Beat the exercise-induced muscle damage
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Abstract
Eccentric exercises are being used widely as a strategy to manage sarcopenia. However, eccentric exercises are linked to increased risk of myofibre damage and delayed recovery. There is elevated muscle soreness, decrease muscle strength and increased levels of muscle-specific circulatory protein. There is a huge variation in the severity of the symptoms after eccentric exercise. Several factors affect the degree and severity of muscle soreness. It includes exercise intensity, duration, mode, muscle group, age, gender, genetics and nutritional status. Therefore, designing a specific individual exercise plan is required to overcome injuries, myofibre damage and muscle soreness. At present, we still do not have enough knowledge about the exact sources and factors that trigger muscle soreness linked with strenuous exercise. Deep insight and identification of the risk factors which predispose individuals at an increased risk of muscle soreness after unaccustomed exercises may be a key to help them by prescribing personalised exercise therapy to speed up recovery and adaptation. Non-steroidal anti-inflammatory drugs are being used widely to manage muscle soreness, pain and tenderness linked with post-exercise complications. But there is more to it than just treating pain. Is there any substantive gain besides pain relief? Can they improve muscle function? Could they prevent muscle soreness or speed up recovery? The current narrative review was planned to discuss the sources and factors that trigger exercise-induced muscle damage. Furthermore, it also provides a comprehensive analysis of the literature concerning the effectiveness of non-steroidal anti-inflammatory drugs in reducing symptom and improving muscle function in exercise-induced muscle soreness.

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Introduction
Muscle fever, or delayed onset muscle soreness (DOMS), is an admirable descriptive term that most people experience after excessive eccentric or unaccustomed exercise, generally lasting 24-48 hours afterwards. Most often, DOMS is so intense that it can feel like a strain, an actual muscle damage. Muscle fever, an excellent term as exercise-induced muscle damage (EIMD), result in sickly greases and sore muscles. Weakness is a manifestation of DOMS that is computable but condensers feel difficult to prove their strength while having tender and achy muscles. The filthiness begins after a little delay, mostly after falling asleep, and then lasts 1-3 days. DOMS is expected to occur only after intensive exercise, in case of starting or resuming an exercise regime, notably weight-training. Strenuous eccentric exercises can lead to myofibre structural disruption, protein degradation, inflammation and impaired coupling (excitation, contraction) mechanism. There is disruption of t-tubule, sarcomeres, z-line, and extracellular matrix. Sarcomere disruption is believed to be due to sarcomere length heterogeneity. Fast twitch fibres are subtle to disruption in z streaming compared to slow-twitch fibres. Due to sarcomere heterogeneity, different sarcomeres resist differently to stress. Extended stress on sarcomere can lead to overstretching of the sarcomere, which turns into broadening and z-line streaming. This is one of the processes by which loss of muscle strength occurs in EIMD. The subjects experience sore, stiffer and tender muscles, most of the symptoms having appeared 24 hours after exercise and then persisting for up to 72 hours. This is accompanied by pain, reduced range of motion (ROM), muscle strength, and power. Creatine kinase (CK) is a marker of EIMD whereas tenascin C is a marker used for connective tissue damage. EIMD can be acute or delayed followed by myofibre remodelling. EIMD seems to relate to age-related, as older adults are more susceptible to myofibre damage compared to the young, as older adults have hampered remodelling and muscle regeneration. Older adult muscle biopsies have shown that strenuous exercise can cause more damage compared to the young adults. A study concluded that older females exhibited three times more myofibre damage after 24 hours of unaccustomed activity compared to young women.
Macrophages, neutrophils and the concentration of plasma interleukin-6 (IL-6) diminished in older men and women.\textsuperscript{11} The joint movement occurs as a result of longitudinal and lateral myofibre force.\textsuperscript{12} Biochemical and structural support is provided by non-contractile structures like extracellular matrix and connective tissues to the skeletal muscles.\textsuperscript{13} The skeletal muscles are linked to the non-contractile structures by costameres, desmin. The desmin and costameres play a vital role in skeletal muscles stability and integrity and thus prevent myofibre injury.\textsuperscript{12} An optimum myofibre injury may be a pre-requisite for adaptation (hypertrophy, muscle restructuring, and strength), but excessive myofibre injury or delayed recovery can enhance the chances of risk for injury, particularly in older adults as they have less effective healing capacity.\textsuperscript{11} Myofibre injury induced by unaccustomed exercises might speed up the rate of desmin degradation. Costameres, desmin and cytoskeletal degradation negatively affect myofibre transmission force result in decreased muscle strength after DOMS.\textsuperscript{12}

The current review was planned to focus on the factors that trigger EIMD. Furthermore, it planned to provide a comprehensive analysis of available literature concerning pharmacological interventions in exercise-induced muscle soreness.

What about Genetics?
Genetics is apparently a consideration. Persons having specific genotypes can have more myofibre damage and DOMS recovery. It means specific gene variability can be associated with delayed healing and profound muscle soreness. The role of genetics is highly varied from person to person. Linkages of genetic mutation and myofibre damage still remains a mystery, and there are certain genetic elements that can have an impact on muscle / tendon injury.\textsuperscript{14} Very limited data is available regarding the association between EIMD and regeneration. The genetic profile of athletes is different from the general population.\textsuperscript{14,15} Furthermore, a specific gene polymorphism -- COL1A1, COL12A1 and COL5A1 genes - is suggested to have a link with the prevalence of ligament / tendon injury.\textsuperscript{16} Different gene expression is suggested to have an important role in inflammation, muscle-wasting, protein synthesis and cell proliferation linked to muscle soreness. IL-1B gene is linked to inflammation, myostatin (MSTN), a gene marker for muscle-wasting and mammalian target of rapamycin (mTOR) gene, is related to protein synthesis and cell proliferation. A study to find the effect of light-emitting diode therapy (LEDT) on gene expression linked with the delayed onset of muscle soreness concluded that LEDT depressed the IL-1β and multiple stress regulatory (MSTR) genes expression and was anti-inflammatory, but depressed the signalling process linked with muscle atrophy. However, gene markers of cell proliferation were increased after LEDT.\textsuperscript{17} Similarly, in another study application of low-level laser therapy (LLLT) reduced the messenger ribonucleic acid (mRNA) of cyclooxygenase-2 (COX-2) induced by exercise.\textsuperscript{18} LLLT is also effective in reducing muscle inflammation and soreness linked with exercise. A study examined the effectiveness of LLLT in exercise-induced muscle soreness in rats' gastrocnemius muscle. Different parameters were used and it was concluded that LLLT of 830nm can have an anti-inflammatory effect on muscle soreness.\textsuperscript{19} The effect of phototherapy and LLLT in reducing muscle soreness, inflammation, improving protein synthesis and gene expression suggested that genetics have a significant role in muscle damage induced by exercise and recovery. However, the potential mechanism behind this association is still unclear.

What about metabolic derangement?
Metabolic derangement is the better subtle approach of expressing as a source of DOMS. Myofibres are small chemical firms that offer some undesirable by-products perhaps at higher intensities beyond their ability to adapt. It sounds generally persuasive, but it is a complex approach. But the main question is what creates metabolic stress? Different studies investigated the numerous obscure molecules generated by myofibres during exercise,\textsuperscript{12,17,20} but are these molecules undoubtedly a manifestation of metabolic degradation? Just due to the fact that myofibres make a substance at some point of exercise does not suggest it is metabolically exhausted. Until now, no study has been able to draw a connection between DOMS and any particular biomarker.

What about Inflammation?
After unaccustomed physical activities, skeletal muscle undergoes a series of events including degeneration, inflammation and recovery. The proposed model of
muscle damage comprised acute and chronic phases. The role of inflammation is either insignificant or complex in the acute phase. However, in the 2nd phase, the inflammatory process may aid in recovery. Data suggests that in the acute phase of DOMS, there is insignificant inflammation. In 2015, a study indicated that inflammation remained steady following workouts. This suggests that inflammation is not a source of exercise muscle soreness. In 2015, a study indicated that in the acute phase of DOMS, there is insignificant inflammation. In 2015, a study indicated that inflammation remained steady following workouts. This suggests that inflammation is not a source of exercise muscle soreness.

The inflammatory process begins in the second stage of muscle injury. A recent study suggested the role of leukocytes in myofibre damage and disturbance of calcium ion (Ca2+) homeostasis. The recent data points out that some trivial inflammation is present in DOMS as a result of unaccustomed physical activity producing pain. It is likely a justification of the repeated bout effect. Unfamiliar physical activity stirs up something troublesome inflammation and the immune system suppresses it over 2-4 days. When you repeat the same physical activity, later on, the immune system is more capable of handling the situation.

What about neurology?
The neurotrophic factor can play a vital role as different previous studies suggested that after unaccustomed exercise, substances are secreted by muscles stimulating nerve growth and are linked with muscle pain. A series of studies on rats suggested that DOMS can be stifled by using a medicine that suppresses neurotrophic factor. A few studies suggested thatDOMS pain is due to growing nerves. Strenuous exercise can develop nerves and that causes muscle discomfort. It was authenticated by averting DOMS with COX-2 inhibitors. Primarily, they prevent neurotrophic growth factors.

What about Dehydration?
Dehydration can aggravate the symptoms as these can accumulate metabolic wastes in the body. A 2005 study to examine the effects of dehydration on the symptoms of muscle soreness induced by eccentric exercise in hyperthermic males concluded that dehydrated participants exhibited increased symptoms of muscle soreness in hot temperature. However, in another study conducted by the same researchers in 2006 for assessing the effects of dehydration on the symptoms of muscle soreness induced by eccentric exercise in normothermic males concluded that dehydrated participants exhibited no increase in symptoms of muscle soreness at normal temperature and in rested state. The specific explanation of DOMS is unidentified and is not adequately revealed. It may be that the body and surrounding temperature have a more influential role in eliciting symptoms of muscle soreness in spite of hydrated or dehydrated state.

Different health issues can aggravate the DOMS symptoms but they are difficult to diagnose or manage. There is no exact way to assess muscle soreness. Sometimes it appears as a part of other symptoms. Extended muscle soreness can be a symptom of other health problems, like Vitamin D deficiency and insomnia. Chronic fatigue syndrome, bone and muscle aches, muscle weakness, fatigue, and lower pain threshold may be the manifestation. Insomnia can make pain worse, in particular, muscle pain and soreness. There is a lack of data regarding sleep deprivation causing muscle aches and becoming vulnerable to DOMS. A 2018 experimental study to find out the effect of sleep deprivation and psychological factors on muscle soreness in 29 healthy females having good sleep and no pain. These subjects were randomly divided into control and sleep restriction group. After experimentally inducing muscle soreness in both groups, the study concluded that the restrictive group had more and multi-site pain compared to the control group.

Role of Anti-inflammatory drugs in DOMS
Numerous risk factors are linked with frequent use of non-steroidal anti-inflammatory drugs (NSAIDs). It may include cardiovascular conditions, gastrointestinal, renal and musculoskeletal disorders. A number of studies suggested that NSAIDs can have a role in managing pain, but these are unable to improve healing time and weakness. Moreover, there is an equivocal result regarding the preventive role of NSAIDs in DOMS. A number of studies tried to find out if NSAIDs could aid in muscle soreness prevention after strenuous exercise. Some researchers indicated that using NSAIDs prophylactically mitigates inflammation, muscle soreness and CK level linked with DOMS. NSAIDs have been shown to moderately limit the pain linked with DOMS. A recent study revealed that NSAIDs were more potent if they were used prophylactically to reduce pain but they failed to limit muscle damage. However, they were able to keep some degree of muscle function. In contrast, some studies suggested that NSAIDs were not
effective, particularly on large muscles.\textsuperscript{31,34,35} Probably it may be due to deficiency of drug absorption in muscle tissues. A study with prophylactic use of NSAIDs failed to reduce pain and muscle damage linked with muscle soreness in running athletes after 48 hours.\textsuperscript{31} Another study reviewed the effects of astaxanthin in reducing joint and muscle soreness following DOMS, and concluded that astaxanthin had no beneficial effect in the acute stage of muscle damage following eccentric exercises.\textsuperscript{28}

The prophylactic utility of NSAIDs is still ambiguous as there are a number of studies concluding no effect on symptoms of DOMS.\textsuperscript{31,34} This disagreement in data may exist because of a variety of methods incorporated for assessment, identification and inducing muscle soreness. Moreover, it is difficult to generalise the result due to variation in the intensity of muscle soreness, eccentric mode or variation in type, dosage and duration of NSAID administration. Future studies with higher doses are warranted.

Moreover, inflammation is a normal physiological mechanism, and taking NSAIDs may inhibit protein synthesis and impair the natural healing process of skeletal muscles. Caution should be exercised for selecting an appropriate pharmacological treatment by considering the individual response and degree of muscle damage. Chronic use of NSAIDs is not recommended as it is linked with adverse consequences.

**Conclusion**

Muscle soreness following unaccustomed exercise is a normal physiological mechanism but it can limit exercise adherence and subsequent benefits of the exercise. A number of factors trigger DOMS, including metabolic stress, degeneration, genetics, gender, neuropathic involvement, nutritional deficiencies, insomnia and dehydration. NSAIDs are widely used to limit DOMS, but do not prevent it. Moreover, the chronic use of NSAIDs can interfere with the healing ability of the muscles. A multi-factorial approach, including pharmacological management, is required as no single remedy is up to the mark so far. Choosing the right treatment option and proper mix-up of interventions and precautions according to individual needs has to be prescribed in consultation with the patient and trainers. When choosing an appropriate exercise plan for older adults, be sure that it is progressive in nature as older adults are more vulnerable to muscle damage.

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**References**