Metabolic consequences of exercise induced muscle damage

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Table of Contents

Abstract……4

Introduction……..5

Physiological changes resulting from exercise induced muscle damage (EIMD)……...6

Mechanism of EIMD – Mechanical and Metabolic stress models……..6

Glucose uptake and insulin sensitivity……9

Glycogen metabolism……..11

Altered metabolic profile……12

Metabolic rate……..14

Mechanical vs. metabolic stress models……..15

Conclusion……...…19

Reference list……20

Table……23

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Abstract

Exercise induced muscle damage (EIMD) is commonly experienced following either a bout of unaccustomed physical activity or following physical activity of greater than normal duration or intensity. The mechanistic factor responsible for the initiation of EIMD is not known; however it is hypothesised to be either mechanical or metabolic in nature. This review summarises what is currently known about the effect of EIMD on muscle metabolism. The most notable metabolic effects of EIMD are decreased insulin sensitivity, prolonged glycogen depletion and an increase in metabolic rate both at rest and during exercise. Based on current knowledge regarding the effects various types of damaging exercise on muscle metabolism, a new model for the initiation of EIMD is proposed. This model states that damage initiation may be either metabolic or mechanical, or a combination of both, depending on the mode, intensity, duration of exercise and training status of the individual.

Introduction

Exercise induced muscle damage (EIMD) is a common occurrence following either unaccustomed physical activity, or activity of great intensity or duration. The symptoms of EIMD are common and easily characterised, and include; stiffness and swelling, decreased force of muscular contraction and delayed onset muscular soreness (DOMS)[1]. In addition, EIMD is often characterised by the presence of the intramuscular enzyme creatine kinase (CK) in the blood[2-11].

The greatest evidence of EIMD has been shown to occur following activities which involve predominantly eccentric muscle actions. Eccentric actions are those actions in which the muscle lengthens under tension, as opposed to concentric actions where the muscle shortens, or isometric actions where the muscle length is unchanged[12]. Normal human motion involves repeated cycles of eccentric and concentric muscle actions known as the stretch shortening cycle (SSC). The SSC functions to conserve energy and decrease the metabolic cost of physical activity[13]. Researchers have used a number of eccentric exercise models to induce and study EIMD. A rather artificial method of inducing EIMD has been the use of protocols in which the exercise component is purely eccentric; these protocols involve resisting the action of a weight or lever[2,4,6], as in eccentric cycling[7,14]. Other protocols have combined concentric and eccentric actions but placed the greater emphasis on the eccentric component. These include bench stepping[15], drop jumps[9,11] and downhill running protocols[8'16]. Other research has examined EIMD following exhaustive exercise containing a large number of SSC contractions, such as marathon running[3,5,10,17-20].

Physiological changes resulting from Exercise Induced Muscle Damage

EIMD results in decreases in a number of measures of physical performance. For example, isometric strength is decreased for up to 2 weeks[21], and isokinetic strength is decreased over a range of angular velocities[1]. Power generation also decreased in studies using both Wingate[22] and vertical jump[23] tests. However, 30m sprint performance was unaffected by moderate EIMD[11]. EIMD also results in increased lactate production and increased heart rate response to submaximal exercise, indicating an increased physiological stress response[24,25].

Histological examination has shown that the initial events in EIMD involve focal disruption of the myofibrils and cytoskeleton, resulting in Z-disk streaming. Damage is also visible in the mitochondria and the sarcoplasmic reticulum[17,20]. This initial disruption is followed by degeneration during which the damaged myofibrillar proteins are acted on by proteases. A number of studies have reported the infiltration of immune cells within 2 to 3 days following injury[14,17], but other researchers have failed to show an immune response[2,10,20]. Regeneration follows with satellite cells becoming centrally located and replacing the damaged myofibrils. The exact time course of muscular regeneration following EIMD has yet to be determined; but one study showed that the regeneration process was not complete 12 weeks after a marathon[20].

Mechanism of EIMD – Mechanical and Metabolic stress models

The causative factors and cellular mechanisms involved in EIMD have as yet been poorly characterised. It has been hypothesised that the muscle injury sequence can be divided into two stages, an initial event which initiates the injury process, followed by the loss of Ca^{2+} homeostasis and the initiation of the Ca^{2+} overload phase[26]. Cytosolic Ca^{2+} levels are closely regulated within muscle cells by a number of Ca^{2+} buffering and translocation mechanisms which are present within the cell. When these mechanisms are overwhelmed following muscle injury, several intrinsic degradative pathways are

activated. These include the activation of a number of Ca^{2+}-dependant proteolytic and phospholipolytic pathways, which degrade structural and contractile myofiber proteins as well as the myofiber membrane[27]. These 2 initial phases of muscle fibre injury are followed by a phagocytic phase, during which the inflammatory response allows the removal of damaged tissue, and the regenerative phase, during which the damaged muscle fibres repair.

The initial event in the EIMD injury process has been the subject of much conjecture, and two general hypotheses have been put forward to explain the initiation of injury. These can be summarised as either the mechanical stress or metabolic stress models[26,27] . The mechanical stress model is the more popular and is commonly accepted as the dominant factor in inducing EIMD. The main argument in support of this model is the fact that EIMD is much more common following eccentric rather than concentric contractions. Eccentric muscle contractions have been shown to produce a greater amount of force than isometric or concentric contractions[28]. In addition there is decreased recruitment of motor units during eccentric as opposed to concentric contractions[29]. It has also been proposed that during muscle lengthening actions the number of attached cross bridges decreases as the muscle fibre length increases[30]. This would result in an increased force per cross bridge, predisposing the contractile proteins to failure. Ultimately these findings imply that during eccentric muscle contractions the mechanical stress per fibre is higher than during concentric actions, and that repeated eccentric contractions may place sufficient mechanical stress on the muscle to induce failure in some fibres.

The metabolic stress model proposes that the initial events in EIMD are caused by metabolic deficiencies within the working muscle, or that these deficiencies increase the vulnerability of the muscle fibre to mechanical stress. During physical activity flux through the glycolytic and oxidative metabolic pathways is increased to match the rate of ATP synthesis to the rate of ATP hydrolysis[31]. However, there is always some reduction in the concentrations of high energy phosphates during

muscular activity[31]. Theoretically then, it is possible that the level of ATP could decrease to concentrations low enough to induce muscle damage, particularly in the face of metabolite depletion or during exercise of particularly high intensity. One mechanism for this type of injury would be the decreased action of the Ca^{2+}-ATPase in the sarcoplasmic reticulum or sarcolemma. This would compromise the removal of Ca^{2+}, causing the elevation of cytosolic [Ca^{2+}] and resulting in a cascade of metabolic events which lead to muscle fibre degeneration[26]. The following studies would seem to support this hypothesis; Duchen et al., (1990)[32] has shown that a reduction in energy supply to cells leads to Ca^{2+} release from internal stores. Duncan et al. (1987)[33] has shown that inhibition of Ca^{2+}-ATPase causes rapid damage to the ultrastructure of muscle. Furthermore it has been shown that ischemia in the absence of any mechanical stress causes structural damage similar to that observed in EIMD[34,35]. Similar structural damage to muscles has also been observed in patients with metabolic defects. Thus it is possible for muscle damage to occur independent of any mechanical trauma.

The most convincing argument against the metabolic stress model is the fact that the metabolic cost of eccentric contraction is less than of concentric and isometric contractions. However, there is a possibility that only localised regions of cells become energy depleted, and that these small foci of metabolic imbalance result in the focal damage to muscle fibres observed in EIMD[26]. Such a hypothesis cannot be disproved by assays which examine the metabolic cost of whole muscle action.

While the actual patho-physiological mechanism of EIMD remains to be elucidated, the consequences of the condition have been much more comprehensively reported. The alterations in neuromuscular function and physical performance which follow EIMD have been recently reviewed by Byrne et al (2004)[1]. The aim of this review is to describe the metabolic consequences of EIMD and based on these observations propose an adjusted model for the initiation of EIMD.

Glucose uptake and insulin sensitivity

Glucose enters muscle cells from the blood by way of glucose transporter proteins. GLUT 1 and GLUT 4 are the major glucose transporters in muscle cells. Basal glucose transport is carried out by GLUT 1 which is permanently located on the membrane. GLUT 4 is stored in intracellular vesicles which are translocated to the cell membrane when additional glucose uptake is required. Translocation occurs in response to either insulin secretion or muscular contraction, and the effects of both of these stimuli are additive[36]. Binding of insulin to membrane bound insulin receptors stimulates the phosphorylation of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), this leads to the activation of phosphatidylinositol 3-kinase (PI3-kinase), which subsequently induces GLUT 4 translocation[37]. Muscular contraction stimulates GLUT 4 translocation via a different pathway, possibly involving AMP-kinase[38]. Physical activity has been shown to increase the sensitivity of skeletal muscle to insulin stimulation. This affect is immediate, following a single bout of exercise and persists for several hours. Regular physical activity can increase whole body and muscle insulin sensitivity, much of this effect can be attributed to the last bout of exercise, but the cumulative effects of regular exercise also play a role in the chronic enhancement of insulin sensitivity[39].

In direct paradox to the above model, Kirwan et al. (1991)[40] used a hyperinsulinemic clamp experiment to show that insulin sensitivity was decreased following treadmill exercise to exhaustion. Subjects experienced muscle soreness and exhibited elevated serum CK levels, leading to the conclusion that the decrease in insulin sensitivity may be related to EIMD. A second study by Kirwan et al. (1992)[8] confirmed this finding; subjects were required to perform either 30 minutes of downhill running or 30 minutes of concentric cycling. The downhill running resulted in marked muscle soreness and increased plasma creatine kinase and also a decrease in insulin sensitivity. None of these findings were present following either the control (no exercise) or concentric exercise interventions. These

results indicate that resting muscle glucose uptake is decreased following EIMD, and have been subsequently confirmed by a number of studies[10,16].

Subsequent efforts to elucidate a mechanism for decreased insulin sensitivity have focused on GLUT4 and cytokine responses to EIMD. A study by Asp et al. (1995)[2] on untrained subjects showed that muscle damage caused by resisting knee flexion resulted in a 17% decrease in muscle GLUT 4 content. However, a subsequent study by Asp et al. (1997)[3] which investigated muscular injury in trained runners following participation in a standard marathon failed to show a decrease in GLUT4 content. This led the authors to hypothesise that muscle damage may have been caused by different mechanisms in the two studies, that EIMD was induced by mechanical stress in the untrained subjects but that in trained subjects who were accustomed to the type of exercise the origin of EIMD was metabolic.

Subsequent attempts to explain the decrease in insulin sensitivity following EIMD have focused on the cytokine molecule tissue necrosis factor α (TNF-α). Several studies have shown that the levels of a number of cytokines, including TNF-α, increase during exercise as an acute inflammatory response[41-43]. Del Aguila et al. (1999)[44] showed using C_2C_{12} muscle cell cultures that TNF-α impairs insulin stimulation of insulin receptor substrate 1 (IRS-1) and phosphatidylinositol-3 (PI3) kinase activation by approx 55%. In a subsequent study del Aguila et al. (2000)[16] showed that eccentric exercise in the form of 30 minutes of downhill running, resulted in impaired insulin signal transduction at the level of IRS-1, PI 3-kinase and Akt-kinase (protein kinase B). It was further shown that TNF-α production was significantly correlated with decreased PI3-kinase activity. These findings have led Kirwan and del Aguila (2003)[45] to hypothesise that the decrease in insulin sensitivity in cells during EIMD results from an acute phase response mediated by TNF-α, released from inflammatory cells in response to disruptions to cellular integrity. There is evidence to suggest that the inflammatory response does not

always occur following EIMD[2,10,20]. TNF-α may also be released from adipocytes within the muscle. Steinacker et al. (2003)[41] have proposed that insulin resistance induced during exhaustive exercise may be a protective mechanism to ensure maintenance of euglycemia during exercise in glycogen depleted conditions.

Glycogen Metabolism

Intramuscular glycogen is an important fuel source during physical activity, particularly activity of long duration such as endurance exercise[36]. It has previously been shown that increases in muscle glycogen content enhance endurance capacity[46] and that the maintenance of intramuscular glycogen stores increases time to fatigue during endurance exercise[47]. It has also been shown that intramuscular glycogen depletion coincides with fatigue during endurance exercise[47]. It is for these reasons that knowledge of the effects of EIMD on muscle glycogen metabolism are important, particularly to athletes who would like to optimise performance.

It is known that repeated muscle contractions lead to the depletion of intramuscular glycogen stores, and this is also shown to be true for eccentric muscle actions[6,48]. However, a number of studies have shown muscle glycogen synthesis to be impaired following eccentric exercise resulting in EIMD[2-4,6,14,17,18,20]. Some studies have even shown muscle glycogen concentrations to be lower 24-48 hours later compared to immediately after the completion of the exercise bout[48], suggesting the complete inhibition of glycogen synthesis. The mechanism of impaired glycogen synthesis is assumed to be related to increased insulin resistance and decreased uptake of glucose into the muscle cell. A number of studies have attempted to relate the decrease in glycogen synthesis to decreased activity of the enzymes hexokinase and glycogen synthase but to date none have been able to show this relationship[18].

Altered metabolic profile

Type II fibres are predominantly glycolytic and type I fibres are predominantly oxidative[36], yet both muscle fibre types have been shown to be equally glycogen depleted following predominantly eccentric exercise[2,3,6], indicating that there is no preferential use of a particular fibre type during eccentric exercise. In a one legged exercise model that required concentric exercise to be performed 2 days after an eccentric exercise bout, Asp et al. (1998)[4] demonstrated an increased use of glycogen in the eccentrically damaged leg. In addition, it was also demonstrated that there was a greater amount of glycogen depletion from type II muscle fibres. In an earlier study, Asp et al. (1997)[3] reported increased muscle glycogen repletion in type II as opposed to type I muscle fibres following a marathon run. These data seem to indicate a preferential use of type II muscle fibres following EIMD. The work of Touminen et al. (1996)[10] supports this conclusion. They showed that following participation in a marathon basal glucose oxidation rates were decreased and that the decrease was compensated for by an increase in free fatty acid oxidation. Using an indirect calorimetry measure they determined that the decrease in glucose oxidation rates observed were as a result of a decrease in oxidative rather than non-oxidative glucose metabolism, a finding which could indicate increased reliance on type II muscle fibers. These effects were shown to be present for 2 weeks following the exercise bout. The findings of Gleeson et al. (1995)[24] and Burgess et al. (Unpublished findings - 1998) lend further weight to this model of altered fibre type recruitment. Both reported an increase RER and a trend towards decreased VO_2 during submaximal exercise following EIMD. These findings are consistent with an increased reliance on type II rather than type I muscle fibres following EIMD.

A possible explanation for these findings would be that EIMD in some way damages some essential component of the oxidative pathway for glucose metabolism, resulting in a compensatory increase in non-oxidative glucose metabolism. A number of studies have noted alterations to mitochondrial structure[17,20] associated with EIMD suggesting that the mitochondrial damage may be the mechanism

whereby the glucose oxidative pathway is disrupted. If EIMD did result in damage to the oxidative pathway of glucose metabolism a change in the metabolic profile of muscle would be expected. This alteration of the metabolic profile could be achieved in one of two ways. Firstly there could be preferential recruitment of type II over type I fibres in an attempt to spare the damaged fibres. Alternatively, if the number of functional type I fibres was decreased due to damage the relative contribution of type II fibres to the metabolic cost would be increased. Damage to the oxidative pathway for glucose metabolism, and a concurrent increase in the use of the non-oxidative pathway, would also provide an alternate explanation for the prolonged depletion of glycogen following EIMD. If glycogen was being used as a preferential fuel source, the glycogen concentration may remain lowered due to increased use rather than impaired repletion. In this way the decrease in insulin sensitivity following EIMD may not be the mechanism of decreased glycogen repletion, but rather a consequence of impaired glucose oxidation.

An alternative hypothesis put forward by Asp et al. (1997)[3] states that damaged muscle has a lower maximal work capacity, and that therefore to generate the same amount of power it must work at a higher relative intensity. Since increasing relative exercise intensity is known to increase the relative utilization of carbohydrate at the expense of fat in undamaged muscle, this mechanism could also explain the increased glycogen use in type II fibres. This hypothesis does not, however, account for the decrease in glucose oxidation at rest observed by Touminen et al[10].

In contrast to both of these hypotheses, an earlier study by O'Reilly et al. (1987)[14] failed to show selective glycogen repletion in either muscle fibre type following eccentric exercise. The exercise protocol used involved untrained subjects performing an eccentric cycling bout. The extent of muscle damage in this study seems to be rather extreme in light of the fact the muscle glycogen stores were not repleted 10 days following the exercise bout. Another possible explanation for the contrasting findings

is that while the other studies involved SSC contractions, the mode of exercise in O'Reilly's study was purely eccentric. Further research is required as to what factors and mechanisms are responsible for changes in muscle metabolic profile during EIMD.

Metabolic rate

A number of researchers have shown that EIMD has a long term effect on muscle metabolism. Studies using magnetic resonance spectroscopy (MRS) have measured the ratio of phosphocreatine to inorganic phosphate (PCr/Pi) in resting muscle following EIMD[49-51]. The results have consistently shown an increase in PCr/Pi following EIMD, assuming equilibrium of the creatine kinase reaction and unchanged values of pH, [ATP] and [creatine]; this would indicate an increase in free [ADP]. The increase in PCr/Pi must reflect either an increase in the concentration of inorganic phosphate in the muscle, possibly as a result of disruptions to the sarcolemma, or a small increase in the resting metabolic rate[51]. The duration of these alterations is between 3 and 7 days. The PCr/Pi level has been shown to be increased, indicating increased metabolism, during exercise at any work level for 2-6 hours following an eccentric exercise bout. PCr/Pi during exercise returns to basal levels 1 to 2 days later[51]. Unfortunately, the majority of studies which have used MRS have used protocols which involve eccentric damage of the wrist flexor muscles; none have been completed describing the effect of more metabolically strenuous exercise such as marathon running on PCr/Pi.

A limited number of studies have been completed attempting to quantify the lactate response to EIMD. Asp et al. (1998)[4] have showed increased lactate release from muscles at rest after EIMD compared to a non-exercised control; this increase was attenuated during exercise. Gleeson et al. (1995,1998)[24,25] has shown an increase in lactate release following EIMD at both maximal and submaximal workloads. These findings again indicate a shift in muscle metabolic profile to an increased reliance on non-oxidative metabolism in response to EIMD.

In an attempt to explain these metabolic changes in response to EIMD Walsh et al. (2001)[52] named the following as potential mechanisms by which oxidative metabolism could be altered.

i. increased resting muscle oxygen utilisation due to muscle damage and subsequent requirement of energy demanding repair processes.
ii. decreased oxygen availability due to restricted diffusion and/or local blood flow
iii. decreased maximal mitochondrial respiration
iv. decreased ADP sensitivity of mitochondrial respiration.

It has been suggested that the presence of inflammatory cells following EIMD may cause competition for glucose taken up from the blood stream within the damaged muscle and that this would result in both decreased glycogen storage and increased glycogen use[6]. However, the presence of inflammatory cells within the muscle following EIMD is an irregular finding, which indicates that increased metabolism due to damage and repair processes cannot always account for these observations.

In an attempt to explain these findings Walsh et al.[52] assessed whether eccentric exercise resulted in decreased oxidative function in muscle fibres using a skinned muscle fibre technique. They failed to show any change in either maximal respiration or respiratory control by ADP. However there was no significant increase in plasma CK in this study, indicating that the exercise protocol may not have been severe enough to illicit the changes they wished to observe. Further research is required to elucidate the mechanism by which metabolism is increased following EIMD.

Mechanical vs. metabolic stress models

Research has thus far failed to conclusively show what initial event causes the cascade of metabolic events that culminates in EIMD. Due to the overwhelming evidence that exercise involving predominantly eccentric muscle contractions is related to EIMD, mechanical strain is the factor most

commonly sited as the cause of EIMD. There are, however, a number of problems with this assumption. It is known that EIMD occurs following unaccustomed exercise as well as exercise of great intensity or duration[1]. Research has conclusively shown that marathon running results in EIMD in trained runners[3,5,10,17-19,52]. The repeat bout effect has been shown to protect subjects exposed to prior eccentric exercise from the effects of EIMD in subsequent exercise bouts[53]. Yet runners who are well trained and have completed a number of marathons still experience soreness following the completion of a marathon. While the repetitive trauma of a great number of SSC contractions must undoubtedly contribute to the EIMD experienced by these runners, it is unlikely that these subjects experience the same type of mechanical damage experienced by untrained individuals performing unaccustomed exercise. It is possible that EIMD can be induced by different mechanisms, either mechanical or metabolic, depending on duration, intensity, and type of exercise performed and the training status of the participant.

Table 1 summarises the differences and similarities in response to various exercise protocols designed to induce EIMD within trained and untrained populations. The table has been divided into those exercise protocols where the stress involved is predominantly mechanical (eccentric cycling, resisting muscle extension, downhill running, drop jumps and bench stepping) and where the stress is predominantly metabolic (marathon running). One of the most apparent differences between the two exercise groups is in the [CK] and muscle soreness response to exercise. Generally mechanical stress type exercise results in [CK] and muscle soreness peaking 24 to 48 hours after the exercise bout and remaining elevated for up to 9 days. In contrast, muscle soreness and serum [CK] following metabolic stress generally peak 24 hours post exercise and subside within 7 days. A study by Vickers et al (2001)[15] comprising 482 subjects illustrated that the time course for muscle soreness was different following either participation in a marathon or bench stepping protocol. He showed that following a marathon run soreness was highest on day 1 and subsided gradually, but that following bench stepping

exercise that the muscle soreness curve had an inverted u shape peaking at 48 hours. It can be argued that differences in the [CK] and pain response are due to differences in the training status of the subjects. However research into the mechanism of the repeat bout effect suggests that it occurs through strengthening of the connective tissue within the muscle. Therefore it can also be argued that being trained protects one from mechanical, but not from the metabolic stress inducing EIMD.

There may also be differences in the inflammatory response to EIMD induced by either mechanical or metabolic stress. There has been differential reporting of the inflammatory response following EIMD with some researchers reporting none at all[2,10,20], and others reporting widespread necrosis[14,17]. In all studies detailing the inflammatory response following marathon running only the earliest has shown any evidence of inflammation. Hikida et al (1984)[17] reported widespread infiltration of leukocytes, phagocytes and macrocytes into the muscle tissue. In contrast to other studies, this study showed evidence of inflammation in the subjects before participation in the race. In addition the muscle biopsy samples for this study were all taken in close proximity which may have been a factor related to the degree of inflammation. All subsequent studies have failed to show inflammation in marathon runners experiencing EIMD. Inflammation and necrosis has been reported following one study making use of a mechanical stress protocol. It may be that inflammation only occurs following excessive muscle damage and that improved training status may also protect against inflammation.

A significant difference between the responses to mechanical and metabolic stress mechanisms is in the metabolic response to EIMD. It has been shown that muscle GLUT4 content is decreased following mechanical strain exercise[2] but not following participation in a marathon[3]. Secondly the shift in muscle metabolic profile in response to EIMD has thus far only been shown to occur in response to exercise which induces metabolic stress. The findings of Warhol et al. (1984)[20] lend particular weight to the argument that the mechanism of muscle damage during marathon running is predominantly

metabolic rather than mechanical. This study aimed to track the time course of morphological changes which occurred in muscle cells following a marathon run. Two or more runners were biopsied at time intervals after the race as follows: same day; 1, 2, 3, 5, 7, and 10 days, 2, 3, 4, 6, 8, 10, and 12 weeks. The author's findings indicated evidence of mitochondrial damage including dissolution of cristae and loss of the mitochondrial matrix. It was further observed that damage was focal and confined to individual sarcomeric units, and that these myofibrillar alteration occurred in fibres depleted of glycogen and lipid. These observations led the authors to conclude that "focal damage may result from metabolic stress of a continued demand in the face of substrate depletion." Another interesting observation was that glycogen repletion correlated with the restoration of mitochondrial architecture and repair of sarcomeric damage. These findings provide physical evidence suggesting that EIMD resulting from marathon running is metabolic rather than mechanical in nature.

It is unlikely that either type of muscle stress, mechanical or metabolic, can occur in isolation from one another, since all muscle actions have metabolic and mechanical components. However, the relative contributions of each type of muscle stress must conceivably differ according to the exercise protocol employed. Therefore when attempting to quantify EIMD the primary type of stress inflicted on the muscle should be considered, since this will have consequences for the subsequent repair and adaptation processes.

Conclusion

The neuromuscular and physiological responses to EIMD have been well characterised, yet it is evident that far less is known about the metabolic response to this condition. A great deal of the research regarding the metabolic consequences of EIMD is conflicting, and as yet there is no model which explains all of these variations. It is logical to assume that if all EIMD cases were the result of the same mechanism of damage, the subsequent neuromuscular, physiological and metabolic effects would be similar. The discrepancies in response to EIMD therefore are indicative of differential damage mechanisms. It is currently hypothesised that EIMD is caused by either a mechanical or a metabolic mechanism. Differences in exercise type, intensity, duration and training status of the participants create a different muscular stress profile for each exercise bout performed, and it is likely that these different stress profiles would each be met with a different stress response. Therefore each of these factors should be considered when quantifying the EIMD response to exercise. Based on apparent differences in the metabolic and muscle soreness responses to exercise, this paper proposes that while EIMD which results from participation in extreme endurance events such as marathon running is the result of both mechanical and metabolic stress, the primarily stress is metabolic in nature.

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Table I – Reported differences in the characteristics of exercise induced muscle damage caused by different exercise protocols.

Reference	Subjects	Protocol	Inflammatory Response	Pain and CK response	Metabolic Effects
Mechanical Strain					
Evans et al., 1986[7]	5 untrained men and 4 trained endurance runners	Eccentric cycling @ 250 W for 45mins	-	Untrained subjects experienced extreme soreness for 1-2 days. Trained runners experienced only mild discomfort. In trained runners CK peaked at day 1 and then returned to normal levels. In untrained subjects CK peaked at day 5 and remained elevated for 9 days. (250U/l vs. 2500U/l)	-
O'Reilly et al., 1987[14]	5 untrained males	3 x 15 min eccentric cycling at 201W	Inflammatory cell infiltration after 10 days, fibers frankly necrotic.	-	EE resulted in significant glycogen depletion which was not restored within 10 days. No selective repletion of type I or type II fibers.
Costill et al, 1990[6]	8 untrained males	One leg performs 10 x 10 eccentric contractions at 120% 1RM. Followed by 60 mins 2 legged cycling at 70% VO2 max.	-	Soreness present for 7 days and peaks at 48 hrs. CK peak measured at 72hrs (6988U/l)	Decreased glycogen storage 72hrs post exercise in EE trained leg.
Kirwan et a., 1992[8]	3 untrained males and 3 untrained females	30mins downhill running on a -17° decline at 60% VO2 max	-	Soreness peaked 48-72 hours after exercise. CK at 48 hrs (273U/l)	Decreased glucose disposal during euglycemic hyperinsulinemic clamp following EE. No difference in serum glucose or FFA concentrations.
Asp et al, 1995[2]	7 untrained males	One legged eccentric exercise by resisting knee flexion enforced by a mechanical ergometer. 4 x 5min sets	No histological evidence of inflammation.	Soreness present for 96 hrs and peaks at 48 hours. CK elevated for 7 days following EE, peak reported on day 7. (587U/l)	Glut 4 content unchanged immediately after exercise, and decreased on days 1 and 2. Glycogen decreased 17% and remained decreased on days 1 and 2.
Semark et al, 1998[11]	25 trained males	7 sets of 10 drop jumps	-	Pain was higher at 24 and 48 hours than at 12 and 72 hours. CK was unchanged throughout.	-
Asp et al, 1998[4]	7 untrained males	One legged eccentric exercise by resisting knee flexion enforced by a mechanical ergometer. 4 x 5min sets	-	Large CK increase peak measured on day 2, not measured further (2211U/l)	EE resulted in decreased muscle glycogen. During subsequent concentric exercise glycogen was more decreased in the EE leg than the control leg. EE caused greater glycogen depletion in type II fibers. GLUT 4 content was not different between legs following EE.

Del Aguila et al, 2000[16]	8 untrained males	30 mins downhill running, -17° gradient @ 80% HRmax	-	-	Glucose disappearance was lower during euglycemic hyperinsulinemic clamp following EE. Indirect calorimetry indicates a decrease in non-oxidative glucose metabolism.
Vickers, 2001[15]	82 untrained males and females and 400 trained males and females	10 minutes of bench stepping while holding sandbags filled to 10% of body weight or a marathon run.	-	Different time course of soreness induced either by running or bench stepping. Soreness peaked at day 1 following a marathon, and 2 to 3 days after bench stepping.	-
Nosaka and Clarkson, 2004[9]	16 untrained males	5 sets of 20 drop jumps	-	Muscle soreness peaked at 48 hours and had not subsided by 96 hours. CK peaked at 24 hours and remained elevated up to 72 hrs.	-
Metabolic Strain					
Sherman et al, 1983[18]	10 well trained marathon runners	Marathon run followed by either rest or exercise during 7 day recovery period.	-	-	Glycogen was decreased following marathon and remained decreased up to 7 days. Decrease was augmented in subjects who exercised during recovery.
Hikida et al, 1983[17]	10 trained male runners	Muscle biopsy samples obtained before, immediately after and 1, 3, 5 and 7 days after a marathon for each subject.	Evidence of muscle damage and inflammation evident before and after participation in the race.	-	Glycogen concentrations were decreased immediately post marathon.
Warhol et al, 1985[20]	40 trained male marathon runners	Muscle biopsies taken from a minimum of 2 subjects on each occasion 1,2,3,5,7,10 days and 2,3,4,6,8,10 and 12 weeks after a marathon run.	Absence of inflammatory cells indicates that acute necrosis did not occur.	-	Fibers had reconstituted glycogen within 1 week. Damage was focal and confined to individual sacromeric units occurred in fibers depleted of glycogen and lipid.
Tuominen et al, 1996[10]	19 trained runners	Marathon run	No indication of inflammation or changes in histological structure.	13x increase in CK 1 day after marathon	Decreased resting glucose oxidation rate (36%), increased resting FFA concentration and oxidation (55%), and increased basal metabolic rate (6%). Muscle glycogen was decreased 37%.
Asp et al, 1997[3]	7 well trained marathon runners	Marathon run	-	CK concentration peaked 1 day after marathon and was recovered within 7 days. (2360U/l)	Glycogen conc. was reduced post race but recovered by day 7. GLUT 4 content was unaltered following

					marathon.
Asp et al, 1999[5]	6 well trained male runners	Marathon run	-	CK peaked 1 day after race and remained elevated on day 2, normal by day 7. (2655U/l)	Muscle glycogen was decreased following the race and remained depleted on day 1 and 2. Returned to normal by day 7. Selective repletion of type IIX compared to type IIA and of type IIA vs. type I fibers.