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Mini Review of Biochemical Basis, Diagnosis and Management of Crush Syndrome

Abdulhalim Hamlah
Faculty of Medicine, Aleppo University, Syria

Abd Alraouf Tarabishy
Department of Chemistry, Faculty of Science, Aleppo University, Syria

Haitham Al-Madhagi*
Department of Chemistry, Faculty of Science, Aleppo University, Syria
Biochemical Technology Program, Dhamar University, Yemen
ORCID: https://orcid.org/0000-0002-3850-244X

Abstract. Crush syndrome (CS) is a metabolic disorder whose victims are individuals suffered from natural disasters such as earthquake or man-made conflicts. CS complications include acute kidney injury and cardiac arrhythmia that collectively end with death if untreated immediately. These complications are accounted for the liberation of damaged muscle tissues contents, primarily myoglobin and potassium. The present mini review discusses the biochemical basis of the development of CS. In addition, diagnosis and management and the application of novel experimental therapeutics of CS are also highlighted.

Keywords: Crush syndrome, rhabdomyolysis, acute kidney injury, arrhythmia, myoglobin

Trumpa gniuždymo sindromo biocheminio pagrindo, diagnozės ir gydymo apžvalga

Santrauka. Gniuždymo sindromas (trumpinys CS) yra metabolinis sutrikimas, kurio aukos yra tie asmenys, kurie nukentėjo nuo gamtinių katastrofų (pvz., žemės drebėjimo) ar nuo žmogiškųjų konfliktų. Prie CS komplikacijų priskiriami ūminiai inkstų sutrikimai ir širdies aritmija. Jei toks simptomų rinkinys skubiai negydomas, galima baigtis – net mirtis. Dėl šių komplikacijų yra atsakingos iš pažeistų raumenų audinių medžiagos išsilaisvinusios substancijos, visų pirma mioglobinas ir kalis. Šioje trumpoje apžvalgoje aptariamas CS raidos biocheminis pagrindas. Taip pat išryškinami tokie aspektai kaip CS diagnozavimas ir gydymas bei naujų eksperimentinių terapinių metodų taikymas.

Raktažodžiai: gniuždymo sindromas, rabdomiolizė, ūminiai inkstų sutrikimai, aritmija, mioglobinas

* Corresponding author: Haitham Al-Madhagibc, Department of Chemistry, Faculty of Science, Aleppo University, Syria; Biochemical Technology Program, Dhamar University, Yemen. E-mail: bio.haitham@gmail.com

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Introduction

Crush syndrome (CS), also known as rhabdomyolysis, is a clinical state characterized by the destruction of striated muscle tissues owing to the pressure imposed for long time liberating their contents into the blood stream. It is caused by either traumatic injuries, whether due to earthquake or man-made accidents/conflicts, or non-traumatic. Among the liberated muscle contents, sarcoplasmic enzymes including lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and creatine kinase (CK), in addition to myoglobin (Mb) and electrolytes were detected in the plasma of CS patients. The most seen clinical symptoms of the affected individuals involve muscle weakness, muscle pain, local swelling of the affected muscles and red-color urine [1]. If no immediate medical intervention was initiated, life-threatening complications are developing and the effected muscles might subject to limb amputation as a result of the pressure-imposed to that body parts. This include acute kidney injury (AKI) and renal failure, severe dehydration and fluid depletion, and cardiac arrhythmias. It is noteworthy that not every muscle trauma can result in rhabdomyolysis and renal failure [2]. Approximately 0.2% of all admissions to care units had CS in UK. Of whom, 75% are males [3].

Biochemical basis

The leakage of myocyte components into bloodstream is the consequence of the depletion of energy in the form of adenosine triphosphate (ATP), creatine phosphate in the short-term and glycogen in the long-term. This represents the strike of events cascade leading to CS [4]. Depleted ATP of myocyte pose serious consequences like the defect in active membrane transport leading to electrolyte imbalance with more ions like calcium being moved to the myocyte. Subsequently, the muscle cells are filled with water molecules as a result of osmosis phenomenon which is a prognostic hallmark of cell death. Besides, increased intracellular calcium levels would activate a number of key enzymes such as proteases and phospholipases which in turn aggravate the myocyte damage through breakdown of intracellular proteins and mitochondrial membrane (damaging the cell's energy factory) and potentiate the generation of excessive reactive oxygen species (ROS). These factors collectively drive the myocyte death and liberating its components [5]. Among the liberated biomolecules, Mb and potassium constitute the most toxic effects leading to CS and its circulatory complications such as renal failure and cardiac arrhythmias (Fig 1). Mb is a single polypeptide composed of 153 amino acids with 17.8 kDa molecular weight. It accounts for about 1–3% of the dry weight of muscles. Mb serves as a muscle reservoir of O_2 received from hemoglobin. In normal circumstances, small Mb concentrations are filtered in the glomerulus and reabsorbed via renal tubules where it is catabolized. Upon AKI, Mb appears in the urine giving rise to the red-color of urine in CS patients [6,7]. The remaining higher Mb concentrations have direct toxic effect to both proximal and distal tubules where in the presence of acidic urine constitute pigmented casts that obstructs renal tubules [8]. In addition, Ferrihemate, a breakdown product of Mb, in the presence of a low pH can generate ROS leading to direct AKI. Furthermore, heme proteins can potentiate renal vasoconstriction, which may have been initiated by hypovolemia and can instigate the overproduction of proinflammatory cytokines [9].

Hyperkalemia, on the flip side, is seen in CS patients as it leaked out of myocytes concomitantly with other electrolytes like phosphate. Hypocalcemia is observed early in CS which is then raised owing to the fact that calcium is entered just prior to cell death. Also, calcium along with phosphate is deposited and calcinating myocyte debris and thus hardening affected muscle areas [10,11]. Hyperkalemia resulted from myocyte degradation causes alteration in cardiac rhythm. Ultimately, patients go into a circulatory shock affecting respiratory gas exchange due to lung edema [12]. Collectively, AKI, electrolyte imbalance and the resulting circulatory collapse can be ended with mortality if untreated.

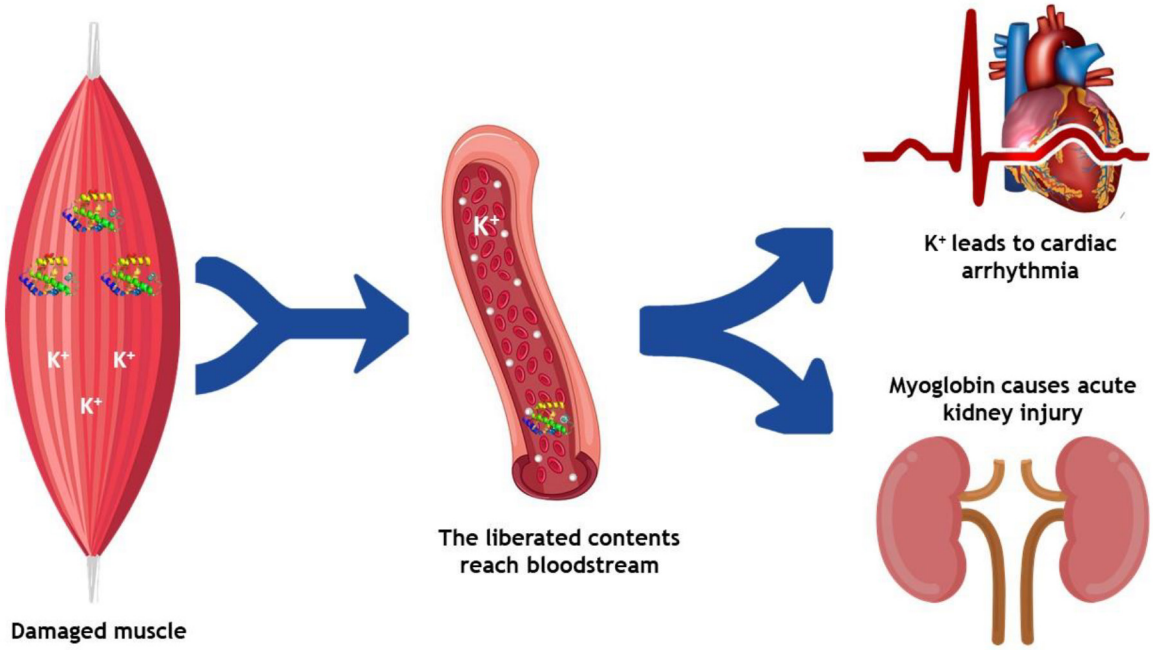

Figure 1. Overview of the biochemical mechanism of CS

Diagnosis

The diagnosis of traumatic CS is usually a straightforward process, given the patients were admitted from damaged regions where natural disasters took place. Nonetheless, a number of laboratory tests are commonly used for the confirmation of CS as summarized in Table 1.

Table 1. Laboratory tests commonly employed for the diagnosis of CS [13]

Laboratory test	Expected finding
CK	Elevated
Mb	Elevated
LDH	Elevated
ALT	Elevated
Creatinine	Elevated
Myoglobinuria	Elevated

CK level elevated to five-time upper normal limit along with the MM-type being the predominant isozyme is critical for CS diagnosis. CK may get increased after 12 h after the occurred injury and return to normal range after 5 days. Mb levels are variable during CS disease course, i.e. given its short half-life (~ 3 h), Mb increases and resolves sooner than CK. Furthermore, Mb is raised only after the overwhelming of the corresponding plasma binding proteins [14].

Management

The medical intervention sought for managing CS focuses on treating the underlying causes of renal failure and arrhythmia. First, correction of blood volume (reversing hypovolemia) through the infusion of appropriate IV fluids should be done. Either lactated Ringer's solution or normal saline (0.9% or 0.45%) is acceptable IV-fluid for resuscitation in CS [15]. Besides, the infused IV fluids might be

coupled to insulin injections in severe cases to ensure the rapid combustion of fuels and the generation of ATP. In injured CS patients, the IV hydration/fluid resuscitation is extremely recommended to begin as early as possible at the site of injury, even before relieving injury if possible, and maintained during patient transport to care unit [16].

Second, $CaCl_2$ or calcium gluconate may be used to deal with hypocalcemia as well as hyperkalemia. Insulin and glucose infusion can facilitate the entry of potassium into cells and thus normalizing the life-threatening hyperkalemia [17].

Besides, several case reports suggested the administration of bicarbonate and loop diuretics so as to avoid fluid overload. These diuretics also potentiate forced alkalization of the formed acidic urine and thus alleviating toxicity of both Mb and uric acid to renal tubules albeit there is no strong clinical evidence that supports the AKI-ameliorating action in CS [18].

Novel experimental therapeutics

Antioxidants and anti-inflammatory agents

Rhodamine and plastoquinone were evaluated for potential antioxidant activity as a therapeutic option against CS. These compounds exhibited limited nephroprotective impact as they mainly neutralized the mitochondrial ROS overproduction [19]. Curcumin, a potent natural antioxidant and anti-inflammatory agent, significantly reduced kidney damage associated with CS. This activity was attributed to reducing the three types of cell death – apoptosis, necroptosis as well as ferroptosis *in vivo* [20].

Fe-chelating agents

The biflavonoid quercetin showed reversal of acute renal failure following rhabdomyolysis in animal models. Because of its radical-scavenging and iron-chelating properties, quercetin protected the rat kidney against the glycerol-induced oxidative stress and resultant renal dysfunction [21]. Moreover, the standard iron-chelator deferoxamine has been demonstrating its benefit in CS-induced experimental animals but the results need to be translated for human use. Such chelators relieve the progression of CS through removing the role of Fe in initiating and propagating the production of ROS through Fenton-chemistry reactions [22].

Other chemical/biological entities

Many drugs and ions exhibited renal-enhancing properties through the upregulation of antioxidant enzymes or inhibiting ROS-generating enzymes *in vivo*. This include dexamethasone [23], nitrite and hydrogen sulphide [24,25], and allopurinol [26]. Alongside, certain proteins such as recombinant human erythropoietin and lactoferrin, monoclonal antibodies like anti-high mobility group box 1 protein antibody and anti-receptor for advanced glycation end products antibody regulate the ongoing inflammation and advanced glycated end-products *in vivo* which constitute an alternative and more-specific actions toward reducing the ROS, advanced glycation end products and inflammation of CS-induced animal models [27].

Conclusion

The damaged myocytes release Mb which pose toxic impact on renal tubules and potassium that eventually leads to cardiac arrhythmia. The individuals afflicted with CS have to immediately get medical intervention, otherwise, mortality is almost unavoidable. IV-fluids must be initiated as soon as possible after saving the affected individuals. Moreover, hyperkalemia must be normalized. The

clinical translation of recent advances regarding the application of monoclonal antibodies and other recombinant proteins as novel therapeutics of CS should be examined.

Author contribution

HAA conceptualized and designed the study, **AH** wrote the diagnosis and management sections, **AAT** wrote the biochemical basis and novel therapeutics sections.

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None declared.

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