Introduction

Resistance exercise can result in localized damage to muscle tissue. This damage may be observed in sarcolemma, basal lamina, as well as, in the contractile elements and the cytoskeleton. Usually the damage is accompanied by release of enzymes such as creatine kinase (CK) and lactate dehydrogenase, myoglobin and other proteins into the blood. Serum CK has been proposed as one of the best indirect indicators of muscle damage due to its ease of identification and the relatively low cost of assays to quantify it. Thus, CK has been used as an indicator of the training intensity and a diagnostic marker of overtraining. However, some issues complicate CK’s use in this manner. There is great interindividual variability in serum CK, which complicates the assignment of reliable reference values for athletes. Furthermore, factors such as training level, muscle groups involved, and gender can influence CK levels to a greater extent than differences in exercise volume completed. This review will detail the process by which resistance exercise induces a rise in circulating CK, illuminate the various factors that affect the CK response to resistance exercise, and discuss the relative usefulness of CK as a marker of training status, in light of these factors.

Keywords: Enzymes, Muscle Damage, Weight Training

The creatine kinase response to resistance exercise

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Abstract

Resistance exercise can result in localized damage to muscle tissue. This damage may be observed in sarcolemma, basal lamina, as well as, in the contractile elements and the cytoskeleton. Usually the damage is accompanied by release of enzymes such as creatine kinase (CK) and lactate dehydrogenase, myoglobin and other proteins into the blood. Serum CK has been proposed as one of the best indirect indicators of muscle damage due to its ease of identification and the relatively low cost of assays to quantify it. Thus, CK has been used as an indicator of the training intensity and a diagnostic marker of overtraining. However, some issues complicate CK’s use in this manner. There is great interindividual variability in serum CK, which complicates the assignment of reliable reference values for athletes. Furthermore, factors such as training level, muscle groups involved, and gender can influence CK levels to a greater extent than differences in exercise volume completed. This review will detail the process by which resistance exercise induces a rise in circulating CK, illuminate the various factors that affect the CK response to resistance exercise, and discuss the relative usefulness of CK as a marker of training status, in light of these factors.

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hours after resistance exercise. From normal resting ranges of 60-400 U·L⁻¹ (see Schlattner et al. 22), CK activity rises by ~100% within 8h after resistance exercise. CK activity continues to rise, reaching levels ranging from 300-6000+ U·L⁻¹, with peak levels seen anywhere from 24 to 96 h after the initial exercise bout 2. The location of that intensity threshold to induce a rise in CK, the time course of the rise in CK, and the extent to which CK rises after exercise, are highly variable and affected by individual factors and exercise variables 23-26.

Individual factors associated with elevated CK

High-responders and genotype

Some individuals studied have been classified as “high-responders” (HR) in light of the much higher rise in CK after resistance exercise as compared to an average, or normal response (NR). Unfortunately, there is no consensus regarding a clinical definition of CK activity to establish an individual as being HR. The distinction between HR and NR has thus far been operationally defined by individual experiments, for example, Heled et al.24 categorized high-responders as those who displayed a post-exercise change in CK≥ the 90th percentile of their cohort. Clarkson et al.27 defined three groups, low (LR), medium (MR) and high (HR), based upon the amount of increase in CK. The LR where those having a peak CK of less than 500 U.l⁻¹, the MR between 500 and 2,000 U.l⁻¹, and the HR were those having a peak CK response of over 2,000 U.l⁻¹. More recently, Chen28 created another group: higher responders (HrR) those exceeding 10,000 U.l⁻¹. It is important to note that this classification diversity could be associated with exercise protocol differences rather than individual (biological) differences. Heled et al.24 used a low intensity, high volume exercise stimulus, while Cleak and Eston29 and Chen28 used a vigorous eccentric exercise protocol. It is possible that the exercise protocol used by Heled et al.24 would not have induced muscle damage to the magnitude of those experiments employing eccentric actions, allowing the classification of subjects into only two groups (Table 1).

However it is defined, the difference between HR and NR...
is thought to be, at least in part, due to genetic variation. Several investigations have sought to identify specific genetic markers for HR. So far, several genetic polymorphisms have been identified as being related to HR, including chemokine ligand 1 and chemokine receptor 2, myosin light chain kinase, insulin-like growth factor II, CK-MM and the ACE genotypes.

α-actinin-3 is an actin-binding protein present in skeletal muscle and represents a major structural component of the Z line in the sarcomere. Owing to its location, it was postulated that this protein may play a role in maintenance of the structural integrity of sarcomeres and muscle cells during eccentric muscle contractions.

Interestingly, the synthesis of α-actinin-3 is encoded for the ACTN3 gene (11q13–q14), which has shown a single nucleotide polymorphism (SNP), called ACTN3 R577X polymorphism, with clinical relevance. Homozygosity of the X-allele results in an absence of ACTN3 expression, with no apparent association with muscle disease phenotypes. Despite this, it has been postulated that the protein may play a role in maintenance of the structural integrity of sarcomeres and muscle cells during eccentric muscle contractions.

Vincent et al. showed that subjects homozygous to the X-allele tended to have higher peak CK values after eccentric exercise when compared to those with a homozygous R-allele. The authors hypothesized that ACTN3-deficient fibers, as observed in homozygous X-allele individuals, could increase muscle damage, inducing a greater increases in CK response to eccentric exercise. Similar results were found by Pimenta et al. when studying soccer professional athletes.

Body composition and sex

Other individual factors that may influence CK response include body composition and sex. In regard to body composition, a higher percent body fat has been found to be related to HR while body mass index was not. It is possible that a higher body fat may provide an indicator of a phenotype related to an intricate relationship between genotypic profile and low habitual physical activity levels, giving poorly conditioned muscles, and then, lead to higher susceptibility to muscle damage after exercise.

Sex may also influence the extent of serum CK increase after exercise. In animal studies, females consistently appear to be less susceptible to muscle damage than males. It appears that estrogen has strong antioxidant properties that help maintain muscle cell membrane permeability after exercise, resulting in a lower rise in serum CK. However, the available human studies have produced markedly different results, where women have either shown no difference in post-exercise serum CK, or displayed higher elevation in serum CK than men.

Exercise factors related to CK

Mechanisms of exercise-induced muscle damage

Experimental evidence implicates two main stressors as causes of exercise-induced muscle damage: mechanical stress and metabolic stress. Mechanical stress placed on muscle during exercise, largely induced by stretching of sarcomeres, causes disruptions in the contractile apparatus, muscle cytoskeleton and sarclemma-associated proteins. Metabolic stress is placed on muscle during exercise due to free radical formation and calcium overload. Elevation in O₂ consumption during exercise leading to increased activity in the electron transport chain, increased semiquinone in the mitochondria and xanthine oxidase in capillary endothelial cells, all of which may lead to increased production of free radicals and consequent damage to cell membranes. Further, muscle may experience an ischemia/reperfusion-like state in the transition from exercise to recovery, which would further enhance free radical production. Calcium levels increase within resting muscle fibers after eccentric contractions, migrating from stretch-activated calcium channels, damaged transverse tubules, and possibly the sarcoplasmic reticulum. This calcium influx consequently activates proteases, phospholipases, lysosomal enzymes, and calpains, all of which increase protein turnover in muscle. Calpains, in particular, are thought to be a primary mediator of muscle damage after eccentric contractions. Mechanical factors have been suggested as those most responsible for muscle injury.

Amount of work performed, surprisingly small effect

The amount of work performed during a resistance exercise bout is often expressed with the term volume load, defined as weight x repetitions x sets. Volume load yields the total tonnage lifted in an exercise session. It would seem logical to presume that a greater volume load lifted in a given exercise session would produce more trauma to the muscles, and thus a higher serum CK activity. Surprisingly, research to date indicates a more complicated relationship between work performed and the rise in serum CK.

Several investigations have noted a positive relationship between workload performed in a resistance exercise bout and serum CK. However, the correlations between the two are generally mild, for example, r=0.44 in one study.

A study by Nosaka and Clarkson provides a classic illustration of the tenuous relationship between work and serum CK elevation. In this experiment, groups of subjects performed 24 maximal eccentric actions of the elbow flexors with either a single arm or both arms simultaneously on an isokinetic dynamometer. It was expected that the group performing exercise with two arms, exercising roughly twice the muscle mass as the comparison group, would display a greater rise in serum CK. Surprisingly, serum CK elevation was similar between groups. Similarly, in diseases where serum CK elevation is associated with tissue damage, such as muscular dystrophy and myocardial infarction, the extent of tissue damage is not strongly correlated with the rise of serum CK. Indeed, animal evidence suggests serum CK elevation is more strongly affected by lymph flow than the extent of tissue injury.

Shorter rest interval related to higher CK in some populations

The rest interval between sets of resistance exercise is an often overlooked factor in resistance exercise. However, sev-
eral studies have found that resistance exercise with short (60s) versus longer (180s) rest intervals between sets may produce a higher rise in serum CK.

Mayhew et al. compared serum creatine kinase concentrations following two sessions that consisted of 10 sets of 10 repetitions at 65% 1RM in leg press with either 1 min or 3 min rest intervals between sets. Significant elevations in serum CK concentrations were demonstrated at 24 hours post-session for both rest conditions. However, serum CK was significantly greater when resting 1 min versus 3 min between sets. This occurred despite the fact that subjects lifted a significantly lower volume load during the 1 min rest protocol. In contrast when volume was held equal between rest conditions, studies have found no difference between shorter vs. longer rest intervals.

A possible explanation for these different findings might be that subjects in the latter two experiments were accustomed to training with 1-2 min rest intervals between sets before the experiment. However, subjects in Mayhew’s study were not.

Training evokes fairly rapid adaptations to exercise. For example, Buresh et al. measured the hormonal response to resistance exercise between groups employing short (1 min) versus long (2.5 min) rest intervals longitudinally, over the course of a 10-week training cycle. While the short rest interval group displayed a significantly higher elevation in post-exercise testosterone and cortisol than was seen in the long rest interval group after one week of training, these differences had disappeared by five weeks of training. Thus it appears that subjects can quickly adapt to training at a specific rest interval, after which post-exercise increases in circulating hormones (and perhaps enzymes) will depend less on the rest interval employed and more on the total amount of work performed. Indeed, such an adaptation would also explain the similarity in CK activity despite differing rest intervals.

Machado and Willardson compared 60 vs. 180s rest intervals in a trained population without equalizing volume between the conditions. Unsurprisingly, subjects lifted a lesser volume load under the conditions with shorter rest. Interestingly, they distinguished subjects’ CK responses between HR and NR. It was found that short rest intervals led to a significantly higher CK activity in HR subjects, but were no different from long rest intervals in NR. Thus there is evidence to support that a shorter rest interval may evoke a higher CK response to resistance exercise, at least in some (HR) individuals (Figure 1).

**Movement speed**

Relatively few studies have examined the effect of velocity of movement on rises in serum CK. One recent study found fast velocity (210°·s⁻¹) eccentric contractions produced a 4.5 higher serum CK activity than slower (30°·s⁻¹) actions given for the same time under tension. Given the positive relationship between force and velocity for eccentric contractions, this finding is understandable. Indeed, fast (180°·s⁻¹) velocity ec-
centric contractions have also been shown to decrease post-exercise torque, activate protein degradation signaling pathways (FOXO1 and FOXO3) and elevate myostatin content\textsuperscript{61} in rat skeletal muscle. These changes, characterized as atrophic\textsuperscript{61}, may contribute to higher CK activity as well. For concentric muscle actions, in which force and velocity are inversely related, it is likely that a slower movement speed would produce higher elevations in serum CK.

**Muscle group - upper body**

Several recent studies\textsuperscript{62-65} have compared upper and lower body exercise, consistently finding of greater elevations in soreness and serum CK following upper body exercise compared to lower body exercise. Most notably, Chen et al.\textsuperscript{62} recent experiment employed the same subjects exercising different (elbow vs. knee, extensor vs. flexor) muscle groups repeatedly. Interestingly, they observed that elevated CK responses occurred after exercise of some muscle groups, but not others, within the same subject. Thus, there is strong evidence to support that the muscle group exercised may be the most important factor in determining CK response.

Exactly why upper body exercise induces a greater rise in CK is still unknown. Jamurtas et al.\textsuperscript{63} proposed that it is likely that people are more often exposed to eccentric actions using the muscles of their lower body in daily activities (i.e. descending stairs, sitting) than the muscles of their upper body.

Chen et al.\textsuperscript{62} noted differences in markers in muscle damage not only between upper body and lower body muscles, but also in antagonist muscle groups around the same joint (e.g., knee extensor versus flexor). From these differences, they concluded that different characteristics of muscle damage between muscles are very specific, and suggested it is ideal to use specific exercise models of specific muscles to understand the nature of muscle damage for a given muscle group.

**Strategies to reduce the rise in serum CK**

**Training status and repeated bout effect**

The most prominent, controllable variable that alters the magnitude of serum CK rise after exercise is familiarization with the activity. Sedentary individuals display greater increases in CK following resistance exercise\textsuperscript{66}. However, one single exposure to a bout of resistance exercise diminishes the rise in CK (and muscle soreness and other markers of muscle damage) to a subsequent bout of the same exercise. This phenomenon has been termed “the repeated bout effect”, and has been demonstrated to occur in many studies\textsuperscript{28,67,68}. The protective effect gained from one bout of exercise is developed within a few days following the initial damaging event.

Adaptations behind the repeated bout effect are thought to include a shift towards greater recruitment of slow-twitch motor units, the generation of new sarcomeres in series, thereby reducing the extent of microtrauma, and a downregulation of inflammation, that would limit the extent of post-exercise cell damage in the days following the exercise\textsuperscript{69,69}. The protective effect of one bout of exercise has been documented to persist for as long as 6 months following the initial exposure\textsuperscript{70}. Thus regular training should provide a powerful resistance to large rises in serum CK activity.

**Aging and muscle fiber type**

Several studies have compared exercise-induced muscle damage responses, including CK activity, among different age groups. Consistently, post-exercise CK activity has been found to be higher in young adults than in either children\textsuperscript{71-73}, or elderly subjects\textsuperscript{75,74} following exercise of the same relative intensity.

A possible explanation for why young adults experience a greater rise in CK activity (as well as other markers of muscle damage) is the difference in muscle fiber type between age groups. Fast-twitch (type II) muscle are more susceptible to exercise-induced muscle damage\textsuperscript{75} and more prevalent in adults than in either children or the elderly\textsuperscript{76-78}. Alternately, the muscles of adults may be more susceptible to damage as they must generate a greater force per fiber during eccentric contractions, owing to the greater body mass of adults vs. children\textsuperscript{71}, and presumably, the elderly.

Interestingly, Gorianovas et al.\textsuperscript{79} recently documented that young adults displayed a greater attenuation of CK activity (and other markers of muscle damage) after a second exposure to eccentric exercise\textsuperscript{79}. In this study, boys (mean age= 11.8 y), young men (mean age= 20.8 y) and elderly men (mean age= 63.2 y) performed two bouts of 100 drop jumps from a 0.5 m height, separated by two weeks. Consistent with previous studies, the young men displayed higher CK activity, perceived soreness, and decreases in voluntarily and electrically-invoked torque than either the boys or elderly men after the first bout. However, the young men also displayed greater decreases in CK activity 24h (young men= -685.2 IU/L, boys= -286.4 IU/L, elderly men= -70.7 IU/L) and 48h (young men= -881.2 IU/L, boys= -205.7 IU/L, elderly men= -206 IU/L) after their second exposure of exercise, relative to the first bout. Thus, while exercise-induced muscle damage and CK activity are greater in young adults, young adults’ muscles may also adapt more readily to exercise.

**Nutritional intervention**

Several studies have investigated the use of dietary supplements as a means to offset exercise-induced muscle damage, as measured by CK activity. Branched chain amino acid (BCAA) supplementation appears to offset rises in serum CK after exercise. BCAA supplementation in subjects who were already ingesting recommended BCAA levels in their diets reduced the rise in CK (and LDH) after either vigorous endurance exercise\textsuperscript{70,80} or resistance exercise\textsuperscript{81}.

It is suggested that phosphocreatine, due to its amphipathic nature, can bind to the plasma membrane increasing its stability\textsuperscript{82,83} and reducing the CK release to serum. However, despite many effects of creatine supplementation, the experimental results are conflicting on the relationship between this supplementation and the integrity of the muscle macrostructure\textsuperscript{84,85}.

Beta hydroxymethylbuterate (HMB) supplementation has been investigated as a means to stabilize muscle cell mem-
branes and reducing the extent of post-exercise damage. Available studies find mixed results, with some reporting an attenuated rise in CK after exercise with HMB supplementation\textsuperscript{86}, while others report no impact\textsuperscript{87} of HMB supplementation. A recent meta-analysis of HMB’s effect on muscle damage concluded that the supplement’s impact on CK was “unclear”\textsuperscript{88}. Additionally, the use of antioxidant supplements has been proposed in recent years\textsuperscript{89}. Experimentation with dietary supplements that may attenuate the extent of muscle damage is ongoing, and represents a dynamic and growing avenue of research.

**Application of cold, heat, massage, and compression**

Immersion in either cold or warm water, ice and compression have been traditionally applied as modalities to assist the recovery from exercise. Briefly cold is theorized to reduce post-exercise inflammation and edema, while heat increases circulation to facilitate the removal of waste products. Available studies indicate that cold application – in the form of cold water immersion\textsuperscript{90}, contrast (cold-hot) immersion\textsuperscript{91} or whole body cryotherapy\textsuperscript{92} can attenuate post-exercise rises in serum CK. A recent study of cold application during (in between sets of) resistance exercise found that while cold application increased the workload completed, it did not alter the rise of serum CK\textsuperscript{93}.

Fewer data support the application of warmth after exercise to reduce serum CK. A recent study of post-exercise warm-water immersion found it to be successful in dampening the rise of serum CK\textsuperscript{94}, however this experiment limited the time of observation to a 6-h post-exercise window, likely too short to observe peak increases in serum CK. Pre-exercise warming has been proposed as a method to blunt exercise-induced muscle damage, possibly by decreasing muscle viscosity or increasing elasticity of the musculotendinous unit. Studies of pre-exercise immersion in warm water have found it may significantly blunt the rise of serum CK\textsuperscript{95}, though this finding is inconsistent\textsuperscript{96}.

Massage after exercise often reduces the post-exercise rise in serum CK, compared to that in a control\textsuperscript{97,98}, though not always\textsuperscript{99}. Compression garments have also been found to effectively reduce the rise in serum CK after exercise\textsuperscript{100,101}. Studies of ice massage have yielded mixed results\textsuperscript{102,103}. In sum, cold therapy, massage, and compression have been found to attenuate post-exercise rises in serum CK. Less evidence supports the tactic of pre-exercise warming to attenuate rises in serum CK.

**Concluding remarks**

Creatine kinase is one of several (LDH, myoglobin, troponin, etc.) markers of exercise-induced muscle damage. In general, studies have found serum CK activity after exercise to poorly related to functional measures of muscle soreness, strength, range of motion, etc\textsuperscript{104}. Post-exercise losses in strength are not coupled to the rise in CK\textsuperscript{105}.

Interpretation of the meaning of CK and other circulating muscle proteins is challenging. Often, a lower rise of CK (or Mb or LDH) after exercise is equated to a less traumatic exercise session, but not always. For example, Viitasalo et al.\textsuperscript{106} found subjects treated with warm jet massage during vigorous power training retained continuous jumping power above levels seen in a control state. However, the authors attributed this observation in part to an increased Mb release seen during the massage treatment. They interpreted the increased release of proteins from muscle as being helpful in the maintenance of neuromuscular performance\textsuperscript{106}. Given the poor relation to functional outcomes, and the question of how to interpret CK’s rise in circulation after exercise, CK appears to be of more use as a qualitative marker that some trauma to skeletal muscle has occurred, rather than a quantitative indicator of the extent of muscle damage.

Based on the available studies, individual differences and exercise variables highly contribute to the extent of CK accumulation. For individual factors, several polymorphisms in genotype that affect the rise in CK have been identified and research to identify more is ongoing. In regards to exercise programming, it appears that a high volume of upper-body exercise, with short rest intervals taken between sets, would tend to produce the greatest increase in CK. Whether this type of protocol would affect clinical outcomes, such as an increased risk exertional rhabdomyolysis is questionable, as there is currently no established link between an exaggerated CK response and exertional rhabdomyolysis. Interestingly, a recent case in the United States, in which 14 high school American football players experienced rhabdomyolysis consisted of just such an exercise bout. During summer training these athletes performed an exercise bout consisting of two upper body exercises: pushups and chair dips. The exercises were performed with virtually no rest, as supersets, and continuously for work intervals of 30s each, and then repeated with decreasing work times until a final work set of 5s each was reached. The consequences of this exercise bout resulted in hospitalization of 14 players, three of whom required an emergency fasciotomy of their Triceps Brachii\textsuperscript{107}.

Noakes\textsuperscript{108} proposed that subjects who displayed abnormally large increases in CK after exercise may have some unrecognized subclinical myopathy. Subsequent work has supported his assertion, finding exaggerated CK responses in conditions such as McCardle’s disease\textsuperscript{109} and calveolinopathies\textsuperscript{110,111}. Thus evaluation of CK pre- and post-exercise may provide a diagnostic tool for the detection of myopathies, with much less invasiveness than required of a muscle biopsy. This may be the most meaningful use of serum CK monitoring.

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