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Review Article

Rhabdomyolysis and It's Imapct on Renal Failure

Jonathan S. Chávez-Iñiguez[1], Gema L. Gómez Hernández[2], Jesús Duarte Mote[3], Victor Lee-Eng Castro[3], Felipe Rodriguez García[4], and Graciela Sánchez Rojas[5]

[1]*Department of Nephrology, University of Guadalajara, Mexico*
[2]*Resident of Internal Medicine "Dr Nicolas San Juan" General Hospital, Autonomus University of the State of Mexico, Mexico*
[3]*Department of Internal Medicine, Autonomus University of the State of Mexico, Mexico*
[4]*Mexican College of Reumathology, Mexico*
[5]*Critical care Nurse, General Hospital "Dr Nicolás San Juan" of Toluca, Mexico*

***Corresponding author**
Gema L. Gómez Hernández, Resident of Internal Medicine "Dr Nicolas San Juan" General Hospital, ISEM, Autonomus University of the State of Mexico, Mexico, Email: gemalizeth17072@gmail.com

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Abstract

The term rhabdomyolysis refers to the destruction of striated muscle; which causes the release of intracellular con-tent as myoglobin, electrolytes, creatine kinase (CPK), lactate dehydrogenase, alanine aminotransferase and aspar-tate aminotransferase into the bloodstream and extracellular fluid. When excessive amounts of myoglobin are re-leased, myoglobin seeps into the glomeruli and reaches the tubules, where it can cause obstruction and kidney failu-re besides direct injury due to direct toxicity. The clinical spectrum of the disease varies from an asymptomatic dis-ease to life-threatening conditions. The causes of rhabdomyolysis are usually easy to identify; however, on some occasions the etiology is evasive. The principal cause of rhabdomyolysis is the direct muscle injury. The base of treatment is aggressive hydration with crystalloids solutions. The use of diuretics and bicarbonate are controversial topics. In this article is reviewed the metabolic effects of rhabdomyolysis and therapeutic options.

INTRODUCTION

The term rhabdomyolysis (RBD), refers to the destruction of striated muscle; which causes the release of intracellular content as myoglobin, electrolytes, creatine kinase (CPK), lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase into the bloodstream and extracellular fluid [1].

When excessive amounts of myoglobin are released, myoglobin seeps into the glomeruli and reaches the tubules, where it can cause obstruction and acute kidney injury (AKI). The clinical spectrum of the disease varies from an asymptomatic disease to life-threatening conditions associated with extreme CPK elevation, electrolyte disturbance, acute renal failure and disseminated intravascular coagulation [1].

The causes of RBD are usually easy to identify; however, on some occasions the etiology is evasive. The principal cause of RBD is the direct muscle injury, for example crush syndrome and prolong immobilization. However, there are another important triggers of muscle injury, as drugs, hereditary syndromes, malignant hyperthermia, neuroleptic malignant syndrome, ketoacidosis diabetic, bacterial and viral infections [2,3].

In the study of Michael Ward in 1988, he included 157 patients with the diagnosis of RBD, 16.5% of them developed AKI. The variables statistically relevant in AKI group were: age and dehydration. Elterman et al., made a retrospective study. They include 318 patients, 79 (24.8%) developed RBD and 56 patients (17.6%) developed AKI stage 1, 0.9% stage 2 and 2.2% stage 3. Besides, they found a weak but statistically significant correlation between peak of CK and real failure [4].

The presence of acute renal failure that warrants replacement therapy ranges from 4% to 33% of cases and mortality ranges from 3% to 50% [5].

The mechanisms studied for the development of AKI during rhabdomyolysis are renal vasoconstriction, (hypovolemia), the formation of intraluminal cylinders due to aciduria and the direct cytotoxicity induced by myoglobin [1,5,6].

The key points, is to provide a review of the literature about rhabdomyolysis and its interaction with renal function, the physiopathological mechanisms responsible, the acute kidney injury secondary to this process and the management that this serious complication entails.

HISTORICAL BACKGROUND

The first known description of rhabdomyolysis is found in the biblical text of the Exodus. The characteristics described are very suggestive of muscle injury secondary to intoxication [3,7].

The first medical description of the syndrome was in Germany in 1908 [3]. The relation between renal injury and rhabdomyolysis was described during the second world war with the presence of renal injury associated with extensive muscular injuries after the bombing of London, where victims of crushing developed acute renal failure [8-12].

Autopsy studies revealed the presence of pigmentary cylinders in the renal tubules; however, by then a relationship between muscle damage and renal failure could not be established. The first description of renal failure and rhabdomyolysis was made during the second world war in London, by Bywaters et al., They describe in a microscopical examination that the main damage was found in tubules and the loops on Henle [10-14].

EPIDEMIOLOGY OF AKI IN RBD

Acute renal injury (AKI), is the most common complication associated with myoglobinuria due to traumatic and non-traumatic rhabdomyolysis [15,16]. AKI due to rhabdomyolysis occurs in 13 to 50% of all cases [17].

According to the literature, the incidence of AKI in patients with rhabdomyolysis varies from 7-25%. Epidemiological studies in intensive care units place mortality between 7-80%, increasing when there is multi-organic failure [3,18].

ETIOLOGY OF RBD

There are multiple potential causes of rhabdomyolysis and they can be divided in different groups according to its mechanism of injury [19]. In table 1 we exposed the most common mechanisms. Traumatic or muscle compression, non traumatic exertional and non traumatic nonexertional causes. Most of the times the specific cause is evident from clinic history or from circumstances preceding the disorder. However, there are situations in which the precipitant may not be as evident but it can be identified by clinic history and laboratory exams [20,21].

TRAUMA OR MUSCLE COMPRESSION

In the study of Melli et al., where evaluated 475 inpatients at Jonhs Hopkins Hospital. They found that 8.8% of all causes were due to trauma being the fourth most frequent etiology [22].

Traumatic causes result in a direct muscle injury and rupture of sarcolemma and due to transmembrane chemical gradient, massive entry of ionized calcium in to the cytoplasm. Furthermore in excessive exercise exists overproduction of heat, leading to energy production alterations. Some examples are described in table 1 [20].

NO TRAUMA BUT ENERGY SUPPLY INSUFFICIENT

RBD occurs when the energy supply is not sufficient to reach demands. Some examples are exposed in table 1 [23,24]. In this context potassium plays an important role in the pathogenesis. When hyperkinetic state occurs muscle increase energy demands then a release of potassium from skeletal muscle cells initiate this lead to local vasodilation, which enhances regional blood flow. On the other hand, the cellular release of potassium is impaired by potassium depletion, as consequence, there is a lesser increase in blood flow resulting in RBD by ischemia [25].

In this subgroup are included patients with metabolic myopathies, inherited disorders such as glycogenolysis, glycolysis or lipid metabolism. Metabolic causes are very rare. In the study of Melli et al., found that metabolic disorders were the 1.8% of all causes [22]. In the study of Tonin et al., evaluated cases of idiopathic myoglobinuria they made 77 biopsies and enzyme defects were found in 36 cases. Carnitine palmitoyltransferase were de most common in 47% [26].

Another causes of RBD without trauma are thermal extremes events as malignant hyperthermia and neuroleptic malignant syndrome [27]. Muscle lesion occurs due to an excessive passage of calcium to extracellular space causing sustained muscle contraction, ATP depletion and hyperkalemia. Something similar occurs in prolong immersion in cold water and hypothermia. The mechanism is severe vasoconstriction and excessive shivering with hypoxia [28].

NO TRAUMA AND NO ENERGY SUPPLY INSUFFICIENT

Drugs

Nonexertional and non traumatic RBD causes are drugs and toxins principally. The illicit drugs have been the principal cause of severe rhabdomyolysis in this group. Alcohol-induced rhabdomyolysis is the most frequent associated with short period of ingest plus prolong immobilization and coma [29].

In the study of Melli et al., the principal cause of RBD in 475 patients was illicit drugs and the second one was medical drugs [19]. It was similar in other studies for instance, Blanco et al., in 2002, studied 52 patients finding that the second cause of rhabdomyolysis was illicit drugs in 15% of cases [30]. Veenstra et al., in 1994, made 7-year-study finding that illicit drugs was the second most frequent cause of severe RBD in the 30% [31].

According to the retrospective review of Food and Drug Administration (FDA) database by Oshima, between 2004 and 2009. He analyzed 8,610 cases of drug-associated RBD. He found that the most frequent medical drug associated was HMG-

Table 1: Mechanisms of rhabdomyolysis.

MECHANISM OF DISEASE	EXAMPLES
TRAUMATIC	Crush syndrome, prolonged immobilization due to coma or conscious individuals forced to lie in one position, torture victims or abuse children, surgical procedures, acute extremity compartment syndrome, high-voltage electrical injury, extensive third-degree burns.
NON TRAUMATIC EXERTIONAL	Extreme exertion, metabolic myopathies, pathologic hyperkinetic states: seizures, delirium tremens, psychotic agitation, amphetamine overdose. Thermal extremes and dysregulation: malignant hyperthermia, neuroleptic malignant syndrome, near drowning/hypothermia.
NON TRAUMATIC NON EXERTIONAL	Drugs: alcohol, heroin, cocaine, amphetamines, methadone, opioid overdose, statins, colchicine. Toxins: snake venoms, insect venoms, mushroom poisoning. Infections: influenza A,B; coxsackievirus, Epstein-Barr, herpes simplex, parainfluenza, Mycoplasma pneumoniae, pyomyositis, Legionella, Salmonella, E. coli, Streptococcus, Clostridium species etc. Electrolyte disordes: hypokalemia, hypocalcemia, diabetic ketoacidosis or nonketotic hyperglycemia.

CoA reductase inhibitors, being simvastatin the most frequent followed by atorvastatin. It was found that the proportion of fatal outcome for HMG-CoA reductase inhibitor with or without concomitant fibric acid derivates were 5.5 (95% CI, 28.-9.3) and 9.7% (95% CI, 8.5-11), respectively. So, concomitant use of these two agents seems to be associated with lower fatal outcome.They also found that the proportion of fatal events were more frequent in patients with renal dysfunction and the high risk groups for fatal outcome were age, younger than 10 years and body weight less than 50kg [32].

In table 2 are exposed the most frequent drugs associated with rhabdomyolysis [33].

Infections

RBD has been associated with different acute infections, viral and bacterial. The most common virus include influenza A and B, coxsackievirus, Epstein-Barr, herpes simplex, parainfluenza, adenovirus, echovirus, and human immunodeficiency virus and cytomegalovirus. Bacterial infections: Legionella, Streptococcus, salmonella, E. coli, leptospirosis, Coxiella Burnetii, clostridium species, leptospirosis, mycoplasma pneumoniae [23,30,34,35].

Electrolyte disorders

Different electrolyte disorders have been associated with RBD. The principal has been hypokalemia and hypophosphatemia. In normal conditions potassium is released from muscle fibers and its rising concentration and increasing muscle blood flow. The mechanism is associated with a depletion of potassium during exercise and as a consequence diminish of blood flow and ischemia [25,36,37].

Endocrine disorders

Some endocrine disorders are related with RBD as diabetes, particularly diabetic ketoacidosis and nonketotic hyperglycemia. Thyroid diseases, such as hyper and hypothyroidism [38,39].

PHYSIOPATHOLOGY OF TISSUE DAMAGED

The muscle cells are surrounded by a cell membrane called sarcolemma. Like all cell membranes, it fulfills several functions; among them maintain the concentration gradients of several cellular components; especially of the electrolytes (sodium, potassium, calcium), to guarantee an adequate cellular functioning, through voltage dependent channels and ATP-dependent pumps. The inability of the sarcolemma to maintain the ionic gradients is the fundamental basis of RBD, this can be caused by alterations of the sea, by direct or indirect damage of the membrane.

Perfusion alterations in muscle cells

Although direct trauma cause muscle injury, damaged muscle groups can evolve to an increase in local pressure and develop a compartmentalization syndrome secondary to the development of edema, which compromises local perfusion. This is where the close monitoring of a patient takes relevance, in order to limit the presence of RBD. This also applies to surgical procedures involving ischemia. Another group of patients that include risk are those with deteriorated alertness, in which the lack of mobilization implies the possibility of ischemia. The time of ischemia is closely related to the development of muscle injury, the muscle supports ischemia up to 2 hours without problem, but when it reaches 4 hours the muscle injuries can be irreversible. By 6 hours there is already muscle necrosis and the possibility of RBD increases [10-12,40].

Exercise, cocaine use and hypothermia cause RBD due to muscle low blood flow [41].

There are several pathophysiological routes of muscle injury, but the most important one is mediated by tissue ischemia.

The factors that contribute to RBD are linked to the increase in intracellular calcium, which up regulates the expression of pro apoptotic factors (cytochrome c, Apoptotic Inductor Factor), activating programmed cell death.

The lesion of the sarcolemma allows the passage of calcium from the extracellular space to the intracellular one. The loss of intracellular sodium by alterations in the functioning of the Na-K ATPase pump decreases the intracellular sodium levels, which increases the calcium gradient, which facilitates its entry into the cell. In addition, the lack of generation of ATP causes the generation of lactate and hydrogen bonds that, by acidifying the intracellular medium, causes the ATP pump to become even more compromised. All of the above contributes to increase intracellular calcium levels.

The increase in intracellular calcium keeps the muscle cell in a condition of continuous contraction, depleting the ATP reserves and leading to the loss of energy cellular reserves [42-47].

Table 2: Frequent drugs associated with rhabdomyolysis.

MEDICAL DRUGS	EXAMPLES
ANTIHYPERLIPIDEMIC AGENTS	Simvastatin, pravastatin, atorvastatin, lovastatin, rosuvastatin, gemfibrozil, bezafibrate, clofifrate
ANTIPSYCHOTICS AND ANTIDEPRESANTS	Amitriptyline, amoxapine, doxepine, haloperidol,lithium, olanzapine, risperidone, fluoxetine
HYPNOTICS AND SEDATIVES	Diazepam, lorazepam, propofol, triazolam, barbiturates
MISCELLANEOUS	Amphotericin B, azathioprime, corticosteroids, fluorochinolones, macrolides, paracetamol, penicilamine, quinidine, succinylcholine, thiazides, trimethoprim-sulfamethoxazole, vasopressin.
ABUSE SUBSTANCES	Alcohol, Amphetamine/metamphetamine, caffeine, cocaine, heroin, ephedrine, methanol, synthetic cannabinoids, toluene.

Modified from: G. Cervellin, et al., Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management, Clin Biochem. 2017. [33].

Once calcium levels have increased inside the cell, it activates several cytoplasmic proteases, activates phospholipase A2 and several neutral proteases (calpain) that degrade the phospholipid membrane and several intracellular organelles including myofibrillar proteins [48].

Resulting in the enzymatic dissolution of the membrane and the formation of free fatty acids that cause direct toxicity and damage sarcolemma, which increases the entry of calcium into the cytoplasm. Finally, the generation of ATP deteriorates, limits the processes of mitochondrial respiration, which closes the vicious circle regarding the deficit of generation of ATP and the consequent structural damage.

In ischemic tissues exists another mechanism of injury. At the time of reperfusion, the damaged tissue releases cytokines, which will recruit activated neutrophils and will cause greater damage by direct injury and generation of free radicals. On the other hand, the conversion of hypoxanthine to xanthine by xanthine oxidase increases the levels of superoxide ions. This second route explains the generalization of the inflammatory process in patients with well localized muscle injuries with the consequent development of systemic inflammatory syndrome, mediated through multiprotein complexes called inflammasomes (mainly the NLRP3) [42].

Once the muscle is injured, intra-sarcoplasmic components, such as potassium and phosphate, are released into the extracellular space, uric acid levels increase, and metabolic acidosis occurs due to the accumulation of lactate.

In fact, hyperkalemia and hypocalcemia are the second cause of death in RBD (the first is renal failure).

The phases of muscular injury are:

1.- Sarcolemmal injury (direct or indirect)

2.- Reperfusion and activation of neutrophils (in case of ischemic injury)

3.-Production and release of free radicals

4.- Release of intracellular components.

A very important component during the physiopathology of RBD is the increase in capillary permeability in reperfused tissue. Some reports consider hypovolemia as a cause of death rather than alterations typical of rhabdomyolysis (up to 66% in some series) [21].

The release of thromboplastin increases the possibility of disseminated intravascular coagulation.

In a late phase, calcium is released from damaged tissues, causing hypercalcemia, also explained by increased levels of parathormone and the synthesis of 1-25 dihydrocolecalciferol by the renal tubules in the recovery phase [21].

Direct muscle damaged

The 10% of patients with electric shock injuries develop RBD; unlike the destructive muscular processes secondary to infectious processes, where the incidence reaches up to 31% in some series. In these cases the direct lesion to the sarcolemma is what explains the process, due to the first thermal affection and the toxic effect direct the second. Malignant hyperthermia or malignant neuroleptic syndrome cause muscle damage due to the presence of a certain degree of muscular hypoperfusion, aggravated by hydroelectrolytic alterations that occur, especially due to severe hypokalemia.The myopathies characterized by alterations in the use of glycogen, lipids, purines or with alterations in mitochondrial functioning, are likely to develop rhabdomyolysis due to problems in the generation of ATP, which affects the functioning of sarcolemma.

Many drugs have been associated with the development of RBD, among the most frequent are lipid-lowering drugs, especially statins. The reduction of the levels of coenzyme Q causes a decrease in the production of ATP, which explains the alterations in the function sarcolemma. [1,13,15]

Ethanol causes RBD by two concomitant mechanisms, one of those is hypoperfusion of muscle groups during acute intoxication secondary to the lack of mobilization, and second one, during the suppression states due to muscular hyperactivity leading to direct damage secondary to problems in calcium uptake from the sarcoplasmic reticulum secondary to inhibition of the Na-K ATP asa pumps. Cocaine in the first instance as mentioned above causes states of hypoperfusion due to vasoconstriction, but evidence of direct damage has also been observed [3].

Different electrolyte alterations can cause direct damage of the sarcolemma and cause RBD. Among them (hypocalcemia, hypophosphatemia, hyponatremia, hypernatremia). Hypokalemia is the most frequent [16].

As explained, all these causes have in common a direct damage to the membrane or indirectly due to alterations in the production of ATP [1].

MECHANISMS OF AKI INDUCED BY RHABDOMYOLYSIS

The development of renal failure during rhabdomyolysis is the most frequent complication [1]. The incidence range from 13 to approximately 50% [1,16, 22]. Several mechanism has been proposed.

Myoglobin is a 17.8 kD protein, responsible for supplying oxygen to the striated muscle, it is freely filtered by the glomeruli, when it enters the tubules it is captured by endocytosis and metabolized [1]. Myoglobin has more affinity for oxygen than hemoglobin. Its function is to bind oxygen and facilitate its delivery to the site of oxidative metabolism in the muscle cell [49]. Myoglobin appears in the urine only when the renal threshold of 0.5 - 1.5 mg/dl is exceeded and grossly visible (obscure urine) when serum myoglobin levels reach 100 mg/dl [49]. We describe the mechanisms studied for the development of AKI.

Direct cytotoxicity

Boutaoud et al., describe two hypotheses to explain the mechanism by which myoglobin can cause renal injury : The first one is about the release of free iron from the myoglobin catalyzing Fenton reactions. This hypothesis came from data showing that desferrioxamine decreased RBD induced AKI in rats [48]. Zager and Burkhat in their studies where they demonstrated that compounds the scavenged hydroxyl radical did not protect cells

from myoglobin injury [50,51]. Furthermore there are some studies confirming the role of myoglobin in renal injury but there are evidence against free iron damaged mechanism according to the study of Nath et al., where heme oxigenase prevent renal failure after induction of rhabdomyolysis in rats [52].

The second hypothesis is about myoglobin redox- cycling-induced lipid peroxidation. Myoglobin by itself can catalyze peroxidation of arachidonic acid and high levels of myoglobin have shown to produce lipid peroxidation [53]. In the study *in vitro* of Boutaud et al., they demonstrate that acetaminophen inhibits hemoprotein-induced lipid peroxidation by reducing ferry heme and decreased oxidant injury in the kidney [54].

In the study of Li et al., in Beijing, China, they used glycerol to induced RBD and AKI in rats. Microarrays were used to identify expressed proteins associated with rhabdomyolysis and AKI and compare with normal tissue. They select transthyretin (TTR) as focus and they found that over expression of TTR could improve renal cell viability and inhibit apoptosis by decreasing accumulation or reactive oxygen species [55].

Renal hypoperfusion and arterial vasoconstriction

Renal hypoperfusion is the product of two phenomena: the decrease intravenous volume secondary to fluid sequestration at the level of damaged muscle masses (and also to hypovolemia) and activation of neuroendocrine systems as renin-angiotensin system, vasopressin and the sympathetic nervous system [1,47] and the local vasoconstrictor effect of myoglobin at the time of filtering at the glomerular level (by activation of endothelin 1, platelet activating factor and tumor necrosis factor alpha). In addition, myoglobin binds to the inactivation of nitric oxide, which causes vasoconstriction and increased renal hypoperfusion [56].

Tubular obstruction

When the myoglobin is filtered by the glomerulus, the water is reabsorbed in the tubules, which generates an increase in the myoglobin concentration and its subsequent precipitation, causing the formation of cylinders and tubular obstruction. The deposit of myoglobin and the formation of the cylinders are increased in the acid medium, hence the need to alkalize the urine. Myoglobin becomes concentrated in renal tubules and it precipitates when it interacts with the Tamm-Horsfall protein. This phenomenon occurs in distal tubules [1,17]. On the other hand, the injured muscle releases adenosine, which at the liver level is transformed into uric acid, which, by increasing the amount filtered at the renal level, favors the damage also by precipitating in the tubules [5,47]. In Figure 1 we illustrate these mechanisms.

CLINICAL PRESENTATION

The clinical spectrum is very broad. The typical RBD triad involves: muscle pain, muscle weakness and reddish-brown urine.

In most patients with rhabdomyolysis with an etiology other than traumatic or ischemic, muscle pain is localized in central muscle groups (shoulders, thighs). However, most of them have no symptoms.

In the clinical examination, the muscle tissue may be swollen and sensitive to palpation, sometimes there is induration and data from the compartmental syndrome should be intentionally sought, such as the most serious complication and urgent attention. Other muscle symptoms include stiffness and cramping. General symptoms are: fever, tachycardia, nausea, vomiting and abdominal pain [21].

Laboratory findings

Urine test: In urine test the reddish-brown urine color is suggestive, however it is only present in only half of cases. (56) The urinary dipstick testing has a sensitivity of 80% for the detection of RBD [22]. Myoglobinuria can be expressed in dipstick test as positive for blood when there are no red cells in the sediment due to it is unable to distinguish between myoglobin and hemoglobin.1 It appears in the urine when the plasma concentration exceeds 1.5 mg/dL. (3) As we mention above visible changes occur once urine levels exceed 100 mg/dl. Myoglobin has a short half-life of only two or three hours and normal levels may return within six to eight hours. In RBD serum levels of myoglobin are elevated before CK elevation and it disappears while CK is still elevated thats de reason why in urine test myoglobin is negative in up to half of patients [21].

It is important to know the differential diagnosis of false positive urinary dipstick test for blood and red color. For instance: hematuria, myoglobinuria, hemoglobinuria, porphyria, bile pigments, food and drugs such as: blackberries, beets, rifampin, doxorubicin, ibuprofen, deferoxamine, nitrofurantoin, chloroquine and methyldopa [1,57]. Proteinuria is a common finding due to the release of myoglobin and other proteins by damaged myocytes [21,58].

Creatine Kinase: In a patient with RBD is has been observed that levels of CK are elevated five or more times the upper limit of normal and there is a weak but statistically significant relation between the levels of CK and the severity of renal injury [1,4].

CK levels range from 1500 to over 100 000 U/L. In the observational study of Veenstra et al., found that renal injury and electrolytical disturbances were more common with levels of CK exceeding 15 000 U/L. 28 The CK is almost entirely of the MM fraction. Creatine kinase has a serum half time of 1.5 days and declines at a constant rate of about 40 to 50 percent of the previous days. It begins to rise within 2 to 12 hours reaching a maximum level within 24 to 72 hours. In the retrospective study of Weibrecht et al., they found a relation between the elevation of aminotransferase and CK level up to 1000 U/L. The incidence of aspartate aminotransferase (AST) was 93.1% and alanine aminotransferase (ALT) was 75%, they also found that AST fall in parallel with CK during the first 6 days. This suggests that skeletal muscle may be a source of AST in rhabdomyolysis [59].

Electrolyte and metabolic disturbances: Hyperkalemia. Elevated potassium levels are the immediate prognostic factor of rhabdomyolysis. The degree and rapid elevation are directly related to the extent of the muscle injury. It is very important to control the etiological factor, thereby preventing the release of potassium. In addition, hyperkalemia is intensified by the coexistence of metabolic acidosis and renal dysfunction. In severe cases rescue hemodialysis is the therapy of choice [1,3,47].

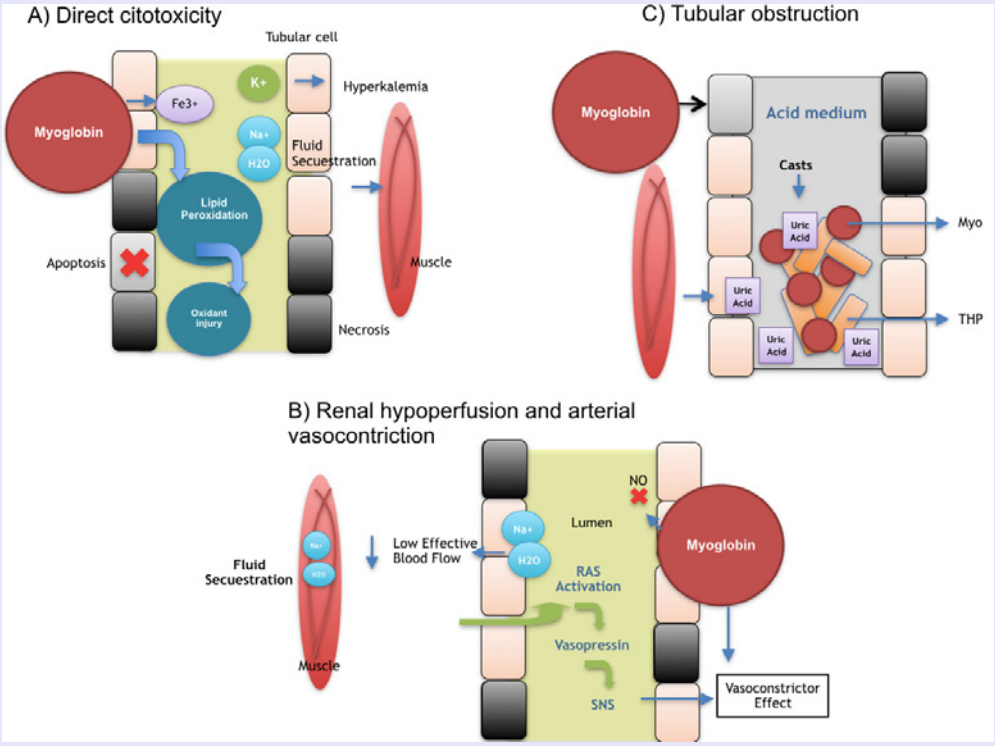

Figure 1 Mechanisms of AKI induced by rhabdomyolysis.
In panel a) We observe direct damaged one of those is the release of free iron from the myoglobin due to fenton reactions and lipid peroxidation causing oxidant injury therefore necrosis and apoptosis. Panel b) Hypoperfusion is due to three mechanisms: 1) Decrease of venous volume secondary to fluid sequestration in damaged muscle and 2) Activation of neuroendocrine systems and local vasoconstriction 3) Inhibition of nitric oxide by myoglobin and vasoconstriction. Panel c), Myoglobin interacts with tamm-horsfall protein and precipitates forming casts causing tubular obstruction. This mechanism is enhanced by acid medium. On the other hand, damaged muscle release uric acid which precipitates un tubules favoring its obstruction.

Hyperkalemia is more common in patients with oliguric acute kidney injury [58].

Hyperphosphatemia. During the breakdown of muscle cells, large amounts of inorganic phosphorus are released into the plasma, which causes hyperphosphatemia. Hyperphosphatemia causes calcium phosphate deposition, in addition to inhibiting renal α-1 hydroxylase, responsible of the production of the active form of vitamin D, leading to hypocalcemia generally asymptomatic [1,3,47].

Hypocalcemia and hypercalcemia. It is secondary to a massive entry of calcium into damaged myocytes and also deposition of calcium salts in damaged muscle decreased bone responsiveness to parathyroid hormone. According to Akmal et al., in their comparative observational study. They compare 15 patients, 7 with RBD and acute kidney injury, 4 with RBD only and 4 with acute renal injury only. All patients had hypocalcemia on admission and it was more pronounced in those with rhabdomyolysis and AKI. Only patients with RBD independent of the presence of AKI, had calcium deposition in soft tissue. Patients with rhabdomyolysis and AKI had hypercalcemia during diuretic phase and high levels of 1,25-dihidroxyvitaminD (1,25(OH)2D), suggesting that muscle may produce this hormone in this patients. They concluded that hypocalcemia occurs in rhabdomyolysis independent of renal failure and is most related to calcium deposition and that elevation of serum levels of 1,25(OH)2D plays an important role in the production of hypercalcemia [60].

On the other hand hypocalcemia during rhabdomyolysis should not be treated unless calcium is used as an antagonist for the cardiac toxic effects of hyperkalemia [61,62].

Hyperuricemia. Purines released from broken muscle nucleic acids are transformed into uric acid in the liver, raising their serum levels [3, 47].

Metabolic acidosis. The release of several organic acids (lactic acid and uric acid) from destroyed muscle cells leads to metabolic acidosis [63-65].

Compartmental syndrome

The muscular fascias are the support of the muscular masses and are low expandable tissues, these same fascias are the cause of the increase of local pressure in the zone of muscular affection. Muscular edema increases local pressure, which further compromises muscle perfusion and closes a vicious circle: greater ischemia injury, greater local pressure, greater vascular compromise and, in the end, aggregated reperfusion injuries [63-65].

Normal compartment pressures range from 0 to 15 mmHg. Clinical muscle ischemia is observed at pressures of 30 to

50 mmHg, myalgia, hypoesthesia and significant functional impairment appear.

Compartmentalization syndrome is characterized by the presence of sensory alterations, local and distal cooling to the lesion and absence of distal pulses [53,63-65].

DIAGNOSIS

Clinical diagnosis. An adequate clinical history and a thorough physical examination will give the diagnosis. However, within the process it is important to highlight some relevant laboratory findings. Due to muscle necrosis, it is the presence of muscle enzymes that contribute to early diagnosis.

The diagnosis of rhabdomyolysis is relatively easy when acute neuromuscular illness is present or dark urine plus a marked acute elevation in serum creatine kinase (CK). As it was mentioned above, CK is typically at least five times the upper limit of normal. The elevation of CK should be considered in the clinical context of the history and examination findings.

Biopsy. Biopsy is the gold standard for diagnosis. However, most of cases is not necessary to make the diagnosis not even start the treatment. In muscle biopsy we will find necrosis, ragged-red fibers and inflammatory cells. Renal biopsy: tubule obstruction with positive myoglobin staining casts, interstitial edema and inflammatory cells [1,66].

Differential diagnosis. Other studies as electromyography (EMG), magnetic resonance imaging (MRI) is not necessary for the diagnosis, only if inflammatory myopathy is suspected [1,47]. On the other hand, there are another pathologies with myalgia, elevated creatine kinase and dark urine. For instance: 1) Myocardial infarction, the points that make this diagnosis less probable are that CK-MM fraction is elevated, in rhabdomyolysis there is no chest pain or electrocardiogram signs of infarction. 2) Hemolysis may result in red-dark urine and may be confused with myoglobinuria. CK is not elevated in rhabdomyolysis. 3) Inflammatory myopathy: this patients may present with myalgia and elevated CK. The evolution is chronic and there is changes in EMG [67,68].

However, there are some rare cases when CK is normal and diagnosis may require histological approach. Faisal et al., reported one case with this presentation. The patient was a man with history of substances abuse, presented with altered mental status, urinalysis showed trace of blood and the color was yellow. He also presented AKI, and CK of 156 U/L at admission and it was always in normal levels. His renal function became worse requiring hemodialysis. Since underlying etiology was unclear biopsy was made and reported multiple myoglobin casts [66].

EVALUATION OF AKI

Once there is evidence of RBD it is important to evaluate the risk of developing AKI. Evidence of muscle damage, CPK levels and evidence of myoglobinuria are the essential data to alert the clinician to the risk of kidney damage. Furthermore levels of myoglobin and CK levels there are also other risk factors that are related to the development of renal failure, which is minimal in patients with normal baseline renal function and a base deficit not beyond -4. Otherwise, patients with a greater base deficit and with some degree of baseline nephropathy, the possibility of renal failure increases.

McMahon et al., develop a risk prediction score to identify patients at greatest risk of renal replacement therapy (RRT) and hospital mortality. They found that the independent predictors were age, female sex, cause of rhabdomyolysis and values of creatinine, CK, phosphate calcium and bicarbonate. Patients with a score less than 5 2.3% died or need RRT, on the other hand those with a sore more than 10, 61.2% died or needed RRT (Table 3).

TREATMENT AND PREVENTION

During the therapeutic approach, the risk of compartment syndrome must first be assessed, the possibility of its development determined, its evolution limited and an early treatment must be considered. It is important to investigate the cause of RBD [1].

The treatment is based on avoiding muscle injury, avoiding sustained ischemia, suspecting the presence of perfusion problems and limiting the development of compartmentalization syndrome, as well as avoiding reperfusion injuries as much as possible.

The fundamental therapeutic basis once the muscle injury and the release of myoglobin are present are based on an aggressive parenteral fluid approach in order to maintain adequate renal perfusion and prevent myoglobin from precipitating in the tubules [45,69]. Patients should have aggressive rehydration with normal saline.1 The rate is 2.5 ml/kg/h and in the first 24-72 hrs continue fluid management with a rate of urine output of 200ml/h or 3ml/kg/h until CK level fall bellow 1000 U/L or [1,70,71]. Patients may require about 10 liters/ day [72]. There are no randomized controlled trials to demonstrate the superiority of 0.9% normal saline versus Ringer's Lactate as the solution of choice in this patients [1].

Table 3: Risk score for mortality and RRT in patients with rhabdomyolysis.

Variable	Score
Age	
≥50 to ≤70	1.5
> 70 to ≤80	2.5
> 80	3
Female sex	1
Initial creatinine, mg/dl	
1.4 to 2.2	1.5
>2.2	3
Initial calcium < 7.5 mg/dl	2
Initial CK > 40 000 U/L	2
Origin not seizures, syncope, exercise, statins, or myositis	3
Initial phosphate	
4.0- 5.4	1.5
>5.4	3
Initial bicarbonate < 19mEq/L	2
Score less or equal than 5 points: Low risk, more or equal than 10 points: High risk. Modified from [77].	

Even thought is it known that normal saline in large amounts may cause metabolic acidosis and in this case worsening AKI. Cho et al., made a prospective study comparing Ringer's lactate and normal saline plus bicarbonate, no effect on peak creatinine kinase level or recovery was observed but more bicarbonate was needed with normal saline than with Ringer's lactate [73].

The use of bicarbonate to alkalinize urine (pH > 6.5), is still controversial. However, it is known that precipitation of myoglobin is increased in acidic urine, reduce tubule injury and ameliorate renal vasoconstriction [1]. It is recommended by some authors if urine pH is less that 6.5 alternate normal saline with 1 liter of 5% dextrose plus 100 mmol of bicarbonate, avoiding potassium and lactate-containing solutions. 1 If sodium bicarbonate is used, ph urine must be measure in 4-6 hrs of treatment and there is no change bicarbonate should be discontinue also if hypocalcemia symptoms develop [1].

At the 2012 meeting for recommendations on the use of mannitol in the handling of crush victims, there was no consensus regarding its usefulness. The addition of a fluid regimen has several purposes: (1) it is a renal blood flow and the glomerular filtration rate, (2) is an osmotic diuretic that attracts fluid from the interstitial space, (3) to the increase of the previous urinary flow the formation of myoglobin cylinders and (4) is a chelator of free radicals [1,64].

Some authors have argued the use of mannitol or the arlkalinization of urine, however until now nobody has been able to verify the benefit of these interventions and its use is rather theoretical. In fact, in the study of Carlos Brown et al., they review 2.038 trauma ICU admissions, they evaluated the use of bicarbonate and mannitol to prevent renal failure. They found that this management did not prevent AKI, dialysis or mortality with a *p* value of 0.27, 0.57 and 0.37, respectively [74].

The use of loop diuretics such as furosemide, increasing tubular flow and decreasing the risk of myoglobin precipitation but acidifying the urinary pH. Its benefit in patients with RBD it is not clear and its used should be in the same manner as in AKI due to other causes.

Chan et al., found that curcumin loaded nanoparticles the anti-AKI effects were: reversed oxidative stress, growth inhibition and cell apoptosis, also down regulation of apoptotic markers Caspase-3 and GRP-78 *in vitro*. *In vivo* reduce serum CK, creatinine, and urea and in biopsy revealed less tubules damage [75].

Renal replacement therapy (RRT), In patients who develop AKI complicated by anuria, severe hyperkalemia, acidosis or volume overdose, RRT may be required [76,77]. Hemodialysis (HD) as a therapeutic modality can be used [78]; usually is implemented in patient with hemodynamic stability, however, most patients with RBD develop acute oliguric and may be with vasoppresors. In these cases continuous renal replacement therapy (CRRT) may be the best option; Zhou et al., found 3 small studies that involved 101 participants, and found that although CRRT showed limited advantages over HD to improve some aspects of kidney function and muscle tissue loss, they found no significant benefits in reducing risk of death [79]. Either modality also can be used to removed large amounts of myoglobin before AKI [80].

Another option of continuous replacement therapy is the use of special filter into the continuous veno-venous hemofiltration (CVVH). The use of CytoSorb emoadsorption device (CytoSorbents Inc.,) has been approved for reducing excessive cytokines, myoglobin, hemoglobin, bilirubin, bacterial toxins, activated complement and other inflammatory mediators. In the case report of Suefke S. et al., they presented a male with acute kidney injury, rhabdomyolysis and sepsis. The CVVH with CytoSorb was used. In total, four consecutive sessions were run over 20 h each. After two days of the last session, levels of cytokines and myoglobin decreased significantly with improve of clinical situation even though kidney function remained impaired after five days on CytoSorb and the patient was discharged at day 13 with ongoing renal failure and RRT. They concluded that future randomized controlled trials are needed to evaluate the benefits of myoglobin removal in this context [81].

Key points:

- RBD is the destruction of muscle tissue and release of intracellular content into the bloodstream with negative impact on clinical status.
- The etiology must be addressed and corrected as son as possible. Detail clinical history and deep interrogation may identify the etiology, specifically when non-traumatic causes are suspected.
- AKI is the most common complication associated RBD and is a strong risk factor to mortality.
- The mechanisms of AKI by RBD included: direct cytotoxicity, renal hypoperfusion, arterial vasoconstriction and tubular obstruction.
- Prevention ant treatment of RBD induced AKI include aggressive hydration, alkalinize urine and in some cases RRT to correct complication due to AKI.

CONCLUSION

Because RBD is a frequent pathology with severe complications, it is important to know its pathophysiology as well as its effects at the renal level since it is the most frequent complication with an important mortality. There are still controversies regarding the treatment. Studies are still needed for prevention and therapeutic measures for this condition.

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