Rhabdomyolysis is a common, but underestimated disease, which can be caused by many different reasons. The best known is a crush syndrome – extensive muscle damage after direct injury, trauma, or compression, very often accompanying natural and manmade disasters e.g. earthquakes, warfare, or everyday accidents. This clinical entity was first described in 1941 when Bywaters and his team were analyzing patients with renal failure and muscle necrosis after a bomb attack, in which many people were buried for several hours [1]. They discovered, in post-mortem examination, the brown pigment in renal tubules – later identified as myoglobin.

The aim

We aimed to address the epidemiology, causes, and treatment, including renal replacement therapy.

Review and Discussion

Epidemiology and etiology

Global rhabdomyolysis mortality is wide – estimated between 2 and 46% and depending on the type of cause, early treatment administration, and the additional comorbid conditions and complications [2]. RM-associated AKI (RM-AKI) frequency has been reported from 17-35% and even to 50% in adults in some studies. In critically sick patients, mortality rates are up to 59% [7-8]. Luckily, most patients recovered and normalized kidney function in a few months [3] but RM-AKI promotes structural changes e.g. glomerulosclerosis and significantly increasing the risk of chronic kidney disease (CKD) in long-term observations.

Because of the complexity of influencing factors, there are many risk groups. The most exposed are morbidly obese patients, chronic users of lipid-lowering drugs, post-operative patients, prolonged and alcohol abusers. Some studies show a higher risk in man vs woman, in African-Americans, patients >60 (and <10) years old [9-10]. Significant factors may be more, but there is still a problem of insufficient detection. There are several ways to categorize causes of rhabdomyolysis e.g.:
• physical / non-physical,
• acquired/inherited.
Regardless of the divisions, the path of the muscle destructions and consequences run similarly.

Mechanisms

There are a few principle mechanisms of kidney injury. Knowledge of these mechanisms has a key role in understanding the whole process and implementing proper treatment.

Oxidative stress

After muscle damage, intracellular fluid is leaked and then sequestrated in extracellular spaces. This causes decreasing...
intravascular volume which gives the signal to activate the renin-angiotensin-alderosterone system (RAAS) and afterward reduce renal blood flow. Increased myoglobin level and its components exert a destructive, cytotoxic effect on the nephron – free iron reacts with peroxide compounds generating reactive oxygen species (ROS) [12]. As we well know, ROS infringes renal tubular integrity. At the same time, other muscle components are releasing into the circulation system – uric acid – which forming deposits of crystals and contributing intratubular impediment.

The second mechanism is lipid membrane components peroxidation- after reacting with a ferryl form of myoglobin (redox-cycling) they are entailing metabolic acidosis which intensifies myoglobin toxicity [5, 12]. This mechanism has become the basis for the use of urine alkalization as therapeutic prevention, as we will discuss in another section.

The diagram below in a simplifying way shows the mechanism of kidney damage (Fig. 1).

**INFLAMMATION**
In the rhabdomyolysis process, damaged muscle cells release a lot of molecules that activating the immune system – among others uric acid, microRNAs, or ligand high mobility group box proteins (HMGB1). These molecules activate dendritic cells, T-lymphocytes, macrophages, Toll-like receptors (TLRs), and nuclear factor kappa beta (NF-κβ). According to this, we have high production of proinflammatory cytokines such as a tumor necrosis factor-alpha (TNF-alpha) [15-17]. Another molecule effects inflammatory reaction in endothelium and the tubular epithelium is myoglobin-derived heme. Exposed cells increasing expression adhesive molecules such as ICAM-1 or VCAM-1 and afterward strengthen the inflammatory response. In consequence, we have the proliferating, pro-fibrotic path, and in the aftermath – glomerulosclerosis.

**INTRATUBULAR OBSTRUCTION AND APOPTOSIS**
Characteristic manifestation in the tubular lumen is pigment deposits – after muscle cell disintegration, myoglobin and the Tamm-Horsfall protein, precipitate and forming tubular casts. Volume depletion and acidic urine Ph promoting this process. Some authors say that aside from preventing apoptosis there is no specific intervention required [12].

**VASOCONSTRICTION**
Most of the above have one combined effect – vasoconstriction. High myoglobin level increasing F2-isoprostane quantity. Fluid sequestration and afterward increasing renal blood flow, activate RAAS. ROS production leads to endothelial dysfunction and then to an imbalance between vasoconstrictors and vasodilators substances. All these factors promote vessel spasm and its consequences [15, 18].

**DIAGNOSIS**
Patients with RM may experience weakness, muscle and joint pain, fatigue, nausea with or without vomiting, diarrhea and many other complaints depends on the main cause of disease. In laboratory tests we can find elevated creatinine kinase (CK) levels – at least five to ten times beyond upper limit and electrolyte abnormalities such as hyperkalemia, hyperphosphatemia, hypocalcemia (at first), after cell destruction – hypercalcemia. Other blood chemistry findings are elevated myoglobin, transaminases, LDH. Serum CK levels gradually increase during the first 12 h, with a peak of 3–5 days [4]. If the myoglobin level in serum exceeding 0.3 mg/L, we have myoglobinuria in urinalysis with tea-colored urine. There is also a tendency to acidic Ph and detectable proteins in the urine sample [5].

When we considering which of those are the best AKI predictors the most often described is CK level [6, 7].
Another predictor that has also been used is myoglobin serum. In their cohort study, Premru and coworkers [6] found that >15 mg/L of myoglobin in the blood was highly associated with the development of AKI, but because of inconclusive data in other studies, it is not the best early prognostic. In the McMahon and co-worker’s study, they created score includes among others: age, gender, etiology, and initial levels of creatinine, calcium, phosphate, serum bicarbonate as a tool to estimate mortality and AKI [11]. Initial CK and myoglobin levels are not corresponding with mortality.

We are currently looking for new markers that can be early predictors. Presently the two of them are on top of the list – neutrophil gelatinase-associated lipocalin (NGAL) and KIM-1.

NGAL is the most widely investigated biomarker – its production quickly increases, as a consequence of toxic or ischemic injury. In several studies, there is evidence that NGAL level could be used as a sensitive predictor of renal injury also correlated with mortality [13-14]. KIM-1 is quite well known as a biomarker increasing in humans with AKI secondary to ischemia due to aggravating body surgeries e.g. cardiac surgery.

However, there is still a lack of data to apply these early biomarkers from studies to clinical practice.

TREATMENT
There are two main groups of therapeutic strategies – classics, such as well known fluid resuscitation, urine alkalinization, diuretics or renal replacement therapies, and new strategies – based on administration anti-oxidant and anti-inflammatory substances or inhibitors vasoconstriction.

CLASSIC STRATEGIES
FLUID THERAPY
Intensive fluid resuscitation is very important in RM-AKI. It should be administrated as soon as possible and should be carried out with monitoring diuresis rate to avoid overloading the circulation or hypovolemia, which can be also harmful. There are a few imprecisions in available studies but in most of them, we have evidence on lower short-term mortality or lower incidence of AKI in RM after receiving early fluids [19, 20]. Michelsen and co-workers, in their review studies, make some recommendations to choose crystalloids instead of colloids because of lower risk of mortality [19]. Against a low level of evidence, they evaluate this recommendation as weak.

DIURETICS
Diuretic administration is still controversial. When, due to fluid therapy, we overhydrate the patient, the necessity of using them is obvious, but in other situations, there is still too little data. The most often we considering loop diuretics and mannitol. Mannitol increases urinary flow and prevents myoglobin precipitation. In some studies, there is data for reducing oxidative stress. Unfortunately, there are mice studies- no randomized trials were conducted on humans. The use of the loop diuretics (furosemide and torasemide) have not to be confirmed as necessarily specific in RM unless there is an additional reason [19, 21].

ALKALINIZATION
From our observation in clinical practice, urine alkalinization by using intravenous natrium bicarbonate is a popular therapeutic method. As the reason for this procedure, we can take available animal studies into account, which show inhibition of myoglobin precipitation and afterward reducing cast formation [22]. However, there is still a limited number of human research or they have been checking alkaline agents in various combinations, so it is impossible to value their results.

RENSAL REPLACEMENT THERAPY (RRT)
High myoglobin level in blood circulation have a crucial influence to further damage. Hence, the assumption that its removal during renal replacement therapy should be a key importance to improve prognosis. Unfortunately plasma exchange, intermittent hemodialysis and conventional hemodialysis has limited evidence of effectiveness. Continuous veno-venous hemofiltration or hemodiafiltration with the super high flux filters and high volumes of hemofiltration have no data at all.

NEW STRATEGIES
IRON CHELATORS AND ANTIOXIDANTS
Considering the mechanisms of damage, antioxidant and iron chelators may be included in the treatment, such as:
- desferrioxamine,
- vitamin E,
- vitamin C,
- acetaminophen,
- NAC (N-acetylcysteine),
- flavonoids.

As in many other cases, these therapeutic options still have too little data for their effectiveness. A list of potential mechanisms of action and available studies is presented in the table 1.

ANTI-INFLAMMATORY TREATMENT
- Liposome-encapsulated clodronate (LEC) – specific depletor of macrophages, which administration reduces apoptosis and preserve renal function (animal studies) by diminution the number of infiltrating macrophages [33-34];
- Suramine – polysulfonated naphthyl urea used in treating sleeping sickness disease; murine studies show a healing accelerating effect after AKI – after administration of this drug mice showed decreased KIM-1 (kidney injury molecule-1) expression, decreased tubular apoptosis and inflammation process by reducing NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) [15,35];
- Pentoxifylline – is a competitive nonselective phosphodiesterase inhibitor[9] which raises intracellular cAMP,
activates protein kinase A, inhibits TNF alpha, and leukotriene production, and decreases inflammation. In rats inhibits mesangial cells proliferation and myofibroblasts differentiation [15, 36];

- MSC (mesenchymal stem cells) – studies suggested that administration of MSC promotes kidney accumulation of protective macrophages, increased IL-10 level (anti-inflammatory interleukin), and reduce pro-inflammatory Il-6 and TNF-alpha [37].

NEW EXTRACORPOREAL BLOOD FILTER, CYTOSORB®

Referring to the different elimination techniques during dialysis, the trials are still underway to find a new type of filter to remove harmful myoglobin from the bloodstream, and thus reduce the frequency and severity of RM-AKI. The Cytosorb® – high-polymer filter with 300ml volume, low-resistance, and molecule selection <55 kD – has promising results caused by adsorbing cytokines such as IL-6, IL-8, and TNF-alpha or myoglobin (17 kD) [38]. The first reports of efficacy in patients with rhabdomyolysis have already appeared, but currently, the most data has been collected on the degree of cytokine reduction in patients in septic shock treated with CRRT only vs Cytosorb [39].

As molecules such as IL-10 are also involved in the uptake of the Cytosorb®, the overall immunomodulatory effect requires further research [40].

CONCLUSIONS

Mechanisms that lead to kidney damage in rhabdomyolysis are complex and must be considered in a multidirectional manner. It seems that the main harmful factor is kidney hypoperfusion secondary to fluid sequestration and vasoconstriction. Not without significance is the effect of increased myoglobin level, leading to intratubular precipitation and activation of the inflammation cascade through the influence of its decay products and afterward increasing the pro-inflammatory agents. The ideal would be to predict and prevent rhabdomyolysis at all, but when it is impossible, the key to successful treatment is its rapid implementation. Therapy should be selected individually, adapting to the triggers, and closely monitoring the patient’s condition. Early implementation of fluid therapy appears to be crucial. In addition, electrolyte

Table 1. AO – antioxidants and IC – iron chelators in RM-AKI treatment, NAC – N-acetylcysteine, ROS – reactive oxygen species MCP-1 – monocyte chemoattractant protein-1

<table>
<thead>
<tr>
<th>Substance</th>
<th>Category</th>
<th>Description</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desferrioxamine</td>
<td>IC</td>
<td>lipid peroxidation inhibitor – reducing myoglobin to its ferrous form; hydrophilic – requires a lipophilic form to reduce nephrotoxicity [23] alternative: deferiprone – the oral form used for ferrous overload by repeated blood transfusions</td>
<td>animal studies, no data about human trials</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>AO</td>
<td>the major lipophilic antioxidants present in cellular membranes and protecting them against lipid peroxidation – theoretically could prevent myoglobin tubular toxicity – impediment: liposolubility implies a low ability to prevent myoglobin oxidation in the urine</td>
<td>animal studies with some efficiency to decrease toxicity [24-26], no animal/human clinical trials</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>AO</td>
<td>water-soluble; reduce oxidative stress and inflammation by (theoretically) blocking the oxidation of myoglobin in urine and antiinflammatory role by inhibiting MCP-1 production</td>
<td>animal (murine) studies with some efficiency to decrease toxicity [24-26], no animal/human clinical trials</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>AO</td>
<td>inhibits lipid peroxidation by reducing ferryl myoglobin and urinary level of F2-isoprostanes some studies have shown benefits not only in prophylaxis but in treatment [28]</td>
<td>mostly murine or rat studies, no clinical data for benefits in human</td>
</tr>
<tr>
<td>NAC</td>
<td>AO</td>
<td>preventing cellular apoptosis by decrease in urinary thiobarbituric acid reactive substances (TBARS) concentrations, a lipid peroxidation marker, and inducing extracellular-signal-regulated kinase (ERK) pathway</td>
<td>lots of research available, but proven efficacy only in animal models [29-30]</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>AO</td>
<td>Probably electron donors with B-ring conjugated chemical structures rich in hydroxyl groups, which have potent antioxidant actions by reacting with and inactivating superoxide anions, oxygen lipid peroxide radicals, and/or stabilizing free radicals [32]</td>
<td>animal studies – largely concentrated on the influence on nerve cells, little data on the effect in people suffering from kidney damage from RM</td>
</tr>
</tbody>
</table>
disturbances should always be detected in the early stages and carefully treated. The use of bicarbonates or diuretics may also be helpful, but especially in the latter case, the indications should be well evaluated, remembering to avoid hypovolemia. RRTs are most often implemented due to water-electrolyte or acid-base disorders. Due to myoglobin kinetics, not all renal replacement methods will be effective. They seem to be the greatest hope of high cut-off treatments, but these are still unproven and require further investigations. Similarly, new diagnostic methods and strategies based on the molecular mechanisms of inflammation required long-term, adequately designed randomized studies.

Until that, classical supportive therapeutic should be recommended.

REFERENCES


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Conflict of interest
Authors declare no conflict of interest

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Received: 28.10.2020
Accepted: 03.12.2020

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article