satellite cell activity, yet the precise regulatory mechanisms in human skeletal muscle are not fully understood (9,30,327). Animal studies have identified several factors that influence satellite cells at different stages of their activity (for detailed reviews see (30,327)). Among these factors, the cyclooxygenase (COX) pathway is one of the most important (31,32,199). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit this pathway. In relation to muscle soreness and/or muscle damage, athletes often use NSAIDs, which highlights the importance of understanding their effect on muscle regeneration (7,91,328).

COX2 inhibitors and the non-selective NSAID ibuprofen reduce hypertrophy of mice and rat skeletal muscle (222,279). In humans, NSAIDs attenuate the satellite cell response to exercise (174,202), which is discussed in more detail below. How NSAIDs or prostaglandins exert their effect on satellite cells is not known.

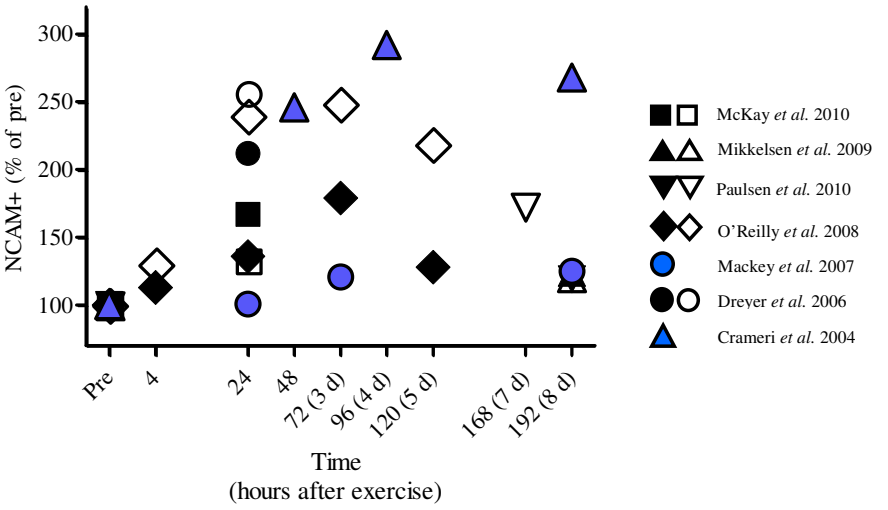

Figure 3: Satellite cell response to a single bout of maximal exercise. The satellite cells were identified by antibodies against NCAM on muscle cross sections from biopsies obtained at different timepoints after exercise. Eccentric exercise was used in all studies except from Mackey *et al.* 2007 (36 km run). Biopsies were obtained from *m. vastus lateralis* except from Paulsen *et al.* 2010 (*m. biceps brachii*). The number of NCAM+ cells is expressed as proportion of total myonuclei (filled symbols) or per muscle fibre (open symbols) and shown as percentage of pre-exercise values.

4.2.1 COX and prostaglandins

The primary function of the COX enzymes is to generate prostaglandins. Prostaglandins (e.g., PGE and PGF) are ubiquitous lipid compounds derived from membrane phospholipids. They regulate smooth muscle tissue, acting as vasodilators to enhance blood flow in a wide range of tissues including the kidneys. They also sensitise nociceptors (pain response), regulate inflammation and fever, and protect the mucus layer in the gastrointestinal tract (104). Among the various COX enzymes, COX1 and COX2 are the most common (83,104). COX1 is constitutively expressed in several cell types, and synthesises prostaglandins that are important for homeostasis. COX2 is induced during cell injury, inflammation and mechanical stretch, and it synthesised prostaglandins that mediate inflammation and pain. Traditional NSAIDs inhibit both COX1 and COX2 isoforms (120). COX2 selective inhibitors have been developed to reduce the adverse effects of traditional NSAIDs on the gastrointestinal tract and the kidneys, while maintaining their analgesic and anti-inflammatory effects (34,309).

4.2.2 COX expression and prostaglandin response to exercise in healthy human muscle

Several studies have investigated the expression of the different COX isoforms in human skeletal muscle, although mainly at the mRNA level. COX1 mRNA is highly expressed in human skeletal muscle (COX1v1 and COX1v2), but it does not respond to exercise or NSAIDs (47,203,318). By contrast, COX2 mRNA is expressed at very low levels at rest, and is either unchanged (47,203) or induced with exercise (45,46,318) and some NSAIDs (47,203). COX3, which constitutes three different splice variants of COX1, is also expressed at very low levels (318). COX1 protein expression remains unchanged with exercise and NSAID treatment (47). COX2 protein is less abundant in skeletal muscle. Immunohistochemical studies have identified both COX1 and COX2 in human skeletal muscle (288,293). However, it is uncertain whether the antibodies used in these studies are specific for the COX enzymes, particularly because COX2 protein expression in human skeletal muscle is very low (47,293). The level of prostaglandins in skeletal muscle increases with resistance exercise, as indicated by the presence of $PGF_{2\alpha}$ in muscle homogenate (300), and PGE_2 efflux from muscle using microdialysis (142). By contrast, PGE_2 does not seem to change following the first hours after eccentric exercise (230).

4.2.3 Effect of NSAIDs on healthy human muscle

4.2.3.1 Muscle function and DOMS following exercise

The effects of NSAIDs on DOMS and recovery of muscle function following exercise have been widely investigated during the last decades (see reviews (4,18,19)). Research on the use of NSAIDs to relieve DOMS has yielded conflicting results. Likewise, the evidence for the effects of NSAIDs on circulating CK activity is inconclusive. Considering the widespread use of NSAIDs among athletes (110,198,311), the effects of NSAIDs on adaptation to exercise training are important to consider. Whether short-term NSAID therapy affects muscle adaptation to training in humans is largely unknown. The discussion below focuses on healthy young humans, but this issue is just as relevant to the elderly and clinical patients who may consume NSAIDs regularly for medicinal purposes.

4.2.3.2 Cellular effects of NSAIDs on human muscle

The cellular effects of exercise combined with NSAIDs on skeletal muscle are not well known. Bourgeois *et al.* (33) demonstrated that consuming the NSAID naproxen for 48 hours following knee extensor exercise did not affect the number of total leucocytes in *m. vastus lateralis* (leucocyte common antigen, CD45+ cells). However, muscular strength returned to baseline more rapidly in response to naproxen compared with the placebo treatment. Treatment with the COX2 specific inhibitor diclofenac for a total of 27 days before and after 20 min step exercise reduced histological abnormalities in muscle (foci of inflammation or necrotic fibres), DOMS and plasma CK activity (224). Animal studies point to a negative effect on skeletal muscle regeneration and adaptation (31,152,204,222,279), whereas evidence from human studies is sparse.

Trappe *et al.* (301) reported that ingestion of ibuprofen for 24 hours following one session of intense eccentric exercise suppressed the increase in mixed muscle protein synthesis rates that normally occurs following exercise. The protein synthesis rate measured 24 hours after exercise, increased by 76% in the placebo group, whereas it remained unchanged in the ibuprofen group. Ibuprofen also suppressed the $PGF_{2\alpha}$ response to exercise (300). Mackey *et al.* (174) showed that ingestion of NSAIDs in humans attenuates the satellite cell response to endurance exercise. In this study, satellite cell number remained unchanged 8 days after a 36-km run in athletes who consumed NSAIDs after exercise. By contrast, satellite cell number was elevated by 27% 8 days after exercise in athletes who consumed placebo. This finding points towards a negative effect of NSAIDs on satellite cell proliferation *in vivo* in humans. This is consistent with reports from animal models that COX enzyme activity is necessary for satellite cell activity and muscle regeneration.

We have also shown that infusion of NSAIDs before, during and for 4.5 hours after eccentric exercise (a total of 7.5 hours) reduces the satellite cell proliferation observed 8 days after exercise (202). A moderate dose of ibuprofen (400 mg/d) during 6 weeks training does not, however, alter muscle hypertrophy, strength or soreness (149). The few human studies using COX2 specific inhibitors have not observed any effect on satellite cells (230) or mixed muscle protein synthesis (48). Burd *et al.* (48) administered celecoxib (600 mg) for 24 hours following a single session of heavy eccentric exercise. Treatment with celecoxib did not alter mixed muscle protein synthesis following exercise (0.06 to 0.11 %/h) compared with the placebo treatment (0.07 to 0.09 %/h). Following eccentric exercise of the elbow flexors, Paulsen *et al*. (230) observed that treatment with celecoxib (400 mg/d) for 7 days did not suppress the increase in numbers of satellite cells or inhibit myofibre regeneration after exercise, when compared to a placebo treated group.

Animal and cell culture studies mainly show that NSAIDs negatively affect satellite cells, hypertrophy and regeneration of skeletal muscle. Results from studies on young, healthy humans indicate either a negative effect (301) or no effect (203) of traditional NSAIDs on muscle protein synthesis (300). Two studies report negative effects of NSAIDs on satellite cells (174,202). Hypertrophy is not reduced following moderate (400 mg/day) doses of ibuprofen (149). Furthermore, COX2 specific inhibitors do not alter muscle protein synthesis (48) or satellite cells (230).

4.3 Inflammation in skeletal muscle: friend or foe?

Current evidence suggests that in healthy young individuals, reducing inflammation by use of NSAIDs may interfere with muscle regeneration or hypertrophy. In contrast, NSAIDs may be beneficial under conditions of excessive or prolonged inflammation. For example, in the elderly, low-grade systemic inflammation may contribute to the loss of muscle mass (termed 'sarcopenia'). In this context, NSAIDs may benefit maintenance of muscle mass (254). Low-grade systemic inflammation that accompanies ageing has attracted a lot of attention during recent years. Levels of inflammatory markers, such as IL-6 and CRP increase slightly with ageing, and these higher levels are correlated with disability and mortality in humans (23,117,231). During 12 weeks of resistance training in elderly people, ibuprofen (3 × 400 mg/day) promoted gains in quadriceps muscle volume and strength (299).

In many chronic disease states, systemic inflammation may contribute to loss of muscle mass (termed 'cachexia'). In animal models of diseases like cancer (125,189) and arthritis (111), NSAIDs help to maintain muscle mass. In these studies, indomethacin (inhibiting COX1 and COX2) and COX2 specific NSAIDs reduce the negative effects of arthritis on body mass, muscle mass and muscle gene expression. Similarly, ibuprofen and indomethacin help to preserve muscle mass in tumor-bearing mice with reduced muscle mass (189).

Summary

Satellite cells are necessary to repair muscle damage. Animal studies show that the COX pathway is essential for this, and that NSAIDs inhibit repair and regeneration. Likewise, in healthy young humans, NSAIDs seem to reduce the capacity to repair muscle damage, since the number of satellite cells is reduced. The biological significance of these findings is that consumption of NSAIDs to alleviate soreness and expedite muscle repair after damage may be contraindicated. Inflammation (or at least a functional COX-pathway) may be necessary for muscle adaptation and regeneration in young, healthy people. Consequently, inhibiting inflammation using NSAIDs may have negative effects on skeletal muscle. Evidence from human studies indicates that consumption of large doses of traditional NSAIDs may negatively affect skeletal muscle in healthy young humans, whereas moderate doses of NSAIDs or COX2 selective inhibitors have apparently no effect. Contrary to this, inhibition of inflammation using NSAIDs may be beneficial in elderly or in individuals with chronic diseases that cause muscle atrophy. The recommendations on use of NSAIDs are therefore likely to differ between subjects, and it seems important to consider health, age and training status of individuals when considering the use of NSAIDs.

CONCLUSIONS

Currently there is no common definition or accepted way to measure the degree of exercise-induced muscle damage. However, both animal and human studies have repeatedly demonstrated that severe exercise-induced muscle damage encompasses myofibrillar disruptions, local inflammation with leucocyte accumulation, segmental myofibre necrosis, and subsequent regeneration involving satellite cell

activation. In humans, the extent of damage and inflammation varies considerably, in contrast to more consistent findings in animal models. There is reasonably solid evidence that unaccustomed, isolated, maximal eccentric actions over large range of motion are necessary to inflict severe exercise-induced damage, including necrosis. Still, some subjects do not display severe damage even after such 'extreme' protocols. Exercise protocols that are closer to exercise used in regular athletic training (e.g., traditional resistance exercise) generally cause minor damage, although some myofibrillar disturbances seem to occur to some degree. Irrespective of the exercise protocol, changes in muscle function (force-generating capacity) seem to be the best marker for the overall level of damage. Thus, if the reduction in muscle force-generating capacity is less than 20% after exercise and recovery is complete in the following 48 hours, the degree of damage is likely to be minor and signs of classical inflammation (i.e., leucocyte accumulation in the muscle tissue) are hardly detectable or absent. Nevertheless, local cytokine production may still occur. By contrast, reductions of muscle force-generating capacity that surpass 50% and prolonged recovery requiring more than one week, indicate severe exercise-induced muscle damage. Consequently, we recommend that investigations of exercise-induced muscle damage should always monitor muscle function until full recovery.

The cytokine response to exercise seems robust, but complex. The circulating concentrations of various cytokines increase during and after exercise, yet the cellular sources of these cytokines are difficult to ascertain. Myofibres have the potential to produce cytokines, but with the exception of IL-6, there is no evidence that other cytokines are released from skeletal muscle into the circulation during exercise. Leucocytes also seem an unlikely major source of circulating cytokines following exercise-induced muscle damage. In the exercised muscles, the increased mRNA expression of cytokines is poorly supported with evidence of increased protein expression. One exception is MCP-1, but this chemokine appears to be produced by stromal cells (macrophages) and satellite cells, rather than by myofibres. Most evidence indicates that the cytokine response to exercise is not necessarily an acute inflammatory response to muscle damage. Instead, cytokines may play a greater role in mediating glucose metabolism and muscle regeneration.

Satellite cells are activated by various types of exercise, both damaging and apparently non-damaging exercise. Thus, the threshold for satellite cell activation is rather low, and the satellite cell response does not seem to be directly related to muscle damage markers. However, only if the initial muscle damage induces a necrotic process in segments of myofibres will the satellite cells leave their position and migrate to the area of damage as (differentiated) myoblasts. The COX pathway by which prostaglandins are synthesised is associated with the satellite cell response, because blocking this pathway in animals reduces the regeneration and growth of skeletal muscle. Although COX2 is essential in animal muscles, selective COX2 inhibitors do not always inhibit muscle regeneration in humans. This could be linked to the fact that both the mRNA and protein levels of COX2 are very low in human skeletal muscle. Non-selective NSAIDs (blocking both COX1 and COX2) can inhibit satellite cells and may affect muscle regeneration and adaptation in young healthy individuals; yet when combined with resistance training, NSAID supplementation facilitate muscle hypertrophy in elderly people.

ADDENDUM

Table 1A: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types of exercise that apparently inflicted *'mild' exercise-induced muscle damage*. In studies with treatment groups, data from the control/placebo group are presented.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group response	*Individual response*					
Bourgeois *et al.* (33)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (single leg), 6 x 10 repetitions; 80-85% of 1 RM.	VL: 1 d	1 d (contra-lateral leg)	No	?	~9% at 1 d	~3% below baseline 2 d after exercise	NA	NA	~750 (1 d)
Féasson *et al.* (90)	30 min downhill running at 12° (~11 $km \cdot h^{-1}$; ~54% of $VO2_{max}$)	VL: 0 h and 1 and 14 d	Pre	No	?	~15% (max power during cycling)	Within 7 d (no tests between day 1 and 7)	Yes	No	~1000 (1 d)
Malm *et al.* (181)	45 min downhill running at either 4° (50% of VO_{2max}) or 8° (max tolerated speed)	VL: 2 d	Control group	No	Higher levels in the epimysium of subjects with DOMS	≤15% (isometric; 1 d; at 8°)	Within 2 d	NA	No	~1000 (1 d; at 8°)
Crameri *et al.* (71)	210 max eccentric actions using the knee-extensors in one randomly chosen leg. The exercise had two phases: 100 actions at $30° \cdot s^{-1}$ and 110 actions at $180° \cdot s^{-1}$. ROM: 10-90°.	VL: 5 h, 1, 4 and 8 d	Pre	Yes (CD68)	-	~16% (isometric)	Within 2 d	Yes	No	NA

Abbreviations: 0° = extended joint; 0 h, immediately after exercise; BB, m biceps brachii; DOMS, delayed onset muscle soreness; EM, electron microscopy; LCA, leucocyte common antigen; MC, mononuclear cells; MPO, myeloperoxidase; NA, not analysed/assessed; VL, m. vastus lateralis; Sol, m. soleus; Gast, m. gastrocnemius; PL, m. peroneus longus; TA, m. tibialis anterior.

Table 1B: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types exercise that apparently inflicted *'moderate' exercise-induced muscle damage*. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group response	*Individual response*					
Fridén *et al.* (103)	Eccentric cycling exercise for 30 min at an intensity corresponding to 80-100% of VO_{2max} during concentric cycling	VL: 0 h and 3 and 6 d	Pre	No	?	~24% (isometric)	Within 6 d	Yes	No	NA
Crenshaw *et al.* (75,76)	Max eccentric actions ($60° \cdot s^{-1}$) with the knee-extensors in one leg until exhaustion; the other (randomly chosen) leg performed concentric work. ROM: 30-120°.	VL: 2 d	2 d ('concentric leg')	No	?	NA	~20% below baseline 2 d after exercise (isometric/ concentric)	Yes	No	NA
Stupka *et al.* (287)	36 eccentric actions of leg press and 100 isolated eccentric actions at 120% of max concentric strength, using the knee-extensors in one leg. ROM: 15-90° (both exercises). The weakest leg evaluated from a pre-test) was exercised.	VL: 1 d	1 d (contra-lateral leg)	Yes (CD68)	-	~31% (concentric)	Within 7 d	Yes	NA	♀: 200-1400, ♂: 300-2100 (range; 4 d)
Beaton *et al.* (24)	240 max eccentric actions ($30° \cdot s^{-1}$) using the knee-extensors in one leg. ROM: 50-110°.	VL: 1 d	1 d (contra-lateral leg)	Yes (CD68; no MPO)	-	~50% (concentric/ isometric)	Within 4 d	Yes	No	120-1300 (range; 3 d)

Table 1B: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types exercise that apparently inflicted *'moderate' exercise-induced muscle damage*. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group	*Individual*					
Beaton *et al.* (25)	300 max eccentric actions ($30° \cdot s^{-1}$) using the knee-extensors in one randomly chosen leg. ROM: 60-120°.	VL: 4 h and 1 d	Pre	Yes (CD68; no MPO and elastase)	-	~54% (isometric)	Within 7 d	Yes	NA (reduced desmin and dystropin staining)	~300 (2 d)
Hubal *et al.* (129)	300 eccentric and concentric actions. The subjects rose from a chair with one randomly chosen leg and lowered the body weight back to a seating position with the other leg (20 cm hip displacement).	VL: 6 h	6 h ('concentric leg')	Yes (MAC387)	-	~32% (isometric)	~23% below baseline 5 d after exercise	NA	NA	NA
Mikkelsen *et al.* (202)	200 max eccentric actions using one leg (knee-extensors); both legs were exercised. The exercise had two phases: 100 actions at $30° \cdot s^{-1}$ and 100 actions at $120° \cdot s^{-1}$. ROM: 10-90°.	VL: 8 d	Pre	No	Yes, 2 of 8 subjects (CD16 and CD68)	~28% (isometric)	Within 8 d	NA	No	~1000 (1 d)
Paulsen *et al.* (229)	300 max eccentric actions using the knee-extensors in one randomly chosen leg. ROM: 30-110°.	VL: 30 min, 4 and 8 h and 1, 4 and 7 d	VL: 30 min, 4 and 8 h and 1, 4 and 7 d	Yes (CD16, CD68)	-	~47% (concentric)	Within 7 d	Yes	Yes (~1%)	~200-25000 (range; 4 d)

Table 1C: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types of exercise that apparently inflicted *'severe' exercise-induced muscle damage*. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group response	*Individual response*					
Hikida *et al.* (121,269)	Marathon (running)	Gast: 0 h and 1, 3, 5, and 7 d	Pre	Yes (EM)	-	~47% (concentric)	> 7 d	Yes	Yes	NA
Jones *et al.* (137,257)	1) Eccentric exercise using the elbow flexors until 50% loss of force 2) Backwards downhill walking (large strain on the calf muscles)	BB and Sol/Gast: 4, 5, 7, 8, 9, 10, 12, 14 and 20 d	No	Yes (MC)	-	>50% (eccentric)	NA	NA	Yes	~750-80000 (range; 4-6 d)
Child *et al.* (60)	70 max eccentric actions ($100°\cdot s^{-1}$) with the knee- extensors in one randomly chosen leg. ROM: almost full extension to almost full flexion (subjects in prone position).	VL: 4 and 7 d	Pre (randomly selected)	Yes (MC)	-	~50% (isometric)	NA	NA	Yes	~16000 (4 d)
Hellsten *et al.* (119)	Max eccentric cycling exercise; 5 x 5 min	VL: 45 min, 1, 2 and 4 d	Pre, 45 min and 2 d	Yes (CD11b)	-	~54% (isometric)	~45% under pre-value 4 d after exercise	NA	NA	~13300 (4 d)
Paulsen *et al.* (154,230)	70 max eccentric actions using the elbow flexors in one randomly chosen arm. ROM: 145-5°.	BB: 1 h and 2, 4 and 7 d	BB: 1 h and 2, 4 and 7 d	Yes (CD68, EM)	-	~50% (isometric)	> 7 d, but within 3 weeks	Yes	Yes	~300-25000 (range; 4 d)

Table 2A: Studies in which *no inflammatory cells (leucocytes) were found* after voluntary exercise in humans. Muscle function was not assessed. In studies with treatment groups, data from the control/placebo group is presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group response	*Individual response*			
Fridén *et al.* (102)	Running down stairs: 10 x 10th floor to ground floor.	Sol: 2 and 7 d	Pre	No	?	Yes	No	NA
Kuipers *et al.* (150)	30, 45 or 60 min of eccentric cycling exercise at ~80% VO_{2max}	VL: 0 h and 1 d	Pre	No	Yes, in two subjects exercising for 45 and 60 min	No	NA	< 200 (unchanged)
Warhol *et al.* (310)	Marathon (running)	Gast: Some hours, 1, 2, 3, 5, 7, and 10 d and 2, 3, 4, 6, 8, 10 and 12 weeks	Control group	No	?	Yes	No	NA
Nurenberg *et al.* (223)	30 min downhill running at 8°; 8 $km \cdot h^{-1}$	Sol, Gast, TA, PL: 2 d	No	No	?	Yes	No	200-1200 (range; 12-36 h)
Malm *et al.* (180)	Eccentric cycling exercise for 30 min at an intensity corresponding to 80-100% of VO_{2max} during concentric cycling (250-300 W).	VL: 0 and 6 h and 1, 2, 4 and 7 d	Pre and control group	No	?	NA	No	~120 (1 d)
Yu *et al.* (324-326)	1) Running down stairs: 15 x 10th floor to ground floor; 2) Eccentric cycling exercise; 3) Downhill running (8°)	Sol: 1 h, 2-3 and 7-8 d	Control group	No	?	Yes	No	< 1000
Crameri *et al.* (72,73)	50 one-leg drop down jumps (45 cm) followed by 80 eccentric actions at 30°·s^{-1} and 80 eccentric actions at 180°·s^{-1}.	0, 2, 4 and 8 d	Contra-lateral leg	No	Yes (CD68; 1 of 8 subjects)	NA	No (1 of 8 subjects)	NA

Dennis *et al.* (81)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (both legs): 4 x 8 reps (to failure in the 4th set) at 80% of 1 RM.	VL: 1 and 3 d	Pre	No	Yes (individual changes were found)	NA	NA	NA
Przybyla *et al.* (246)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (both legs): 4 x 8 reps (to failure in the 4th set) at 80% of 1 RM.	VL: 3 d	Pre	No	?	NA	NA	NA

Table 2B: Studies in which *inflammatory cells (leucocytes) were found* after voluntary exercise in humans. Muscle function was not assessed. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Myofibrillar disruptions	Signs of necrosis	Peak CK ($IU \cdot L^{-1}$)
				Group response	*Individual response*			
O'Reilly *et al.* (226)	Eccentric cycling for 45 min (3 x 15 min) at 70-90% of VO_{2max} (~180-220 W)	VL: 0 h and 10 d	Pre	Yes (EM)	-	Yes	Yes	NA
Costill *et al.* (70)	Eccentric actions using the knee-extensors in one leg; 10 x 10 repetitions with 120% of 1 RM. 30 min after the eccentric exercise the subjects performed a cycling exercise to deplete their glycogen stores (both legs).	VL: 1.5 h and 1 and 3 d	1.5 h and 1 and 3 d (contra-lateral leg)	Yes (MC)	-	NA	NA	~7000 (3 d)
Stauber *et al.* (283)	70 max eccentric action (120°·-1) using the elbow flexors in the non-dominant arm. ROM: 120°.	BB: 2 d	2 d (contra-lateral arm)	Yes (MC)	-	NA	Yes (~2%)	NA
Widrick *et al.* (320)	Eccentric actions using the knee-extensors in one leg; sets of 6 repetitions until failure with 120% of 1 RM. Subjects had the evening before performed a cycling exercise to deplete their glycogen stores (both legs).	VL: 0 and 6 h and 1 and 3 d	0, 6 h and 1 and 3 d (contra-lateral leg)	Yes (MC)	-	NA	Yes	< 300 (unchanged)
Crenshaw *et al.* (74)	Ultramarathon footrace (160 km)	Gast: 1 d	No	Yes (EM)	-	Yes	Yes (~1%)	NA

Fielding *et al.* (92)	45 min downhill running at 16°; 75% max heart rate.	VL: 45 min and 5 d	Pre	Yes (neutrophils)	-	Yes	NA	~300 (1 d)
O'Grady *et al.* (224)	20 min eccentric stepping exercise; step height vas 110% of the lower leg length.	VL: 12 d (right leg)	Pre (left leg)	Yes (MC)	-	NA	Yes	~1800 (3 d)
Stupka *et al.* (286)	Eccentric actions using the knee-extensors in one leg; leg press 3x12 and knee-extension 9x12 at 120% of 1 RM.	VL: 2 d	VL: 2 d	Yes (LCA; increase only in males)	-	Yes	No	♀: ~600 ♂: ~1000 (6 d)
Peterson *et al.* (241); Trappe *et al.* (302)	10-14 sets of 10 actions with the knee-extensors in the non-dominant leg. Load: 120% of max concentric strength. ROM: 0-90°.	VL: 1 d	Pre (contra-lateral leg)	Yes (CD68, not CD15)	-	NA	NA	~2250 (5 d)
Mahoney *et al.* (177)	300 max eccentric actions ($120°\cdot s^{-1}$) using the knee-extensors in the non-dominant leg. ROM: 30-90°.	VL: 3 h and 2 d	Pre	Yes (CD68, MPO)	-	Yes	NA	~300 (2 d)
MacNiel *et al.* (175)	150 max eccentric actions ($120°\cdot s^{-1}$) using the knee-extensors in the right leg. ROM: 30-90°.	VL: 3 h and 2 d	Pre (left leg)	Yes (CD68, MPO)	-	NA	NA	~500 (2 d)

Table 5. Summary of changes in cytokines and markers of muscle damage after exercise.

Reference	Exercise mode	Cytokine	Time of peak Δ	Function	Time of peak Δ	Protein	Time of peak Δ
Buford *et al.* (45)	Downhill running	IL-6 mRNA IL-8 mRNA	6% ↑, 3 h 8% ↑, 3 h			Serum CK	6× ↑, 1 d
Kingsley *et al.* (145)	Downhill running	Serum IL-6	1.2× ↑, 0 h			Plasma CK Plasma Mb	2× ↑, 1 d 80% ↑, 0 h
Malm *et al.* (181)	Downhill running						
	4° gradient	IL-6, LIF protein in muscle	No change	Strength Soreness [b]	No change 2, 0 h	Serum CK	70% ↑, 1 d
	8° gradient	IL-6, LIF protein in muscle	No change	Strength Soreness [b]	15%↓, 1 d 3, 0 h	Serum CK	4.6× ↑, 4 d
Malm *et al.* (180)	Eccentric cycling	IL-1β protein in muscle	60% ↑, 0 h			Plasma CK	1.2× ↑, 1 d
Chen *et al.* (59)	Eccentric contractions of the quadriceps	MCP-1 mRNA	25×↑, 4–8 h	Strength	9% ↓, 3 d		
Ross *et al.* (256)	Eccentric contractions of the quadriceps	MCP-1 mRNA IL-6 mRNA IL-8 mRNA	1.3× ↑, 3 h 70% ↑, 3 h 1.2× ↑, 3 h			Serum Mb	2.3× ↑, 3 h
Paulsen *et al.* (228)	Eccentric contractions of the quadriceps	Plasma M-CSF Plasma IL-6 Plasma G-CSF Plasma MCP-1	50% ↑, 0 h 4× ↑, 6 h 70% ↑, 6 h 1.6× ↑, 6 h	Strength	34%↓ 6 h 24%↓ 4 d	Serum CK	50× ↑, 4 d
Childs *et al.* (61)	Eccentric contractions of the elbow flexors	Plasma IL-6	4× ↑, 2 d			Serum CK Serum Mb Serum LDH	20× ↑, 3 d 4× ↑, 2 d 5× ↑, 3 d
Phillips *et al.* (242)	Eccentric contractions of the elbow flexors	Serum IL-6	1.5× ↑, 1 h	Soreness [a]	35 mm	Serum CK	2.4× ↑, 3 d
Peake *et al.* (234)	Eccentric contractions of the elbow flexors						
	Submaximal	Serum IL-6 Serum sTNFαR1	80% ↑, 3 h 40% ↑, 3 h	Strength Soreness [a]	10% ↓, 1 d 15 mm, 2 d	Plasma CK Plasma Mb	2.4× ↑, 4 d 100% ↑, 3 h
	Maximal	Serum IL-6 Serum sTNFαR1	40% ↑, 3 h 50% ↑, 3 h	Strength Soreness [a]	40% ↓, 1 d 21 mm, 2 d	Plasma CK Plasma Mb	1.3× ↑, 4 d 60% ↑, 3 h
Bruunsgaard *et al.* (43)	Concentric cycling Eccentric cycling	Serum IL-6 Serum IL-6	50% ↑, 2 h 4.5× ↑, 2 h			Serum CK Serum CK	No change 55× ↑, 4 d
Peake *et al.*	Level running	Plasma IL-6	4× ↑, 0 h			Plasma CK	20% ↑, 0 h

(233,235,236)		Plasma IL-1ra	1.3× ↑, 1 h			Plasma Mb	1.1× ↑, 1 h
		Plasma IL-10	No change				
	Downhill running	Plasma IL-6	4.6× ↑, 0 h			Plasma CK	60% ↑, 0 h
		Plasma IL-1ra	2.4× ↑, 1 h			Plasma Mb	18× ↑, 1 h
		Plasma IL-10	No change				
Croisier *et al.* (77)	Eccentric contractions of the quadriceps						
	Bout 1	Plasma IL-6	7× ↑, 0.5 h			Serum Mb	290× ↑, 0.5 h
	Bout 2	Plasma IL-6	7× ↑, 0.5 h			Serum Mb	No change
Hirose *et al.* (124)	Eccentric contractions of the elbow flexors						
	Bout 1	Plasma G-CSF	60% ↑, 3 d	Strength	43% ↓, 2 d	Plasma CK	60× ↑, 4 d
				Soreness [a]	37 mm, 2 d	Plasma Mb	20× ↑, 4 d
	Bout 2	Plasma G-CSF	25% ↑, 3 d	Strength	19% ↓, 2 d	Plasma CK	No change
				Soreness [a]	20 mm, 2 d	Plasma Mb	No change
Hubal *et al.* (129)	Contractions of the quadriceps						
	Bout 1						
	Concentric	MCP-1 mRNA	9.2× higher (vs. concentric)				
	Eccentric			Strength	35% ↓, 3 d		
		IL-1R mRNA	5× higher (vs. concentric)				
	Bout 2						
	Concentric	MCP-1 mRNA	0.7× higher (vs. Bout 1)	Strength	22% ↓, 3 d		
		IL-1R	1.1× higher (vs. Bout 1)				
	Eccentric	MCP-1 mRNA	2.6× higher (vs. Bout 1)				
		IL-1R	1.9× higher (vs. Bout 1)				
Smith *et al.* (277)	Downhill running						
	Bout 1	Serum IL-6	6 pg/mL, 12 h			Serum CK	~900 U/L, 1 d
		Serum IL-10	0.8 pg/mL, 12 h				
		Serum MCP-1	103 pg/mL, 12 h			Serum CK	~340 U/L, 1 d
		Serum MIP-1β	42 pg/mL, 12 h				
	Bout 2	Serum IL-6	12 pg/mL, 12 h				
		Serum IL-10	1.6 pg/mL, 12 h				
		Serum MCP-1	93 pg/mL, 12 h				
		Serum MIP-1β	50 pg/mL, 12 h				

N.B. Only muscle function > 1 day post-exercise is reported because changes in strength < 1 day post-exercise most likely represent acute changes in muscle fatigue rather than damage *per se*. [a] Soreness was assessed using a visual analogue scale measured in millimeters (mm). [b] Soreness was assessed on a scale from 0–10.

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