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Rhabdomyolysis-associated Acute Kidney Injury: from pathogenic mechanisms to the therapeutic use of sorbents

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Short title: Rhabdomyolysis-associated AKI

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Abstract

Background: Rhabdomyolysis is a pathological process that results from the breakdown of skeletal muscle fibers, leading to the release of intracellular contents such as myoglobin, creatine kinase, potassium, and phosphate into the systemic circulation. One of the most critical and life-threatening complications of Rhabdomyolysis is Acute Kidney Injury (RA-AKI), which occurs in 10-50% of patients with severe rhabdomyolysis.

Summary: The mechanisms of RA-AKI include myoglobin-induced oxidative injury, tubular obstruction by casts, renal vasoconstriction, hypoperfusion, and triggering of the inflammatory response. The mainstay of therapy is fluid resuscitation and early conservative interventions to prevent myoglobin precipitation in the tubular lumen. Emerging interventions using Renal Replacement Therapy (RRT) using selected types of membranes represent a significant advancement in the management of the most severe forms of RA-AKI. Hemoadsorption alone or in series with a RRT circuit (Sequential Therapies) offers a promising approach for a more efficient and faster removal of myoglobin, addressing one of the primary drivers of kidney injury. Furthermore, cytokine adsorption could offer a dual beneficial effect by reducing the systemic inflammatory response that exacerbates kidney damage during rhabdomyolysis.

Key messages: The aim of this narrative review is to analyze the causes and the pathogenic mechanisms of RA-AKI and to explore the therapeutic role of specific RRT modalities and sorbent-based extracorporeal therapies.

Introduction

Rhabdomyolysis is characterized by the breakdown of skeletal muscle fibers, leading to the release of intracellular components, particularly myoglobin into the bloodstream. This can result from a wide range of causes including trauma, extreme physical exercise, drug toxicity, seizures, infections, and ischemia-reperfusion injury [1].

Myoglobin, a 17 kDa oxygen binding protein, is known to play a key role in the development of Rhabdomyolyis-associated Acute Kidney Injury (RA-AKI) due to its direct nephrotoxic activity on tubular epithelial cells at high concentrations. Of note, when muscle damage is more severe, the risk of RA-AKI increases with a reported incidence as high as 50% [2].

The pathophysiology of RA-AKI is complex and multifactorial, involving direct myoglobin toxicity, oxidative stress, renal ischemia, and triggering of inflammatory processes [3]. Traditional management strategies focus on fluid resuscitation and correction of electrolyte imbalances. However, there is a growing interest to evaluate the role of extracorporeal therapies for the management of RA-AKI: in this setting, the main purpose is to induce a faster clearance of both myoglobin and inflammatory cytokines that are involved in the pathogenic mechanisms of this life-threatening syndrome.

The aim of this narrative review is to summarize the recent findings on RA-AKI pathogenesis, highlighting new potential therapeutical approaches including different modalities of Renal Replacement Therapies (RRT) used alone or in combination with sorbents, according to the recent definition of sequential therapies.

Main Text

Definition, epidemiology and causes of RA-AKI

Likewise all the other forms of AKI, RA-AKI should be classified and graded according to the KDIGO 2012 criteria based on both serum creatinine levels and urinary output [4,5]. This classification allows a better risk stratification strategy including the identification of patients at high risk of need for RRT and of worse outcome. However, in RA-AKI, the KDIGO criteria should be combined with the identification in the serum of specific biomarkers of muscle injury such as myoglobin and Creatine Kinase (CK). Even though the detection of myoglobin in the serum is considered pathognomonic for rhabdomyolysis, CK is considered a more useful marker for diagnosis and severity assessment, due to its delayed clearance [6]. Of note, rhabdomyolysis is commonly diagnosed by referring to specific CK cut-off values, the majority of which is a level >1000 U/L or at least five times above the upper limit of normal reference values [7]. A recent consensus paper concerning the use of hemoadsorption in RA-AKI [8] suggested the definition of severe rhabdomyolysis in the presence of CK level > 5.000 U/L and myoglobin >10.000 ng/ml. Moreover, in the case that both parameters could be available, myoglobin should be interpreted with priority considering that, apart its use as biomarker, this protein can directly contribute to the development of AKI due to its direct toxic effects on tubular epithelial cells [8].

Several previous studies showed the association of AKI with different causes of rhabdomyolyis. In particular, an increasing rate of in-hospital mortality and development of AKI requiring RRT has been shown for the following causes: myopathy/myositis, severe exercise, seizures/syncope, statin-associated myopathy, trauma, immobilization, surgery (orthopedic, cardiac, vascular, abdominal, toracic), burns, sepsis, compartment syndrome and cardiac arrest [9].

Pathogenic mechanisms of RA-AKI

The main pathogenic mechanisms of RA-AKI are represented in Figure 1 and briefly discussed below.

Myoglobin-Induced Tubular Toxicity and Oxidative Stress

Myoglobin is the primary mediator of renal injury in rhabdomyolysis: after being released into the circulation, myoglobin is freely filtered by the glomeruli due to its small size (~17 kDa). However, under conditions of hypovolemia or acidosis, the concentration of filtered myoglobin is increased, overwhelming kidney's reabsorptive capacity. Myoglobin toxicity can be mainly ascribed to its heme component which dissociates and releases free iron, catalyzing the Fenton reaction and finally generating Reactive Oxygen Species (ROS) [6].

The triggering of oxidative stress leads to lipid peroxidation and mitochondrial dysfunction within kidney tubular epithelial cells [7]. Studies in animal models of RA-AKI have demonstrated that the administration of iron chelators or anti-oxidants such as N-acetylcysteine can significantly reduce myoglobin-induced oxidative injury, emphasizing the pivotal role of ROS in the pathogenesis of RA-AKI [10]. Histological evidence from renal biopsies obtained from rhabdomyolysis patients frequently revealed the presence of Acute Tubular Necrosis (ATN), characterized by a prominent oxidative damage in proximal tubular epithelial cells [11].

Tubular Obstruction and Cast Formation

The combination of high levels of myoglobin with Tamm-Horsfall Protein (THP), the most abundant urinary molecule in both physiologic and pathologic conditions, can facilitate the formation of casts within tubular lumen, especially in the presence of an acidic environment. Cast precipitation leads to the obstruction of urinary flow primarily in the distal convoluted tubules and collecting ducts, where pH is lower [12]. Myoglobin-THP interaction is responsible not only for cast formation and for tubular obstruction, but also contributes to elevated intratubular pressure, which in turn reduces Glomerular Filtration Rate (GFR), thus exacerbating the loss of renal function. In autopsy examinations of patients died for rhabdomyolysis, obstructive myoglobin-containing casts are frequently observed, confirming the direct role of tubular obstruction in the pathophysiology of RA-AKI [2]. Furthermore, since acidic conditions worsen this process, urinary alkalinization could be considered a valid therapeutic strategy [13].

Renal Vasoconstriction and Ischemic Damage

The pathogenesis of RA-AKI could also be influenced by severe alterations of renal hemodynamics. In rhabdomyolysis, the release of vasoactive substances such as endothelin-1, together with the depletion of vasodilators like nitric oxide (NO), results in significant renal vasoconstriction [14]. Myoglobin, particularly in its oxidized form, has been shown to scavenge NO, reducing its bioavailability and contributing to endothelial dysfunction and vasoconstriction [15]. This biological process, combined with the presence of hypovolemia and systemic inflammation, worsens renal ischemia and consequently tubular injury. Several studies demonstrated that the administration of endothelin receptor antagonists or NO donors could improve renal blood flow, thus reducing the development and the severity of AKI in experimental models of rhabdomyolysis [16].

Systemic Inflammation and Cytokine Release

Rhabdomyolysis is also associated with a systemic inflammatory response characterized by increased circulating levels of cytokines such as TNF-α, IL-6, and IL-1β [2]. These mediators contribute to endothelial activation, increased vascular permeability, and tubular apoptotic cell death. The innate immune response is triggered by Damage-Associated Molecular Patterns (DAMPs) released from necrotic muscle cells, further amplifying inflammation and promoting tissue leukocyte infiltration [17]. This cytokine-driven inflammatory response is a critical factor in the development and maintenance of RA-AKI, particularly in the concomitant presence of sepsis and/or multiple organ failure. Elevated levels of TNF-α and IL-6 have been correlated with worse renal outcomes in patients with rhabdomyolysis, suggesting that targeting these cytokines could offer therapeutic benefits [18]. Moreover, as reported in other forms of AKI and in particular that related to sepsis, TNF-α, IL-6 and other inflammatory mediators such as IL-18, Fas-Ligand, and CD40-Ligand are not only biomarkers of inflammation and worse outcomes, but also mediators of microvascular endothelial and tubular epithelial cell injury [19]. Indeed, these cytokines can interact with specific counter-receptors located on the surface of kidney resident cells, triggering different detrimental biological processes such as mitochondrial dysfunction, caspase activation, inflammation, apoptosis, and senescence [19]. These processes driven by inflammatory cytokines may enhance myoglobin-induced endothelial and tubular damage, thus sustaining RA-AKI.

Therapeutic approaches for RA-AKI

A brief overview of conservative therapies and extracorporeal blood purification approaches for RA-AKI are described in Figure 2 and reported below. The aim of the conservative therapeutic approaches is the limitation of AKI incidence, particularly the most severe forms requiring RRT. The purpose of RRT and other adsorption-based extracorporeal blood purification therapies is obviously the replacement of renal function, but also the possible protection of the kidney from the deleterious activities of myoglobin and inflammatory cytokines.

Conservative Therapeutic Approaches for RA-AKI

Fluid Resuscitation

The cornerstone of RA-AKI management is early and aggressive fluid resuscitation. The primary objective is restoring intravascular volume, maintaining renal perfusion, and diluting nephrotoxins such as myoglobin and inflammatory mediators. Isotonic saline is the fluid of choice, as it can expand intravascular volume without exacerbating hyperkalemia, a common complication observed during rhabdomyolysis [20]. Fluid resuscitation aims to maintain a urinary output of at least 200-300 mL/hour to prevent the precipitation of myoglobin in the tubular lumen. Although fluid therapy is widely accepted, the optimal volume and rate of infusion still remains a matter of debate. Some guidelines suggest a fluid administration rate of 10-12 liters per day for the first 24-48 hours in patients at high risk for RA-AKI, whereas others recommend titration based on urinary output and hemodynamic parameters [13]. From a quantitative point of view, an aggressive rate of fluid resuscitation may result in volume overload, respiratory failure, worsening of cardiac function and, hypothetically, oedema-induced multiple organ failure including AKI. Based on these considerations, recent Randomized Clinical Trials (RCTs), have clearly demonstrated a significant association between volume overload and mortality [21]. On the other hand, the choice of fluid composition is crucial to avoid or to limit RA-AKI: according to the Stewart approach, high chloride concentration may alter

strong ion difference (SID) and consequently the acid-base balance favouring the development of hyperchloremic acidosis: this acid-base modification may trigger other adverse events such as immunological alterations, gastrointestinal dysfunction, and AKI correlated with decreased renal blood flow [22].

Urinary Alkalinization

The choice of fluid composition has also a strong impact on urinary alkalinization, a key mechanism to avoid intratubular myoglobin cast formation. In this context, alkalinizing urine with sodium bicarbonate to reach a pH ≥6.5 is a long-standing therapeutic approach aimed to prevent the precipitation of myoglobin and uric acid in the tubules [23]. By increasing the solubility of these nephrotoxic substances, urinary alkalinization may antagonize the vasoconstrictive effect of myoglobin and reduce the risk of tubular obstruction, lipid peroxidation and the clinical persistence of RA-AKI. However, clinical evidence supporting the routinary use of bicarbonate therapy remains controversial: some studies have shown a reduction of AKI incidence, whereas others have found no significant difference in outcomes compared to saline alone [24]. It should be acknowledged that sodium bicarbonate administration may lead to an increased risk of metabolic alkalosis, hypocalcemia, and as already stated, volume overload, suggesting that this strategy should be judiciously used in selected patients at the right time and with a personalized therapeutic approach [25].

Electrolyte Management

Rhabdomyolysis frequently leads to the release of intracellular potassium, phosphate, and uric acid into the bloodstream, resulting in hyperkalemia, hyperphosphatemia, and hyperuricemia, all of which can worsen renal injury [26]. Of interest, hyperkalemia is a life-threatening complication that requires prompt correction to prevent fatal cardiac arrhythmias. The management of hyperkalemia typically involves the use of calcium gluconate, insulin with glucose, sodium bicarbonate, and new potassium-binders such as patiromer and sodium zirconium cyclosilicate. In the most severe cases or when conservative measures fail, RRT may be necessary to remove the excess of potassium and to correct acid-base imbalance [27].

Diuretics

The use of diuretics in the management of RA-AKI remains controversial. Although intravenous fluid resuscitation is widely accepted as the first line of treatment, the role of diuretics, particularly mannitol and loop diuretics like furosemide, is far to be fully elucidated [13].

Mannitol is an osmotic diuretic that is used in RA-AKI with the aim of increasing urinary output, reducing intratubular myoglobin precipitation, cast formation and scavenging free radicals, thereby minimizing tubular cell injury [28,29]. However, evidence supporting its efficacy in improving renal outcomes or reducing mortality is limited. Some studies have suggested that mannitol may be beneficial when administered after adequate fluid resuscitation, but the lack of RCTs makes its routinary use uncertain. Clinical investigations assessing mannitol's efficacy in preventing heme-associated AKI are limited by their retrospective design, frequent co-administration of bicarbonate, and inconsistent results across studies [30-33]. Additionally, mannitol should be avoided in patients with oliguria, as it can exacerbate renal dysfunction. Excessive administration of mannitol, particularly in individuals with impaired renal function and consequent reduced clearance, may result in significant alterations in fluid and electrolyte balance, including the development of hyperosmolarity, intravascular volume expansion, and hyperosmolar hyponatremia [28].

The consequent rise in plasma osmolality can induce a passive transcellular shift of potassium, thereby increasing its serum concentrations. In patients receiving mannitol, regular monitoring of the plasma osmolal gap is also essential. Therapy should be discontinued if the osmolal gap exceeds 55 mOsm/kg, as this may indicate excessive accumulation and heightened risk of toxicity. Furthermore, mannitol should be withdrawn if the intended diuretic response, defined as a urinary output of approximately 200–300 mL/hour, is not achieved. Finally, accumulation of mannitol exceeding 200 g/day has been associated with a potential worsening of tubular toxicity and renal vasoconstriction.

Loop diuretics are also used to increase urinary output in RA-AKI: however, the administration of furosemide is still controversial. Loop diuretics can lead to increased urinary acidosis and

hypercalciuria, both factors potentially able to accelerate the precipitation of myoglobin in the tubular lumen [34-36]. For these reasons, to date the only indication for the use of loop diuretics in RA-AKI is fluid overload.

Antioxidants

As previously discussed, a significant role in the pathogenic mechanisms of RA-AKI is sustained by lipid peroxidation of tubular cells with generation of ROS [3]. In this perspective, antioxidants may represent an additional therapeutic strategy in the management of RA-AKI by inhibition of lipid peroxidation in tubular cells and redox cycling between ferric and ferryl myoglobin. In this setting, some pharmacologic agents that inhibit myoglobin-redox cycling may represent the best additive therapeutic intervention for patients affected by the most severe form of disease [10]. Preclinical studies have demonstrated that acetaminophen inhibits lipid peroxidation and improves renal function [10]. Furthermore, other antioxidants have shown efficacy in animal models, neutralizing the harmful effect of myoglobin on kidney injury such as N-acetylcysteine, vitamin E, vitamin C [10]. N-acetylcysteine (NAC) works as a precursor of intracellular glutathione and sulfhydryl (GSH) groups, exerting potent antioxidant properties through its scavenging activity on ROS. Furthermore, in experimental rat models, NAC has been shown to attenuate renal injury by inhibiting cellular apoptosis and mitigating oxidative stress [37]. Vitamin E (α-tocopherol) is the primary lipophilic antioxidant placed within cellular membranes, where it plays a crucial role in protecting against lipid peroxidation. Due to these characteristics, it has been proposed as a potential protective agent against myoglobin-induced tubular toxicity [38]. However, due to its lipophilic nature, its effectiveness in preventing the initial oxidation of myoglobin in urine is limited [38]. Vitamin C (ascorbic acid) also exhibits antioxidant properties, with the added advantage of being water-soluble, which likely enables it to inhibit the oxidation of myoglobin in urine [3] and may also reduce proteinuria and hyperuricemia.

<u>Renal Replacement Therapies (RRT) and Plasma Exchange (PEX)</u>

The volume of distribution of myoglobin in the human body remains unclear but it is estimated to be compartmentalized into two primary pools: the first pool is in equilibrium with the vascular compartment that corresponds to approximately 10% of total body weight, and the second one within muscle tissue, which is more difficult to quantify. Based on this consideration, myoglobin clearance is influenced by renal residual function of patients affected by rhabdomyolysis as well as by artificial clearance provided by RRT: both natural and artificial clearance should be carefully evaluated in this setting. Moreover, the vascular and muscle tissue compartments reach the steady-state slowly: for this reason, an extracorporeal blood purification therapy with high efficiency will result in a faster decline of circulating myoglobin levels, thus favouring an intermittent treatment approach. Conversely, a less efficient system, capable of maintaining steady-state plasma myoglobin concentration, may be effective in managing ongoing myoglobin release, requiring continuous treatment [39]. Taking together the data present in the current literature suggest that both intermittent (including a prolonged intermittent strategy) and continuous treatments can be effective in myoglobin removal: however, a strict evaluation of myoglobin plasma levels is strongly recommended together with parameters of renal function and, if allowed by clinical practice and assay availability, inflammatory mediators involved in RA-AKI.

Another important point to consider is the well-known difference in myoglobin clearance between diffusion- and convection-based techniques. Indeed, as already stated, myoglobin is a middle molecule with a molecular weight of about 17 kDa: however, due to its non-spherical shape and electrical charge distribution, its effective hydrodynamic radius is larger than expected based on the Einstein–Stokes equation. As a result, myoglobin exhibits a very low diffusion coefficient, necessitating convective transport for a more efficient clearance. Additionally, its steric properties lead to partial rejection by membrane pores, further limiting its removal via classical dialysis techniques [40]. Concerning convective modalities, another potential limitation is that the theoretic Sieving Coefficient (SC) for myoglobin should range between 0.4 and 0.6 in the presence of ideal conditions such as those observed in aqueous solutions and in the absence of concentration

polarization. However, several factors such as plasma protein interference, high filtration fraction and membrane pore size variability may significantly reduce SC below 0.1, leading to negligible final clearance despite high filtration volumes. Moreover, the use of high convective volume aimed to increase myoglobin and inflammatory cytokine removal could enhance the concentration polarization effect, leading to a significant decrease of clearances due to the formation of a protein cake on the membrane, in particular when Regional Citrate Anticoagulation (RCA) is not chosen as strategy to avoid circuit clotting [41].

Despite clearance efficiency, another relevant point to avoid the protraction of kidney damage is the rate of myoglobin removal. In this setting, the modification of membrane characteristics has been explored in several studies. Considering the effective hydrodynamic radius of myoglobin, high-flux and high-permeability membrane are hypothetically effective in facilitating its removal [42]. An enhanced myoglobin clearance has been demonstrated by using high-permeability dialysis [43] and high-flux hemofiltration [44]. Furthermore, more advanced hyper-permeable dialyzers, such as High Cut-Off (HCO) and Medium Cut-Off (MCO) membranes, offer additional myoglobin removal capabilities [40]. HCO dialyzers exhibit superior clearance compared to high-flux membranes [41] but their use is associated with unintended removal of albumin [45] and coagulation factors [46], which may complicate the clinical condition especially in critically ill patients with severe rhabdomyolysis. MCO are also defined as High Retention Onset (HRO) membranes capable of "internal hemodiafiltration" due to a particular pore composition: this characteristic of enhanced internal convection may allow a more efficient removal of middle molecules including myoglobin [47]. In addition, several studies demonstrated that MCO membranes are also able to remove inflammatory cytokines more efficiently than high flux hemodialysis [48], with a further potential protective effect on RA-AKI.

Last, PEX has been explored as an alternative technique, achieving higher SC than standard high-flux hemofiltration. However, considering the intermittent activity of PEX and the need of its combination with hemodialysis in the presence of AKI, the overall clearance remains limited, making it an inefficient strategy for effective myoglobin removal in this clinical setting.

Use of Sorbents and Sequential Therapies

An alternative modality for myoglobin removal is the use of adsorption-based techniques with polymeric devices. This strategy employs porous beads capable of adsorbing hydrophobic molecules up to 60 kDa in size, including cytokines, bilirubin and, of course, myoglobin [49,50]. As already discussed, this dual ability to remove myoglobin and inflammatory cytokines presents a potential advantage, as both molecules may contribute to the pathogenic mechanisms of RA-AKI [51]. Generally, sorbents present several differences associated with packing density, bead design and porosity, particle diameter, interparticle porosity, path tortuosity, length/diameter and fluid viscosity. However, sorbents exploit the same physical properties to reduce blood levels of different toxins: indeed, the interaction between sorbents and a specific molecule is based on the presence of van der Waals forces, ionic bonds and/or hydrophobic bonds. Similarly to the concept of clearance in diffusive and convective hemodialysis, adsorption-based removal of a substance is related to the knowledge of the Mass Transfer Zone (MTZ) and solute adsorption isotherm curves. For this reason, it is mandatory to perform kinetic studies with specific sorbents potentially able to remove one or more toxic molecules.

Based on the previous observations, the effectiveness of myoglobin removal by direct hemoadsorption has been evaluated by assessing the percentage reduction of plasma levels at each passage through a specific sorbent: initially 80% reduction was observed, which then declined to 40%, 20%, 15%, and 12% at 30 minutes, 2 hours, 4 hours, and 8 hours, respectively [52]. The overall clearance is determined by the plasma flow rate and the percentage reduction of myoglobin, which itself is influenced by its plasma concentration. Of interest, the saturation kinetics of hemoadsorption appears to be independent from myoglobin concentration, suggesting the presence of a competitive binding by other circulating molecules to adsorption sites within the cartridge. As a result, the efficacy of myoglobin removal decreases over the time, and the sorbent should ideally be replaced

every 8 to 12 hours to maintain effective removal when a further reduction of plasma levels is required. However, it should be emphasized that the saturation of adsorptive properties and consequently the timing of cartridge replacement are strongly influenced by the persistence of the causes of rhabdomyolysis with an unceasing endogenous release of myoglobin in the bloodstream. Another relevant point is that in some studies, the control group received CVVHD with a high cut-off hemofilter using high blood and dialysate flow rates for consecutive 48 hours: in this setting, the rationale is trying to enhance myoglobin and inflammatory cytokine removal by increasing membrane pore size. However, in comparison to the high-cut-off hemofilter, myoglobin reduction by adsorption cartridges (CytoSorb) was more efficient [52].

The Consensus Statement by the Hemoadsorbtion in Rhabdomyolysis Task Force confirmed that hemoadsorption could be considered a valid option for removing myoglobin in rhabdomyolysis [8]. When myoglobin level is higher than a cut-off of 10.000 ng/ml, hemoadsorption should be considered as soon as possible (within 24 h of admission) and the cartridge should be replaced every 8–12 h until myoglobin reaches level lower than this cut-off. In addition, hemoadsorption should be continued until the myoglobin concentrations are stably lower than 5000 ng/ml. In the case that myoglobin level cannot be easily determined for local organization reasons, hemoadsorption discontinuation should be based on clinical trend and CK levels. Taken together, these data suggest that a closer evaluation of biomarker levels (myoglobin and when not available CK) could help not only to better understand the process of care of RA-AKI patients, but also to determine the saturation point of the cartridge in correlation with endogenous myoglobin release, and consequently the best moment for cartridge replacement.

Recently, in the prospective Cyto-SOLVE study (NCT04913298) that included patients with severe rhabdomyolysis (plasma myoglobin > 5000 ng/ml), Graf et al. showed that the CytoSorb cartridge efficiently eliminated myoglobin: however, the adsorption capacity rapidly decreased after 3 hours, suggesting that an early change of the adsorber might increase the efficacy in patients with severe rhabdomyolysis [53]. Furthermore, Grafe et al. showed that the use of CytoSorb might positively affect renal recovery in patients with severe rhabdomyolysis (myoglobin levels >10,000 ng/ml) under RRT. Of interest, the probability of renal function recovery was significantly higher in the group treated with Cytosorb (31.4%) in comparison to control group (11.4%). Similar results were observed considering patients who survived 30 days (kidney recovery in the Cytosorb group 61.1% vs. 37.6% in the control group) [54]. Another case series of patients with RA-AKI subjected to hemoadsorption using CytoSorb demonstrated an improvement of renal function and a reduction of need for prolonged RRT [55]. However, despite these promising results, large-scale RCTs enrolling a larger number of RA-AKI patients are still needed to confirm the efficacy of hemoadsorption in this clinical setting.

An additional attractive hypothesis is that sorbents could simultaneously remove from the bloodstream myoglobin and inflammatory cytokines: as already discussed, inflammatory mediators can act as DAMPs on kidney resident endothelial and tubular epithelial cells, thus perpetuating tissue damage during RA-AKI. CytoSorb and other approaches such as Coupled Plasma-Filtration and Adsorption (CPFA) in which adsorption is performed on plasma after separation from cells and not on whole blood, have been shown to efficiently remove inflammatory cytokines [56].

Last, sorbent technology can be used alone or in series with standard RRT in an artificial circuit that has been recently defined as “sequential therapy”. Sequential therapies have been adopted mostly in sepsis-associated AKI in which the classical RRT is coupled with a sorbent able to remove whole bacteria/virus, bacterial products such as endotoxin or inflammatory mediators and DAMPs [57]. In the setting of RA-AKI, patients can achieve at the same time a correct balance of fluids, electrolytes and acid-base as well as clearance of waste products by diffusive and/or convective therapies, together with a more efficient and faster removal of myoglobin and inflammatory cytokines by cartridge adsorption. Data from the presented clinical studies paved the way to hypothesize the use of sorbents not only in sequential therapies with RRT, but also their potential protective effect in the prevention of AKI episodes consequent to rhabdomyolysis when used alone. However, the use of sorbent-based therapies in RA-AKI represents a promising advancement, but several challenges

remain to be fully explored. Determining the optimal timing and patient selection for these interventions is critical, as delays in starting extracorporeal therapies may reduce their efficacy. Furthermore, the high cost and limited availability of sorbent cartridges may limit their widespread adoption, particularly in resource-limited settings [58]. Further research is needed to refine these technologies and develop standardized treatment protocols for their use in RA-AKI.

Conclusions

RA-AKI remains a challenging clinical condition in critically ill patients due to its multifactorial causes and pathogenic mechanisms, including direct tubular toxicity of myoglobin, oxidative stress, tubular obstruction and tissue hypoperfusion. The mainstay of therapeutic treatments continues to be aggressive fluid resuscitation and early conservative interventions to prevent myoglobin precipitation in the tubular lumen. Traditional therapeutic strategies, including fluid therapy and urinary alkalinization, aim to dilute myoglobin concentrations and enhance renal perfusion, but their efficacy in the most severe cases is often limited. Emerging dialysis-based interventions using selected types of membranes represent a significant advancement in the management of RA-AKI. Hemoadsorption offers a promising approach for a more efficient and faster removal of myoglobin from the bloodstream, addressing one of the primary drivers of kidney injury. Furthermore, cytokine adsorption could offer a dual beneficial effect by reducing the systemic inflammatory response that exacerbates kidney damage during rhabdomyolysis.

Statements

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Conflict of Interest Statement

VC was a member of the journal's Editorial Board at the time of submission. All the other authors have no conflicts of interest to declare.

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Authors Contributions

EN and MM wrote the paper and designed the figures. VC conceived the paper and contributed to writing part of the manuscript. All the authors approved the final version of the manuscript.

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Figure Legends

Fig. 1. Different causes and pathogenic mechanisms of Rhabdomyolysis-Associated Acute Kidney Injury (RA-AKI), (created with Biorender)

Fig. 2. Natural (diuresis) and artificial (renal replacement therapy and/or hemoadsorption alone or combined in sequential therapies) clearance of myoglobin during Rhabdomyolysis-Associated Acute Kidney Injury (RA-AKI), (created with Biorender).

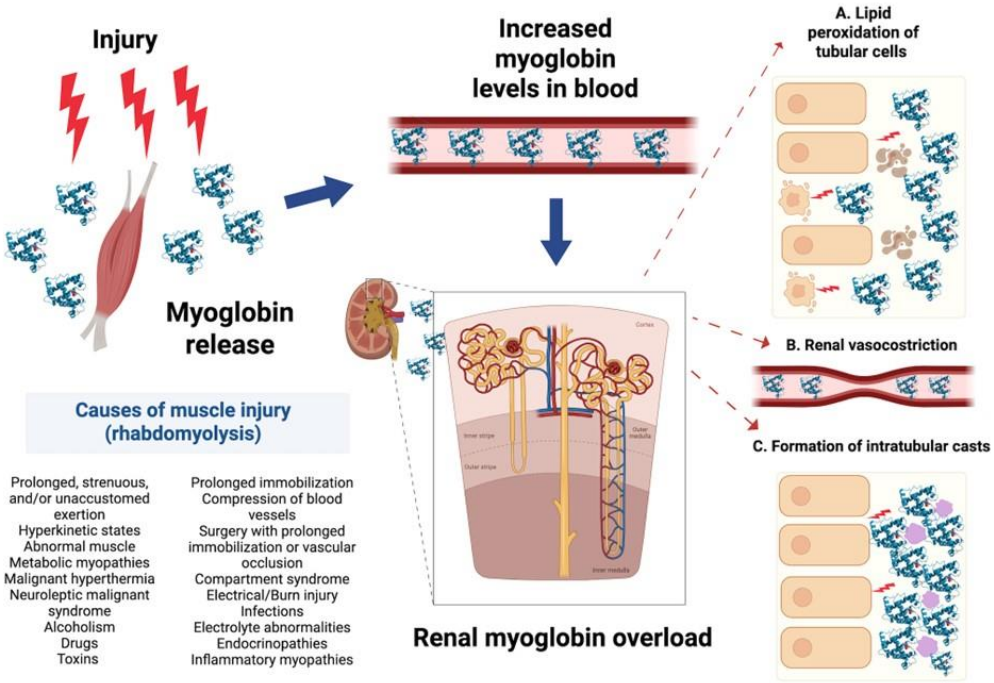

Figure 1

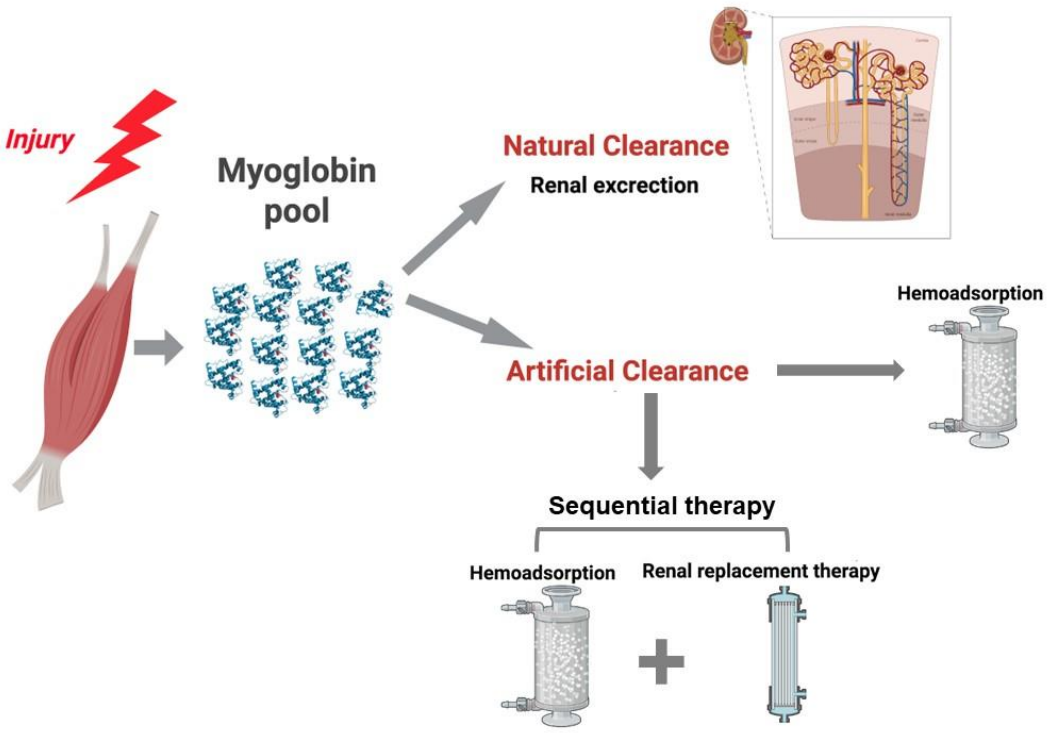

Figure 2