Non-traumatic and non-drug-induced rhabdomyolysis

Genovefa Kolovou[1], Philip Cokkinos[1], Helen Bilianou[2], Vana Kolovou[1,3], Niki Katsiki[4], Sophie Mavrogeni[1]

[1]Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece
[2]Cardiology Department, Tzanio Hospital, Piraeus, Greece
[3]Molecular Immunology Laboratory, Onassis Cardiac Surgery Center, Athens, Greece
[4]First Department of Internal Medicine, Division of Endocrinology-Metabolism,
 Diabetes Center, AHEPA University Hospital, Thessaloniki, Greece

Corresponding author:
Philip Cokkinos MD, FRCP,
FESC
Cardiology Division
Onassis Cardiac
Surgery Centre
356 Sygrou Avenue
176 74 Athens, Greece
Phone: +30 210 9493549
Fax: +30 210 9493336
E-mail: philipcokkinos@
yahoo.com

Abstract

Rhabdomyolysis (RM), a fortunately rare disease of the striated muscle cells, is a complication of non-traumatic (congenital (glycogen storage disease, discrete mitochondrial myopathies and various muscular dystrophies) or acquired (alcoholic myopathy, systemic diseases, arterial occlusion, viral illness or bacterial sepsis)) and traumatic conditions. Additionally, RM can occur in some individuals under specific circumstances such as toxic substance use and illicit drug abuse. Lipid-lowering drugs in particular are capable of causing RM. This comprehensive review will focus on non-traumatic and non-drug-induced RM. Moreover, the pathology of RM, its clinical manifestation and biochemical effects, and finally its management will be discussed.

Key words: rhabdomyolysis, myoglobulin, dystrophy, myopathy.

Introduction

The term "rhabdomyolysis" (RM) first entered PubMed in 1959 [1], although its first clinical description appeared more than a thousand years ago [2]. Fortunately a rare disease, it usually presents as a complication of non-traumatic (congenital (glycogen storage diseases, mitochondrial myopathies and muscular dystrophies) or acquired (alcoholic myopathy, systemic disease, artery occlusion, viral or bacterial illness)) and traumatic conditions. Additionally, RM may occur in some individuals under specific circumstances such as toxic substance use and illicit drug abuse. Lipid-lowering drugs may also cause RM [3].

Recognizing underlying disorders presenting with RM, particularly genetic disorders, is a diagnostic challenge: these diseases are uncommon and present with a wide range of symptoms. Despite this challenge, timely diagnosis and appropriate laboratory evaluation are crucial for the prevention of new episodes [4]. Early identification of RM is especially crucial for the prevention of acute kidney disease (AKD) as RM is a severe, potentially life-threatening condition with a mortality rate of ~10% which is even higher in patients with AKD [5]. Clinically, RM presents with muscle aches and weakness, oedema and dark-red urine discoloration. Many patients experience only one episode of RM; patients with more than one episode, additionally to the above-described symptoms, complain of exercise intolerance and fatigue and may have

a positive family history for myopathy. Typically, in RM, the increase of serum creatine kinase (CK) is > 10 times the normal upper limit (ULN). If AKD is present then creatinine elevation, red urine discoloration [6], oliguria (rarely anuria) and electrolyte abnormalities are observed [7]. However, the clinical symptoms are often non-specific, and red-coloured urine is usually the first indication of RM [8].

RM is defined as necrosis of muscle cells which leads to: 1) leakage of intracellular substances to the extracellular fluid and bloodstream and 2) uncontrolled entry of extracellular substances into damaged muscle cells, principally calcium. Both reactions can cause various systemic complications [9]. This review will focus on non-traumatic and non-drug-induced RM.

Rhabdomyolysis in genetic disorders

RM can occur in patients with underlying genetic conditions such as glycogen storage diseases (GSDs), mitochondrial myopathies, and muscular dystrophies, which are a diverse group of ailments resulting in progressive muscle atrophy and weakness [10]. In most cases the diagnosis of congenital myopathy may be obvious because the affected individual has already some level of muscle weakness, although exercise-induced cramps may be the only presenting symptoms. Below we briefly analyze the examples of muscle myopathies which more frequently than other GSDs induce RM.

Glycogen storage disease

Glycogen is a form of carbohydrate and in humans is stored in skeletal muscle (~500 g) and liver (~100 g) cells [11]. Glycogen storage is controlled by feedback-mediated inhibition of glycogen synthase to prevent exaggerated glycogen accumulation. There are more than 13 types of GSD, which are classified with Roman numerals and, if the name of the person who first reported it is known, the disease is called accordingly [11].

McArdle disease (GSD-V)

GSD-V is the most common disorder of muscle glycogenesis and is caused by mutations (autosomal recessive) in the *PYGM* gene which encodes glycogen phosphorylase [12, 13] resulting in an inability of converting muscle glycogen into glucose-1-phosphate. This produces glycogen accumulation within skeletal muscle cells. Typically, McArdle disease presents in the first two decades of life with exercise intolerance and muscle cramps (occurring within the first few minutes of physical effort), episodes of RM, and the second-wind phenomenon [12, 13]. Additional

clinical features may involve muscle hypertrophy and permanent muscle weakness, mainly shoulder girdle and axial [13–15]. De Stefano *et al.* [16] observed a decrease in the rate of oxidative phosphorylation in muscle cells of patients with GSD-V due to reduced delivery of glycogen phosphorylase to their mitochondria and impaired anaerobic glycolysis. Moreover, subjects with McArdle disease frequently develop insulin resistance which leads to impaired glucose uptake, impaired glycogen production, and alterations in fuel oxidation. During exercise, a rise in lactate and ammonia occurs, causing fatigue and exercise intolerance even in the first minutes of physical effort and a disproportional increase in heart rate. Notably, insulin sensitivity decreases with age and this may partially explain the disease's late onset in some cases [17]. Moreover, Haller *et al.* [18] showed that in patients with GSD-V the Na^+-K^+ pump may be impaired, and this further limits exercise capacity by inducing a failure of skeletal muscle cell membrane excitability.

RM may present in approximately 50% of GSD-V patients but it is likely that only a few develop AKD. Park *et al.* reported recurrent episodes of RM after seizures in a Korean patient with *PYGM* mutations [19].

Stimulators of RM in patients with GSD-V include the continuation of physical activity despite symptoms, intense exertion [20, 21], viral infections and seizures [19, 22].

Tarui disease (GSD-VII)

Tarui disease is caused by a mutation (autosomal recessive) in the *PFKM* gene encoding phosphofructokinase (PFK) which catalyses the conversion of fructose-6-phosphate to fructose-1,6-diphosphate. PFK deficiency causes myopathy and/or haemolysis and may be asymptomatic. Four clinical subclasses of Tarui disease have been identified: classical, infantile, late-onset, and haemolytic [23]. Patients with the classical presentation complain of muscle cramps and aches, physical intolerance, accompanied by nausea and vomiting. Jaundice, elevated CK levels, hyperuricaemia, and increased serum bilirubin can also be seen. Early presentation of Tarui disease may manifest as "floppy babies", arthrogryposis and mental retardation. Infants affected with Tarui disease may die within the first year of their lives. Late onset presents usually in the fifth decade and leads to severe disability. The haemolytic form features haemolytic anaemia. The combination of haemolytic anaemia and myopathy should raise the suspicion of GSD-VII [24, 25].

Stimulators of RM in patients with GSD-VII include intense exercise, particularly isometric muscle contraction [25].

GSD-IX

GSD-IX (also called GSD-IXb or GSD-IXd) is caused by deficiency of the phosphorylase kinase (PhK) which is encoded by the *PHKB* gene [26]. PhK is involved in glycogen [27]. There are two types of PhK deficiency, liver PhK and muscle PhK. The former is characterized by exercise intolerance, myalgia, muscle cramps, progressive muscle weakness and episodes of RM.

Stimulators of RM in patients with GSD-IX: exaggerated physical effort.

GSD-X

GSD-X is caused by a mutation (autosomal recessive) in the *PGAM2* gene and is characterized by a reduction of phosphoglycerate mutase (PGAM). Usually, symptoms do not present in daily activities but after exaggerated physical effort with muscle pains, myoglobinuria and RM.

Stimulators of RM in patients with GSD-X: exaggerated physical effort [28–31].

GSD-XII

GSD-XII, or aldolase A, deficiency is caused by mutations (autosomal recessive) in the *ALDOA* gene and is characterized by lack of production of dihydroxyacetone phosphate and glyceraldehyde 3-phosphate from fructose 1,6-bisphosphate, due to the deficiency of the aldolase A isoform [32, 33]. It usually affects muscle cells and erythrocytes. Patients may present with haemolytic anaemia, muscle pains, exercise intolerance, fatigue and episodes of RM [33–35], which can appear in the first months of life [32, 34].

Stimulators of RM in patients with GSD-XII include fever and infections [32–36].

Mitochondrial myopathies

Impaired oxidative phosphorylation and reduction of adenosine triphosphate (ATP) production are the two main defects of mitochondrial diseases [37]. These disorders belong to the most severe inborn metabolic diseases, which may be present even in newborns and young children. The enzymes involved in respiratory chain complexes and ATP synthase are encoded by maternally transmitted mitochondrial DNA (*mtDNA*) and nuclear DNA (*nDNA*). Thus, pathogenic mutations can therefore reside in both nuclear and mitochondrial genomes. According to mitochondrial myopathies [38–40], fortunately episodes of RM are infrequent and only a few examples will be analysed below. Generally, mitochondrial myopathy can be classified into 5 groups: 1) mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [38], 2) myoclonus epilepsy associated with ragged-red fibres (MERRF) [41, 42], 3) Kearns-Sayre syndrome (KISS) [43], 4) chronic progressive external ophthalmoplegia (CPEO) [44], and 5) neurogenic weakness with ataxia and retinitis pigmentosa (NARP) [45, 46].

The stimulators leading to RM in patients with MELAS, MERRF, KISS, CPEO or NARP syndromes are similar and include strenuous physical exertion, fever and infection [47, 48].

MELAS syndrome

The MELAS syndrome was first described by HW Koenigsberg [49] but the name was given in 1984 by Pavlakis *et al.* [50]. Approximately 80% of affected individuals are carriers of the mitochondrial transporter (tRNA) *m.3243A>G* gene. The frequency of this mutation in the general population is about 1/15,000 births. Affected individuals may develop diabetes mellitus, deafness, encephalopathy, seizers, stroke-like episodes, partially reversible blindness, short stature and exercise intolerance [38, 47, 48]. Nearly 22% of affected individuals will die before the age of 18.

MERRF syndrome

The MERRF syndrome is a multisystem disorder characterized by myoclonus (often the first presentation) [41, 42]. The *mtDNA* gene *MT-TK* encoding tRNA^{Lys} is the gene most commonly associated with MERRF and is maternally transmitted. Affected individuals may also present with generalized epilepsy, ataxia, sensorineural hearing loss, myopathy, peripheral neuropathy, dementia, short stature, exercise intolerance, and optic atrophy. Ragged-red fibres (RRF) are found in muscle biopsy or an *mtDNA* pathogenic variant identified. Less frequent clinical features include cardiomyopathy, pigmentary retinopathy, pyramidal signs, ophthalmoparesis and lipomatosis [41, 42].

KISS syndrome

The KISS syndrome has a typical onset before the age of 20 and manifests with progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction block, hyperproteinorrhachia or ataxia [43].

CPEO

Patients with CPEO usually present with progressive paralysis of the external eye muscles resulting in limited sideways or upwards gaze, muscle fatigue and weakness, exercise intolerance and psychiatric disorders [44].

NARP

NARP was first described by Holt *et al.* [51] and presents with ptosis, external ophthalmoplegia,

proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus.

Muscular dystrophies

DMD

Mutations of the dystrophin gene are the cause of 2 harmful and still incurable diseases, Duchenne (DMD) Becker (BMD) muscular dystrophies [52, 53]. Dystrophinopathies are sex-linked disorders. The lack of dystrophin destabilizes the muscle membrane, leading to clinical features of delayed motor development, calf hypertrophy, joint contractures, and progressive muscle weakness leading to scoliosis, cardiomyopathy, respiratory insufficiency, severe physical disability and reduced life expectancy, with death occurring before the third or fourth decade of life [52, 54–59]. DMD affects 1/3,500–5,000 live-born males; it is the most common type of muscular dystrophy in childhood [57, 58]. Dystrophin is an important part of the dystrophin-associated glycoprotein complex, is associated with other cytoskeletal proteins [60], and is essential for cell survival via its transmembrane signalling function and modulation of vasomotor response to physical activity [61].

Other genetic disorders

Carnitine palmitoyltransferase deficiency II (CPTII)

Other genetic (autosomal recessive) metabolic disorders which are associated with RM include CPTII deficiency [62–65], which affects adolescents and young adults and is characterized by recurrent myoglobinuria, muscle aches, and stiffness induced by exercise, fasting, infection, exposure to cold and stress. The condition may be silent until the first episode of RM.

Malignant hyperthermia (MH)

A genetic disorder which manifests as a hyper-metabolic response to potent inhalation agents (halothane, isoflurane, sevoflurane, desflurane), the depolarizing muscle relaxant succinylcholine, and to stressors such as strenuous exercise and heat [66–68].

The two genes that have been definitively associated with MH causative mutations are *RYR1* and *CACNA1S* [69, 70]. MH may occur at any time during anaesthesia as well as in the early postoperative period [71]. Larach *et al.* found that increased temperature was among the first three early signs in 63.5% of MH reactions [72]. Hyperthermia can result in a temperature up to, or greater than, 44°C and lead to vital organ dysfunction (heart failure, compartment syndrome, see below), and disseminated intravascular coagulation, which is the usual cause of death [73]. Experimental evidence suggests that the signs and symptoms of MH are associated with an uncontrolled release of intracellular Ca^{2+} from the skeletal muscle sarcoplasmic reticulum [74].

Rhabdomyolysis in acquired diseases

Acquired diseases which can cause RM are mainly endocrine disorders, various infections, muscle ischaemia and severe agitation. RM can be precipitated by electrolyte wasting, thyroid storm, increased sympathetic stimulation and metabolic demands forcing the body into hyper-metabolism [75–77].

Endocrine disorders

Hypothyroidism

Hypothyroidism may cause hypothyroid myopathy and rarely RM [75]. Clinical symptoms such as myalgias, proximal muscle weakness and cramps usually resolve after the normalization of thyroid hormones. The exact cause of RM in hypothyroidism is still not clarified. It is believed that impaired glycogenolysis, impaired mitochondrial oxidative metabolism or triglyceride turnover in thyroxine deficiency may be the responsible mechanisms [78–80]. Katipoglu *et al.* [81] describe a case of RM complicated by AKD in a patient who developed hypothyroidism after stopping l-thyroxine, which he was taking after undergoing total thyroidectomy for papillary thyroid cancer. The pathophysiology of AKD due to hypothyroidism may be explained by a decrease in cardiac output, which leads to reduced renal blood supply and the decrease of glomerular filtration rate (GFR) [80]. On the other hand, T3 (triiodothyronine) may directly affect systemic (including renal) vascular resistance. Moreover, brain natriuretic peptide (produced mainly from the ventricles in response to volume expansion, pressure overload, and elevated end diastolic pressure) levels have been found to be influenced by free T3 and T4 (thyroxine) [82, 83]. It has also been shown that T4 regulates Na^+/Ca^{2+} channels and Na^+/K^+-ATPase activity (see below) in the nephron sarcoplasmic reticulum [84–86]. Of note, haemodialysis patients are likely to have an increased risk for hypothyroidism-induced RM due to the presence of comorbidities such as electrolyte imbalance, diabetes mellitus, and drug interactions (statins, antihypertensives, and antiarrhythmics) [86]. Another important mechanism of RM in hypothyroidism is the coexistence of statin therapy with potentially decreased drug catabolism, resulting in higher serum statin levels [87]. Also, amiodarone (a class III antiarrhythmic

drug) may induce clinical hypothyroidism in approximately 5% of treated patients. Thus, hypothyroidism must be considered in the aetiological assessment of RM in these patients.

Hyperthyroidism

Hyperthyroidism may present as indolent proximal weakness, idiopathic ocular myositis or polymyositis [88, 89]. Painless thyroiditis is characterized by transient thyrotoxicosis lasting 2–4 weeks, followed by hypothyroidism for 1–3 months, and then resolution. Patients with painless thyroiditis usually do not require treatment during the hyperthyroid or hypothyroid phase because thyroid dysfunction is transient and rarely severe. However, if thyrotoxicosis leads to hypokalaemia, generalized muscle weakness (thyrotoxic periodic paralysis), RM and cardiac arrhythmias, including life-threatening ventricular tachycardia, may ensue [90]. The decreased potassium release from muscle cells due to hypokalaemia can decrease blood flow to muscles, leading to ischaemic RM [91]; see below. Chang *et al.* [92] describe a 61-year-old man with thyrotoxicosis, lower extremity paralysis and severe hypokalaemia. Despite attempts to correct potassium levels he developed pulseless polymorphic ventricular tachycardia (resuscitated with defibrillation), AKD and RM. The authors explain the cause of RM by 2 mechanisms, namely severe hypokalaemia and increased CK secondly to chest compressions and defibrillation. The release of CK after cardioversion indicates increased skeletal muscle damage and may predispose patients to RM [93–95]. Moreover, RM induced by hyperthyroidism may be present in individuals after exercise. Summachiwakij and Sachmechi describe RM in a patient with Graves disease induced by non-strenuous exercise [96].

Hyper/hypoparathyroidism

Hyperparathyroidism may cause muscle weakness (dropped head syndrome), muscle pain, or ischaemic, calcifying myopathy [97, 98].

Muscle involvement in hypoparathyroidism may present as myopathy, neuromyotonia, or RM. Sumnu *et al.* [99] describe the case of a 26-year-old epileptic male with leg myalgias, cramps, nausea, vomiting, and decreased urine output. He was admitted to the emergency department several times over 6 months and eventually diagnosed with primary hypoparathyroidism and AKD secondary to severe RM.

Diabetes mellitus

Diabetes is known to predispose to RM in patients with hyperosmolarity. Diabetes mellitus may cause diabetic myopathy [100–102] with a wide range of abnormalities, such as painless muscle wasting (diabetic amyotrophy), muscle inflammation, ischaemia, infarction, fibrosis, fatty atrophy, haemorrhage and diabetic myonecrosis, a self-limiting condition with acute onset of oedema and severely painful muscle necrosis. Usually, myonecrosis occurs in poorly controlled diabetes [103, 104]. The development of RM in diabetic patients depends on the severity of serum hyperosmolarity and the presence of hypernatraemia [77, 105]. Another mechanism which may provoke episodes of RM is through chronic kidney dysfunction, often present in diabetic patients, and comorbidities such as electrolyte imbalance and drug interactions (antihyperlipidemic, antihypertensives, and antiarrhythmics). Of note, hypolipidemic drugs (statin and/or fibrates), which many of these patients are taking, may provoke RM [106]. Antidiabetic drugs may also cause RM. Slim *et al.* report a case of a patient who developed severe RM after receiving pioglitazone [107] and Yokoyama *et al.* [108] report such a case after troglitazone. Potential risk factors identified in these cases include concomitant therapy with fibrate, alcohol abuse, and asymptomatic mild CK elevation prior to initiating therapy.

Adrenal insufficiency

RM is reported rarely in patients with acute adrenal insufficiency and may present as myopathy, hyperkalaemic neuromyopathy and hyponatraemia with sodium concentration reported as low as 97 mmol/l [109]. Convulsions because of hyponatraemia can also cause muscle damage and a subsequent rise in CK. Lau and Yong describe a patient with acute primary adrenal insufficiency and severe hyponatraemia complicated by RM and AKD [110].

Bacterial, viral and fungal infections

Potentially all bacterial, viral and fungal infections can lead to RM [111–114]. Particularly, viral infections may cause various complications involving skeletal muscle, from non-specific myalgias to severe myositis and RM. Tanaka *et al.* [115] identified the influenza virus as an implicated agent in nearly 33% of known virus-induced RM. RM has been described in infections from *Staphylococcus aureus*, *Mycoplasma pneumoniae*, tuberculosis, tetanus, *Salmonella*, *Brucella*, *Legionella* and others [116–122]. Infectious conditions destroy muscle tissue by toxin production or direct bacterial invasion.

Muscle ischaemia

Conditions of generalized ischaemia and hypoxaemia, such as cardiogenic shock, CO poison-

ing and status asthmaticus, are possible causes of RM, as they are associated with insufficient ATP production and sarcolemma dysfunction due to limited cellular oxygen delivery [123]. Localized compression, arterial thrombosis, prolonged vascular occlusion during surgical operations, air emboli and severe sickle cell crisis are other causes of RM. However, many events which eventually lead to RM due to muscle ischaemia occur during the reperfusion phase. After circulation is restored, large amounts of potentially toxic intracellular content are released into the bloodstream.

Conditions with agitation

Conditions with severe agitation, such as protracted myoclonic seizures in status epilepticus, delirium tremens, and the use of psychostimulant drugs may lead to RM [19, 42, 124, 125]. Severe agitation results in a state where ATP production cannot keep up with cellular demand, leading to depletion of energy supply and eventually cellular death.

The above listed causes of RM, and their relative prevalence, are summarised in Table I.

Rhabdomyolysis pathology

Independently of what causes RM, the consequences are the same. The increase in concentration of intracellular ionized calcium is the most harmful pathological process, is activated in RM and is critical for muscle cell survival. Muscle cell membrane damage allows leakage of intracellular ingredients (proteins, glycogen, carbonic anhydrase, CK, aldolase, lactate dehydrogenase and electrolytes) to extracellular fluid and thence the bloodstream. On the other hand, membrane damage permits the uncontrolled flow of calcium into the cytoplasm [126, 127].

Proteins

Myoglobin (Mb) is the fundamental muscle cell protein and is composed of globin (a polypeptide chain of 153 amino acids) and of one molecule of haem. The Mb molecular weight is 18,800 daltons, one-fourth of haemoglobin [1, 9, 128] and is present in both heart and in the skeletal muscles. The Mb concentration in these cells depends on the work performed by the tissue. For example, in people living at high altitude the concentration of Mb in the cells is increased. Also, in marine mammals Mb concentration is approximately 10 times higher than that of terrestrial mammals, giving them the ability to dive to great sea depths.

Mb is responsible for temporary oxygen storage [129] and correlates with cytochrome C oxidase expression, as well as capillary density [130, 131].

When muscle anoxia is present, Mb decreases the demand for glycolytic processes by releasing its oxygen content and allowing a continuance of much more efficient oxidative breakdown of lactate, pyruvate and similar metabolites. Plasma Mb concentration is around 0.003 mg/dl. However, Mb may escape from damaged skeletal cells and bind to haptoglobin. Damage of more than 100 g of skeletal muscle leads to haptoglobin binding capacity saturation [129, 132–134] and circulating Mb becomes "free" to be filtered by the kidneys, where it acts directly on the nephrons, causing distal renal tubular necrosis. The half-life of Mb is

Table I. Causes and relative prevalence of non-traumatic, non-drug-induced rhabdomyolysis [11–125]

Cause	Prevalence
Genetic disorders:	
Glycogen storage disease (per live births)	
GSD-V McArdle disease	1/100,000
GDD-VII Tarui disease	< 1/1,000,000
GSD-IX	1/100,000
GSD-X	1/20,000–40,000
GSD-XII	1/20,000–43,000
Other:	
CTPII	1–9/100,000
Malignant hyperthermia	1/5,000–50,000
Mitochondrial myopathies:	
MELAS syndrome	1-–9/1,000,000
MERRF syndrome	0.9/100,000
KISS syndrome	Unclear; low
CPEO	1/30,000
NARF	1/36,000–40,000
Muscular dystrophies:	
DMD Duchenne	1/3,500 males
BMD Becker	1/18,000–31,000 males
Acquired diseases:	
Hypo/hyperthyroidism	4–5%
Hypo/hyperparathyroidism	25–66/100,000
Diabetes mellitus	8.6%
Adrenal insufficiency	4.4–6/1,000,000
Infection	Up to 15% in sepsis
Muscle ischaemia	29.9/100,000
Agitation	8–15% in myoclonus

Genovefa Kolovou, Philip Cokkinos, Helen Bilianou, Vana Kolovou, Niki Katsiki, Sophie Mavrogeni

2–3 h. Following muscle injury, Mb serum concentration increases within 1–3 h, peaks within 8–12 h, and then returns to normal concentration within 24 h [128]. Additionally, in RM increased levels of heavy-chain myosin fragments are observed and other proteases such as lactate dehydrogenase, aspartate aminotransferase (AST) and decreased levels of albumin (see below). In patients with RM, Mb concentration is not a diagnostic or prognostic criterion [134].

Free oxygen radicals

The increase in concentration of intracellular ionized calcium which occurs in RM may activate various vasoactive molecules and proteases, leading to the production of reactive oxygen species (ROS) [134]. The injured muscle cell is attacked by activated neutrophils, which increase the damage by releasing proteases and free radicals [135], resulting in an inflammatory, self-sustaining myolytic reaction rather than pure necrosis. These processes take place only after blood flow into the damaged tissue is restored.

Glycogen

The main muscle carbohydrate is glycogen. During RM blood glycogen levels may be raised and glycosuria may be present [136].

Carbonic anhydrase III

Carbonic anhydrase III (CA III) is a metalloenzyme found mainly in skeletal muscle, liver and adipose tissue. Its physiological role is to catalyze carbon dioxide and water to form bicarbonate and protons. CA III is considered as a biomarker of muscle ischaemia/necrosis [137, 138]. Lippi et al. [139] observed increased CA III levels in healthy men who performed 21-km runs. Of note, the MB myocardial isoenzyme of creatine phosphokinase (CK-MB, see below) is also higher as compared to pre-run levels.

CK

CK is an enzyme present in all types of muscle and its increased concentration in plasma is a marker of RM: after muscle damage, CK is released into the circulation [93, 140]. The main function of CK is to catalyse the transportation of one phosphate group from creatinine to adenosine diphosphate (ADP), resulting in ATP [128, 141]. There are 3 CK isoenzymes: muscle-type (CK-MM), brain-type (CK-BB) and CK-MB. After muscle injury CK is elevated within the first 12 h, peaks within the first 3 days, and returns to baseline levels 3–5 days later [128, 141]. The increase of CK-MM concentration in some cases can reach even 100,000 IU/ml or more [128, 141]. Plasma CK elevation lasts longer than the Mb elevation (Mb is rapidly metabolized by the liver; see above) [128, 141]. Therefore, tests evaluating Mb concentration in plasma or urine are not very helpful.

Calcium

Ionized calcium can be found in both extracellular and intracellular compartments of the human body. Its concentration in the extracellular space is significantly higher compared with the intracellular space (~10,000 times higher). Major factors causing the shifting of ionized calcium from the extracellular to the intracellular space are either energy depletion in the muscle cell or rupture of the membrane's continuity (ionized calcium influx from the extracellular space into the cell due to its chemical gradient) [127, 142, 143]. The increased intracellular concentration of ionized calcium leads to overwork and overuse of the cell's energy. These two provoke increased sarcoplasmic influx of ionized sodium, chloride and water retention. The above result in cellular swelling and eventual destruction [144]. Ionized calcium further penetrates into the cell in exchange for ionized sodium to protect the increased intracellular sodium concentration [145]. Moreover, once muscle cells are injured, two major processes take place: 1) ATP leaks from cells causing ATPase pump dysfunction and further increase in ionized sodium, which activates the $2Na^+/Ca^{2+}$ exchanger to correct ionic abnormalities [123, 128] and 2) the mitochondria release stored ionized calcium into the cytoplasm as a rescue measure [146]. All the above cause persistent contraction, ATP depletion, exhaustion and eventually cellular death.

Potassium

Muscle cells contain a significant amount of potassium and when disruption of the cell's membrane occurs its escape into the circulation results in hyperkalaemia: potassium levels higher than 8.5 mEq/l can cause cardiac arrhythmias (e.g. ventricular fibrillation) and sudden death] [91, 123, 128].

Compartment syndrome

On top of all the processes described above, the compartment syndrome may develop. As was already mentioned, failure of the transmembrane pump systems leads to muscle cell swelling. Then, intracompartmental pressure rises and may provoke additional damage and necrosis which due to anatomical particularities (non-communicating, closed systems) may require a fasciotomy [147–149].

Clinical and biochemical effects of rhabdomyolysis

As was already mentioned, RM is a severe and potentially life-threatening condition. There are various clinical and biochemical consequences of RM induced by muscle cell damage, such as the following: 1) fluid overload in the affected limb(s), reaching even 10 l/limb. This results in severe hypovolaemia and hypernatraemia, which may lead to hypovolaemic shock and/or acute renal failure [150]; 2) hyperalbuminaemia caused by hypovolaemia (later changes to hypoalbuminaemia due to inflammation, malnutrition, fluid overload); 3) acidosis provoked by lactic acid escape from the cells [151] which worsens hyperkalaemia and allows intratubular precipitation of Mb and uric acid; 4) severe hypocalcaemia due to release from the storage site and hyperphosphataemia, which may lead to cardiac arrhythmias, muscular contractions or seizures [152]; 5) release of nucleosides into the bloodstream (metabolized in the liver to purines, i.e. xanthine, hypoxanthine, and uric acid, which further stimulates tubular obstruction); 6) release of proteases into the bloodstream may cause hepatic dysfunction in 25% of patients with RM [153]; 7) acute kidney injury (AKI, see below); and 8) disseminated intravascular coagulation as a result of the activation of the coagulation cascade by components released from damaged muscles, which may be responsible for haemorrhagic complications.

RM-induced AKI

The pathophysiology of RM-induced AKI is believed to be caused mainly by 3 mechanisms: renal vasoconstriction, intratubular cast formation, and Mb toxicity [154, 155].

Reduced renal blood flow causes renal vasoconstriction and secondary activation of the renin–angiotensin–aldosterone system. Also, the decrease in renal blood flow promotes cast formation. On the other hand, Mb and its breakdown compounds such as iron exert direct a cytotoxic effect on the nephron [142]. Additionally, iron in the Mb oxidizes lipid membrane components and causes lipid peroxidation, called redox cycling [142]. The presence of metabolic acidosis promotes cast formation, tubular obstruction and pronounced Mb nephrotoxicity [156].

Rhabdomyolysis management

Management of RM is presently based on observations from retrospective studies, case reports, and case series which describe various RM treatments, particularly for AKI complications. The most significant intervention in RM, which may save the life of the patient, is to preserve diuresis by considerable hydration, use of mannitol, urine alkalization and forced diuresis [86, 157]. Immediate fluid resuscitation to restore and preserve renal perfusion and increase urine flow rate [132] is critical. Potassium or lactate-containing solutions should be avoided because of the risk of RM-associated hyperkalaemia and lactic acidosis [133]. Urine alkalinisation with sodium bicarbonate (not needed in patients with good urinary response) is helpful for decreasing cast formation, diminishing the nephrotoxic effects of Mb, inhibiting lipid peroxidation, and decreasing the risk of hyperkalaemia [133, 146, 158]. Hyperkalaemia treatment should be initiated with IV insulin, glucose and calcium. In some cases, dialysis may be an option. Hypercalcaemia responds to saline diuresis and IV furosemide [133, 146]. In cases with RM-induced hyperphosphataemia greater than 7 mg/dl oral phosphate binders may be administered. Hypophosphataemia, which may occur late in RM, requires treatment only when the serum level is below 1 mg/dl [150]. Dialysis should be considered as a lifesaving procedure for patients with severely elevated serum potassium, persistent acidosis, or oliguric AKI with fluid overload [158]. For the better management of renal replacement therapy in RM-induced AKI see Guidelines of Kidney Disease Improving Global Outcomes (KDIGO Clinical Practice Guideline for Acute Kidney Injury. [http://www.kidney-international.org).

Conclusions

Rhabdomyolysis is a severe and potentially life-threatening condition, fortunately presenting infrequently. Early identification is key to timely treatment. Recognizing underlying abnormalities, particularly genetic disorders, is a diagnostic challenge. Familiarity with RM pathophysiology leads to its better management, particularly for renal replacement interventions in RM-induced AKI.

Conflict of interest

The authors declare no conflict of interest.

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