

Exertional Rhabdomyolysis

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Received: 20.06.2019

Accepted: 02.07.2019

Summary

Rhabdomyolysis is a clinical syndrome characterized by the destruction of striated muscular tissue and the dumping of the intracellular content of the muscle that presents with muscle pain due to myositis, loss of strength and muscular edema. It is characterized by the high elevation of creatine kinase, myoglobin, dehydrogenated lactate and it can cause important complications, especially renal complications. According to the CK figures, always higher than 5000 IU / l, which are at the beginning of the table, rhabdomyolysis is classified as light and severe.

From the point of view of sport, among the various etiological causes that can cause it, it is interesting to focus on stress-induced rhabdomyolysis.

This work reviews the etiology of the clinical picture, paying special attention to exercise as a trigger of the syndrome and the characteristics of the type of exercise (physical condition and experience of the athlete, intensity and duration of physical exercise, type of exercise, environmental conditions, etc.) that can cause it.

Although the causes of rhabdomyolysis are very varied and different, the final pathogenic pathway leading to muscle destruction is common to all and has to do with the alteration in the regulation of intracellular electrolytes and especially with cytoplasmic calcium levels.

Currently, in addition to the analytical diagnosis, ultrasound allows a rapid diagnosis and the observation of the evolution of the picture. Rhabdomyolysis shows muscle involvement patterns that are described in this work.

Different prevention strategies are described based on the execution of an adequate physical exercise (type, intensity and duration of the exercise), measures related to nutrition and feeding, as well as measures related to environmental and educational factors.

Finally, is presented the immediate treatment of the symptoms, with necessary hospitalization in some cases, and recommendations on re-incorporation to training and sports competition.

Key words:

Rhabdomyolysis. Effort. Exercise. Muscle. Muscle injury. Ultrasound. Prevention. Treatment.

Rabdomiolisis inducida por esfuerzo

Resumen

La rabdomiolisis es un síndrome clínico caracterizado por la destrucción de tejido muscular estriado y el vertido del contenido intracelular del mismo que cursa con dolor muscular por miositis, pérdida de fuerza y edema muscular. Se caracteriza por la elevación muy importante de creatinquinasa, mioglobina, lactato deshidrogenado y puede provocar importantes complicaciones, fundamentalmente renales. En función de las cifras de CK, siempre superiores a 5000 UI/l, que se encuentran en el inicio del cuadro la rabdomiolisis se clasifica en ligera y severa.

De entre las diversas causas etiológicas que la pueden provocar, desde el punto de vista del deporte, interesa la rabdomiolisis inducida por esfuerzo.

Este trabajo revisa la etiología del cuadro, prestando especial atención al ejercicio como desencadenante o coadyuvante del síndrome y a las características del tipo de ejercicio (condición física y experiencia del deportista, intensidad y duración del ejercicio físico, tipo de ejercicio, condiciones ambientales, etc.) que pueden provocarla.

Aunque las causas de la rabdomiolisis son muy variadas y diferentes, la vía patogénica final que conduce a la destrucción muscular es común a todas y tiene que ver con la alteración en la regulación de los electrolitos intracelulares y especialmente con los niveles de calcio citoplasmático.

Además del diagnóstico analítico, actualmente, la ecografía permite un diagnóstico rápido y la observación de la evolución del cuadro. La rabdomiolisis muestra patrones de afectación muscular que se describen en el trabajo.

Se describen las estrategias de prevención basadas en la realización de un ejercicio físico adecuado (tipo, intensidad y duración del ejercicio), medidas relacionadas con la nutrición y alimentación, medidas relacionadas con los factores ambientales y medidas educativas.

Por último, se presenta el tratamiento inmediato del cuadro, con hospitalización necesaria en algunos casos, y las recomendaciones sobre re-incorporación al entrenamiento y a la competición deportiva.

Palabras clave:

Rabdomiolisis. Esfuerzo. Ejercicio. Músculo. Lesión muscular. Ecografía. Prevención. Tratamiento.

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Introduction

Rhabdomyolysis is a medical condition which consists of the breakdown of striated muscle tissue and the release of intracellular muscle components, creatine kinase (CK), myoglobin, lactate dehydrogenase (LDH), electrolytes, etc., into the extracellular fluid and bloodstream.

Among other symptoms, patients present muscle pain, calling for differential diagnosis to rule out other conditions. Some authors differentiate between myopathy (general muscle disease), myalgia (pain without rise in CK), myositis (with rise in CK) and rhabdomyolysis (symptoms: pain, swelling and loss of strength, significant rise in CK and occasionally myoglobinuria and kidney impairment)¹.

At present, mild rhabdomyolysis should be considered a clinical syndrome characterized by acute pain, loss of muscle strength and edema, accompanied by a rise in CK to at least 5 times the basal value (>1000 IU/L), and severe rhabdomyolysis is when these symptoms are accompanied by myoglobinuria and acute kidney failure, provided that concomitant diseases such as myocardial infarction, stroke, status epilepticus, chronic kidney failure and neuromuscular diseases have been counted out².

Exertional or exercise-induced rhabdomyolysis (exRML) meets all the clinical requisites outlined above, but must be preceded by exercise, not necessarily excessive or unhabitual, over the limits of fatigue, performed voluntarily or otherwise, with a rise in CK over the subsequent 12-36 hours, a peak level at 3-4 days and normalization after a few weeks of rest.

The condition also produces myoglobinemia and myoglobinuria, but for many authors laboratory quantification is not necessary and the criteria set out in the preceding paragraph are sufficient for diagnosis³.

There are no reliable data on the prevalence of this syndrome and significant discrepancies exist according to baseline studies. In the US, 26,000 cases/year have been reported, of which 47% meet the diagnostic criteria for exRML, although other studies give lower percentages^{4,5}.

Rhabdomyolysis patients present both local and general symptoms. The most important local symptoms are muscle pain, loss of strength, edema and muscle fatigue. The general symptoms are malaise, fever, nausea, vomiting, confusion, choluria, delirium, anuria and heart arrhythmia⁶.

On occasions, the CK level can increase up to 50 times or more above normal resting values.

In most cases, rhabdomyolysis is a mild condition which ceases with outpatients medical treatment, analgesics and rest.

More rarely, it gives rise to complications which may endanger the patient's life, such as: acute kidney failure, compartment syndrome, disseminated intravascular coagulation, hypovolemia and electrolyte disorders (hyperkalemia, hyperphosphatemia, hypercalcemia from the outset and delayed hypercalcemia)¹.

The most common and feared complication is acute kidney failure due to the vasoconstriction caused by the endotoxins released as a result of muscle fiber breakdown, hypovolemia and myoglobinuria, which lead to a decrease in the glomerular filtration rate⁷. It has been estimated that between 10% and 30% of patients with exRML develop this serious complication⁸.

Table 1. Causes of rhabdomyolysis.

Acquired
- Drugs/Toxins
- Ethanol
- Infections
- Exercise
- Trauma:
Crush syndrome
Compartment syndrome
- Ischemia
- Metabolic disorders
- Neurological disorders:
Status epilepticus
Status dystonicus
- Idiopathic

Table 2. Causes of rhabdomyolysis.

Genetic
- Muscle metabolism disorders
Fat metabolism
Carbohydrate metabolism
- Mitochondrial disorders
Complexes I and II
Cytochrome b
- Disruption of the release of intramuscular calcium
- Muscular Dystrophies

Etiology

The causes of rhabdomyolysis can be divided into acquired (Table 1) and hereditary (Table 2). A third group would be rhabdomyolysis caused by anesthetics like propofol and volatile anesthetics.

The most important causes are^{1,6,9,10}:

Recreational drugs

The recreational drugs which may cause rhabdomyolysis include alcohol, heroin, methadone, barbiturates, cocaine, amphetamines and benzodiazepines.

Alcohol can induce rhabdomyolysis through a combination of mechanisms, including myotoxicity, electrolyte derangement and immobilization.

Cocaine produces vasospasm and ischemia, coma with muscular compression and myofibrillar damage.

Hypnotics, barbiturates and benzodiazepines may cause depression of the central nervous system with prolonged immobilization and muscular compression, resulting in hypoxia and muscle damage^{11,12}.

Medications

Salicylates, fibrates, neuroleptics, anesthetics, propofol, corticosteroids, antidepressants, etc., may cause rhabdomyolysis.

Statin therapy has also been associated with the condition, suggesting the involvement of such mechanisms as sarcolemmal lipid disorders, protein disorders and Q10 coenzyme deficiency. The risk of triggering rhabdomyolysis is increased when associated with fibrates¹³.

Trauma

Crushing, the sudden deceleration which takes place in car crashes, falls, high-voltage electric shocks and third-degree burns are particular risk factors.

Extreme temperatures

The body can withstand a maximum internal temperature of about 42°C for a period of between 45 minutes and 8 hours. Cell destruction occurs rapidly at high temperatures. The causes of excessive heat include heatstroke, neuroleptic malignant syndrome and malignant hypothermia¹⁵.

Although rare, exposure to cold temperatures, with or without hypothermia, can also lead to rhabdomyolysis¹⁶.

Muscle ischemia

Situations which can trigger rhabdomyolysis include the compression of blood vessels (tourniquets), thrombosis, embolism and compartment syndrome.

Muscle ischemia interferes with the release of oxygen to the cells, limiting the production of energy (ATP). If maintained for a long time, this can cause necrosis of the muscle cells¹⁷.

Prolonged immobilization

Prolonged immobilization for various causes (coma, alcohol-induced unconsciousness, anesthesia) can lead to rhabdomyolysis.

The primary mechanism involved is the reperfusion of damaged tissue following a period of ischemia and the release of intracellular content into the general bloodstream.

Cases of patients with morbid obesity, diabetes, high blood pressure and undergoing prolonged surgery have been reported¹⁸.

Infections

The most common infections are those caused by influenza virus types A and B. Other viruses which can induce rhabdomyolysis include HIV, Epstein-Barr, cytomegalovirus, herpes simplex and varicella-zoster.

Bacteria such as *Legionella*, *Salmonella*, *Streptococcus*, *Staphylococcus*, *Mycoplasma*, *Leptospira* and *Escherichia coli*, fungal infections and malaria may also be involved¹⁹.

The mechanisms proposed include tissue hypoxia, the activation of lysosomes and endotoxins.

Electrolyte and endocrine disorders

Electrolyte disorders, such as hyponatremia, hypernatremia, hypokalemia, and hypophosphatemia, may cause rhabdomyolysis due to alterations in the cell membrane, primarily by affecting the operation of the sodium-potassium pump.

Endocrine disorders, such as hypothyroidism, hyperthyroidism, diabetic ketoacidosis and diabetic coma, may also be behind the syndrome⁹.

Genetic disorders

Family history, repeated episodes with not particularly intense exercise and very high levels of CK which remain high for a long time may point in the direction of this cause. In these cases, rhabdomyolysis may be the first sign of genetic myopathy³.

Rhabdomyolysis may be induced by alterations in the carbohydrate metabolism, such as a deficiency of myophosphorylase (McArdle's disease), phosphorylase kinase, phosphofructokinase or lactate dehydrogenase, or alterations in the lipid metabolism, such as a shortage of carnitine palmitoyltransferase I and II, and others like MADA deficiency, Duchenne muscular dystrophy or malignant hyperthermia.

In recent years, mutations have been identified in the LPIN1 gene in children and the RYR1 gene in adults. Variants/polymorphisms of the ACTN3 gene have also been reported, as have other polymorphisms in a number of other genes which may be related to rhabdomyolysis and especially with exercise-induced rhabdomyolysis: CK-MM, MYLK^{20,21}.

Physical exercise

Exercise in itself or in combination with one or more of the factors noted above can cause rhabdomyolysis.

The factors which can precipitate or contribute to the syndrome are^{22,23}:

- The experience and fitness level of the athlete. People with less experience and who are less physically fit more frequently present episodes of rhabdomyolysis.
- The intensity and duration of exercise; high intensity exercise in people unaccustomed to exercise or a particular type of exercise would seem to generate a greater risk.
- The type of exercise. Eccentric contractions, whether in strength or dynamic exercise, are directly related to rhabdomyolysis. The sports in which this condition most commonly appears include marathon, triathlon, football, weightlifting and CrossFit.
- Hot environments and dehydration.
- Electrolyte disorders, as indicated above.
- Nutritional problems, such as insufficient protein intake in strict vegetarian or vegan athletes and in athletes who employ extreme carbohydrate loading strategies.
- Other factors already mentioned, such as genetic factors, medications, particularly statins in combination with fibrates, psychiatric medications and infections.

Most studies show a lower incidence of rhabdomyolysis in women compared to men; this is probably due to the protective effect of estrogen²⁴.

Pathophysiology

Although the causes of rhabdomyolysis are very varied and different, the final pathogenetic pathway leading to muscle breakdown is common to all of them and is associated with alteration of intracellular electrolyte regulation and especially with cytoplasmic calcium levels.

Although the pathophysiology is common no matter what the cause, with specific reference to exRML, various alterations are triggered following excessive, intense, fast, new forms of exercise in those unaccustomed to exercise which, alone or in combination, can precipitate the condition.

Damage to the membrane of muscle fibers (sarcolemma) or an increase in the permeability of this membrane together with a decrease in energy production (ATP) alters the mechanisms which regulate intracellular electrolytes. Of the complex regulatory mechanisms, the most important are the exchangers $\text{Na}^+/\text{K}^+\text{ATPase}$ and $\text{Na}^+/\text{Ca}^{2+}\text{ATPase}$, and the pump $\text{Ca}^{2+}\text{ATPase}$ ³. Energy depletion (ATP) or cytoplasmic membrane injury/rupture causes dysfunction in the exchanger $\text{Na}^+/\text{K}^+\text{ATPase}$ and the pump $\text{Ca}^{2+}\text{ATPase}$ in the sarcolemma, and those regulatory mechanisms which act in the membranes of the internal organs of muscle fibers (sarcoplasmic reticulum and mitochondria).

This leads to an increase in the Na^+ in the cytoplasm, which then triggers failure of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, thereby increasing the concentration of intracytoplasmic Ca^{+10} .

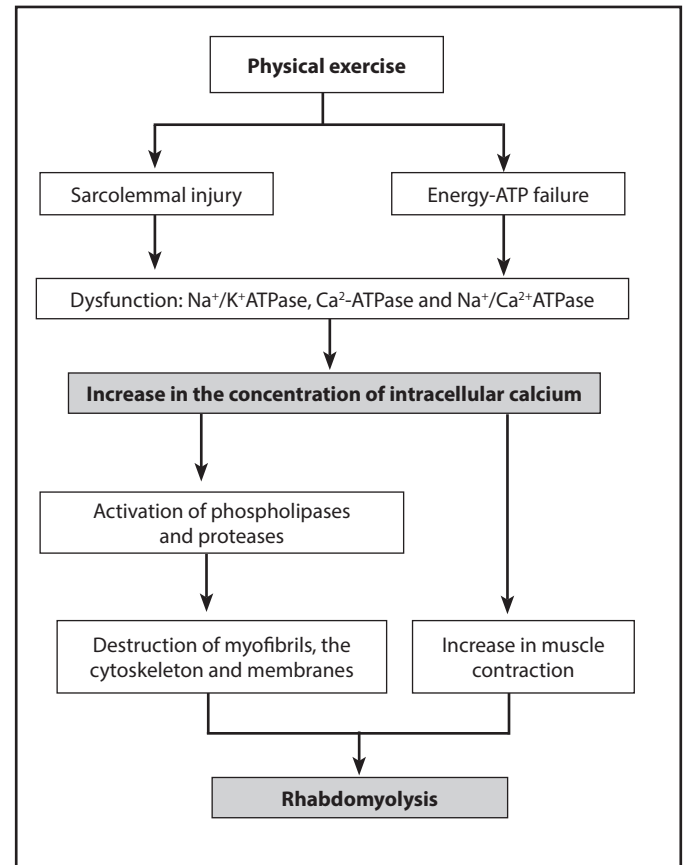
The $\text{Na}^+/\text{Ca}^{2+}$ pump needs energy, accentuating the ATP deficit, which in turn affects the $\text{Ca}^{2+}\text{ATPase}$ and causes it to malfunction, increasing calcium concentration in the cytoplasm to an extreme. This leads to increased muscle contraction, which further depletes ATP and activates calcium-dependent proteases and phospholipases. These then initiate destruction of the myofibrils, the cytoskeleton and the proteins of the cell membranes²³.

This produces cell apoptosis and release of the cell contents (calcium, potassium, phosphates, aldolases, myoglobin, CK, LDH, etc. (Figure 1)) into the extracellular medium and bloodstream. In severe cases of rhabdomyolysis, this can lead to serious complications, such as acute kidney failure, heart arrhythmias or disseminated intravascular coagulation.

Changes in the ultrasound pattern for rhabdomyolysis

The sonographic signs describing rhabdomyolysis have increased over recent years due to different articles which have been published. Initially, rhabdomyolysis was characterized by a decrease in echogenicity and local disorganization of the injured muscle²⁵. Later, further sonogra-

Figure 1. Diagram of the pathophysiology of exercise-induced rhabdomyolysis.



phic diagnosis data relating to the syndrome indicated intramuscular hyperechoic areas, which were believed to be due to hypercontractile muscle fibers in the acute stage. Complete loss of muscle texture in the muscle involved, with reduced echogenicity, normal vascularity and preservation of the muscle boundary, was sometimes observed. These findings made it necessary to perform differential diagnosis with muscle strain and muscle tear, although muscle texture is preserved in these cases²⁶. More recent publications²⁷ describe a reverse image where the muscle septa are shown as distended and hypoechoic, and the muscle fibers appear relatively hyperechoic. Furthermore, the formation of hypoechoic/anechoic intramuscular areas usually occurs when there is breakage of the muscle fibers representing edema or bleeding²⁸.

Ultrasound signs specific to the cause of rhabdomyolysis

In sporting contexts, other causes of rhabdomyolysis in addition to muscle trauma need to be considered, such as intense or strenuous physical activity and ischemia associated with compartment syndromes. The ultrasonic signs may be specific to the cause behind rhabdomyolysis.

Rhabdomyolysis associated with muscle trauma is characterized by the presence of ground glass-like or cloudy images, together with irregular anechoic areas in the muscular and intramuscular periphery (Figure 2). Generally, the muscle fibers are uneven and heterogeneous, and there are usually no blood flow signals²⁷.

However, when rhabdomyolysis occurs as a result of strenuous exercise in physically unprepared patients, areas of lower echogenicity (ground glass or cloudy image) with hyperechoic intramuscular areas, creating an environment of muscular disorganization, are observed (Figures 3 and 4). The diameter of the muscle fascia also increases, covering uneven anechoic areas in the muscular and intramuscular periphery, with no signals of blood flow compatible with edema. Doppler ultra-

sonography reveals normal vascularization with preservation of waves and flow velocities²⁷.

Finally, in cases of rhabdomyolysis associated with a compartment syndrome, an increased volume of striated muscle with reduced flow velocity in the distal arteries is observed. The muscle presents a heteroechoic pattern and sometimes dissection of the aponeurosis (Figure 5).

Prevention

Rhabdomyolysis prevention should consist of steering clear of the pathophysiological mechanisms which trigger the muscle injury itself and the complications which can come afterwards.

Figure 2. This cross-sectional image of rectus femoris and vastus lateralis muscle contusion shows the presence of hyperechoic images with loss of fibrillar pattern and anechoic areas with uneven edges on the periphery of each muscle.

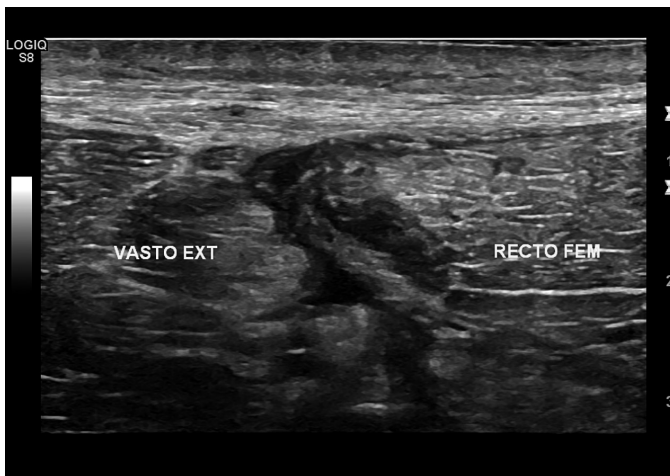


Figure 3. This cross-sectional image of the back of the thigh shows areas with lower echogenicity and intramuscular hyperechoic areas on the surface. Note that the hyperechogenicity of the muscle is similar to that of the semimembranosus tendon (arrow) and the sciatic nerve (SN).

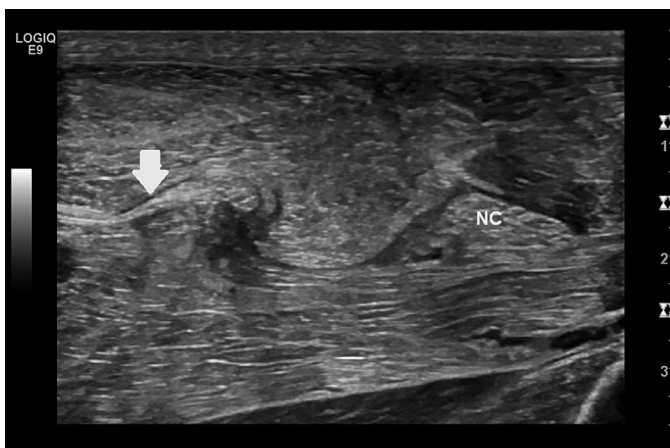


Figure 4. In a cross-sectional examination, ground glass opacities can be seen in the muscle belly.

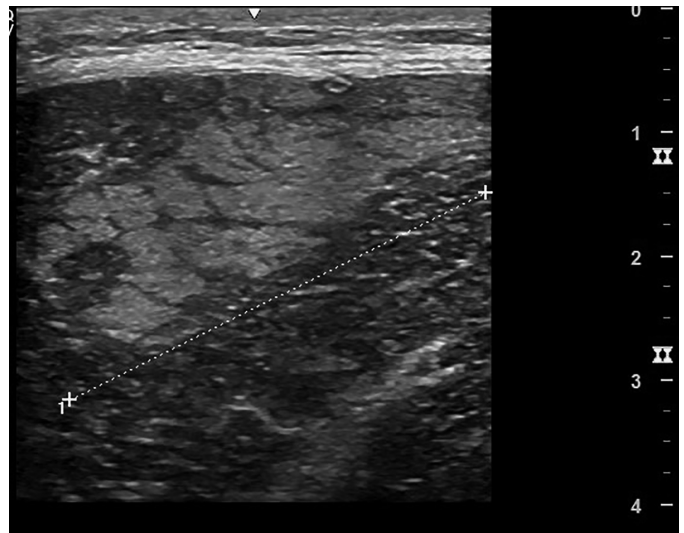
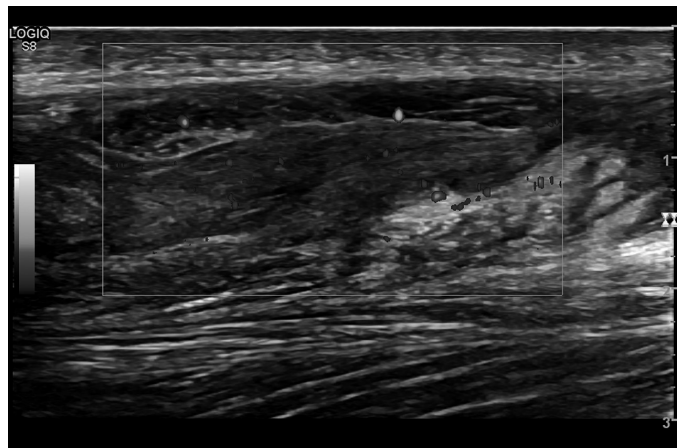


Figure 5. In a short-axis examination of the gastrocnemius muscle, a heteroechoic pattern and an increase in muscle volume can be observed.



Adequate physical exercise

The exercise carried out should be adapted to the individual's level of fitness and specifically prescribed in terms of the intensity, duration and type of exercise, and how it should be performed. Variations in these variables can lead to muscle damage and, ultimately, rhabdomyolysis.

Generally, those less fit are at more risk of suffering rhabdomyolysis, which is uncommon in top-level athletes²⁹. Preventive measures, therefore, need to be considered more in the earlier stages of fitness training.

The progression of exertion from the start of each training or competition session is an important factor, as is a suitable warm-up stage, which is the first preventive measure to take into account³⁰ and one of the most effective.

Type of exercise

Exercises with a greater eccentric component are prone to cause greater muscle damage, increasing CK and LDH levels, especially exercises which involve jumping, running on land at different gradients or muscle training consisting of squats and arm and shoulder extensions with heavy weights or a lot of repetitions²³. It has been shown that sports such as marathon running, triathlon, football and CrossFit involve a greater risk of both muscle injury and rhabdomyolysis^{23,31}.

As a preventive measure, it is advisable to start with a low number of repetitions and only 1-2 sets, and gradually increase the repetitions and sets of exercises with a greater eccentric component, using the onset of pain the day after training as a control variable²³.

Exercise intensity

Higher intensity exercises increase the risk of muscle damage and rhabdomyolysis, especially in less fit athletes, whose exercise-induced adaptive responses are poorer, thereby exposing them further. For this reason, the intensity of exercise should be increased gradually according to how the athlete tolerates and assimilates it, particularly controlling loads in the initial phases of training programs.

Duration of exercise

Longer exercises (like marathon running, triathlon, etc.) expose athletes to the risk of greater muscle damage and increase the risk of rhabdomyolysis. It is advisable to exercise for progressively longer periods of time, apply a weekly frequency which permits full physical recovery and perform exercises which involve an eccentric component in line with the athlete's muscular development³¹.

Food and nutrition

Carbohydrate and protein intake must be adapted to the intensity, duration and type of exercise in order not only to improve performance but also to prevent excessive muscle damage resulting from an energy deficit, which can lead to rhabdomyolysis.

Exercises which involve a greater eccentric component and last longer lead to greater catabolism and call for a greater supply of protein (1.5-2.0 g protein/kg of body weight) and carbohydrates to enhance structural and functional muscle, and liver and muscle glycogen recovery³².

Electrolyte and fluid imbalances (chiefly hyponatremia and hypokalemia) increase the risk of rhabdomyolysis, particularly when exercising in hot environments that induce greater sweating and electrolyte loss, which interferes with fatigue and muscle damage³. Proper hydration and mineral supplementation prevent the nutritional imbalances which predispose athletes to excessive muscle damage.

Finally, since the exercises which most predispose athletes to rhabdomyolysis also lead to an increase in oxidative processes which affect energy and muscle function, they may also affect kidney function if major oxidative damage occurs. This potential situation makes it advisable to increase the intake of antioxidants (vitamin C, coenzyme Q10) to prevent the consequences that could lead to these forms of muscle and kidney damage which accompany and complicate rhabdomyolysis³³.

Environmental factors

Exercise conducted in excessively hot environments can cause varying degrees of dehydration and even heatstroke. Such scenarios produce greater muscle damage, which becomes more complicated the higher the level of dehydration and electrolyte loss²³, thereby increasing the risk of rhabdomyolysis.

Adequate fluid and electrolyte replacement minimizes health risks when exercising in hotter environments.

Educational measures

Rhabdomyolysis is considered a serious complication of exercise, so coaches, physical education teachers and athletes themselves should have a good knowledge of its clinical features and be aware of the risks associated with the condition. Familiarization with preventive measures would prevent the appearance of the syndrome and its complications, helping to preserve athletes' health.

Treatment

The treatment of rhabdomyolysis in the acute phase, with significant enzymatic alterations, can be differentiated from treatment once the analytical figures and ultrasound images have returned to normal and sporting activity can be considered again.

Here, we are more interested in exertional rhabdomyolysis, about which not much literature nor many guidelines have been published^{34,35}, possibly due to its low prevalence.

Studies of the condition when related to sport, conducted with significant sets of hospital admissions, although few cases, with average CK figures on admission of more than 30,000 IU/L^{34,35} report an

Table 3. General criteria for resuming sporting activity.

Biological criteria	<ul style="list-style-type: none"> • Follow-up ultrasound (essential) • Follow-up MRI (not essential) • No pain at the site of the injury • CK blood test
Functional criteria	<ul style="list-style-type: none"> • Full joint mobility • All kinds of contraction without pain • Stretches without pain • Load bearing without pain • No pain after exercise • No signs of inflammation after exercise • No neurological signs
Sporting criteria	<ul style="list-style-type: none"> • No pain in basic movements • No pain in specific movements or technical sport movements • Adequate athletic performance
Psychological criteria	<ul style="list-style-type: none"> • No negative symptoms (fear, apprehension, distress, etc.)

Adapted from: Fernández TF, Guillén P. *Arch Med Deporte*. 2017³⁶.

Table 4. Positive criteria for an optimum return to competition.

<ul style="list-style-type: none"> • Positive factors for quick reincorporation • No strength deficit compared to the uninjured limb • No flexibility deficit compared to the injured limb • No problem completing more than one training session • Normal ultrasound and MRI scans
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Source: adapted from Servicios Médicos del FC Barcelona. *Apunts Med Esport*. 2009³⁷.

absence of major complications like severe kidney damage, electrolyte disorders, compartment syndrome, disseminated intravascular coagulation, arrhythmias and seizures.

In such cases, initial treatment consists of fluid therapy and alkalinization, and the patients are discharged after an average of 2.5 days.

Once the acute phase has ended, complete rest from physical activity until the test results and ultrasound images return to normal is usually sufficient, bar the administration of analgesics in the event of pain.

As for resuming sporting activity, the guidelines set out in Table 3 can be applied, the progressive application of workloads to the injured area, starting out with very low intensities and progressing according to the tolerance of each load tried, being recommended. In lower limbs, it is very useful to start with anti-gravity exercise (in a swimming pool) before beginning bicycle exercise, leaving running for the final phase of recovery.

Table 4 shows the most important positive criteria for returning to competition.

Conflict of interest

The authors have no conflict of interest whatsoever.

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