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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.

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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 mitocondria. These are octameric proteins known as macro-CK because of their large molecular size[19] from polymerization of isoenzymes CK-MM and CK-BB with IgG in type I and with mitocondrial CK in type II.[20] 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 isoenzymes are found in patients with malignant proliferation.[21–23] 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.[24] CK-MB increases in acute myocardial infarction,[25] and CK-BB increases in brain damage.[26] Mitocondrial CK is raised in mitochondrial myopathies.[27]

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.[28] 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.[29]

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 synemine, paranemin and nestin), vinmentin (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 telethonin (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,[42] this does not correlate with CK levels[43]; but some studies do not report any differences in the CK serum values between black and white athletes.[44] Anyway, CK activity is related to body mass[45] and physical activity, with resting levels higher in athletes than in sedentary subjects, given the regular training that athletes undergo.[46,47]

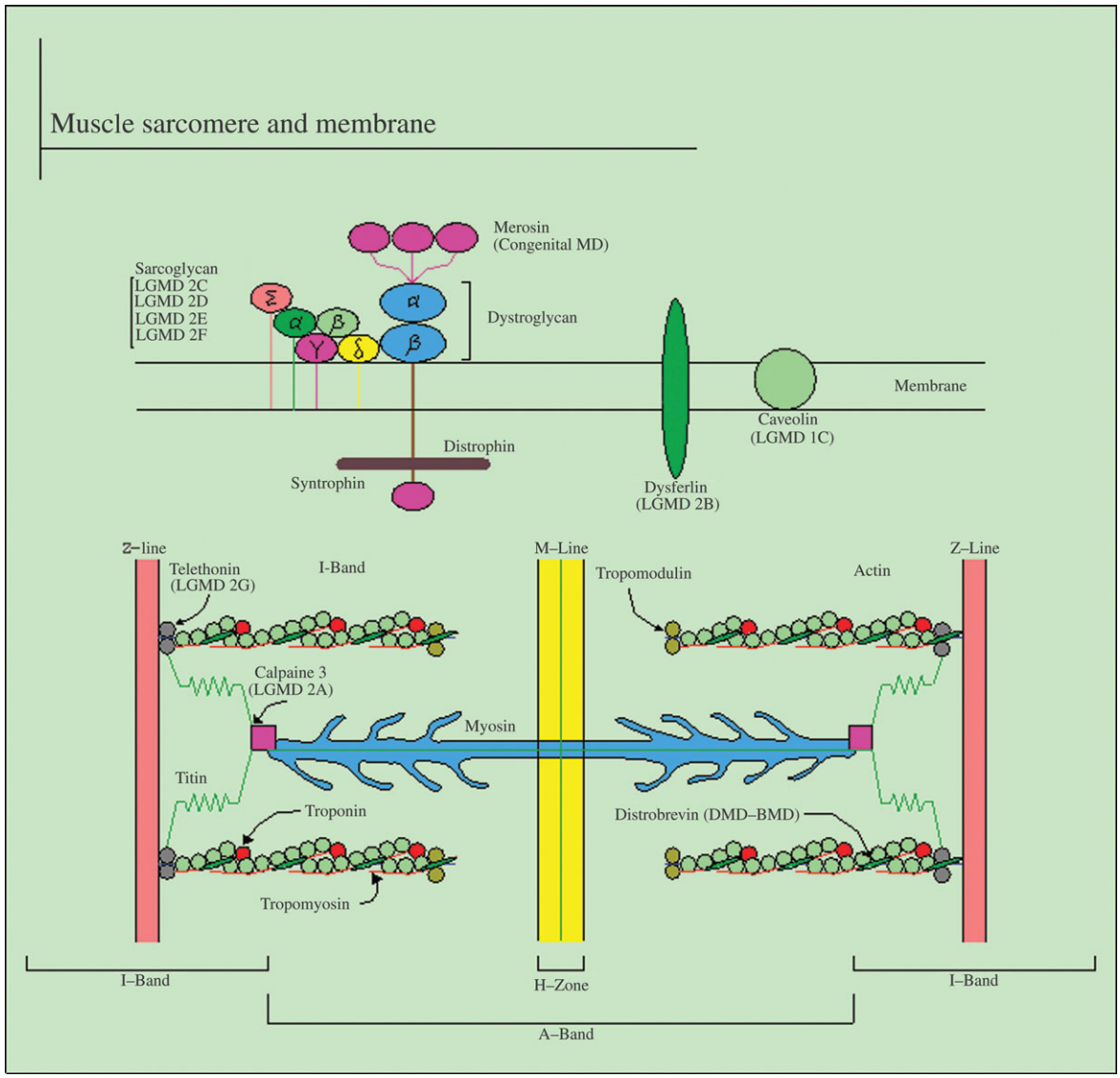

Fig. 1 Proteins related to muscular dystrophies and localization in the sarcomere.

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, cardiomyopathies 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 atrophy[55] and amyotrophic lateral sclerosis[56] show marked elevation of CK-BB. Elevated CK has also been described in various neuromuscular conditions as a result of muscle damage and necrosis[57] 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 deficiency[64] 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 myopathy[66,67] or polymyositis,[68] which have levels of CK similar to the ones seen in myocardial infarction.

Table 1 CK values usually found in some muscular pathology

Muscular pathology	CK value increases
Duchenne and Becker dystrophies	25–200-fold
Limb-girdle muscular dystrophy	10–100-fold
FSHD	2–7-fold
Distal myopathy	3-fold
Endocrine myopathy	Up to 10-fold
Congenital myopathies	Slight increase
Metabolic myopathy	Slight increase
Mitochondrial myopathy	Slight increase
Drug-induced myopathies	Slight or no increase

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.[69] Many authors suggest to assess thyroid function in patients with muscle weakness or elevation of CK, although clinical signs of hypothyroidism may be absent.[70,71]

Infective rhabdomyolysis can be another cause of unexplained serum CK increase, most frequently seen in patients with respiratory tract infections[72] and cytomegalovirus infections.[73] Moreover, in paediatric patients, an increase in serum mitochondrial CK can be associated with rotavirus gastroenteritis, probably reflecting the diffusive intestinal epithelial cell damage.[74]

In crush syndrome,[75] CK serum levels have been used as a prognostic tool.[76] 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.[77,78] 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.[79] The risk of exertional rhabdomyolysis is higher in anabolic androgenic steroids users.[80,81]

Other causes of serum CK elevation can be intramuscular injections, with the magnitude of serum CK elevation proportional to the injection volume[82] and the drug injected.[83] In compartment syndrome,[84] 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.[85] Increased CK levels have been observed following convulsive seizures,[86,87] heat stroke,[88] administration of statins, which can lead to rhabdomyolysis when used alone,[89] or following interaction with other drugs.[90] Rhabdomyolysis has been observed following the ingestion of herbal medicine.[91]

Physiological CK elevation

Strenuous exercise that damages skeletal muscle cell structure at the level of sarcolemma and Z-disks[92] results in an increase in total CK.[93,94] 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 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 running[96] 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 musclar 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 boxers[115] 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.[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.[117] Manual lymph drainage after treadmill exercise is associated with faster decrease in the serum levels of muscle enzymes.[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.[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 *et al.*,[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.[121] Other authors demonstrated that, in most of these patients, hyperCKemia probably does not imply disease,[122] and patients without skeletal muscle abnormalities on muscle biopsy may have idiopathic hyperCKemia (IH).[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.[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.[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.[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.[127]

Serum CK activity is also markedly increased in the pre-clinical stages of some muscle diseases.[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.[129,130] In the same group, the defects of mitocondrial transport,[131] of beta-oxidation,[132] of Krebs cycle,[133] and of respiratory chain[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[135] and myoadenilate deaminase deficiency, who can have serum CK levels only slightly elevated and can slowly develop myalgia and progressive weakness.[136] The defects of glycogen storage affect the glycolytic or the glycogenolytic pathway, causing myopathy with hyperCKemia.[137] A form of persistent asymptomatic hyperCKemia can be due to desmin abnormalities and has been reported in patients with only mild neuromuscular abnormalities.[138] 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[139] and paramyotonia congenita[140] was made following an exercise test. Becker muscular dystrophy,[141,142] FSHD,[143] and limb-girdle muscular dystrophy[144] 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[145] or limb-girdle muscular dystrophy.[146] 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.[147]

Some studies focused on the quality of life in patients with IH or mild symptoms because of myopathies. Reijneveld *et al.*[148] 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.[149] Strength training seems to be safe for patients with FSHD, even though the evidence for routine exercise prescription is still insufficient.[150,151]

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.[152] Athletes have higher resting CK when compared with untrained subjects,[153] 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.[154]

Also, the most marked increase in CK occurs in the less-trained subjects.[155] 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.[112] However, marked CK increase is reported after exertional rhabdomyolysis following marathon running[156] and is often even greater when the exercise is strenuous in cold weather.[157] The risk of skeletal muscle injuries is increased when athletes use androgenic steroids or creatine supplements.[158,159] In addition a large increase in serum CK levels combined with reduced exercise tolerance could be a marker of overtraining.[160] 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.[161] 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.[162]

Noakes,[163] in 1987, hypothesized that subjects with abnormally large increase in serum CK activity after exercise may have unrecognized subclinical myopathy.[163] This is indeed the case in some metabolic myopathies such as McArdles, disease,[164] or mutation in some sarcolemmal protein such as caveolin-3[165,166] and alpha-dystroglycan, with a correlation between the reduction of protein expression and the clinical phenotype,[167] or cytoskeleton[168] and components of nuclear envelope as lamins.[169,170] In conclusion, persistent CK elevation must be carefully investigated[171] 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.[172] Unexplained exertional limitation including myalgia, fatigue or dyspnoea could be a sign of myopathy.[173]

Patients misdiagnosed with fibromyalgia may rarely have a myopathy.[174] 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.[175] In other instances, the myopathy could have a prevalent cardiac phenotype.[176] Athletes are at a higher risk of injuries during sport activities if there is muscle weakness.[177] Therefore, even the less severe myopathies could cause pain and muscle imbalance in athletes.[178]

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.*[178] diagnosed FSHD in a baseball player complaining of shoulder pain. In other athletes, biopsy-proven myopathies were the cause of unexplained exercise impairment.[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.[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),[183] limb-girdle muscular dystrophy type 1A (myotilin),[183] nemaline myopathy (actin, tropomyosin and nebulin),[184] desmin-related myopathy (desmin),[184] and other myopathies (plectin).[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.[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.[187] The determination of lactate during and after stress test is another simple method to detect the impairment of oxidative metabolism of mitocondrial myopathies[188,189] and McArdle's disease,[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,[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;

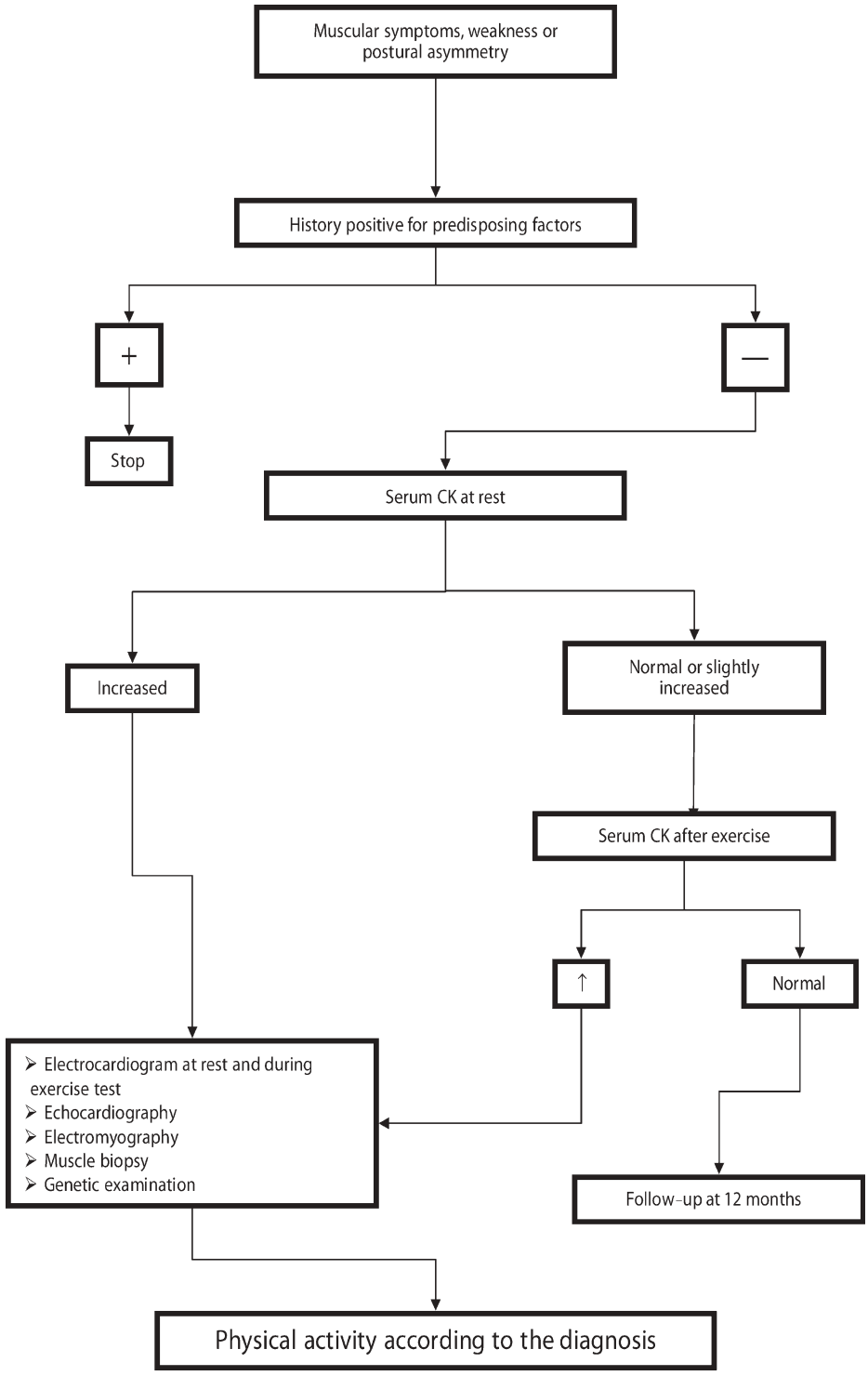

Fig. 2 Algorithm for detection of muscle pathology in subject with hyperCKemia.

(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 mitocondrial 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.

References

1 Szumilak D, Sulowicz W, Walatek B (1998) Rhabdomyolysis: clinical features, causes, complications and treatment. *Przegl Lek*, **55**, 274–279.
2 Mokuno K, Riku S, Sugimura K, Takahashi A, Kato K, Osugi S (1987) Serum creatine kinase isoenzymes in Duchenne muscular dystrophy determined by sensitive enzyme immunoassay methods. *Muscle Nerve*, **10**, 459–463.
3 Wolf PL, Lott JA, Nitti GJ *et al.* (1987) Changes in serum enzymes, lactate and haptoglobin following acute physical stress in international-class athletes. *Clin Biochem*, **20**, 73–77.
4 Priest JB, Oei TO, Moorehead WR (1982) Exercise-induce changes in common laboratory test. *Am J Clin Pathol*, **77**, 285–289.
5 Ide M, Tajima F, Forusawa K *et al.* (1999) Weelchair marathon racin causes striated muscle distress in individuals with spinal cord injury. *Arch Phys Med Rehabil*, **80**, 324–327.
6 Munjal DD, McFadden JA, Matix PA *et al.* (1983) Changes in serum myoglobin, total creatine kinase, lactate dehydrogenase and creatine kinase MB levels in runners. *Clin Biochem*, **16**, 195–199
7 Boros-Hatfaludy S, Fekete G, Apor P (1986) Metabolic enzyme activity patterns in muscle biopsy samples in different athletes. *Eur J Appl Physiol Occup Physiol*, **55**, 334–338.
8 MacDougall JD, Hicks AL, Mac Donald JR *et al.* (1998) Muscle performance and enzymatic adaptations to sprint interval training. *J Appl Physiol*, **84**, 2138–2142.

9 Linossier MT, Dormois D, Perier C *et al*. (1997) Enzyme adaptation of human skeletal muscle during bicycle short-sprint training and detraining. *Acta Physiol Scand*, **161**, 439–445.
10 Klapcinska B, Iskra J, Poprzecki S *et al*. (2001) The effects of sprint (300 m) running on plasma lactate, uric acid, creatine kinase and lactate dehydrogenase in competitive hurdlers and untrained men. *J Sports Med Phys Fitness*, **41**, 306–311.
11 Ohkuwa T, Saito M, Miyamura M (1984) Plasma LDH and CK activities after 400 mt sprinting by well-trained sprint runners. *Eur J Appl Physiol*, **52**, 296–299.
12 Szabo A, Romvari R, Bogner P *et al*. (2003) Metabolic changes induced by regular submaximal aerobic exercise in meat-type rabbits. *Acta Vet Hung*, **51**, 503–512.
13 Fink R, Luttgau HC (1976) An evaluation of the membrane constants and the potassium conductance in metabolically exhausted muscle fibres. *J Physiol*, **263**, 215–238.
14 Fink R, Hase S, Luttgau HC, Wettwer E (1983) The effect of cellular energy reserves and internal calcium ions on the potassium conductance in skeletal muscle of the frog. *J Physiol*, **336**, 211–228.
15 Ponraj D, Gopalakrishnakone P (1996) Establishment of an animal model for myoglobinuria by use of a myotoxin from pseudechis australis (king brown snake) venom in mice. *Lab Anim Sci*, **46**, 393–398.
16 Nakada K, Nakada F, Ito E, Inoue F (1984) Quantification of myonecrosis and comparison of necrotic activity of snake venoms by determination of creatine phosphokinase activity in mice sera. *Toxicon*, **22**, 921–930.
17 Lopes-Ferreira M, Nunez J, Rucavado A *et al*. (2001) Skeletal muscle necrosis and regeneration after injection of thalassophryne nattereri (niquim) fish venom in mice. *Int J Pathol*, **82**, 55–64.
18 Angelini C (2004) Limb-girdle muscular dystrophies: heterogeneity of clinical phenotypes and pathogenetic mechanisms. *Acta Myol*, **23**, 130–136.
19 Takagi Y, Yasuhara T, Gomi K (2001) Creatine kinase and its isozymes. *Rinsho Byori*, **116**, 52–61.
20 Ruiz Gines MA, Calafell Mas MF, Ruiz Gines JA, Fernandez Rodriquez E (2006) Macro creatine kinase: illness marker. Practical guide for the management. *Ann Med Interne*, **23**, 272–275.
21 Laureys M, Sion JP, Slabbynck H *et al*. (1991) Macromolecular creatine kinase type 1: a serum marker associated with disease. *Clin Chem*, **37**, 430–434.
22 Lee KN, Csako G, Bernhardt P, Elin RJ (1994) Relevance of macro creatine kinase type 1 and type 2 isoenzymes to laboratory and clinical data. *Clin Chem*, **40**, 1278–1283.
23 Stein W, Bohner J, Renn W, Maulbetsch R (1985) Macro creatine kinase type 2: results of a prospective study in hospitalized patients. *Clin Chem*, **31**, 1959–1964.
24 Nigro G, Comi LI, Limongelli FM *et al*. (1983) Prospective study of X-linked progressive muscular dystrophy in Campania. *Muscle Nerve*, **6**, 253–262.
25 Borrayo-Sanchez G, Sosa Jarero F, Borja-Teran B, Isordia–Salas I, Arguero-Sanchez R (2006) Qualitative determination of markers for myocardiac necrosis during pre-hospital admission for acute coronary syndrome. *Cir Cir*, **74**, 231–235.
26 Pfeiffer FE, Homburger HA, Yanagihara T (1983) Creatine kinase BB isoenzyme in CSF in neurologic disease. Measurement by radioimmunoassay. *Arch Neurol* **40**, 169–172.
27 Stadhouders AM, Jap PH, Winkler HP, Eppenberg HM, Wallimann T (1994) Mitochondrial creatine kinase: a major constituent of pathological inclusions seen in mitochondrial myopathies. *Proc Nat Acad Sci USA*, **91**, 5089–5093.
28 Hornemann T, Kempa S, Himmel M, Hayess K, Furst DO, Walliman T (2003) Muscle-type creatine kinase interacts with central domains of the M-band proteins myomesin and M-protein. *J Mol Biol*, **332**, 877–887.
29 Hornemann T, Stolz M, Walliman T (2000) Isoenzyme-specific interaction of muscle-type creatine kinase with the sarcomeric M-line is mediated by NH_2-terminal lysine charge-clamps. *J Cell Biol*, **149**, 1225–1234.
30 Stomme JH, Rustad P, Steensland H, Theodorsen L, Urdal P (2004) Reference intervals for eight enzymes in blood of adult females and males measured in accordance with the international Federation of Clinical Chemistry reference system at 37°C: part of the Nordic Reference Interval Project. *Scand J Clin Lab Invest*, **64**, 371–384.

31 Foxall CD, Emery AE (1975) Changes in creatine kinase and its isoenzymes in human fetal muscle during development. *J Neurol Sci*, **24**, 483–492.
32 Bayer PM, Gabi F, Gergely T, Zazgornik J (1977) Isoenzymes of creatine kinase in the perinatal period. *J Clin Chem Clin Biochem*, **15**, 349–352.
33 Chemnitz G, Navermann L, Schmidt E, Schmidt FW, Lobers J (1979) Creatine kinase (EC-No.2.7.3.2) and creatine kinase isoenzymes during pregnancy and labor and in the cord blood. *Clin Biochem*, **12**, 277–281.
34 Leiserowitz GS, Evans AT, Samuele SJ, Omand K, Kost JG (1992) Creatine kinase and its MB isoenzyme in the third trimester and the peripartum period. *J Report Med*, **37**, 910–916.
35 Borges O, Essen-Gustavsson B (1989) Enzyme activities in type I and II muscle fibres of human skeletal muscle in relation to age and torque development. *Acta Physiol Scand*, **136**, 29–36.
36 Tietz NW, Shuey DF, Wekstein DR (1992) Laboratory values in fit aging individuals-sexagenarians though centenarians. *Clin Chem*, **38**, 1167–1185.
37 Fu FH, You CY, Kong ZW (2002) Acute changes in selected serum enzyme and metabolite concentrations in 12-yr to 14 yr old athletes after an all-out 100 m swimming sprint. *Percept Motor Skills*, **95**, 1171–1178.
38 Amelink GJ, Kamp HH, Bar PR (1988) Creatine kinase isoenzyme profiles after exercise in the rat: sex-linked differences in leakage of CKMM. *Pflugers Arch*, **412**, 417–421.
39 Tiidus PM (2000) Estrogen and gender effects on muscle damage, inflammation and oxidative stress. *Can J Appl Physiol*, **25**, 274–287.
40 Amelink GJ, Koot RW, Erich WB, Van Gijn J, Bar PR (1990) Sex-linked variation in creatine kinase release, and its dependence on oestradiol, can be demonstrated in an *in-vitro* rat skeletal muscle preparation. *Acta Physiol Scand*, **138**, 115–124.
41 Wong ET, Cobb C, Umehara MK *et al.* (1983) Heterogeneity of serum creatine kinase activity among racial and gender groups of the population. *Am J Clin Pathol*, **79**, 582–586.
42 Schuttle JE, Townsend EJ, Hugg J, Shoup RF, Malina RM, Blomqvist CG (1984) Density of lean body mass is greater in blacks than in whites. *J Appl Physiol*, **56**, 1647–1649.
43 Worral JG, Phongsathorn V, Hooper RJ, Paice EW (1990) Racial variation in serum creatine kinase unrelated to lean body mass. *Br J Rheumatol*, **29**, 371–373.
44 Eliakim A, Nemet D, Shenkman L (1995) Serum enzyme activities following long-distance running: comparison between Ethiopian and white athletes. *Isr J Med Sci*, **31**, 657–659.
45 Swaminathan R, Ho CS, Donnan SP (1988) Body composition and plasma creatine kinase activity. *Ann Clin Biochem*, **25**, 389–391.
46 Fallon KE, Sivyer G, Sivyer K, Dare A (1999) The biochemistry of runners in a 1600 km ultramarathon. *Br J Sports Med*, **33**, 264–269.
47 Hortobagyi T, Denhan T (1989) Variability in creatine kinase: methodological, exercise and clinically related factors. *Int J Sports Med*, **10**, 69–80.
48 Makinen TM, Rintamaki H, Karpakka J, Komulainen J, Hissa R (1998) Submaximal exercise in the cold: does cooling potentiate the development of muscle injuries in the rat? *Comp Biochem Physiol A Mol Integr Physiol*, **121**, 273–278.
49 Hina K, Kusachi S, Iwasaki K *et al.* (1997) Use of serum creatine kinase MM isoforms for predicting the progression of left ventricular dilatation in patients with hypertrophic cardiomyopathy. *Jpn Circ J*, **61**, 315–322.
50 Kloss R, Keller HE, Stober T, Emde H, Schimrigk K (1985) Creatine kinase BB activity in the serum of patients with cerebrovascular diseases. *Nervenarzt*, **56**, 417–422.
51 Hoffman EP, Clemens PR (1996) HyperCKemic, proximal muscular dystrophies and the dystrophin membrane cytoskeleton, including dystrophinopathies, sarcoglycanopathies and merosinopathies. *Curr Opin Rheumatol*, **8**, 528–538.
52 Rajappa M, Sharma A (2005) Biomarkers of cardiac injury: an update. *Angiology*, **56**, 677–691.
53 Galla JM, Mahaffey KW, Sapp SK *et al.* (2006) Elevated creatine kinase-MB with normal creatine kinase predicts worse outcomes in patients with acute coronary syndromes: results from 4 large clinical trials. *Am Heart J*, **151**, 16–24.

54 Bell RD, Rosenberg RN, Ting R, Mukherjee A, Stone MJ, Willerson JT (1978) Creatine kinase BB isoenzyme levels by radioimmunoassay in patients with neurological disease. *Ann Neurol*, **3**, 52–59.
55 Rudnik-Schoneborn S, Lutzenrath S, Borkowska J, Karwanska A, Hausmanowa-Petrusewicz I, Zerres K (1998) Analysis of creatine kinase activity in 504 patients with proximal spinal muscular atrophy types I–III from the point of view of progression and severity. *Eur Neurol*, **39**, 154–162.
56 Ilzecka J, Stelmasiak Z (2003) Creatine kinase activity in amiotrophic lateral sclerosis patients. *Neurol Sci*, **24**, 286–287.
57 Nakada K, Nakada F, Ito E, Inoue F (1984) Quantification of myonecrosis and comparison of necrotic activity of snake venoms by determination of creatine phosphokinase activity in mice sera. *Toxicon*, **22**, 921–930.
58 Fierro B, Daniele O, Aloisio A *et al.* (1997) Evoked potential study in facio-scapulo-humeral muscular dystrophy. *Acta Neurol Scand*, **95**, 346–350.
59 Merlini L, Sabatelli P, Columbaro M *et al.* (2005) Hyper-CK-emia as the sole manifestation of myotonic dystrophy type 2. *Muscle Nerve*, **31**, 764–767.
60 Engel AG, Orawa E (2004) Chapter 34: Dystrophinopathies. In Engel AG, Franzini C, Armstrong H (eds) *Myology*, (Aggiungere: McGraw-Hill) 3rd ed., 978.
61 El-Bohy AA, Wong BL (2005) The diagnosis of muscular dystrophy. *Pediatr Ann*, **34**, 525–530.
62 Rowland Lewis P (1993) *Trattato di neurologia*. Merrit, 589–594.
63 Zatz M, Rapaport D, Vainzof M *et al.* (1991) Serum creatine-kinase (CK) and pyruvate-kinase (PK) activities in Duchenne (DMD) as compared with Becker (BMD) muscular dystrophy. *J Neurol Sci*, **102**, 190–196.
64 Chariot P, Bignani O (2003) Skeletal muscle disorders associated with selenium deficiency in humans. *Muscle Nerve*, **27**, 662–668.
65 Chahin N, Selcen D, Engel AG (2005) Sporadic late onset nemaline myopathy. *Neurology*, **65**, 1158–1164.
66 Taylor MR, Slavov D, Ku L *et al.* (2007) Prevalence of desmin mutations in dilated cardiomyopathy. *Circulation*, **13**, 1244–1251. Epub 2007, Feb 26.
67 Olive M, Goldfarb L, Moreno D *et al.* (2004) Desmin-related myopathy: clinical, electrophysiological, radiological, neuropathological and genetic studies. *J Neurol Sci*, **219**, 125–137.
68 Strongwater SL, Annesley T, Schitzer TJ (1983) Myocardial involvement in polymyositis. *J Rheumatol*, **10**, 459–463.
69 Hekimsoy Z, Oktem IK (2005) Serum creatine kinase levels in overt and subclinical hypothyroidism. *Endocr Res*, **31**, 171–175.
70 Scott KR, Simmons Z, Boyer PJ (2002) Hypothyroid myopathy with a strikingly elevated serum creatine kinase level. *Muscle Nerve*, **26**, 141–144.
71 Madariaga MG (2002) Polymyositis-like syndrome in hypothyroidism: review of cases reported over the past twenty-five years. *Thyroid*, **12**, 331–336.
72 Blanco JR, Zabaiza M, Salcedo J, Echeverria L, Garcia A, Vallejo M (2002) Rhabdomyolysis of infectious and noninfectious causes. *South Med J*, **95**, 542–544.
73 Sato K, Yoneda M, Hayashi K, Nakagawa H, Higuchi I (2006) A steroid-responsive case of severe rhabdomyolysis associated with cytomegalovirus infection. *Rinsho Shinkelgaku*, **46**, 312–316.
74 Hoshino T, Hosokawa N, Kumasaka K, Kawano K (2001) The relationship of serum mitochondrial creatine kinase and rotavirus gastroenteritis in pediatric patients. *Rinsho Byori*, **49**, 597–602.
75 Malinoski DJ, Slater MS, Mullins RJ (2004) Crush injury and rhabdomyolysis. *Crit Care Clin*, **20**, 171–192.
76 de Meyer AR, Fikkers BG, de Keijzer MH, van Engelen BG, Drenth JP (2003) Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5-year intensive care survey. *Intensive Care Med*, **29**, 1121–1125.
77 Liu J, Zhang Z, Yang Z, Li F, Yan P, Liu Y (1996) Effect of freezing and hypoxia on serum creatine kinase activity in rats. *Space Med Med Eng (Beijing)*, **9**, 291–294.

78 Grissom CK, Radwin MI, Scholand MB, Harmston CH, Muetterties MC, Bywater TJ (2004) Hypercapnia increases core temperature cooling rate during snow burial. *J Appl Physiol*, **96**, 1365–1370.

79 Krivickas LS (2006) Recurrent rhabdomyolysis in a collegiate athlete: a case report. *Med Sci Sports Exerc*, **38**, 407–410.

80 Braseth NR, Allison EJ Jr, Gough JE (2001) Exertional rhabdomyolysis in a body builder abusing anabolic androgenic steroids. *Eur J Emerg Med*, **8**, 155–157.

81 Daniels JM, van Westerloo DJ, de Hon OM, Frissen PH (2006) Rhabdomyolysis in a body-builder using steroids. *Ned Tijdschr Geneeskd*, **150**, 1077–1080.

82 Diness V (1985) Local tissue damage after intramuscular injections in rabbits and pigs: quantitation by determination of creatine kinase activity at injection sites. *Acta Pharmacol Toxicol*, **56**, 410–415.

83 Montero Perez FJ, Munoz Avila J, Berlango Jimenez A *et al.* (1996) Increase of blood levels of creative kinase following intramuscular injection. *Med Clin (Barc)*, **107**, 649–654

84 Ihedioha U, Sinha S, Campbell AC (2005) Do creatine kinase (CK) levels influence the diagnosis or outcome in patients with compartment syndrome? *Scott Med J*, **50**, 158–159.

85 Yousef MA, Vaida S, Somri M *et al.* (2006) Changes in creatine phosphokinase (CK) concentrations after minor and major surgeries in children. *Br J Anaesth*, **96**, 786–789.

86 Chesson AL, Kasarskis EJ, Small VW (1983) Postictal elevation of serum creatine kinase level. *Arch Neurol*, **40**, 315–317.

87 Wyllie E, Lueders H, Pippenger C, VanLente F (1985) Postictal serum creatine kinase in the diagnosis of seizure disorders. *Arch Neurol*, **42**, 123–126.

88 Alzeer AH, el-Hazmi MA, Warsy AS, Ansari ZA, Yrkendi MS (1997) Serum enzymes in heat stroke: prognostic implication. *Clin Chem*, **43**, 1182–1187.

89 Magalhaes ME (2005) Mechanisms of rhabdomyolysis with statins. *Arq Bras Cardiol*, **85**, 42–44.

90 Ricaurte B, Guirguis A, Taylor HC, Zabriskie D (2006) Simvastatin–amiodarone interaction resulting in rhabdomyolysis, azotemia and possible hepatotoxicity. *Ann Pharmacother*, **40**, 753–757.

91 Mansi IA, Huang J (2004) Rhabdomyolysis in response to weight-loss herbal medicine. *Am J Sci*, **327**, 356–357.

92 Thorsten H, Martin S, Theo W (2000) Isoenzyme-specific interaction of muscle-type creatine kinase with the sarcomeric M-line is mediated by NH_2–terminal lysine charge-clamps. *J Cell Biol*, **149**, 1225–1234.

93 Noakes TD (1987) Effect of exercise on serum enzyme activities in humans. *Sports Med*, **4**, 245–267.

94 Epstein Y (1995) Clinical significance of serum creatine phosphokinase activity levels following exercise. *Isr J Med Sci*, **31**, 698–699.

95 Bijsterbosch MK, Duursma AM, Smit MJ, Bos OJ, Bouma JM, Gruber M (1985) Several dehydrogenases and kinases compete for endocytosis from plasma by rat tissues. *Biochem J*, **229**, 409–417.

96 Nuviala RJ, Roda L, Lapieza MG, Boned B, Giner A (1992) Serum enzymes activities at rest and after a marathon race. *J Sports Med Phys Fitness*, **32**, 180–186.

97 Denvir MA, Galloway PJ, Meighan AS *et al.* (1999) Changes in skeletal and cardiac muscle enzymes during the Scottish Coast to Coast Triathlon. *Scott Med J*, **44**, 49–51.

98 Malm C, Sjodin TL, Sjoberg B *et al.* (2004) Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol*, **556**, 983–1000.

99 Totsuka M, Nakaji S, Suzuki K, Sugawara K, Sato K (2002) Break point of serum creatine kinase release after endurance exercise. *J Appl Physiol*, **93**, 1280–1286.

100 Kratz A, Lewandrowski KB, Siegel AJ *et al.* (2002) Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers. *Am J Clin Pathol*, **118**, 856–863.

101 Fallon KE, Sivyer G, Sivyer K, Dare A (1999) The biochemistry of runners in a 1600 km ultramarathon. *Br J Sports Med*, **33**, 264–269.

102 Hortobagyi T, Denhan T (1989) Variability in creatine kinase: methodological, exercise and clinically related factors. *Int J Sports Med*, **10**, 69–80.

103 Vincent HK, Vincent KR (1997) The effect of training status on the serum creatine kinase response, soreness and muscle function following resistance exercise. *Int J Sports Med*, **18**, 431–437.

104 Fehrenbach E, Niess AM, Schlotz E, Passek F, Dickhuth HH, Northoff H (2000) Transcriptional and translational regulation of heat shock proteins in leukocytes of endurance runners. *J Appl Physiol*, **89**, 704–710.

105 Garry JP, McShane JM (2000) Postcompetition elevation of muscle enzyme levels in professional football players. *Med Gen Med*, **3**, E4.

106 Karamizrak SO, Ergen E, Tore IR, Akgun N (1994) Changes in serum creatine kinase, lactate dehydrogenase and aldolase activities following supramaximal exercise in athletes. *J Sports Med Phys Fitness*, **34**, 141–146.

107 Garry JP, McShane JM (2000) Postcompetition elevation of muscle enzyme levels in professional football players. *Med Gen Med*, **2**, E4.

108 Hurley BF, Redmond RA, Pratley RE, Treuth MS, Rogers MA, Goldberg AP (1995) Effects of strength training on muscle hypertrophy and muscle cell disruption in older men. *Int J Sports Med*, **16**, 378–384.

109 Serrão FV, Foerster B, Spada S *et al.* (2003) Functional changes of human quadriceps muscle injured by eccentric exercise. *Braz J Med Biol Res*, **36**, 781–786.

110 Staubli M, Roessler B, Kochli HP, Peheim E, Straub PW (1985) Creatine kinase and creatine kinase MB in endurance runners and in patients with myocardial infarction. *Eur J Appl Physiol Occup Physiol*, **54**, 40–45.

111 Hyatt JP, Clarkson PM (1998) Creatine kinase release and clearance using MM variants following repeated bouts of eccentric exercise. *Med Sci Sports Exerc*, **30**, 1059–1065.

112 Helers GG, Ball TE, Liston L (2002) Creatine kinase levels are elevated during 2-A-day practices in collegiate football players. *Athletic Training*, **37**, 151–156.

113 Smith LL, Fulmer MG, Holbert D *et al.* (1994) The impact of a repeated bout of eccentric exercise on muscular strenght, muscle soreness and creatine kinase. *Br J Sports Med*, **28**, 267–271.

114 Noakes TD, Kotzenberg G, McArthur PS, Dykman J (1983) Elevated serum creatine kinase MB and creatine kinase BB-isoenzyme fractions after ultra-marathon running. *Eur J Appl Physiol Occup Physiol*, **52**, 75–79.

115 Brayne CE, Dow L, Calloway SP, Thompson RJ (1982) Blood creatine kinase isoenzyme BB in boxers. *Lancet*, **2**, 1308–1309.

116 Koutedakis Y, Raafat A, Sharp NC, Rosmarin MN, Beard MJ, Robbins SW (1993) Serum enzyme activities in individuals with different levels of physical fitness. *J Sports Med Phys Fitness*, **33**, 252–257.

117 Havas E, Komulainen J, Vihko V (1997) Exercise-induced increase in serum creatine kinase is modified by subsequent bed rest. *Int J Sports Med*, **18**, 578–582.

118 Schillinger A, Koenig D, Haefele C *et al.* (2006) Effect of manual lymph drainage on the course of serum levels of muscle enzymes after treadmill exercise. *Am J Phys Med Rehabil*, **85**, 516–520.

119 Coombes JS, McNaughton LR (2000) Effects of branched-chain amino acid supplementation on serum creatine kinase and lactate dehydrogenase after prolonged exercise. *J Sports Med Phys Fitness*, **40**, 240–246.

120 Galassi G, Rowland LP, Hays AP, Hopkins LC, Di Mauro S (1987) High serum levels of creatine kinase: asymptomatic prelude to distal myopathy. *Muscle Nerve*, **10**, 346–350.

121 Joy JL, Oh SJ (1989) Asymptomatic hyper-CK-emia: an electrophysiologic and histopathologic study. *Muscle Nerve*, **12**, 206–209.

122 Wokke JH (2003) Raised creatine-kinase serum activity: not necessarily a sign of disease. *Ned Tijdschr Geneeskd*, **147**, 1998–2000.

123 Prelle A, Tancredi L, Sciacco M *et al.* (2002) Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum greatine kinase levels. *J Neurol*, **249**, 305–311.

124 Capasso M, De Angelis MV, Di Muzio A *et al.* (2006) Familial idiopathic hyper-CK-emia: an underrecognized condition. *Muscle Nerve*, **33**, 760–765.

125 Reijneveld JC, Notermans NC, Linssen WH, Wokke JH (2000) Benign prognosis in idiopathic hyper-CK-emia. *Muscle Nerve*, **23**, 575–579.

126 Dabby R, Sadeh M, Herman O *et al.* (2006) Asymptomatic or minimally symptomatic hyperCKemia: histopathologic correlates. *Isr Med Assoc J*, **8**, 110–113.
127 Kleppe B, Reimers CD, Altmann C, Pongratz DE (1995) Findings in 100 patients with idiopathic increase in serum creatine kinase activity. *Med Klin*, **90**, 623–627.
128 Miyoshi K, Kawai H, Iwasa M, Kusaka K, Nishino H (1986) Autosomal recessive distal muscular dystrophy as a new type of progressive muscular dystrophy. Seventeen cases in eight families including an autopsied case. *Brain*, **109**, 31–54.
129 Faigel HC (1995) Carnitine palmitoyltransferase deficiency in a college athlete: a case report and literature review. *J Am Coll Health*, **44**, 51–54.
130 Dupond JL, de Wazieres B, Monnier G, Closs F, Desmurs H (1992) Silent exercise-induced enzymatic myopathies at rest in adults. A cause of confusion with fibromyalgia. *Presse Med*, **6**, 974–978.
131 Vielhaber S, Feistner H, Wels J *et al.* (2004) Primary carnitine deficiency: adult onset lipid storage myopathy with a mild clinical course. *J Clin Neurosci*, **11**, 919–924.
132 Woldseth B, Rootwelt T (2006) Mitochondrial beta-oxidation defects. *Tidsskr Nor Laegeforen*, **126**, 756–759.
133 Deschauer M, Gizatullina Z, Schuize A *et al.* (2006) Molecular and biochemical investigations in fumarase deficiency. *Mol Genet Metab*, **88**, 146–152.
134 Di Mauro S (2006) Mitochondrial myopathies. *Curr Opin Rheumatol*, **18**, 636–641.
135 Sciacco M, Prelle A, Comi GP *et al.* (2001) Retrospective study of a large population of patients affected with mitochondrial disorders: clinical, morphological and molecular genetic evaluation. *J Neurol*, **248**, 778–788.
136 Abe M, Higuchi I, Morisaki H, Morisaki T, Osama M (2000) Myoadenilate deaminase deficiency with progressive muscle weakness and atrophy caused by new missense mutations in AMPD1 gene: case report in a Japanese patient. *Neuromuscul Disord*, **10**, 472–477.
137 Tsujino S, Nonaka I, Di Mauro S (2000) Glycogen storage myopathies. *Neurol Clin*, **18**, 125–150.
138 Prelle A, Rigoletto C, Moggio M *et al.* (1996) Asymptomatic familial hyperCKemia associated with desmin accumulation in skeletal muscle. *J Neurol Sci*, **140**, 132–136.
139 Weinberg J, Curl LA, Kunci RW, McFarland EG (1999) Occult presentation of myotonia congenital in a 15-year-old athlete. *Am J Sports Med*, **27**, 529–531.
140 Fredericson M, Kim BJ, Date ES (2004) Disabling foot cramping in a runner secondary to paramyotonia congenital: a case report. *Foot Ankle Int*, **25**, 510–512.
141 Drouet A, Leturcq F, Guilloton L, Delage H, Ribot C (2002) Muscular exercise intolerance syndrome in Becker muscular dystrophy. *Presse Med*, **31**, 197–201.
142 Minetti C, Tanji K, Chang HW *et al.* (1993) Dystrophinopathy in two young boys with exercise-induced cramps and myoglobinuria. *Eur J Pediatr*, **152**, 848–851.
143 Bushby KM, Pollitt C, Johnson MA, Rogers MT, Chinnery PF (1998) Muscle pain as a prominent feature of a facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. *Neuromuscul Disord*, **8**, 574–579.
144 Carbone I, Bruno C, Sotgia F *et al.* (2000) Mutation in the CAV3 gene causes partial caveolin-3 deficiency and hyperCKemia. *Neurology*, **54**, 1373–1376.
145 Arbustini E, Pilotto A, Repetto A *et al.* (2002) Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. *J Am Coll Cardiol*, **39**, 981–990.
146 Kuru S, Yasuma F, Wakayama T *et al.* (2004) A patient with limb girdle muscular dystrophy type 2B (LGMD2B) manifesting cardiomyopathy. *Rinsho Shinkeigaku*, **44**, 375–378.
147 Weglinski MR, Wedel DJ, Engel AG (1997) Malignant hyperthermia testing in patients with persistently increased serum creatine kinase levels. *Anesth Analg*, **84**, 1038–1041.
148 Reijneveld JC, TeBoekhorst BC, Zonderland ML, Kalmijn S, Notermans NC (2002) Response to exercise of patients with idiopathic hyperCKemia. *Muscle Nerve*, **26**, 832–837.
149 Lue YJ, Chen SS (2000) The strength and functional performance in patients with facioscapulohumeral muscular dystrophy. *Kaohsiung J Med Sci*, **16**, 248–254.
150 van der Kool EL, Vogels OJ, van Asseldonk RJ *et al.* (2004) Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology*, **63**, 702–708.
151 van der Kool EL, Lindeman E, Riphagen I (2005) Strength training and aerobic exercise training for muscle disease. *Cochrane Database Syst Rev*, **25**, CD003907.

152 Brancaccio P, Limongelli FM, Maffulli N (2006) Monitoring of serum enzymes in sport. *Br J Sports Med*, **40**, 96–97.

153 Koutedakis Y, Raafat A, Sharp NC, Rosmarin MN, Beard MJ, Robbins SW (1993) Serum enzyme activities in individuals with different levels of physical fitness. *J Sports Med Phys Fitness*, **33**, 252–257.

154 Vincent HK, Vincent KR (1997) The effect of training status on the serum creatine kinase response, soreness and muscle function following resistance exercise. *Int J Sports Med*, **18**, 431–437.

155 Maxwell JH, Bllor CM (1981) Effects of conditioning on exertional rhabdomyolysis and serum creatine kinase after severe exercise. *Enzyme*, **26**, 177–181.

156 Kratz A, Lewandrowski KB, Siegel AJ *et al*. (2002) Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers. *Am J Clin Pathol*, **118**, 856–863.

157 Lin AC, Lin CM, Wang TM, Leu JG (2005) Rhabdomyolysis in 119 students after repetitive exercise. *Br J Sports Med*, **39**, e3.

158 Braseth NR, Allison EJ Jr, Gough JE (2001) Exertional rhabdomyolysis in a body builder abusing anabolic androgenic steroids. *Eur J Emerg Med*, **8**, 155–157.

159 Sheth NP, Sennet B, Berns JS (2006) Rhabdomyolysis and acute renal failure following arthroscopic knee surgery in a collegiate football player taking creatine supplementation. *Clin Nephrol*, **65**, 134–137.

160 Hartmann U, Mester J (2000) Training and overtraining markers in selected sport events. *Med Sci Sports Exerc*, **31**, 209–215.

161 Margaritis I, Tessier F, Verdera F, Bermon S, Marconnet P (1999) Muscle enzyme release does not predict muscle function impairment after triathlon. *J Sports Med Phys Fitness*, **39**, 133–139.

162 Hartmann U, Mester J (2000) Training and overtraining markers in selected sport events. *Med Sci Sports Exerc*, **32**, 209–215.

163 Noakes TD (1987) Effect of exercise on serum enzyme activities in human. *Sports Med*, **4**, 245–267.

164 Bruno C, Bertini E, Santorelli FM, DiMauro S (2000) HyperCKemia as the only sign of McArdle' disease in a child. *J Child Neurol*, **15**, 137–138.

165 Woodman SE, Sotgia F, Galbiati F, Minetti C Lisanti MP (2004) Caveolinopathies: mutations in caveolin-3 cause four distinct autosomal dominant muscle diseases. *Neurology*, **62**, 538–543.

166 Carbone I, Bruno C, Sotgia F *et al*. (2000) Mutation in the CAV-3 gene causes partila caveolin-3 deficiency and hyperCKemia. *Neurology*, **54**, 1373–1376.

167 Brown SC, Torelli S, Brockington M *et al*. (2004) Abnormalities in alpha-dystroglycan expression in MDC1C and LGMD2I muscular dystophies. *Am J Pathol*, **164**, 727–737.

168 Ramaekers FC, Bosman FT (2004) The cytoskeleton and disease. *J Pathol*, **204**, 351–354.

169 Worman HJ (2005) Components of the nuclear envelope and their role in human disease. *Novartis Found Symp*, **264**, 35–42.

170 Broers JL, Hutchison CJ, Ramaekers FC (2004) Laminopathies. *J Pathol*, **204**, 478–488.

171 Finsterer J, Neuhuber W, Mittendorfer B (2004) Reconsidering idiopathic CK-elevation. *Int J Neurosci*, **114**, 1333–1342.

172 Drouet A, Leturcq F, Guilloton L, Delage H, Ribot C (2002) Muscular exercise intolerance syndrome in Becker muscular dystrophy. *Presse Med*, **31**, 197–201.

173 Flaherty KR, Wald J, Weisman IM *et al*. (2001) Unexplained exertional limitation. *Am J Respir Crit Care Med*, **164**, 425–432.

174 DeSouza RA, Cardenas RJ, Lindler TU, De La Fuente FA, Mayorquin FJ, Trochtenberg DS (2004) Mitocondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS): a mitocondrial disorder presents as fibromyalgia. *South Med J*, **97**, 528–531.

175 Mahjneh I, Haravuori H, Paetau A, Anderson LV, Saarinen A, Somer H (2003) A distinct phenotype of distal myopathy in a large Finnish family. *Neurology*, **61**, 87–92.

176 Kuru S, Yasuma F, Wakayama T *et al*. (2004) A patient with limb girdle muscular dystrophy type 2B (LGMD2B) manifesting cardiomyopathy. *Rinsho Shinkeigaku*, **44**, 375–378.

177 Wang HK, Cochrane T (2001) Mobility impairment, muscle imbalance, muscle weakness, scapular asymmetry and shoulder injury in elite volleyball athletes. *J Sports Med Phys Fitness*, **41**, 403–410.
178 Kaar S, Hazard D, Miller BS (2005) Facioscapulohumeral muscular dystrophy presenting as shoulder pain in a baseball player. *Arthroscopy*, **21**, 1145.
179 Cavanagh NP, Preece MA (1981) Calf hypertrophy and asimmetry in female carriers of X-linked Duchenne muscular dystrophy: an over-diagnosed clinical manifestation. *Clin Genet*, **20**, 168–172.
180 Mahjneh I, Haravuori H, Paetau A *et al.* (2003) A distinct phenotype of distal myopathy in a large Finnish family. *Neurology*, **61**, 87–92.
181 Bonnemann CG, Bushby K (2002) Chapter 37: The limb-girdle muscular dystrophies. In Engel AG, Franzini C, Armstrong H (eds) *Myology*, (Aggiungere: McGraw-Hill) 3rd ed., 1089–1092.
182 Moreira ES, Wiltshire TJ, Faulkner G *et al.* (2000) Limb girdle muscular dystrophy type 2G is caused bymutation in the gene encoding the sarcomeric protein telethonin. *Nat Genet*, **24**, 163.
183 Hauser MA, Horrigan SK, Salmikangas P *et al.* (2000) Myotilin is mutated in limb girdle muscular dystrophy type 1A. *Hum Mol Genet*, **9**, 2141.
184 Laing NG (1999) Inherited disorders of sarcomeric proteins. *Curr Opin Neurol*, **12**, 513.
185 Fuchs E, Yang Y (1999) Crossroads on cytoskeletal highways. *Cell*, **98**, 547.
186 Vercelli L, Mongini T, Tupler R *et al.* (2006) Selective hypotrophy of pectoralis muscle reveals an atypical case of FSHD. *Basic Appl Myol*, **16**, 62.
187 Burnett JR, Crooke MJ, Delahunt JW, Feek CM (1994) Serum enzymes in hypothyroidism. *N Z Med J*, **107**, 355–356.
188 Finsterer J, Milvav E (2004) Stress lactate in mitochondrial myopathy under constant unadjusted workload. *Eur J Neurol*, **11**, 811–816.
189 Finsterer J, Milvav E (2002) Lactate stress testing in 155 patients with mitochondriopathy. *Can J Neurol Sci*, **29**, 49–53.
190 Lofberg M, Lindholm H, Naveri H *et al.* (2001) ATP, phosphocreatine and lactate in exercising muscle in mitochondrial disease and Mc'Ardle's disease. *Neuromuscul Disord*, **11**, 370–375.
191 De Bleecker (2005) How to approach the patient with muscular symptoms in the general neurological practice? *Acta Neurol Belg*, **105**, 18–22.
192 Gaines RF, Pueschel SM, Sassaman EA, Driscoll JL (1982) Effect of exercise on serum creatine kinase in carriers of Duchenne muscular dystrophy. *J Med Genet*, **19**, 4–7.
193 Feng J, Yan J, Buzin CH *et al.* (2002) Mutation in the dystrophin gene are associated with sporadic dilated cardiomypathy. *Mol Genet Metab*, **77**, 119–126.
194 Olsen DB, Gideon P, Jeppesen TD, Vissing J (2006) Leg muscle involvement in facioscapulohumeral muscular dystrophy assessed by MRI. *J Neurol*, **253**, 1437–1441.