



(REVIEW ARTICLE)

## Behavior of skeletal muscle after severe burn injury

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### Abstract

Severe burn injuries (BI) represent a public health problem in the world, especially children, most of cases due to hot liquids. In these situations, it tends to be more superficial and extensive injuries. BI above 40% of total body surface area are considered extensive and result in local and systemic responses. After an extensive BI, a persistent hypermetabolic and catabolic state begins, resulting several alterations in skeletal muscle. Since skeletal muscle is as a reservoir of amino acids in organisms, catabolic states occurs a protein metabolism deviation to the site of injury and to essential metabolism, resulting in loss of muscular mass and atrophy. The muscular connective tissue wrap also suffers the changes in favor of accompanying the morphological alterations of muscle fibers. Besides that, the skeletal muscle regeneration depends on a delicate balance between systemic inflammatory response, and muscle regulatory and atrophy factors. Thus, the aim of this review is contribute to understanding of these relationships.

**Keywords:** Skeletal muscle; Burn injury; Metabolism; Inflammation; Atrophy; Regeneration.

### 1. Introduction

Severe burn injuries (BI) represent a public health problem. The incidence of this type of injury is high in all age groups, especially children and due to hot liquids in most of cases. In these situations, it tends to be more superficial and extensive injuries, resulting in systemic consequences as increased metabolism and protein catabolism. In view of this question, several studies should be conducted to understand the systemic consequences of extensive BI.

In children who have suffered severe BI, the musculoskeletal system may be prejudiced; resulting in a delay in the growth when compared with who do not suffered the injury promoted by a persistent hypermetabolic state with consequent protein catabolism and muscle atrophy.

Since skeletal muscle is as a reservoir of amino acids in organisms, catabolic states occurs a protein metabolism deviation to the site of injury and to essential metabolism, resulting in loss of muscular mass and atrophy. The muscular connective tissue wrap also suffers changes in favor of accompanying the morphological alterations of muscle fibers. Besides that, the skeletal muscle regeneration depends on a delicate balance between systemic inflammatory response, and muscle regulatory and atrophy factors.

This review paper we discuss the relationship between severe burns and the systemic consequences that affect skeletal muscle tissue. Experimental model of burn injury assays, as well as articles involving human suffered burn injury were mentioned. This review was structured in topics, aiming a comprehensive and actual view of the metabolic mechanisms related to the systemic consequences in skeletal muscle after severe burn injury.

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### 1.1. Incidence and classification of burn injuries

World Health Organization (WHO) defines burn injury as a skin injury or in other organic tissues [1], resulting in varying degrees of tissue loss with local and systemic clinical repercussions [2]. WHO indicates that there are approximately 265,000 deaths per year due to BI, this type of injury be the 11th cause of death in children 1 to 9 years of age and the fifth most common cause of nonfatal injuries in childhood. The infant mortality by BI is 7 times higher in developing and underdeveloped countries than in developed countries [1].

Children are more vulnerable to BI risk, since they are less aware of danger, have reduced reflex capacity compared to adults, and are less able to react quickly and properly. In addition, children's natural curiosity increases with the development of motor activity and skills, so the younger the child, the greater the risk of BI [3].

Epidemiological studies in the treatment center for burn injuries show that scalds by outpouring of warm substances in children are one of the most common accident; predominating second degree BI in domestic environments, and the thorax is the most affected site [2,4–7]. Among the most common accidents are boiling water in the kitchen, hot water bath, hot drinks and cooking oil. In these case, the lesions are usually more superficial, but more extensive [2,8].

BI can be classified according to its extent, location, depth, pathophysiological status, age, and social and individual circumstances of the patient [8,9]. Depth lesion classification is the most common. In first degree lesions, the superficial layer of the dermis is affected, and it is characterized by erythema, swelling, local pain, without bubbles; while in the second degree lesions occur in the deeper layers of the dermis, appearing bubbles, detachment of layers, erythema, pain and swelling. Finally, in the third degree lesions all the layers of dermis are affected, reaching muscles and bones [10].

In first-degree BI, healing occurs within 7 days, and in the second degree it may vary from 7 to 21 days, depending on whether superficial or deep, and third degree usually there is no spontaneous cure, requiring surgical intervention [9]. Depth and extent of the total body surface area (TBSA) are important factors that influence patient survival and systemic responses [6]; so the longer the TBSA is, the greater the risk of systemic repercussions [2,8,11,12].

### 1.2. Systemic responses due to BI

BI above 40% of TBSA are considered extensive and result in local and systemic responses, as hormonal and metabolic alterations [2,11,12]. Extensive BI are followed by long periods of stress, inflammation and hypermetabolism; characterized by increase of body temperature, glycolysis, myofibrillar proteolysis, glycogenolysis and lipolysis [13]. The increase of catecholamines, glucocorticoids, glucagon and dopamine secretion are responsible for initiating the hypermetabolic response [13,14].

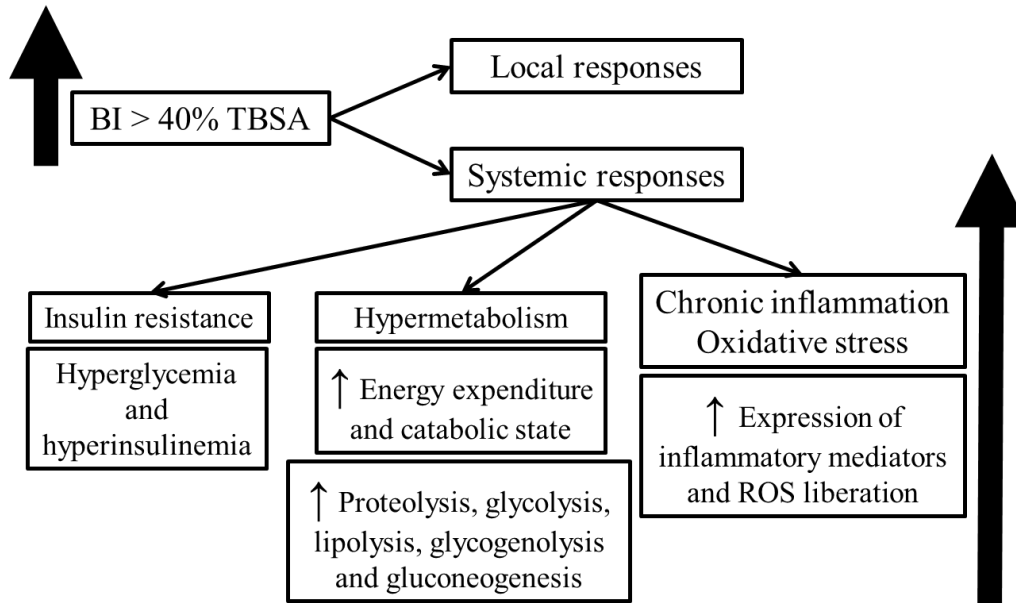
In an early phase to an extensive BI response, a hyperglycemic state occurs, followed by a late phase with a predominance of protein hypermetabolism [15]. Other alterations, such as fever, hyperdynamic blood circulation, gastrointestinal barrier deficiency with passage of bacteria and toxins into bloodstream are also observed. In addition, dehydration due to exudation in the area of the injury leads to hydroelectrolytic imbalance [2].

Amidst extensive BI pathophysiology, the expression of inflammatory mediators and a decrease in the level of anabolic hormones contribute to a significant increase in catabolic state and energy expenditure [12]. Children who have suffer extensive BI have an increase of up to 100% in energy expenditure when compared to healthy children [16]. BI in children have two main differences when compared to adults. First, children suffer greater fluid loss than adults [17], because the skin layers are thinner and have a smaller amount of insulating subcutaneous tissue than older children and adults [3]. In addition, children need follow-up until full growth [17] as persistent protein catabolism may contribute to the delay in growth for up to two years after BI [13,18]. And the presence of contractures limit the range of movement, resulting in functional limitation and inadequate musculoskeletal growth [17], increasing the risk of bone deformities [19].

The response after severe BI is characterized by a hypermetabolic state that always varies increasing the larger the affected TBSA. In BI above 40% of TBSA, there is a protein catabolic state that persists for at least one year after BI [20]. Such factors contribute to muscle protein loss, bone mineral density, and total bone mineral content [12]. Oliveira *et al* [21] verified changes in the condyle of the mandible of young *Wistar* rats submitted to scalding injury (SI) of 45% of TBSA, and observed that bone remodeling was affected, with a decrease in bone mineral density and alteration of bone morphology affecting the growth of the mandibular condyle.

In face of these consequences, hypermetabolism and chronic systemic inflammatory response induce insulin resistance, which is maintained for up to three years after BI [13]. According to Atiyeh *et al.* [15], the second most prominent BI response is metabolic stress due to hyperglycemia and the first is hypermetabolism.

Hyperinsulinemia and hyperglycemia are hallmarks of insulin resistance soon after BI [22]. Hyperglycemia remains as a result of increased hepatic gluconeogenesis and glucose substrate [15]. Such metabolic changes lead to decreased anabolic action of insulin, increased glucose release, lipolysis in adipose tissue, hepatic gluconeogenesis and proteolysis in skeletal muscle [23], in order to provide increased glucose availability in an attempt to enhance the energy source to glucose-dependent tissues [24] thus providing a cycle in the body.



**Figure 1** Extension of burn injury and main systemic alterations. Extensive BI leads to local and systemic responses. As chronic inflammation and oxidative stress with increased expression of several inflammatory mediators and release of reactive oxygen species. Hypermetabolism with consequent increase of energy expenditure and catabolic state, such as: proteolysis, glycolysis, lipolysis, gluconeogenesis and glycogenolysis. And insulin resistance with increased serological parameters such as hyperinsulinemia and hyperglycemia. These systemic responses remain for long periods, according to TBSA.

## 2. Impacts of severe BI on skeletal muscle

This topic brings the systemic consequences of the extensive burn injury to the skeletal muscle, and also how regeneration occurs with consequent remodeling of the connective tissue wrap. Finally followed by processes of atrophy, inflammation and oxidative stress that may occur in this tissue during hypermetabolism state.

### 2.1. Systemic effects of BI on skeletal muscle

The skeletal muscles development, with the exception of some craniofacial and esophageal muscles, is derived from precursor cells of the paraxial mesoderm, from somites originating on the sides of the neural tube of the embryo, during the embryogenesis of vertebrates [25]. Expression of progenitor genes for cell cycle entry or arrest, as well as cell differentiation, occurs in response to signals from the neural tube, notochord, and mesoderm. Signaling factors have effects on the expression of genes in the myotome domains; whose signaling pathways regulate a cascade of molecules in order to coordinate and balance the proliferation, differentiation, and specification of the myogenic lineage during vertebrate development [26].

Postnatal muscle growth occurs through the fusion of satellite cells with preexisting muscle fibers. The satellite cells are located at the periphery of the muscle fibers between the basement membrane and the plasma membrane; following a mechanism similar to that occurring in muscle recovery and repair [27]. Proteolysis in skeletal muscle and

consequent reduction of muscle mass are characteristic of denervation, cachexia [28], diabetes, renal failure and AIDS [29], cancer, sepsis, and extensive BI [15,30]. After an extensive BI, a persistent hypermetabolic state begins, resulting in skeletal muscle atrophy, decreased muscle mass and function. Such complications are considered the main complications of this type of injury [15,31]. The balance between catabolism and protein anabolism, as a consequence of more than 40 % of TBSA in BI undergoes reorganization [16]. Skeletal muscle, which is an endogenous protein reservoir, undergoes increased proteolysis and the amino acids resulting from this process are destined for essential metabolisms as well as the restoration of BI [2,16].

The flow of protein synthesis to the BI site becomes five times greater than that of the muscular protein stock replenishment. The muscular catabolism, associated with hypermetabolism, is maintained for several months after BI and subsequent healing [16], making skeletal muscle function as a primary source of amino acids, serving as a substrate for energy production in gluconeogenesis during a hypermetabolic state [32]. Thus, increased glucose flux is directed to BI restoration so that glucose is consumed during anaerobic metabolism by fibroblasts, endothelial cells, and inflammatory cells at the site [15].

In order to provide glucose to vital organs during hypermetabolism, gluconeogenesis is increased in the liver and glucose, which is a substrate for such organs, comes from lipolysis and myofibrillar proteolysis. However, in healthy subjects, postprandial glucose metabolism increases blood glucose concentration and stimulates the release of insulin by the beta cells of the pancreas. Insulin mediates the uptake of glucose into muscle and adipose tissue by suppressing hepatic gluconeogenesis and maintaining glycemic homeostasis. In extensive BI cases there is a significant metabolic alteration of energetic substrate and hyperglycemia cannot suppress gluconeogenesis [13]. Therefore, both degradation and muscle protein synthesis are increased. Thus, degradation exceeds protein synthesis, resulting in more loss than protein gain [15]. Therefore, the persistent hypermetabolic state due to large BI leads to increased muscle proteolysis [33] and such damage brings about the need for regeneration of this tissue [26].

## **2.2. Regeneration of skeletal muscle after BI**

Postnatal muscle growth and muscle regeneration occur through the fusion of satellite cells with preexisting muscle fibers; such cells are located at the periphery of the muscle fibers between the basement membrane and the plasma membrane [27]. Satellite cells provide skeletal striated muscle with the ability to respond from physiological stimuli such as exercise to severe injury. However, muscular regenerative capacity is limited by the exhaustion of the population of these cells, which can lead to muscle deterioration [26]. So after a myotrauma, rupture of basal lamina occurs and consequent migration of the satellite cells to the region of the lesion. Such processes are mediated by inflammatory cytokines [25] and regulatory myogenic factors [26].

The regeneration of a muscle injury has three phases: destruction, repair and remodeling. In the destruction phase, inflammatory cells, such as lymphocytes and macrophages, phagocytose the necrotic muscle fibers [34]. In the repair, the satellite cells, which were in quiescence, are activated and return to the cell cycle within 2 hours after the injury. After 2 to 3 days, these cells initiate proliferation (or amplification) process, where occur cell division, and one daughter cell differs in myoblast while the other cell replenishes the pool of stem cells and returns to the state of quiescence [26,34].

Within 5 to 7 days after injury, differentiation occurs, where myoblasts are withdrawn from the cell cycle, forming small basophilic myotubes with a centralized nucleus, characteristic of muscle regeneration. In the next phase, fusion of myoblasts occurs in myotubes and the growth of myofibers with centralized nuclei. In the remodeling, maturation of myofibers occurs and the nuclei to the periphery, characteristic of mature muscle fibers, since sarcoplasm is filled with contractile myofilaments organized as myofibrils, and restoration of cellular architecture occurs within 2 weeks after injury [26,34].

All events involved in muscle regeneration are coordinated by the expression of regulatory myogenic factors (MRFs): MyoD, Myf5, Mrf6 and Myogenin. These are nuclear transcription factors expressed sequentially during myogenesis [35]. At the beginning of myogenesis, satellite cells, when activated, express markers such as paired-box protein 7 (Pax7), while active cells in early stages of myogenesis express helix-loop-helix transcription factors such as Myf5 and MyoD [36], both with increase of expression within two to six hours of a muscle injury [26].

MyoD is released in stages of primary myogenesis, in satellite cell activation and myoblast proliferation, participating actively until differentiation of these cells [37,38], and these phases are marked by the increased expression of this protein, with peak in its production three days after an injury [39]. Myogenin is involved in secondary stages of myogenesis, from differentiation [40]. The expression of Myf5 is later, with peaks within five days of the lesion, and

has similar expression to Myogenin [26]. The severe BI causes increased MyoD and Myogenin immunoeexpression in skeletal muscle of young rats [41].

Like MRFs, the insulin-like growth factor (IGF) is also associated with the regulation of muscle regenerative capacity, participating in the hypertrophy of this tissue [42]. IGFs are peptides structurally related to insulin and include IGF1 and IGF2. The main target tissue of these growth factors is skeletal muscle, stimulating hypertrophy and inhibiting muscle atrophy [36].

IGF-1 is an important regulator of postnatal growth and its isoform, IGF-1Ea, participates as a muscle regeneration regulator by increasing the activity of satellite cells, preserving the integrity of the fibers and prolonging the regenerative potential of skeletal muscle [43]. Under physiological conditions, the level of anabolic hormone IGF-1 in the tissues inhibits the degradation of myofibrillar proteins. Catabolic states caused by long BI, lead to a decrease in IGF-1 levels, favoring an increase in myofibrillar catabolism [44].

### 2.3. Remodeling of skeletal muscle after BI

The skeletal muscle tissue consists of contractile, elongated, striated, multinucleate fibers with peripheral nuclei. The cytoplasm or sarcoplasm consists mainly of myofibrils that extend throughout the fiber and this myofibrils arrangement is responsible for the transverse striations [25]. The individual myofibers are connected by a connective tissue composed of three levels of wraps called endomysium, perimysium and epimysium. Each muscle fiber is connected at both ends by connective tissue called tendon [45].

In paper with rats submitted to SI of 45% of TBSA, the Sham group presented equidistant, polygonal, regular sized muscle fibers with peripheral nuclei. While 14 days after SI, the animals presented rounded, degenerating, irregular contours and varied sizes of the fibers, and increase of distance between fibers [41,46], fibers in process of splitting [41] besides inflammatory cells from vessels with vascular congestion [47]. There are also changes in the collagen type, after 4 and 14 days of SI, this authors observed the presence of collagen type III, which is an immature collagen characteristic of regeneration processes [41]. And the changes in muscle tissue that promote muscle mass decrease also lead to alterations in the muscle phenotype, accompanied by a change in the type of collagen from I to III [48].

Furthermore, efficient muscle repair requires the migration and proliferation of fibroblasts in order to produce new temporary components of the extracellular matrix, such as several types of collagen, fibronectin, elastin and laminin. These elements serve to stabilize the tissue, and act as a scaffold for the new fibers [49]. The amount of extracellular collagen is determined by the balance between synthesis and degradation [50]. According to Uemura et al. [51], metalloproteinases (MMPs) degrade components of the extracellular matrix and basement membranes, such as interstitial collagen, fibronectin, laminin and proteoglycans [52], this family of enzymes have the capacity to act both in physiological and pathological processes and its performance is a prerequisite for tissue remodeling and its expression may respond to growth factors and inflammatory cytokines [53].

Fusion of satellite cells in skeletal muscle to form new contractile fibers is a key step in the process that relates to metalloproteases [54], since the distribution of muscle strength and the process of muscular contraction depend on the collagen of the intra, inter and extra-muscular connective tissue [55]. MMP2 and MMP9 assist in myotube formation by migrating and differentiation of satellite cells in both muscle cells cultured *in vitro* and in animal models *in vivo* [56]. These both enzymes are characteristic in skeletal muscle injuries, even at distant sites from where the injury occurred because of their relationship to the degradation of basement membranes. MMP2 is capable of degrading components of the extracellular matrix such as elastin, fibronectin and collagens type I, II, III and IV. [57].

### 2.4. Atrophy of skeletal muscle after BI

In skeletal muscle, there are pathways responsible for regular proteolysis, such as lysosomal, calcium-dependent and ubiquitin-proteasome-dependent pathways [58]. Among such mechanisms the most notable in with accelerated proteolysis states is the ubiquitin-proteasome system (UPS) [30], that during muscle atrophy acts to reduce protein synthesis and increase protein degradation [59].

The proteolytic action of UPS is ATP-dependent and involves ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase enzyme (E3). E3 transmits specific substrate for gene expression of two muscle-specific enzymes, muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx, also known as atrogin-1) [60–62], leading to the primary regulation of muscle proteolysis under muscular atrophy conditions-induced, such as immobilization, denervation or systemic response to extensive BI [58]. In experimental models of animals submitted to extensive BI, have shown that muscular atrophy occurs by protein catabolism from the action of the proteases

dependent on calcium activation; by apoptosis and the ubiquitin-proteasome system [63]. In this condition, there is greater expression of the MuRF1 and MAFbx enzymes [58].

UPS pathway is not able to degrade intact proteins, suggesting that there is another system responsible for initiating degradation, probably a result of increased caspase-3 or calcium-dependent enzymes. UPS initiates the proteolytic action from the binding of free ubiquitin (Ub) molecules to the enzyme E1, and then Ub molecule is transferred to the enzyme E2. Ub molecule is then catalyzed by E3 and conjugated to the target myofibrillar protein by a protein-enzyme binding isopeptide in up to a minimum of four molecules. Finally, the 26S proteasome is capable of recognizing the signal in order to degrade the target protein and cleaves it in small oligonucleotides [29].

Recent studies have shown the specific function of each of E3 ligases, so that MuRF1 preferentially interacts with muscle structural proteins and promotes degradation of sarcomere proteins such as titin, myosin, nebulin and troponin [64]. In contrast, MAFbx interacts with MRFs, modulating myoblast differentiation, protein synthesis and muscle growth. This enzyme acts inhibiting the differentiation of myotubes by their interaction with MyoD. Similarly to this process, MAFbx binds to Myogenin promoting myotube degradation. In this way, both E3 ligases contribute to remodeling activity, atrophy and muscular metabolism [65].

Thus, skeletal muscle mass is regulated by balancing the rates of protein synthesis and degradation. Some of the signaling pathways that mediate this delicate balance include: Akt-mTOR, Akt-GSK3b, Akt-FoxO, and myostatin. Akt can be activated by insulin and IGF-1 to regulate protein synthesis and protein degradation. For the FoxO pathway, Akt is phosphorylated and activates the FoxO3 transcription factor of this family. Activation of FoxO3 induces the transcription and activation of ubiquitin ligaments MuRF1 and MAFbx and consequent increase of myofibrillar proteolysis [66].

The increase of anabolic hormones such as insulin and IGF-1 acts on the regulation mechanism of MuRF1 and MAFbx decreasing the expression level of both and consequently acting in the reduction of skeletal muscle atrophy [66]. In experimental model of extensive SI occurs an increase in mRNA expression for MuRF1 occurs four days after injury, as well as an increase of MAFbx at 14 days post-injury [41]. The regulation of transcription of MAFbx and MuRF1 is closely linked to the metabolic and inflammatory state of cells, and in well-coordinated signaling events [29].

## **2.5. Inflammation and oxidative stress in skeletal muscle after BI**

The increase in expression of several inflammatory cytokines after extensive BI promotes the start and maintenance of hypermetabolism, compromising the structure and function of several tissues, such as muscle, skin, heart, immune system and liver [67]. In skeletal muscle, these cytokines contribute to the induction of muscle proteolysis, even in muscles not directly injured, resulting in mass deficit and consequent muscular atrophy [28]. The cause that results in hypermetabolism is still not well understood, however, it is known that interleukins, such as IL-1 and IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ), arachidonic acid metabolites via cyclooxygenase and reactive species of oxygen, are some of the complexes that participate in this state [15].

In muscle, the systemic inflammatory response acts in order to optimize myogenesis by phagocytosis of cellular debris by macrophages, release of cytokines and growth factors [39]. Macrophages play a decisive role in the removal of necrotic or lesioned tissues, along with fibroblasts, producing complementary chemotactic signals (cytokines and growth factors) to attract circulating inflammatory cells. Inflammatory cytokines, such as interleukin-1beta (IL-1b-), IL-6, IL-8, TNF- $\alpha$ , are important in modulating chemotaxis for injured muscle [45].

COX-2 is responsible for muscle fiber growth during regeneration, but is not required for constant maintenance of muscle fiber size. It also acts on satellite cell activation, regulation of myoblast proliferation and apoptosis [39]. In the skeletal muscle, prostaglandins are synthesized and catalyzed by COX-2, regulating muscle regeneration by inflammation response modulation such as synthesis and degradation proteins [68].

In patients who suffered 20 to 60% TBSA of BI, serum levels of IL-1, IL-6, IL-8 and TNF- $\alpha$  were found to be higher when compared to clinically healthy individuals [63]. In a study using an experimental model of SI of 45% TBSA in rats occurs an increase in iNOS and TNF- $\alpha$  gene expression in distal skeletal muscle, after 4 and 14, respectively [41].

Muscle degeneration after BI as a result of the systemic inflammatory response is associated with the release of reactive oxygen species. After 14 days of SI of 45% TBSA, an increase in the COX-2 immuno-expression and the marker for oxidative stress 8OHdG in muscle distant from the lesion site was noted [47]. During oxidative stress processes occurs reactive oxygen species (ROS) formation, which are produced from the oxidative deterioration of

proteins, lipids and DNA [69]. ROS can be produced mainly in the mitochondria and the endoplasmic reticulum [70] and the damage generated by ROS is linked to severe degenerative conditions [71]. Among the main ROS are free oxygen radicals, such as hydroxyl (HO) capable of interacting with DNA strands, causing the addition of DNA bases, generating a variety of oxidation products [72].

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### 3. Conclusion

In face of an extensive or severe BI, skeletal muscle behavior will pass by changes, such as morphological alterations of the muscle fibers, reorganization of it with changes in the connective tissue surround them, oxidative stress, inflammatory process and muscle catabolism that can cause atrophy of this tissue. Indeed, there will be a need for repair with increased expression of myogenesis genes.

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### Compliance with ethical standards

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#### *Disclosure of conflict of interest*

The authors declare no conflict of interest. And all authors have made substantial contributions to the article.

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