Preventative Strategies for Exercise-Induced Muscle Damage

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ABSTRACT: Eccentric exercise is part of regular rehabilitation and sports training. Unaccustomed eccentric exercise causes muscle damage that presents as delayed soreness, strength and range of motion loss, swelling, and increased passive stiffness. These symptoms reduce the ability to exercise and might be harmful if further exercise is continued. Several interventions such as warm-up, stretching, massage, acupuncture, anti-inflammatory drugs, and estrogen supplements have been researched in order to find interventions that successfully alleviate the severity of muscle damage. The results are controversial due mainly to the variety of exercise-induced muscle damage protocols, the types of intervention protocols, and the doses of application. From a practical point of view prevention strategies are preferred by practitioners because they reduce time lost from training, reduce the cost of treatment, and reduce the risk of further injury. For that reason, this article emphasizes the mechanism of initial events and the factors involving the severity of muscle damage. Research on the prevention of eccentric exercise-induced muscle damage is reviewed and discussed. Appropriate preventative strategies for muscle damage from eccentric exercise are suggested.

KEY WORDS: eccentric exercise-induced muscle damage, delayed-onset muscle soreness, repeated bout effect, prevention of DOMS

I. INTRODUCTION

Muscle damage resulting from exercise commonly occurs when the exercise involves an unaccustomed "lengthening" eccentric contraction. This type of exercise is difficult to avoid for several reasons. First, rehabilitation practitioners often prescribe eccentric exercise in the initial stage of treatment in rehabilitation programs because it elicits less fatigue and pain than concentric contraction at the same workload.[1,2] Second, coaches usually combine concentric and eccentric contraction in training programs because this provides greater strength gains than concentric exercise alone, particularly when the eccentric exercise is emphasized.[3] In addition, eccentric contraction is also a part of regular exercise when smooth movement is required. Unaccustomed eccentric exercise appears to result in muscle damage and, consequently, causes soreness sensation and strength and functional movement loss. The symptoms of muscle damage usually subside within a week and might not affect daily living in healthy individuals. However, when the symptoms of muscle damage occur in patients undergoing rehabilitation, or in athletes, this might disrupt the rehabilitation or training program, as well as sport performance. Several researchers have investigated interventions thought to reduce and/or prevent the severity of muscle damage. From a clinical point of view,

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preventative intervention is preferred because it reduces the cost of treatment, time lost from training or rehabilitation, and the likelihood of sustaining further injury, and it also maintains the ability to exercise. Therefore, this article reviews the initial mechanisms of muscle damage and analyses-related factors, and proposes possible strategies for prevention. Previous research related to preventative strategies is discussed.

In this article, we use the term "eccentric exercise" to indicate the type of exercise that induces muscle damage. The term "severity of muscle damage" indicates the magnitude of the symptoms after eccentric exercise, including soreness sensation, strength and range of motion loss, swelling, and tenderness. In terms of muscle damage from eccentric exercise, soreness sensation was the major concern in earlier research[4–6] because the symptoms after eccentric exercise are usually termed "delayed-onset muscle soreness". However, other symptoms, such as strength and range of motion loss, need to be considered because they might have more impact on athletes or patients than soreness sensation, and they may take longer to recover from. This article considers the other symptoms of muscle damage such as strength and range of motion loss, swelling, tenderness, and stiffness, along with soreness sensation after exercise-induced muscle damage.

Several reviews of eccentric exercise-induced muscle damage have been published in the past 15 years, so the reader is encouraged to refer to these for information on the mechanisms and etiology of exercise-induced muscle fiber injury, muscle function and adaptation after exercise-induced muscle damage, treatment strategies, and performance factors.[7–14] No reviews, however, have dealt with preventative strategies for muscle damage from eccentric exercise.

Literature for this review was located using three electronic databases (PubMed, SPORT Discus, and ProQuest 5000 International), in addition to manual journal searches. The electronic databases provided access to biomedical and sports-related journals, serial publications, books, theses, conference papers, and related research published since 1985. The key phrases used to search the databases included delayed-onset muscle soreness (DOMS), mechanisms of DOMS, sports performance and DOMS, DOMS treatments, DOMS and prevention, DOMS and exercise, and repeated bout effect. Articles not published in English and/or in scientific journals, articles that focused on the psychological effects of DOMS, or articles on the effects of treatments after performing exercise-induced muscle damage were not included in this review. The criteria for inclusion were

- Articles must have used normal, healthy participants. Age, gender, and fitness differences were not excluding factors
- Articles must have discussed the possible mechanisms of initial events of DOMS, factors inducing DOMS, and the impacts on exercise performance
- Articles must have investigated preventative interventions in reducing the severity of DOMS.

A. Signs and Symptoms of Muscle Damage

Even though eccentric contractions result in less fatigue and pain than concentric contractions immediately after exercise,[1,2] eccentric contractions have been shown to produce specific and long-lasting effects on soreness sensation and muscle functions.[15–17] It is well known that eccentric exercise causes muscle damage.[8,10,12,18] The specific and long-lasting effects resulting from lengthening contractions (a contraction that happens when an external torque is greater than an internal torque within muscle) include delayed-onset soreness sensation, prolonged strength loss, reduced range of motion, and increased passive stiffness. Several reviews have described the nature and time course of these changes.[11,19] In brief, soreness sensation appears 24 hours after exercise, peaks at 2 to 3 days after exercise, and slowly recovers but does not fully subside until 8 to 10 days after exercise.[11] Strength dramatically reduces immediately after exercise, and slowly recovers up to 80% of the pre-exercise strength 10 days after exercise.[11] Range of motion reduces as the damaged muscles shorten spontaneously (decreased relaxed muscle length) and are unable to fully contract voluntarily (decreased active range of motion). The spontaneous muscle shortening occurs immediately after exercise and peaks on day 3 after exercise. Muscle loses the ability to contract maximally immediately after exercise and gradually recovers. The loss of range of motion measurements appear to return to baseline within 10 days after exercise.[11] The increase in passive stiffness peaks on day 2 after exercise and returns to pre-exercise values on day 10.[20] To illustrate the changes, the time course of soreness sensation, range of motion, muscle strength, and passive stiffness described in the earlier literatures is presented in Figure 1.

Careful interpretation is needed, because the data presented in Figure 1 are based on muscle damage to the elbow flexors (from two sets of 35 maximal eccentric contractions, with 5 minutes rest between each set).[11,20] The time course and the severity of muscle damage in other muscles with different exercise-induced muscle damage protocols would be slightly different.[18,21,22] It is clear, however, that the adverse effects of eccentric exercise last longer than 10 days and have an impact on functional movements.

B. Impact of Muscle Damage on Sports Performance

Strength, range of motion, and a feeling of competence are important factors in performing sports and exercise. Unaccustomed eccentric exercise causes adverse effects on these factors.[18,21,23–26] Moreover, soreness sensation is aggravated during movements, especially when the eccentric contraction is involved. Eccentric exercise, therefore, may cause significant reduction in performance during training and competition and/or increase the risk of further injury. The impact of muscle damage from eccentric exercise on athletic performance in terms of biomechanics has been reviewed recently by Cheung et al.[9] The perception of functional impairment, joint kinematics, strength and power, altered recruitment patterns, and injury risk factors in healthy adults were emphasized.

Despite obvious changes in soreness sensation and biomechanical properties of muscle, reviews on the impact of muscle damage resulting from eccentric exercise on physiological and metabolism parameters are controversial. Dolezal et al[27] reported an increase in resting metabolic rate at 24 hours

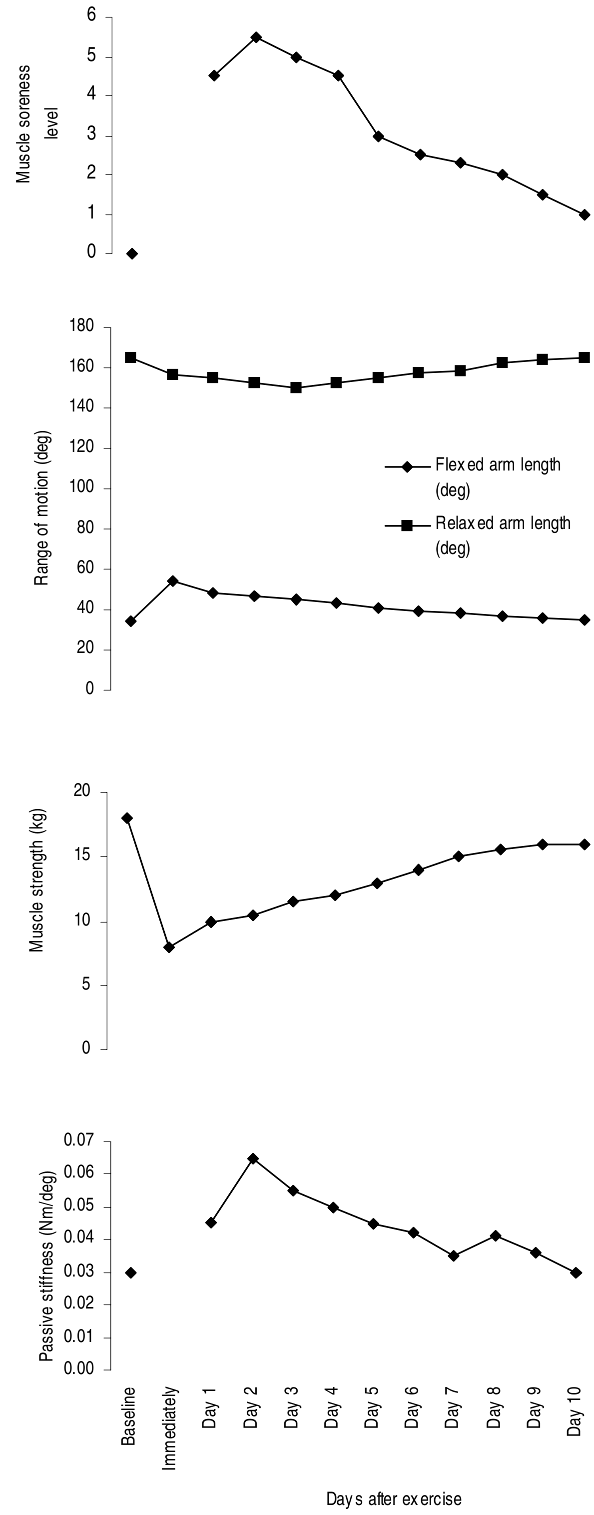

FIGURE 1. The parameters indicating the severity of muscle soreness (soreness sensation, range of motion, muscle strength, and passive stiffness) in elbow flexor muscles. Data were compared among pre-exercise, immediately postexercise, and follow-up for 10 days. Data were modified from Clarkson et al[11] and Howell et al.[20]

(18%) and 48 hours (11%) after eccentric exercise. The muscle damage was induced by using a leg press exercise for eight sets at the subjects' 6-RM. The symptoms of muscle damage were similar in trained and untrained groups, except that the untrained group showed a higher magnitude in creatine kinase and soreness sensation. Walsh et al,[28] however, reported that after eccentric exercise (eccentric cycling for 30 minutes), muscle oxygen utilization and local oxygen transport (measured by near infrared spectroscopy), and muscle fiber respiration at rest (measured from biopsy) of the vastus lateralis muscle were unchanged.

In addition, previous research has reported an increase in physiological and metabolic responses from healthy, untrained men indicating exercise stress parameters (ie, minute volume, breathing frequency, respiratory exchange ratio, heart rate, rating of perceived exertion, venous blood lactate concentration, and plasma cortisol concentration) during cycling 2 days after eccentric exercise.[29,30] Even though the changes in these physiological parameters indicated an earlier onset of fatigue and more stressful exercise than in normal circumstances, the cycling efficiency, as measured by oxygen uptake[29,30] and time to exhaustion,[29] were not different. The results of the Gleeson et al[29,30] study might be due to the muscle damage in these two studies being induced by bench stepping (involving mainly the quadriceps).[31] The subsequent exercise test for the efficiency was cycling (involving all muscles of the legs—ie, quadriceps, gluteus maximus, gastrocnemious, hamstrings, and dorsiflexors).[31] In fact, if athletes perform eccentric exercise with several muscles during training, it is possible that the exercise efficiency on the subsequent day might be impaired. This notion is supported by Calbet et al[32] who reported an increase in running cost (8%) 48 hours after a duathlon (five kilometres running, 16 kilometres cycling, and two kilometres running). However, 7 days after the duathlon, the running economy had nearly returned to the baseline.

C. The Importance of Preventative Strategies to Reduce Muscle Damage

Coaches, athletes, and medical practitioners are well aware of the symptoms of muscle damage after eccentric exercise because it clearly affects subsequent exercise or performance (ie, strength, power, range of motion, and probably exercise economy). If muscle damage does occur, the following problems are of importance:

- How long is an appropriate recovery period?
- What is (are) the main factor(s) to determine when an athlete can start their training again?
- How much does the treatment cost?
- Is an athlete likely to get a related injury, such as a muscle tear, if the rest time is not enough?
- Are there any long-term effects from muscle damage if such damage happens repeatedly?
- How much do the symptoms of muscle damage affect performance?
- Is a reduction of soreness sensation a good indicator to restart training? Muscle weakness requires longer recovery and might have more impact on performance than soreness sensation.

To avoid the above problems, preventative strategies are required. A comprehensive understanding of the initial mechanisms of exercise-induced muscle damage is necessary to investigate appropriate intervention. This article, therefore, reviews briefly the initial event of exercise-induced muscle damage and the factors that contribute to the magnitude of muscle damage.

II. THE MECHANISMS AND FACTORS CONTRIBUTING TO MUSCLE DAMAGE

A. Initial Events of Muscle Damage From Lengthening Exercise

Many theories have been proposed to explain muscle damage, including inflammation,[33] muscle spasm,[34] metabolic,[35] and mechanical theories.[36] Recently, several authors have reviewed the initial events of exercise-induced muscle damage[12,37–39] and stated that the mechanical theory appears to be the most likely explanation.

Friden and Lieber[13] hypothesized that high tension from eccentric contraction might stretch or break the intermediate filaments (desmin and dystropin). The intermediate filaments are responsible for maintaining the sarcomeres in register/

alignment[38] and may fail when the non-homogeneous lengthening of sarcomeres occurs.[8] The disruption of these intermediate filaments would expose degraded Z-proteins and globular proteins, and then activated lysosomal enzymes, causing further degradation and eventually Z-disk dissipation.[40] Changes in ultrastructure such as focal damage have been observed using electron microscopy.[41] Clarkson and Hubal[12(ps53)] have described the changes in ultrastructural integrity as "Z-line streaming, Z-lines out of register, loss in thick myofilaments, loss in mitochondria in areas that showed abnormalities, and disturbed arrangement of filaments at the A-band." In addition, Abraham[42] reported an increase in the ratio of hydroxyproline/creatinine (OHP/Cr) in 24-hour urine collection which indicated the disruption of the connective tissue elements in the muscles and/or their attachments. In an animal study, however, Hasselman et al[43] showed the disruption of both muscle fibers and connective tissue only at a high intensity of exercise (actively stretched at 10 cm/s to 90% of the force required to fail). A lower intensity of exercise (70% and 80% of the same relative force) showed only evidence of muscle fiber disruption.

Proske and Morgan[39] described the series of events leading to muscle damage from eccentric exercise, suggesting that lengthening contraction with mechanical overload from eccentric exercise caused overstretched sarcomeres. The sarcomeres are disrupted and cause the optimum length to shift to a longer length. When the disrupted sarcomeres are spread widely, membrane damage occurs. The damage of muscle fibers in series (sarcomeres) and membrane (connective tissues) causes local contracture and increases in stiffness. The damage of muscle fibers and connective tissues lead to several symptoms of muscle damage, such as strength and range of motion loss, tenderness, edema, and soreness.[39]

B. Factors Related to the Magnitude of Muscle Damage

Several researchers have investigated the factors involved in the magnitude of muscle damage.[41,42,44,45] Information that has been reported is useful for coaches and health care practitioners in designing eccentric exercise programs at early stages of training or rehabilitation sessions in order to minimize muscle damage.

A number of factors have been linked to the severity of muscle damage. An individual's characteristics, such as muscle strength or physical fitness level, are not related to the response to eccentric exercise-induced muscle damage.[12] Genetics, as investigated in research on identical twins, is also not a predisposing factor in the severity of muscle damage.[46] Muscle properties, such as passive stiffness, have been reported as having a positive relationship with the magnitude of muscle damage.[18] In a study by Leivseth et al,[47] the stiffer muscles demonstrated less sarcomere numbers and muscle length and increased mechanical energy loss during passive movement than did normal muscles. Therefore, stiff muscles might reduce the ability to withstand elongation and may be more likely to develop injuries (which generally occur during muscle elongation).[47] Nevertheless, there is no published study on the relationship between other properties of muscle on the severity of muscle damage, such as active stiffness, tendon stiffness, creep, and stress relaxation.

Several mechanical factors involving exercise prescription have been investigated, such as velocity,[48] intensity,[49–51] duration of exercise,[49] resting period,[52] starting position,[53,54] and muscle attachment.[45] Kulig et al[48] compared fast and slow eccentric movement of elbow flexors at the same work load (60% 1-RM) and duration (144 s). Fifty-eight percent of participants reported soreness sensation in the arm that performed fast movement, whereas none of the participants reported soreness sensation in the arm that performed a slow protocol. The results are questionable due to the exercise muscles (elbow flexors) and the exercise protocol (Fast: 2-s eccentric movement plus 2-s concentric movement per 1 repetition, 36 repetitions; Slow: 10-s eccentric movement plus 2-s concentric movement per 1 repetition, 12 repetitions). Elbow flexors consist of both one-joint (brachialis) and two-joint (biceps brachii) muscles, which are recruited differently at different velocities. The brachialis was more active during the slow movement protocol, whereas the biceps brachii were more active during the fast protocol.[48] Kulig et al[48] did not compare the same muscle when comparing the two velocities. The number of repetitions might be a more important factor in the severity of muscle damage than the velocity of exercise. As a result, the recommendation to decrease the velocity of eccentric exercise to reduce the severity of muscle soreness is questionable.

At the same exercise velocity, biarticular and monoarticular muscles respond to the same eccentric exercise protocol differently. Prior et al[45] investigated muscle injuries in four muscles (vastus lateralis, vastus medialis, vastus intermediate, and rectus femoris) by using magnetic resonance. The four muscles were activated equally during eccentric exercise (similar muscle transverse relaxation of water protons [T_2]) but the rectus femoris showed a greater level of muscle injury on the following days (greater delayed T_2) than the other muscles. The results showed that the biarticular muscle was likely to experience more damage than the monoarticular muscle when exercised at the same velocity. Prior et al[45] proposed that the greater injury to rectus femoris might have been due to the position of exercise. In this study, participants sat on the seat and exercised their quadriceps eccentrically. The seated position might restrict the ability of rectus femoris to transfer force between the hip and knee joints. Interestingly, the results also indicated that the level of muscle activation during exercise was not a unique determinant of muscle injury.

The starting position of exercise and/or the initial muscle length is another factor thought to be involved in the magnitude of muscle damage. Newham et al[53] and Nosaka and Sakamoto[54] compared two different starting positions with the same range of motion (short and long muscle range, 50–130° and 100–180°, respectively). The participants reported more soreness and demonstrated more strength and range of motion loss, and more swelling in the long muscle length condition than in the short muscle length condition. The images from the magnetic resonance and ultrasound also showed greater damage in the long muscle length condition.[54] At a longer muscle length, both bicep brachii and brachialis contributed to torque, whereas at the shorter length, brachialis had the greater contribution.[55] As a result, the more muscle involved in the exercise protocol, the more muscle damage that occurred.

Other factors that may affect the magnitude of muscle damage include intensity of exercise, number of repetitions, and the length of rest period between each set. Previous research on the severity of muscle damage has agreed that intensity of exercise is the most important factor.[49–51] In a study by Nosaka and Newton,[51] the high intensity of exercise (100% of maximum isometric contraction) produced more severity of muscle damage than the low intensity of exercise (50% of maximum isometric contraction), as measured by isometric muscle strength, range of motion, upper arm circumference, and plasma creatine kinase activity. High intensity of exercise also required longer periods of time to recover. In a study by Nosaka et al,[50] at the high intensity of exercise (maximal eccentric contraction) an increase in the number of repetitions (12, 24, and 60 repetitions) did not affect soreness sensation but did produce more severity of muscle damage, as indicated by an increase in strength and range of motion loss as well as the level of plasma creatine kinase.[50] In a study by Tiidus and Ianuzzo,[49] the high intensity and short duration exercise (80% 10-RM, 170 repetitions) resulted in greater serum enzyme activities (LDH, CK, and GOT) and soreness sensation than for the low-intensity and long-duration exercise (30% 10-RM, 545 repetitions). Nevertheless, the rest period between each eccentric exercise (0 s, 15 s, 5 min, and 10 min) did not affect the severity of muscle damage.[52] Therefore, increases in intensity and duration of exercise seem to produce more severity of muscle damage, with intensity having a more pronounced effect.

III. PREVENTATIVE STRATEGIES TO REDUCE MUSCLE DAMAGE

Several interventions have been proposed as preventative or as treatment strategies for eccentric exercise-induced muscle damage, including acupuncture,[56] ultrasound,[57,58] cryotherapy,[59] compression,[24,60] anti-inflammatory drugs,[61] hyperbaric oxygen therapy,[62] warm-up,[5,63] stretching,[4,5,64] and massage.[65–68] These strategies, as treatments, have been reviewed extensively,[9,69–73] but none of these strategies have been evaluated in terms of effectiveness as preventative interventions.

A. Repeated Bout of Exercise (Eccentric Exercise)

The "repeated bout effect" is believed to be the most effective strategy in preventing muscle damage from eccentric exercise. The repeated bout effect refers to "the protective adaptation to a single bout of eccentric exercise."[71] The protective adaptation is known to markedly reduce the severity of muscle damage, as indicated by soreness sensation and strength and range of motion loss, when these symptoms of the second bout of eccentric exercise are compared with the initial bout.[74–77]

The repeated bout effect has been shown to produce a rapid adaptation of muscle properties which happens while the damage process is still occurring (within 1 day after the initial bout of eccentric exercise).[75,78–80] However, how long the protective effect lasts is uncertain. Byrnes et al[81] and Nosaka et al[82] reported that the repeated bout effect did not last longer than 6 weeks. Lund et al[83] stated from their pilot work that the repeated bout effect did not appear after 8 to 10 weeks (data was not shown in the article). Nosaka et al[84] reported that the protective effect of elbow flexors (24 maximal eccentric actions) lasted for at least 6 months (see Table 1). Interestingly, the effectiveness of the repeated bout seems to be greater the sooner it was repeated after the initial bout of eccentric exercise. Repeated exercise when muscle has not fully recovered (Day 1, 2, 3, 4, and 6 after the initial bout) has been shown to neither exaggerate the damage nor delay the recovery rate.[75,76,78–80,85] These results can be interpreted as indicating that there are some rapid adaptations that fully protect muscle damage from the second bout of eccentric exercise. The results from previous research have shown that the sooner the repeated bout is performed the less severe the symptoms of muscle damage will be (see Table 1).

Several studies have shown that the initial bout of eccentric exercise produced a protective adaptation on muscle regardless of the severity of muscle damage of the initial bout.[76,79,86,87] A small number of contractions (as little as two maximal eccentric contractions) showed a slightly protective adaptation on the following 24 maximal eccentric contractions (performed 2 weeks later).[86] It should be noted that the two eccentric contractions protocol of the initial bout did not produce muscle damage. However, the effectiveness of the repeated bout effect of the two contractions was less than the 6 and 24 maximal eccentric contractions.[86] Interestingly, there were no significant differences of the repeated bout effects between the 6 and the 24 maximal eccentric contractions. Therefore, the low intensity of the initial bout as indicated by low repetitions (such as 16%,[79] 20%,[87] 25%,[86] 42%,[76] and 60%[87] of the subsequent bout) is effective in producing the repeated bout effect, as indicated by less swelling and range of motion and strength loss. Nevertheless, in the studies of Nosaka et al[86] and Paddon-Jones and Quigley[88] the low volume of eccentric exercise did not reduce the soreness sensation when compared with the first bout (soreness level of the first bout was 1.1 cm.).[86,88] This might be due to the low volume of the first bout of exercise being too small to cause soreness sensation.

There is evidence that high-intensity exercise (maximal contraction) is a more pronounced factor on the repeated bout effect than the number of repetitions. For example, Nosaka et al[89] reported that low-intensity eccentric training (50% of 1-RM) did not produce the repeated bout effect on the subsequent maximal bout. Therefore, high intensity of the initial bout eccentric exercise is necessary for providing repeated bout effects.

The repeated bout effect was specific to the exercised muscle[90] but not specific to the pattern of exercise.[91,92] In a study by Eston et al,[90] the knee extensors exercise (100 maximal eccentric contractions) showed protective effects on downhill running 2 weeks later. In two studies, downhill running showed a repeated bout effect on subsequent downhill running, regardless of the stride length.[91,92] However, in the Connolly et al study,[93] there was no evidence of crossover effects to the contralateral limb. Therefore, to maximize the effectiveness of the protective adaptation on the repeated bout without severe damage of muscle from the initial bout, the initial eccentric exercise program should be high intensity (maximal eccentric contraction), have low repetitions (at least 15% of the repetitions of the subsequent exercise), and be specific to the muscle group. The subsequent bout should be repeated within 2 to 6 weeks (after muscle weakness recovers).

TABLE 1
Time Course of Muscle Adaptation of the Repeated Bout Effect

	Exercise intensity		Repeated bout effect (% reduction from the initial bout)				
Timing	Muscles	Intensity of eccentric exercise	Soreness	Maximum isometric contraction	Range of motion	Circumference	Image
2 weeks[94]	Hamstrings	6 sets of 10 repetitions at 60% MVC	83% s	0% s	—	—	—
3 weeks[81]	Quadriceps	30 min downhill running (slope –10°)	58% s	—	—	—	—
6 weeks[81]	Quadriceps	30 min downhill running (slope –10°)	64% s	—	—	—	—
8 weeks[100]	Elbow flexors	5 sets of 10 repetitions at 110% of 10 RM	30% s	—	—	—	20% s
9 weeks[81]	Quadriceps	30 min downhill running (slope –10°)	20%	—	—	—	—
6 months[84]	Elbow flexors	24 maximal eccentric contractions	30% s	24% s	S	43% s	35% s
9 months[84]	Elbow flexors	24 maximal eccentric contractions	13%	20% s	S	20%	NS
12 months[84]	Elbow flexors	24 maximal eccentric contractions	20%	11%	NS	0%	NS

Note: The exercise bouts occurred at least 2 weeks apart. MVC = maximum voluntary contraction, RM = repetitive maximum, NS = nonsignificant, S = significant.

Recently, several articles have reviewed the possible adaptative mechanisms of the repeated bout effect.[12,71,93] The proposed mechanisms have included neural, mechanical, and cellular adaptations.[71] Neural adaptation could occur by an increase in motor unit activation, a change in motor unit recruitment, and an increased synchrony of motor firing.[94] Mechanical adaptation could occur by increasing muscle stiffness from the adaptation in the cytoskeletal proteins responsible for maintaining the alignment and structure of sarcomeres.[71] Cellular adaptation could occur by a longitudinal addition of sarcomeres, an adaptation in inflammatory response, and an adaptation to maintain E–C coupling.[71]

The neural adaptation theory is the most widely investigated of the three theories. Some research has supported this theory by reporting a reduction of fast-twitch motor unit activation during the subsequent exercise bout (3 days later).[74] Much research, however, has not supported this theory. For example, a study of McHugh et al[94] reported that EMG per unit torque and median frequency showed no difference between the initial and the repeated bout of eccentric exercises (2 weeks apart). Therefore, there was no evidence of an increase in motor unit recruitment or activation. Nosaka et al[89] reported the repeated bout effect in electrically stimulated eccentric contraction. The changes in symptoms of muscle damage (maximal voluntary isometric force, range of motion, plasma creatine kinase and aspirate aminotransferase activities, upper arm circumference, muscle thickness from ultrasonography, and muscle soreness) from the subsequent electrically stimulated eccentric contractions were smaller than for the symptoms from the initial electrically stimulated eccentric contraction (2 weeks later). The electrical stimulation was applied at the same muscle sites by the same conditions for the initial and the subsequent bouts. The peak force of the stimulation was the same between the two bouts. As a result, the pattern of motor unit activation was exactly the same between bouts, but the symptoms of muscle damage were different. The lack of crossover effect did not support the central neural adaptation theory.[93]

There is little published on the mechanical theory of the repeated bout effects and there is suggestion that mechanical adaptation of muscle might present by the change of muscle stiffness.[71] The change in active stiffness contributes to changes of the stretch reflex, level of muscle activation, and passive joint properties,[95] whereas the change in passive stiffness contributes to changes of cross-links between the actin and myosin filaments, and series and elastic components of muscle.[96] There have been no reports on the effects of eccentric exercise on active stiffness, either through a single bout or as a training effect. Howell et al[20] reported a change in passive stiffness after eccentric exercise. Passive stiffness increased nearly twofold immediately after elbow eccentric exercise and remained elevated for 3 days (see Fig. 1). A rapid decrease in passive stiffness then occurred on days 4 to 6, but the degree of stiffness did not return to the baseline completely until ten days after eccentric exercise. At this period of time, whereas passive stiffness was still higher than the normal level, the repeated bout effect had already occurred. Therefore, one might conclude that a high level of passive stiffness produces a protective effect on the subsequent bout of eccentric exercise. This notion is contrary to that of McHugh et al,[18] who reported that the stiff participants experienced more severity of muscle damage than the compliant participants. McHugh[71(p92)] also stated in his recent review that "less stiffness was thought to enable greater sarcomere shortening thereby avoiding sarcomere strain." In fact, the increase of passive stiffness after eccentric exercise was thought to be one of the protective effects preventing muscle from further damage.[10] Therefore, more evidence on the mechanical theory is needed to investigate the effects of eccentric training on muscle stiffness, the time course of elevated passive stiffness after eccentric exercise, and the repeated bout effect on passive stiffness.

The cellular theory is another theory used to explain the repeated bout effect.[71] Cellular adaptation after initial eccentric exercise is thought to be due to the longitudinal addition of sarcomeres, as shown by the shift of optimal length to the right (longer muscle length).[97] The change in sarcomere numbers connected in the series of muscle fibres was considered the most plastic property of muscle and these could be changed within days after changes in activity patterns.[98] However, there are a number of questions that need to be addressed:

- What is the least amount of time to produce an increase in the number of sarcomeres?
- Can the longitudinal addition of sarcomeres happen within a day after eccentric exercise (because the repeated bout effect occurred 24 hours after the initial bout)?[78]
- Can the longitudinal addition of sarcomeres occur due to low-intensity stimulation (because the repeated bout effect occurred when the initial bout was low intensity—8% of the subsequent bout)?[86]
- How long does the shift to the longer length of muscle last (because the repeated bout effect lasts for 6 months)?[84]

Armstrong et al[99] proposed another theory that is used to explain the repeated bout effect. This theory is based on the idea that the high mechanical lengthening overload on muscle fibres from the initial bout results in damage only to the weak muscle fibres. Therefore, the strong fibres remain. The existence of strong fibres might be responsible for reducing severity of muscle damage for the subsequent bout of eccentric exercise. As a result, repeated bout effects (the less severity of muscle damage) can be seen as early as the first day after the initial bout.[78] In the study by Foley et al,[100] the prolonged loss in muscle volume (7–10%, 2–8 weeks after the initial bout) was thought to be a result of the extinction of weak fibers within the muscle compartment. The shift to the longer muscle length, as reported by Brockett et al,[97] might be the length of the remaining strong fibres, not from the longitudinal addition of sarcomere. The protective mechanism that lasted for 6 months, as reported by Nosaka et al,[84] might be a consequence of the time that muscle has built up weak fibres and returned to a normal combination between the weak and strong fibers. Therefore, the protective effect from the strong fibers alone disappeared. The decrease in motor unit activation (30%) and median frequency (20%) reported by Chen[74] might also be the result of the vanishing of the weak fibres. The pronounced effect of the high intensity (maximal contractions), not the number of repetitions, might be another reason to support this theory because the high intensity of exercise is more likely to damage the weak fibres than the number of repetitions.

B. Training

In an early report, Hill[101] stated that training was the only way to reduce the severity of muscle damage. Contrary to Hill's[101] suggestion, a single bout of eccentric exercise provides a protective effect on a subsequent bout (known as the repeated bout effect). Regular eccentric exercise training, however, seems not to provide a protective benefit on the severity of muscle damage on subsequent eccentric exercise.

The published literature on the effect of training on severity of muscle damage does not support the common belief that training can prevent muscle damage from eccentric exercise. Concentric training was reported to increase the susceptibility of muscle damage.[16,102,103] The protective effect of eccentric training, however, is still uncertain. Balnave and Thompson[104] reported that downhill running once a week for 8 weeks reduced muscle damage. When eccentric training was compared with concentric training, Nosaka and Newton[105] reported no difference in the symptoms of muscle damage between groups. If concentric training did increase the severity of muscle damage as reported by other studies, [16,102,103] eccentric training in the Nosaka and Newton[105] study might provide the same results, because the data were not compared with a nontraining group.

An increase in muscle stiffness may be the mechanism responsible for increasing the severity of muscle damage after training. A positive relationship has been reported between active stiffness and isometric and concentric ($r = 0.6$–0.8), but not eccentric, contraction.[106] Similarly, a positive relationship has been reported between passive stiffness and isometric ($r = 0.6$)[107] and concentric contraction ($r = 0.5$).[108] There have been no reports on the relationship between passive stiffness and eccentric contraction. Even though a stiff musculotendinous unit is more efficient in force transmission generated by the muscle to the bone, the stiff muscles might be more susceptible to the strain imposed by the lengthening contraction than the complaint muscle. Stiff muscles have been reported to reduce the ability of muscle fibres to absorb energy.[47] The reduced ability of muscle fibres to absorb energy during lengthening contractions might cause more strain on the myofibril than on the compliant muscles. Moreover, a positive relationship has been reported between passive stiffness and the severity of muscle damage. McHugh et al[18] attributed passive stiffness to tendon-aponeurosis extensibility and stated that the aponeurosis rupture was responsible for greater damage in the stiff muscles than the compliant muscles. Therefore, any intervention that increases muscle stiffness might also increase the susceptibility of the muscle to damage. Klinge et al[109] reported that isometric training of the hamstring muscles increased both strength (43%) and passive stiffness (data were not shown). In the same way, eccentric training was reported to increase active stiffness.[110] Although these studies did not directly investigate the effect of training on the severity of muscle damage, their results could indicate that stiffness might be a mechanism responsible for the more vulnerable musculotendinous unit after training.

C. Pre-exercise Activities (Warm-Up, Stretching, and Massage)

Warm-up, stretching, and massage are commonly recommended before exercise or competition to improve performance and reduce the risk of injury. Unfortunately, the scientific data to support this belief are not widely evident. Warm-up has been shown to elevate muscle temperature,[111] increase muscle blood flow,[65] and increase neurological excitability.[112] Stretching has been shown to increase flexibility.[113] Research has shown that massage can increase muscle blood flow,[114] muscle temperature,[115] and muscle flexibility, and reduce tissue adhesion.[116,117] The benefits of such pre-exercise activities might help to reduce injury risk factors. Unfortunately, there are limited published studies in this area.

A search of the literature identified only one published research paper on the effects of warm-up on the severity of muscle damage.[63] Nosaka and Clarkson[63] found that both high (100 repetitions of maximal concentric contraction) and low (100 repetitions of minimal concentric contraction) intensities of warm-up could reduce the magnitude of muscle damage, as indicated by reduced soreness sensation, strength and range of motion loss, swelling, and creatine kinase activity. The authors proposed that warm-up might help to increase muscle temperature and circulation, and consequently, increase muscle and connective tissue elasticity. The proposed mechanism that warm-up could increase musculotendinous unit elasticity (reduce muscle stiffness) was not investigated in this study. If passive stiffness is the mechanism responsible for the severity of muscle damage, the results from this study indicate that the warm-up program might need to address specific muscles because a general warm-up (running) was not shown to affect passive stiffness.[111] If active stiffness is the mechanism responsible for the severity of muscle damage, a general warm-up might help to reduce the severity of muscle damage. As McNair and Stanley[95] reported, a reduction of active stiffness was achieved after jogging. To date, there are no published papers on the effects of general warm-up on the magnitude of muscle damage and the effects of a specific warm-up on passive stiffness.

Several authors have investigated the effects of pre-exercise stretching on the magnitude of muscle damage,[4,5,64,118] and a recent review has summarized the finding.[70] Unfortunately, most researchers found that static stretching did not help to reduce the magnitude of muscle damage. The ineffectiveness of stretching on the severity of muscle damage might be that stretching has no effects on passive[109,119,120] and active[121] stiffness. No research on the effects of other types of stretching (eg, ballistic, proprioceptive neuromuscular facilitation, and dynamic stretching) on muscle stiffness and the severity of muscle damage was found.

No published studies have reported the effects of pre-exercise massage on the severity of muscle damage. Massage can increase muscle temperature[115] and blood flow[114], which might help to increase muscle compliance and reduce muscle stiffness. Nevertheless, the only research on the effects of massage on passive stiffness did not support this claim.[122] Massage involves several techniques such as effleurage, petrissage, and friction. Each technique is used for different purposes and provides different effects. Stanley et al[122] used an effleurage technique for 10 minutes on the hamstring muscles and did not find any change in passive stiffness. Generally, massage therapists use effleurage techniques to stimulate the parasympathetic nervous system and evoke the relaxation response. Therefore, the massage technique used in Stanley et al's study might not be appropriate. Petrissage and friction are techniques aimed to mobilize deep muscle tissue or the skin and subcutaneous tissue and increase local circulation. From a clinical point of view, these techniques might be more appropriate in reducing muscle stiffness, and, consequently, reducing the severity of muscle damage.

There was only one published research article on the combined effects of warm-up, stretching, and massage on the severity of muscle damage. Rodenburg et al[67] reported that the combination of warm-up and stretching before eccentric exercise, and massage after exercise, was effective in reducing the severity of muscle damage. Unfortunately, the researchers did not compare the effect of each treatment alone. The results of Rodenburg et al[67] suggest the benefit of warm-up only being given because stretching showed no effect on the severity of muscle damage at all. Massage was also unlikely to provide any benefit because massage was applied immediately after eccentric exercise. Immediately after eccentric exercise, muscle does not need more blood flow to eliminate waste products, such as lactic acid, because eccentric exercise does not produce a lot of waste products.[8] Therefore, it was not clear which intervention provided the benefit for preventing muscle damage in this study.

D. Pharmaceutical Substances

The role of several chemical substances (eg, anti-inflammatory drugs, antioxidants, herbs, nutritional supplements) has been researched in relation to preventing or reducing the severity of muscle damage. The use of anti-inflammatory drugs such as aspirin, diclofenac, ibuprofen, naproxen, and ketoprofen was emphasized in the recent literature reviewed by Connolly et al.[69] Comparisons the effectiveness of different anti-inflammatory drugs on the severity of muscle damage was difficult due to the variety of anti-inflammatory drugs used, doses, time to provide drugs, intensity and protocol of eccentric exercise-induced muscle damage, and the initial characteristic of participants. Research on the prophylactic effects of the anti-inflammatory drugs (ibuprofen,[61] naproxen,[23] and flurbiprofen[123]), however, indicated that only ibuprofen (three doses, 400 mg each, in 24 hours, for a total of 1200 mg) showed preventative effects on eccentric exercise-induced muscle damage by reducing soreness sensation and strength and range of motion loss.[61] Interestingly, the prophylactic application of ibuprofen in this study showed a faster effect in relieving the symptoms of muscle damage than did the therapeutic treatment.

There have been attempts to investigate the effects of several substances used to prevent the symptoms of muscle damage, such as fish oil,[124] ethanol,[125] herbs,[126] and pollen extract.[127] Fish oil was thought to decrease the inflammatory process.[124] Ethanol was thought to reduce a leakage of muscle proteins after eccentric exercise.[125] An herb (*Arnica*) was commonly used for any type of soft tissue trauma.[126] Unfortunately, none of these substances was effective in reducing the severity of muscle damage. Pollen extract is a free radical–scavenging preparation that was thought to attenuate or eliminate tissue destruction.[127] The pollen extract was reported to reduce soreness sensation and lower the concentration of lipid peroxides (reduce the level of free radicals). However, the authors did not investigate the other symptoms of muscle damage, such as strength and range of motion loss.

E. Estrogen

Several researchers have reported less severity of muscle soreness in females than in males.[41,44,128] Reduced severity of muscle soreness in women was also found in research that compared women who were contraceptive users with eumenorrheic non-oral contraceptive users.[129,130] This observation has been explained as being related to the protective effects of estrogen on cardiac and smooth muscles in premenopausal females when they are compared with age-matched males.[73] The protective effects of estrogen on muscle damage might be that estrogen defends against oxygen free radicals and reduces the susceptibility of muscle membrane to being damaged.[131] Estrogen also acts as a membrane stabilizer and gene regulator.[73] The potential protective role of estrogen on muscle damage from eccentric exercise has been reviewed recently.[73,131]

It is important to note that the majority of previous research on the effects of estrogen on muscle damage reported only a reduction in soreness perception. When other indirect parameters, such as strength, range of motion, circumference, and serum creatine kinase activity in the oral contraceptive and non–oral contraceptive user groups were compared, no differences **in** these parameters were found.[130] Therefore, the effectiveness of estrogen on preventing muscle damage is questionable. Moreover, research in this area compared males and females who might actually have more differences in muscle properties than the effects of estrogen alone. The comparison between the oral contraceptive and non–oral contraceptive users might show the effects of estrogen at different levels. If estrogen provides a long-term protective effect, women who are non–oral contraceptive users still have high estrogen levels during the regular menstrual cycle that might provide the chronic protective effects on muscle damage. Tiidus[131] recommended that research should compare the menopausal women who received estrogen supplement with those who received non-estrogen supplement. However, menopausal women are considered a special population who might have a change in muscle properties due to aging. Further research that compares male participants who are provided with estrogen with male participants who do not receive estrogen is needed. Such research might lead to more understanding of the effects of estrogen on muscle damage and lead to more practical use of estrogen.

IV. PRACTICAL RECOMMENDATIONS FOR THE HEALTH CARE PRACTITIONER

To prevent and/or reduce the severity of muscle damage from unaccustomed eccentric exercise, on the basis of the previous research, medical practitioners and coaches should recommend to their patients in rehabilitation programs or to athletes that they perform a specific warm-up regularly on muscles that are predominantly used in the rehabilitation program or sport. A "light" specific eccentric exercise following a specific warm-up (at least 15% of the number of repetitions of the real eccentric exercise at maximum contraction, low velocity, and short muscle length position) that produces a "low" severity of muscle damage is recommended. This light eccentric exercise will produce a repeated bout effect that also helps to reduce the severity of muscle damage. The next eccentric exercise session should be 2 weeks later in order to recover from strength loss. If eccentric training needs to be performed before 2 weeks, the intensity of eccentric exercise should be low (50–60% of maximal isometric voluntary contraction).

It is important to note that when chemical substances are administered to prevent or relieve the symptoms of muscle damage, one should be aware of the side effects that might be harmful. Long-term use of anti-inflammatory drugs has resulted in an increased risk of stomach ulcers, kidney failure, and liver damage.[61] Estrogen might be beneficial for female patients or athletes, but the effects on male patients or athletes are uncertain. For these reasons, the use of chemical substances might not be an appropriate strategy in reducing the severity of muscle damage.

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REFERENCES

1. Horstmann T, Mayer F, Maschmann J, Niess A, Roecker K, et al. Metabolic reaction after concentric and eccentric endurance-exercise of the knee and ankle. Med Sci Sports Exerc 2001;33(5):791–795.
2. Hollander D, Durand R, Trynicki J, Larock D, Castracane V, et al. RPE, pain, and physiological adjustment to concentric and eccentric contractions. Med Sci Sports Exerc 2003;35(6):1017–1025.
3. Hilliard-Robertson P, Schneider S, Bishop S, Guilliams M. Strength gains following different combined concentric and eccentric exercise regimens. Aviat Space Environ Med 2003;74(4):342–347.
4. Johansson P, Lindstrom L, Sundelin G, Lindstrom B. The effects of preexercise stretching on muscular soreness, tenderness and force loss following heavy eccentric exercise. Scand J Med Sci Sports 1999;9:219–225.
5. High D, Howley E, Franks B. The effects of static stretching and warm-up on prevention of delayed-

onset muscle soreness. Res Q Exerc Sport 1989;60(4): 357–361.
6. Hilbert J, Sforzo G, Swensen T. The effects of massage on delayed onset muscle soreness. Br J Sports Med 2003;37:72–75.
7. Armstrong R. Initial events in exercise-induced muscular injury. Med Sci Sports Exerc 1990;22(4):429–435.
8. Armstrong R, Warren G, Warren J. Mechanisms of exercise-induced muscle fibre injury. Sports Med 1991;12(3):184–207.
9. Cheung K, Hume P, Maxwell L. Delayed onset muscle soreness: treatment strategies and performance factors. Sports Med 2003;33(2):145–164.
10. Clarkson P, Sayers S. Etiology of exercise-induced muscle damage. Can J Appl Physiol 1999;24(3):234–248.
11. Clarkson P, Nosaka K, Braun B. Muscle function after exercise-induced muscle damage and rapid adaptation. Med Sci Sports Exerc 1992;24(5):512–520.
12. Clarkson P, Hubal M. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil 2002;81(11 Suppl):S52–S69.
13. Friden J, Lieber R. Structural and mechanical basis of exercise-induced muscle injury. Med Sci Sports Exerc 1992;24(5):521–530.
14. Tiidus P. Massage and ultrasound as therapeutic modalities in exercise-induced muscle damage. Can J Appl Physiol 1999;24(3):267–278.
15. Newham D, Mills K, Quigley B, Edwards R. Pain and fatigue after concentric and eccentric exercise contractions. Clin Sci 1983;64:55–62.
16. Whitehead N, Allen T, Morgan D, Proske U. Damage to human muscle from eccentric exercise after training with concentric exercise. J Physiol 1998;512(2): 615–620.
17. Sayers S, Knight C, Clarkson P. Neuromuscular variables affecting the magnitude of force loss after eccentric exercise. J Sports Sci 2003;21:403–410.
18. McHugh MP, Connolly DA, Eston RG, Kremenic I, Nicholas SJ, et al. The role of passive muscle stiffness in symptoms of exercise-induced muscle damage. Am J Sports Med 1999;27(5):594–599.
19. Ebbeling C, Clarkson P. Exercise-induced muscle damage and adaptation. Sports Med 1989;7:207–234.
20. Howell J, Chleboun G, Conaaster R. Muscle stiffness, strength loss, swelling and soreness following exercise-induced injury in humans. J Physiol 1993; 464:183–196.
21. Brown S, Child R, Donnelly A, Saxton J, Day S. Changes in human skeletal muscle contractile function following stimulated eccentric exercise. Eur J Appl Physiol 1996;72(5–6):515–521.
22. Vickers A. Time course of muscle soreness following different types of exercise. BMC Musculoskelet Disord 2001;2(1):5.
23. Bourgeois J, MacDougall D, MacDonald J, Tarnopolsky M. Naproxen does not alter indices of muscle damage in resistance-trained men. Med Sci Sports Exerc 1999;31(1):4–9.
24. Chleboun G, Howell J, Baker H, Ballard T, Graham J, et al. Intermittent pneumatic compression effect on eccentric exercise-induced swelling, stiffness, and strength loss. Arch Phys Med Rehabil 1995;76:744–749.
25. Cleak M, Eston R. Muscle soreness, swelling, stiffness and strength loss after intense eccentric exercise. Br J Sports Med 1992;26(4):267–272.
26. Crenshaw A, Karlsson S, Styf J, Backlund T, Friden J. Knee extension torque and intramuscular pressure of the vastus lateralis muscle during eccentric and concentric activities. Eur J Appl Physiol Occup Physiol 1995;70(1):13–19.
27. Dolezal B, Potteiger J, Jacobsen D, Benedict S. Muscle damage and resting metabolic rate after acute resistance exercise with an eccentric overload. Med Sci Sports Exerc 2000;32(7):1202–1207.
28. Walsh B, Tonkonogi M, Malm C, Ekblom B, Sahlin K. Effect of eccentric exercise on muscle oxidative metabolism in humans. Med Sci Sports Exerc 2001; 33(3):436–441.
29. Gleeson M, Blannin A, Walsh N, Field C, Pritchard J. Effect of exercise-induced muscle damage on the blood lactate response to incremental exercise in humans. Eur J Appl Physiol Occup Physiol 1998;77(3): 292–295.
30. Gleeson M, Blannin A, Zhu B, Brooks S, Cave R. Cardiorespiratory, hormonal and haematological responses to submaximal cycling performed 2 days after eccentric or concentric exercise bouts. J Sports Sci 1995;13(6):471–479.
31. Hamill J, Knutzen K. Biomechanical basis of human movement. Baltimore: Williams & Wilkins; 1995.
32. Calbet J, Chavarren J, Dorado C. Running economy and delayed onset muscle soreness. J Sports Med Phys Fitness 2001;41(1):18–26.
33. Smith L. Acute inflammation: the underlying mechanism in delayed onset muscle soreness? Med Sci Sports Exerc 1991;23:542–551.
34. deVries H, Housh T. Physiology of exercise: for physical education, athletics and exercise science. Madison: Brown & Benchmark; 1996.
35. Evans W, Cannon J. The metabolic effects of exercise-induced muscle damage. Exerc Sport Sci Rev 1991;19:99–125.
36. Armstrong R. Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. Med Sci Sports Exerc 1984;16:529–538.
37. Lieber R, Friden J. Mechanisms of muscle injury after eccentric contraction. J Sci Med Sport 1999;2(3): 253–265.
38. Morgan D, Allen D. Early events in stretch-induced muscle damage. J Appl Physiol 1999;87(6):2007–2015.
39. Proske U, Morgan D. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. J Physiol 2001;537(Pt 2): 333–345.
40. Faulkner J, Brooks S, Opiteck J. Injury to skeletal muscle fiber during contractions: conditions of occurrence and prevention. Phys Ther 1993;73:911–921.

41. Stupka N, Lowther S, Chorneyko K, Bourgeois J, Hogben C, et al. Gender differences in muscle inflammation after eccentric exercise. J Appl Physiol 2000; 89(6):2325–2332.
42. Abraham W. Factors in delayed muscle soreness. Med Sci Sports Exerc 1977;9(1):11–20.
43. Hasselman C, Best T, Seaber A, Garrett WJ. A threshold and continuum of injury during active stretch of rabbit skeletal muscle. Am J Sports Med 1995;23(1): 65–73.
44. MacIntyre D, Reid W, Lyster D, McKenzie D. Different effects of strenuous eccentric exercise on the accumulation of neutrophils in muscle in women and men. Eur J Appl Physiol 2000;81(1–2):47–53.
45. Prior B, Jayaraman R, Reid R, Cooper T, Foley J, et al. Biarticular and monoarticular activation and injury in human quadriceps muscle. Eur J Appl Physiol 2001;85(1–2):185–190.
46. Giulbin J, Gaffney P. Identical twins are discordant for markers of eccentric exercise-induced muscle damage. Int J Sports Med 2002;23:471–476.
47. Leivseth G, Tindall A, Lovaas E, Reikeraas O. Change in muscle stiffness caused by reduced joint mobility. Scand J Med Sci Sports 1993;3:28–36.
48. Kulig K, Powers C, Shellock F, Terk M. The effects of eccentric velocity on activation of elbow flexors: evaluation by magnetic resonance imaging. Med Sci Sports Exerc 2001;33(2):196–200.
49. Tiidus P, Ianuzzo C. Effects of intensity and duration of muscular exercise on delayed soreness and serum enzyme activities. Med Sci Sports Exerc 1983; 15(6):461–465.
50. Nosaka K, Newton M, Sacco P. Delayed-onset muscle soreness does not reflect the magnitude of eccentric exercise-induced muscle damage. Scand J Med Sci Sports 2002;12(6):337–346.
51. Nosaka K, Newton M. Difference in the magnitude of muscle damage between maximal and submaximal eccentric loading. J Strength Cond Res 2002;16(2): 202–208.
52. Teague B, Schwane J. Effect of intermittent eccentric contractions on symptoms of muscle microinjury. Med Sci Sports Exerc 1995;27(10):1378–1384.
53. Newham D, Jones D, Ghosh G, Aurora P. Muscle fatigue and pain after eccentric contractions at long and short length. Clin Sci (Lond) 1988;74(5):553–557.
54. Nosaka K, Sakamoto K. Effect of elbow joint angle on the magnitude of muscle damage to the elbow flexors. Med Sci Sports Exerc 2001;33(1):22–29.
55. Kawakami Y, Nakazawa K, Fujimoto T, Nozaki D, Miyashita M, et al. Specific tension of elbow flexor and extensor muscles based on magnetic resonance imaging. Eur J Appl Physiol Occup Physiol 1994; 68(2):139–147.
56. Barles P, Robinson J, Allen J, Baxter G. Lack of effect of acupuncture upon signs and symptoms of delayed onset muscle soreness. Clin Physiol 2000; 20(6):449–456.
57. Ciccone C, Leggin B, Callamaro J. Effects of ultrasound and trolamine salicylate phonophoresis on delayed-onset muscle soreness. Phys Ther 1991;71(9): 675–678.
58. Craig J, Bradley J, Walsh D, Baxter G, Allen J. Delayed onset muscle soreness: lack of effect of therapeutic ultrasound in humans. Arch Phys Med Rehabil 1999;80(3):318–323.
59. Eston RG, Peters D. Effects of cold water immersion on the symptoms of exercise induced muscle damage. J Sports Sci 1999;17(3):231–238.
60. Kraemer W, Bush J, Wickham R, Denegar C, Gomez A, et al. Influence of compression therapy on symptoms following soft tissue injury from maximal eccentric exercise. J Orthop Sports Phys Ther 2001;31(6):282–290.
61. Hasson S, Daniels J, Divine J, Niebuhr B, Richmond S, et al. Effects of ibuprofen use on muscle soreness, damage, and performance: a preliminary investigation. Med Sci Sports Exerc 1993;25(1):9–17.
62. Mekjavic I, Exner J, Tesch P, Eiken O. Hyperbaric oxygen therapy does not affect recovery from delayed onset muscle soreness. Med Sci Sports Exerc 2000; 32(3):558–563.
63. Nosaka K, Clarkson P. Influence of previous concentric exercise on eccentric exercise-induced muscle damage. J Sports Sci 1997;15:477–483.
64. Lund H, Vestergaard-Poulsen P, Kanstrup I, Sejrsen P. The effects of passive stretching on delayed onset muscle soreness, and other detrimental effects following eccentric exercise. Scand J Med Sci Sports 1998; 8:216–221.
65. Tiidus P, Shoemaker J. Effleurage massage, muscle blood flow and long term post-exercise recovery. Int J Sports Med 1995;16(7):478–483.
66. Smith L, Keating M, Holbert D, Spra**ttt** [[?]] D, McCammon M, et al. The effects of athlete massage on delayed onset muscle soreness, creatine kinase and neutrophil count: a preliminary report. J Orthop Sports Phys Ther 1994;19(2):93–99.
67. Rodenburg J, Steenbeek D, Schiereck P, Bar P. Warm-up, stretching and massage diminish harmful effects of eccentric exercise. Int J Sports Med 1994;15:414–419.
68. Lightfoot J, Char D, McDermont J, Goya C. Immediate post-exercise massage does not attenuate delayed onset of muscle soreness. J Strength Cond Res 1997; 11(12):119–124.
69. Connolly D, Sayers S, McHugh M. Treatment and prevention of delayed onset muscle soreness. J Strength Cond Res 2003;17(1):197–208.
70. Herbert R, Gabriel M. Effects of stretching before and after exercising on muscle soreness and risk of injury: systemic review. Br J Sports Med 2002;325:1–5.
71. McHugh M. Recent advances in the understanding of the repeated bout effect: the protective effect against muscle damage from a single bout of eccentric exercise. Scand J Med Sci Sports 2003;13(2):88–97.
72. Tiidus P. Manual massage and recovery of muscle function following exercise: a literature review. J Orthop Sports Phys Ther 1997;25:107–112.
73. Kendall B, Eston R. Exercise-induced muscle damage

and the potential protective role of estrogen. Sports Med 2002;32(2):103–123.
74. Chen T. Effects of a second bout of maximal eccentric exercise on muscle damage and electromyographic activity. Eur J Appl Physiol 2003;89(2):115–121.
75. Nosaka K, Newton M. Repeated eccentric exercise bouts do not exacerbate muscle damage and repair. J Strength Cond Res 2002;16(1):117–122.
76. Chen T, Hsieh S. The effects of repeated maximal voluntary isokinetic eccentric exercise on recovery from muscle damage. Res Q Exerc Sport 2000;71(3): 260–266.
77. Cleary M, Kimura I, Sitler M, Kendrick Z. Temporal pattern of the repeated bout effect of eccentric exercise on delayed-onset muscle soreness. J Athl Train 2002; 37(1):32–36.
78. Chen T, Hsieh S. Effects of a 7-day eccentric training period on muscle damage and inflammation. Med Sci Sports Exerc 2001;33(10):1732–1738.
79. Paddon-Jones D, Muthalib M, Jenkins D. The effects of a repeated bout of eccentric exercise on indices of muscle damage and delayed onset muscle soreness. J Sci Med Sport 2000;3(1):35–43.
80. Smith L, Fulmer M, Holbert D, McCammon M, Houmard J, et al. The impact of a repeated bout of eccentric exercise on muscular strength, muscle soreness and creatine kinase. Br J Sports Med 1994;28(4): 267–271.
81. Byrnes W, Clarkson P, White J, Hsieh S, Frykman P, et al. Delayed onset muscle soreness following repeated bouts of downhill running. J Appl Physiol 1985;59(3): 710–715.
82. Nosaka K, Clarkson P, McGuiggin M, Byrne J. Time course of muscle adaptation after high force eccentric exercise. Eur J Appl Physiol Occup Physiol 1991;63(1): 70–76.
83. Lund H, Vestergaard-Poulsen P, Kanstrup I, Sejrsen P. Isokinetic eccentric exercise as a model to induce and reproduce pathophysiological alterations related to delayed onset muscle soreness. Scand J Med Sci Sports 1998;8(4):208–215.
84. Nosaka K, Sakamoto K, Newton M, Sacco P. How long does the protective effect on eccentric exercise-induced muscle damage last? Med Sci Sports Exerc 2001;33(9):1490–1495.
85. Mair J, Mayr M, Muller E, Koller A, Haid C, et al. Rapid adaptation to eccentric exercise-induced muscle damage. Int J Sports Med 1995;16(6):352–356.
86. Nosaka K, Sakamoto K, Newton M, Sacco P. The repeated bout effect of reduced-load eccentric exercise on elbow flexor muscle damage. Eur J Appl Physiol 2001;85(1–2):34–40.
87. Brown S, Child R, Day S, Donnelly A. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. J Sports Sci 1997;15(2):215–222.
88. Paddon-Jones D, Quigley B. Effect of cryotherapy on muscle soreness and strength following eccentric exercise. Int J Sports Med 1997;18(8):588–593.
89. Nosaka K, Newton M, Sacco P. Responses of human elbow flexor muscles to electrically stimulated forced lengthening exercise. Acta Physiol Scand 2002;174(2): 137–145.
90. Eston R, Finney S, Baker S, Baltzopoulos V. Muscle tenderness and peak torque changes after downhill running following a prior bout of isokinetic eccentric exercise. J Sports Sci 1996;14(4):291–299.
91. Rowlands A, Eston R, Tilzey C. Effect of stride length manipulation on symptoms of exercise-induced muscle damage and the repeated bout effect. J Sports Sci 2001;19(5):333–340.
92. Eston R, Lemmey A, McHugh P, Byrne C, Walsh S. Effect of stride length on symptoms of exercise-induced muscle damage during a repeated bout of downhill running. Scand J Med Sci Sports 2000;10(4):199–204.
93. Connolly D, Reed B, McHugh M. The repeated bout effect: does evidence for a crossover effect exist? J Sports Sci Med 2002;1:80–86.
94. McHugh MP, Connolly D, Eston R, Gartman E, Gleim G. Electromyographic analysis of repeated bouts of eccentric exercise. J Sports Sci 2001;19:163–170.
95. McNair P, Stanley S. Effect of passive stretching and jogging on the series muscle stiffness and range of motion of the ankle joint. Br J Sports Med 1996;30: 313–318.
96. Gajdosik R. Passive extensibility of skeletal muscle: review of the literature with clinical implications. Clin Biomech (Bristol, Avon) 2001;16(2):87–101.
97. Brockett C, Morgan D, Proske U. Human hamstring muscles adapt to eccentric exercise by changing optimum length. Med Sci Sports Exerc 2001;33(5): 783–790.
98. Morgan D, Brockett C, Gregory J, Proske U. The role of the length-tension curve in the control of movement. Adv Exp Med Biol 2002;508:489–494.
99. Armstrong R, Ogilvie R, Schwane J. Eccentric exercise-induced injury to rat skeletal muscle. J Appl Physiol 1983;54(1):80–93.
100. Foley J, Jayaraman R, Prior B, Pivarnik J, Meyer R. MR measurements of muscle damage and adaptation after eccentric exercise. J Appl Physiol 1999;87(6): 2311–2318.
101. Hill A. The mechanics of voluntary muscle. Lancet 1951;261:947–954.
102. Ploutz-Snyder L, Tesch P, Dudley G. Increased vulnerability to eccentric exercise-induced dysfunction and muscle injury after concentric training. Arch Phys Med Rehabil 1998;79(1):58–61.
103. Gleeson N, Eston R, Marginson V, McHugh M. Effects of prior concentric training on eccentric exercise induced muscle damage. Br J Sports Med 2003; 37(2):119–125.
104. Balnave C, Thompson M. Effect of training on eccentric exercise-induced muscle damage. J Appl Physiol 1993;75(4):1545–1551.
105. Nosaka K, Newton M. Concentric or eccentric training effect on eccentric exercise-induced muscle damage. Med Sci Sports Exerc 2002;34(1):63–69.

106. Wilson G, Murphy A, Pryor J. Musculotendinous stiffness: its relationship to eccentric, isometric and concentric performance. J Appl Physiol 1994;76(6): 2714–2719.
107. Kubo K, Kanehisa H, Fukunaga T. Is passive stiffness in human muscles related to the elasticity of tendon structures? Eur J Appl Physiol 2001;85:226–232.
108. Gajdosik R. Relationship between passive properties of the calf muscles and plantarflexion concentric isokinetic torque characteristics. Eur J Appl Physiol 2002;87(3):220–227.
109. Klinge K, Magnusson S, Simonsen E, Aagaard P, Klausen K, et al. The effects of strength and flexibility training on skeletal muscle electromyographic activity, stiffness, and viscoelastic stress relaxation response. Am J Sports Med 1997;25(5):710–716.
110. Pousson M, van Hoecke J, Boubel F. Changes in elastic characteristics of human muscle induced by eccentric exercise. J Biomech 1990;23(4):343–348.
111. Magnusson S, Aagaard P, Larsson B, Kjaer M. Passive energy absorption by human muscle-tendon unit is unaffected by increase in intramuscular temperature. J Appl Physiol 2000;88:1215–1220.
112. Shellock F, Prentice W. Warming-up and stretching for improved physical performance and prevention of sports-related injuries. Sports Med 1985;2:267–278.
113. Smith C. The warm-up procedure: to stretch or not to stretch. A brief review. J Orthop Sports Phys Ther 1994;19(1):12–17.
114. Hansen T, Kristensen J. Effect of massage, shortwave diathermy and ultrasound upon 133Xe disappearance rate from muscle and subcutaneous tissue in the human calf. Scand J Med Sci Sports 1973;5:179–182.
115. Drust B, Atkinson G, Gregson W, French D, Binningsley D. The effects of massage on intra muscular temperature in the vastus lateralis in humans. Int J Sports Med 2003;24(6):395–399.
116. Nordschow M, Bierman W. The influence of manual massage on muscle relaxation: effect on trunk flexion. J Am Phys Ther 1962;42(10):653–657.
117. Braverman D, Schulman R. Massage techniques in rehabilitation medicine. Phys Med Rehabil Clin N Am 1999;10(3):631–649.
118. Wessel J, Wan A. Effect of stretching on the intensity of delayed-onset muscle soreness. Clin J Sport Med 1994;4:83–87.
119. Magnusson S. Passive properties of human skeletal muscle during stretch manoeuvres. Med Sci Sports Exerc 1998;8:65–77.
120. Halbertsma J, van Bolhuis A, Goeken L. Sport stretching: effects on passive muscle stiffness of short hamstrings. Arch Phys Med Rehabil 1996;77:688–692.
121. Cornwell A, Nelson A. The acute effects of passive stretching on active musculotendinous stiffness. Med Sci Sports Exerc 1997;29:s281.
122. Stanley S, Purdam C, Bond T, McNair P. Passive tension and stiffness properties of the ankle plantar flexors: the effects of massage. In: XVIIIth Congress of the International Society of Biomechanics; 2001 July; Zurich.
123. Semark A, Noakes T, St Clair Gibson A, Lambert M. The effect of a prophylactic dose of flurbiprofen on muscle soreness and sprinting performance in trained subjects. J Sports Sci 1999;17(3):197–203.
124. Lenn J, Uhl T, Mattacola C, Boissonneault G, Yates J, et al. The effects of fish oil and isoflavones on delayed onset muscle soreness. Med Sci Sports Exerc 2002;34(10):1605–1613.
125. Clarkson P, Reichsman F. The effect of ethanol on exercise-induced muscle damage. J Stud Alcohol 1990;51(1):19–23.
126. Vickers A, Fisher P, Smith C, Wyllie S, Lewith G. Homeopathy for delayed onset muscle soreness: a randomised double blind placebo controlled trial. Br J Sports Med 1997;31(4):304–307.
127. Krotkiewski M, Brzezinska Z, Liu B, Grimby G, Palm S. Prevention of muscle soreness by pretreatment with antioxidants. Scand J Med Sci Sports 1994;4:191–199.
128. Dannecker E, Koltyn K, Riley J, Robinson M. Sex differences in delayed onset muscle soreness. J Sports Med Phys Fitness 2003;43(1):78–84.
129. Carter A, Dobridge J, Hackney A. Influence of estrogen on markers of muscle tissue damage following eccentric exercise. Fiziol Cheloveka 2001;27(5):133–137.
130. Thompson H, Hyatt J, De Souza M, Clarkson P. The effects of oral contraceptives on delayed onset muscle soreness following exercise. Contraception 1997;56(2): 59–65.
131. Tiidus P. Influence of estrogen on skeletal muscle damage, inflammation, and repair. Exerc Sport Sci Rev 2003;31(1):40–44.