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A REVIEW ON CLINICAL IMPLICATIONS OF MUSCULAR CREATINE KINASE AND RESPONSE TO EXERCISE

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ABSTRACT

Creatine kinase is a controller of cellular homeostasis. CK and its cytosolic and mitochondrial subunits is compartment specific which play their role in cardiac muscles, skeletal muscles, brain and other tissues. Under situations of compromised cellular energy state of ischemia, oxidative stress and calcium overload, mitochondrial Creatine kinase exquisites susceptibility to oxidative modifications and the compensatory up regulation of its gene expression, in some cases leading to accumulation of crystalline Mt-CK inclusion bodies in mitochondria that are the clinical hallmarks for mitochondrial cytopathies.Asymptomatic hyper CK emiais an incidental finding in a patient without muscle related symptoms or with only insignificant nonspecific muscle symptoms like cramps, spasms and fatigue that do not significantly affect daily life activities. The diagnosis of congenital muscular dystrophy requires the concurrence of expertise in multiple specialties available in a few centres worldwide that have achieved sufficient experience with the different CMD subtypes. Metabolic muscle disruption is seen due to heavy exercise, researchers studied exercise related elevation of CK in different groups on the basis of different factors effecting CK.

KEY WORDS

Creatine kinase, Adenine Nucleotide Translocaor, ATP, Cytosolic and mitochondrial CK

INTRODUCTION

Creatine kinase (CK, *EC 2.7.3.2*), a central controller of cellular energy homeostasis is formed by reversible interconversion of creatine into phosphocreatine. It builds up a large pool of rapidly diffusing phosphocreatine for temporal and spatial buffering of ATP (Ellington, 1989).It is a compact enzyme of around 82 kilo dalton found in cytosol and mitochondria of tissues where energy demands are high. CK is composed of two polypeptide subunits of around 42 kDa in cytosol, and two types of subunit are found: muscle type M and brain type B. Muscle specific cytosolic (MCK) is expressed in sarcomeric skeletal and cardiac muscles and ubiquitous brain specific cytosolic (BCK) is expressed in brain, neuronal tissues and other non muscle and non cardiac tissues.These subunits allow the formation of three tissue specific isoenzymes: CK-MB (cardiac muscle), CK-MM (skeletal muscle), and CK-BB (brain). The ratio of skeletal muscle: 98% MM and 2% MB and cardiac muscle: 70-80% MM and 20-30%MB, in brain it is predominantly BB. In mitochondria there are two specific forms of mitochondrial CK (Mt-CK): a non sarcomeric type ubiquitous Mt-CK expressed in various tissues such as brain, smoothmuscle, and sperm, and a sarcomericMt-CK expressed in cardiac

and skeletal muscle, these two localize to the intermembrane space of mitochondria(Jacobs *et al.*, 1964; Sturk, 1990).

The expression of tissue specific and temporal creatine kinase is regulated bymyocyte specific enhancer binding factor 2(Buskin and Hauschka SD, 1989; Hobson *et al.*, 1990) myogenic differentiation factor D (Lassar*et al.*, 1989), specificity protein 1 (Shen *et al.*, 2002) and hypoxia inducible factor (Glover *et al*., 2013). Evidence from some in vitro studieshas shown that the cytosolic and mitochondrialCreatine kinase expression is modulated by estrogens receptor mediated gene activation (Wu *et al*., 1992; Payne *et al*., 1993;Sukovich*et al*., 1994).

Creatine kinasecompartment specific and are found in mitochondrias Mt-CK (Fig), uMt-CK, and cytosol MM-CK, BB-CK, MB-CK. They are either associated with ATP delivering processes, oxidative phosphorylation or glycolysis and ATPconsuming processes ATPases, to maintain local ADP and ATP ratio. They occur in soluble form to maintain global cytosolic ADP/ATP. A large cytosolic phosphocreatine pool of up to 30 mM is built up by CK from creatine, using ATP from oxidative phosphorylation in heart or glycolysis in fast twitch glycolytic muscle. The large phosphocreatine pool is used as a temporal energy buffer to maintain constant global and local ATP/ ADP ratio over a wide range of workload. The greater diffusibility of phosphocreatine, as compared to ATP, along with localized CK isoenzymesis used for energy buffering that is for an energy shuttle between ATP providing or consuming processes. This looks more effective for polarized cells and has very high or localized ATP consumption (V.A. 1978;Bessman*et al*., 1981;Wallimann, 1996;Ovadi*et al*., 2000;Schlattner*et al*., 2004).

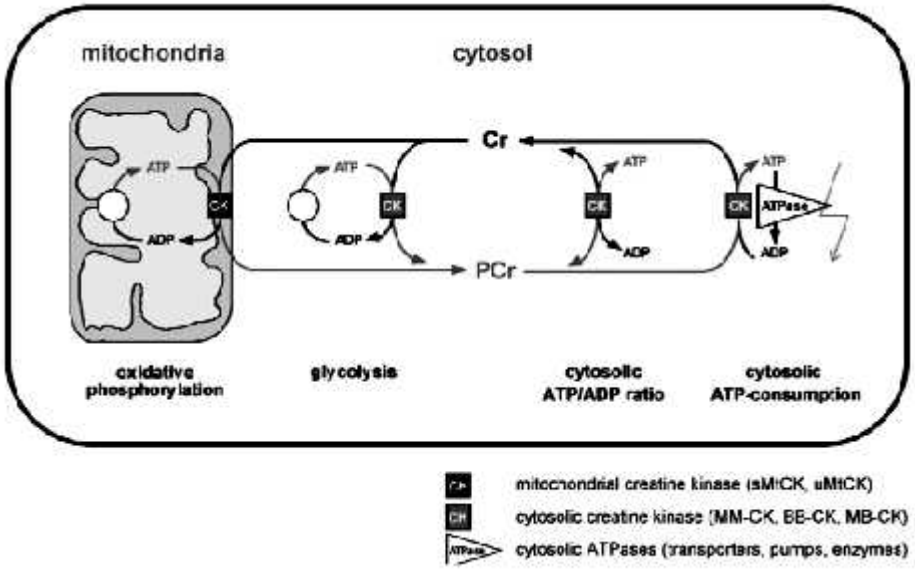

Figure 1: Compartment specific cytosolic and mitochondrial CK activity

CLINICAL IMPLICATIONS OF CK ND ITS ISOENZYMES

CK activity is shown to bea potential biomarker of cardiac muscle injury (Dreyfus, 1960). CK appears in blood 3 to 9 hours after an acute myocardial infarction, reaches the extreme value in blood in 10 to 20 hours and returns to normal in approximately 72 hours (Penttilä*et al.*, 2000). The sensitivity of this biomarker is very high when blood is drawn early after the onset of disease. Sorensen,(1963)reported a sensitivity of 98% when blood was drawn within 72 hours after the onset of acute myocardial infarction. It was demonstrated that patients with high CK activity amount in the third day had a worse prognosis. Total CK activity may be related to the extent of myocardial infarction and diagnosis (Shell *et al.*, 1971; Sobel *et al*., 1972). This

biomarker is characterized by low specificity, as its activity increases considerably in liver, biliary tract, kidneys and skeletal muscles diseases.

CK-MB

CK-MB originates from the variety ofcombination of the M (muscle) and B (brain) isoforms. CK-MB is normally undetectable or very low in the blood, increases in heart and skeletal muscle diseases by showing highest concentration in cardiac muscle i.e., approximately 22% of the total CK content of myocardium compared to approximately 1-3% in the skeletal muscle (Panteghini, 1995). Several studies confirmed CK-MB sub forms providinganunswerving and precise diagnosis with high accuracy in the first hours of onset of cardiac symptoms (Puleo *et al*., 1990; Wu *et al*., 1992; Zimmerman *et al*., 1999). Roe *et al*. (1972)developed a zone electrophoresis technique to identify and enumerateserum or plasma for CK-MB isoenzyme. Using anion exchange column chromatography, this biomarker was measured successfully(Mercer, 1974). Roberts *et al*. (1976)developed a radioimmunoassay for CK isoenzymes. The assays to measure the enzymatic activity of CK-MB represented important advances particularly in terms of improved specificity (Bruns, 1983).

The introduction of immunologic determination of CK-MB mass was an important improvement, which nearly replaced the conventional enzymatic assay. The first immunoassay for CK-MB mass was developed by Chan,(1985) and found to be more sensitive than the measurement of enzymatic activity. This antibody was successively paired with an antibody to the CK-MB B subunit. Now this two step mass immunoassay is used by all automated immunoassay instrumentation. CK-MB mass enumeration has the advantage to be more stable than the enzyme activity after storage and appears to be more sensitive by increasing in plasma and serum more rapidly than CK or CK-MB (Murthy *et al.,* 1986;Bakker *et al*., 1993). It isnot satisfactorily rapid when compared to myoglobin in the early diagnosis of acute myocardial infarction, mostly in the first 6 hours after the onset of symptoms. As for the enzymatic activity, the mass value of CK-MB also increases in many conditions other than acute myocardial injury. Serum CK-MB mass measurement/total CK activity ratio was proposed to identify false positive elevations of CK-MB arising from skeletal muscle (El *et al*., 1986; Pierce and Jaffe, 1986). Ratios between 3 and 5 represented a gray zone. Rapid enzyme immunoassays for direct mass measurement of CK-MB mass as µg/L were developed. It issuggested that these immunoassays were less susceptible to analytical interference and that measurement of CK-MB mass concentration was better suited for infarct sizing than measurement of catalytic activity (Brandt *et al*., 1990; Jorgensen *et al*., 1990; Delanghe*et al*., 1990).

MACRO CK

Macro CK is one of the most common macroenzymes, with a higher molecular mass than the corresponding enzymes that are normally found in serum (Miffin*et al.,* 1985; Sturk and Sanders, 1990; Galasso *et al*., 1993). Itis found in two forms; Macro CK type 1 is an enzyme antibody complex with a molecular weight greater than 200 kDa, and is formed by 1 of the CK isoenzymes most often CK-BB and immunoglobulin most often IgG with a kappa light chainrarely IgA and very often IgM (Laureys*et al*., 1991) Macro CK type 2 is notbound to immunoglobulin,formed by a separate gene (Whelan, 1983). Macro CK type 2 is a polymer of mitochondrial CK with a molecular mass greater than 300 kDa (Stein *et al*., 1985;Mercer andTalamo, 1985).Both macro CK types 1 and 2 are well recognized to cause false elevation of CK-MB which leads to diagnostic uncertainty and unnecessary investigation for myocardial injury. The detection of macro CK requires additional biochemical tests that are needed to establish the appropriate diagnosis. Liu and his colleagues,(2010) presented a case report of 2 patients with macro CK type 1 and the other with macro CK type 2 to stress the general clinical situations and diagnostic impasse that clinicians encountered when evaluating patients with macro CK. The conditions related to macro CKand the phenomenon of high CK-MB activity

out of proportion to total CK were discussed. They also showed thatmacro CK type 2 is detected in up to 3.7% of hospitalized patients. The presence of macro CK type 2 can be a cautionof occult malignancies, a reduced prognostic symbol in patients with a malignancy or anindication of the severity of an underlying illness (Remaley*et al*., 1989; Galasso *et al.*, 1993; Lee *et al.*, 1994;Grobble*et al*., 1995). In their findings macro CK could occur in healthy individuals or a marker of certain diseases like autoimmune diseases, cancer, severe liver disease, and serious illness. It is important to identify macro CK in patients with symptoms mimicking ACS to avoid needless specialist consultations and invasive procedures. In spite ofthe worth of troponin assays, confirmation is mandatory to replace CK and CK isoenzymes by troponins in AMI and ACS diagnosis. It is important for clinicians to understand the biochemistry and clinical significance of macro CK in the context of modern laboratory medicine.

MITOCHONDRIAL CK

Mitochondria are not only the powerhouse of the cell, butalso an important regulatory system like Ca^{2+} management and apoptosis (Scheffler, 2001;Newmeyer, 2003). The basic function is the organization of mitochondrial membranes and sub compartments, the distribution of proteins as well as transport and diffusion pathways across the membranes and compartments of mitochondria. Specific functions are based on large proteolipid complexes, and Mt-CK seems participant in a specific type of multifunctional complex.Mt-CK is localized in the peripheral intermembrane space and the cristae space, observed with immunogold electron microscopy. Mt-CK links into octamers that bind to mitochondrial membranes and form proteolipid complexes with VDAC and ANT in contact site complexes or with ANT only in cristae complexes. Interaction of Mt-CK with ANT is indirect and involves common cardiolipin patches. The interaction with VDAC is direct and regulated by Ca^{2+} (Schlattner, 2001). The membrane bound Mt-CK is favored by the large membrane surface and the high affinity of octameric Mt-CK to cardiolipin and VDAC (Schlattner andWallimann, 2000;Schlattner, 2001). The proteolipid complexes cause direct exchange of Mt-CK substrates and products. In contact site complexes, the substrate channelling allows a constant supply of substrates and removal of products at the Mt-CK active site. There is an ATP/ADP exchange in cristae complexthat is facilitated through direct channelling to the active site of Mt-CK, while creatine and phosphocreatine diffuse along the cristae space to reach VDAC (Scheffler, 2001). In compromised cellular energy state, which are often linked to ischemia, oxidative stress and calcium overload, twocharacteristics of mitochondrial creatine kinase are particularly relevant: its exquisite susceptibility to oxidative modifications and the compensatory up regulation of its gene expression, in some cases leading to accumulation of crystalline Mt-CK inclusion bodies in mitochondria that are the clinical hallmarks for mitochondrial cytopathies. Both of the events may impair or reinforce the functions of mitochondrial Mt-CK complexes in cellular energy supply and protection of mitochondria form the so called permeability transition leading to apoptosis or necrosis.

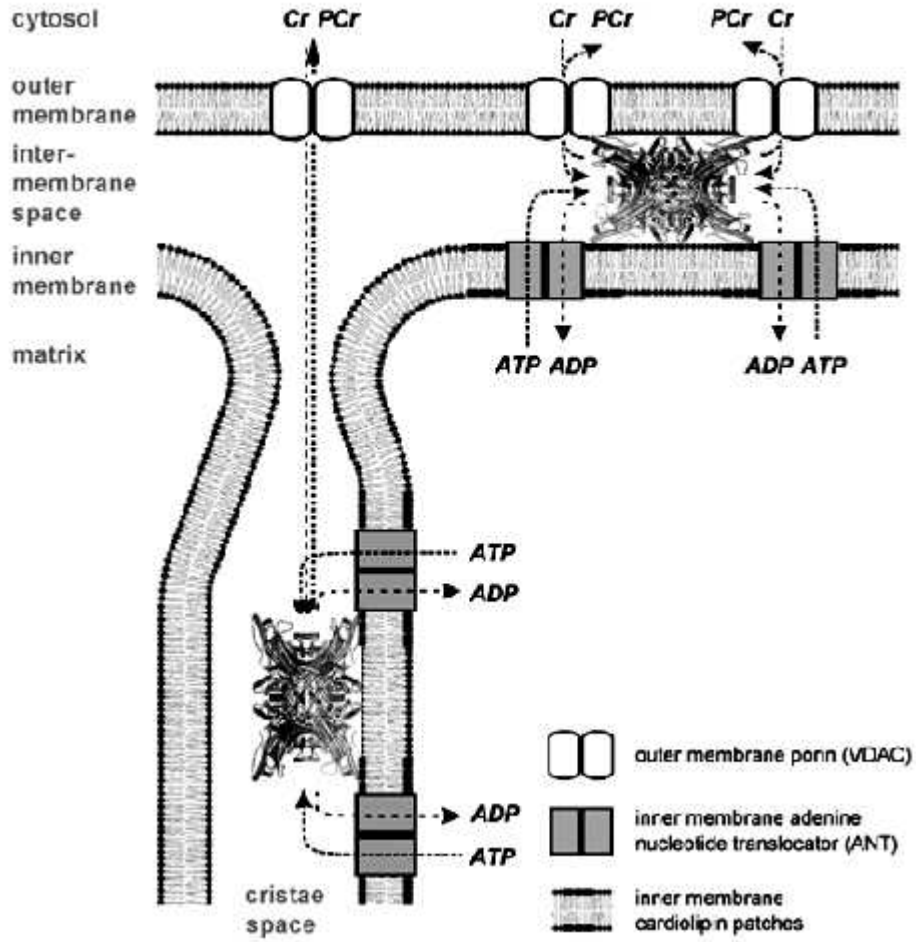

Figure 2: Compartment specific activity of mitochondrial CK

EXERCISE RELATED CK

Mechanical muscle damage of varying degree is due to unusual exercise, mainly eccentric muscle contractions (Brown *et al*., 1999). Metabolic muscle disturbance is due to release of cellular components through a cascade of events which begin with exhaustion of ATP which results in the escape of extracellular calcium ions into intracellular space due to both Na-K ATPase and Ca^{2+}-ATPase pump dysfunction. Intracellular proteinases activity enhances and muscle protein degradation and increase cell permeability which allows some cell contents to leak into the circulation (Huerta, 2005; Khan, 2009). The process of mechanical and metabolic commenced muscle disturbance is not completely understood; it is thought to consist of a complex range of pathways which involve increased oxidative stress, inflammatory and immune responses. In most cases, isolated mild to moderate damage in healthy individuals does not appear to cause further problems and many studies have demonstrated that the body is capable of clearing released muscle components back to baseline levels within 7–9 days (Totsuka, 2002; Sayers, 2003; Saks, 2008) (Figures a–c).

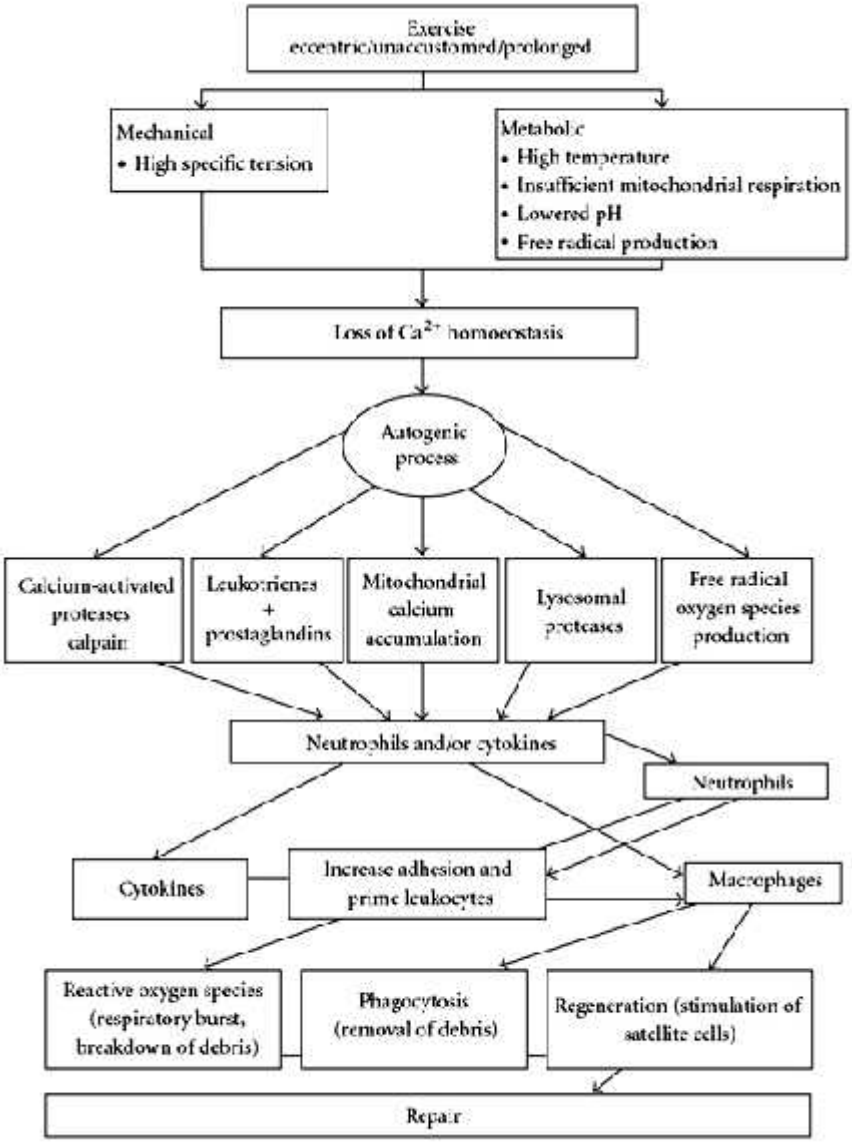

Figure 3: Theoretical model of muscle damage and repair cycle reproduced from Kendall and Eston

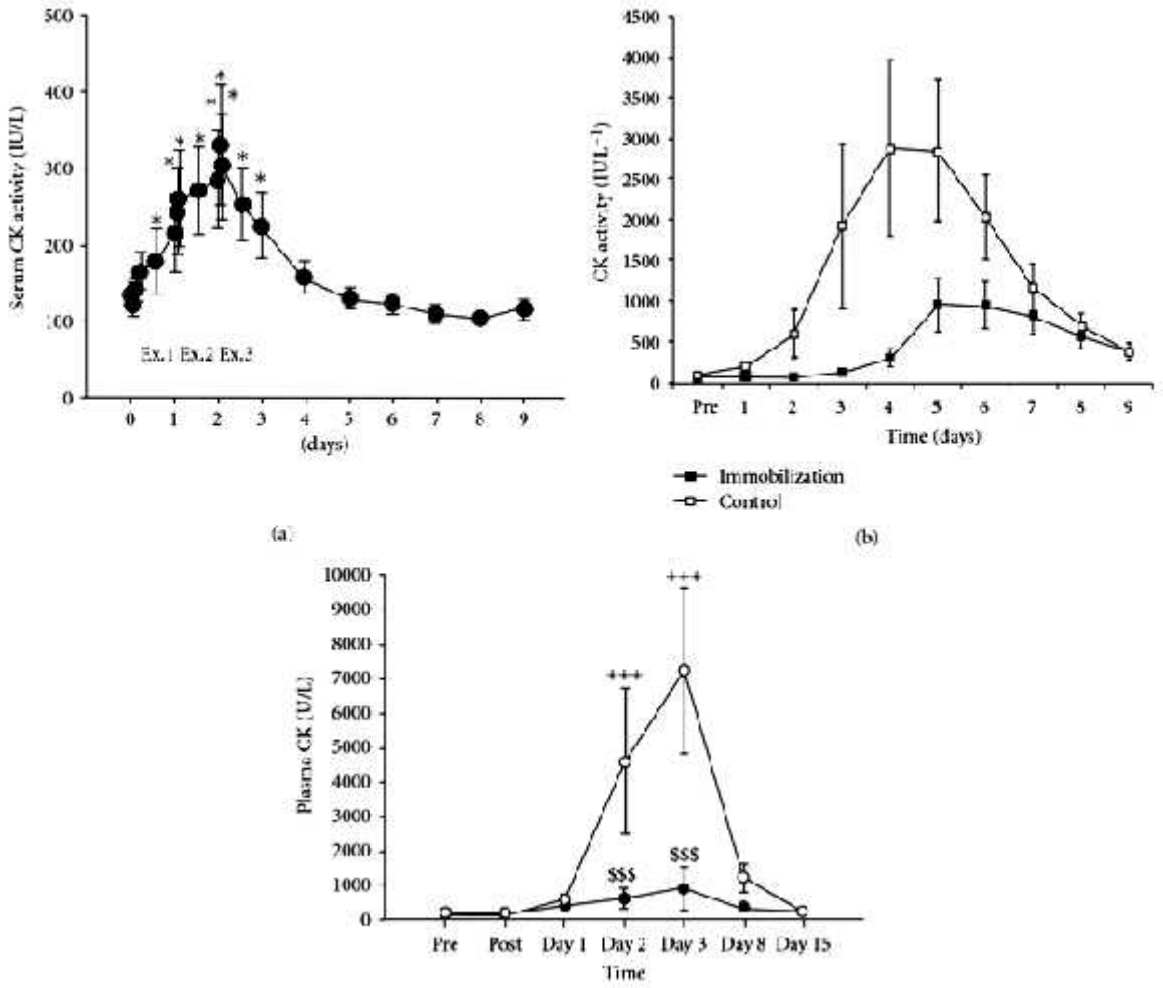

Figure 4: Graphical representation of elevated and baseline CK levels

(a) Changes in serum CK activity during 90-minute cycling exercise on three consecutive days.

(b) CK response to eccentric exercise between immobilisation and control group. PRE refers to the baseline period before exercise. Days 1-4 represent the 4-day immobilization and days 5-9 are the recovery period.

(c) CK activity in women and in men before, immediately after, and 15 days after step exercise +++

Significant difference from preexercise level (P <0.001).Significant difference between men and women (P <0.001).

Some individual's studies have been classified as high responders in light of the much higher rise in CK after resistance exercise as compared to an average or normal response. There is no consensus about a clinical definition of CK activity to found an individual as being high responder. The difference between high responders (HR) and normal responders (NR) has been defined by individual experiments. Heled *et al.*(2007) categorized high responders to those whodisplayed a post exercise change in CK≥ the 90th percentile of their cohort. Clarkson *et al.*(1992) classified three groups, low responders (LR), medium responders (MR) and high responders (HR), based on the degree of increase in CK. The LR where those having a peak CK of less than 500 U.l(1), the MR 500-2,000 U.l(1), and the HR were those having a peak CK response of >2,000 U.l(1). Chen, 2006in his study created another group of 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.* (2007) used a low intensity, high volume exercise stimulus, while Cleak andEston,(1992) and Chen,(2006) used a dynamic eccentric exercise protocol. It is possible that the exercise protocol used by Heled *et al.*(2007) would not have induced muscle damage to the extent of those experiments using eccentric actions, allowing the classification of subjects into only two groups (Table 1).

Table 1: sample classification and criteria for recognizing CK response to resistance exercise

Work	Classification (U.L^{-1})					Decision Criteria for Classification	Exercise Protocol
	Low response	Medium response	Normal response	High response	Higher response		
Clarkson et al 1992	<500	500-2000	No	<2000	No	Discretionary	
Chen 2006	<300	500-2000	No	2000-10000	>10000	Discretionary	30 eccentric contractions with the elbow flexors of nondominant arm.
Heled et al 2007	No	No	<230	≥230	No	ΔCK≥90th percentile	stepping up and down two stairs (30-cm height each) for 5 min at a pace of 54 steps/min followed by 15 knee bends completed within 1 min (3-s count down and 2-s count up were done to increase the eccentric contraction time) A backpack weighted at 30% of their body weight was worn during both tests.
Totsuka et al 2002	<300	No	No	>500	No	Discretionary	90 min of bicycling at a set absolute workload (1.5 kp, at 60 rpm) on 3 consecutive days
Machado & Willardson, 2010	No	No	<556.2^1 and <442.3^2	≥556.2^1 and ≥442.3^2	No	ΔCK≥90th percentile	Three sets with 10RM loads were completed for the chest press, cable pulldown, biceps curl, triceps extension, leg extension, and prone leg curl
Do Carmo et al 2011	No	No	<475.1	≥475.1	No	CKpeak ≥90th percentile	4 sets of biceps curl at 85% of 1-RM with 1 minute rest interval length between sets. The subjects were instructed to extend the elbows from an elbow flexed (50°) to an extended position (170°) and return to the flexed position in 3 s (~1 s to concentric and ~2 s to eccentric phase).

^{1}CKpeak1; ^{2}CKpeak3, referring to resistance exercise with 1 min and 3 min rest intervals, respectively.

Other individual factors influence CK response are body composition and sex, amount of work performed, nutritional status, aging and muscle type. Scientistshave studied most of these factors in relation to exercise to show their effect on creatine kinase.

There are several factors that are associated with the elevated CK. These include high responders and genotype, body composition and sex, amount of work performed.

EXERCISE FACTORS ASSOCIATED WITH CK

Mechanical and metabolic stress muscle during exercise cause disruptions in the contractile apparatus, muscle cytoskeleton and sarcolemma associated proteins. Elevated O_2 consumption during exercise leads to increased activity in the electron transport chainand xanthine oxidase in capillary endothelial cells, so there is an increased production of free radicals and consequent damage to cell membranes. Further, muscle may experience an ischemia or reperfusion like state in the transition from exercise to recoverywhich would then 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 sarcoplasmicreticulum.

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 (Koch *et al.,* 2014).

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. A greater volume load lifted in a given exercise session would produce more trauma to the muscles, and thus a higher serum CK activity.

Nosaka and Clarkson,(1992) in his study illustrated the relation between work and elevated serum CK. Serum CK was similar within the groups exercising with their two arms and those with their elbows only. 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.

CONCLUSION

Creatine kinase is a central controller of cellular energy homeostasis.Individual differences and exercise variables highly contribute to the extent of CK accumulation.For individual factors, several polymorphisms ingenotype 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 tendto produce the greatest increase in CK. This type of protocol would affect clinical outcomes, such as an increased risk exertional rhabdomyolysis is questionable, as there is at present no established link between an exaggerated CK response and exertion rhabdomyolysis. Studies have found serum CK activity after exercise to poorly related to functional measures of muscle soreness, strength, range of motion. Post exercise losses in strength are not coupled to the rise in CK. Given the poor relation to functional outcomes, and the question of how to interpret CK 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 ofmuscle damage.

Many questionsremain unanswered, mainly concerning the optima cut-offsand timing of serial sampling.So further studies may be possible in this regard and in genetics; sequencing of the genes of CK and its isoform related genes to find the mutations, familial disorders, phenotype genotype correlations. Researchers have experimented about diagnosis of CK related disease but there is a need of monitoring of CK, therapeutic and prognostic studies also.

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