# Exertional Rhabdomyolysis 177

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**Abstract**

Rhabdomyolysis syndrome has many acquired pathophysiological causes, resulting in a common pathway of muscle tissue degradation and the dispersing of its components onto circulation, causing systemic effects such as electrolyte abnormalities, arrhythmia, kidney injury, compartment syndrome, and DIC. Exertional rhabdomyolysis (ER) is the most common cause among young persons. It is related to several risk factors such as temperature extremes, humidity, dehydration, fatigue, asthma, HMG-CoA reductase inhibitors (statins) consumption, and congenital defects such as sickle-cell trait and myopathy. Although usually ER has a rather benign course, complications should be anticipated and referred, and a high index of suspicion is recommended. Guidelines for diagnosis and management are provided.

## Introduction

Rhabdomyolysis means the breakdown of striated muscle tissue. However, rhabdomyolysis syndrome is characterized by additional dispersing of the tissue's intracellular components into the circulatory system. These components include electrolytes, purines, enzymes (such as creatine kinase – CK), and myoglobin. This syndrome is associated with different pathophysiologies including exertion, infections, metabolic diseases, drugs, medications, toxins, and injuries. The syndrome can vary from an asymptomatic elevation of blood CK level to acute kidney failure and death.

## Pathophysiology

There are several causes of rhabdomyolysis (see Table 1), but they all appear to lead to a final common pathway, which is the breakdown of muscle tissue, destruction of the myocyte, and distribution of its components into the circulatory system. In the normal myocyte, a low level of calcium is maintained by the $Ca^{2+}$ ATPase pump, which concentrates intracellular calcium into the sarcoplasmic reticulum and the mitochondria, and Na/Ca exchanger ion channel, powered by sodium influx, due to the gradient created by Na/K+ ATPase pump. All these mechanisms depend, directly or indirectly, on ATP as a source of energy. The lack of ATP causes the cell's homeostasis to collapse, as the intracellular calcium level increases. In turn, the rise of calcium level activates intracellular proteolytic enzymes, degrading the myocyte. As the cell breaks down, large quantities of potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase (LDH), aspartate transferase (AST), and urate leak into circulation (Brancaccio et al. 2010; Better and Abassi 2011). As more than 100 g of degraded muscle tissue overwhelm the plasma's myoglobin-binding capacity, free myoglobin causes renal morbidity by several mechanisms (Bosch et al. 2009; Plotnikov et al. 2009; Hendgen-Cotta et al. 2010).

There is a large variety of causes for rhabdomyolysis, all leading to muscle ischemia and cell breakdown. The most common causes in the adult population are illicit drugs, alcohol abuse, medications, muscle diseases, trauma, neuroleptic malignant syndrome (NMS), seizures, and immobility (Melli et al. 2005). Among pediatric patients, the most common causes are viral myositis, trauma, connective tissue diseases, exercise, and drug overdose (Mannix et al. 2006).

Strenuous exercise, especially in relatively untrained persons, e.g., marathon runners (Clarkson 2007), military recruits (Alpers and Jones 2010; Landau et al. 2012), and inmates in correctional facilities (Greene and Anders 1990), may result in acute severe rhabdomyolysis. It is reported in voluntary setups, such as highly motivated athletes or inexperienced exercisers (especially on sporadic occasions rather than as a part of a training program). Less voluntary setups are also reported, such as personal trainer (pushing the trainer beyond what he would normally

**Table 1** Causes for rhabdomyolysis (by mechanism)

| |
|---|
| 1. Increased energy demand |
| 1.1. Exercise (especially strenuous exercise) |
| 1.2. Heat stroke |
| 1.3. Acute psychosis |
| 1.4. Seizures; Status epilepticus |
| 1.5. Status dystonicus |
| 1.6. Status asthmaticus |
| 1.7. Delirium tremens |
| 2. Decreased energy production |
| 2.1. Dystrophies |
| 2.2. Metabolic enzyme deficiencies |
| 2.3. Mitochondrial function disorders |
| 2.4. Hypokalemia |
| 2.5. Hypophosphatemia |
| 3. Direct muscle injury |
| 3.1. Crush injury (trauma) |
| 3.2. Electrical injury |
| 3.3. 3rd degree burns |
| 3.4. Inflammatory myopathy |
| 3.5. Temperature extremes (hyper/hypothermia) |
| 3.6. Hyper/hyponatremia |
| 4. Decreased oxygen delivery |
| 4.1. Arterial thrombus; emboli |
| 4.2. Surgery; prolonged immobilization |
| 4.3. Trauma |
| 4.4. Shock |
| 4.5. Sickle cell trait/crisis |
| 5. Infections |
| 5.1. Viral |
| 5.2. Bacterial |
| 5.3. Fungal |
| 6. Endocrine abnormalities |
| 6.1. Diabetic keto-acidosis; non-ketotic hyperosmolar state |
| 6.2. Addison's disease |
| 6.3. Hyperaldosteronism |
| 6.4. Hypo/hyperthyroidism |
| 7. Drugs and medications |
| 7.1. Substance abuse (MDMA, amphetamine, heroin, methdone, cocaine, PCP, LSD) |
| 7.2. Alcohol; ethylene glycol |
| 7.3. Sedative/hypnotic drugs (barbiturates, benzodiazepines) |
| 8. Toxins |
| 8.1. Carbon mono-oxide (CO). |
| 8.2. Venom – snake; spider; bee; wasp |
| 8.3. Quail eating |

endure) (Springer and Clarkson 2003, 2013), military training (2013), physical punishment in correctional facilities or educational institutes (Greene and Anders 1990), and overexertion facilitated by the use of stimulating recreational drugs such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) (Richards 2000). The least voluntary muscle exercise such as seizures (Gupta et al. 2010), status epilepticus, acute psychosis (Coryell et al. 1978), status dystonicus, or status asthmaticus (Carroll and Zucker 2007) may lead to a severe form of acute rhabdomyolysis.

The primary mechanism is ATP supply-demand discordance, meaning the inability to supply the muscle's increased demand of energy by the circulatory system, leading to the inability of the muscle to maintain normal membrane homeostasis. Moreover, Clarkson and Hubal also proclaim that exercise-induced muscle damage is caused by eccentric contractions (e.g., running downhill), leading to tearing of muscle fibers (Clarkson and Hubal 2002). Repetitive, high-intensity exercises, especially those involving eccentric effort (contraction while the muscle is lengthening) such as push-ups, curl-ups, squat stands, cycling, and downhill running or walking, are correlated with ER (Sayers and Clarkson 2002). The more strenuous or prolonged the exercise, more damage will be caused (Patel et al. 2009). There is a lack of clear concordance between biochemical markers and both the intensity of the exercise (Clarkson 2007) and rhabdomyolysis complications, mainly acute kidney injury (Schiff et al. 1978; Clarkson and Eichner 2006). The correlation between the most important marker, which is serum's CK, and the chief toxic agent, which is myoglobin, is nonlinear, thus making the determination of the severity and susceptibility to complication a complex issue.

Risk factors for ER (see Table 2) are extreme heat and humidity (Landau et al. 2012), dehydration, hypokalemia (often resulting from excessive sweating), sickle-cell trait (especially in combination with high altitude) (Makaryus et al. 2007), exercise-induced asthma, or pre-exertion fatigue. Low-intensity exercise-induced rhabdomyolysis

**Table 2** Risk factors for exertional rhabdomyolysis and its complication

| High validity | | Low validity |
|---|---|---|
| Temperature extremes | Eccentric exercise | Viral infection |
| Humidity | Fatigue | Hyperthyroidism |
| Dehydration | Myopathies (see Table 3) | Performance-enhancing substances (e.g., creatine, amino acids, and ephedrine) |
| Shock | Statins | Stretching after eccentric exercise |
| Sickle-cell trait | NSAID | |
| Exercise-induced asthma | Licorice | |

cases have also been reported, but the mechanism remains unknown (Gagliano et al. 2009).HMG-CoA reductase inhibitors (statins) often cause exercise intolerance, myalgia, and hyper-CK-emia, but a resulting full-blown ER is considered relatively rare (Escobar et al. 2008; Fernandez et al. 2011), though it had been reported (Meador and Huey 2010; Semple 2012). In addition, a viral infection prior to exertion (Marinella 1998; Sevketoglu et al. 2011), a metabolic/endocrine disorder (e.g., hyperthyroidism Kim et al. 2012), and the consumption of performance-enhancing compounds (Sandhu et al. 2002; Meador and Huey 2010) have been suggested to be precipitating factors to this syndrome. Due to the variability of the clinical severity, laboratory values, and outcome in athletes performing similar exertion, several authors have suggested that ER is the result of a "perfect storm," combining several factors abovementioned (Clarkson 2007; Cleary et al. 2011).

Special attention should be paid to the possibility of a genetic predisposition to exercise intolerance, resulting in a wide spectrum starting from asymptomatic hyper-CK-emia to severe ER, followed by serious complications. Genetic polymorphisms, such as the genotypes of CK-MM, angiotensin-converting enzyme (ACE), and myosin light-chain kinase (MLCK), are associated with excessive release of CK during exercise up to sixfold of normal and are possibly connected to

**Table 3** Genetic myopathies related to exertional rhabdomyolysis (Elsayed and Reilly 2010; Quinlivan and Jungbluth 2012)

| |
|---|
| 1. Muscular dystrophies |
| 1.1 Duchene |
| 1.2 Becker |
| 1.3 Limb-girdle muscular dystrophy 2B/2I |
| 2. Congenital enzyme deficiencies |
| 2.1 Lipid metabolism |
| 2.1.1 Carnitine cycle |
| 2.1.1.1 Primary carnitine deficiency |
| 2.1.1.2 Carnitine palmitoyltransferase I (CPT I) deficiency |
| 2.1.1.3 Carnitine palmitoyltransferase II (CPT II) deficiency |
| 2.1.2 Acyl-CoA dehydrogenase deficiency |
| 2.1.2.1 Long chain 3-hydroxy acyl CoA dehydrogenase (LCHAD) deficiency |
| 2.1.2.2 Very long chain Acyl CoA dehydrogenase (VLCAD) deficiency |
| 2.1.2.3 Short chain Acyl CoA dehydrogenase (SCAD) deficiency |
| 2.1.3 Mitochondrial trifunctional protein deficiency |
| 2.1.4 Phosphatidic acid phosphatase deficiency |
| 2.2 Glycogen metabolism |
| 2.2.1 McArdle disease (glycogen storage disease type 5) |
| 2.2.2 Tauri disease (glycogen storage disease type 7) |
| 2.2.3 Lactate dehydrogenase deficiency |
| 2.2.4 Phosphorylase kinase deficiency |
| 2.2.5 Phosphoglycerate mutase deficiency |
| 2.2.6 Phosphoglycerate kinase deficiency |
| 2.2.7 β-Enolase deficiency |
| 2.2.8 Glycogen synthase deficiency |
| 2.2.9 Distal glycogenoses |
| 2.3 Potassium related |
| 2.3.1 11-Hydroxylase deficiency |
| 3. Core myopathies |
| 3.1 Central core disease (CCD) |
| 3.2 Multi-minicore disease (MmD) |
| 3.3 Centronuclear myopathy (CNM) |
| 4. Connective tissue diseases |
| 4.1 Polymyositis |
| 4.2 Dermatomyositis |
| 4.3 Inclusion body myositis |
| 4.4 Neurosarcoidosis |

ER (Elsayed and Reilly 2010). High index of suspicion for myopathies should be practiced in young patients or in recurrent ER, searching for muscle dystrophies, mitochondrial defects,

malignant hyperthermia susceptibility, and metabolic disorders (Liang and Nishino 2010; Quinlivan and Jungbluth 2012).

Regarding the incidence of ER, Alpers and Jones conducted a cohort in a medical center servicing a grand military base, resulting in 22.2/100,000 trainees per year, while former authors reported an incidence of up to 39 % among recruits (Alpers and Jones 2010; Landau et al. 2012). The true incidence of ER in the general population is currently unknown and is believed by many authors to be highly underestimated and underreported, due to the similarity of its symptoms to those of normal exercise.

## Temperature-Related Exertional Rhabdomyolysis

A thermal maximum of body core temperature of 42 °C (107.6 °F) for 45 min to 8 h was established to be the maximal level and duration of heat muscle cells can endure without being damaged (Bynum et al. 1978). The higher the heat a body will absorb or produce, a higher and faster extent of cellular destruction will occur (Khan 2009).

Heat-related ER has several pathways that all share a common hypermetabolic state that includes a high demand for ATP; accelerated chemical, oxidative, and mechanical stress of muscle; and increased level of intracellular calcium (Capacchione and Muldoon 2009):

- Exercise may lead to exertional heat illness or even ***exertional heat stroke*** (Bouchama and Knochel 2002; Yeo 2004). Heat strokes, related to hypercatabolic state, occur usually in a hot and humid climate and in persons unaccustomed to the climate nor to the level of exertion (Quinlivan and Jungbluth 2012).
- ***Malignant hyperthermia*** syndrome is a condition usually ascribed as a genetic susceptibility to anesthetic drugs, causing hyperthermia, increased metabolic rate, elevated respiratory rate and pulse, rigidity, and rhabdomyolysis. It may also be triggered by exercise (exercise-induced malignant hyperpyrexia) (Brukner 2008). Its most common known genetic mutation is connected with predisposition to ER (Capacchione and Muldoon 2009; Carsana 2013).
- ***Neuroleptic malignant syndrome*** may result in muscle damage, on the cellular level. In neuroleptic malignant syndrome, the mechanism suggested is that neuroleptic medications induce abnormal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis, and hyperthermia (Adnet et al. 2000; Hadad et al. 2003).
- Exertion in warm environment and excessive sweating can lead to severe electrolyte abnormalities, which disrupt the cell's membrane homeostasis, mainly by disturbing the Na/K+ ATPase pump. Hyponatremia (Trimarchi et al. 1999), hypernatremia (Denman 2007), hypokalemia (von Vigier et al. 2010), and hypophosphatemia (Kutlu et al. 2011) may result in rhabdomyolysis. It has been suggested that extreme exercise with intense fluid consumption by athletes may cause hyponatremia-induced rhabdomyolysis (Siegel 2006). Polydipsia alone can initiate dilutional hyponatremia followed by rhabdomyolysis as well (Strachan et al. 2007). Other electrolyte abnormalities initiating rhabdomyolysis, which are caused by exertion, seem to require additional predisposition (e.g., hypophosphatemia caused by diabetic ketoacidosis).

## Congenital Predisposition to Exertional Rhabdomyolysis

There are several genetic disorders leading to ER:

- ***Inherited dystrophies*** – Although usually presented as muscle weakness in early childhood to adolescence, dystrophinopathies may present in a milder form as exercise-induced cramps, with little histological changes (Quinlivan and Jungbluth 2012). Duchenne or Becker's muscular dystrophy-related ER (Amato and Griggs 2011) are the most common, especially among males, however, not exclusively; in these disorders muscle cramps

usually occur after, but not during, exercise, as myalgia is present both during and after. Myoglobinuria is usually mild. Other dystrophies such as limb-girdle muscular dystrophy were also reported to cause ER (Quinlivan and Jungbluth 2012).

- ***Metabolic and mitochondrial enzyme deficiencies*** – Since lipids are the main fuel of low-intensity exercise, replaced by carbohydrates at the crossover level of 48 % $VO_2$ max, the restriction of lipid or carbohydrate metabolism due to genetic enzymes defects is highly correlated with exercise intolerance and rhabdomyolysis (Elsayed and Reilly 2010). Lipid metabolism disorders may involve the carnitine cycle (most notably carnitine palmitoyltransferase II (CPT II) deficiency) or acyl-CoA dehydrogenase deficiency (e.g., very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency). Carbohydrate metabolism disorders usually involve glycogen storage diseases (most notably type 5 (McArdle disease) and type 7 (Tauri disease)). Although all these diseases vary significantly in terms of their clinical severity, they are all consistent in that they may flare up as a result of exertion, fasting, or increased metabolic demands (e.g., infection).
- ***Exercise intolerance myopathies*** – Some inherited myopathies may not lead to isolated rhabdomyolysis, but only to exercise intolerance and myalgia. RYR-1 gene mutation (causing also susceptibility to malignant hyperthermia) (Carsana 2013) is connected to central core disease (CCD), multi-minicore disease (MmD), and centronuclear myopathy (CNM) (Quinlivan and Jungbluth 2012). Usually, these disorders will present themselves in early childhood.
- ***Connective tissue disorders*** – Although ER related to polymyositis, dermatomyositis (Yen et al. 2005), and inclusion body myositis is rare, it has been described. Inflammatory myopathy can present with very high CK levels, but not as high as those found in muscle dystrophies (Elsayed and Reilly 2010).

Careful history taking may reveal genetic defects predisposing to exercise intolerance with or without ER. The diagnosis is usually made by a muscle biopsy, followed by histochemical, immunohistochemical, and mitochondrial respiration studies, by metabolic tests, or by genetic analysis. All these myopathies are specified in Table 3. Further information regarding the genetics, clinical features, diagnosis, treatment, and prognosis is beyond the scope of this chapter.

## Clinical Presentation

Due to the various possible causes, there are a large variety of rhabdomyolysis' clinical presentations. These may range from severe symptoms, when muscle damage is extensive, to subclinical, when the damage is minor.

A classical triad of muscle aches, weakness, and dark, tea-colored urine, with suspected clues of muscle damage, is described, especially in pediatrics (Al-Ismaili et al. 2011), and is highly suggestive of the diagnosis. Careful history taking may reveal dark, tea-colored urine; however, it could be apparent in only ~50 % of the patients (Alpers and Jones 2010) or less. Other specific symptoms include muscle tenderness, muscle cramps, swelling, stiffness, weakness, and even loss of function of the affected muscles. The most common muscle groups involved are postural muscles, such as the lower back, thighs, and calves (Galvez et al. 2008). Note that muscle swelling might not be apparent until after intravenous (IV) fluid rehydration. Other symptoms may be of nonspecific nature, such as abdominal pain, fever, malaise, nausea, and vomiting. Depending on the underlying cause, a deterioration of mental status may occur (e.g., hyperthermia, trauma, toxins or drugs, infections, electrolyte abnormality, or urea-induced encephalopathy).

Physical examination may be obscure, revealing limb indurations or skin changes due to ischemic damage of involved tissues (e.g., blisters, discoloration). However, muscle involvement might not reveal any notable signs.

Rhabdomyolysis can be an incidental finding of a laboratory test. Anyhow, an effort should be made attempting to find the underlying cause and treat it.

## Diagnosis

In general, a high index of suspicion is crucial for diagnosing rhabdomyolysis, since a classic presentation such as muscular swelling, pain, and tenderness may not be eminent, or even absent. However, the history taking often implies this diagnosis when dealing with ER, especially among previously healthy, young patients. The definitive diagnosis is made by supporting laboratory tests including serum CK and urine myoglobin. A skeletal muscle biopsy could be used to establish the diagnosis, but is not, usually, obligatory.

### Serum CK (Creatine Kinase)

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to the muscles. Serum CK begins to rise approximately 2–12 h after the onset of muscle injury, peaks within 24–72 h, and then declines gradually in 7–10 days. A persistent elevated level of CK suggests continuing muscle injury, development of a compartment syndrome, or continuous muscle stress (e.g., prolonged exercise or infection) (Brancaccio et al. 2010). A clear agreed level of serum CK that is evident to diagnose rhabdomyolysis is yet to be established as consensus. A CK level higher than five times its normal value is accepted by many authors as a diagnostic criterion. Notice that some studies establish the low specificity of serum CK levels. Kenney et al. followed a cohort of 499 young healthy military recruits with CK elevation ten times of normal, of which none were diagnosed as ER, and suggest either coexisting myoglobinuria or CK level of 50-folds of normal as a diagnostic threshold (Kenney et al. 2012). CK level is simple to measure, and its level correlates to myoglobin, LDH, AST, and ALT levels in an exertion setup; thus, it is used as a surrogate marker for muscle damage (Clarkson et al. 2006). However, whether it is a reliable predictor of kidney injury in the setup of ER remains controversial (de Meijer et al. 2003; Clarkson and Eichner 2006).

### Serum and Urine Myoglobin

Myoglobin is normally bound to plasma globulins and is maintained at a low serum level up of 0–0.003 mg/dL (Hendgen-Cotta et al. 2010). Once circulating myoglobin levels have exceeded 0.5–1.5 mg/dL, it overwhelms its physiological homeostatic mechanism: the plasma protein binding capacity, the renal proximal tubule endocytosis rate, and the metabolism rate. At this saturation level, myoglobin is rapidly excreted in the urine (Bosch et al. 2009; Sorrentino et al. 2011). Myoglobinuria is pathognomonic to rhabdomyolysis, but is not necessarily visible. Elevated serum myoglobin and myoglobinuria are reliable and specific indicators for rhabdomyolysis, but because of several reasons, the diagnostic usage of them is limited. Firstly, serum myoglobin level kinematics is swift – it rises and drops much faster than CK level (in 1–6 h), thus results in a low negative predictive value and may not be used as a ruling out test. Secondly, myoglobinuria is not always visible or may be resolved early; a urine myoglobin level of 100 mg/dL is required to cause tea- or cola-colored urine. In addition, detecting myoglobinuria is commonly done using urine dipstick tests (orthotoluidine), which also react with the globin fragment of hemoglobin, and accordingly is a nonspecific test (e.g., hematuria). Rodríguez-Capote et al. published a systemic review which concluded a high sensitivity, but poor specificity of myoglobinuria as a rhabdomyolysis marker (Rodriguez-Capote et al. 2009). Immunoassay is more sensitive and specific than dipstick, but is often not readily available, and it may take days to obtain results. Thus, neither serum myoglobin nor myoglobinuria is sensitive or specific parameters to establish a diagnosis.

### Blood Chemistry

Extended chemistry test may find raised levels of muscle enzymes such as lactate dehydrogenase (LDH), aldolase, carbonic anhydrase III, and aminotransferases. In particular, aspartate aminotransferase with normal level of alanine aminotransferase can indicate the occurrence of

rhabdomyolysis. An elevated level of troponin I subtype is found in 50 % of rhabdomyolysis cases, while it is normal in inflammatory and chronic myopathies, in which troponin T subtype and CK levels are elevated (Brancaccio et al. 2010). Serum creatinine level rises more rapidly in rhabdomyolysis-associated kidney injury, comparing other causes of kidney injury, especially among muscular young patients. In concordance, the blood urea nitrogen (BUN) to creatinine ratio is typically low (Bosch et al. 2009). Electrolyte abnormalities related to rhabdomyolysis (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia) may be found in a simple blood chemistry test.

## Imaging

Rhabdomyolysis is usually diagnosed as a clinical syndrome, with a combination of supporting laboratory tests; thus, imaging is usually not used as a diagnostic modality. However, in less clear cases, in which the diagnosis is not definite, it had been reported that several imaging tests may prove useful. Bone scintigraphy may demonstrate Tc-99m-labeled diphosphonate reacting with released calcium (due to sarcolemmal disruption) in muscle tissue (Walsh and Fan 2009). Magnetic resonance imaging (MRI) may demonstrate decreased signal using T1 weighted images, increased signal using T2 weighted images, and a contrast between damaged and unharmed muscles using STIR images (which suppresses fat tissue signal). Computed tomography (CT) images may demonstrate diffuse areas of low attenuation in the muscle and tissue swelling due to edema and defined intramuscular hypodense foci suggesting tissue necrosis. Ultrasound (US sonography) may reveal hypoechoic areas attributed to inflammation and fluid infiltration (Moratalla et al. 2008; Mian et al. 2011). MRI had proved to be almost 100 % sensitive, as other modalities were inferior (Lamminen et al. 1989). None of these techniques are highly specific concerning rhabdomyolysis. All techniques may also be used to demonstrate macroscopic findings of the kidney, if affected.

Often, ER is isolated to a specific muscle group. When considering a fasciotomy, MRI or bone scintigraphy could demonstrate the affected muscles (Lim et al. 2008) and serve as decision-making tool (Moratalla et al. 2008; Zhang et al. 2011) to avoid unnecessary interventions.

## Muscle Biopsy

Muscle biopsy can confirm the diagnosis of rhabdomyolysis, but is not necessary. The histopathological findings are dependent on the underlying etiology and will include evidence of a necrotic process, meaning loss of cell nucleus and muscular stria. Muscle biopsy may reveal a metabolic disorder, which may be the underlying cause of rhabdomyolysis, especially in recurrent episodes, and should be considered among young patients (Hannah-Shmouni et al. 2012).

## Investigations for Precipitating Factors

Diagnosing rhabdomyolysis must be followed by a search for the cause. When discussing rhabdomyolysis in general, the underlying cause might be obscure, while when dealing with ER, it may be revealed by a careful history taking. However, several precipitating factors should not be overlooked, since ER or intolerance to physical activity at various levels may be the outcome of sickle-cell trait, viral infections (e.g., influenza or coxsackie virus) (Marinella 1998; Sevketoglu et al. 2011), exertional or non-exertional hyperthermia, electrolyte abnormalities, prescription medications, drugs, or toxins. Moreover, inherited muscle dystrophies, metabolic enzyme deficiencies, or mitochondrial or malignant hyperthermia diseases may present themselves for the first time as ER, thus should be suspected, especially in young patients, history of exertion insufficient in explaining the clinical severity or unexplained recurrent episodes. Chronic symptoms involving both muscular and other major systems such as cardiac or neurological systems should also raise a suspicion for a metabolic enzyme deficiency.

Aside from careful history and physical examination, there is not a clear protocol which tests should be attempted. Core temperature should be monitored. Blood chemistry test will map the serum's CK levels and reveal electrolyte abnormalities. If an infection is suspected, complete blood count (CBC), cultures, and serological studies are appropriate. If drugs or toxins are a possibility, toxicological screening should be performed. If an endocrine disorder is suggested, blood chemistry and endocrine assay are to be carried out to confirm. Genetic analysis (Quinlivan and Jungbluth 2012), muscle biopsy (Hannah-Shmouni et al. 2012), and the modified forearm ischemic exercise test (Tarnopolsky et al. 2003) may be indicated in patients with suspected genetic metabolic or myopathic disorders. Malignant hyperthermia can be detected by performing a caffeine-halothane contracture test (CHCT), although currently genetic tests already in use may spare the need for this invasive procedure (Litman and Rosenberg 2005). Imaging modalities, as described earlier, may assist in determining the affected muscle groups, establishing diagnosis, demonstrating kidney involvement, and considering appropriate interventions.

## Other Investigations

Although its diagnostic sensitivity and specificity to detect electrolyte abnormalities is not high, ECG monitoring is essential to detect related cardiac arrhythmias (Montague et al. 2008). Arterial blood gas analysis may reveal metabolic acidosis. CBC, blood chemistry, liver and kidney function tests, prothrombin time (PT), and activated partial thromboplastin time (aPTT) may be useful laboratory tests and should be considered, particularly when acute kidney failure or disseminated intravascular coagulation (DIC) is suspected.

## Complications

***Volume depletion*** is caused by leakage of intravascular fluid into a third space, in this case into the muscle tissue, due to interference of the cellular electrolyte homeostasis. This process facilitates further the depletion of available ATP, creating a viscous circle, resulting in further tissue damage, hypovolemia, and even hypovolemic shock. In extensive rhabdomyolysis, hypovolemia is comparable to that occurring in patients with extensive burns (over 60 % of body surface) (Better and Abassi 2011) or major vessel bleeding.

***Compartment syndrome*** is defined as increased intra-compartmental pressure. It is caused by the same mechanism as volume depletion, causing oxygen deprivation of the muscle. The syndrome clinically presents with muscle pain (sometimes out of proportion to observed injury), weakness, paresthesia or hypoesthesia, pallor, turgor, and tightness of affected muscles. Note that compartment syndrome may present in a milder manner, as a non-acute occurrence, such as chronic exertional compartment syndrome. When the compartmental pressure substantially exceeds the capillary refill pressure, usually at a compartmental pressure of over 30 mmHg (which can be measured using several invasive applications King et al. 2010), for more than 8 h, or higher pressures for lesser time, it may result in muscular necrosis followed by permanent neuromuscular damage. It may involve future long-term dysfunction of the musculoskeletal system, including permanent disability, contractures, posture. and gait disturbances (Campbell 2008).

***Acute kidney injury*** (***AKI***) is common in rhabdomyolysis patients. About one-third to one-half of rhabdomyolysis patients will develop acute kidney injury (Lima et al. 2008), as 7–10 % of all acute kidney injuries occurring are due to rhabdomyolysis (Bosch et al. 2009). Kidney injury may sometimes present only several days after the initial impact.

The mechanisms are not fully understood:

- Due to depletion of intravascular volume, the renin-angiotensin system is activated, causing vasopressin secretion and sympathetic activity, causing renal vasoconstriction. Other inflammatory factors such as endothelin-1, thromboxane A2, and TNF-α and the depletion of nitric oxide contribute further to renal vasoconstriction.

- Myoglobin interacts with Tamm-Horsfall protein, creating casts, obstructing the tubuli, along with sloughed destroyed cells from tubular necrosis (Lima et al. 2008; Bosch et al. 2009; Plotnikov et al. 2009; Hendgen-Cotta et al. 2010). This process is more vigorous in an acidic environment, thus suggesting urine alkalization as a method of treatment.
- Myoglobin is a direct nephrotoxic factor due to its activity as peroxidase-like enzyme, causing uncontrolled oxidation of biomolecules, lipid peroxidation, and generation of isoprostanes. The nephrotoxic effect and cellular damage are caused also by the unbalanced conversion of the ferrous oxide ($Fe^{2+}$) of the heme group into ferric oxide ($Fe^{3+}$), generating hydroxyl radicals (Boutaud and Roberts 2011).

However, it appears that ER has a substantially decreased risk of resulting in AKI, compared with non-exertional rhabdomyolysis (less than half of AKI rate), suggesting additional contributing factors, perhaps related to the underlying cause itself (Alpers and Jones 2010). As mentioned above, CK level or myoglobinuria alone is not considered to be a reliable predicting factor (Schiff et al. 1978; Clarkson and Eichner 2006; Clarkson et al. 2006; Clarkson 2007; George et al. 2010).

***Arrhythmias*** may occur due to electrolyte abnormalities, mainly hyperkalemia and hypocalcemia. Careful monitoring and early intervention are crucial in order to prevent arrhythmias and cardiac arrest. Note that most electrolyte abnormalities, especially hypocalcemia of the early phase or rhabdomyolysis (Bosch et al. 2009), might present very early in the pathogenesis of the underlying cause.

***Acidosis*** is mainly caused by the deprivation of oxygen from involved tissues, resulting in lactic acidosis. However, the kidney injury most probably will prompt the situation rapidly (Better and Abassi 2011). Another mechanism is unmonitored usage of loop diuretics (Better and Stein 1990). When suspecting additional substance abuse, keep in mind that acidosis may also be caused as a direct or secondary outcome by many drugs (Liamis et al. 2010). The acidic urine will promote, as mentioned, the forming of casts by myoglobin interacting with Tamm-Horsfall proteins.

***Disseminated intravascular coagulation*** (***DIC***) may be initiated by the components of necrotic muscle tissue, resulting in diffuse internal hemorrhage (Khan 2009).

## Management and Treatment

Although there is no sufficient level I evidence, meaning randomized controlled trials, regarding the management of rhabdomyolysis patients, there are many series of retrospective clinical studies, case reports, and animal models. The most important issues of the treatment are vigorous fluid resuscitation, elimination of the underlying cause, and prevention of complications.

### Prehospital Care

Once deciding the occurrence of rhabdomyolysis is probable, aggressive fluid resuscitation is indicated. 1–1.5 L/h of normal saline should be infused, using a large-bore catheter. Potassium or lactate containing solutions are contraindicated due to the risk of hyperkalemia or lactic acidosis. This early intervention, infusing fluids vigorously, prior to evacuation to a medical center (Gunal et al. 2004) or up to 6 h of admission (Zager 1996), is reported to reduce the incidence of acute renal failure (ARF). The longer it takes to initiate rehydration, the higher the probability of ARF to develop (Odeh 1991; Adiseshiah et al. 1992). In comparison, when discussing rhabdomyolysis caused by massive crush disasters, several series proved better results (meaning decreased risk of renal replacement therapy required) when intravenous rehydration was applied prior to complete extraction of injured patient from the scene, using sometimes only one available limb (Better and Stein 1990; Gunal et al. 2004).

## Hospital Care

As discussed previously, thorough history and physical examination are crucial for diagnosing ER, as well as its underlying cause, precipitating factors, risk factors, and complications. Nevertheless, they should not delay aggressive fluid resuscitation, if not started prior to the intake. Vital signs, urine output, serum electrolytes, and CK levels should be monitored continuously, at intensive care setup if needed. In patients prone to heart condition due to preexisting disease or in elderly patients, careful hemodynamic monitoring is indicated due to the risk of fluid overload.

The chief objective of treatment is to achieve vigorous diuresis and dilution of the toxic products, using aggressive IV rehydration. A 1–1.5 L/h infusion of normal saline is required for initial resuscitation, followed by 300–500 mL/h once hemodynamic stability had been achieved. The measure for success is achieving the goal of 200–300 mL/h of urine and serum CK levels lower than 1,000 IU/L. Note that the desired CK level is not agreed upon by all protocols, indicating that the serum level will rise only 2–4 h after the primary insult and reach its peak level only after 24–72 h.

Although yet to be supported by randomized control trials, bicarbonate and mannitol therapy with saline hydration is advised in order to prevent acute kidney injury. Sodium bicarbonate is used for urinary alkalization, achieving several goals:

- Reduction of the nephrotoxic affect of myoglobin to the tubuli, due to the inhibition of reduction-oxidation cycling of myoglobin and lipid peroxidation (Bosch et al. 2009).
- Reduction of casts' formation because the precipitation of myoglobin with Tamm-Horsfall protein into a complex is precipitated by acidic urine and suppressed by an alkaline environment (Lima et al. 2008; Bosch et al. 2009).
- Sodium bicarbonate is a treatment for hyperkalemia.

The disadvantages of this therapy lie in the reduction of ionized calcium, which might exacerbate the symptoms of hypocalcemia, which is common in the early stage of rhabdomyolysis (Bosch et al. 2009), or by facilitating hypokalemia, common among crush-injured patients (due to potassium loss in the urine) (Gunal et al. 2004). Sodium bicarbonate solution is to be administrated at rate of 100 mL/h, till achieving a goal of urine pH >6.5 maintained and till myoglobinuria is resolved (Better and Stein 1990). Electrolyte levels (especially calcium and potassium), serum bicarbonate levels, and urine pH levels should be monitored during this treatment. If symptomatic hypocalcemia develops or urine pH resists treatment for more than 6 h, alkalization should be discontinued.

Mannitol is beneficial due to several reasons:

- As an osmotic agent, it draws interstitial fluid back to the intravascular compartment, improving hypovolemia, muscle swelling, and nerve compression.
- It is suggested to increase renal blood flow and glomerular filtration rate by osmotic diuresis, assisting in flushing the tubuli from nephrotoxic agents.
- It reduces free radical level as a scavenger (Bosch et al. 2009).

Mannitol therapy should be initiated only after intravascular volume is restored and should be withheld in patients with oliguria. Mannitol is to be administrated as 20 % infusion, starting with a loading dose of 0.5 g/kg during a 15 min period, followed by 0.1 g/kg/h infusion rate. However, there is no randomized controlled study that proves the yield of mannitol in this scenario, nor reports specific to ER, and some studies have found no benefit (Brown et al. 2004). It should be considered in light of the risk for osmotic nephrosis, due to renal vasoconstriction and tubular toxicity when mannitol serum level exceeds 1,000 mg/dL (Doi et al. 2003). Urine and serum pH levels, plasma osmolality, and osmolal gap should be monitored. Acetazolamide should be added if the serum pH is >7.45 or urinary pH remains lower than 6.0 (Better and Stein 1990; Khan 2009), and

treatment discontinued if sufficient diuresis is not achieved, or serum osmolal gap exceeds 55 mOsm/kg (equals to 1,000 mg/dL serum level) (Doi et al. 2003; Bosch et al. 2009). Although not in exertion setup, Terpilowski and Criddle suggested CK >20,000 IU/L as a threshold to start bicarbonate and mannitol therapy (Terpilowski and Criddle 2004).

The use of loop diuretics (e.g., furosemide) or recombinant B-natriuretic peptide (nesiritide) in rhabdomyolysis is controversial. Loop diuretics acidify the urine, which is not beneficial, except as a possible treatment in the case of iatrogenic metabolic acidosis caused by excessive use of normal saline (Ho et al. 2001). There is not enough supporting evidence of their yield-reducing mortality, reducing the need for renal replacement therapy or shortening the time of hospitalization (Karajala et al. 2009).

## Treatment of Any Reversible Cause of Muscle Damage

The major aim of treatment is to stop any progressing muscle destruction. Any toxin, infection, trauma, or hyperthermia must be diagnosed and treated as early as possible. Drugs and toxins should be eliminated and detoxified using gastric lavage, antidotes, and/or hemodialysis, and hypoxia must be corrected. Infections should be treated using broad-spectrum antimicrobial agents until the causative organism is isolated and diagnosed. Surgical eradication of infectious foci should be considered (e.g., abscess drainage, soft tissue debridement, or removal of infected foreign body). Muscle compartment syndrome is to be treated with fasciotomy. However, note that pressure relief may involve reperfusion injury. Hyperthermia is treated with external cooling measures and benzodiazepines to control muscular hyperactivity. In malignant hyperthermia, anesthetics should be discontinued, and the patient should be treated with dantrolene sodium; the usual initial dose is 2.5–4.0 mg/kg, followed by a maintenance dose of 1 mg/kg every 4 h for up to 48 h to avoid reoccurrence of the disease (Khan 2009). Electrolyte and metabolic abnormalities that cause rhabdomyolysis (e.g., hyponatremia, hypernatremia, hyperglycemia, hypocalcemia, and hypophosphatemia) should be corrected as soon as possible.

## Return to Normal Activity

Although there are no standardized guidelines for return to normal activity after an episode of ER, it is accepted by most researchers that the absence of symptoms and the decline of CK levels (with no consensus concerning the cutoff value) are advised prior to the return to exercises (Thoenes 2010). However, some authors recommend physical therapy to expedite early return to activity (Baxter and Moore 2003). According to Eichner, gradual preconditioning can be initiated, once muscle soreness and stiffness resolve and the CK levels are less than 5,000 IU/L (Eichner 2008). O'Connor et al. recommend a risk stratification and a classification into high or low risk for recurrence, using the criteria specified in Table 4 (O'Connor et al. 2008). Patients with low risk for recurrence should return to light activity for a minimum of 1 week, only after 72 h minimum of complete rest and the decrease of CK level to less than five times the upper level of normality. Only then and after recurrent medical follow-up a gradual return to normal activity should be permitted. During the recovery time, all patients should avoid possibly nephrotoxic drugs (most common NSAID), calcium supplements, and sulfa (Thoenes 2010). Return to physical activity should be done gradually, preconditioning any novel level of exertion in a period of minimum 1–2 weeks. Patients should be educated to pay close attention to symptoms (cramping, tenderness, turgor, fatigue, and especially colored urine) and report if any to a medical authority. Patients classified as high risk (e.g., sickle-cell trait, inherited myopathy) should return to activity at utmost caution, more gradually, taking longer periods of rest before and after exertion and be instructed

**Table 4** Discriminatory factors for ER recurrence probability (O'Connor, et al. 2008)

| High risk[a] | Low risk[b] |
|---|---|
| Delayed recovery (>1 week) while activity is restricted | Rapid clinical recovery + CK normalization after exercise restriction |
| CK >5 times the upper limit of normal range, despite 2-week rest | Well-trained athlete with a history of extremely intense training causing the ER episode |
| Acute kidney injury | Other athletes from the group/team also diagnosed as ER by the same training |
| Personal/familial history of ER | No personal/familial history of ER |
| Personal/familial history of recurrent muscle cramps | No personal/familial history of recurrent muscle cramps |
| Personal/familial history of sickle-cell disease/trait | Drug/dietary supplement potentially contributing to ER |
| ER episode after low/moderate exertion | Suspected viral/infectious disease prior to ER episode |
| Personal history of heat stroke | No personal history of heat injury |
| Serum CK peak >100,000 U/L | |

[a]Minimum one factor will be considered as high risk for recurrence
[b]No high-risk factors, minimum one factor will be defined as low risk for recurrence

to avoid hot and humid climate. It is advised to adopt further medical follow-up, especially in patients with high risk for recurrence.

## Prognosis

The prognosis of ER differs widely, between full recovery and no sequels, chronic muscle damage, and dysfunction and chronic renal failure. It is heavily dependent on the underlying cause and the complications of the initial injury. As there are no long-term follow-up prospective studies regarding the prognosis, the available evidence suggests that ER has good prognosis, if treated early and vigorously, including full recovery of renal damage. However, if recurrence risk is not taken into consideration, residual symptoms often occur, with less favorable long-term prognosis.

## Conclusion

Exertional rhabdomyolysis is a well-described, dangerous, and not uncommon medical situation, thus should not be overlooked, but included, within the sport's medical doctor differential diagnosis for muscle pain and loss of function. Ignoring it may have devastating results, as its diagnosis and treatment can be established relatively easily, achieving good prognosis in the majority of patients.

## Cross-References


- ▶ Compartment Syndromes of Thigh and Lower Leg
- ▶ Ironman Triathlon: Medical Considerations
- ▶ Ultramarathon Running Injuries


## References


(2013) Update: exertional rhabdomyolysis, active component, U.S. Armed Forces 2008–2012. MSMR 20 (3):21–24

Adiseshiah M, Round JM, Jones DA (1992) Reperfusion injury in skeletal muscle: a prospective study in patients with acute limb ischaemia and claudicants treated by revascularization. Br J Surg 79(10): 1026–1029

Adnet P, Lestavel P, Krivosic-Horber R (2000) Neuroleptic malignant syndrome. Br J Anaesth 85(1):129–135

Al-Ismaili Z, Piccioni M, Zappitelli M (2011) Rhabdomyolysis: pathogenesis of renal injury and management. Pediatr Nephrol 26(10):1781–1788

Alpers JP, Jones LK Jr (2010) Natural history of exertional rhabdomyolysis: a population-based analysis. Muscle Nerve 42(4):487–491

Amato AA, Griggs RC (2011) Overview of the muscular dystrophies. Handb Clin Neurol 101:1–9

Baxter RE, Moore JH (2003) Diagnosis and treatment of acute exertional rhabdomyolysis. J Orthop Sports Phys Ther 33(3):104–108

Better OS, Abassi ZA (2011) Early fluid resuscitation in patients with rhabdomyolysis. Nat Rev Nephrol 7 (7):416–422

Better OS, Stein JH (1990) Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med 322(12):825–829
Bosch X, Poch E, Grau JM (2009) Rhabdomyolysis and acute kidney injury. N Engl J Med 361(1):62–72
Bouchama A, Knochel JP (2002) Heat stroke. N Engl J Med 346(25):1978–1988
Boutaud O, Roberts LJ (2011) Mechanism-based therapeutic approaches to rhabdomyolysis-induced renal failure. Free Radic Biol Med 51(5):1062–1067
Brancaccio P, Lippi G, Maffulli N (2010) Biochemical markers of muscular damage. Clin Chem Lab Med 48(6):757–767
Brown CV, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC (2004) Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma 56(6):1191–1196
Brukner P (2008) Clinical sports medicine. Nicole Meehan
Bynum GD, Pandolf KB, Schuette WH, Goldman RF, Lees DE, Whang-Peng J, Atkinson ER, Bull JM (1978) Induced hyperthermia in sedated humans and the concept of critical thermal maximum. Am J Physiol 235(5): R228–R236
Campbell WC, Canale ST, Beaty JH (2008) Operative orthopaedics, 12th edn. Mosby Elsevier, Philadelphia, pp 2311–2321
Capacchione JF, Muldoon SM (2009) The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. Anesth Analg 109 (4):1065–1069
Carroll CL, Zucker AR (2007) The increased cost of complications in children with status asthmaticus. Pediatr Pulmonol 42(10):914–919
Carsana A (2013) Exercise-induced rhabdomyolysis and stress-induced malignant hyperthermia events, association with malignant hyperthermia susceptibility, and RYR1 gene sequence variations. Sci World J 2013:531465
Clarkson PM (2007) Exertional rhabdomyolysis and acute renal failure in marathon runners. Sports Med 37 (4–5):361–363
Clarkson PM, Eichner ER (2006) Exertional rhabdomyolysis: does elevated blood creatine kinase foretell renal failure? Curr Sports Med Rep 5(2):57–60
Clarkson PM, Hubal MJ (2002) Exercise-induced muscle damage in humans. Am J Phys Med Rehabil 81 (11 Suppl):S52–S69
Clarkson PM, Kearns AK, Rouzier P, Rubin R, Thompson PD (2006) Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc 38(4):623–627
Cleary MA et al (2011) Exertional rhabdomyolysis in an adolescent athlete during preseason conditioning: a perfect storm. J Strength Cond Res 25(12): 3506–3513
Coryell W, Norby LH, Cohen LH (1978) Psychosis-induced rhabdomyolysis. Lancet 2(8085):381–382
de Meijer 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 (7):1121–1125
Denman JP (2007) Hypernatraemia and rhabdomyolysis. Med J Aust 187(9):527–528
Doi K, Ogawa N, Suzuki E, Noiri E, Fujita T (2003) Mannitol-induced acute renal failure. Am J Med 115 (7):593–594
Eichner ER (2008) Exertional rhabdomyolysis. Curr Sports Med Rep 7(1):3–4
Elsayed EF, Reilly RF (2010) Rhabdomyolysis: a review, with emphasis on the pediatric population. Pediatr Nephrol 25(1):7–18
Escobar C, Echarri R, Barrios V (2008) Relative safety profiles of high dose statin regimens. Vasc Health Risk Manag 4(3):525–533
Fernandez G et al (2011) Statin myopathy: a common dilemma not reflected in clinical trials. Cleve Clin J Med 78(6):393–403
Gagliano M, Corona D, Giuffrida G, Giaquinta A, Tallarita T, Zerbo D, Sorbello M, Paratore A, Virgilio C, Cappellani A, Veroux P, Veroux M (2009) Low-intensity body building exercise induced rhabdomyolysis: a case report. Cases J 2(1):7
Galvez R, Stacy J, Howley A (2008) Exertional rhabdomyolysis in seven division-1 swimming athletes. Clin J Sport Med 18(4):366–368
George M, Delgaudio A, Salhanick SD (2010) Exertional rhabdomyolysis–when should we start worrying? Case reports and literature review. Pediatr Emerg Care 26 (11):864–866
Greene JT, Anders DL (1990) Exertional rhabdomyolysis in two prison inmates. J Med Assoc Ga 79(10): 743–746
Gunal AI, Celiker H, Dogukan A, Ozalp G, Kirciman E, Simsekli H, Gunay I, Demircin M, Belhan O, Yildirim MA, Sever MS (2004) Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. J Am Soc Nephrol 15 (7):1862–1867
Gupta P, Singh VP, Chatterjee S, Agarwal AK (2010) Acute renal failure resulting from rhabdomyolysis following a seizure. Singapore Med J 51(4): e79–e80
Hadad E, Weinbroum AA, Ben-Abraham R (2003) Drug-induced hyperthermia and muscle rigidity: a practical approach. Eur J Emerg Med 10(2):149–154
Hannah-Shmouni F, McLeod K, Sirrs S (2012) Recurrent exercise-induced rhabdomyolysis. CMAJ 184(4):426–430
Hendgen-Cotta UB, Flogel U, Kelm M, Rassaf T (2010) Unmasking the Janus face of myoglobin in health and disease. J Exp Biol 213(Pt 16):2734–2740
Ho AM, Karmakar MK, Contardi LH, Ng SS, Hewson JR (2001) Excessive use of normal saline in managing traumatized patients in shock: a preventable contributor to acidosis. J Trauma 51(1):173–177
Karajala V, Mansour W, Kellum JA (2009) Diuretics in acute kidney injury. Minerva Anestesiol 75(5):251–257

Kenney K, Landau ME, Gonzalez RS, Hundertmark J, O'Brien K, Campbell WW (2012) Serum creatine kinase after exercise: drawing the line between physiological response and exertional rhabdomyolysis. Muscle Nerve 45(3):356–362

Khan FY (2009) Rhabdomyolysis: a review of the literature. Neth J Med 67(9):272–283

Kim HR, Kim SH, Oh DJ (2012) Rhabdomyolysis after a regular exercise session in a patient with Graves' disease. Nephrology (Carlton) 17(3):307–308

King TW, Lerman OZ, Carter JJ, Warren SM (2010) Exertional compartment syndrome of the thigh: a rare diagnosis and literature review. J Emerg Med 39(2): e93–e99

Kutlu AO, Kara C, Cetinkaya S (2011) Rhabdomyolysis without detectable myoglobulinuria due to severe hypophosphatemia in diabetic ketoacidosis. Pediatr Emerg Care 27(6):537–538

Lamminen AE, Hekali PE, Tiula E, Suramo I, Korhola OA (1989) Acute rhabdomyolysis: evaluation with magnetic resonance imaging compared with computed tomography and ultrasonography. Br J Radiol 62 (736):326–330

Landau ME, Kenney K, Deuster P, Campbell W (2012) Exertional rhabdomyolysis: a clinical review with a focus on genetic influences. J Clin Neuromuscul Dis 13(3):122–136

Liamis G, Milionis HJ, Elisaf M (2010) Pharmacologically-induced metabolic acidosis: a review. Drug Saf 33(5):371–391

Liang WC, Nishino I (2010) State of the art in muscle lipid diseases. Acta Myol 29(2):351–356

Lim ST, Sohn MH, Jeong HJ, Yim CY (2008) Lithotomy position-related rhabdomyolysis of gluteus maximus muscles demonstrated by bone scintigraphy. Clin Nucl Med 33(1):58–60

Lima RS, da Silva Junior GB, Liborio AB, Daher Ede F (2008) Acute kidney injury due to rhabdomyolysis. Saudi J Kidney Dis Transpl 19(5):721–729

Litman RS, Rosenberg H (2005) Malignant hyperthermia: update on susceptibility testing. JAMA 293 (23):2918–2924

Makaryus JN, Catanzaro JN, Katona KC (2007) Exertional rhabdomyolysis and renal failure in patients with sickle cell trait: is it time to change our approach? Hematology 12(4):349–352

Mannix R, Tan ML, Wright R, Baskin M (2006) Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics 118(5):2119–2125

Manji H, Howard RS, Miller DH, Hirsch NP, Carr L, Bhatia K, Quinn N, Marsden CD (1998 Feb) Status dystonicus: the syndrome and its management. Brain 121(Pt 2):243–252

Marinella MA (1998) Exertional rhabdomyolysis after recent coxsackie B virus infection. South Med J 91 (11):1057–1059

Meador BM, Huey KA (2010) Statin-associated myopathy and its exacerbation with exercise. Muscle Nerve 42(4):469–479

Melli G, Chaudhry V, Cornblath DR (2005) Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore) 84(6):377–385

Mian AZ, Saito N, Sakai O (2011) Rhabdomyolysis of the head and neck: computed tomography and magnetic resonance imaging findings. Dentomaxillofac Radiol 40(6):390–392

Montague BT, Ouellette JR, Buller GK (2008) Retrospective review of the frequency of ECG changes in hyperkalemia. Clin J Am Soc Nephrol 3(2):324–330

Moratalla MB, Braun P, Fornas GM (2008) Importance of MRI in the diagnosis and treatment of rhabdomyolysis. Eur J Radiol 65(2):311–315

O'Connor FG, Brennan FH Jr, Campbell W, Heled Y, Deuster P (2008) Return to physical activity after exertional rhabdomyolysis. Curr Sports Med Rep 7(6):328–331

Odeh M (1991) The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. N Engl J Med 324(20):1417–1422

Patel DR, Gyamfi R, Torres A (2009) Exertional rhabdomyolysis and acute kidney injury. Phys Sportsmed 37 (1):71–79

Plotnikov EY, Chupyrkina AA, Pevzner IB, Isaev NK, Zorov DB (2009) Myoglobin causes oxidative stress, increase of NO production and dysfunction of kidney's mitochondria. Biochim Biophys Acta 1792 (8):796–803

Quinlivan R, Jungbluth H (2012) Myopathic causes of exercise intolerance with rhabdomyolysis. Dev Med Child Neurol 54(10):886–891

Richards JR (2000) Rhabdomyolysis and drugs of abuse. J Emerg Med 19(1):51–56

Rodriguez-Capote K, Balion CM, Hill SA, Cleve R, Yang L, El Sharif A (2009) Utility of urine myoglobin for the prediction of acute renal failure in patients with suspected rhabdomyolysis: a systematic review. Clin Chem 55(12):2190–2197

Sandhu RS et al (2002) Renal failure and exercise-induced rhabdomyolysis in patients taking performance-enhancing compounds. J Trauma 53(4):761–763; discussion 763-4

Sayers SP, Clarkson PM (2002) Exercise-induced rhabdomyolysis. Curr Sports Med Rep 1(2):59–60

Schiff HB, MacSearraigh ET, Kallmeyer JC (1978) Myoglobinuria, rhabdomyolysis and marathon running. Q J Med 47(188):463–472

Semple SJ (2012) Statin therapy, myopathy and exercise–a case report. Lipids Health Dis 11:40

Sevketoglu E, Kural B, Beskardes AE, Hatipoglu S (2011) Exertional rhabdomyolysis after influenza A (H3N2) infection in a basketball player boy. Ann Trop Paediatr 31(1):93–96

Siegel AJ (2006) Exercise-associated hyponatremia: role of cytokines. Am J Med 119(7 Suppl 1):S74–S78

Sorrentino SA, Kielstein JT, Lukasz A, Sorrentino JN, Gohrbandt B, Haller H, Schmidt BM (2011) High permeability dialysis membrane allows effective removal of myoglobin in acute kidney injury resulting from rhabdomyolysis. Crit Care Med 39(1):184–186

Springer BL, Clarkson PM (2003) Two cases of exertional rhabdomyolysis precipitated by personal trainers. Med Sci Sports Exerc 35(9):1499–1502

Strachan P, Prisco D, Multz AS (2007) Recurrent rhabdomyolysis associated with polydipsia-induced hyponatremia – a case report and review of the literature. Gen Hosp Psychiatry 29(2):172–174

Tarnopolsky M et al (2003) Diagnostic utility of a modified forearm ischemic exercise test and technical issues relevant to exercise testing. Muscle Nerve 27 (3):359–366

Terpilowski J, Criddle L (2004) Rhabdomyolysis following a gunshot wound and one trauma center's protocol and guidelines. J Emerg Nurs 30(1):36–41

Thoenes M (2010) Rhabdomyolysis: when exercising becomes a risk. J Pediatr Health Care 24(3):189–193

Trimarchi H, Gonzalez J, Olivero J (1999) Hyponatremia-associated rhabdomyolysis. Nephron 82(3):274–277

von Vigier RO, Ortisi MT, La Manna A, Bianchetti MG, Bettinelli A (2010) Hypokalemic rhabdomyolysis in congenital tubular disorders: a case series and a systematic review. Pediatr Nephrol 25(5):861–866

Walsh S, Fan SL (2009) Visualising rhabdomyolysis. Lancet 373(9658):154

Yen TH, Lai PC, Chen CC, Hsueh S, Huang JY (2005) Renal involvement in patients with polymyositis and dermatomyositis. Int J Clin Pract 59(2):188–193

Yeo TP (2004) Heat stroke: a comprehensive review. AACN Clin Issues 15(2):280–293

Zager RA (1996) Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int 49(2):314–326

Zhang L, Fang ZJ, Liu F, Fu P, Tao Y, Li ZY, Song B (2011) Magnetic resonance imaging and magnetic resonance angiography in severe crush syndrome with consideration of fasciotomy or amputation: a novel diagnostic tool. Chin Med J (Engl) 124(13):2068–2070