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REVIEW

Molecular Mechanisms of Rhabdomyolysis-Induced Kidney Injury: From Bench to Bedside

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Rhabdomyolysis-induced acute kidney injury (RIAKI) occurs following damage to the muscular sarcolemma sheath, resulting in the leakage of myoglobin and other metabolites that cause kidney damage. Currently, the sole recommended clinical treatment for RIAKI is aggressive fluid resuscitation, but other potential therapies, including pretreatments for those at risk for developing RIAKI, are under investigation. This review outlines the mechanisms and clinical significance of RIAKI, investigational treatments and their specific targets, and the status of ongoing research trials.

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Acute skeletal muscle destruction, termed rhabdomyolysis, can be caused by a variety of etiologies, often in austere environments. Examples include crush injury after an earthquake or blast injury, overexertion during intense athletic activity, and various forms of ischemia-reperfusion injury, including stasis and compression due to general anesthesia, obtundation by other drugs, or vascular occlusion from a tourniquet or thromboembolism.[1,2] Once skeletal muscle contents are in circulation, a well-understood sequence of events occurs, involving the release and potentially lethal accumulation of toxins, including potassium, lactic acid, and myoglobin, leading to multiple organ failures, most notably acute kidney injury (AKI). This phenomenon, referred to as RIAKI, is a common complication affecting up to 46% of patients hospitalized and 80% of those requiring intensive care unit for rhabdomyolysis.[3,4] Even with excellent care, mortality is greater than 15%.[5] The incidence of RIAKI has increased 10-fold in the last decade,[6] fueled in part by popular interest in studio fitness training, such as CrossFit.[7-10] RIAKI is a significant comorbidity for injured soldiers who are are 3 to 4 times more likely to develop rhabdomyolysis than civilians.[11] It is also common in critically ill patients with COVID-19, because COVID-AKI shares many features with RIAKI even without specific markers of RIAKI.[12-19]

RIAKI takes on greater importance as the leading cause of death in immediate survivors of earthquakes. Nearly 400 million people live in cities in earthquake-prone areas, a number that is projected to double by 2050, making RIAKI treatment strategies an essential part of any disaster relief plan. The Renal Disaster Relief Task Force has contributed substantially to saving lives during natural disasters by establishing permanent networks for support as well as response plans.[20-22] However, despite these efforts and more than 50 years of mechanistic insight, significant challenges imposed by austere care environments and investigative limitations have prevented specific therapy for RIAKI from reaching the bedside. Treatment is limited to supportive care, emphasizing early intravenous fluid administration, reduction of serum potassium, and forced diuresis.[2] Studies demonstrate benefits from these treatments, including reduction in need for dialysis,[1,5] but this moderately effective supportive care for RIAKI requires highly trained personnel, extensive access to medical supplies, and advanced modalities such as dialysis.[23] Specific, molecular mechanism-based treatment would be expected to reduce these barriers.

Recent advances in kidney physiology and interest in improving care in austere environments have advanced mechanistic knowledge and brought new hope for

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specific therapy. Herein, we review these challenges and respective advances, focusing on how knowledge gained from preclinical studies can be translated into therapies to improve clinical management in humans. We first present known molecular mechanisms of RIAKI and how these can be used to develop novel therapies. We then briefly summarize current treatment paradigms, emphasizing challenges and shortcomings, and identify potential future directions.

Mechanisms of Rhabdomyolysis-Induced Kidney Injury: Avenues for Novel Therapies

Animal Models of RIAKI

The importance of RIAKI in veterinary medicine is an indication of a critically conserved balance between kidney function and muscle integrity. Many domesticated species develop RIAKI, including racing greyhound dogs, cattle, and horses. Equine exertional rhabdomyolysis (“tying-up” or “azoturia”) develops after intense physical effort or resuming physical work following a long period of inactivity.[24] Physical symptoms in horses are similar to those in humans and include stiff movements, dark reddish urine, and swollen, tender muscles. Exertional rhabdomyolysis is also observed in captured wild animals, including flamingos, baboons, and pronghorn, in response to stress and physical efforts to escape.[25] The conserved nature of this critical muscle-kidney response supports the use of animal models for investigation. In rodents, RIAKI may be induced by direct infusion of myoglobin,[26] administration of drugs that have rhabdomyolysis as an adverse effect (e.g., ciprofloxacin and atorvastatin),[27] crush injury or vascular occlusion,[28] or destruction of muscle by intramuscular glycerol injection.[29–35] It is vital to contextualize mechanistic insights obtained from animal models as folllows: systemic inflammation may be altered, for example, in a glycerol-treated rodent compared with a human with a crush injury.

Primary Injury by Myoglobin

Damage to the sarcolemma sheath of muscle impairs cellular impermeability to sodium and calcium ions, affecting the sodium potassium pump and calcium transporter functionality.[36,37] The resultant high intracellular calcium concentration activates calcium-dependent enzymes that further disrupt cellular structure and allow leakage of myoglobin and other proteins and metabolites into the bloodstream, which can increase vascular permeability leading to interstitial edema and systemic intravascular hypovolemia.[38] Myoglobin is readily filtered into the proximal tubule of the kidney. The route of released myoglobin from muscle to AKI mechanism is illustrated in Figure 1.

As myoglobin transits the nephron, it causes injury at 2 primary points followed by cascading effects. Proximal tubule cells internalize myoglobin via their apical endocytic complex, composed of megalin, cubilin, and amnionless.[39] Within tubular epithelial cells (TECs), heme oxygenase-1 catalyzes the breakdown of heme to iron, carbon monoxide, and biliverdin.[40] Iron in excess of heme oxygenase capacity combines with hydrogen peroxide to create ferric (Fe(3+)) iron. When ferric iron storage capacity is reached, free ferric iron increases hydroxyl ion concentrations via the iron redox cycle; this results in increased formation of reactive oxygen species (ROS) and peroxidation of tubular cell membrane lipids. In addition to iron-mediated hydroxyl radical production, ROS are also generated via the redox cycle creation of lipid peroxidation from excessive myoglobin and other nephrotoxins released from the muscle.[41]

Beyond the proximal convoluted tubule, in the thick ascending limb of the loop of Henle, urinary myoglobin combines with Tamm-Horsfall protein, forming a precipitate. This pH-dependent precipitate forms tubular casts that occlude the distal tubule.[26,42] Although the extent to which AKI depends on this mechanism is controversial, tubular cast obstruction is believed to increase intratubular pressure to above interstitial pressure, reducing vascular inflow and perfusion, promoting inflammation, and directly reducing glomerular filtration rate by altering Starling forces.[43–45]

Intravascular hypovolemia and hypotension are induced by post-trauma muscular edema, leading to sympathetic and renin-angiotensin system-mediated vasoconstriction due to increased angiotensin II, compounding kidney ischemia by impairing the release of vasodilating nitric oxide.[2] Kidney micropuncture in glycerol-induced RIAKI rats demonstrated that low kidney intratubular hydrostatic pressure failed to clear tubular casts; therefore, tubular casts are a consequence of reduced intratubular pressure rather than a cause.[46] Pressure is related to vascular tone; increased vasopressin, noradrenaline, and adrenaline lead to kidney arteriole vasoconstriction, potentially as a compensatory mechanism for tubular obstruction.[47,48] With decreased glomerular filtration rate, urine output decreases, reducing myoglobin’s excretion. Tubular myoglobin concentration rises, augmenting apoptosis and necrosis of TECs as ROS increases. The resultant kidney tubule pathology observed in RIAKI is associated with insufficient compensatory response as follows: inadequate levels of free-radical scavengers, excessive neutrophil adhesion and cytokine release, and impaired microvascular blood flow.[49] Thus myoglobin directly causes injury to tubular epithelial

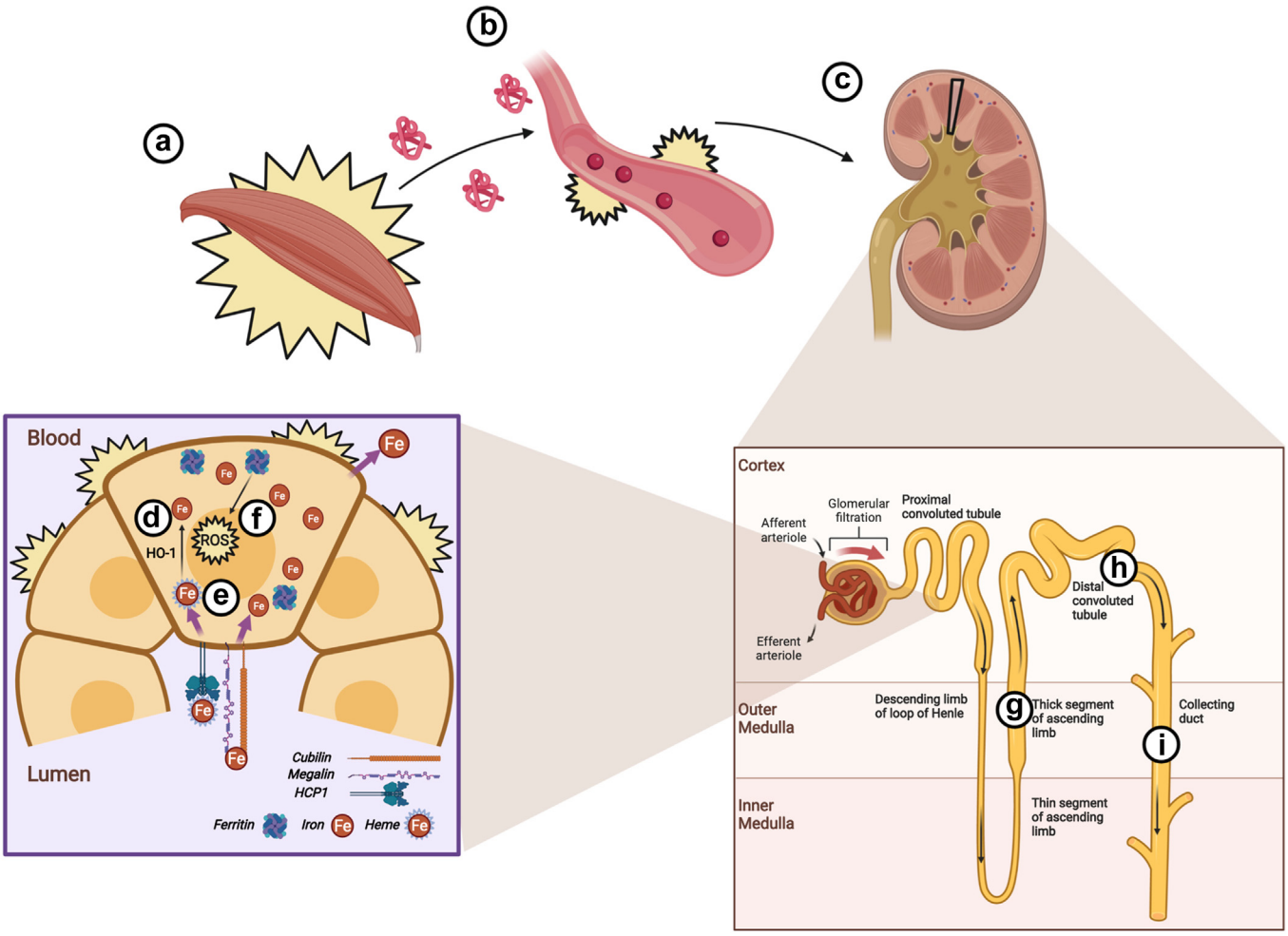

Figure 1. Rhabdomyolysis-induced acute kidney injury is caused by myoglobin. (a) Muscle takes damage and releases myoglobin and other metabolites into circulation. (b) Myoglobin is circulated to the kidney for filtration, causing capillary damage and hypovolemia en route. (c) Myoglobin reaches the kidney and is filtered by the glomerulus. (d) Heme oxygenase-1 degrades heme transported into the proximal tubule by Heme carrier protein 1 to release free ferrous iron. (e) Iron bound to substrates, including myoglobin, is transported into the proximal kidney tubule by megalin and cubilin, further increasing the concentration of free ferrous iron. (f) Ferritin, which oxidizes Fe(2+) to Fe(3+) and stores it, fails to keep up with incoming free ferrous. Fe(2+) reacts with hydrogen peroxide in the Fenton reaction, producing hydroxyl radicals, lipid peroxidation, and overwhelming superoxide dismutase activity, resulting in the formation of damaging reactive oxygen species (ROS). (g) Myoglobin combines with Tamm-Horsfall protein (THP), found in the thick segment of the ascending limb, forming a precipitate. (h) THP-Myoglobin precipitate forms obstructive tubular casts in the distal convoluted tubule. (i) Urine output decreases, resulting in reduced potassium excretion and perturbation of water, pH, and sodium balances, putting further pressure on the vascular system. ROS, reactive oxygen species.

cells and indirectly compounds the injury by direct and indirect vascular effects, including the release of local vasoconstrictors in the vasa recta and peritubular capillaries.[50]

Immune-Mediated Mechanisms

In addition to processes directly related to myoglobin toxicity, products released from skeletal muscle and TEC damage act as immunogenic damage-associated molecular patterns, activating resident macrophages and recruiting circulating immune cells into the kidney interstitium. These cells then produce inflammatory cytokines and additional cytotoxic molecules, resulting in a positive feedback loop, potentiating cell damage. Immune activation is thought to be an essential aspect of RIAKI; however, the immune system's role in RIAKI is still not well understood, and although specific therapies targeting immune cells have been tested in preclinical studies, no translation has occurred. Becuase the immune response represents a "second hit," i.e., a dysfunctional, secondary response to injury, treatments do not necessarily need to be administered immediately after injury, offering a highly translational window for intervention. In this section, we discuss proposed and potential immune-mediated mechanisms of RIAKI and how these may be exploited to develop specific therapies.

Because adaptive immunity takes a week or more to respond to injury, The critical immune mediation to RIAKI is thought to be primarily innate immune-driven. AKI immunology suffers from limited clinical

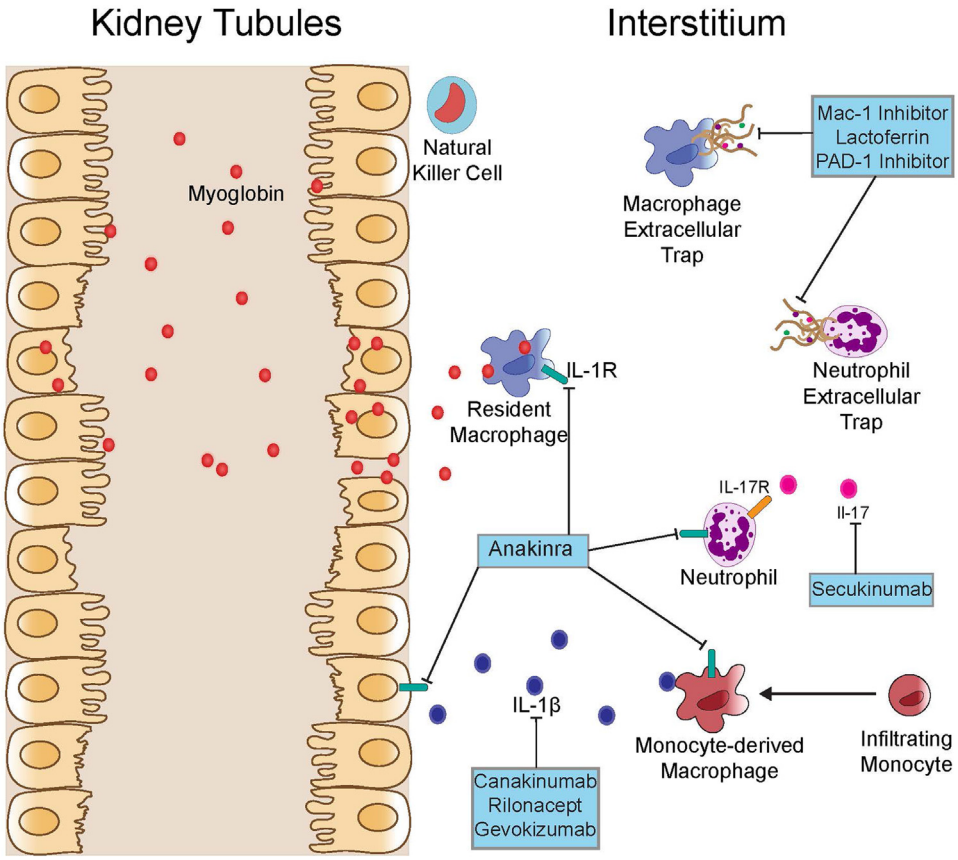

Figure 2. Kidney inflammation during RIAKI and associated molecular targets. Myoglobin from the tubular system infiltrates into the interstitial space, resulting in immune activation. Studies thus far demonstrate that primarily innate immune cells are involved in kidney inflammation during RIAKI. These cells include monocytes, macrophages, natural killer cells, and neutrophils. Resident macrophages express IL-1β receptor, activation of which promotes production of inflammatory cytokines and cytotoxic macrophage extracellular traps, similar to neutrophil extracellular traps. Depicted in this figure are several potential molecular targets that have not yet been investigated in RIAKI. IL-β, interleukin 1 beta; IL-R, interleukin receptor.

data because the field is highly dependent on tissue studies, and biopsies are rarely performed in AKI.[51,52] Thorough immunophenotyping throughout the course of kidney injury in animal models has not been conducted. Case data available demonstrate macrophage (innate) infiltration[53,54] but also T-cell infiltration, suggesting the possibility that there may be adaptive immune involvement.[55] The involvement of immune cells in kidney inflammation during RIAKI is depicted in Figure 2.

Macrophages. Studies performed in rodent models of RIAKI have focused primarily on macrophages, which expand shortly after rhabdomyolysis.[54,56-58] Macrophages are highly heterogeneous innate immune cells with numerous functions,[59] including inflammatory cytokine production, pathogen phagocytosis, ROS generation, tissue repair, and cellular debris scavenging. They can be derived from circulating monocytes that transmigrate into the tissue or from kidney-resident cells of the reticuloendothelial system.[56,57,60]

Macrophages are producers of the most potent proinflammatory cytokine, interleukin 1 beta (IL-1β). IL-1β is an apical inflammatory signaling mediator, because its production is required to generate a mature immune response.[61] However, dysregulated IL-1β production is deleterious. Signaling through the IL-1β receptor results in the transcription of additional inflammatory cytokines.[61] Macrophage-derived IL-1β induces pathology in diabetes,[62] cholestasis,[63] and sepsis.[64] In the kidney, macrophages produce IL-1β during intravenous contrast-induced AKI, inhibition of which prevents kidney injury.[65] In addition, myoglobin induces IL-1β production in macrophages *in vitro*.[56] Lastly, IL-1β induces production of extracellular matrix components in kidney organoids, suggesting a role in the development of fibrosis.[66] Though IL-1β inhibition led to decreased fibrosis and improved glomerular filtration rate in obesity-associated CKD,[67] to our knowledge, no studies have deleted IL-1β specifically from macrophages, which would provide key insight into the mechanisms of macrophage-mediated kidney injury.

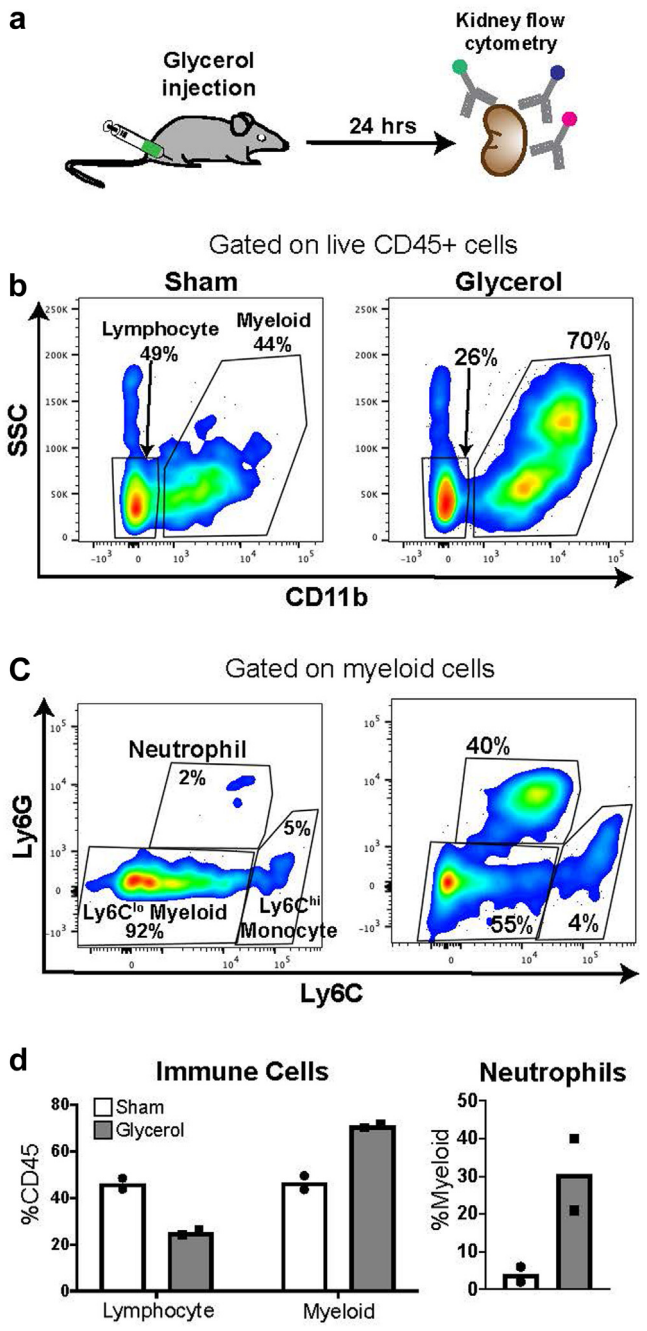

Figure 3. Neutrophils infiltrate the kidney in a mouse model of RIAKI. (a) Schematic of a RIAKI mouse model, generated by glycerol injection into the anterior thigh after 4 hours of water deprivation, resulting in rhabdomyolysis and acute kidney injury. The kidney immune landscape was then characterized by flow cytometry 24 hours after injection. (b) Representative flow cytometry plots depicting immune cells (live, single cell, CD45+), identifying kidney lymphocytes (CD11b-) and myeloid cells (CD11b+) from glycerol- or saline-treated mice. (c) Representative flow cytometry plots depicting different myeloid cell populations from glycerol-treated or saline-treated mice. By gating on CD11b+ myeloid cells, Ly6CloLy6G- myeloid cells (mainly resident macrophages), Ly6ChiLy6G- monocytes (inflammatory monocytes), and Ly6CmidLy6G+ neutrophils were identified. (d) Quantification of kidney immune cells 24 hrs after glycerol injection, demonstrating an increase in myeloid cells, particularly neutrophils, in glycerol-injected mice. $n = 2$/group. CD, cluster of differentiation; CD11b, integrin alpha M; CD45, Protein tyrosine phosphatase, receptor type, C.

Neutrophils. Neutrophils are the most abundant leukocyte population in the circulation and are first responders to injury and infection. Though these cells are essential for an appropriate infection response, inappropriate recruitment can cause tissue damage and drive organ dysfunction during several diseases, such as cancer,[68] atherosclerosis,[69] Alzheimer's disease,[70] and systemic lupus erythematosus.[71] These cells are potent ROS generators, produce a myriad of inflammatory cytokines, phagocytose bacteria, and form cytotoxic neutrophil extracellular traps. Neutrophils accumulate in the kidney during ischemia-repurfusion injury,[72] and neutrophil depletion attenuates kidney damage following ischemia-repurfusion injury.[73] Our laboratory has recently observed a significant increase in neutrophils 24 hours after RIAKI following muscular glycerol injection (Figure 3). However, no studies have investigated the role of neutrophils in RIAKI.

RIAKI Diagnosis and Treatment

Diagnostic Criteria

The most used clinical test for rhabdomyolysis is the measurement of plasma creatine kinase. Typically, a level greater than 10,000 IU/l is considered diagnostic confirmation of severe rhabdomyolysis and an increased risk for RIAKI.[74] However, measuring creatine kinase alone may give a partial and late view of the problem. Hidden compartment syndrome (i.e., compartment syndrome not clinically obvious initially) is an uncommon yet serious condition that can be overlooked in evaluation of a trauma patient and obscure the value of creatinine kinase evaluation. This is especially true for trauma or surgical patients, but can occur in young healthy athletes.[75] Therefore, urine or plasma myoglobin may be useful in certain clinical scenarios. It should also be noted that serum creatinine should not be used to estimate glomerular filtration rate in the context of massive muscle breakdown, which results in a large amount phosphocreatinine (which is converted to creatinine) released into the circulation.

Current Treatment Paradigms

The standard of care for acute rhabdomyolysis is fluid resuscitation directed toward preventing TEC injury by promoting the excretion of myoglobin. Aggressive fluid resuscitation with balanced salt solutions such as normal saline or lactated Ringer's is the first step. Although protocols vary, we demonstrated success using a protocol with initial bolus infusion of 1 to 2 liters followed by additional fluid at a rate of up to 1l/hr, adjusted to urine output, pH, and other physiologic parameters.[76] The goal is to restore intravascular volume and dilute intratubular myoglobin, preventing tubular cell injury. Though this may be challenging in

austere trauma conditions (e.g., earthquakes, combat zones), experiences from previous natural disasters suggest that immediate hydration into a protruding limb before extraction may be life-saving, considering that extraction could take well over an hour.[77,78] Up to 10 liters of intravenous fluid may be required in the first 48 hours of treatment, yet comorbid conditions such as respiratory distress syndrome or chronic heart failure may limit the amount of fluid an injured person can receive, emphasizing the importance of individualized treatment strategy and careful clinical monitoring.

Treatment protocols often include sodium bicarbonate and mannitol in addition to intravenous fluid, sometimes guided by plasma and urine acid-base balance to provide optimal conditions for myoglobin solubility and promotion of excretion in urine. Myoglobin precipitates in acidic urine, leading to the use of bicarbonate. Mannitol, an osmotic diuretic, increases urine flow and serves as a ROS scavenger,[79] reducing TEC exposure. We conducted a 10-year retrospective study of surgical patients with creatinine kinase levels over 10,000 IU/L, which suggested that protocolized treatment with fluid and the latter adjunctive therapies reduces the development of RIAKI.[76] However, there remains controversy regarding this strategy. Clinical evidence to support these claims is based on few and small patient cohorts. In addition, they are challenged by the most extensive retrospective study of trauma-induced rhabdomyolysis, which showed no change in kidney failure, dialysis, or mortality after treatment with bicarbonate and mannitol.[80] The methodologic heterogeneity of these conflicting reports and lack of an adequately randomized controlled trial prevent definitive conclusions from being drawn. Lastly, the potential benefit of bicarbonate should be weighed against the risk of promoting calcium phosphate precipitation in muscle. Thus, although the standard of care is guided by mechanistic insight, a greater understanding of connections and disconnects between injury due to intratubular myoglobin and plasma volume, plasma pH, and osmotic diuretic use is necessary.

Extracorporeal technologies such as dialysis also play a role in RIAKI treatment. Dialysis is necessary once kidney failure is established or significant hyperkalemia occurs. Indeed, a newly liberated crushed extremity containing 150 mEq/l of intracellular potassium can produce hyperkalemia which can only be resolved with some form of dialysis. The challenge of providing dialysis in epidemics, disasters and military environments has driven innovation in use and design of dialysis equipment, including redesign or repurposing of fluidics and pumps,[81-83] sorbent-based dialyzers,[84,85] and extended use of critical care-based equipment.[86,87] As with specific medical therapy, current evidence for these technologies is preliminary, but tantalizing.

Developing Mechanism-Based Treatments for RIAKI

The intervention window for preventing RIAKI is unknown but suspected to be within hours following injury as AKI develops quickly; therefore, treatments with rapid effects that can be readily administered are of utmost importance.[88]

Inhibition of Myoglobin Endocytosis. A well-characterized endocytic complex composed of megalin, cubilin, and amnionless transports many filtered proteins, including myoglobin, into TEC.[39] Removing or blocking megalin activity prevents tubular myoglobin uptake.[39] Mice with proximal tubule-specific megalin deletion are profoundly protected from myoglobin and demonstrate greater than 10-fold more myoglobin clearance than wild type mice. Our laboratory has recently identified a kidney dipeptidase inhibitor, cilastatin, with similar megalin-inhibitory characteristics.[89] Administering cilastatin at the time of glycerol-induced rhabdomyolysis in mice results in a renoprotective effect, which recapitulates the effect seen in megalin-deleted mice.[90] This efficacy of contemporaneous administration of cilastatin with RIAKI indicates a novel postinjury treatment for rhabdomyolysis to prevent kidney injury if given in a limited window following muscular trauma. Cilastatin is currently approved by the United States Food and Drug Administration for another indication and is nearly nontoxic; therefore, it is an promising drug for additional studies in related models and clinical trials.

Oxidative Damage Amelioration. ROS generated during RIAKI have been the target of several drug therapies, primarily antioxidants, designed to reduce ROS in vivo by inhibiting or scavenging, thereby protecting cells from further damage. Acetaminophen, an inhibitor of the formation of peroxide-generated radicals, was found to decrease ROS damage in the kidney and improve kidney function by counteracting lipid peroxidation and reducing global free radicals in a rat model of RIAKI. However, in high doses, it may generate n-acetyl-p-benzoquinone imine, a toxic byproduct.[91,92] In some studies involving chronic kidney disease, n-acetyl cysteine has been shown to beneficially increase ROS scavenging and improve cardiovascular and kidney function.[93] Other studies show no effect of n-acetyl cysteine on serum creatinine and other markers of kidney function.[94,95] The use of n-acetyl cysteine to ameliorate RIAKI is, therefore, controversial.

Table 1. RIAKI treatments (current and proposed) and their molecular targets

Current therapies				
Treatment	Molecular target	Investigated in RIAKI?	Investigation stage	Reference(s)
Intravenous fluid	Tubular flow	Y	Current recommended treatment	76
Sodium bicarbonate	Tubular pH, myoglobin precipitation	Y	Current treatment at some centers	76,80
Mannitol	Tubular flow, ROS	Y	Current treatment at some centers	76,80
Proposed therapies				
Treatment	Molecular target	Investigated in RIAKI?	Investigation stage	Reference(s)
Cilastatin	Megalin/tubular endocytosis	Y	Preclinical	89,90
High flux dialysis	Myoglobin	Y	Phase I - NCT01467180	128
N Acetylcystine	Reactive oxygen species	Y	Phase II - NCT00391911	93-95
CytoSorb device	Myoglobin	Y	Phase II - NCT02111018	129,130
Peptidyl arginine deaminase	NET/MET formation	N-lupus	Preclinical	131
Brensocatib	Dipeptidyl peptidase-1	N- brochiectasis	Phase II - NCT03218917	112
Secukinumab	IL-17A	N-rheumatoid diseases	FDA approved for rheumatoid diseases	132
Lactoferrin	MET formation	Y	Preclinical	58
Anti-Mac-1 antibody	Mac-1	Y	Preclinical	58
Canakinumab	IL-1B	N-CKD	Phase III - NCT01327846	103
Anakinra	IL-1B	N-inflammation in CKD	Phase II - NCT00420290, Phase II - NCT02278562	133
Rilonacept	IL-1B	N-inflammation in CKD	Phase II - NCT00897715	134
Gevokizumab	IL-1B	N-Type 2 diabetic kidney disease	Phase II - EudraCT2013–003610–41	135

CKD, chronic kidney disease; IL-B, interleukin beta; MET, macrophage extracellular traps; NET, neutrophil extracellular traps; RIAKI, rhabdomyolysis-induced acute kidney injury; ROS, reactive oxygen species; Y, yes.

Glutathione oxidation-reduction cycling is the object of other potential treatments for oxidative stress, including selenium. Glutathione peroxidase (and other reductases) are selenium-dependent enzymes that reduce superoxides.[96] Selenium also increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha, critical to many cellular metabolic pathways, including mitochondrial biogenesis.[97] Providing pre-RIAKI dietary selenium to rats increased kidney superoxide dismutase and nitric oxide with reduced proteinuria, but other classical markers for AKI such as plasma urea and creatinine remained unchanged.[98] Reduced proteinuria may result in less myoglobin clearance, and with unchanged creatinine levels, it is unlikely that this method of selenium administration is the most effective treatment.

Antioxidant vitamins C and E have been widely tested in AKI. Vitamin C reduced oxidative stress, kidney damage, tubular cast formation, and proteinuria in RIAKI, but vitamin E only inhibited lipid peroxidation with no subsequent improvement in kidney function or cellular condition.[99] Curcumin delivered as an oral dietary supplement in rats following RIAKI has been found in one study to reduce kidney cell apoptosis and oxidative stress via regulation of 5′ adenosine monophosphate-activated protein kinase, Nrf2/HO01, and PI3K/Akt pathways.[35] Future renoprotective treatments may also come from mitochondria-targeted and global antioxidants that have successfully reduced ROS in other tissues, including mitochondrial-derived peptides like humanin and the superoxide dismutase stimulant metformin.[100] At current, the most promising global antioxidants affecting AKI appear to be vitamin C and curcumin, both of which have low toxicity and are readily abundant, but targeting moieties discussed later in this paper may improve the effectiveness of these and other antioxidants in treating AKI.

Immune-Targeting Treatments. Despite the centrality of IL-1β to RIAKI and other forms of AKI, no studies have assessed whether targeting IL-1β can improve outcomes after RIAKI. However, translational investigation is suggested, because several inhibitors of IL-1β signaling are approved for the treatment of inflammatory disease in humans. These include canakinumab (an IL-1β-neutralizing antibody),[101] anakinra (a recombinant IL-1β receptor antagonist), rilonacept (an IL-1β-neutralizing small molecule), and gevokizumab (an IL-1β-binding antibody). Several clinical trials investigating the efficacy of these treatments for non-AKI kidney disease are ongoing or were recently completed.[102] For example, the Canakinumab Antiinflammatory Thrombosis Outcomes Study demonstrated decreased cardiovascular events in patients with CKD.[103] In addition, canakinumab decreased proteinuria in a patient with kidney amyloidosis.[104] CD44-overexpression stimulates IL-1β, but targeting these cells to counter increased IL-1β with elamipretide (SS-31) conjugated to nanopolyplexes reduced oxidative stress, inflammatory response, and apoptosis in tubular cells affected by AKI.[105]

Macrophages can also release cytotoxic molecules, which are essential for killing pathogens but can also damage surrounding tissue. A recent study in rodents demonstrated that kidney macrophages release their

cellular contents during RIAKI, producing cytotoxic extracellular traps, called "macrophage extracellular traps" (METs).[58] METs are similar to extracellular traps produced by neutrophils (termed neutrophil extracellular traps), which are potently bactericidal[106] but can be aberrantly produced during conditions of sterile inflammation, such as cancer,[68] Alzheimer's disease,[70] and systemic lupus erythematosus,[107] leading to tissue damage. During RIAKI, platelets and iron induce MET formation, which is dependent on integrin αMβ2 (also referred to as Mac-1).[58] MET inhibition prevents TEC damage in RIAKI, presenting multiple therapeutic targets. A Mac-1 inhibitor was demonstrated to prevent cytokine storm and pathological damage in a mouse model of sepsis.[108] In addition, lactoferrin, a naturally occurring glycoprotein with antibacterial properties, inhibited platelet-induced METs.[58] Lastly, there are several inhibitors of peptidyl arginine deiminase, a key enzyme for neutrophil extracellular trap (and presumably MET) formation.[109,110]

Neutrophils present an unexplored cellular target for RIAKI. Several therapies targeting neutrophils are currently under investigation or already Food and Drug Administration approved.[111] Brensocatib inhibits dipeptidyl peptidase-1, an enzyme key in activating neutrophil serine proteases. A recently published phase II clinical trial (NCT03218917) demonstrated that brensocatib administration was associated with increased time to first exacerbation in patients with bronchiectasis.[112] In addition, secukinumab is a monoclonal antibody against IL-17A, which is important for neutrophil activation. Secukinumab is Food and Drug Administration-approved for psoriatic arthritis, psoriasis, and ankylosing spondylitis.[113] To our knowledge, no studies have investigated the efficacy of these treatments in inflammatory kidney disease. This presents an exciting avenue for future RIAKI treatments.

Kidney-Targeted Delivery Systems. Kidney-targeted delivery systems, including nanoparticles (NPs) and microbubbles (MBs), are recent advances in medical technology to deliver drugs, proteins, and other pharmaceutical payloads to prevent and treat kidney dysfunction. Both NPs and MBs have benefits versus nonconjugated treatments as follows: they improve bioactivity and targeting and reduce toxicity and adverse side effects associated with other methods of treatment administration.[114] NPs are generally 1 to 100 nm in diameter; though there is variation in how they are constructed, typically, a multifunctional "backbone" or envelope structure is bound to therapeutic and targeting moieties. Either the backbone alone or additional structural motifs may be added to target the molecule to the kidney specifically. The unique physiology of filtration and reabsorption in the kidney offers the potential for precise targeting, which may increase the efficacy of agents which have broad, systemic mechanisms, such as antioxidants.[115,116] Although there are currently no clinically approved kidney-targeted NPs, NP treatment of rodent *in vivo* models of glycerol-induced rhabdomyolysis has produced promising results. AKI induced by ischemia-reperfusion injury has been the treatment focus of several NPs, including triptolide-encapsulated, resveratrol-conjugated, polyethylene glycol-treated ceria conjugated to atorvastatin, and oltipraz-loaded poly lactic-co-glycolic acid NPs.[105,117-120] Kidney clearable nanochelators designed to reduce excess iron have successfully targeted rat kidneys, with a 7-fold increase in urinary iron excretion, indicating a potential mechanism of reduced ROS creation and proximal tubule damage via the Fenton reaction.[121] In addition, dextran, dendrimer, and poly lactic-co-glycolic acid-polyethylene glycol NPs, cationic quantum dots, and carbon nanotubes have been used to target kidney tubular cells in chronic kidney disease and may be options to treat RIAKI.[115] Overall, the ability to specifically target the kidney and perhaps the proximal tubule renders NPs a promising emerging area. These targeting strategies may ameliorate many of the dose-limiting and treatment-limiting off-target effects of otherwise effective drugs.

Using selenium and rutin-coated gold NPs to pretreat before causing glycerol-induced rhabdomyolysis also showed favorable outcomes. Selenium NPs reduced elevated creatinine, serum creatine phosphokinase, and damage severity compared to injured but not uninjured rats, which was similar to what was observed using rutin-coated gold NP pretreatment.[122] Curcumin-conjugated polyethylene glycol NPs were used to assess treatment efficacy in a human in vitro (HK-2 cells) and rodent *in vivo* model. Curcumin-NPs reduced oxidative stress and cellular apoptosis *in vitro*; creatinine, serum creatine phosphokinase, and the severity of kidney tubule damage were reduced to control levels *in vivo*.[123] Quercetin-derived treatments such as rutin, ubiquinol (MitoQ), and plastoquinone (SkQ1) have also been used to reduce ROS via novel mechanisms that are still not fully understood but have produced promising results in other injury paradigms, suggesting that they may be worth considering for trials in AKI treatment.[100,124]

MBs have been used since the 1990s to facilitate ultrasound imaging. MBs are 1 to 10 μm in diameter, comprised of a gas core surrounded by a protein, lipid, or polymer envelope embedded with targeting molecules.[125] MBs can be used to deliver treatment agents

targeted to specific organs by applying ultrasound to the target, either destroying the bubble membrane or increasing local vascular permeability to facilitate uptake.[126] Targeting moieties that have been employed include *Smad 7*, *miR 433*, *NFκB*, *siTNFα*, and VEGFR2.[127] MBs have not yet been shown to ameliorate AKI, but modifications to the MB to improve its time in circulation have been proposed as potential carriers for treatments. This modality offers promise, especially with the widespread adoption of handheld ultrasound for clinical use; however, additional research into specific targets and protocols will be required.

Current Treatments for RIAKI, Clinical Trials, and Proposed Preclinical Therapies

Conclusion

In Table 1 we provide a summary of current approved therapies for RIAKI as well as several novel therapies in various stages of investigation. Muscular trauma, particularly following crush injury, results in rhabdomyolysis and AKI primarily through proximal tubule endocytosis of myoglobin and subsequent immune-driven response. Current clinically approved treatments are limited, but recent research advances provide promising new avenues to improved treatment, including inhibition of myoglobin endocytosis, prevention and treatment of oxidative damage, and immune cell targets. Technology-related advances in NP and MB delivery may further enhance outcomes. Advancements in these areas would potentially prevent the long-term effects caused by the transition of AKI later to CKD.

DISCLOSURE

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