Proceedings of Scientific Research Universidad Anáhuac, 2025, 5(10): 27-38.
ISSN-e: 2954-3541.

Review Article

Muscle Atrophy Secondary to Spinal Cord Injury: A Global Understanding

Diego Bustamante-Laguna[a1], Ivan Ignacio-Mejia[b2], Humberto Carrasco-Vargas[b3], Marco Antonio Vargas-Hernández[b4], Antonio Ibarra[a,b5*]

[a] Universidad Anáhuac México, Centro de Investigación en Ciencias de la Salud (CICSA), Estado de México.
[b] Secretaría de la Defensa Nacional, Escuela Militar de Graduados en Sanidad, Ciudad de México.

ID ORCID:

[1]https://orcid.org/0009-0005-3273-7757, [2]https://orcid.org/0000-0003-3792-4613, [3]https://orcid.org/0000-0001-6365-064X, [4]https://orcid.org/0000-0002-2518-2803, [5]https://orcid.org/0000-0003-2489-4689

https://doi.org/10.36105/psrua.2025v5n10.03

ABSTRACT

Introduction: Spinal cord injuries are widely acknowledged for their profound impact on quality of life. Consequently, there is a particular interest in comprehending the molecular and genetic pathophysiological mechanisms that are distinctly associated with the development of muscle complications, such as atrophy. These complications are crucial features of spinal cord injury, leading to further mobility limitations and systemic disturbances in cellular homeostasis. **Objectives:** The present review aims to elucidate the molecular and inflammatory mechanisms involved in muscle atrophy that contribute to the deterioration of individuals with spinal cord injury. Furthermore, the current therapeutic options for this condition will be explored in this review, with the aim of providing a comprehensive approach to muscle atrophy in spinal cord injury and identifying potential therapeutic targets. **Materials and Methods:** This narrative literature review was conducted through online research in PubMed, SciELO, and Web of Science between October 2023 and January 2024. A search was conducted using keywords such as “spinal cord injury,” “muscle atrophy,” “oxidative stress,” and “skeletal muscle,” with the use of Boolean operators to refine the search. A total of 48 studies were selected based on specific criteria. **Conclusions:** The process of muscle atrophy that occurs after a spinal cord injury is characterized by the disruption of motor signals, which in turn results in damage to the neuromuscular junction. Furthermore, this process gives rise to a calcium imbalance, as well as the activation of pathways that lead to cell death and protein breakdown. Inflammatory cytokines have been demonstrated to promote catabolism by inhibiting protein synthesis and inducing atrogenes such as MuRF1 and MAFbx. Calcium-dependent enzymes have been demonstrated to contribute to protein degradation, thereby driving progressive muscle loss. These findings underscore the significance of timely, multidisciplinary interventions —integrating pharmacological, rehabilitative, and molecular strategies— to preserve muscle function and enhance outcomes in individuals with SCI.

Key words: muscle atrophy; spinal cord injury; treatment.

* *Corresponding author:* Antonio Ibarra. Universidad Anáhuac México, Centro de Investigación en Ciencias de la Salud (CICSA). Address: Av. Universidad Anáhuac núm. 46, Lomas Anáhuac, 52786. Huixquilucan, Estado de México, México. Tel.: +52 55 5627 0210 ext. 8524. Email: jose.ibarra@anahuac.mx

Received: March 6, 2025.
Accepted: September 3, 2025.

RESUMEN

Introducción: en el presente estudio se aborda una introducción al tema en cuestión. Las lesiones de la médula espinal se caracterizan por su repercusión en la calidad de vida de los pacientes, por lo tanto, resulta de particular interés comprender los mecanismos patológicos moleculares y genéticos fuertemente asociados al desarrollo de complicaciones musculares, tales como la atrofia. Estas complicaciones son características esenciales de las lesiones medulares, ocasionando restricciones adicionales en la movilidad y alteraciones sistémicas en el equilibrio celular**. Objetivos:** El propósito de la presente revisión es esclarecer los mecanismos moleculares e inflamatorios implicados en la atrofia muscular, contribuyendo así a la degeneración de las personas afectadas por lesiones de la médula espinal. En este estudio, se explorarán las opciones terapéuticas actuales con el objetivo de proporcionar un enfoque integral al estudio de la atrofia muscular en la lesión de la médula espinal y de identificar potenciales dianas terapéuticas. **Métodos y materiales empleados:** Este estudio constituye una revisión narrativa de la literatura, llevada a cabo mediante una exhaustiva investigación en línea en las bases de datos PubMed, SciELO y Web of Science, entre los meses de octubre de 2023 y enero de 2024. Se emplearon palabras clave como "lesión de la médula espinal", "atrofia muscular", "estrés oxidativo" y "músculo esquelético", utilizando operadores booleanos para refinar la búsqueda. El presente estudio aborda un total de 48 estudios seleccionados mediante criterios específicos. **Conclusiones:** La atrofia muscular posterior a la lesión medular se caracteriza por la interrupción de las señales motoras, lo que resulta en la afectación de las uniones neuromusculares, un desequilibrio en el calcio y la activación de vías de muerte celular y degradación de proteínas. El incremento de los factores inflamatorios estimula el catabolismo a través de la inhibición de la síntesis de proteínas y la activación de los genes reguladores de la degradación muscular, tales como MuRF1 y MAFbx. Las enzimas dependientes de calcio contribuyen a la degradación de las proteínas, lo que resulta en una pérdida progresiva de la masa muscular. Los hallazgos subrayan la relevancia de las intervenciones multidisciplinarias tempranas, que integran estrategias farmacológicas, de rehabilitación y moleculares, con el propósito de preservar la función muscular y optimizar los resultados en individuos con lesión medular.

Palabras clave: atrofia muscular; lesión medular; tratamiento.

INTRODUCTION

Spinal cord injury (SCI) is a devastating condition in which anatomical or electrophysiological disruption of the spinal cord interrupts the communication between the central nervous system and the peripheral nervous system.[1] This disruption leads to motor neuron dysfunction distal to the injury site, resulting in various physical impairments, with muscle atrophy being one of the most frequent.[2] Beyond the loss of neural input and output, inflammatory and signaling pathways play a significant role in long-term complications often associated with muscular and bone dysfunction, leading to a continuously worsening condition and, eventually, a downturn in the prognosis after SCI.

SCI etiology, according to Yanbo Liu *et al.,*[3] is mostly attributed to traumatic causes such as falls, violent acts, and transit-related injuries. The most prevalent and incidental level of damage is the cervical region, which is also related to the most significant disability. Given the trend of increasing global life expectancy over the last decades (reaching up to 73.5 years in 2019), the average age of individuals with SCI tends to increase. With a worldwide prevalence of around 20.6 million cases estimated in 2019 and very high medical management costs per individual, SCI is a matter of concern for global public health.[4]

SCI can be classified based on the injury mechanism and the chronological stages in which it presents. Regarding the first classification, non-traumatic SCI occurs when neuronal deterioration is mediated by immune-related, degenerative or infectious mechanisms. In contrast, traumatic SCI involves functional and physical interruption resulting from the external application of force conditioning, a complete or partial neuronal dysfunction distal to the injured segment.[5]

In this last case, the sudden application of force to the spinal cord not only damages the neuronal tissue, but also compromises blood vessels and adjacent structures such as bone, muscles and connective tissue, resulting in ischemia and the release of multiple proinflammatory mediators that will condition and perpetuate the dysfunction. In terms of chronological classification, the time from injury up to 48 hours is designated as the acute stage of SCI, between 48 hours and 14 days as subacute, 14 days to 6 months as intermediate, and after 6 months of clinical progression, it is considered a chronic lesion.[5] Throughout this process, depending on its stage, individuals with SCI experience

https://doi.org/10.36105/psrua.2025v5n10.03

varying degrees of inflammation and activation of signaling pathways. The inflammatory process, which is ongoing, has consequences for both damaged tissue and the potential for new long-term complications related to musculoskeletal dysfunction. These include the loss of muscle mass and, eventually, muscle atrophy. The chronological stages of SCI facilitate a pathophysiological understanding of immunological mechanisms and emphasize the significance of time-dependent medical therapies that prevent individuals from progressing to muscular complications.

In view of the considerable clinical implications of spinal cord injury, a thorough review of the mechanisms of muscle atrophy is both appropriate and necessary. The topic has been identified as being of significant relevance, primarily due to three key factors. Firstly, there is the increasing global prevalence of the condition. Secondly, there is the ageing population. Thirdly, and finally, there is the impact of muscle atrophy on long-term functionality. The physical consequences of muscle atrophy are twofold. Firstly, it limits mobility and independence. Secondly, it contributes to secondary complications.

These include, but are not limited to, insulin resistance, osteoporosis and cardiovascular disease. The latter two have been shown to drastically worsen prognosis and increase healthcare costs. Despite the advances made in the field of medicine, this narrative review offers a structured synthesis of the existing evidence, highlighting the gaps in literature and identifying emerging therapeutic approaches tailored to the mechanism of muscle atrophy. The objective of this review is twofold: firstly, to integrate epidemiological data, molecular insights and current treatment strategies; and secondly, to support evidence-based care and guide future research.

METHODOLOGY AND MATERIALS

This is a narrative literature review performed through online research in PubMed, SciELO, and Web of Science between October 2023 and January 2024. Keywords such as "spinal cord injury," "muscle atrophy," "oxidative stress," and "skeletal muscle" were used. Boolean operators were used in the following combinations: "spinal cord injury AND muscle atrophy", "spinal cord injury" AND "muscle atrophy" AND "oxidative stress" AND "molecular mechanisms", IF ("spinal cord injury" AND "muscle atrophy") THEN "oxidative stress". The selection criteria included English and Spanish language publications, evidence-based, especially focusing on muscle atrophy after SCI. Publications in languages other than English or Spanish were excluded. Articles that did not meet the eligibility criteria were excluded and classified, with reasons including insufficient data, non-indexed articles, and studies published in languages other than English or Spanish. Selected articles were published in journals related to immunology, oxidative stress, neuroscience, neurorehabilitation, molecular science, and neurology, between 2000 and 2024. Articles focused on prognosis, psychological impact, economic involvement, future aiming, and ethics were also excluded from this literature review.

Results of the search: A total of 294 records were initially identified. 150 from PubMed, 20 from SciELO, and 124 from Web of Science. After removing 84 duplicates, 210 records remained. A screening review of 210 documents was conducted by examining titles and abstracts, leading to the exclusion of 120 articles. Twenty of the remaining documents were not retrieved. The 70 remaining articles underwent a full text evaluation to determine if they met the inclusion criteria or not. Finally, 48 studies were selected (Figure 1). No automation tools were used in the process.

RESULTS

Muscle atrophy

Skeletal muscle is a key component of physiological metabolic homeostasis, including energy metabolism, thermogenesis, as well as mechanical and protective functions. Since 40% of our total body weight is muscle, representing approximately 50% of the total protein body mass-it is expected that any pathological process might trigger consequences that not only affect muscular tissue but also impact multiple metabolic processes and molecular pathways.[6]

Muscular tissue is composed of excitable contractile myofibers, which can be classified into three types based on their oxidative rate: Type I (slow oxidative rate), also known as red muscle fibers; Type IIa (fast oxidative rate); and Type IIb (fast glycolytic rate), also called white muscle fibers, which are capable of hydrolyzing ATP faster than type I fibers.[6]

The term "muscle atrophy" is defined as a skeletal muscle disorder characterized by the progressive deterioration of functionality and muscle mass decline. The categorization of this condition may be facilitated by its underlying etiology, which can be defined as the causative agents that precipitate the onset of the disease. In this instance, etiology is

constituted by congenital diseases, which are characterized by the presence of protein mutations. These mutations are the primary causative agents of muscle atrophy. However, the present review highlights that acquired muscular dysfunction may also result from malnutrition, sepsis, or neural disconnection causing muscular atrophy. In such cases, the underlying condition and the person's immobilization create an imbalance between protein synthesis and degradation, triggered by multiple signaling pathways, such as the sphingosine 1-phosphate signaling axis activated by the release of TNFα in acute inflammation affecting skeletal muscle myotubes. The result of these events is the promotion of cellular apoptosis, muscle wasting, weakness, and muscle atrophy, thereby perpetuating muscular dysfunction and clinically leading to a decline in mobility.[6-9] Histologically, atrophied muscle is characterized by a significant reduction in myofiber diameters and a hypereosinophilic sarcoplasm. However, in denervation atrophy, as observed in SCI, the characteristic histologic feature includes myofibers that are compressed and have crowded nuclei, along with the.

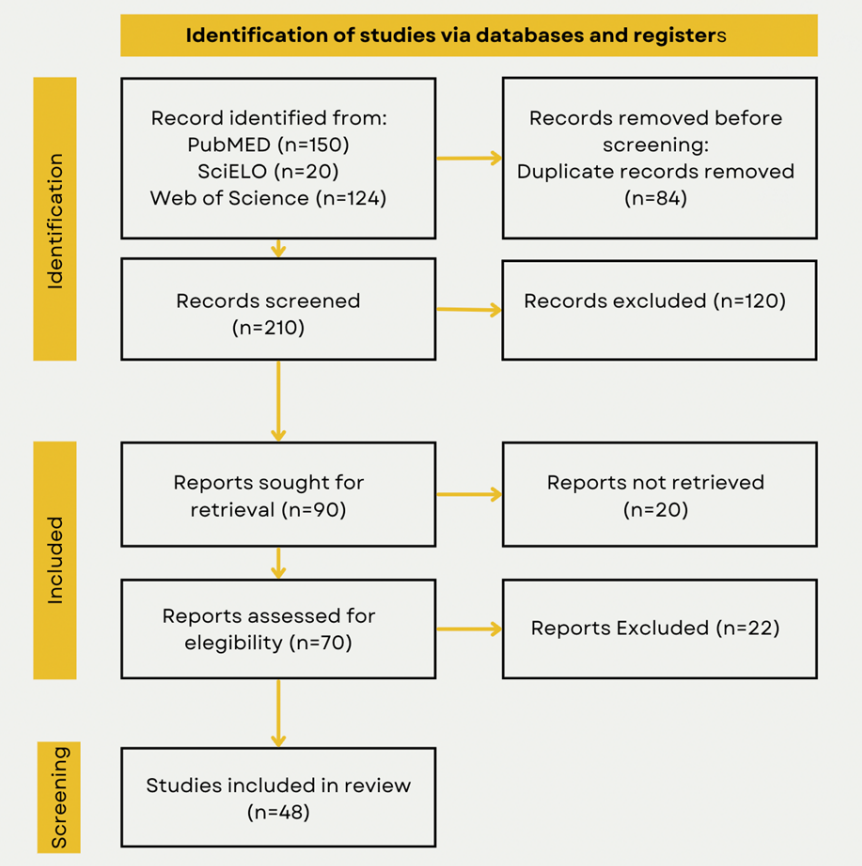

Figure 1. Prisma research flow diagram, 210 articles were screened, from PubMED, SciELO and Web of Science, after assessing eligibility, only 48 studies were included.

Loss of organelles and changes in muscular cell types. It is important to note that in animal models, a specific tendency to change the type of muscle fiber has been observed in type II fibers in cases of atrophy secondary to disuse, cachexia and malnutrition.[10]

After SCI, the disconnection of the neural network and the resulting lack of muscular movement lead to atrophy. In the complex neuronal relation between the spinal cord and skeletal muscle, there are three types of motor neurons that are crucial in the pathophysiology of muscular

https://doi.org/10.36105/psrua.2025v5n10.03

atrophy: Alpha, Beta and Gamma motor neurons. Since alpha motor neurons contain extrafusal fibers and are found predominantly at neuromuscular junctions, they act as force regulators. Gamma motor neurons have intrafusal fibers distributed largely in muscle spindles which act as somatosensorial mechanoreceptors, therefore modulating the length of muscular fibers during contraction. Finally, Beta motor neurons contain both extrafusal and intrafusal fibers.[7,8] Studies have shown that whenever there is a sudden neuronal interruption, motor neurons can become highly excited promoting deep hyperreflexia and even spasticity.[9] With the interruption of the synaptic communication between any given motor neuron and its corresponding neuromuscular junction, the motor endplate undergoes a degeneration process, resulting in the inability to eliminate acetylcholine, consequently leading to the accumulation of substrates such as calcium and the initiation of apoptotic processes in skeletal muscle.[9]

Consequently, the process of muscle atrophy after any SCI is not solely attributable to a sudden absence of neural input; it is also associated with various molecular pathways and molecular phenomena, including mitochondrial dysfunction, increased oxidative stress, inflammation, and the activation of multiple proteolytic enzymes that contribute to muscle wasting, cell apoptosis, and muscle atrophy.

Signaling Pathways, Inflammation and Proinflammatory Cytokines Involved in Muscle Atrophy

Muscle atrophy is a condition mediated by "atrogens", which are activated through various proteolytic pathways associated with this pathological process.[9] Given the complexity of the factors involved in these associated mechanisms, it is essential to understand some of the key elements intimately related to this common complication of SCI.

After a traumatic event involving the spinal cord, multiple factors and signaling pathways are activated to respond to the macro and microscopic damage caused by the initial insult. Although these elements initially aim to contain further damage and eliminate cellular debris, they eventually contribute to the perpetuation and development of muscle atrophy. Cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1/6 (IL-1, IL-6), and tumor necrosis factor-like weak apoptosis inducer (TWEAK) act as pro-inflammatory mediators and are directly linked to muscle catabolism through the down-regulation of mRNA translation and blockage of muscle protein synthesis by inhibiting the PI3K/Akt pathway and promoting the transcription of atrophy-related genes (e.g. MuRF1, MAFbx).[11]

Following SCI, an increased intracellular calcium concentration has been identified as the starting point of a cascade of events that culminate in the participation of calcium-dependent proteases called calpains. These enzymes function as catalysts in proteolytic processes and contribute to the inhibition of various signaling pathways that ultimately result in muscle destruction.[11] The role of Calpain in calcium-mediated protein decomposition is to inhibit and catalyze the proteolytic events involved in muscle atrophy. Caspases are implicated in the loss of muscle fibers, as they play an essential role in apoptosis.[12] Additionally, the recruitment and activation rate of autophagic lysosomes that degrade protein-based material, is particularly important. These lysosomes show heightened activity during SCI and have preference for glycolytic type II muscle fibers in their autophagic process, as seen in Figure 2.[13]

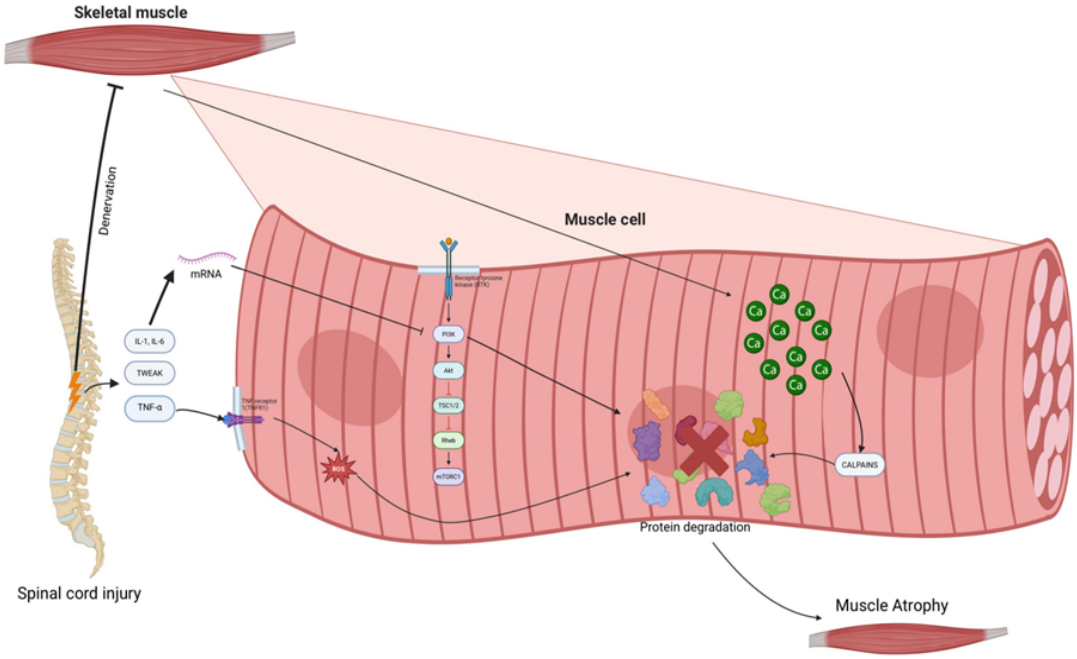

FIGURE 2. This image illustrates the complex network of molecular pathways leading to muscle atrophy following spinal cord injury (SCI). Key pro-inflammatory cytokines: TNF-α, IL-1/6, and TWEAK, initiate cascades that inhibit anabolic pathways such as PI3K/Akt and promote protein degradation via calpains, caspases, autophagy, and the ubiquitin-proteasome system. This intricate interplay underscores the multifactorial nature of SCI-induced muscle atrophy. Figure self-made in Biorender. IL: interleukin, mRNA: messenger ribonucleic acid, TWEAK: tumor necrosis factor-like weak inducer of apoptosis, TNF: tumor necrosis factor, PI3K: phosphatidylinositol 3-kinase, ROS: reactive oxygen species, mTORC1: mechanistic target of rapamycin complex 1, Ca: Calcium, Rheb: Ras homolog enriched in brain.

Another mechanism of muscle atrophy and catabolic induction is the ubiquitin-proteasome system, which consists of various enzymes and proteins that work together to degrade proteins, including ubiquitin itself, and a 26S proteasome responsible for degrading the polypeptides formed by the system, thereby promoting protein replacement.[6] Some ubiquitin-related proteins are of special interest because of their transcription factors, such as O-type forkhead transcription factor (FOXO), which plays an essential role in muscle atrophy by participating in many protein destruction pathways.[14]

The function of the Ubiquitin-E3 ligase muscle ring finger-1 (MuRf1) is of particular interest, as this gene has been found to be profoundly linked to muscle mass loss in recent studies and is recognized as a molecular marker of muscle atrophy. Another strongly involved ligase is muscle atrophy F-box/MAFbx (Atrogin-1), which has been observed to act as a mediator of myofibril degradation, making it a key component of these pathophysiological mechanisms.[15] It is worth mentioning that in many animal models, the expression of these factors can be significantly increased following SCI.[6,15,16]

Despite the existence of multiple catabolic mechanisms involved in SCI, we can also find factors that activate anabolic pathways, such as the signaling stream mediated by insulin-like growth factor-1 (IGF-1) that results in the activation of phosphatidylinositol-3 kinase (PI3K)/Akt, promoting hypertrophy and nerve regeneration.[9] Unfortunately, inflammation caused by SCI can significantly affect the concentration of substrates needed for these anabolic functions, thus impairing these capabilities and ultimately preventing muscle mass regeneration. Additionally, it has been observed that this down-regulation can persist chronically in subjects with a complete spinal cord section.[16]

As previously mentioned, there is a very complex interaction between molecules, genes and signaling pathways that lead to muscle mass reduction. Among them, TNF-α has multiple physiological functions related to immunity and inflammatory response. In addition, it is also known for

https://doi.org/10.36105/psrua.2025v5n10.03

its involvement in apoptotic events when it is attached to the TNF receptor-1 (TNFR1). This results in the activation of multiple substrates that trigger the production and accumulation of reactive oxygen species, the transcription of proapoptotic protein mediators, and the activation and recruitment of caspases, which are closely linked to myofibrillar degradation and muscle mass loss.[17,18]

Additionally, individuals with pathological signaling pathway activation secondary to SCI present several mechanisms that promote muscle atrophy. Among these, myostatin, within the TGFβ superfamily, is of particular interest due to its expression being limited to skeletal muscle.[19] Myostatin regulates the transcription of genes such as MuRF1 and Atrogin1 through the phosphorylation of Smad complexes (Smad2/Smad3, and later Smad4), limiting muscle growth and playing a major role in muscle mass loss.[9,19] Equally important, there are multiple types of tissue and cell bodies capable of secreting interleukin-6 (IL-6), including adipocytes, cardiomyocytes, leucocytes and even skeletal muscle.[18] Specifically in skeletal muscle tissue, IL-6 plays an important role in the activation of muscle satellite cells. By doing so, it contributes to the development of new muscle cells; however, it has been observed that constant and long-term exposure to IL -6, in conjunction with other factors such as TNF-alpha, can promote muscle atrophy.[9,18]

This phenomenon also applies to TWEAK, belonging to the TNF superfamily, which is primarily produced in tissues undergoing active inflammation, such as the muscle and connective tissue involved in SCI. It is also linked to proteolysis and oxidative stress through nuclear factor kappa-light-chain-enhancer of B cells (NF-kappa-B).[9] In addition, fibroblast growth factor-inducible 14 (Fn14) acts as a TWEAK receptor, and the binding of these two components has been proven to induce tissue remodeling and fibrosis.[20] Thus, both TWEAK and TWEAK/Fn14 are involved in the pathological remodeling of skeletal muscle, leading to atrophy through their continuous activity in injured individuals.

Oxidative stress and Mitochondrial dysfunction

Mitochondrial biogenesis is regulated by various factors, including peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), a transcriptional coactivator that is highly expressed in skeletal muscle. Through various signaling pathways, PGC-1α can increase the transcription of mitochondrial genes in response to certain stimuli, such as increased energy demand, as seen in SCI.[9,21] Moreover, PGC-1α is closely linked to the upregulation in antioxidant factors. Thus, PGC-1α provides oxidative stress protection not only through mitochondrial regulation and functions such as reactive oxygen species (ROS) detoxification and oxidative phosphorylation but also by promoting diverse antioxidant substrates that prevent oxidative damage and ensure mitochondrial survival.[21]

However, PGC-1α levels can significantly decrease with inflammation. Mitochondrial dysfunction invariably leads to an imbalance in the production and elimination of reactive oxygen species (ROS), which consequently promotes signaling and proapoptotic pathways in muscle cells.[9] It is known that due to mitochondrial function, ROS are inevitably produced, however, this production coexists in a delicate balance with their elimination through antioxidant agents. Therefore, any stimulus that aggravates this balance results in the accumulation of ROS and is reflected in the deterioration of cellular functions.[22]

Finally, in conditions with long-term inflammatory environments, such as SCI, the downregulation of PGC1-α might perpetuate and increase oxidative damage. In addition to the harmful mechanisms triggered by inflammation that can inevitably result in muscle atrophy, it is important to note that muscle atrophy itself is also related to an increase in oxidative stress, creating a self-sustaining inflammatory loop initiated by the initial injury and further perpetuated by muscle atrophy.[23] Exogenous antioxidant therapy (e.g. vitamin D) has been recommend recently to reduce or reverse oxidative stress and support the muscular rehabilitation of individuals after SCI.

Bone Implications in Muscle Atrophy

The lack of motion in the limbs following a SCI, which leads to the absence of mechanical stress, has a particularly negative impact on the physiological functions of the bone, since mechanical stress is one of the main promoters of bone remodeling.[24]

Moreover, the delicate balance between bone formation and resorption depends on multiple factors that stimulate complex signaling pathways, resulting in cell differentiation into either osteoclasts or osteoblasts. On one hand, osteoblasts can produce macrophage-colony stimulating factor (M-CSF) and RANKL, which, when combined with RANK, trigger a signaling cascade leading to the differentiation of osteoclasts. These osteoclasts, along with cathepsin k and hydrochloric acid, are responsible for bone resorption. On the other hand, the recruitment of

osteoblasts leads to the formation of new bone segments along with osteocytes.[25]

When limb motility is lost, the mechanical stimuli that the bone is designed to carry is no longer available. Therefore, in the absence of these mechanical stimuli, osteocytes will not produce signals that promote bone remodeling, leading to a decrease in bone tissue, osteoporosis, and a greater risk of fracture.[24,25] Interestingly, elevated IL-6 concentrations have been identified in individuals with SCI, attributed to osteoclast-like cell stimulation observed in bone marrow cultures of people with paraplegia.[25] Some studies suggest that the loss of bone quality may begin shortly after an SCI and can persist chronically if not adequately addressed.[24,26]

Systemic Implications of Muscle Atrophy

Beyond the outcomes that specifically concern the musculoskeletal system, there are multiple systemic repercussions that can substantially deteriorate the prognosis of the SCI individuals. The inability to perform certain activities due to SCI leads to a significantly sedentary lifestyle. Given the musculoskeletal conditions resulting from SCI, there is a tendency towards insulin resistance and alterations in carbohydrate metabolism, as well as difficulty in thermoregulation and accumulation of adipose tissue. These factors may lead to a higher incidence of cardiometabolic morbidities, atherosclerosis, dyslipidemias, chronic renal disease, among other conditions, compared to people without SCI.[27–29] There has also been a clear association between low muscle mass and cardiovascular events, specifically in SCI individuals with cervical or thoracic injuries that compromise the cardiorespiratory function. Physical rehabilitation to maintain muscle mass has been proven to improve pulmonary capacity and systemic cardiovascular function.[29]

Pharmacological management approach

To date, no pharmacological strategies have demonstrated significant reduction or reversal of muscle atrophy. Nonetheless, given the number of signaling pathways involved in the pathophysiology of this process, several therapeutic options are currently available, and some others are still under study, which could radically change the outcomes for individuals with SCI.

As previously mentioned, muscle atrophy in SCI involves the disruption of many molecular pathways. Due to the variety of these alterations, there are as many clinical approaches as there are disturbances. For instance, it has been identified that up to 60% of men who have suffered an SCI present with gonadal dysfunction and, as a result, a decrease in total testosterone levels.[15]

Testosterone, an androgen with anabolic effect, is strongly linked to the maintenance of proper musculoskeletal function. It not only contributes to increasing muscle mass but has also been observed to promote protein synthesis by activating PI3K/Akt pathways, thereby decreasing the expression of MAFbx, FOXO1, MuRF1, and other genes involved in muscle atrophy.[15,16,30,31]

Additionally, testosterone is involved in neuronal recovery processes and is known to have neuroprotective characteristics against oxidative stress.[32] However, it is important to consider the risks involved in testosterone hormone therapy, with one of the main concerns being prostate growth in males.[14] As a result, this therapy is not yet a viable option to prevent muscle wasting and atrophy on its own, as it requires further studies.

It is evident that mitochondrial dysfunction, in conjunction with the subsequent accumulation of ROS, constitutes a pivotal factor in the progressive decline in muscle function and mass. Consequently, a therapeutic approach that has been proposed is the utilization of antioxidants. It has been hypothesized that the utilization of vitamins, including but not limited to vitamin E and vitamin D, may result in a reduction in the prevalence of muscle atrophy. It has been determined that the incorporation of polyphenols could play a pivotal role in the prevention of mitochondrial dysfunction. This process involves the elimination of the accumulation of ROS and the reduction of the pro-inflammatory stimulus that promotes and perpetuates skeletal muscle damage.[33]

Various other options have been explored as part of the pharmacological approach to muscle atrophy, targeting the signaling pathways involved in this condition. For instance, pharmacological agents that inhibit myostatin, which, as previously discussed, is an important factor restricting muscle growth through the regulation of genes linked to muscle atrophy, although they have not been proven to be completely effective in SCI management. It has been hypothesized that the potential exists for the utilization of β2-agonists to promote protein synthesis and activate PI3K/Akt signaling pathways, thereby achieving anabolic benefits.[14,19,34] However, despite their individually promising therapeutic effects, these approaches are not sufficient to completely meet the needs of an individual with muscle atrophy secondary to SCI, as there is currently

https://doi.org/10.36105/psrua.2025v5n10.03

no pharmacological option available that can address the complex signaling network involved in this condition.[16]

Genetic, cellular and other managements in development and study

The possibility of a genetic approach to the management of muscular atrophy has significantly developed over the last few decades. However, current limitations in this field still represent a hurdle for its implementation as a definitive treatment.

The potential exists for the application of both muscle-derived and non-muscle-derived stem cells to mitigate this complication. In addition, endeavors to identify efficacious therapies for the management of muscle atrophy have resulted in the exploration of strategies such as the controlled use of tetanus neurotoxin. These have the capacity to be transported by the axon after their internalization at the neuromuscular junction, thereby activating a series of complex mechanisms that lead to the disinhibition of the involved motor neurons.[35,36] However, despite being excellent therapeutic alternatives, they still have technical complications that prevent their full therapeutic implementation.[33,35]

Functional Electrical Stimulation

Functional Electrical Stimulation (FES) involves the application of controlled electrical impulses to neuromuscular junctions and muscle fibers via surface electrodes to induce muscular contraction. It is widely used as a rehabilitation and injury prevention technique. When combined with resistance training, this electrical stimulation can be a highly effective therapeutic resource, resulting in muscular hypertrophy and improving overall bone and muscle health.[37,38] There are several modalities for this electrostimulation therapy, including FES-cycling, FES-rowing, FES-assisted, and electro stimulated resistance training (NMEST-RT).[38]

Maintaining proper muscle function through FES has been shown to increase muscle mass, improve blood circulation, and enhance cardiorespiratory performance. It is also associated with a reduction in complications related to muscle atrophy, such as fractures, venous thrombosis, and glucose intolerance.[39,40] Furthermore, evidence suggests that FES can be combined with other therapies, such as blood flow restriction, to achieve positive effects and long-term results.[41]

The integration of assistive technologies with therapeutic approaches has proven to be highly beneficial for individuals' functionality. Despite partial or complete denervation secondary to an SCI, upper motor stimulus may still be produced. In recent years, work has focused on developing neuromechanical prosthetic models, designed to replicate or enhance the mechanical or neurological function of extremities affected by the lack of neural input, acting as exoskeleton that promote functional recovery.[42,43]

It is worth mentioning that even with the growing development of devices featuring neuromechanical technology, any instrument that facilitates the performance of activities for the individuals is considered an assistive device, whether it is a wheelchair or a robotic device. Despite the availability of multiple assistive devices, physical rehabilitation and muscular resistance exercises are essential components of the comprehensive management of SCI individuals, as they have proven to be especially effective in preserving muscle mass and preventing complications.[44]

Physical Rehabilitation

The fundamental principle of physical rehabilitation lies in the systematic repetition of movements, with or without resistance, aimed at improving physical capacity and muscle strength.[45] Evidence supports the necessity of physical therapy in individuals with muscle atrophy secondary to spinal cord dysfunction, regardless of whether it is of traumatic origin.[46] However, an interdisciplinary approach is crucial for creating a personalized program that adjusts the required number of sessions, intensity, and exercises to the specific needs of everyone, according to the severity of their condition. Thus, extremely encouraging results can be obtained, which, when combined with the previously mentioned therapeutic efforts, can drastically change both the prognosis and the quality of life of people with spinal cord injury.[45,47,48]

CONCLUSION

Spinal cord injury (SCI) induces profound skeletal muscle atrophy through mechanisms that extend beyond the loss of neural stimulation. Current evidence demonstrates that muscle wasting is driven by a complex interaction of chronic inflammation, mitochondrial dysfunction, oxidative stress, and proteolytic systems such as the ubiquitin-proteasome pathway, calpains, and caspases. Proinflammatory cytokines,

including TNF-α, IL-6, and TWEAK, not only inhibit anabolic signaling pathways like PI3K/Akt but also promote the expression of key atrogenes such as MuRF1 and Atrogin-1, directly contributing to protein degradation. These changes affect type II muscle fibers and are compounded by elevated intracellular calcium levels, which exacerbate apoptotic and autophagic activity. Although anabolic pathways mediated by IGF-1 attempt to counteract muscle loss, their effects are limited by the persistent inflammatory environment. Furthermore, the downregulation of PGC-1α disrupts mitochondrial biogenesis and antioxidant defense, intensifying oxidative damage. Collectively, these findings highlight the multifactorial nature of muscle atrophy in SCI and establish the need for targeted therapeutic strategies that address the underlying molecular mechanisms to preserve muscle mass and improve systemic outcomes in affected individuals. Clinical implications of the present study urge physicians to implement multidisciplinary clinical approach; clinicians must consider not only musculoskeletal rehabilitation but also systemic monitoring and intervention to mitigate secondary muscle atrophy complications. Early personalized interventions integrating pharmacological, rehabilitative, and assistive technology to optimize patient outcomes and preserve long-term functionality. Future research should focus on the identification of molecular targets and biomarkers to guide tailored therapies.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. James SL, Bannick MS, Montjoy-Venning WC, Lucchesi LR, Dandona L, Dandona R, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Jan 1;18[1]:56–87. https://doi.org/10.1016/S1474-4422(18)30415-0
2. Badhiwala JH, Wilson JR, Fehlings MG. Global burden of traumatic brain and spinal cord injury. 18, The Lancet Neurology. Lancet Publishing Group; 2019:24–5. https://doi.org/10.1016/s1474-4422(18)30444-7
3. 3Liu Y, Yang X, He Z, Li J, Li Y, Wu Y, et al. Spinal cord injury: global burden from 1990 to 2019 and projections up to 2030 using Bayesian age-period-cohort analysis. 14, Frontiers in Neurology. Frontiers Media; 2023. https://doi.org/10.3389/fneur.2023.1304153
4. Ding W, Hu S, Wang P, Kang H, Peng R, Dong Y. Spinal Cord Injury: The Global Incidence, Prevalence, and Disability from the Global Burden of Disease Study 2019. Spine [Phila Pa 1976]. 2022 Nov 1;47[21]:1532–40. https://doi.org/10.1097/brs.0000000000004417
5. Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. 3, Nature Reviews Disease Primers. Nature Publishing Group; 2017. https://doi.org/10.1038/nrdp.2017.18
6. Yin L, Li N, Jia W, Wang N, Liang M, Yang X, et al. Skeletal muscle atrophy: From mechanisms to treatments. 172, Pharmacological Research. Academic Press; 2021. https://doi.org/10.1016/j.phrs.2021.105807
7. Friese A, Kaltschmidt JA, Ladle DR, Sigrist M, Jessell TM, Arber S. Gamma and alpha motor neurons distinguished by expression of transcription factor Err3 [Internet]. 2009 Jun. Available from: https://doi.org/10.1073/pnas.0906809106
8. Ninfali C, Siles L, Darling DS, Postigo A. Regulation of muscle atrophy-related genes by the opposing transcriptional activities of ZEB1/CtBP and FOXO3. Nucleic Acids Res. 2018;46[20]:10697–708. https://doi.org/10.1093/nar/gky835
9. Tong T, Marino JS, Li JJ, Yang DG, C-j Z, Y-z P. Open access edited by Mechanism of skeletal muscle atrophy after spinal cord injury: A narrative review. 2023:1099143. https://doi.org/10.3389/fnut.2023.1099143
10. Torrie A. Crabbs. Skeletal Muscle - Atrophy [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25035576
11. Cohen S. Role of calpains in promoting desmin filaments depolymerization and muscle atrophy. 1867, Biochimica et Biophysica Acta - Molecular Cell Research. Elsevier B.V.; 2020. https://doi.org/10.1016/j.bbamcr.2020.118788
12. Singh A, Yadav A, Phogat J, Dabur R. Dynamics and Interplay between Autophagy and Ubiquitin-proteasome system Coordination in Skeletal Muscle Atrophy. Curr Mol Pharmacol. 2021 Aug 9;15[3]:475–86. https://doi.org/10.2174/1874467214666210806163851
13. Franco-Romero A, Sandri M. Role of autophagy in muscle disease. Mol Aspects Med. 2021 Dec 1;82. https://doi.org/10.1016/j.mam.2021.101041
14. Ji Y, Li M, Chang M, Liu R, Qiu J, Wang K. Inflammation: Roles in Skeletal Muscle Atrophy. 11, Antioxidants. MDPI; 2022. https://doi.org/10.3390/antiox11091686

https://doi.org/10.36105/psrua.2025v5n10.03

15. Otzel DM, Lee J, Ye F, Borst SE, Yarrow JF. Activity-based physical rehabilitation with adjuvant testosterone to promote neuromuscular recovery after spinal cord injury. 19, International Journal of Molecular Sciences. MDPI AG; 2018. https://doi.org/10.3390/ijms19061701
16. Otzel DM, Kok HJ, Graham ZA, Barton ER, Yarrow JF. Pharmacologic approaches to prevent skeletal muscle atrophy after spinal cord injury. 60, Current Opinion in Pharmacology. Elsevier Ltd; 202:193–9. https://doi.org/10.1016/j.coph.2021.07.023
17. Idriss HT, Naismith JH. TNFα and the TNF receptor superfamily: Structure-function relationship[s]. Microsc Res Tech. 2000 Aug 1;50[3]:184–95. https://doi.org/10.1002/1097-0029(20000801)50:3%3C184::AID-JEMT2%3E3.0.CO;2-H
18. Drasites KP, Shams R, Zaman V, Matzelle D, Shields DC, Garner DP, et al. Review pathophysiology, biomarkers, and therapeutic modalities associated with skeletal muscle loss following spinal cord injury. 10, Brain Sciences. MDPI AG; 2020:1–13. https://doi.org/10.3390/brainsci10120933
19. Abati E, Manini A, Comi G Pietro, Corti S. Inhibition of myostatin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases. 79, Cellular and Molecular Life Sciences. Springer Science and Business Media Deutschland GmbH; 2022. https://doi.org/10.1007/s00018-022-04408-w
20. Zhang Y, Zeng W, Xia Y. TWEAK/Fn14 axis is an important player in fibrosis. 236, Journal of Cellular Physiology. Wiley-Liss Inc.; 2021:3304–16. https://doi.org/10.1002/jcp.30089
21. Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S, Sandhu MA. PGC-1 α, Inflammation, and Oxidative Stress: An Integrative View in Metabolism. Oxid Med Cell Longev. 2020. https://doi.org/10.1155/2020/1452696
22. Zhang B, Pan C, Feng C, Yan C, Yu Y, Chen Z. Role of mitochondrial reactive oxygen species in homeostasis regulation. 27, Redox Report. Taylor and Francis Ltd.; 2022:45–52. https://doi.org/10.1080/13510002.2022.2046423
23. Savikj M, Kostovski E, Lundell LS, Iversen PO, Massart J, Widegren U. Altered oxidative stress and antioxidant defense in skeletal muscle during the first year following spinal cord injury. Physiol Rep. 2019;7[16]. https://doi.org/10.14814/phy2.14218
24. Abdelrahman S, Ireland A, Winter EM, Purcell M, Coupaud S. Osteoporosis after spinal cord injury: aetiology, effects and therapeutic approaches [Internet]. Available from: http://www.ismni.org
25. Shams R, Drasites KP, Zaman V, Matzelle D, Shields DC, Garner DP, et al. The pathophysiology of osteoporosis after spinal cord injury. 22 International Journal of Molecular Sciences. MDPI AG; 2021. https://doi.org/10.3390/ijms22063057
26. Choi H, Chang SY, Yoo J, Lim SH, Hong BY, Kim JS. Correlation Between Duration from Injury and Bone Mineral Density in Individuals with Spinal Cord Injury. Ann Rehabil Med. 2021 Feb 1;45[1]:1–6. https://doi.org/10.5535/arm.20169
27. Peterson MD, Berri M, Lin P, Kamdar N, Rodriguez G, Mahmoudi E. Cardiovascular and metabolic morbidity following spinal cord injury. Spine Journal. 2021 Sep 1;21[9]:1520–7. https://doi.org/10.1016/j.spinee.2021.05.014
28. Smith DL, Yarar-Fisher C. Contributors to Metabolic Disease Risk Following Spinal Cord Injury. 4, Current Physical Medicine and Rehabilitation Reports. Springer; 2016:190–9. https://doi.org/10.1007/s40141-016-0124-7
29. Gibbs JC, Gagnon DH, Bergquist AJ, Arel J, Cervinka T, El-Kotob R. Rehabilitation Interventions to modify endocrine-metabolic disease risk in Individuals with chronic Spinal cord injury living in the Community [RIISC]: A systematic review and scoping perspective. Journal of Spinal Cord Medicine. 2017 Nov 2;40[6]:733–47. https://doi.org/10.1080/10790268.2017.1350341
30. Holman ME, Gorgey AS. Testosterone and Resistance Training Improve Muscle Quality in Spinal Cord Injury. Med Sci Sports Exerc. 2019 Aug 1;51[8]:1591–8. https://doi.org/10.1249/mss.0000000000001975
31. Gorgey AS, Lester RM, Ghatas MP, Sisturn SN, Lavis T. Dietary manipulation and testosterone replacement therapy may explain changes in body composition after spinal cord injury: A retrospective case report. World J Clin Cases. 2019 Sep 1;7[17]:2427–37. https://doi.org/10.12998/wjcc.v7.i17.2427 https://doi.org/10.12998/wjcc.v7.i17.2427
32. Sengelaub DR, Han Q, Liu NK, MacZuga MA, Szalavari V, Valencia SA, et al. Protective Effects of Estradiol and Dihydrotestosterone following Spinal Cord Injury. J Neurotrauma. 2018 Mar 15;35[6]:825–41. https://doi.org/10.1089/neu.2017.5329
33. Huang L, Li M, Deng C, Qiu J, Wang K, Chang M, et al. Potential Therapeutic Strategies for Skeletal Muscle Atrophy. 12, Antioxidants. MDPI; 2023.
34. Scholpa NE, Simmons EC, Tilley DG, Schnellmann RG. β2-adrenergic receptor-mediated mitochondrial biogenesis improves skeletal muscle recovery following

spinal cord injury. Exp Neurol. 2019 Dec 1;322. https://doi.org/10.3390/antiox12010044

35. Kutschenko A, Manig A, Mönnich A, Bryl B, Alexander CS, Deutschland M, et al. Intramuscular tetanus neurotoxin reverses muscle atrophy: a randomized controlled trial in dogs with spinal cord injury. J Cachexia Sarcopenia Muscle. 2022 Feb 1;13[1]:443–53. https://doi.org/10.1002/jcsm.12836
36. Megighian A, Pirazzini M, Fabris F, Rossetto O, Montecucco C. Tetanus and tetanus neurotoxin: From peripheral uptake to central nervous tissue targets. Journal of Neurochemistry. John Wiley and Sons Inc; 2021.1244–53. https://doi.org/10.1111/jnc.15330
37. Chandrasekaran S, Davis J, Bersch I, Goldberg G, Gorgey AS. Electrical stimulation and denervated muscles after spinal cord injury. 15, Neural Regeneration Research. Wolters Kluwer Medknow Publications; 2020:1397–407. https://doi.org/10.4103/1673-5374.274326
38. Atkins KD, Bickel CS. Effects of functional electrical stimulation on muscle health after spinal cord injury. 60, Current Opinion in Pharmacology. Elsevier Ltd; 2021: 226–31. https://doi.org/10.1016/j.coph.2021.07.025
39. Thomaz SR, Cipriano G, Formiga MF, Fachin-Martins E, Cipriano GFB, Martins WR, et al. Effect of electrical stimulation on muscle atrophy and spasticity in patients with spinal cord injury – a systematic review with meta-analysis. 57, Spinal Cord. Nature Publishing Group; 2019:258–66. https://doi.org/10.1038/s41393-019-0250-z
40. Gorgey AS, Khalil RE, Davis JC, Carter W, Gill R, Rivers J, et al. Skeletal muscle hypertrophy and attenuation of cardio-metabolic risk factors [SHARC] using functional electrical stimulation-lower extremity cycling in persons with spinal cord injury: Study protocol for a randomized clinical trial. Trials. 2019 Aug 23;20[1]. https://doi.org/10.1186/s13063-019-3560-8
41. Skiba GH, Andrade SF, Rodacki AF. Effects of functional electro-stimulation combined with blood flow restriction in affected muscles by spinal cord injury. Neurological Sciences. 2022 Jan 1;43[1]:603–13. https://doi.org/10.1007/s10072-021-05307-x
42. Pizzolato C, Saxby DJ, Palipana D, Diamond LE, Barrett RS, Teng YD, et al. Neuromusculoskeletal modeling-based prostheses for recovery after spinal cord injury. Front Neurorobot. 2019;13. https://doi.org/10.3389/fnbot.2019.00097
43. Nistor-Cseppento CD, Gherle A, Negrut N, Bungau SG, Sabau AM, Radu AF, et al. The Outcomes of Robotic Rehabilitation Assisted Devices Following Spinal Cord Injury and the Prevention of Secondary Associated Complications. 58, Medicina [Lithuania]. MDPI; 2022. https://doi.org/10.3390/medicina58101447
44. de Sire A, Moggio L, Marotta N, Curci C, Lippi L, Invernizzi M, et al. Impact of rehabilitation on volumetric muscle loss in subjects with traumatic spinal cord injury: A systematic review. 52, NeuroRehabilitation. IOS Press BV; 2023:365–86. https://doi.org/10.3233/NRE-220277
45. Hurst C, Robinson SM, Witham MD, Dodds RM, Granic A, Buckland C. Resistance exercise as a treatment for sarcopenia: Prescription and delivery. 51, Age and Ageing. Oxford University Press; 2022. https://doi.org/10.1093/ageing/afac003
46. Mirea A, Leanca MC, Onose G, Sporea C, Padure L, Shelby ES, et al. Physical Therapy and Nusinersen Impact on Spinal Muscular Atrophy Rehabilitative Outcome. Frontiers in Bioscience - Landmark. 2022 Jun 1;27[6]. https://doi.org/10.31083/j.fbl2706179
47. Lu L, Mao L, Feng Y, Ainsworth BE, Liu Y, Chen N. Effects of different exercise training modes on muscle strength and physical performance in older people with sarcopenia: a systematic review and meta-analysis. BMC Geriatr. 2021 Dec 1;21[1]. https://doi.org/10.1186/s12877-021-02642-8
48. Jones MA, McEwen IR, Hansen L. Use of Power Mobility for a Young Child with Spinal Muscular Atrophy. 2003.