

Persistent HyperCKemia in Athletes

Paola Brancaccio¹,
Nicola Maffulli²,
Luisa Politano³,
Giuseppe Lippi⁴,
Francesco Mario Limongelli¹

¹Seconda Università di Napoli, Servizio di Medicina dello Sport, Department of Experimental Medicine, Centre of Excellence of Cardiovascular Disease, Napoli, Italy (PB, GL, FML)

²Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Centre for Sports and Exercise Medicine, Mile End Hospital, London E1 4DG, England (NM)

³Seconda Università di Napoli, Servizio di Cardiomiologia e genetica medica, Department of Experimental Medicine, Centre of Excellence of Cardiovascular Disease, Napoli, Italy (LP)

⁴U.O. Diagnostica Ematochimica, Dipartimento di Patologia e Medicina di Laboratorio, Azienda Ospedaliero-Universitaria di Parma, Italy

Corresponding author:

Paolo Brancaccio MD
Servizio di Medicina dello Sport
Via Costantinopoli, 16 - Napoli - Italy
Tel. 328 8963153
pabranca@libero.it

Summary

We compared the effects of exercise on serum levels of creatin kinase (CK) in athletes with persistent hyperCKemia at rest (CK group) and in healthy athletes (control group).

Prospective controlled study.

Eighteen male Caucasian athletes with high serum CK levels at rest (CK between 80 and 150 U/L) and 25 male Caucasian athletes with normal serum CK levels at rest (CK between 10 and 80 U/L)

Main Outcome Measures. Blood samples were collected at rest, 30 minutes, 6 hours, 24 hours, 48 hours and 72 hours after a progressive cycloergometer test to exhaustion. The levels of serum CK and its isoenzymes were measured.

In the control group, serum CK values at rest were normal (48.18 ± 14.14 U/L). After exercise, they increased slightly, though they always remained <80 U/L, decreasing to the rest level after 48 hours. The CK group had serum CK levels at rest higher than normal (116.56 ± 33.30 U/L). Serum CK levels were still

outwith the normal range after 48 hours (130.11 ± 46.95 U/L) and 72 hours (116.55 ± 24.84 U/L). Serum CK levels were significantly different in both groups both before and after progressive cycloergometer test to exhaustion.

In athletes with high serum CK levels at rest, serum CK levels remained elevated and had a different kinetics after exercise when compared with healthy athletes.

Key Words: Hyperckemia, Primitive Myopathy, Muscular Enzymes.

Background

Creatine kinase (CK) is located in the sarcolemma and mitochondrial intermembrane space of healthy muscle cells. It catalyzes the movement of phosphate from phosphocreatine to adenosine diphosphate, forming adenosine triphosphate (ATP) and creatine (1).

Human tissues contain three dimer isoenzymes, MM, MB and BB, located respectively in skeletal muscle, heart and brain. In serum, total CK is provided mainly by the MM fraction. In health, serum CK concentration is dependent on race, gender (2,3), age (4), muscle mass (5) and physical activity (6), with higher values in black men and athletes.

Strenuous exercise that damages skeletal muscle cell structure at the level of sarcolemma and Z disks (7) results in an increase in total CK (8,9). CK leaks into the interstitial fluid, is uptaken by the lymphatic system, and returns into the circulation. Hence, daily training may result in persistent serum elevation of CK (10), and resting serum CK levels are higher in athletes (11,12). However, if athletes and sedentary subjects undertake the same physical exercise test, the serum CK levels of athletes are lower than those recorded in matched healthy control subjects (13,14). Also, a large increase of serum CK levels combined with reduced exercise tolerance could be a marker of overtraining (15). Elevated plasma levels of CK are observed in various neuromuscular conditions as a result of muscle damage and necrosis. A sustained increase in serum CK is often the results of myopathies, with levels depending on severity and course of the disease (16). CK levels, though still high, are less elevated in neurogenic disorders (17).

Persistently high serum CK levels at rest may be encountered in individuals with idiopathic hyperCKemia (18), but it is also possible that subjects with abnormal increase in serum CK after exercise may have an unrecognised subclinical myopathy (19). Exercise does not result in more extensive muscle damage in patients with idiopathic hyperCKemia than in healthy controls (20). In some female patients heterozygous for Duchenne mus-

cular dystrophy, serum CK levels after exercise may be better indicators of carrier status than resting levels (21). This study investigated the effect of exercise on serum CK levels in athletes with persistent hyperCKemia at rest compared with a control group of healthy athletes.

Methods

All procedures were approved by the local ethics committee, and all participants gave written informed consent to participate in the study.

Subjects

All the athletes involved in the present study had attended a routine pre-participation screening session, and had undergone routine exercise testing (19, 22, 23). We recruited 18 male Caucasian athletes playing different sports (mean age 27.31 ± 10.33 years; weight 79.92 ± 17.42 Kg; height 180.38 ± 6.64) and high serum CK levels at rest (CK between 80 and 150 U/L) (CK group). We also recruited a control group (C group) consisting of 25 male Caucasian athletes playing different sports (mean age 23.79 ± 8.72 year; weight 70.07 ± 7.66 Kg; height 172.21 ± 7.04) and normal serum CK levels at rest (CK between 10 and 80 U/L). After establishing that the CK group had persistently elevated serum CK levels at rest, all athletes underwent 15 days of abstention from athletic activities before another blood sample was taken to establish the basal levels of CK. Before entering the study, each participant completed a questionnaire to determine whether factors in their lifestyle could account for increased in CK levels.

Protocols

The blood collected was transported immediately to the laboratory, centrifuged, and the assay performed using a spectrometric monotest method (EOS 880 CGA Strumenti Scientifici, Firenze, Italy) at 25°C according to the manufacturer's instructions. We used the reference values of 10–80 U/L as normal. Isoenzymatic evaluation was performed by agarose-gel electrophoresis and determined by Beckman Appraise Densitometer System method [Helena Laboratories Europe Biosciences SAS 1 Platinum, Assago (MI), Italy]. The reference values for the various isoenzymes are CK-MB: 0–4.8%, CK-MM: 0–80%, and CK-BB: 0 % of total CK.

Exercise test All subjects underwent an electrically braked cycloergometer (SECA, Hamburg, Germany) at 60–70 RPM to exhaustion. Each test started with a 2 minute warm up with a load of 25 watt, with an increment of 25 watt every 2 minutes to exhaustion. This was followed by 1 minute of warm down at a load of 25 watt, and by 4 minutes of rest while supine.

To assess CK and its isoenzymes activity (CK-MM, CK-MB, CK-BB), blood samples were taken at rest, 30 minutes, 6 hours, 24 hours, 48 hours and 72 hours after the test.

Assessment of serum lactic acid levels were made at rest, immediately after completion of the test, and 5 and 30 minutes later. The athletes who showed high serum CK values at rest or after exercise underwent careful clinical examination to evaluate localised hypotonic or hypotrophic muscles in the pelvic and upper limb girdle to ascertain whether signs of muscle weakness were present.

All athletes also underwent clinical and echocardiographic examination to identify genetic muscular pathology phenotypically expressed as a cardiomyopathy (24). If a myopathy was diagnosed they received genetic counselling.

Statistics: Statistical analysis was performed by SPSS statistical package for Windows, release 10.0 (Chicago, IL, USA). Descriptive statistics were calculated. Comparison between the values of CK obtained in the two groups before and after exercise was performed by paired Student's *t* test for different samples. Differences were considered statistically significant when $p < 0.05$.

Results

After completing the questionnaire, two athletes from the CK group were excluded from the study, since they had had mononucleosis three months before our investigation. We also excluded three further athletes whose serum CK levels returned to normal after the 15 day rest period. Therefore, the CK group includes 13 athletes who completed the cycloergometer test to exhaustion.

The athletes in the CK group reached a mean 191.67 ± 25 W at exhaustion. The athletes in the C group reached a mean work of 227.27 ± 36.15 W. ($p = 0.02$).

The resting values of lactic acid were not significantly different between the two groups (2.5 vs 2.3 mmol/L). At exhaustion (7.2 vs 8 mmol/L) however, after 5 minutes of recovery (8.1 vs 7.6 mmol/L), and after 30 minutes of recovery (4.9 vs 3.8 mmol/L), they were significantly higher in the CK group than in the C group ($0.05 < p < 0.01$).

In the control group, the CK values at rest were within the URL (48.18 ± 14.14 U/L). After exercise, they increased slightly (30' post test = 55.06 ± 17.74 U/L; 6 h post test = 55.46 ± 22.26 U/L; 24h post test = 53.50 ± 22.67 U/L), although they always remain lower than 80 U/L, decreasing to the rest level after 48 hours (48 hours 49.69 ± 21.90 U/L; 72 hours 42.00 ± 14.14 U/L) (Fig. 1). The CK group always had serum CK levels at rest higher than normal (116.56 ± 33.30 U/L). After the test, serum CK levels were always increased (30' post test = 137.89 ± 59.48 U/L; 6h post test = 145.68 ± 51.52 U/L; 24h post test = 136.16 ± 60.29 U/L), and did not return to the normal range (< 80 U/L) after 48 hours (130.11 ± 46.95 U/L) and 72 hours (116.55 ± 24.84 U/L) (fig. 1). The two groups had both before and after the test serum CK levels significantly different (rest: $p = 0.00$; 30': $p = 0.00$; 6h: $p = 0.00$; 24h: $p = 0.00$; 48h: $p = 0.00$; 72h: $p = 0.01$). Although most of the serum CK released after exercise was of the CK-MM fraction, 7 subjects in the CK group showed small amounts of CK-MB isoenzyme ($< 5\%$). None of the subjects of the C group had detectable levels of this isoenzyme.

None of the athletes in control group referred muscular symptoms. Nine subjects in the CK group reported in the questionnaire muscular symptoms such as fatigue, pain and cramp after intensive training. One athlete had CK values 48 hours after the test lower than the rest values and reported muscular weakness after exercise. Other 4 subjects in the CK group had only slightly hyperckemia without muscular symptoms or fatigue.

The most common signs at examination were clinical features of involvement of the pelvic muscles (glutei and adductors), stiffness and muscle soreness of the upper and

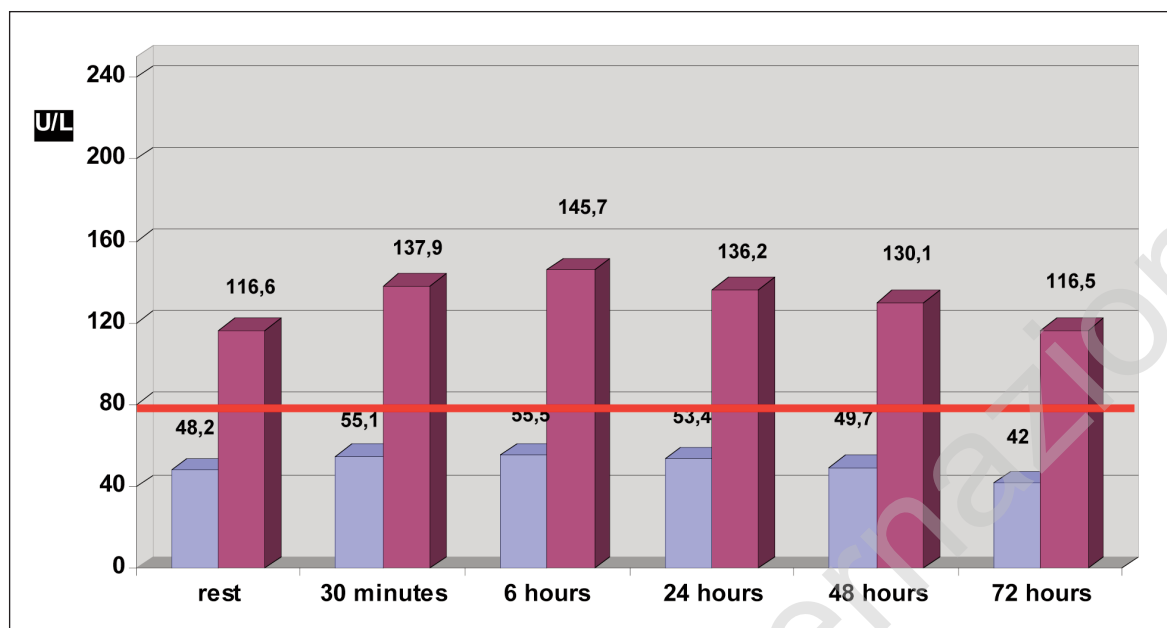


Figure 1 - Serum CK levels after exercise in the control group and in the CK group.

lower extremity with the involvement of deltoid, infraspinatus, biceps and periscapular muscles leading to scapular winging (Table 1). Some subjects had minimal facial involvement with a “transverse smile”, and occasional myalgia and muscle cramps.

All subjects were assessed by a Clinical Genetics consultant, who formulated the diagnoses reported in Table 2.

Discussion

Increased serum levels of CK from rhabdomyolysis are found during and after exercise (25, 26). In this instance, the high levels of CK are correlated with physical training status, but high levels of CK after a period of complete rest are unexpected both in athletes and in sedentary subjects. In our study, the elevated serum CK levels in the group with hyperCKemia persisted after exercise and did not return to normal range after 48 hours. Seven athletes of the CK group had clinical signs of Facioscapulohumeral muscular dystrophy (FSHD). In our study, most subjects exhibited relatively modest elevations of serum CK. However,

Table 1 - Clinical criteria used for myologic evaluation of subjects with persistent hyperCKhaemia.

- Skeletal anomalies
- Localized hypotrophy or hypertrophy
- Weakness of hip or shoulder muscles
- Scapular winging
- Myotonic disease
- Muscle contractures and cramps

Table 2 - Diagnoses formulated in the athletes in our study.

ATHLETE	SPORT	AGE	SEX	DIAGNOSIS
D. D.	RUNNING	33	M	Scapulohumeral dystrophy
V. I.	FOOTBALL	14	M	Limb-Girdle myopathy
G. P.	RUNNING	26	M	Limb-Girdle myopathy
S. D.	RUNNING	42	M	Facioscapulohumeral myopathy
G. G.	SWIMMING	17	M	Facioscapulohumeral myopathy
G. F.	SWIMMING	21	M	Facioscapulohumeral myopathy
G. M.	FITNESS	28	M	Facioscapulohumeral myopathy
F. C.	BASKET	17	M	Facioscapulohumeral myopathy
R. M.	FITNESS	23	M	Facioscapulohumeral myopathy
G. L.	RUNNING	50	M	Facioscapulohumeral myopathy
G. R.	CALCIO	33	M	To be defined
C. M.	BODY-BUILDING	28	M	To be defined
T. S.	RUNNING	17	M	CoQ10 deficiency Myopathy

in presymptomatic patients, the serum CK level might be slightly elevated. In one subject, muscular symptoms became suddenly worse after increasing training loads, and we suspected a CoQ10 deficiency Myopathy, as he referred that a brother had died for cerebellar ataxia the year before. Other two subjects (M.C. and G.R.) showed hyperCKemia at rest and after exercise, and clear signs of progressive muscle involvement. However, we have not been able to formulate a conclusive diagnosis.

Accurate history taking can evidence symptoms, such as fatigue, pain and cramp after intensive training, which athletes often underestimate, but can be the first signs of muscle disease. Another sign that can reveal a myopathy is isolated hypotrophy of a muscle usually involved in training (27).

In our study, athletes with hyperCKemia exhibited a response to progressive exercise to exhaustion within normal limits, even though the control group performed better. The assessment of the serum CK levels at rest is a simple and non invasive method to identify subjects with muscle disease without exercise intolerance in a preclinical stage of pathology.

Often, the high serum levels of CK are considered normal in asymptomatic athletes because clinicians know that they are influenced by training, while they can be a sign of silent disease. Indeed, CK serum levels are almost always elevated even in the preclinical stages of frank myopathy (28). The interpretation of CKemia at rest is difficult in athletes because, for a clear interpretation of the results, athletes need to abstain from training course for at least three days. In athletes with sign of silent myopathy, serum CK levels had a different kinetics after exercise compared with healthy athletes. In the control group, serum CK levels increase slightly after exercise, but remained lower than 80 U/L, decreasing to the resting values after 48 hours. The CK group had serum CK levels significantly higher than normal, and, after the test, did not return to normal range (< 80U/L), increasing for 48 hours after exercise (fig. 1). Symptoms such as unexplained exertional limitation can be a manifestation of biopsy-proven myopathies (29), but, in this instance, the evaluation of CK at rest and after exertion could be a simple and non invasive method towards diagnosis.

After genetic consultation, once a diagnosis has been formulated, it may be necessary to perform a muscle biopsy, although athletes often refuse to become "patients" until their underlying condition becomes clinically manifest. Early diagnosis is important because it is difficult to evaluate the risks of sporting activities: it is possible that repeated intense prolonged exercise may produce negative effects (27), as it does not induce the physiological muscle adaptations to physical training given the continuous loss of muscle proteins. 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 allow ample recovery to favour adequate recovery.

In the future, it might be interesting to study and quantify the type of exercise more suited to athletes with myopathy, and the intensity of exercise not dangerous for the progression of the pathology. Our results, although interesting, are partially limited by the relatively small number of individuals studied, and need of confirmation in a larger population. Moreover, since we did not perform skeletal muscle biopsy, we cannot assess the relationship between serum CK, clinical pictures, and histopathological features.

Conclusion

Evaluation of serum CK levels at rest, and the study of its kinetics after exercise help to identify myopathies often going undiagnosed in athletes. Clinical and laboratory findings should help the physician to identify athletes with pre-clinical disease.

References

1. Wyss M, Kaddurah-Daouk R "Creatine and creatine metabolism" *Physiol Rev* 2000; 80:1107-1213
2. Gledhill RF, Van der Merwe CA, Greyling M, Van Niekerk MM Race-gender differences in serum creatine kinase activity: a study among South Africans *J Neurol Neurosurg Psychiatry* 1988; 5:301-304
3. Clarkson PM, Hubal MJ Are women less susceptible to exercise-induced muscle damage? *Curr Opin Clin Nutr Metab Care* 2001; 4:527-531
4. Fu FH, You CY, Kong ZW 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* 2002; 95:1171-1178
5. Garcia W Elevated creatine phosphokinase levels associated with large muscle mass. Another pitfall in evaluating clinical significance of total serum CPK activity *YAMA* 1974; 228:1395-1396
6. Meltzer HV Factors affecting serum creatine phosphokinase levels in the general population: the role of race, activity and age *Clin Chim Acta* 1971; 33:165-172
7. Hornemann T, Stolz M, Wallimann T. Isoenzyme-specific interaction of muscle-type creatine kinase with the sarcomeric M-line is mediated by NH₂-terminal lysine charge-clamps. *The Journal of Cell Biology* 2000; 149:1225-1234
8. Noakes TD Effect of exercise on serum enzyme activities in humans *Sports Med* 1987; 4:245-267
9. Epstein Y. Clinical significance of serum creatine phosphokinase activity levels following exercise. *Isr J Med Sci* 1995; 31:698-699
10. Kratz A, Lewandrowski KB, Siegel AJ, Chun KY, Flood JG, Van Cott EM, Lee-Lewandrowski E Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers *Am J Clin Pathol* 2002; 118: 856-863
11. Fallon KE, Sivyer G, Sivyer K, Dare A The biochemistry of runners in a 1600 km ultramarathon *Br J Sports Med* 1999; 33: 264-269
12. Hortobagyi T, Denhan T, Variability in creatine kinase: methodological, exercise and clinically related factors *Int J Sports Med* 1989; 10:69-80
13. Karamizrak SO, Ergen E, Tore IR, Akgun N, Changes in serum creatine kinase, lactate dehydrogenase and aldolase activities following supramaximal exercise in athletes *J Sports Med Phys Fitness* 1994; 34:141-146
14. Garry JP, McShane JM Postcompetition evaluation of muscle enzyme levels in professional football players *MedGenMed* 2000; 3:2-4
15. Hartmann U, Mester J Training and overtraining markers in selected sport events *Med Sci Sports Exerc* 2000; 31:209-215
16. Engel A.G., Franzini-Armstrong C "Myology" Mc Graw Hill third edition vol II p. 978 2004

17. Szlachcic Y, Adkins RH, Waters RL, Govindarajan S, Wang J, Yee F, Greenwood J Incidence and clinical correlates of increased serum creatine kinase levels in persons with spinal cord injury J Spinal Cord Med 2002; 25:156-160
18. Capasso M, De Angelis MV, Di Muzio A, Scarciolla O, Pace M, Stupia L, Comi GP, Uncini A. Familial idiopathic hyperkemia: an unrecognized condition Muscle Nerve 2006; 33:760-765
19. P.Brancaccio, F.M. Limongelli, N. Maffulli Monitoring of serum enzymes in sport Br J Sports Med. 2006; 40:96-97
20. Reijneveld JC, Te Boekhorst BC, Zonderland ML, Kalmijn S, Notermans NC Response to exercise of patients with idiopathic hyper-ck-emia Muscle Nerve 2002; 26:832-837
21. Gaines RF, Puschel SM, Sassaman EA, Driscoll JL Effect of exercise on serum creatine kinase in carriers of Duchenne muscular dystrophy J Med Genet 1982; 19:4-7
22. Pigozzi F, Spataro A, Alabiso A, Parisi A, Rizzo M, Fagnani F, Di Salvo V, Massazza G, Maffulli N. Role of exercise stress test in master athletes. Br J Sports Med 2005; 39:527-531
23. Pigozzi F, Spataro A, Fagnani F, Maffulli N. Preparticipation screening for the detection of cardiovascular abnormalities that may cause sudden death in competitive athletes. Br J Sports Med 2003; 37:4-5
24. Feng J, Yan J, Buzin CH et al. Mutation in the dystrophin gene are associated with sporadic dilated cardiomyopathy Mal Genet Metab 2002; 77:119-126
25. Boffi FM, Cittar J, Balskus J, et al Training induced apoptosis in skeletal muscle. Equine Vet J Suppl 2002; 34: 275-278
26. Maxwell JH, Bloor CM Effects of conditioning on exertional rhabdomyolysis and serum creatine kinase after severe exercise. Enzyme 1981; 26:177-181
27. L. Vercelli, T. Mongini, R. Tupler, N. Oliviero, E. Vittonatto, R. Mutani, L. Palmucci "Selective hypotrophy of pectoralis muscle reveals an atypical case of FSHD" Basic and Applied Myology 2006; 16: 62
28. Miyoshi K, Kawai H, Iwasa M, Kusaka K, Nishino H Autosomal recessive distal muscular dystrophy as a new type of progressive muscular dystrophy. Seventeen cases in eight families including an autopsied case. Brain 1986; 109:31-54
29. Kevin R. Flaherty, Jhon Wald, Idelle M. Weisman, R. Jorge Zeballos, M. Anthony Schork, Mila Blaivas, Melvyn Rubenfire and Fernando J. Martinez "Unexplained exertional limitation: characterization of patients with a mitochondrial myopathy" Am J Respir Crit Care Med 2001; 164:425-432