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Review

Exercise-induced rhabdomyolysis mechanisms and prevention: A literature review

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Abstract

Exercise-induced rhabdomyolysis (exRML), a pathophysiological condition of skeletal muscle cell damage that may cause acute renal failure and in some cases death. Increased Ca^{2+} level in cells along with functional degradation of cell signaling system and cell matrix have been suggested as the major pathological mechanisms associated with exRML. The onset of exRML may be exhibited in athletes as well as in general population. Previous studies have reported that possible causes of exRML were associated with excessive eccentric contractions in high temperature, abnormal electrolytes balance, and nutritional deficiencies possible genetic defects. However, the underlying mechanisms of exRML have not been clearly established among health professionals or sports medicine personnel. Therefore, we reviewed the possible mechanisms and correlated prevention of exRML, while providing useful and practical information for the athlete and general exercising population.

Keywords: Acute renal failure; Calcium (Ca^{2+}); Creatine kinase; Myoglobin (Mb); Rhabdomyolysis

1. Introduction

The number of people participating in regular as well as organized exercise programs has been continuously increasing. The increase in popularity of physical activity and exercise may be due to positive effects on physical and mental health. However, excessive or intense exercise beyond the extent of personal or physical limits may induce various types of musculoskeletal damage, including exercise-induced rhabdomyolysis (exRML), a pathophysiological condition of skeletal muscle cell damage.[1] exRML may be manifested by an increase in creatine kinase (CK) or myoglobin (Mb), seeping into the blood stream through damaged cell membrane as results of excessive or intense exercise.[1] exRML may lead to acute renal failure (ARF), liver dysfunction, compartment syndrome, heart failure, arrhythmias, electrolyte imbalance, and in severe cases also to death.[2,3] exRML can occur via highly intense and prolonged exercise or due to sudden and excessive contraction of skeletal muscles. Symptoms of exRML are similar to those of delayed onset muscle soreness that can be easily overlooked.[4] Despite its importance, people who participate in exercise may not be aware of exRML. Therefore, the purposes of this review are to provide exercising population with information about the possible mechanisms of exRML and offer preventive strategies to avoid exRML based on results of previously conducted studies.

2. Pathophysiology of exRML

2.1. Role of calcium in the pathogenesis of exRML

Ca^{2+} has been suggested as an important factor in the pathogenesis of exRML (Fig. 1). Numerous studies[5,6] have shown increased levels of Ca^{2+} in cells of exRML patients. The concentration of Ca^{2+} should remain at nano-molar levels under resting conditions. Ca^{2+} would increase to mille-molar levels through cell activation and muscle contraction during exercise.[7] Ryanodine receptors in the sarcoplasmic reticulum, dihydropyridine receptors (i.e., voltage-gated L-type Ca^{2+} channels), and Ca^{2+} pump are the 3 major pathways controlling the Ca^{2+} in skeletal muscle cells.[8–10] Transient receptor potential channel (non-selective cation

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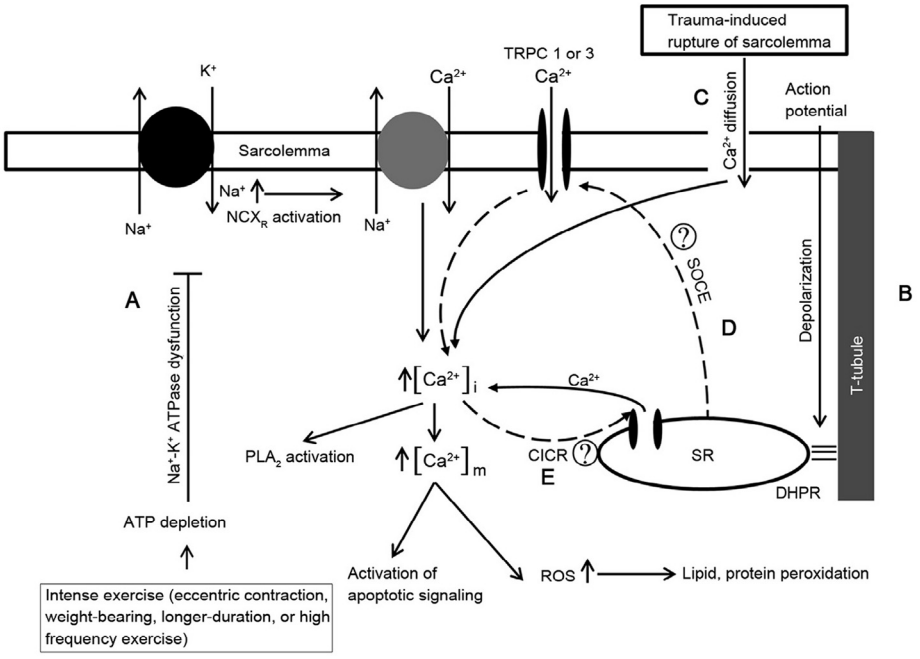

Fig. 1. The pathophysiological mechanism of rhabdomyolysis focusing on the increase of Ca^{2+}. A: Deficiency of ATP due to high intensity exercise and continuous muscle contraction could induce the dysfunction of Na^{+}-K^{+} ATPase, causing subsequent activation of reverse mode Na^{+}-Ca^{2+} exchanger; B: Depolarization of sarcolemma and T-tubule by an action potential could activate dihydropyridine receptor and promote the secretion of Ca^{2+} via ryanodine receptor in sarcoplasmic reticulum; C: The increase of Ca^{2+} due to Ca^{2+} diffused by the rupture of sarcolemma from trauma; D: The entry of store-operated Ca^{2+} through transient receptor potential Channel 1 or transient receptor potential Channel 3 with reduced levels of Ca^{2+} in the sarcoplasmic reticulum; E: The secretion of Ca^{2+} (Ca^{2+}-induced Ca^{2+} release) from sarcoplasmic reticulum in accordance with the increase of Ca^{2+} in sarcoplasm. → represents activation; ⟞ represents inhibition, - - → represents candidate mechanisms in the regulation of Ca^{2+}. ATP = adenosine triphosphate; CICR = Ca^{2+}-induced Ca^{2+} release; DHPR = dihydropyridine receptor; NCX_R = Na^{+}-Ca^{2+} exchanger; PLA_2 = phospholipase A_2; ROS = reactive oxygen species; SOCE = store-operated Ca^{2+} entry; SR = sarcoplasmic reticulum; TRPC = transient receptor potential cation channels.

channel),[11] Ca^{2+}-induced Ca^{2+} release,[12] and Na^{+}-Ca^{2+} exchanger[13] contribute to the control of Ca^{2+}. Increased Ca^{2+} concentration has been reported in the sarcoplasm of exRML patients[6] with deficiency or depletion of adenosine triphosphate (ATP) due to intensity of exercise. ATP is continuously synthesized during exercise. When the amount of ATP is severely depleted, ATP-dependent ion transporter may be affected.[14] ATP-dependent transporters of skeletal muscle cells are Na^{+}-K^{+} ATPase[15] and Ca^{2+} ATPase[16] ion transporters. When skeletal muscle cells are excited, Na^{+} influx through the voltage-gated Na^{+} channel creates an action potential, resulting in similar amounts of K^{+} efflux through the K^{+} channel. The movement of these ions strengthens the capacity of Na^{+}-K^{+} ATPase to readjust the distribution of ions in the sarcoplasm.[15] The efflux of Na^{+} and the influx of K^{+} become ATP-dependent and move in the opposite direction of the concentration gradient. If the amount of ATP is deficient or insufficient, the activity of Na^{+}-K^{+} ATPase would be reduced. Decreased amount of ATP could cause dysfunction of the Na^{+}-K^{+} ATPase,[14] resulting in an increased level of Na^{+} in the cells.[17] Normal function of Na^{+}-K^{+} would activate Na^{+}-Ca^{2+} exchanger in the forward mode (Ca^{2+} extrusion). However, due to the dysfunction of Na^{+}-K^{+} ATPase, increased level of Na^{+} in cells would activate the reverse mode of Na^{+}-Ca^{2+} exchanger (Ca^{2+} influx), thereby increasing the level of Ca^{2+} in the cells.[18] During the cycle of contraction and relaxation of skeletal muscle, Ca^{2+} in the sarcoplasm repeatedly gain sentry through the Ca^{2+} pump in the membrane of sarcoplasmic reticulum.[7] Normal function of the Ca^{2+} pump requires the hydrolysis of ATP.[19,20] If the amount of ATP is insufficient, the Ca^{2+} pump would result in abnormal function. Zhang[21] suggested that dysfunction of ion regulation proteins as, a Na^{+}-K^{+} ATPase, Na^{+}-Ca^{2+} exchanger, and Ca^{2+} pump in skeletal muscle may be strongly related to rhabdomyolysis (RML).

Ca^{2+}-induced Ca^{2+} release has been detected earlier than inositol 1,4,5-triphosphate-induced Ca^{2+} release for the reservation or mobilization of Ca^{2+} in the sarcoplasm.[12] Ca^{2+}-induced Ca^{2+} release is not the primary Ca^{2+} control mechanism in the skeletal muscles. It is achieved via protein–protein interaction of voltage sensor dihydropyridine receptor of the T-tubule with the Ca^{2+} release channel ryanodine receptor of the sarcoplasmic reticulum membrane.[22,23] According to the Ca^{2+}-induced Ca^{2+} release mechanism, membrane depolarization caused by the action potential increases the levels of Ca^{2+} in the sarcoplasm, thus releasing Ca^{2+} from the Ca^{2+} store (sarcoplasmic reticulum). Ryanodine receptor and inositol 1,4,5-triphosphate are both associated with Ca^{2+}-induced Ca^{2+} release.[12] Due to consistent contraction of skeletal muscles, increased level of Ca^{2+} in the sarcoplasm may activate Ca^{2+}-induced Ca^{2+} release, which may have asynergistic effect and subsequently increase the level of Ca^{2+} even more. Transient receptor potential channels are non-selective cation channels permeable to Na^{+} and Ca^{2+}.[7] In skeletal muscles, transient receptor potential canonical

(TRPC) Types 1 and 3 have been identified, with TRPC3 being reported to interact with ryanodine receptor.[24,25] The activation of store-operated Ca^{2+} entry by TRPC1/3 with a Ca^{2+} deficiency of the sarcoplasmic reticulum due to ryanodine receptor or inositol 1,4,5-triphosphate activation may increase the levels of Ca^{2+} in the sarcoplasm.[26,27] The malignant hyperthermia is characterized by an increase in RML[28] and store operated cation channels involving TRPC3 accelerated activation by malignant hyperthermia.[29] This leads to increasing intracellular Ca^{2+} and indicates that store operated cation channels and/or TRPC3 is contributing to the development of RML.

Increased level of Ca^{2+} has been reported to have influence on the activation of proteases and phospholipase A_2.[30,31] These responses are strongly associated with damage or decomposition of phospholipids of the cell membrane,[32] which could induce damage to the cell membrane and reveal toxicity caused by several types of molecular efflux.[5] In addition, the increase in Ca^{2+} concentration in the mitochondria due to chemical gradient of Ca^{2+} between the sarcoplasm and mitochondria may be another plausible mechanism of damage.[20,33] This reaction could promote the creation of reactive oxygen species (ROS) in the mitochondria,[34] which could damage proteins, lipids, and nucleic acids.[35,36] This type of damage could reduce the synthesis of cell membrane, proteins, and/or ATP.[34] The increase of Ca^{2+} in the sarcoplasm and mitochondria may amplify the signaling of apoptosis and promoting cell death.[37–39] Furthermore, rupture of muscular cell membrane caused by injury, toxicity, or exercise may induce the influx of Ca^{2+} into cells due to concentration gradient, contributing to the elevation of Ca^{2+} concentration in the sarcoplasm.[20,37] Therefore, the increase in Ca^{2+} in cells may induce exRML by creating energy, while controlling the cell signaling pathway system through interactions that may cause cell death.

2.2. Role of myoglobin in exRML-induced ARF

Among complications of exRML, ARF has shown the greatest incidence rate increase.[40,41] Park et al.[42] reported that 10%–30% of exRML patients may have accompanying ARF, making exRML a clinically important condition due to strong correlation between ARF and death. ARF from exRML may be caused by the delay of treatment due to failure of recognizing severe muscle damage and the presence of renal diseases or age-related biological decline.[43] While the pathogenesis of an ARF originating from exRML has not been clearly recognized, previous studies have suggested an association between increased Mb and K^+ ion and uric acid affecting the glomerulus of kidneys.[40] Particularly Mb could easily permeate the glomerular membrane and subsequently increase the amount of Mb as results of continued muscle damage.[44]

The mechanism of exRML-induced ARF may be referred to vasoconstriction. Necrosis in muscular tissues may create additional space for increased accumulation of intravascular fluid and generate hypovolemia,[45,46] that may activate sympathetic tone and renin angiotensin–aldosterone system, inducing vasoconstriction and activate additional vasoactivator (e.g., endothelin 1, vasopressin) that are known to suppress vasodilation induced by protaglandins.[47–49] Damage to muscles promotes extrication of endotoxins and cytokines into systemic circulation and thus promoting vasoconstriction.[50,51] Mb also plays an important role in decreasing nitric oxide and vasodilation.[52,53] Under these conditions, the creation of ATP would be reduced resulting in vasoconstriction, renal ischemia, and reduction in oxygen.[45]

Cast formation is a contributor in the development of exRML-induced ARF.[37,44] Deficit in ATP may cause necrosis of epithelial cells, accumulation of dead cells in the tubular lumen, resulting in the precipitation of Mb and formation of casts.[47,54] Mb is filtrated at the renal glomeruli.[55] The increase in Mb in pre-urine is accompanied by acidification, and thus, increasing the accumulation of Mb and Mb cast formation in the distal convoluted tubules.[56] The accumulation of Mb induces constriction of blood vessels and initiates ischemia, reducing the function of renal tubules in filtering metabolites and waste products.[53] The accumulation of Mb also creates ROS and induces lipid peroxidation that produces cell membrane and blood vessels in kidneys causing temporary or chronic impairment of normal kidney function.[57,58]

2.3. Primary factors

During exercise, factors that may cause exRML include the exercise experience of participants, level of physical fitness, the intensity, duration, and types of exercises. Line and Rust[59] reported that exRML tends to appear more often in people with little or no exercise experience or in athletes who are less trained than others. In addition, a positive relationship was found between exRML and soldiers performing sedentary duties compared to trained soldiers.[60] Paul et al.[61] reported that highly experienced weight-lifters exhibited relatively lower levels of CK and Mb than less experienced weight-lifters.

Other important factors in exRML are the intensity and duration of exercises. Clarkson[62] found that the typical onset of exRML was extreme muscle soreness and brown colored urine in 12-year-old boys who performed squat jumps 250–500 times. Moeckel-Cole and Clarkson[63] also reported the onset of exRML in college soccer players who conducted highly intense weight training and performed 300 squat jumps. In addition, Russo and Bass[64] reported exRML in a 17-year-old male basketball player who had CK level of 241,026 U/L after completing 800 sit-ups, 400 push-ups, and a 3.2 km run. The determinations of exRML manifested from other sources are summarized in Table 1.

The type of exercise is also considered an important factor in the development of exRML. It has been found that eccentric contraction of muscles may cause exRML more often than concentric contraction.[40,65,66] Kinematic factors of tension, changes in the length of eccentric contraction of the muscle, and attenuation of the bonding between contractile proteins have been suggested to explain these findings.[57,67] According to a previous study,[66] muscle soreness along with the appearance of CK or Mb in the blood appeared often in the blood after exercises containing an excessive component of eccentric contractions. Prolonged and high intensity exercises (e.g., marathon, triathlon,

Table 1
Case reports of exercise-induced rhabdomyolysis.

Researcher	Subject	Exercise mode	Symptom	Complication
Park et al.[43]	20 years male	Scuba diving	Vomiting, CK 12,054 U/L, Mb 3000 mg/mL	ARF
Clarkson[62]	12 years male	Weight training	Brown urine, CK 92,115 U/L, AST 1520 U/L	None
Moeckel-Coke and Clarkson[63]	18 years male	Weight training	Brown urine, CK 130,899 U/L	None
DeFilippis et al. [143]	24 years female	Stationary bike	Brown urine, CK 161,550 U/L, AST 1983 U/L	ARF, compartment syndrome
Goubier et al.[144]	30 years male	Weight training	Sever muscle pain, muscle edema, CK 113,260 U/L, LDH 790 U/L	None
Kim et al.[145]	28 years male	Weight training	Edema, muscle pain, CK 52,240 U/L, LDH 2277 U/L	Hepatitis
Gagliano et al.[146]	30 years male	Bodybuilding	CK 70,920 U/L, LDH 4981 U/L, Mb 1702 U/L	ARF
Inklebarger et al.[85]	63 years male	Stationary bike	Sever muscle pain, brown urine, CK 38,120 U/L, Mb 5330 U/L	None
Thoenes[147]	17 years male	Stationary bike	Brown urine, sever muscle pain, CK is not suggested	None
Karre and Gujral[148]	24 years male	Low intensity exercise	Joint pain, brown urine, CK 214,356 U/L, Mb 1347 mg/mL	None
MacDonald et al.[149]	26.7 years (19–40 years), $n = 17$	Weight training	Muscle aches, some subjects had hematuria and proteinuria, CK 1800–220,000 U/L	Unknown
Pierson et al.[150]	25 years male	Weight training	CK 31,950 U/L, Mb 50 ng/mL	Not present
Summachiwakij and Sachmechi[151]	33 years male with Grave's disease	Non-strenuous exercise	Brown urine, AST 993 U/L, ALT 228 U/L, LDH 2330 U/L, CK 98,407 U/L	Not present

Abbreviations: ALT = alanine aminotransferase; ARF = acute renal failure; AST = aspartate aminotransferase; CK = creatine kinase; LDH = lactate dehydrogenase; Mb = myoglobin.

soccer, body-building, or Crossfit) have been reported to activate exRML.[45,58,59]

2.4. Secondary factors

2.4.1. Hot environments

Exertional heat stroke syndrome induced fever and encephalopathy (delirium, seizures, and coma) as well as the muscle weakness could lead to exRML.[37] A hyperthermal environments may increase body temperature above 42°C accompanied by liquation of the lipids constituting the muscle cell membrane disturbance by suppressing the process of internal oxidative phosphorylation or inducing protein denaturation in the mitochondria, resulting in hemodynamic changes and subordinate activation of inflammatory cytokines that may be responsible for exRML.[41] Excessive exercise in high humidity and temperature has been reported to be the most severe condition that induces exRML.[44] Soldiers and athletes were reported to have more exRML compared to general population.[68] Soldiers who undergo special force physical training or ranger activities with long distance marching in hot outdoor environments[69,70] and athletes who are exposed to high heat in outdoor environments when participating in long activities for hours, such as marathon or triathlon, might be particularly susceptible to exRML.[71,72]

2.4.2. Electrolyte imbalance

Aizawa et al.[73] reported expression of exRML in a 22-year-old male soldier who presented with fever, retching, and fatigue after highly intense physical training for 3 days. They suggested that electrolyte imbalance (hypokalemia or hyponatremia) may have produced these symptoms.[73] K^+ ion generally would increase blood flow to the contracting muscles during exercise. However, in the case of excessive exercise in high temperatures, the body may compromise its homeostasis to control body heat. As a result, potential hypokalemia may be generated due to sweating, therefore reducing the blood flow to the muscles and induced exRML.[74] According to Park et al.[42] hypokalemia may lead to exRML by changing voltage of safety film on the cell membrane by impeding the synthesis of muscle energy substrates such as glycogen. Na^+ is closely associated with muscle contraction and Na^+-K^+ ATPase may be markedly reduced in a high temperature environment, resulting in exRML.[75] It has been reported that exRML was induced in body builders who avoided Na^+ and water intake to generate a contrasting contour of muscles, which affected the electrolyte imbalance.[76]

2.4.3. Sex

The incidence of exRML in males has been reported to be higher compared to females.[72,77,78] A female group was reported to have less increase in CK level than the male group.[79] In menopausal women, the secretion of CK and lactate dehydrogenase (LDH) were diminished in the group taking estrogen hormone supplement.[80] The incidence of exRML was reported to be lower in female athletes than in male athletes.[77] A report from the U.S. Centers for Disease Control and Prevention also reported that exRML was observed in 32 men, but not in 84 women among 16,506 fire fighters who participated in a physical strength examination.[81] In an epidemiological investigation of exRML in high school students, male students were found to have more cases of exRML than female students.[66] At 24 h post marathon, the level of CK in the male group was 3322 IU/L that was significantly higher than in the female group constituting 946 IU/L.[82] Therefore, males are more vulnerable to exRML than females. It was reported that estrogen with similar structure as vitamin E may have suppressed oxidative stress due to exercise, thus squelching the activation of calpain, a protein with function of diminishing the infiltration of inflammatory cells such as neutrophil leukocyte and macrophages.[83,84]

2.4.4. Nutritional problems

Dietary composition of vegetarians with exRML has been discussed previously.[85] The amount of ingested protein has been reported to cause variation in the degree of exRML,[86] suggest-

ing that exRML may be associated with deficiency of protein in the diet. Vegetarian athletes, who do not consume proper amount of protein with their meals may potentially develop exRML.[87] One young athlete manifested with exRML together with high levels of CK, muscle pains, discomfort, temporary tachycardia, and retching was found to have been on vegetarian diet.[86] Therefore, healthy diet containing proper amount of protein is required to prevent exRML.

Besides proteins, carbohydrate intake may also play a role in exRML. One male marathoner in his 30s who controlled carbohydrate intake through glycogen loading died from heat stroke accompanied with exRML and increased levels of CK after finishing the race.[77] According to Bank,[88] among track and field athletes who exhibited brown urine after glycogen loading, were reported to develop ARF. The manifestation of exRML appeared to originate from acidification and reduction of normal energy stores in muscles by increasing lactic acid as results of an increase in glycogen.[77] Although the exact mechanism has not been determined, it is possible that track and field athletes are more vulnerable to myoglobinuria attributed to glycogen loading.[88] Park et al.[42] suggested that hypokalemia induced by increased insulin from excessive intake of carbohydrate may be a possible reason for exRML in a body builder after finishing exercise.

2.4.5. Creatine supplements and alcohol

Creatine supplements have been used by athletes who require muscle power in a short time and by general public who may wish to increase the muscle mass.[89] Creatine is endogenous energy substrates that can be taken additionally as supplements.[90] The intake of 20–25 g/day of creatine for 5–7 days is recommended. However, over 80% of athletes appear to take much larger amount of the supplements than recommended.[89] Such excessive intake may cause imbalance in body water, triggering muscle cramps or dehydration, which may be the root cause of renal failure or exRML. A male weight-lifter was reported to have renal failure and compartment syndrome including exRML after taking high doses of creatine supplement.[91] A case of recurrence of steroid-responsive nephrotic syndrome along with reduced creatinine clearance rate caused by the intake of creatine supplement was also reported.[92]

The excessive use of medication for medical or entertainment purposes can also cause RML. Excessive exercise while taking drugs for medical reasons may lead to potentially adverse drug reactions. A rare case of induced RML by statin (medication administered for patients to control hyperlipidemia) was also reported.[93] It was found that statins may impede the activation of ATP and coenzyme Q10 (antioxidant), making the muscle cell membrane susceptible to damage.[44] Similarly, steroids typically used by athletes may also induce RML and liver damage.[94,95] Recently, indication of RML was reported in a person who performed exercise after taking synephrine (similar to phenylpropanolamine or ephedrine) contained in supplements used for weight loss.[96] Compartment syndrome with RML was also reported in a soldier who took ephedrine after completion of physical training.[97] In addition, a woman in her 50s exhibited RML together with symptoms of extreme pain, muscle hyposthenia, and loss of weight and muscle power after taking oriental medicine containing *Herba Ephedrae* who later died.[98]

RML may be induced by ingestion of drugs such as heroin, cocaine, amphetamine, and cyclosporine (immunosuppressive agent after organ transplantation).[44] Alcohol may also cause RML by aggravating damage to muscles created by exercise. It was reported that alcohol ingestion after exercise may worsen edema, soreness, and dehydration.[99] Alcohol aggravates muscle damages by innate immunoreactions of the body influenced by differentiated activation of inflammatory cells during process of recovery from muscle damage.[100]

2.4.6. Other factors

Various diseases may also affect exRML. A young teenager who participated in a weight lifting training had exRML due to an influenza virus.[101] In addition, a young basketball player presented with exRML after taking medication to treat influenza.[102] Although the exact cause of exRML symptoms needs further clarification, it is possible that viral infection may play a role in the cases of exRML.

Genetic deficiency of metabolic factors may also be implicated in RML. McArdle's disease, a deficiency of myophosphorylase related to the metabolism of carbohydrate, may impede the supply of energy sources required for exercise due to the deficiency of enzymes essential for glycolysis and glycogenolysis.[103] Reduction or absence of glycolysis and glycogenolysis would have a negative influence on the synthesis of ATP as illustrated in Fig. 1. Fatty acid oxidation disorders such as the disturbance of β-oxidation and other enzyme shave also been linked to RML.[104,105] Fatty acid oxidation is an important energy metabolism system in skeletal muscles, heart, liver, and kidneys.[106]

Deficiency of carnitine palmitoyltransferase II may cause RML via synthesis of ATP related to lipid metabolism during aerobic exercise.[107] Deficiency of carnitine palmitoyltransferase II is a common cause of myopathy, resulting in RML in adults.[108]

Mutations of *LPIN 1* gene have been suggested as a novel factor in recurrent RML,[109] and are associated with the muscle specific phosphatidic acid phosphatase, a key regulator in triglyceride biosynthesis.[110] This gene, predominantly expressed in muscle and adipose tissues,[111] affected recurring RML in children.[112] The prognosis of *LPIN 1* deficiency has been considered as a negative outcome, causing death in one-third of patients with RML.[113]

3. Symptoms and diagnoses

The symptoms of exRML may vary individually. However, changes in the color of urine and muscle soreness are common.[114,115] When RML occurs, excessive Mb contained in the urine may exhibit myoglobinuria with dark colors. Extreme muscle soreness is accompanied by cramps or muscular stiffness, nausea, headache, and fatigue.[44,115]

Blood tests and urinalysis have been adopted to diagnose for exRML. CK, Mb, LDH, aspartate aminotransferase (AST), troponin, and aldolase in blood are examined via various blood

tests that also include tests for CK and Mb. CK is the most sensitive indicator of RML. The normal level of CK is at 22–198 U/L. Depending on the degree of RML, the level of CK could increase up to 10,000–200,000 U/L.[58] CK level of 3,000,000 U/L was observed in 1 case report.[115] Thus, CK level in blood has been adopted as an indicator of RML. However, some studies have questioned the diagnosis employing CK.[116] It was reported that CK may be sensitive but not specific for RML.[117] The National Lipid Association's Muscle Safety Expert Panel provided the level of CK to diagnose RML into 3 categories: 1) levels less than 10 times of the upper limit of normal (ULN) was classified as mild; 2) levels of 10–49 times of ULN was classified as moderate; and 3) levels exceeding 50 times of ULN have been classified as marked.[116]

Since Mb can be quickly removed from the serum, it has a relatively low reliability as an indicator for RML diagnosis.[58,118] In urinalysis, the ratio of nitrogen and creatinine has been determined to be positive when diagnosing for RML. The normal ratio of nitrogen and creatinine is 10:1. This ratio may decrease below 6:1 depending on the symptoms of RML.[44] In addition, electrolyte balance, arterial blood gas examination, muscle biopsy, and/or electrocardiogram are used for the diagnosis of RML.[119] Controversy exists that addresses possible and viable use of biomarkers for detection of RML. Thus, the determination of RML depends on symptoms recognized by exercise participants. Previous study has suggested to seek diagnosis and treatment when pain accompanied with dark urine color are observed 24–48 h after exercise.[120]

4. Rehabilitation protocol

Rehabilitation programs related to RML were introduced by Randall et al.[68] The initial rehabilitation program should be composed of exercise containing gradual resistive exercises to activate cell function and prevent energy deficiency. This would enable the exercise intensity of muscles to be placed below an aerobiosis. In general, the range of motion of joints should improve simultaneously. During the 1st stage of a rehabilitation program, manual efforts to secure a range of motions of joints may require some form of discomfort and perhaps some pain. Before recovering from complete joint mobilization, the 2nd stage of rehabilitation should increase gradually. The distal portion of the upper or lower part of the body should be manipulated gradually with very low intensity from 5 to 15 min using a non-weight bearing equipment. If no feeling of discomfort or pain is present within 24 h after the exercise, the 3rd stage of the rehabilitation program could be introduced. In the 3rd stage of the rehabilitation program, isotonic exercises such as stretching of the joints, modified flexion and extension of joints, or bench press should be gradually introduced. Modified flexion and extension of joints should start from forward tilted position with both hands touching the wall, and then proceed to a table, a footboard, or chairs, and finally to the floor to increase the joint mobility and exercise intensity. In the 4th stage of the rehabilitation program, one set of limited flexion and extension of the joints should be performed together with the normal exercise program. The limits of flexion and extension of joints is to restore performance capability before determination of RML without loss of range of motion of joints or pain.[68]

Guidelines of O'Connor et al.[121] divide the rehabilitation program in 3 phases for athletes at low risk for RML. In Phase 1, CK and urinalysis are monitored during moderate resting. In Phase 2, the guidelines suggest the initiation of physical activity. In Phase 3, the guidelines suggest a gradual comeback to sports activity. They recommend 72 h of rest and ample water intake after the onset of RML in Phase 1. Eight hours of sleep has been recommended together with remaining in a heat-controlled environment in the presence of RML when accompanied with heat injury. Monitoring of CK and urinalysis every 72 h has also been recommended. Light physical activities in Phase 2 could be initiated after urinalysis results reveal CK levels below 5 times of the normal level. In cases where CK or the results of urinalysis are not normalized within 2 weeks, medical consultation was recommended. For Phase 2, physical activities considering self-paced distance should be practiced. The Phase 3 could be initiated along with necessary follow-ups when no clinical symptoms a represent during a 1-week follow-up in Phase 2. The rehabilitation program after the onset of RML should be advanced gradually while carefully monitoring symptoms (CK, pains, *etc*.).

5. Prevention guidelines

5.1. Consideration of exercise program components

It has been suggested that warm-up may be the best approach to improve exercise adherence, as it provides the participant with pre-practice of the actions required for corresponding exercises or games. Warm-ups could also reduce the chance or occurrence of musculoskeletal damage.[122] It may also be useful to utilize the same amount of time for warm-up and cool-down as demanded factual exercise or game.

Several studies have reported that periodic repetition of eccentric exercises could reduce the level of muscle damage, inducing positive changes in blood markers such as CK or LDH as well as diminished pains of the muscles.[123–125] To make these changes, several factors should be considered, including the interval time between each exercise, the number of repeated eccentric contractions, length of muscles, and the types of exercise. Various mechanisms related to repeated-bout effect[120] have been reported. Changes to muscle fibers and the nervous system would require additional motor units for successful eccentric contractions. Thus, muscles should be adapted by considering not only dynamic factors such as length-tension changes, but also reduction in intracellular events such as inflammatory reaction generated from damage or function of excitation-contraction coupling (E-C coupling) to prevent the onset of exRML.[126,127]

What type of exercise could prevent exRML? The answer to this question is not clear. However, it may be easy to identify the types of exercises that may promote exRML. CK is a crucial indicator for the diagnosis of exRML. High-intensity, longer-duration, and weight-bearing exercise (eccentric contraction and downhill running) have been found to be responsible for the increase in CK concentration,[128] especially in men who are

lacking physical strength.[129] Thus, the type and intensity of exercise must be considered prudently before participating in exercises training program.

5.2. Education of exercise-induced rhabdomyolysis

Generalized guidelines for identification of exRML have not been established. Individuals participating in exercise requiring greater or more intense eccentric contraction of muscles should understand the danger and potential exRML to prevent this condition.[66] It is also important to educate coaches and others who are involved in training of athletes about the symptoms and signs of exRML. Lack of descriptions regarding the exRML in exercise physiology books and books addressing physical training are warranted.[63] Knowledge of exRML would enhance coaches and other professional of athletes in each field to recognize quickly when exRML may occur.[130]

5.3. Prudence in participating in exercise when having communicable diseases

Regular exercise may become a risk factor in individuals prone and susceptible to disease. Individuals with mild disease including communicable diseases should refrain from exercise, or at least limit the scope of the exercise. In cases of viral diseases including diarrhea or vomiting, exercise and training should be modified or abstain from training to prevent possible development of exRML.[130] Symptoms that are similar to those of influenza or communicable diseases should be considered to avoid further complications.[4]

5.4. Environmental factors to be considered in outdoor exercises

Many previous studies have reported that sufficient intake of water is effective in preventing heat induced disorders. Normal hydration could ensure the homeostasis of body temperature.[131,132] These relatively simple and common sense measures may prevent heat induced disorders and subsequently reduce the risk and onset of exRML. Since the degree of water loss in a high temperature environment is usually higher, coaches and other professional in the field should continually observe athletes to prevent exRML. In addition, clothing heat production needs to be considered as well. American football players often presented with exRML attributed to their heavy and thick uniforms.[133] When participating in exercise in high temperature, wearing clothing and uniforms that would assist and aid in heat dissipation and provide a cooling mechanism should be considered.[134]

5.5. Consideration of alimentation

Excessive exercise consumes large amounts of body energy. Thus, supplying the body with major nutrients after completing exercise, including protein, carbohydrates, and fat, is preferable and prudent practice. When muscles are damaged, catabolic state may aggravate the damage. These changes could be diminished by proper intake of balanced nutrients.[135] To promote the recovery and regeneration of damaged muscles, ingesting protein together with carbohydrate is more effective since carbohydrate improves the rate of glycogen synthesis.[136,137] Sweating and muscular contraction may induce excessive loss of electrolytes as results of intense exercise or training. Thus, drinking fluids containing electrolytes during and after exercise is desirable.[138] Proper maintenance of fluids and nutrients after completing exercise could provide damaged muscles with necessary fuel for recovery and regeneration and prevent the potential to develop RML.

RML is also known to be associated with oxidative stress. Proper intake of exogenous antioxidants could be another way to prevent the onset of RML. Intake of antioxidants, oxidative stress caused by ROS may be reduced and prevent the damage or failure of kidneys.[139] Since RML is related to oxidative stress, the uptake of coenzyme Q10 may improve the activation of endogenous antioxidants such as glutathione, superoxide dismutase, and catalase and consequently reduce the levels of CK and LDH in blood.[140] Water soluble antioxidant vitamin C may contribute at least partially in preventing renal failure and morphological damage to kidneys due to vitamin C's action that may prevent ARF induced by RML.[141] In another study, it was suggested that RML could be prevented via exogenous intake of antioxidants vitamin C by also reducing CK.[142]

6. Conclusion

When accompanied by various complications, exRML can lead to severe medical conditions. Therefore, it is important to know the related information about exRML as well as various kinds of exercise induced risk factors associated with exRML. Swift and timely measures indicative of symptoms could prevent medical and clinical complications. Return to the training and exercise through a basic rehabilitation protocol after suffering from exRML should be encouraged to prevent the exRML condition. The intent of this review is to provide athletes, coaches, training and medical professional, as well as general population with information necessary to identify various conditions that may lead to exRML as well as how to prevent it. Further studies on the mechanism of exRML are warranted to establish prudent or better guidelines to prevent future cases of exRML.

Authors' contributions

DJS, JK, and JL searched the related studies and contributed to the writing of the manuscript. SK, HYR, and KSC helped to draft the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

None of the authors declare competing financial interests.

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