Review article

The syndrome of rhabdomyolysis: Pathophysiology and diagnosis

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Abstract

Rhabdomyolysis is defined as a pathological condition of skeletal muscle cell damage leading to the release of toxic intracellular material into the blood circulation. Its major causes include trauma, ischemia, drugs, toxins, metabolic disorders, and infections. The pathophysiological hallmark of the syndrome is an increase in intracellular free ionized calcium due to either cellular energy depletion, or direct plasma membrane rupture. The increased intracellular calcium activates several proteases, intensifies skeletal muscle cell contractility, induces mitochondrial dysfunction, and increases the production of reactive oxygen species, ultimately resulting in skeletal muscle cell death. Clinically, the syndrome presents with severe muscular pain, weakness and myoglobinuria. Increased myoglobin and creatine phosphokinase as a consequence of muscular cell death are the major laboratory findings, which, in combination with the clinical presentation, lead the clinician to the final diagnosis of the syndrome.
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Keywords: Rhabdomyolysis; Calcium; Energy depletion; Cell death; Diagnosis

Contents

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1. Introduction

Rhabdomyolysis is a pathological syndrome caused by skeletal muscle cell damage which affects the integrity of the cellular membrane and leads to the release of toxic intracellular constituents into the blood circulation. Its main causes include trauma, ischemia, drugs, toxins, metabolic disorders, and infections [1–7]. The clinical presentation of rhabdomyolysis varies from an asymptomatic increase in creatine phosphokinase (CPK) to severe acute renal failure and hypovolemic shock [8–12]. Typically, rhabdomyolysis presents with muscular pain, weakness, and reddish-brown discoloration of urine.

Rhabdomyolysis has been known since ancient times. In the Old Testament, a plague that affected the Israelites after consumption of quails during their exodus from Egypt (Book of Numbers, 11:31–35) is reported [13]. In more recent years, the first report of rhabdomyolysis caused by compression (crush syndrome) was during the earthquake in Sicily in 1908 [5]. Similar reports exist in the German literature during the First World War [5]. The first systematic recording of the syndrome was done by the British investigators Bywaters and Beall, who followed the clinical course of four victims of the bombing of London during the Battle of England in 1940 and realized that these individuals developed acute renal failure [14]. The investigators attributed the acute renal failure to rhabdomyolysis due to compression, without discovering, however, the cause of their observation. A few decades later, it was found that the renal damage had been caused by the nephrotoxic effect of myoglobin, which is released from muscle cells during rhabdomyolysis. The non-traumatic causes of rhabdomyolysis were identified only in the 1970s [5].

In this review, the molecular and cellular mechanisms involved in the pathophysiology of the syndrome of rhabdomyolysis are summarized. The clinical manifestations and the major laboratory findings of the syndrome are also presented.

2. Etiology of rhabdomyolysis

2.1. Homeostasis of intracellular calcium

The concentration of free ionized calcium in the extracellular space $[Ca^{2+}]c$ is 10,000 times higher than that in the intracellular space [15]. Because of this chemical gradient, even minimal changes in the permeability of the cellular membrane for Ca^{2+} are capable of inducing significant changes in its intracellular concentration with unfavorable consequences for the functional integrity of the cell [16]. Therefore, the cell has to maintain the homeostasis of intracellular calcium with great precision. For this purpose, it is equipped with a group of special regulatory proteins that are divided into: (a) non-membrane proteins, which are soluble in the cytoplasm, and (b) transmembrane proteins, which constitute the main regulators of calcium concentration [15,16].

The transmembrane proteins consist of a series of carrier proteins that are located either at the plasma membrane of the muscle cell (sarcolemma) or at the membranes of intracellular organelles, notably the sarcoplasmic reticulum and mitochondria [17]. The plasma membrane carrier proteins include the Ca^{2+} channels, the $2Na^+/Ca^{2+}$ exchanger, and Ca^{2+} ATPase pump [2]. Ca^{2+} channels and the $2Na^+/Ca^{2+}$ exchanger facilitate the energy-consuming entrance of Ca^{2+} into the cytoplasm, whereas the Ca^{2+} ATPase pump
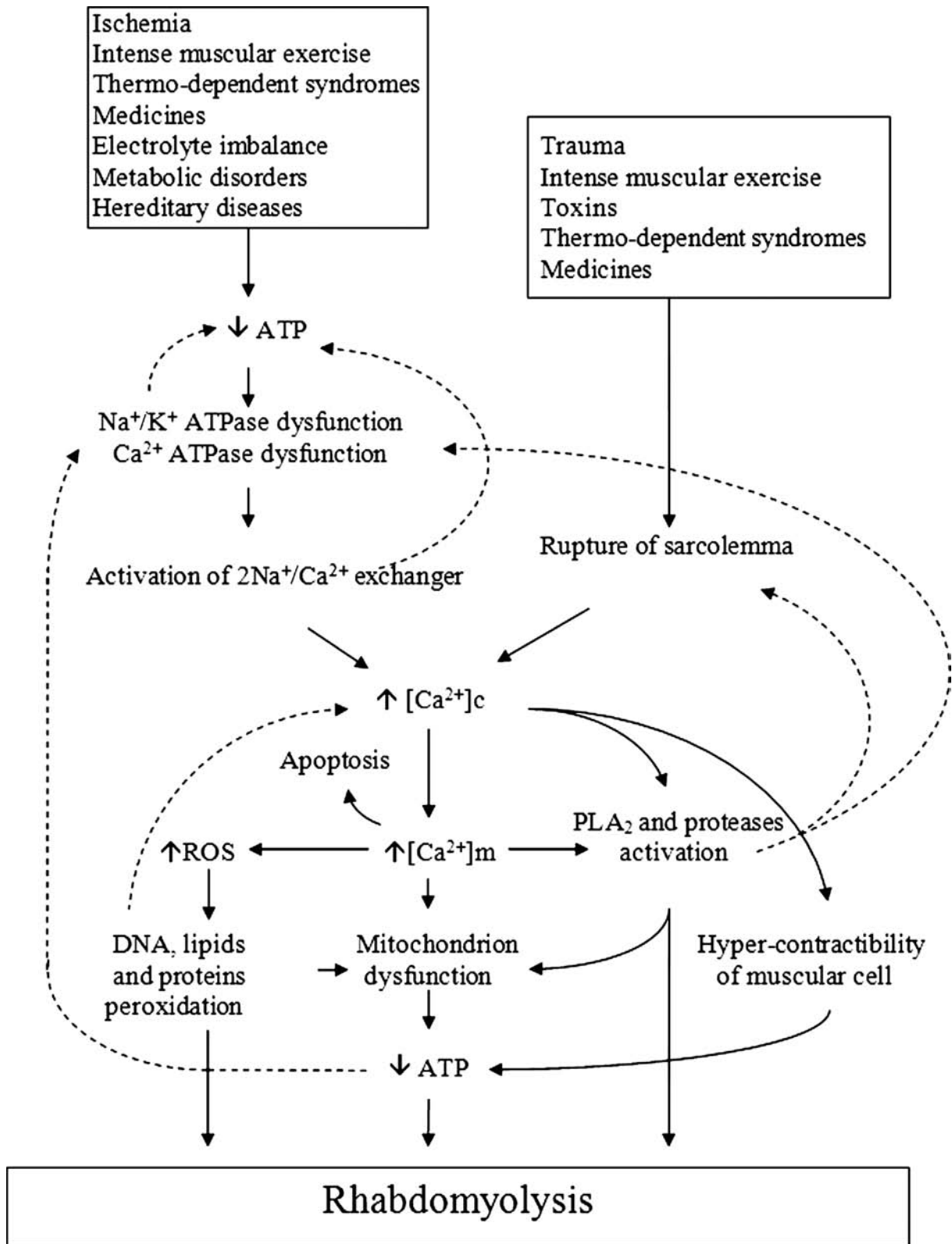
Fig. 1. Pathophysiological mechanisms involved in the syndrome of rhabdomyolysis. The decreased production of ATP and rupture of sarcolemma increase free ionized cytoplasmic and mitochondrial calcium. The increased calcium initiates a complex network of downstream intracellular cascades leading to rhabdomyolysis and, consequently, the release of toxic intracellular substances into the extracellular fluid. $[Ca^{2+}]c$: cytoplasmic Ca^{2+}, $[Ca^{2+}]m$: mitochondrial Ca^{2+}, ROS: reactive oxygen species, PLA_2: phospholipase A_2,- - -: feedback.

Table 1
Causes of rhabdomyolysis

Hereditary	Deficiency of glycolysis or glycogenolytic enzymes (e.g. McArdle's disease)
	Abnormal metabolism of lipids
	Other genetic malfunctions (e.g., idiopathic rhabdomyolysis, malignant hyperthermia, neuroleptic malignant syndrome)
Acquired	
Traumatic	
Intense muscular exercise	Marathon, intense military training, myoclonus, status epilepticus, status asthmaticus, tetanus, acute dystonia
Direct muscular damage	Crush syndrome, accidents (traffic, occupational), natural disasters (earthquakes), burns, frostbite, electric shock
Non-traumatic	
Ischemic	Compression, thrombosis, obstruction of blood flow (arterial embolism, sickle cell crisis, etc.)
Drugs	Alcohol, statins, fibrates, heroin, cocaine, methadone, amphetamines, benzodiazepines, barbiturates, antidepressants, antipsychotics, antihistaminics, amphotericin B, paracetamol, diuretics, corticosteroids, azathioprine, salicylates, theophylline, vasopressin, phenytoin, quinidine
Toxins	Snake poison, bee/wasp sting, spider bite, Haff disease (i.e., sudden rhabdomyolysis 24 h after the consumption of fish), consumption of quails
Thermo-dependent syndromes	Toxic shock syndrome, heat shock
Metabolic diseases	Diabetic acidosis, diabetic hyperosmolar nonketotic coma, hypothyroidism
Electrolyte disorders	Hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypernatremia
Inflammatory myopathies	Polymyositis, dermatomyositis
Infections	Bacteria (*E. coli*, *Shigella*, *Salmonella*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, β-hemolytic streptococcus A, *Clostridium*, etc.)
	Viruses (Influenza A and B, CMV, HSV, EBV, HIV, Coxsackie, etc.)
Other causes	Anticholinergic syndrome, cessation of L-dopa intake

facilitates the energy-consuming transportation of Ca^{2+} to the extracellular space [15]. In the sarcoplasmic reticulum, the Ca^{2+} ATPase pump is responsible for the entrance of Ca^{2+}, while Ca^{2+} release to the cytoplasm is achieved with a complex transmembrane transport mechanism [18]. The Ca^{2+} is brought into the mitochondria with the Ca^{2+} uniporter, and the release of Ca^{2+} into the cytoplasm is primarily accomplished by the $2Na^+/Ca^{2+}$ exchanger [16].

2.2. Mechanisms of intracellular calcium increase

The major causes of increased intracellular calcium are multiple and often interrelated. However, they share a common pathogenetic basis that involves either the energy depletion in the muscle cell or the plasma membrane (sarcolemma) rupture (Fig. 1).

2.2.1. Reduction in energy production
The reduction in energy production is mirrored in a decrease in adenosine triphosphate (ATP) and causes dysfunction of the energy-dependent ion pumps, such as Na^+/K^+ ATPase and Ca^{2+} ATPase in the sarcolemma, as well as in other intracellular membranes [17,19]. Na^+/K^+ ATPase pump dysfunction results, in turn, in an increase in intracellular Na^+ concentration [19,20]. Following intracellular Na^+ increase, the cell increases the activity of the $2Na^+/Ca^{2+}$ exchanger, which removes the excess intracellular Na^+ from the cytoplasm by exchanging it with Ca^{2+}, ultimately increasing the cytoplasmic calcium [1,20]. As the $2Na^+/Ca^{2+}$ exchanger requires energy in order to function properly, the energy deficit of the cell is accentuated [1,5]. In this setting, the Ca^{2+} ATPase, which under normal circumstances releases any surplus of intracellular Ca^{2+} into the extracellular space, becomes dysfunctional, further increasing the $[Ca^{2+}]c$ [3].

The sarcoplasmic reticulum and the mitochondria constitute the most important intracellular depots of free ionized calcium. Their main role is to store the excess cytoplasmic calcium so that its concentration in the cytoplasm is maintained at low levels with respect to its concentration in the extracellular space [16]. As mentioned, these organelles are equipped with special transmembrane calcium transport mechanisms (Ca^{2+} ATPase and Ca^{2+} uniporter, respectively) that hydrolyze ATP for proper functioning [18,21,22]. The decreased energy production that occurs in rhabdomyolysis impedes their functioning, thereby sustaining $[Ca^{2+}]c$ in high levels [3,23].

2.2.2. Rupture of plasma membrane
Several factors directly affect the membrane of the muscle cell and cause interruption of its continuity, resulting in a massive influx of extracellular calcium into the cytoplasm driven by its chemical gradient [24]. In addition, the progressive damage of the sarcoplasmic reticulum and mitochondria during cellular death promotes the release of stored calcium ions into the cytoplasm [3,25,26]. The reduced release of Ca^{2+} into the extracellular fluid, in combination with their inadequate intracellular storage and increased entry into the cytoplasm, leads to the overloading of the muscle cell with Ca^{2+}. Once $[Ca^{2+}]c$ exceeds a certain critical limit, the cascade of cellular death is activated [22,27,28].

2.3. Causes of rhabdomyolysis

As shown in Table 1, the causes of rhabdomyolysis can be classified as hereditary and acquired ones. The hereditary diseases mainly involve a lack or insufficiency of various enzymes that directly or indirectly participate in the catabolism of various energy macromolecules (e.g., carbohydrates, lipids) [2]. The most frequent hereditary disease

related to rhabdomyolysis is McArdle's disease, in which the muscle phosphorylase, an enzyme essential for glycogenolysis, is underproduced [29,30].

The acquired causes are further classified as traumatic or non-traumatic [5]. The traumatic ones (e.g., crush syndrome, accidents, natural disasters, intense muscular exercise) result in direct muscle injury and rupture of the sarcolemma and, because of the transmembrane chemical gradient, massive entry of ionized calcium into the cytoplasm. In addition, during exhausting physical exercise, beside mechanical muscle injury, overproduction of heat also occurs, leading to heat injury, which disturbs the energy production by the intracellular enzymatic systems (Fig. 1).

The non-traumatic causes are the most frequent causes of rhabdomyolysis during peacetime. Alcohol abuse, various drugs (e.g., hypolipidemic agents, amphetamines, antipsychotics, diuretics), seizures, and coma are considered to be the leading ones [9,12,24,31–33]. Rhabdomyolysis of ischemic origin is caused by a decreased oxygen supply to the cells, which is essential for the production of energy [1]. Metabolic and electrolytic disorders lead to a deficiency of mitochondrial enzymatic systems that are responsible for the oxidative phosphorylation and production of ATP, whereas in infections and inflammatory myopathies the released toxins stimulate the production of cytokines (e.g., TNF-a, IL-1) that directly affect and disrupt the cellular membrane [34,35]. With regard to drugs and thermic syndromes, they can either impede the production of energy or cause lysis of the plasma membrane [36–39] (Fig. 1).

3. Pathophysiological mechanisms of rhabdomyolysis

Despite the fact that the causes of rhabdomyolysis are numerous, the final pathogenetic pathway is common, characterized by an increase in free ionized calcium in the cytoplasm [1]. The increased $[Ca^{2+}]c$ initiates a chain of downstream reactions that eventually lead to the destruction of the muscle cell (Fig. 1).

3.1. Activation of phospholipase A_2

Increased $[Ca^{2+}]c$ activates phospholipase A_2 (PLA2) and various neutral proteases (e.g., calpain) [20,40–43] that degrade the cellular phospholipid membranes (e.g., plasma membrane, mitochondrial membrane) and various intracellular organelles [44,45]. Following the enzymatic dissolution of membrane phospholipids, lysophosphatides and free fatty acids are produced that either cause direct toxic damage to the sarcolemma and other intracellular membranes or affect the function of cell membrane carrier proteins, leading to the entry of Ca^{2+} into the cytoplasm [3,23].

3.2. Persistent contractility of the muscular cell

Increased $[Ca^{2+}]c$ maintains the muscle cell in a condition of continuous contraction, resulting in severe ATP depletion and progressive exhaustion of the cellular energy reserves [1,5,17,46].

3.3. Increase in mitochondrial calcium — mitochondrial dysfunction

The abrupt increase in $[Ca^{2+}]c$ contributes to an increase in mitochondrial calcium $[Ca^{2+}]m$ because of its chemical gradient between the cytoplasm and mitochondrion [16,22,47]. As mentioned the mitochondrion acts as a "safety reservoir" that succeeds in storing large quantities of Ca^{2+} when their concentration in the cytoplasm is excessively
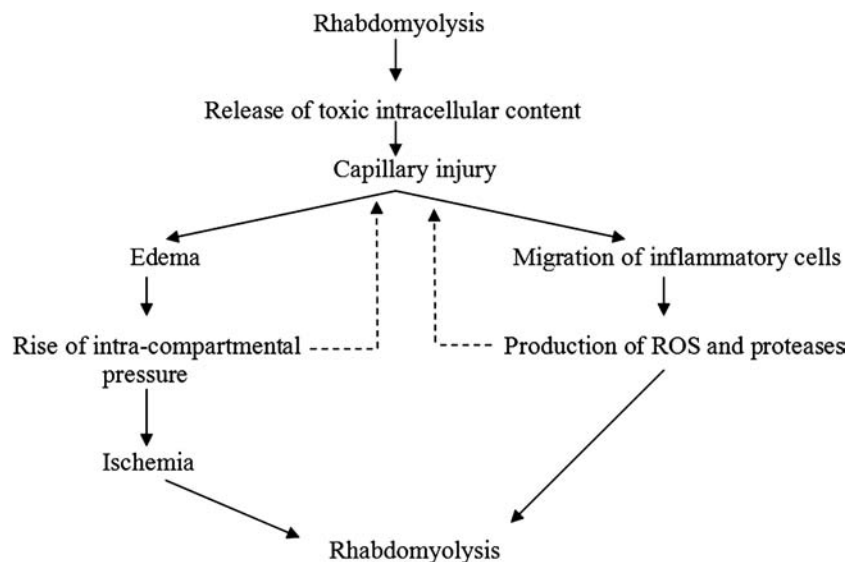

Fig. 2. The release of toxic intracellular substances into the extracellular space damages the regional capillary circulation, resulting in local edema and migration of circulating leukocytes to the lesion area. Edema increases the intra-compartmental pressure and the leukocytes produce reactive oxygen species (ROS), ultimately accentuating the inflammatory and necrotic process.

increased [2,22]. In this way, the cell saves precious time in order to confront the actual cause of $[Ca^{2+}]c$ increase. If this cause persists for a long time, the overloading of the mitochondrion with Ca^{2+} adversely affects its structural and functional integrity (dysfunction of oxidative phosphorylation), eventually impairing the production of ATP [16]. Such a reduction in ATP worsens the dysfunction of the Ca^{2+} carrier proteins in the sarcolemma and intracellular organelles, thereby initiating a self-perpetuating, vicious circle [2].

3.4. Free radical production-oxidative stress

Increased mitochondrial calcium $[Ca^{2+}]m$ leads to increased production of reactive oxygen species (ROS, e.g. O_2, $OH\cdot$, H_2O_2) [47]. Physiologically, during the electron transfer in the respiratory chain in the mitochondria, roughly 2% of the reduced oxygen is transformed to peroxide anion (O_2^-) and other ROS [48]. ROS constitute a broad group of chemical substances that include free oxygen radicals (e.g. O_2^-, $OH\cdot$) and certain substances (e.g. H_2O_2, NO) which, even though they are not free oxygen radicals, are powerful oxidant factors and can potentially cause the production of free oxygen radicals [43,49]. The free radicals carry in their exterior orbit one or more unpaired electrons, which makes them very reactive chemical substances as they have a strong tendency to pair off their unpaired electron, causing oxidation [49–52].

The human organism possesses an abundance of endogenous antioxidant (reductive) systems, such as the superoxide radical dismoutase, catalase, and glutathione [49,52,53]. When the antioxidant capacity of endogenous systems is reduced, the cell is bombarded with ROS and a condition called oxidative stress develops [54].

ROS oxidate the various biomolecules of the cell, such as proteins, lipids, and nucleic acids, leading to structural and functional impairment of the cells [55–57]. Given that proteins and lipids are basic structural components of biological membranes and intracellular organelles, their destruction influences the integrity of the sarcolemma and intracellular membranes, as well as the functioning of various intracellular organelles, such as mitochondria and sarcoplasmic reticulum [25,52]. Ultimately, cytoplasmic calcium increases [47,58].

Moreover, ROS induce mutations in both nuclear and mitochondrial DNA [52,59,60]. The modification of nuclear
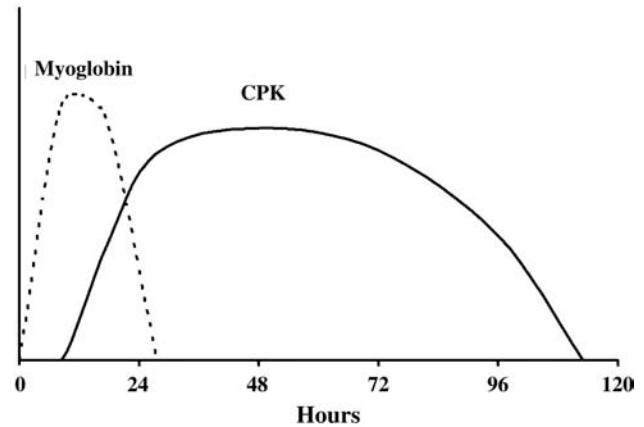

Fig. 3. Variations of myoglobin and creatine phosphokinase (CPK) during the course of rhabdomyolysis. Myoglobin is the first enzyme that increases, but, due to its rapid clearance from the plasma, it returns to normal levels within the first 24 h after the onset of symptoms. CPK increases a few hours later than myoglobin, reaches its peak value within the first 24 h, and remains at these levels for 3 days. Even though the detection of myoglobin in the serum is considered pathognomonic for the syndrome of rhabdomyolysis, CPK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscular injury due to its delayed clearance from the plasma.

DNA leads to functional disorganization of the muscle cell, whereas mutations of mitochondrial DNA, which contains the coding sequences for the respiratory chain proteins, leads to structural and functional degeneration of the electron transport system, ultimately resulting in reduced ATP production [24].

3.5. Apoptosis

Also increased mitochondrial calcium $[Ca^{2+}]m$ upregulates the expression of pro-apoptotic factors (e.g., cytochrome *c*, AIF), thereby triggering apoptotic cell death [22,24,28,61,62].

3.6. Cell death

The result of the abovementioned complex and self-reinforcing reactions is the lysis of muscle cells and the release of their toxic content into the extracellular space (Fig. 2). The concentration of toxic substances in the microenvironment of the muscle cell causes damage to the adjacent capillaries, inducing local edema, increase in intracompartmental pressure and, eventually, regional ischemia [3,10]. This ischemia further augments the energy depletion, thereby destroying more capillaries. The circulating leukocytes adhere to the destroyed capillaries, become activated, and transmigrate to the destroyed muscle cells, where they release ROS and proteolytic enzymes, ultimately aggravating cellular impairment [57,63].

Notably, in ischemic injury (e.g., crush syndrome, arterial embolism, thrombosis), the destruction of the muscle cells does not take place during ischemia, but mainly during the

Table 2
Urine findings in rhabdomyolysis

General urinalysis	
Dipstick	
Heme	Positive (usually 3+ or 4+)
pH	Acidic (usually 5–6)
Proteins	Positive
Color	Reddish-brown
Microscopic analysis	Absent or very few red blood cells
Urine radioimmunoassay	Myoglobinuria
Urine sediment	Myoglobin casts, dead epithelial cells

phase of reperfusion [23,64]. This "paradoxical" phenomenon is attributed to the fact that oxygen and neutrophils are delivered to the destroyed muscular tissue mainly during reperfusion, thereby accentuating the generation of ROS [5,49].

4. Clinical presentation

Even though the final diagnosis of rhabdomyolysis is established by laboratory findings, alertness to the syndrome is essential for prompt diagnosis. The clinical spectrum of rhabdomyolysis is rather wide. The typical triad of symptoms involves muscular pain, weakness, and reddish-brown urine [4,24,31]. In 50% of the cases, the pain is focused on the central muscle groups (thighs, shoulders). However, more than half of the patients do not report muscular symptoms. The reddish-brown color of urine is due to myoglobinuria and constitutes a powerful diagnostic element [24]. Nonetheless, it is observed in approximately half of the cases and its absence does not exclude the syndrome. Muscular stiffness and seizures have also been reported. In more severe cases of rhabdomyolysis, general symptoms, such as malaise, fever, tachycardia, nausea, and vomiting, can be observed [65].

In the clinical examination, muscles may be swollen and sensitive during palpation, while changes in the color of skin compatible with compression necrosis may occur [24,66].

5. Laboratory findings

Due to the muscle cell necrosis and dissolution, several substances are released into the plasma (e.g., myoglobin, CPK, electrolytes, protein and non-protein substances), the detection of which contributes to the early diagnosis of the syndrome.

Table 3
Biochemical findings in rhabdomyolysis (▲ Increase, ▼ Decrease)

Myoglobin	▲
CPK	▲
CPK-MM	▲
Potassium (K^+)	▲
Phosphorus (P)	▲
Calcium (Ca^{2+})	Initially ▼ Later ▲
Uric acid	▲
pH	▼
Carbonic anhydrase	▲
Myosin-heavy chains	▲
LDH, SGOT, aldolase	▲
Albumin	▼
Hematocrit	▼
Intravascular volume	▼
Anion gap	▲
Creatinine	▲
Urea/creatinine ratio	Initially ▼ Later ▲
Platelets	▼
Fibrinogen degrading products (FDP)	▲
Prothrombin time (PT)	▲

5.1. Urinalysis (Table 2)

Myoglobin is composed of globin, a polypeptide chain of 135 amino acids, and a molecule of heme. The molecule of heme contains a ring of protoporphyrin that has a divalent ferrum cation (Fe^{2+}) in the center. The molecular weight of myoglobin is approximately 18 kD, one-fourth that of hemoglobin [35]. The role of myoglobin is to transport oxygen to the mitochondria of skeletal and heart muscles in conditions of low partial pressure of oxygen [3,6].

The excretion of myoglobin mainly occurs through the renal system. Initially, it is filtered at the renal glomerulus and then resorbed by the convoluted tubules and degraded into globin and heme via proteolysis. Globin breaks down into amino acids, while heme degrades into a ring of proto-porphyrin and a divalent Fe^+ cation, which are stored in the form of ferritin so that they can be re-used by the organism. As happens with every low molecular weight protein, a small quantity of filtered myoglobin (0.01–5%) is normally excreted with urine. The normal concentration of myoglobin in the serum is below 100 μg/L and in urine below 10 μg/L [6].

During rhabdomyolysis a portion of the myoglobin from skeletal muscle cells enters the plasma (myoglobinemia) [1]. The low binding affinity of serum for myoglobin and the small molecular weight of myoglobin contribute to the increased glomerular filtering of the molecule. The higher concentration of myoglobin in the preurine increases the reabsorbing capacity of epithelial cells of the renal glo-merulus, tying to limit the excretion of myoglobin into the urine and protect the kidney from its nephrotoxic effect. When, however, the concentration of myoglobin in the preurine exceeds the reabsorbing capacity of glomerular cells, an excessive amount of myoglobulin appears in the urine (myoglobinuria). Myoglobinuria may be detected either with a urine dipstick (microscopic myoglobinuria) or macroscopically as reddish-brown urine in the case of severe rhabdomyolysis [3,24,67].

The half-life of myoglobin is particularly short (2–3 h) since its clearance from the plasma is achieved rapidly through renal excretion or catabolism to bilirubin [4,31]. In rhabdomyolysis, the level of myoglobin in the serum increases within 1–3 h, reaches its peak in 8–12 h, and then returns to normal within 24 h after the onset of the injury (Fig. 3). Thus, the detection of myoglobin in the blood or urine is pathognomonic for the diagnosis of rhabdomyolysis, provided that it is made in the initial phases of the syndrome (i.e., within the first 24 h) [12,68].

5.1.1. General urinalysis

Urine dipstick: When serum myoglobin exceeds 0.3 mg/ L, it becomes detectable with a urine dipstick, which is a particularly cheap and sensitive test [2,6]. A urine dipstick detects heme-rich molecules, known as hemoproteins. More specifically, it contains an organic peroxide and *o*-toluidine; heme acts as hyperoxidase and releases the oxygen of organic peroxide, which then oxidates *o*-toluidine into an

azure colored product, leading to a positive result. The main drawback of this technique is that it cannot distinguish whether the actual cause of a positive result is hemoglobin, myoglobin, or hemoglobin-rich red blood cells [65].

The pH of urine in rhabdomyolysis is acidic. The acidic pH of urine plays a significant role in the formation of myoglobin cylinders and crystals of uric acid, as well as in the extraction of heme from myoglobin, which is the major cause of acute renal failure [65,69].

In 45% of the cases of rhabdomyolysis, the urine dipstick can be found to be positive for the presence of protein. Proteinuria is due to the release of myoglobin and other proteins by the disrupted muscle cells.

Color of urine: Macroscopic myoglobinuria (reddish-brown urine) is observed when the concentration of plasma myoglobin exceeds 300 mg/L [4].

Microscopic examination of urine: In the microscopic examination of urine, red blood cells are relatively few (<5 per high-power field) [69]. The microscopic examination is mostly used for the exclusion of hematuria in the case of positive urine dipstick test.

### 5.1.2. Other urine examinations

Radioimmunoassay methods: The final diagnosis of myoglobinemia and myoglobinuria is established with immunologic and radioimmunologic methods, in which special antibodies against myoglobin are used [65].

Urine sediment: In the examination of urine sediment, myoglobin casts and dead epithelial cells are detected [24,69].

5.2. Biochemical findings

5.2.1. High creatinine phosphokinase

Increased levels of serum CPK constitute the diagnostic hallmark of rhabdomyolysis [31]. CPK is active in skeletal muscles and catalyzes the transportation of one phosphate group from creatinine (CP) to ADP, resulting in ATP and creatinine (C) (Table 3) [70,71].

$$CP + ADP \overset{CPK}{\rightleftarrows} C + ATP$$
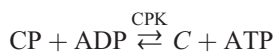
Three isoenzymes of CPK exist: (a) CPK-MM, which is mainly found in skeletal muscles, but also in smaller amounts in the myocardium; (b) CPK-MB, which is mainly found in myocardium; and (c) CPK-BB, which is mainly found in the brain and kidneys [2]. CPK-MM is most often increased in rhabdomyolysis [70]. CPK is elevated in the first 12 h after the onset of rhabdomyolysis. The peak is observed during the first 3 days, and it returns to baseline levels 3–5 days after cessation of the injury [2] (Fig. 3). Therefore, CPK, and more specifically CPK-MM isoenzyme, represent more reliable markers than myoglobin for the diagnosis and estimation of the degree of muscular damage since they remain at high levels for longer periods of time (half-life 1.5 days) than serum myoglobin [2,3,5,64].

Although it is not clear whether CPK levels can be used as a prognostic factor for the development of acute renal failure, if CPK does not exceed 5000 U/L during the first 3 days after the onset of injury, the probability of developing acute renal failure is generally considered to be low [6,7,12]. In cases where rhabdomyolysis leads to acute renal failure, CPK may exceed 15,000 U/L and, on rare occasions, 70,000 U/L; in extreme situations, it can reach even 3,000,000 U/l [69,72].

5.2.2. Hyperkalemia

Hyperkalemia constitutes the most life-threatening electrolyte imbalance. Given that 98% of potassium (K^+) is found in the intracellular space and that 60–70% of the total cellular mass of the human body consists of skeletal muscle cells, even an acute necrosis of only 100 g of muscular mass could potentially increase serum K^+ by 1 mEq/L. Moreover, hyperkalemia during rhabdomyolysis is intensified by the coexistent metabolic acidosis and renal dysfunction, which in combination with hypocalcemia, may cause fatal ventricular arrhythmias [10,35].

5.2.3. Hyperphosphatemia — early hypocalcemia–late hypercalcemia

During the disruption of muscle cells, inorganic and organic phosphoric components are dissolved and large amounts of inorganic phosphorus are released into the plasma, leading to hyperphosphatemia [35,66,73]. Hyperphosphatemia causes the deposition of calcium phosphate onto the destroyed muscle cells and other tissues [7]. Furthermore, by suspending the enzyme 1a-hydroxylase of kidneys, which is responsible for the production of the active form of vitamin D, it leads to early hypocalcemia, which is usually asymptomatic.

Upon complete cellular necrosis, the calcium initially entrapped in the cytoplasm of muscle cells is released back into the plasma. This, in combination with the secondary hyperparathyroidism that develops due to early hypocalcemia and high levels of vitamin D (produced in great quantities by the glomerular cells), leads to the manifestation of late hypercalcemia [2,74,75].

5.2.4. Hyperuricemia

Purines, which derive from muscle cell nucleic acids breakdown, are transformed into uric acid in the liver, and this uric acid may exceed 40 mg/dl [35,69]. Such magnitude of

Table 4
Differential diagnosis of myoglobulinuria, hemoglobinuria, and hematuria

	Myoglobinuria	Hemoglobinuria	Hematuria
Cause	Rhabdomyolysis	Hemolysis	
Cloudy serum	−	+	−
Urine dipstick	+	+	+
Microscopic examination for red blood cells	−	−	+
High levels of serum CPK	+	−	−

hyperuricemia is typically observed in rhabdomyolysis, while it seldom occurs in other conditions of hyperuricemia [66,67].

5.2.5. Metabolic acidosis

The release of various organic acids (e.g., lactic, uric acid) from the destroyed muscle cell leads to metabolic acidosis, further intensifying the hyperkalemia [31,35,40].

5.2.6. Increased levels of carbonic anhydrase III

Carbonic anhydrase III has a higher specificity for the diagnosis of muscular injury than serum myoglobin and CPK as it is found exclusively in the skeletal muscles [2]. However, its measurement is difficult and expensive and, thus, rarely applied in daily clinical practice [4].

5.2.7. Increased heavy-chain myosin fragment

Heavy-chain myosin fragments also constitute specific markers for the diagnosis of rhabdomyolysis [4]. Their serum levels increase within 4–7 days after the beginning of injury and remain high until the 12th day, permitting the late diagnosis of rhabdomyolysis [7]. However, this test is not widely available.

5.2.8. Increases in other enzymes

The elevation of various muscle enzymes, such as lactate dehydrogenase (LDH), aspartate aminotransferase (SGOT), and aldolase, is a quite common finding in rhabdomyolysis [2]. Even though these enzymes are usually the first laboratory finding that supports the diagnosis of rhabdomyolysis, they have very low specificity since they increase in a variety of diseases [66,67,70].

5.2.9. Hypoalbuminemia and anemia

Hypoalbuminemia is a poor prognostic sign in rhabdomyolysis because it reflects capillary damage and the release of albumin into the extravascular space [67]. Sometimes, the capillary injury can be so serious as to cause the accumulation of red blood cells in the interstitial space, resulting in an acute decrease in hematocrit and hypovolemic shock [67]. Nevertheless, in cases of an acute declination of hematocrit, the possibility of bleeding or hemolysis must first be excluded.

5.2.10. Contraction of intravascular volume

The destruction of muscle cells results in the creation of a "third space" where substantial amounts of water and Na^+ are concentrated, causing hypovolemia [35]. Hypovolemia, if not treated immediately, can lead to acute renal failure and hypovolemic shock [64].

5.2.11. Elevated anion gap

The anion gap is the difference between serum cations and anions $[Na^+-(Cl^-+HCO_3)]$ and is normally 12 ± 2 mmol/l. In rhabdomyolysis, the release of organic and phosphoric acids from the muscle cell increases the anion gap due to the overproduction of organic acids [31,69].

5.2.12. Urea/creatinine ratio

Creatinine (C) is produced in the muscle cells from phosphocreatinine (CP) by the non-enzymatic reduction of one phosphate group and one molecule of water. Then, the creatinine is released into the plasma and excreted by the kidneys. The amount of creatinine removed with the urine does not vary much from day to day for a healthy individual and, hence, represents a valuable indicator of total body muscle mass. In rhabdomyolysis, the levels of plasma creatinine increase disproportionately in relation to the increases in urea and, as a result, the urea/creatinine ratio, which is normally 10:1, decreases to 5:1 or even less [1,66,69]. At the later stages of rhabdomyolysis, the proteins released by the dead muscle cells are catabolized, thereby increasing the production of urea. In this setting, the urea/creatinine ratio returns to normal or even above normal [69].

5.2.13. Coagulation disorders

In rare cases, thrombocytopenia, increased fibrinogen degradation products (FDP), and extended prothrombin time (PT) may be observed [4,24].

6. Conclusions and diagnostic approach

Rhabdomyolysis constitutes a severe medical emergency that requires prompt diagnosis so that its life-threatening complications can be avoided. Although the etiology is multifactorial, all of the potential causes share the same pathophysiological pathway, which involves an increase in intracellular calcium. Physicians should be aware of all the pathogenetic mechanisms described above as they are strongly linked to the clinical manifestation and laboratory findings of the disease.

With regard to the diagnosis of the syndrome, the occurrence of central or diffuse myalgia and the presence of darkly colored urine or a heme-positive urine dipstick, in combination with elevated serum and urine myoglobin and increased CPK and CPK-MM, represent strong diagnostic elements [2,68]. In the absence of clinical findings, but with a positive urine dipstick test for heme, hematuria must first be excluded by urine microscopy. For the differential diagnosis between myoglobinuria and hemoglobinuria, CPK and CPK-MM must be determined because these enzymes increase exclusively in rhabdomyolysis. Another useful test for the differential diagnosis between hemoglobinuria and myoglobinuria is macroscopic serum inspection; in hemoglobinuria the serum is darkly colored but in myoglobinuria it is transparent [2] (Table 4).

7. Learning points

1. Rhabdomyolysis is a pathological condition defined as severe skeletal muscle cell damage leading to the release of toxic intracellular material into the blood circulation.
2. Its major causes include trauma, ischemia, drugs, toxins, metabolic disorders, and infections.

3. The major pathophysiological characteristic of the syndrome is an increase in intracellular free ionized calcium, due to either cellular energy depletion or direct plasma membrane rupture.
4. Clinically, the syndrome presents with severe muscle pain, decreased muscle strength, and myoglobinuria.
5. The increased myoglobin and CPK, due to muscle cell death, are the major laboratory findings, which, in combination with the clinical manifestation, lead the clinician to the final diagnosis of the syndrome.

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