Serum enzymes

Monitoring of serum enzymes in sport

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Monitoring of creatine kinase and lactate dehydrogenase can reveal the state of the muscle and its biochemical adaptation to physical load

Functional assessment of athletes' fitness includes a variety of variables. Serum creatine kinase (CK) and lactate dehydrogenase (LDH) give an indication of the degree of metabolic adaptation to physical training of skeletal muscles. Both enzymes are involved in muscle metabolism, and their serum concentration is normally very low, a result of physiological wear and tear of the cell. They increase considerably after intensive exercise and in muscle pathology.[1 2]

Changes in serum activity of muscle enzymes have been reported in normal subjects and athletes after strenuous exercise.[3–6] The amount of enzyme efflux from muscle tissue to serum can be influenced by physical exercise.[7] Also, there are ethnic differences,[8] and the differences between the sexes have been attributed to the protective effects of oestrogen on muscle cell membrane.[9]

Muscle biopsy findings have evidenced different activity of total LDH and LDH isozymes in endurance and strength athletes. The former had lower total LDH with a prevalence of LDH1–2 isoenzyme activity compared with the latter, who showed higher total LDH and prevalence of LDH5 activity. In addition, LDH and CK activity measured by needle biopsy showed different behaviour before and after training, and changes due to different protocols and intensity and level of training.[10–13] This is especially true for CK, the isoenzymes of which can be identified in different organs: CK1(BB) is mainly from the brain, CK2(MB) is mainly cardiac, and CK3(MM) is mainly from skeletal muscle.

Monitoring of CK and characterisation of its isoenzymes is widely used in the diagnosis of cardiomyopathies, encephalopathies, and muscle disease.[14–16] CK activity may increase after treatment with cholesterol lowering drugs, asthma, hypothyroidism, recreational drug use, and anabolic androgenic steroid abuse.[17] Also, increased CK activity from rhabdomyolysis is found during and after exercise.[18 19] In this instance, high CK activity correlates with physical training status, with large increases in CK after exercise. Most data on CK monitoring come from long distance runners, although short intense periods of sports activity seem to induce increases in serum CK, especially if eccentric muscle contractions have been involved.[12] In these instances, the high serum CK activity is a consequence of damage to sarcolemmal membrane.[20 21] The damage is probably proportional to the duration and intensity of the contraction, and is related to the severity of muscle soreness. A peak is reached 24 hours after the end of the exercise, and CK activity may stay raised for 48–72 hours.

High serum CK activity in apparently healthy subjects at rest and without other factors should therefore prompt further investigations; once secondary rhabdomyolysis is excluded, it may be a sign of a genetic muscle disease.[22] Muscle biopsy is helpful for diagnosis in asymptomatic subjects with high serum CK activity: 18% of such patients had a muscle disease, 38.6% non-specific muscle anomalies, and 31.6% were normal.[23 24]

High CK activity after a period of complete rest in an athlete is unexpected, as physical training also exerts a positive effect on the sarcolemma. Most data from the literature evidence that the resting CK activity is higher in athletes, but, in the absence of trauma, drugs, or other pathologies, increases after exercise are lower than those recorded in matched healthy control subjects.[25] Hence, persistently high CK activity may be a sign of a subclinical genetic muscle disease, which training loads may evidence through the onset of symptoms such as profound fatigue and abnormal contractions.[26]

Recently, several studies have identified numerous muscle diseases with a variety of clinical manifestations. For example, Mongini *et al*[27] have documented a patient with high serum CK activity with mild myoglobinuria at rest and decreased muscle function associated with changes in α sarcoglycan. Also, other patients have shown McArdle syndrome, and some patients with muscle dystrophy show mutation of the gene for caveolin.[28] In others, high serum CK activity may be a sign of malignant hyperthermia, with no significant relation between the basal serum CK activity and the severity of the condition.[29] In some patients, the muscle condition may be phenotypically expressed as a cardiomyopathy.[30]

High serum CK activity in an athlete after absolute rest and without any further predisposing factors should prompt a full diagnostic work up with particular regard 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 symmetry of the inferior angle of the scapula and the iliac spines.[31–33] Stiffness and muscle soreness are a normal consequence of physical training. However, if they are resistant to rest and massage, or recur too often, they should prompt a diagnostic work up.

Further minimally invasive investigations include examination of the isoenzymes of CK (CK-MM, CK-MB, CK-BB) and LDH (LDH1, LDH2, LDH3, LDH4, LDH5) at rest and after exercise. In healthy athletes, serum CK activity peaks six hours after exercise and returns to normal within 48 hours.

> ''A symptomatically high CK activity may be a predictor of late onset cardiomyopathy''

Normally, only CK-MM is present in the serum; the presence of other isoenzymes should be considered suspicious. CK-MB is present in ultramarathon runners,[34] and CK-BB in boxers,[35] but the presence of these isoenzymes at rest or after a laboratory exercise test should be considered a sign of pathology. A symptomatically high CK activity may be a predictor of late onset cardiomyopathy, which can be difficult to identify, especially in subjects who practice endurance sports. In these instances, it may be necessary to perform serial echocardiography to identify the possible onset of the condition.

The isoenzymes of LDH give a different picture from CK with regard to metabolic adaptation to exercise, with different profiles in power and endurance athletes. Therefore the study of the isoenzymes of CK and LDH produces information not only on the state of the muscle but also on its biochemical adaptation to physical load. Often patients with persistent high CK activity also have altered LDH profiles. The protocol for studying an athlete with recurrent muscle problems with known high CK activity should include accurate clinical examination to detect the

asymmetries outlined above, together with localised atrophic or hypotonic muscles. Echocardiography may reveal heart problems, which can themselves be responsible for high CK activity, as some genetic cardiomyopathies may present late with cardiac involvement.[36] A maximal exercise test should be performed to evaluate CK and LDH isoenzymes at baseline, 30 minutes, six hours, 24 hours, 48 hours, and 72 hours after the tests. In this way, it is possible to study the serum kinetics of these enzymes. The evaluation should also include serum lactate concentrations at baseline, at peak effort, and 5–10 minutes after the tests.[37] A urinalysis should reveal exercise myoglobinuria.[38] If CK and LDH activities are persistently altered, then it may be necessary to perform a muscle biopsy. If the subject is asymptomatic and if light microscopy reveals no gross morphological changes at muscle biopsy, biochemical and genetic tests must be performed to exclude a pre-clinical or carrier status of a genetic disease or a metabolic disorder such as carnitine palmitoyltransferase deficiency.[39] If these tests are negative, then idiopathic high CK activity may be present. To our knowledge, there are no studies on the effects of repeated exercise bouts on athletes with persistent high CK activity. Therefore, if the athlete is totally asymptomatic, it is difficult to evaluate the risks of sporting activities. It is, however, possible that repeated 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. Indeed, in muscles of syntrophin deficient subjects after exercise, muscle hypertrophy occurs with formation of abnormal neuromuscular junctions.[40]

It is probably safe to counsel the athlete to continue to undertake physical activity at a lower intensity, so as to prevent muscle damage from high intensity exercise, and allowing ample recovery time.

In conclusion, further clinical examination and investigations should be performed to identify the possible causes of muscle pathology at the basis of persistent high serum CK activity. In this respect, athletes with persistently high CK activity at rest should be considered exactly as all other subjects in the same condition and directly undergo muscle biopsy to try to achieve a diagnosis.

Once a diagnosis has been formulated, physical activity should be tailored to the physical and sporting needs of the individual. However, to date this can only be undertaken on a trial and error basis.

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