Creatine kinase monitoring in sport medicine

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Areas of general agreement: Total creatine kinase (CK) levels depend on age, gender, race, muscle mass, physical activity and climatic condition. High levels of serum CK in apparently healthy subjects may be correlated with physical training status, as they depend on sarcomeric damage: strenuous exercise that damages skeletal muscle cells results in increased total serum CK. The highest post-exercise serum enzyme activities are found after prolonged exercise such as ultradistance marathon running or weight-bearing exercises and downhill running, which include eccentric muscular contractions. Total serum CK activity is markedly elevated for 24 h after the exercise bout and, when patients rest, it gradually returns to basal levels. Persistently increased serum CK levels are occasionally encountered in healthy individuals and are also markedly increased in the pre-clinical stages of muscle diseases.

Areas that are controversial: Some authors, studying subjects with high levels of CK at rest, observed that, years later, subjects developed muscle weakness and suggested that early myopathy may be asymptomatic. Others demonstrated that, in most of these patients, hyperCKemia probably does not imply disease. In many instances, the diagnosis is not formulated following routine examination with the patients at rest, as symptoms become manifest only after exercise. Some authors think that strength training seems to be safe for patients with myopathy, even though the evidence for routine exercise prescription is still insufficient. Others believe that, in these conditions, intense prolonged exercise may produce negative effects, as it does not induce the physiological muscle adaptations to physical training given the continuous loss of muscle proteins.

Growing points: High CK serum 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 signs may indicate subclinical muscle disease, which training loads may evidence through the onset of profound fatigue. It is probably safe to counsel 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 ample recovery to favour adequate recovery.
Areas timely for developing research: CK values show great variability among individuals. Some athletes are low responders to physical training, with chronically low CK serum levels. Some athletes are high responders, with higher values of enzyme: the relationship among level of training, muscle size, fibre type and CK release after exercise should be investigated further. In addition, more details about hyperCKemia could come from the evaluation of the kinetics of CK after stress in healthy athletes with high levels of CK due to exercise, comparing the results with the ones obtained from athletes with persistent hyperCKemia at rest. Finally, it would be important to quantify the type of exercise more suited to athletes with myopathy and the intensity of exercise not dangerous for the progression of the pathology.

Keywords: creatine kinase/muscular enzymes/myopathy/stress test

Introduction

The serum level of skeletal muscle enzymes is a marker of the functional status of muscle tissue and varies widely in both pathological and physiological conditions. An increase in these enzymes may represent an index of cellular necrosis and tissue damage following acute and chronic muscle injuries.\(^1,^2\) Changes in serum levels of muscular enzymes and isoenzymes are also found in normal subjects and in athletes after strenuous exercise\(^3–^6\); the amount of enzyme from muscle tissue to blood can be influenced by physical exercise.\(^7\) Muscle creatine kinase (CK) activity measured from needle muscle biopsies shows different behaviour before and after training,\(^8,^9\) and the serum level of CK changes according to different protocols and to the intensity and level of training.\(^10–^12\)

The serum CK level can be raised from the damage of the muscle tissue as a consequence of intense prolonged training. This may be a consequence of both metabolic and mechanical causes. Indeed, metabolically exhausted muscle fibres exhibit a decrease in the membrane resistance following an increase in the internal free calcium ions, which promotes the activation of the potassium channel.\(^13,^14\) Another mechanism could be the local tissue damage with sarcomeric degeneration from Z-disk fragmentation. CK is an indicator of muscle necrosis, increasing with its extent.\(^15–^17\)

The study of CK in sport medicine allows to obtain information on the state of the muscle. High levels of serum CK in apparently healthy subjects may be correlated with physical training status. However, if these levels persist at rest, it may be a sign of subclinical muscle disease, which training loads may evidence through the onset of symptoms such as profound fatigue.\(^18\)
Background

CK is a dimeric globular protein consisting of two subunits with a molecular mass of 43 kDa. It buffers cellular ATP and ADP concentrations by catalysing the reversible exchange of high-energy phosphate bonds between phosphocreatine and ADP produced during contraction. At least five isoforms of CK exist: three isoenzymes in cytoplasm (CK-MM, CK-MB and CK-BB) and two isoenzymes (non-sarcomeric and sarcomeric) in mitochondria. These are octameric proteins known as macro-CK because of their large molecular size from polymerization of isoenzymes CK-MM and CK-BB with IgG in type I and with mitochondrial CK in type II. The presence of macro-CK isoenzymes has a prognostic value: macro-CK type I is present in patients who developed cardiovascular or autoimmune process, whereas macro-CK type II isoforms are found in patients with malignant proliferation.

CK isoenzymes give specific information on injured tissue because of their tissue distribution. In fact, CK-MM is found in several domains of the myofibre where ATP consumption is high and is a marker of muscle disease. CK-MB increases in acute myocardial infarction, and CK-BB increases in brain damage. Mitochondrial CK is raised in mitochondrial myopathies.

MM-CK is specifically bound to the myofibrillar M-Line structure located in the sarcomere, a complex structure containing at least 28 different proteins. A sarcomere is bordered at each end by a dark narrow line known as the Z-line. Each Z-line bisects a lighter I-band, which is shared between adjacent sarcomeres. At the centre of the sarcomere is the dark A-band bisected by a less dense H-zone. In the middle of the H-zone lies a narrow band of higher density, the M-line. This site accounts for 5–10% of the total CK-MM: there are two pairs of highly conserved lysine residues, which are necessary and sufficient to mediate the isoenzyme-specific binding of CK into the M-line structure and which probably depend on the energy state of the muscle as the binding properties change according to pH. The M-line region appears to be the only myofibrillar structure which connects thick filaments (myosin) directly with each other, providing physical stability between thick filaments during contraction.

Furthermore, the presence of MM-CK suggests that the M-line has a structural and enzymatic role to regenerate ATP at sites of high-energy consumption, thus providing myosin with sufficient ATP to work even under strenuous conditions.

The Z-line is located at the end of the sarcomere, forming the junction between one sarcomere and the next. It contains numerous components, which contribute to anchoring the thin filaments (mainly
composed of actin) in Z-line. It contains several other proteins, including Myotilin, which have been implicated in limb-girdle muscular dystrophy type 1A. Moreover, there are transverse filaments connecting myofibrils with each other at neighbouring Z- and M-lines, respectively, and with the sarcolemma, possibly contributing to transmission of force along the fibril, even though sarcomeres have been damaged or overstretched. The major constituent of the intermediate filaments is desmin (and the associated synemin, paranemin and nestin), vinmin- tin (which is not expressed in mature muscle), syncolin, Skelemin and Plectin, whose absence is associated with muscular dystrophy. A third set of filaments in muscle, constituted by titin, plays two crucial roles in the sarcomere: it provides a template for the precise organization of the myofibrillar proteins during development and determines the mechanical behaviour of the muscle. Titin extends to the entire length of a half-sarcomere, from Z-line to M-line, and interacts with teletho- nin (or titin-cap) (Fig. 1), implicated in limb-girdle muscular dystrophy type 2G.

Therefore, the high serum levels of CK depend on sarcomeric damage arising either from strenuous exercise or from muscular pathology. Accurate history and a correct diagnostic approach help the physician to formulate the correct diagnosis.

Serum CK in healthy subjects

In normal serum, total CK is provided mainly by the skeletal muscle and is almost only of the MM fraction. Total CK levels depend on age, gender, race, muscle mass, physical activity and climatic condition. The 2.5 and 97.5 percentile reference limits have recently been revisited.30 During foetal life, CK activity is provided mainly by the BB isoenzyme, changing to MM predominance during foetal development.31 In the newborn, CK serum levels are higher than those in adults and are dependent on gestational age, with values that reach adult levels within the first 10 days of life.32 In women, CK activity decreases during pregnancy, but increases in late gestation with high values of CK-MB.33,34 Young adult males have high serum levels of CK,35 which decline slightly with age during the geriatric period.36 There are marked sex differences in CK serum levels at rest,37 with lower values in females than in males. After muscular exercise, sex-linked differences are still present,38 and oestrogen may be an important factor in maintaining post-exercise membrane stability, thus limiting CK leakage from the damaged muscle.39,40 Black men usually have higher values than Caucasians,41 and, although black men usually have an higher body weight and a denser
lean body mass, this does not correlate with CK levels; but some studies do not report any differences in the CK serum values between black and white athletes. Anyway, CK activity is related to body mass and physical activity, with resting levels higher in athletes than in sedentary subjects, given the regular training that athletes undergo.

Fig. 1 Proteins related to muscular dystrophies and localization in the sarcomere.
Cold weather induces higher serum CK increases following a standard exercise bout when compared with the same exercise bout at warmer temperatures.48

**CK elevation in pathology**

Monitoring of CK and characterization of its isoenzymes are widely used in the diagnosis of myopathies, cardiomypathies and encephalopathies.49–51 CK, and especially its MB isoenzyme, is a reliable marker of myocardial necrosis, offering great sensitivity to detect infarct extension to predict worse prognosis.52,53

Patients with neurological conditions such as acute cerebrovascular accidents,54 proximal spinal muscular atrophy55 and amyotrophic lateral sclerosis56 show marked elevation of CK-BB. Elevated CK has also been described in various neuromuscular conditions as a result of muscle damage and necrosis57 and in many muscular dystrophies such as facioscapulohumeral dystrophy (FSHD) and myotonic dystrophy.58,59

Primary skeletal muscle disorder manifests with pain, fatigue, weakness, and serum CK elevation.60 The levels of serum CK are different in various myopathies according to the type of disease and the stage of pathology (Table 1). Muscular dystrophy shows the highest CK levels.61,62 The low CK levels occur in the late stages of the condition because muscle tissue has almost totally undergone fibrotic changes.63 Other muscular pathologies, such as selenium deficiency64 or nemaline myopathy,65 often present only slightly elevated serum enzyme levels. Pain and weakness with mild elevation of enzymes can be due even to the myocardial involvement in other pathology as dilated cardiomyopathy in desmin-related myopathy66,67 or polymyositis,68 which have levels of CK similar to the ones seen in myocardial infarction.

<table>
<thead>
<tr>
<th>Muscular pathology</th>
<th>CK value increases</th>
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<tbody>
<tr>
<td>Duchenne and Becker dystrophies</td>
<td>25–200-fold</td>
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<tr>
<td>Limb-girdle muscular dystrophy</td>
<td>10–100-fold</td>
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<tr>
<td>FSHD</td>
<td>2–7-fold</td>
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<tr>
<td>Distal myopathy</td>
<td>3-fold</td>
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<tr>
<td>Endocrine myopathy</td>
<td>Up to 10-fold</td>
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<td>Congenital myopathies</td>
<td>Slight increase</td>
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<td>Metabolic myopathy</td>
<td>Slight increase</td>
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<tr>
<td>Mitochondrial myopathy</td>
<td>Slight increase</td>
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<tr>
<td>Drug-induced myopathies</td>
<td>Slight or no increase</td>
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Hypothyroidism is a common cause of endocrine myopathy and should be considered in patients with unexplained persistent elevation of serum muscle enzymes, which are higher in patients with overt hypothyroidism and lower in subclinical hypothyroidism. Many authors suggest to assess thyroid function in patients with muscle weakness or elevation of CK, although clinical signs of hypothyroidism may be absent.

Infective rhabdomyolysis can be another cause of unexplained serum CK increase, most frequently seen in patients with respiratory tract infections and cytomegalovirus infections. Moreover, in paediatric patients, an increase in serum mitochondrial CK can be associated with rotavirus gastroenteritis, probably reflecting the diffusive intestinal epithelial cell damage.

In crush syndrome, CK serum levels have been used as a prognostic tool. In prolonged exposure to cold, as in the victims of avalanche, crush injury to the muscles combines with hypoxia and hypercapnia (secondary to rebreathing and hypothermia) to produce high serum levels of CK. A common cause of exercise-induced rhabdomyolysis is carnitine palmitoyltransferase deficiency, which impairs mitochondrial oxidation of long-chain fatty acids, often detected by a chance finding of elevated CK levels. The risk of exertional rhabdomyolysis is higher in anabolic androgenic steroids users.

Other causes of serum CK elevation can be intramuscular injections, with the magnitude of serum CK elevation proportional to the injection volume and the drug injected. In compartment syndrome, CK levels are useful to formulate the diagnosis. At surgery, local muscle tissue damage occurs, with CK levels significantly higher in major surgery than in minor procedures. Increased CK levels have been observed following convulsive seizures, heat stroke, administration of statins, which can lead to rhabdomyolysis when used alone, or following interaction with other drugs. Rhabdomyolysis has been observed following the ingestion of herbal medicine.

**Physiological CK elevation**

Strenuous exercise that damages skeletal muscle cell structure at the level of sarcolemma and Z-disks results in an increase in total CK. When exercise intensity is mild to moderate, the muscle tissue is exercised without marked changes in the membrane permeability: when the exercise intensity exceeds this range, membrane permeability changes and enzymes are released. The boundary of the range of exercise intensity which the muscle tissue can withstand is its break point: when loading exceeds a certain limit of muscle ability, CK leaks into the bloodstream.
the interstitial fluid, is taken up by the lymphatic system and returned into the circulation.95

Many factors determine the degree to which serum enzyme activities increase during and after exercise. The highest post-exercise serum enzyme activities are found after very prolonged competitive exercise such as ultradistance marathon running96 or triathlon events.97 Weight-bearing exercises, which include eccentric muscular contractions such as downhill running, induce the greatest increases in serum enzyme activities.98 There is a breakpoint at 300–500 IU/l of CK serum release after exercise, and the levels of enzyme are associated with distinctive individual muscular properties. Subjects can be classified into high and low responders. In high responders, the cross-sectional area and volume of the quadriceps femoris muscle were significantly lower than those in low responders.99 Daily training may result in persistent serum elevation of CK,100 and resting CK levels are higher in athletes,101,102 but the significant increases of CK occurred after exercise are usually lower in trained subjects when compared with untrained subjects.103–105 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.106,107

The time of CK release into and clearance from plasma depends on the level of training, type, intensity and duration of exercise. Peak serum CK levels of about 2-fold above baseline occur 8 h after strength training.108 Increased CK levels after eccentric exercise are associated with muscle injury, with a pronounced increase between 2 and 7 days after exercise.109

After prolonged exercise, total serum CK activity is markedly elevated for 24 h after the exercise bout when subjects rest and remains elevated for 48 h when subjects train in the first week post-exercise.110 The release of CK following eccentric exercise peaked 96 h after the exercise bout, and an additional bout of exercise produces only small increases, probably from accelerated enzymatic clearance.111 More intense activity, such as a twice daily football training, leads to significant increase of CK during the fourth day of training. CK levels decrease between days 4 and 10, probably an adaptation to training.112 A bout of exercise performed 48 h after an initial bout does not change the time course of the CK leakage.113

Normally, only CK-MM is present in the serum, but prolonged and strenuous exercise increases the serum activity of all three CK-isoenzymes in the absence of myocardial damage.114 Probably, the BB-fraction found in boxers115 is a sign of cerebral damage.

CK serum levels reach their highest values only 5 min after a cycloergometer test, demonstrating that exercise duration rather than fitness
levels seems to be related to serum CK, aspartate aminotransferase (AST) and alanin aminotransferase (ALT) activities.\textsuperscript{116}

The decrease in the serum enzyme levels 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.\textsuperscript{117} Manual lymph drainage after treadmill exercise is associated with faster decrease in the serum levels of muscle enzymes.\textsuperscript{118} 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.\textsuperscript{119}

### Persistent HyperCKemia

Persistently increased serum CK levels are occasionally encountered in healthy individuals. Subjects often do not present any clinical manifestation of a neuromuscular disorder or any condition known to be associated with increased serum CK levels. Galassi \textit{et al.},\textsuperscript{120} studying subjects with high levels of CK at rest, observed that, years later, subjects developed weakness. They suggest that early myopathy may be asymptomatic.\textsuperscript{121} Other authors demonstrated that, in most of these patients, hyperCKemia probably does not imply disease,\textsuperscript{122} and patients without skeletal muscle abnormalities on muscle biopsy may have idiopathic hyperCKemia (IH).\textsuperscript{123} Familial IH is a benign genetically heterogeneous (although normally autosomal dominant) condition often ascribed to caveolin-3 gene mutations, with a higher penetrance in men.\textsuperscript{124} In a long-term study of IH patients, there was no clinical deterioration on electromyography (EMG), and muscle biopsy demonstrated only minor, non-diagnostic abnormalities.\textsuperscript{125} Recently, 40 subjects with persistent asymptomatic IH underwent clinical and laboratory investigations, electromyography and muscle biopsy: pathological findings were found in 55% of them, and a diagnosis of muscular dystrophy was made in three subjects.\textsuperscript{126} However, as the diagnosis of muscular dystrophy does not depend on the level of CK, a full workup may well be indicated in patients with unexplained high enzymatic serum levels of CK.\textsuperscript{127}

Serum CK activity is also markedly increased in the pre-clinical stages of some muscle diseases.\textsuperscript{128} In the group of mitochondrial myopathies, carnitine palmitoyltransferase deficiency has been detected from elevated CK levels in routine blood tests, especially after exercise. This myopathy is one of the most common causes of rhabdomyolysis and severe exercise induced myalgia.\textsuperscript{129,130} In the same group, the defects of mitochondrial transport,\textsuperscript{131} of beta-oxidation,\textsuperscript{132} of Krebs cycle,\textsuperscript{133} and of respiratory chain\textsuperscript{134} are other disorders that can
manifest by increased CK. Even mild or recurrent hyperCKemia may indicate a metabolic disease, as is the case in patients with mitochondrial myopathy and myoadenilate deaminase deficiency, who can have serum CK levels only slightly elevated and can slowly develop myalgia and progressive weakness. The defects of glycogen storage affect the glycolytic or the glycogenolytic pathway, causing myopathy with hyperCKemia. A form of persistent asymptomatic hyperCKemia can be due to desmin abnormalities and has been reported in patients with only mild neuromuscular abnormalities. In many instances, the diagnosis is not formulated following routine examination with the patients at rest, as the symptoms become manifest only after exercise. For example, in two case reports, the patients were athletes in whom muscle symptoms such as pain and cramping developed insidiously after severe exercise: the diagnosis of myotonia and paramyotonia congenita was made following an exercise test. Becker muscular dystrophy, FSHD, and limb-girdle muscular dystrophy exhibit persistent hyperCKemia and exertional muscle pain. In some instances, the elevated serum CK levels are associated with myocardial pathology because the myopathy manifests with dilated cardiomyopathy, as in lamin A/C gene defects or limb-girdle muscular dystrophy. Furthermore, malignant hyperthermia may sometimes cause unexplained, persistently increased serum CK levels in otherwise healthy subjects, with no significant correlation between the magnitude of CK increase and the severity of malignant hyperthermia.

Some studies focused on the quality of life in patients with IH or mild symptoms because of myopathies. Reijneveld et al. studied the response to exercise in subjects with IH: exercise does not result in more extensive damage when compared with healthy subjects, even though long-term data were not available. Other authors studied the effect of exercise in FSHD. Strength training seems to be safe for patients with FSHD, even though the evidence for routine exercise prescription is still insufficient.

**Monitoring of serum CK in sport**

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 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.
Also, the most marked increase in CK occurs in the less-trained subjects. Other authors attribute this behaviour to training adaptation and identified a relationship between peak power and release of CK with the athletes achieving the lowest peak power showing the greatest increase in CK. However, marked CK increase is reported after exertional rhabdomyolysis following marathon running and is often even greater when the exercise is strenuous in cold weather. The risk of skeletal muscle injuries is increased when athletes use androgenic steroids or creatine supplements. In addition a large increase in serum CK levels combined with reduced exercise tolerance could be a marker of overtraining. However, muscle recovery cannot be evaluated by changes in serum CK levels, as there is no correlation between serum enzyme leakage and muscular performance impairment after exercise. In addition, CK values show great variability, and athletes with chronically low CK serum levels (low responders) have low variability when compared with those who have higher values (high responders). Therefore, the diagnosis of overtraining becomes possible only if a large increase is observed in combination with reduced exercise tolerance.

Noakes, in 1987, hypothesized that subjects with abnormally large increase in serum CK activity after exercise may have unrecognized subclinical myopathy. This is indeed the case in some metabolic myopathies such as McArdles disease, or mutation in some sarcoplasmic protein such as caveolin-3 and alpha-dystroglycan, with a correlation between the reduction of protein expression and the clinical phenotype, or cytoskeleton and components of nuclear envelope as lamins. In conclusion, persistent CK elevation must be carefully investigated and could be important to evaluate CK serum activity at rest and after exercise to identify silent myopathies. In fact, if a genetic trait predisposes to exertional rhabdomyolysis, the myopathy could be symptomatic only after exercise, as seen in the early stage of Becker’s syndrome. Unexplained exertional limitation including myalgia, fatigue or dyspnoea could be a sign of myopathy.

Patients misdiagnosed with fibromyalgia may rarely have a myopathy. In these patients, before performing a muscle biopsy, measurements of CK serum levels can be the first laboratory sign of muscle disease.

Sometimes, the asymmetry of muscular involvement shows myopathic features, and the pathology is evident at careful clinical examination. In other instances, the myopathy could have a prevalent cardiac phenotype. Athletes are at a higher risk of injuries during sport activities if there is muscle weakness. Therefore, even the less severe myopathies could cause pain and muscle imbalance in athletes.
Persistent hyperCKemia in athletes

Stiffness, muscle soreness and pain are normal features of physical training: often, both athletes and coaches pay little attention to these symptoms. However, if they are resistant to rest and massage, or recur too frequently, they should prompt a diagnostic workup. Sometimes, these are the only signs of a silent myopathy. Kaar et al. \textsuperscript{178} diagnosed FSHD in a baseball player complaining of shoulder pain. In other athletes, biopsy-proven myopathies were the cause of unexplained exercise impairment. \textsuperscript{179} In these instances, evaluation of CK at rest and after exertion could be a simple and non-invasive method to guide diagnosis.

High CK serum 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 evaluation of the symmetric position of the inferior angle of the scapula and the iliac spines. \textsuperscript{180–182} Mutation in sarcomeric proteins is the prime cause of a major class of disease that affects cardiac function, such as familial hypertrophic cardiomyopathy, or leads to a variety of other myopathies including limb-girdle muscular dystrophy type 2G (telethonin), \textsuperscript{183} limb-girdle muscular dystrophy type 1A (myotilin), \textsuperscript{183} nemaline myopathy (actin, tropomyosin and nebulin), \textsuperscript{184} desmin-related myopathy (desmin), \textsuperscript{184} and other myopathies (plectin). \textsuperscript{185} In these subjects, repeated intense prolonged exercise does not induce the physiological muscle adaptations to physical training given the continuous loss of muscle proteins. \textsuperscript{186}

In addition, although the increase in serum levels of CK is the most useful screening laboratory test to identify myopathies, some cause no increase in CK, and CK increase does not occur only in myopathies. \textsuperscript{187} The determination of lactate during and after stress test is another simple method to detect the impairment of oxidative metabolism of mitochondrial myopathies \textsuperscript{188,189} and McArdle’s disease, \textsuperscript{190} as the sensitivity of method seems to be higher than the resting values determination. Therefore, the approach to subjects with muscular symptoms must be multidisciplinary, \textsuperscript{191} and athletes with recurrent muscle disease or persistently high CK at rest should be considered exactly as all other subjects in the same condition and undergo clinical and instrumental examination to achieve a diagnosis with (Fig. 2):

(i) accurate history taking to identify predisposing factor or familiarity of the pathology;

(ii) assessment of serum CK levels after at least 1 week of rest;
Algorithm for detection of muscle pathology in subject with hyperCKemia.

1. Muscular symptoms, weakness or postural asymmetry
   - History positive for predisposing factors
     - +
       - Stop
     - -
       - Serum CK at rest
         - Increased
           - Electrocardiogram at rest and during exercise test
             - Echocardiography
             - Electromyography
             - Muscle biopsy
             - Genetic examination
         - Normal or slightly increased
           - Serum CK after exercise
             - Up
               - Follow-up at 12 months
             - Normal
               - Physical activity according to the diagnosis
(iii) physical examination to identify postural asymmetries;
(iv) assessment of serum CK levels after exercise, as in some myopathies, post-exercise serum CK levels may be a better indicator of carrier status than rest CK serum levels\(^ {192}\);
(v) measurements of lactic acid after stress, which has a high sensitivity and specificity in mitochondrial myopathies;
(vi) echocardiography to identify genetic muscular pathology phenotypically expressed as a cardiomyopathy\(^ {193}\);
(vii) electromyographic examination;
(viii) magnetic resonance imaging to study muscle involvement in myopathies, which cannot be detected by manual muscle strength testing\(^ {194}\);
(ix) muscle biopsy;
(x) protein analyses and genetic testing.

**Concluding remarks**

It is probably safe to counsel 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 ample recovery to favour adequate recovery. Accurate history taking and clinical examination should help to clarify whether more invasive investigations, including muscle biopsies, should be considered.

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