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Should Creatine Kinase be tested at baseline in athletes?

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Abstract

Creatine kinase (CK) level depends on muscle mass, age, race, physical activity and various pathologies involving the muscles or the heart. Resistance training elicits the greatest release of CK, and is the best way to attain muscle hypertrophy. The highest post-exercise serum enzyme level is found after prolonged exercise such as ultradistance marathon running or weight-bearing exercises and downhill running, which produce eccentric muscular contractions. Persistently elevated CK levels in apparently healthy subjects may indicate a late-onset underlying condition. The decrease in the serum enzyme level depends on the period of rest after exercise, as short-term physical inactivity may reduce the lymphatic transport of CK and the release of the enzyme from the muscle fibres. We discuss the source and level of CK in various situations, the different CK isoenzymes and also when to test for an underlying myopathy or other pathologies which may impact the long-term athletic performance. It is likely safe for athletes with suspected myopathy to continue physical activity at a lower intensity to prevent muscle damage, and allow appropriate rest to favour recovery. Thyroid dysfunctions and drug-induced myopathies should be ruled out. History and clinical examination could help clarify whether other muscle-directed investigations are required.

Keywords: creatine kinase, athlete, physical training, rhabdomyolysis, myopathy, statins

Creatine kinase - biological functions

Creatine kinase (CK) is a crucial enzyme in the metabolism of creatine, catalyzing the formation of creatine phosphate and ADP from creatine and ATP (Fig. 1).

Creatine (Cr), or N-aminoiminomethyl-N-methylglycine, is mainly but not exclusively synthesized in the pancreas and in the kidney, which have high AGAT (L-arginine:glycine amidinotransferase) activity, as well as in the cells of the liver, where high concentrations of GAMT (S-adenosyl-L-methionine: *N*-guanidinoacetate methyltransferase) can be found. From the organs of synthesis, creatine is transported via the bloodstream to the tissues which use creatine (mainly the brain and muscles), where both the endogenously synthesized creatine and the creatine derived from dietary sources is taken up by a creatine transporter (CRTR, or SLC6A8), a sodium dependent system enhanced by insulin (Stockler-Ipsiroglu et al., 2016; Lange at al., 2020).

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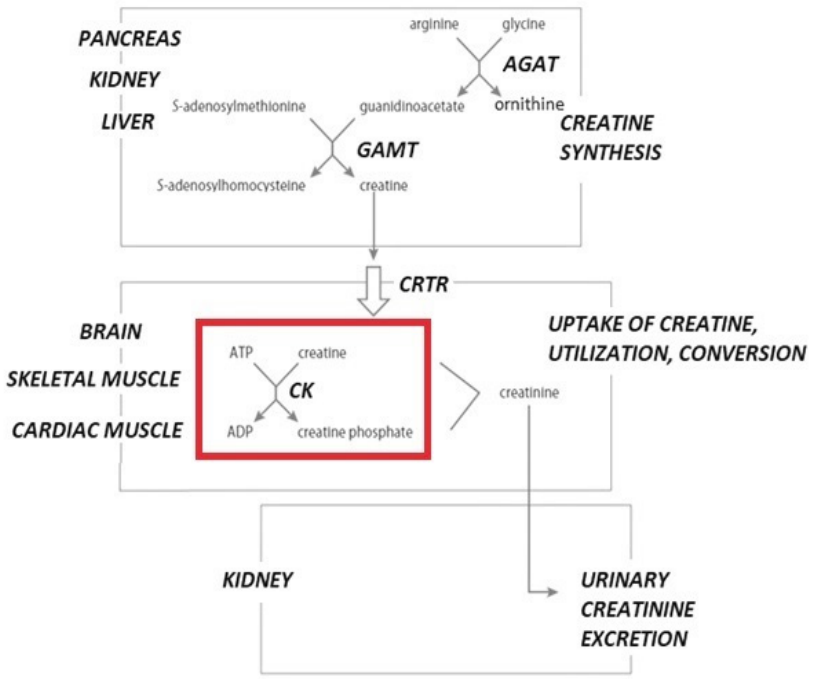

Fig. 1 – Metabolic pathway of creatine/creatine phosphate involving CK (image adapted after Stockler-Ipsiroglu et al., 2016). Legend: AGAT, L-arginine: glycine amidinotransferase; GAMT, *N*-guanidinoacetate methyltransferase; CRTR, creatine transporter; ATP, adenosine triphosphate; ADP, adenosine diphosphate; CK, creatine kinase

CK is a compact enzyme found both in the cytosol and in the mitochondria of tissues, where energy demands are high. In the cytosol, CK is composed of two polypeptide subunits, which can be of two types: M (muscle type) and B (brain type). These subunits allow the formation of three tissue-specific isoenzymes: CK-MB (cardiac muscle), CK-MM (skeletal muscle) and CK-BB (brain) (Schlattner et al., 2006).

CK is also found in macroenzymes. Macro-CK type 1 is a complex of CK (most often CK-BB) and immunoglobulin (most often IgG) and is typically greater than 200 kDa in size. Macro-CK type 2 is a polymer of Mt-CK (mitochondrial creatine kinase – an isoenzyme found in the mitochondria between the inner and outer membranes, with a molecular mass greater than 300 kDa). These forms of CK are expressed during disease and/or a dysfunction. For example, macro-CK 1 is associated with cardiovascular and autoimmune disease and macro-CK 2 with cancer (Liu et al., 2010).

In normal serum, total CK is represented almost entirely by CK-MM of muscular origin. Total CK levels depend on age, gender, race, muscle mass, physical activity, climatic condition and various pathologies involving the muscles or the heart (Stomme et al., 2004). CK values vary greatly among individuals. At rest, CK values are much lower in females than in males. The sex-linked differences are also present after exercise; estrogen is likely involved in maintaining post-exercise membrane stability, thus limiting CK leakage from the damaged muscle cells (Stomme et al., 2004; Enns & Tiidus, 2010).

During prolonged intense training, the damage of muscle tissue leads to an increase in the level of serum CK. This may be a consequence of both metabolic and mechanical factors (Amelink et al 1988; Fu et al 2002). The impact of physical training may vary on CK values between athletes. The type of exercise also influences CK values. The highest values are seen after prolonged exercise such as ultramarathon, weight-bearing exercise and downhill running (Brancaccio et al., 2007). An explanation could reside in the decrease of the membrane resistance of a metabolically exhausted fiber after an increase in Ca^{2+} ions leading to K channel activation (Brancaccio et al., 2007; Fink & Luttgau, 1976).

Persistently elevated CK levels in apparently healthy subjects may indicate an underlying condition with late onset. In some athletes with asymptomatically high CK values, the type of training, muscle size and the predominantly involved muscle fiber type should be assessed (Brancaccio et al., 2007; Munjal et al., 1983).

Creatine kinase and muscle activity

Creatine kinase (CK) level depends on the muscle mass, age (Table I), race, physical activity, and various pathologies involving the muscles or the heart. CK values vary greatly among individuals.

Serum CK activity and the profile of the isoenzyme are important indicators of the occurrence of muscle cell necrosis and tissue damage due to disease or trauma.

While the level of CK is important, there is no consensus regarding the upper limit of the reference range. Regular preventative exercise with relatively constant muscle stress is often not associated with CK increases (Kindermann, 2016). Nevertheless, CK should be assessed after one week free of exercise, which is difficult to impose to elite

athletes (Kindermann, 2016). CK should be assessed along with the liver enzymes, and a parallel increase of the TGO transaminase (of muscle origin) could be orientating as well, mostly when the CK level exceeds 3-4 times the upper limit of the reference range (Kindermann, 2016).

Table I
Reference values for CK at different ages (Department of Clinical Biology and Anatomopathology, Academic Hospital - Vrije University Brussel, 2001).

Age	Male (IU/L, 37˚C)	Female (IU/L, 37˚C)
0-3 days	up to 3-4 times the adult values	
< 1 year	up to 2 times the adult values	
1-3 years	60-305	
4-6 years	75-230	
7-9 years	60-365	
10-11 years	55-215	80-230
12-13 years	60-330	50-295
14-15 years	60-335	50-240
16-19 years	55-370	45-230
> 19 years	< 145	< 130

Moderate-intensity exercise, mainly of long duration, may increase CK levels to meet the criteria for rhabdomyolysis; eccentric muscle contractions, such as weight lifting or downhill running, could also lead to rhabdomyolysis (Latham et al., 2008). The potential complications are disquieting for the treating physician. Nevertheless, the clinical significance is unclear, as neither renal complications of rhabdomyolysis, nor correlations between the CK level and renal dysfunction have been observed (Latham et al., 2008). The patient should be instructed to report symptoms such as myalgia, weakness or dark urine, and CK should be further monitored.

Resistance training elicits the greatest release of CK, but it is also the best way to attain muscle hypertrophy. Thus, the enzyme is normally confined to the muscle cell - so the question arises: is the reason for the elevated CK levels after exercise the muscle damage and loss of muscle cell integrity, or is there some other molecular explanation reflecting a temporal disturbance of muscle processes? (Brancaccio et al., 2007).

Some individuals might have high levels of serum CK compared to other similar individuals when following the same exercise protocol (including moderate exercise), even when main comparability factors such as gender, age, and training status are accounted for in data analysis. In certain cases, this variability may indicate underlying myositis, but in many others the cause is unknown. There appears to be no established link between habitual exercise or acute high-intensity eccentric exercise and the high incidence of kidney dysfunction or muscle disorder in normal healthy individuals, even in the presence of CK levels >20000 IU/L. The contribution of additional factors such as genetic disposition, environmental conditions, or disease may increase the risk of exertional rhabdomyolysis, resulting in acute renal failure. Individuals who regularly participate in high-volume, intense exercise tend to have significantly raised baseline levels of CK compared to sedentary and moderately active individuals. Raised levels of serum CK were also found in regularly exercising pre-menopausal women compared to similar sedentary individuals; this suggests that CK flux into the serum is a natural and normal reaction to regular exercise (Clarkson et al., 2006).

Myofibrillar CK-MM is bound to the M-line of the sarcoplasmic reticulum of myofibrils and is also found in the I-band sarcomeres providing support for muscle energy requirements. Animal studies on mice lacking the isoenzyme CK-MM have shown that the mice are viable, but have impaired muscle function upon challenge, proving that CK-MM at the M-band is required for optimal contractile response and physiological performance (Lange et al., 2020).

Apart from the myomesin family members, which are the major structural linkers in the M-band, several other proteins (titin, obscurin and others) were found in this region of the sarcomere (Fig. 2). CK-MM (the muscle isoform of creatine kinase) was shown to bind to the central domains of both myomesin and M-proteins and is very likely the cause for the electron dense signal that is picked up in electron micrographs as M-lines (González-Morales et al., 2017; Lange et al., 2020).

Factors such as extreme temperatures, alcohol abuse, or sporadic strenuous exercise (such as ultramarathons) can result in more severe disturbance and may require medical intervention to prevent permanent renal damage, primarily due to the nephrotoxic effects of myoglobin (Khan, 2009). The highest post-exercise serum enzyme activity is found after prolonged exercise such as ultradistance marathon running or weight-bearing exercises and downhill running, which produce eccentric muscular contractions. There is a breakpoint at 300-500 IU/L of CK serum release after exercise, and the level of the enzyme is associated with distinctive individual muscular properties. Daily training may result in persistent serum elevation of CK, and resting CK levels are higher in athletes, but the significant post-exercise increases of CK are usually lower in trained subjects when compared with untrained subjects. In fact, if athletes and sedentary subjects undertake the same physical exercise test, the CK levels of athletes are lower than those recorded in matched healthy control subjects (Karamizrak et al., 1994).

Total serum CK activity is markedly elevated for 24 h after a prolonged exercise bout, and remains markedly elevated for 48 h when subjects train in the first week post-exercise. The release of CK following eccentric exercise peaks 96 h after the exercise bout, and an additional exercise session produces only small increases of serum CK, probably from accelerated enzymatic clearance. More intense activity, such as two football training sessions a day, leads to a significant increase of CK during the fourth day of training. CK levels decrease between days 4 and 10, which could be an adaptation to training. A bout of exercise performed 48 h after an initial bout does not change the time course of the CK leakage (Smith et al., 1994).

The decrease in the serum enzyme level depends on the period of rest after exercise, as short-term physical inactivity may reduce both the lymphatic transport of CK and the release of the enzyme from the muscle fibres. Manual lymph drainage after treadmill exercise is associated with a faster decrease in the serum levels of

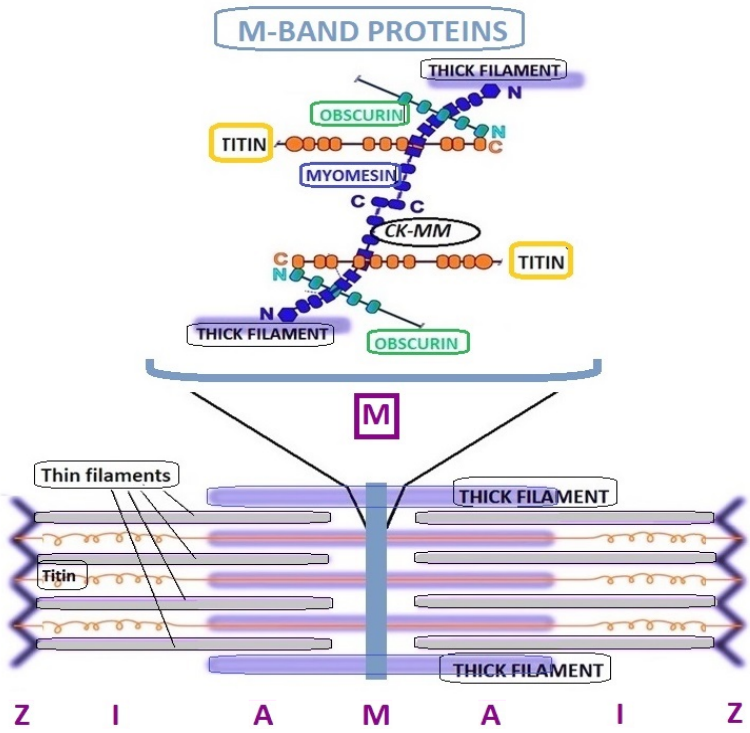

Fig. 2 – The sarcomere - the basic unit of a myofibril - with the M-band at the centre (image adapted after Lange et al., 2020). Legend: Z, Z-discs; I, I-band linking systems; A, A-bands; M, M-bands.

muscle enzymes. Another factor that may reduce muscle damage and serum concentrations of CK following prolonged exercise is supplementation with branched-chain amino acids, often used in sports (Schillinger et al., 2006; Coombes & McNaughton, 2000).

Persistently increased serum CK levels are occasionally encountered in healthy individuals. CK values are also markedly increased in the pre-clinical stages of muscle diseases. In some studies on subjects with high levels of CK at rest, muscle weakness developed after several years, suggesting that early myopathy may be asymptomatic. Nevertheless, other studies on patients with elevated resting serum CK values demonstrated that in most cases, hyperCKemia probably does not imply disease. Frequently, the diagnosis is not formulated following routine examination with the patients at rest, as symptoms become manifest only after exercise (Smith et al., 1994).

In athletes, the study of CK at rest and after exercise could be an important tool for coaches and clinicians. Athletes have higher resting CK values when compared with untrained subjects, probably because of the greater muscle mass and the daily training performed. However, after exercise, CK serum activity depends on the level of training: although athletes experience greater muscle soreness when compared with untrained subjects, their peak serum activity is lower. Furthermore, the most marked increase in CK occurs in the less trained subjects.

High serum CK levels in athletes following absolute rest and without any further predisposing factors should prompt a full diagnostic workup with special regards to signs of muscle weakness or other simple signs that, in both athletes and sedentary subjects, are not always promptly evident. These include cranial asymmetry and asymmetric position of the inferior angle of the scapulae and the iliac spines. Mutation in sarcomeric proteins is the prime cause of a major class of genetic diseases that affect cardiac function, such as familial hypertrophic cardiomyopathy, or lead to a variety of other myopathies including limb-girdle muscular dystrophy type 2G (telethonin), limb-girdle muscular dystrophy type 1A (myotilin), nemaline myopathy (actin, tropomyosin and nebulin), desmin-related myopathy (desmin), and other myopathies (plectin). In these subjects, repeated intense prolonged exercise does not induce the physiological muscle adaptations to physical training, given the continuous loss of muscle proteins (Laing 1999; Morimoto 2008). Muscle mass growth occurs by hypertrophy via growth hormone and testosterone. While hypertrophy is readily reversible, loss of muscle cells as a result of damage would be progressively more serious (Brown et al., 1999).

Statins are impact factors that may be associated with increased CK levels in amateur athletes who may take these cholesterol lowering drugs as part of a healthier lifestyle (Laufs et al., 2015). About 5% of statin users have muscle symptoms of different severity, from muscle pain and isolated increased CK to rhabdomyolysis (Laufs et al., 2015; Mancini et al, 2016). There are several types of grading the statin-induced muscle symptoms and a simple CK elevation should be weighed against the long-term benefit on survival, i.e. prevention of cardiovascular events (Rosenson, 2014). The patients with a four-time CK increase should discontinue the administered statins (Stroes et al., 2015). In patients with mild, incidentally found CK increments, both thyroid function and the

exercise level should be checked, and a long-term follow-up is required (Stroes et al., 2015). Amongst the common medications, several can be associated with myopathy (for instance oral antifungals for athlete's foot such as itraconazole, miconazole; beta-blockers and others). In healthy individuals, other factors which may increase CK - such as the use of recreational drugs (cocaine, etc.), chronic alcohol consumption or binge drinking - should also be taken into account.

Discussions

The molecular mechanisms that result in CK release from muscle after mild exercise are unclear. More clarification could provide important information for athletes concerned about muscle hypertrophy, performance, and the importance of periods of rest between exercise sessions. Future studies should include an exploration of ethnic variations in CK levels in response to exercise. In the absence of any mechanical muscle damage, a question remains - whether raised CK after exercise does represent a degree of actual muscle damage or some form of disruption in energy control processes, or some other molecular reaction mechanism should be subject to further studies.

Conclusions

1. It is likely safe to advise athletes with suspected myopathy to continue to undertake physical activity at a lower intensity, so as to prevent muscle damage from high intensity exercise and allow appropriate rest to favour adequate recovery.

2. The patient's history and the clinical examination should help to clarify whether more invasive investigations, including muscle biopsies, should be performed.

Conflict of interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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