

Macro Creatine Kinase (macro CK) in Clinical Practice

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Creatine kinase (CK) is an important enzyme involved in energy metabolism. CK is found in the cytosol and mitochondria of various tissues, mainly those with increased energy necessities as skeletal muscle, cardiac muscle and brain, but also in visceral tissues. CK is a dimeric molecule composed of two identical or different subunits, type M - muscular and type B - brain. The combination of M and B subunits leads to formation of three isozymes: CK - MM found mainly in the skeletal muscle, CK - BB found mainly in the brain and CK - MB found mainly in the cardiac muscle, but also in small quantities in the skeletal muscle. The serum increase of different isozymes of CK is a consequence of cell disruption in various clinical situations like physical training, rhabdomyolysis, myositis, muscular dystrophy, myocardial infarction and others, CK being an important biomarker for this diseases. Macro CK is a complex of CK and immunoglobulin (macro CK type 1) or a polymer of mitochondrial CK (macro CK type 2) that induces false and persistent elevation of CK levels that could mislead the clinician. We present a review of the literature concerning the appearance and clinical significance of macro CK.

Keywords: creatine kinase, pathologies, outcome

Creatine kinase (CK) is an important enzyme involved in energy metabolism by generation and transportation of high - energy phosphates [1-3]. CK catalyzes the reversible transformation of ATP + creatine in ADP and phosphocreatine [1,3]. CK is a dimeric globular protein of 43 kDa who expresses different isozymes that could be classified according to the combination of component subunits or according intracellular expression [1-4]. CK has two possible subunits: type M - muscular and type B - brain and the combination of two identical or different subunits leads to three isozymes of CK: CK - MM found mainly in the skeletal muscle, CK - BB found mainly in the brain and in other visceral tissues, CK - MB found mainly in the cardiac muscle and in small quantities in the skeletal muscle [1-4]. According to the intracellular expression there are five isozymes of CK: three cytosolic - the muscular isoforms expressed in the skeletal (CK - MM) and cardiac muscle (CK - MB) and the ubiquitous brain isoform expressed in the brain and in non-muscular tissue (CK- BB) - and two mitochondrial - the muscle specific (sarcomeric) and the ubiquitous form (non-sarcomeric) [2-4].

The normal serum levels of CK have considerable variations influenced by age, gender, race and physical activity [1,3,5]. According to race, adult black males have higher levels of CK, according to gender males have higher levels of CK compared with females and according to the level of physical activity, males and females athletes have the upper limit of CK two to six times higher than the matching non athlete population [3,5,6]. There are also differences in the upper limit of CK between athletes who practice different sports (highest in soccer players in comparison with swimmers) [3,5].

The main reason for increased serum levels of CK is a skeletal muscle lesion and it is possible to find elevation of CK after intramuscular injections and intense exercise [1,3], but usually significant increases of CK are found in major muscular or neuromuscular pathology as polymyositis,

dermatomyositis, rhabdomyolysis, muscular dystrophies, drug-induced myopathies, seizures, malignant hyperthermia, malignant neuroleptic syndrome [7-11] in association with the increase of other enzymes as lactate dehydrogenase (LDH), aldolase or muscular components as myoglobin, being very problematic for patients with impaired renal function, especially if they need to go under surgery [12-14]. High levels are often encountered in case of bone fractures which needs extensive muscle and periosteum trauma and in aggressive tumors that have invaded the muscle tissue [15-18]. CK levels are useful not only for the diagnosis but also for monitoring these conditions. It is important to emphasize that persistent increases in CK in athletes after rest, even without symptoms, could indicate a muscular disease in early preclinical phase or muscular impairment function [3,19]. Amongst drug-induced muscular reactions, statin associated muscular symptoms (SAMS) are very frequent (7-29% of all treated patients) and a major cause of statin therapy non-adherence or discontinuation (65-75%) [8]. Due to the worldwide use of statins for prevention of cardiovascular events, the number of patients affected by SAMS is very high and continues to grow as statin therapy is extending, raising important issues in then subgroup of patients having chronic renal failure [20,21] but the majority of patients will have normal or slightly elevated CK levels [10,22]. In contrast, true myopathy induced by statins, defined by an increase of CK more than 10 times the upper limit of normal is less frequent - 1 case in 1000-10000 treated patients [1,10].

In the general population it is possible to have patients with idiopathic hyper-CKemia induced by a benign autosomal dominant genetic condition [3]. This patients do not have muscular symptoms and muscle biopsy and electromyography are usually normal [3].

In the myocardium CK - MB is increased proportionally to the total CK (15-30%) in comparison to the skeletal

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muscle (5-7%) and the increase of CK -MB is a good indicator of a myocardial lesion (as acute coronary syndrome, myocarditis, cardiac surgery), but less specific and less sensitive than troponins (the current golden standard) because skeletal muscle lesion, kidney failure and other visceral conditions could induce elevated CK - MB [1,23,24]. CK - MB levels are increased in first hours after a myocardial lesion with a peak at 24 hours and they return back to normal after approximately 48 hours due to the short half - life [1,23]. A new increase of CK - MB is suggestive of a new myocardial lesion as reinfarction [1,23]. Higher levels of CK - MB in patients with acute coronary syndrome are associated with higher rate of complications and higher mortality [1,23].

CK - BB is increased in neurologic or neuromuscular conditions as stroke, amyotrophic lateral sclerosis [1,3].

CK is metabolized by proteolysis in the local tissue or in the local lymph nodes [1]. For lab testing, fasting it is not necessary, but it is better to obtain blood samples at least one hour after minor muscle lesions as intramuscular injection in order to avoid minor elevation of CK produced by this situation [1]. In order to obtain valid, reliable results, the laboratory measurement should use standardized tests and follow the established reference measurement procedures (RMPs) [25]. CK measurement is considered now satisfactorily standardized [25].

An important cause for false, persistently elevated levels of CK and/or CK - MB is the apparition of macroCK. If normal CK is a globular dimeric protein with molecular weight of 43 kDa, macroCK is an octameric protein that is a complex formed by CK - MM and CK - MB with an immunoglobulin (Ig) usually Ig G with a kappa light chain, but sometimes Ig A or Ig M - type I of macroCK (molecular weight >200 kDa) or a polymer of mitochondrial CK - type II of macroCK (molecular weight >300 kDa) [3,4,9,26-28]. The electrophoretic separation using agarose gel is useful for detecting normal CK and macroCK and immunofixation with antisera against Ig G is used for type I macroCK [3,22,26-30]. Type I of macroCK is migrating between CK - MM and CK - MB (anodal type of macroCK) and type II of macroCK is migrating cathodic to CK - MM (cathodal type of macroCK) [4,22,26-30]. Two other methods were proposed for the detection of macroCK and other macro enzymes: polyethylene glycol (PEG) precipitation and ultrafiltration [31,32]. Sometimes, patients with type I macroCK have false high levels of CK - MB, with an increase ratio of CK - MB/total CK or even CK - MB level higher than the total level of CK, that mimics a myocardial lesion as the acute coronary syndrome and testing troponins levels is recommend to clarify this type of situations with major clinical consequences [4,26-29]. There are reports about macroCK in multiple members of a family, possible by transplacental transfer of Ig G against CK from mother to the child [4,25]. The prevalence of macroCK type I was reported to range between 0.23 and 2.3% in several studies involving blood donors or randomly selected patients [27-29]. Type I of macroCK is associated with cardiovascular or inflammatory diseases as ulcerative colitis or even true inflammatory muscular conditions as myositis and sometimes malignancies [3,4,22,25-28]. The prevalence of macroCK type I seems to be higher in patients over 70 years compared with other age groups and in females compared to males [29,30]. Type II of macroCK was found with a similar prevalence of 0.4-3.7% in hospitalized patients [28,29]; this type of macroCK is associated with critically ill patients, malignant diseases that are sometimes disseminated or liver cirrhosis [4,27-32].

Usually the laboratory findings in macroCK type I are: markedly increased levels of total CK (more than 500 U/

L), CK - MB present and frequently increased, CK - BB rarely detected [4,28]. In macroCK type II, total CK is could be low (less than 100 U/L) or increased, CK - MB may be present and sometimes is increased and even higher than total CK, CK - BB is detectable in around one third of the patients [4,28,33]. MacroCK is one of the most frequent macroenzymes found in patients and healthy persons all over the world as macromaylase, macro lactate dehydrogenase (LDH), macro aspartate aminotransferase (ASAT) [4]. First reports about an abnormal CK were published between 1970 and 1980 and macroCK type I (complex of CK and Ig) was the first described and soon after that, data were published about macroCK type II of mitochondrial origin [4,37-41]. An important clinical issue is the concomitant presence in the serum of some patients of macroCK and other macroenzymes as macroamylase, macroLDH, macroASAT, situation that is misleading the clinician and make differential diagnosis more difficult [34,36,42,43]. A particular situation is found in HIV/AIDS patients where is possible to find multiple macroenzymes induced by hypergammaglobulinemia of the disease or by the antiviral treatments [3,34,35]. Macro CK type I is significantly more frequent in patients (adults and children) with ulcerative colitis compared with patients with Crohn's disease, making the detection of macroCK type I a good tool for differential diagnosis between different types of inflammatory bowel diseases [44-46].

Conclusions

MacroCK is a frequent cause of false elevated levels of CK and/or CK - MB that could mislead the clinician by raising the suspicion of acute coronary syndrome or significant lesions of skeletal muscles (myopathy, myositis, rhabdomyolysis). There are two known types of macroCK: type I that is a complex of CK and CK - MB with Ig G (usually) with molecular weight > 200 kDa, this type being associated with cardiovascular, inflammatory and sometimes malignant diseases and type II macroCK that is a polymer of mitochondrial CK, with molecular weight > 300 kDa and is associated with malignant diseases and critically ill patients. The presence of macroCK is suspected when high levels of total CK and/or CK - MB are found in patients without other clinical or laboratory abnormalities and it is demonstrated by using electrophoretic separation in agarose gel or other techniques as polyethylene glycol precipitation or ultrafiltration. Older patients and females seems to be more affected by this situation. MacroCK could be present alone or associated with other macroenzymes. The significance of macroCK presence it is not completely understood, but it is an important differential diagnosis for cardiac and muscular diseases, macroCK type 2 is associated with malignant diseases and in some clinical situations as inflammatory bowel diseases, the presence of macroCK could help the differential diagnosis of diseases from the same group.

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