Review article

**The Influence of Risk Factors on Acute Kidney Injury in Rhabdomyolysis Patients: A Comprehensive Review**

**Abstract**

Rhabdomyolysis is a condition that arises when there is damage to skeletal muscle and its degradation substances are released into the circulation. One serious consequence of this disease is acute kidney injury (AKI). This exercise goes over the etiology, pathophysiology, and clinical manifestations of rhabdomyolysis. The pathophysiology for rhabdomyolysis depends on an increase in total ionized calcium in the cytoplasm. Muscular trauma is rhabdomyolysis's most frequent reason. Reduction often occurring causes include deficiencies in muscle enzymes, anomalies in electrolytes, endocrinopathies, drugs, toxins, and viral origins. Three of the major symptoms are tea-coloured urine, weakness, and myalgia. The most accurate test indicative of muscle injury is an elevated level of plasma creatine kinase. In addition to medicines, overdoses, infections, muscular ischemia, abnormalities in metabolism and electrolytes, genetic problems, prolonged periods of bed rest or activity, and temperature-induced illnesses like NMS and MH are some potential causes of the syndrome, even if physical trauma is the primary cause. Early detection and assessment are essential for preventing AKI and improving patient outcomes. A positive prognosis is associated with rhabdomyolysis syndrome when it is recognized early and the necessary treatment is started soon. Early and intensive hydration should be a part of the treatment for patients with rhabdomyolysis. The various causes of rhabdomyolysis share the same pathophysiological pathway, which involves an increase in intracellular calcium, even if the disease's genesis is complex.

**Key Words:** Rhabdomyolysis, Acute Kidney Injury (AKI), Skeletal Muscle Damage, Myoglobinuria, Creatine Kinase

**Introduction:**

Skeletal muscle integrity is disrupted by the illness known as rhabdomyolysis. Due to this disruption, the bloodstream is exposed to myoglobin, cytokines, aldolase, lactate dehydrogenase and electrolytes. The most frequent side effect of rhabdomyolysis is acute kidney injury, which is generally brought by multiple organ failure [1-2]. Acute kidney damage (AKI) can result from myoglobinuria, which intensifies the severity of rhabdomyolysis, shock, hypocalcaemia, hyponatremia, hypophosphatemia and peripheral neuropathy [3-4]. There are both traumatic and non-traumatic causes of rhabdomyolysis. Crush syndrome, which can result from accidents, earthquakes, and natural causes, is a major cause of traumatic rhabdomyolysis. Many non-traumatic reasons are seizures, alcohol, and drugs [5]. The research demonstrates that rhabdomyolysis can arise from various sources, including trauma, but the ultimate cause of muscle damage and necrosis [6].

As kidney diseases do not cause specific symptoms, it leads to delayed diagnoses. Therefore, many patients admit only with elevation in serum urea and creatinine which necessitates determining the acuity of the event [62]. Although the precise mechanism underlying acute kidney damage caused by rhabdomyolysis is uncertain, experimental data indicates that tubular obstruction, ischaemic tubule damage and intrarenal vasoconstriction are the key factors affected [7]. It has been found that mortality rates among patients inside the critical care unit are 22% when AKI is absent and 59% when it is present [8]. In cases of traumatic rhabdomyolysis, crush syndrome occurs in 30 to 50% of cases [9]. In patients with AKI, aggressive fluid therapy is essential because it replenishes the vascular bed, which improves renal perfusion [10]. Bicarbonate replacement and fluid resuscitation are essential in preventing AKI due to rhabdomyolysis [11]. Rhabdomyolysis can lead to AKI due to the release of free haemoglobin and myoglobin, regardless of the source. The glomerulus easily filters both myoglobin and haemoglobin have the potential to directly damage tubular cells by producing oxygen-free radicals, cast precipitation, and tubular blockage.

**ETIOLOGY:**

Depending on the age, rhabdomyolysis can have a variety of causes. In children, the most frequently mentioned aetiologies are trauma, viral Infections medications, and exercise, while the most frequently reported reasons in adults are trauma, drugs, and infections [12-13]. There are many causes that cause rhabdomyolysis including statins, trauma, temperature, muscle ischemia, infection and cytochrome p450 enzymes [1]. Results indicate that rhabdomyolysis patients who are older are more likely to have AKI [14]. Combining statins with other frequently given medications can complicate statin therapy by raising the chance of myopathy and rhabdomyolysis. About 60% of cases of statin-induced rhabdomyolysis are associated with medication interactions. These interactions frequently occur because the cytochrome P450 system metabolizes both statins and frequently co-administered medications [15]. Nonetheless, not every statin has the same physiochemical characteristics. Although cytochrome P450 3A4 does not metabolize pravastatin, fluvastatin, or rosuvastatin, it does metabolize some statins, including atorvastatin, simvastatin, and lovastatin. These statins are therefore known as 3A4 substrates and are subject to phase I metabolism.[16].

The pharmacokinetics of simvastatin and atorvastatin, two 3A4 substrates, were significantly altered when given with different 3A4 inhibitors; the incidence of myopathy increased by up to five times. It is noteworthy that whilst cerivastatin and fenofibrate were responsible for 88% (533 of 606) of the reports of rhabdomyolysis, their use alone only accounted for 2.3% (14 of 606) of the cases of rhabdomyolysis using statin and fibrate treatment [65]. According to new research, gemfibrozil's capacity to prevent statin glucuronidation may contribute to the elevated myotoxicity observed with gemfibrozil/statin therapy by slowing down the rate at which statins are eliminated from the body and raising their plasma concentrations [17-19]. Rhabdomyolysis caused by trauma can also result from high-voltage electrical injuries, such as those caused by lightning strikes or electrocution. Rhabdomyolysis is thought to occur in up to 10% of people who survive the original electrical injury [20].

Bacterial rhabdomyolysis is usually associated with Legionella bacteria [1]. The development of rhabdomyolysis has also been linked to viral infections, most frequently influenza A and B viruses [21].  In patients who had rhabdomyolysis, AKI was linked to increased rates of opiate and cocaine usage. An overdose of opioids can result in hypotension, which can cause AKI in rhabdomyolysis [22]. Additionally, patients who experienced RM as a result of severe consumption of alcohol, bee stings, or sepsis were more likely to develop stage II–III AKI. The severe AKI group had a higher observation frequency of patients with RM due to acute drinking, bee stings, and sepsis than from other causes [23]. It was determined that the primary risk factors of AKI with rhabdomyolysis were decreased levels of calcium, higher urine OB, AST, and uric acid levels, and multiple organ failure with underlying illnesses. [24]. Higher rates of rhabdomyolysis after exercise or effort may also be attributed to increased temperature and humidity [25]. Rhabdomyolysis can be brought on by heat stroke, NMS, and MH. It’s interesting to note that females almost never have exertional heat stroke, possibly as a result of women's higher oestrogen levels protecting their muscles [26]. However, these factors which cause rhabdomyolysis could contribute to the risk factors for acute, severe kidney damage, when the patient does not treat properly for rhabdomyolysis. Practically women are more prone to acute kidney injury than males and trauma is also most leading factor for acute kidney injury. Rhabdomyolysis-induced [acute kidney injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/acute-kidney-failure) occurs following damage to the [muscular sarcolemma](https://www.sciencedirect.com/topics/medicine-and-dentistry/sarcolemma) sheath, resulting in the leakage of [myoglobin](https://www.sciencedirect.com/topics/medicine-and-dentistry/myoglobin) and other metabolites that cause [kidney damage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/kidney-injury). Currently, the sole recommended clinical treatment for the injury is aggressive [fluid resuscitation](https://www.sciencedirect.com/topics/medicine-and-dentistry/fluid-resuscitation), but other potential therapies, including pretreatments for those at risk for developing the injury, are under investigation [63].

**PATHOPHYSIOLOGY:**

Although there are several reasons for rhabdomyolysis, the primary cause of muscle damage and necrosis involves direct myocyte death or a breakdown in the energy source of the muscle cell. Actin-myosin linkage is created when too much calcium enters the sarcoplasm, and Contraction of muscles is an active process utilizing adenosine triphosphate (ATP). The intracellular electrolyte homeostasis is lost upon any lesion that compromises the ATP, Ion pathways and the plasma membrane. Proteases and phospholipases that are dependent on calcium are also activated by an excess of intracellular calcium, which leads to the disintegration of cell membranes and the disturbance of ion channels, such as the Na and ca pump and the Na + ca  exchangers. Reperfusion releases many organic acids, creatine kinase, phosphate, potassium, myoglobin, and other breakdown products in blood circulation. It also induces mylosis necrosis of the muscle fibres. Leukocytes move into the damaged muscle and create more cytokines, free radicals, and prostaglandins [27].

The causes of rhabdomyolysis-induced acute kidney damage (AKI) are complicated. Excess myoglobin produced during rhabdomyolysis causes oxidative damage to lipids. This leads directly to renal vasoconstriction by allowing the over-release of endothelin, thromboxane A2, isoprostanes (vasoconstrictors), decreased nitric oxide (vasodilators), necrotic tumour factor-alpha, and endothelin (vasodilators). Myoglobinuria, or brown-reddish tea-coloured urine, is caused by excess myoglobinuria after rhabdomyolysis, which surpasses the renal metabolic threshold. The following conditions can lead to the development of AKI: ischemia, cellular damage in PCT, volume depletion, intrarenal vasoconstriction, and the development of the myoglobin-Tamm-Horsfall protein complex limits DCT activity. [28]. Renal impairment brought on by rhabdomyolysis is accompanied by renal vasoconstriction, tubular toxicity, and luminal blockage. An increasing body of research indicates that lipid peroxidation-induced kidney damage plays a significant role in the aetiology of renal failure. Examined is the suggested pivotal role of free iron in this process. According to recent research, the heme core of myoglobin can cause kidney damage and lipid peroxidation without releasing free iron. This is because the heme group undergoes redox cycling from ferrous to ferric and Ferryl oxidation states. Alkaline circumstances prevent lipid peroxidation brought on by myoglobin by stabilizing the reactive Ferrell myoglobin complex [29]. Rhabdomyolysis-induced Aki in spite of a normal CPK. This is a rare presentation because rhabdomyolysis is normally indicated by elevated CPK levels, which are typically confirmed by raised CPK of at least five times the upper limit of normal [30].

Ischemia is the most typical cause of AKI. Damage caused by ischaemia is especially prone to affect the kidney, since it can cause endothelial damage, constriction of the blood vessels, and the start of inflammatory processes. Anaemia reduces blood supply to essential nephron structures, which contributes to this susceptibility. The connections between blood vessels and renal tubules in the kidney's outer medulla may help to explain some of this sensitivity. When efficient renal perfusion declines, the epithelial cells can't keep up the levels of intracellular ATP needed for vital cell functions. When ATP is depleted, cells become injured and may die by necrosis or apoptosis if they deserve enough an ischemic insult can affect any section of the nephron, but proximal tubular cells are more commonly injured [31]. By direct microbial invasion of the tubular epithelia or white cell tubular cast development, infections can result in obstructive AKI and ATI/ATN. There is always an associated interstitial nephritis. Adenovirus nephropathy in transplant or immunocompromised patients, as well as coronaviruses (such as COVID-19 and influenza) and ATI in the setting of polyomavirus, CMV, or adenovirus [ 32-33].



Figure :- mechanism of acute kidney injury



Figure 2-acute kidney damage due to ischemia

**Diagnosis:**

A targeted laboratory evaluation and prompt clinician recognition of the risk of rhabdomyolysis are crucial for early identification and treatment of the condition, which can greatly improve prognosis. In order to obtain an early diagnosis, ultrasound might partially induce the likelihood of rhabdomyolysis. One common examination technique for muscle soreness is ultrasound. Clinicians should confirm blood CK levels and conduct additional research into the likelihood of rhabdomyolysis when ultrasound detects suspected indications of the condition in order to identify and treat rhabdomyolysis as soon as possible. When rhabdomyolysis is examined under a microscope, extensive vacuolization and destruction of the microfibrillar architecture may be seen. Muscle texture will become blurry in ultrasound imaging due to the breakdown of muscle fibre structure; a significant number of vacuoles scattered throughout the cells will increase the muscle's echo, giving the appearance of ground glass. Consequently, "blurred muscle fibre structure, ground glass-like changes" is an ultrasonography symptom that is specific to rhabdomyolysis and was present in every case [34-37].

The most accurate and sensitive marker of muscle damage is an elevated blood creatinine (CK) level, which is typically between 45 and 170 U/L. There exists a clear correlation between the degree of elevation and the severity of the injury. Rhabdomyolysis is commonly diagnosed in laboratories using serum creatinine levels multiple times at the baseline when there is no brain or cardiac damage. According to some experts, the gold standard for diagnosing exertional rhabdomyolysis should be a blood CK level of more than 12,000 U/L. Acute rhabdomyolysis patients may have serum CK levels greater than 100,000 U/L, and skeletal muscle damage usually results in elevated CK-MM band isoenzymes [38-40]. Only if the history suggests that there is a urinary tract obstruction should renal ultrasonography be performed, as it may show signs of a postrenal source of acute kidney injury [41]. Prerenal azotaemia is diagnosed by fractional elimination of sodium and urea. Acute kidney failure may have a prerenal aetiology if sodium fractional excretion is less than 1%; however, a number higher than 2% indicates an underlying cause.

The effectiveness of this test can be significantly impacted by acute glomerulonephritis, cirrhosis, contrast-induced nephropathy, sepsis, myoglobinuria, diuretic use of medications, and congestive heart failure. The effectiveness of this test can be significantly impacted by acute glomerulonephritis, cirrhosis, contrast-induced nephropathy, sepsis, myoglobinuria, diuretic use of medications, and congestive heart failure [42-43]. The initial indicators of damage to the kidneys that have been hypothesized throughout the past few decades include urine cystatin C urinary Kidney Injury Molecule-1 (KIM-1) [56], urine interleukin 18 (IL-18), and urinary/plasma neutrophil gelatinase-associated lipocalin (NGAL). A small number of biomarkers have been incorporated into clinical practice, despite being examined in various contexts. Numerous studies have demonstrated NGAL's value for earlier AKI evaluation, severity evaluation, and dialysis requirement prediction. Tissue inhibition for metalloproteinases-2 (TIMP-2), cell cycle arrest biomarkers, and insulin-like growing factor-binding protein 7 (IGFBP7) have recently surfaced, providing mechanistic insight into the physiopathology of AKI and boosting expectations for early identification and treatment [44].

**EPIDEMIOLOGY:**

According to the emergence of comorbidities, AKI is associated with a more severe hospital course, according to an analysis of over 100,000 hospitalizations nationwide related to rhabdomyolysis. In our study, 24% of hospitalizations related to rhabdomyolysis had an overall incidence of AKI. Previous data, based on limited population studies, revealed a wide range of incidence (10–67%), which may vary depending on the etiology of rhabdomyolysis [64]. It has been noted that individuals with combat-injury-induced rhabdomyolysis and all-cause rhabdomyolysis have greater fatality rates when they have AKI [45]. ARF is thought to develop in 10%–40% of rhabdomyolysis patients, and rhabdomyolysis may be the cause of up to 15% of ARF cases overall [46]. According to earlier research, the proportion of kids with rhabdomyolysis who go on to develop ARF could be as high as 42%–50% [47].

**TREATMENT:**

Regardless of the underlying cause, when rhabdomyolysis is suspected, one of the most important therapy goals is to prevent severe renal injury [48]. The best defence against azotaemia is to drink enough water, 1.5 L/h. Additionally, drugs like statins that are known to raise the risk of rhabdomyolysis must be stopped right away.[49]. To minimize damage to the kidneys and muscles in compartment syndrome, fasciotomy can be necessary. Intravenous fluid therapy with balanced crystalloid or 0.9% NaCl at dosages up to 1.5 L/h is the primary line therapy for patients having rhabdomyolysis. This is carried out to produce a diuresis of 300 mL/h. Because vigorous fluid therapy refills the vascular bed and restores renal perfusion, it is very beneficial for patients with AKI [50-52]. RRT may be necessary for this situation as CK and myoglobin levels rise. Patients with rhabdomyolysis may get continual replacement kidney treatment or daily haemodialysis. [53-54]. The use of diuretics in fluid treatment is still debatable. Mannitol and loop diuretics are the ones we think of most frequently.

Mannitol inhibits myoglobin precipitation and promotes urine flow. Until there is a further justification, the use of loop diuretics (furosemide and torsemide) in RM has not been proven to be specifically indicated [55-56]. Anti-inflammatory agent: Liposome-encapsulated clodronate (LEC), a specific macrophage depletor, reduces apoptosis and improves renal function by decreasing the number of invasion macrophages. {animal studies} [57-58]. Anti-oxidant-By lowering ferric myoglobin to its reduced form, acetaminophen, a peroxidase substrate, prevents lipid peroxidation. Due to the fact that myoglobin deposits were equally prevalent in treated and untreated kidneys, the benefits of acetaminophen were not dependent on the reduction of muscle injury. Fascinatingly, this effect was shown when acetaminophen was administered both before and after the damage was caused, suggesting that this medication can be utilized for both prophylaxis and treatment [59-60]. Unfortunately, there is very little use of flavonoids in the treatment of AKI because of their low permeability and water solubility. Improved water solubility- the effectiveness and availability of flavonoids can be enhanced using nanocarriers. Zhang et al. synthesized water-soluble eupafolin nanoparticles (NPs) by reducing the particle size of the original eupafolin without endangering normal renal cells. This was accomplished by utilizing polyvinyl alcohol (PVA) and Eudragit E100. Furthermore, eupafolin NPs' enhanced anti-oxidant and anti-inflammatory qualities can stop kidney damage brought on by LPS [61].

**PREVENTION AND FOLLOW-UP OF AKI:**

A recent study indicates that risk categorization for AKI can help minimize the occurrence of AKI and facilitate the implementation of appropriate care, even though there is currently no proof of benefit for long-term renal outcomes. Phased treatment of acute kidney injury (AKI) should start with community-based risk assessment and prevention, move on to hospital-based AKI avoidance and management optimisation, and find with Acute Disease Quality Initiative (ADQI) surveillance and prevention of CKD progression and RECAUTION. "Quality Improvement for AKI" was the topic of discussion at the most recent Acute Disease Quality Initiative (ADQI) meeting. Healthcare providers should identify individuals who are at risk and carry out preventive measures to lower the incidence of AKI, as it is thought that at least 50% of AKI episodes start in a community setting. According to the ADQI consensus and the KDIGO guidelines, individuals with an incident of AKI should see a nephrologist within three months of the episode to monitor renal recovery and/or kidney disease progression. It is important to base the outlook and outcome assessment on proteinuria and kidney function along with medication reconciliation, patient education on avoiding nephrotoxic medicines, and the implementation of preventive measures to stop the progression of chronic renal disease. To find high-risk patients, the best time for nephrology follow-up, and strategies to enhance patient outcomes, more research is needed. [62].

**CONCLUSION:**

The intricate process of rhabdomyolysis is linked to both morbidity and mortality. In addition to medicines, overdoses, infections, muscular ischemia, abnormalities in metabolism and electrolytes, genetic problems, prolonged periods of bed rest or activity, and temperature-induced illnesses like NMS and MH are some potential causes of the syndrome, even if physical trauma is the primary cause. It offers a significant understanding of the complex interactions influencing the development of AKI in rhabdomyolysis patients. Early detection and assessment are essential for preventing AKI and improving patient outcomes. These results could assist in avoiding and treating RM patients with AKI**.**

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