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Spinal Cord Injury: Emergency Assessment, Multidisciplinary Management, Rehabilitation, and Long-Term Care-An Updated Review.

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Abstract

Background: Spinal cord injury (SCI) is a cause of disability. It can produce motor, sensory, and autonomic dysfunction and affect bladder and bowel control, respiratory function, and well-being. The initial mechanical injury is followed by secondary processes, including ischemia, inflammation, oxidative stress, excitotoxicity, and tissue damage.

Aim: This review examines the assessment and management of SCI, with attention to emergency care, pharmacological and surgical treatment, rehabilitation, nursing, long-term support, and regenerative strategies.

Content: The review outlines spinal cord anatomy and the primary and secondary mechanisms of injury. It discusses the acute, subacute, intermediate, and chronic phases and considers treatment approaches aimed at limiting secondary damage, decompressing and stabilizing the spine, managing pain and spasticity, and preventing complications. The roles of rehabilitation, physical and occupational therapy, assistive devices, and psychosocial support are also addressed. In addition, the review summarizes tissue-engineering strategies using natural, synthetic, and hybrid biomaterials, as well as cell-based approaches involving neural stem or progenitor cells, mesenchymal stromal cells, dental pulp stem cells, oral mucosa stem cells, olfactory ensheathing cells, and induced pluripotent stem cells. Signaling pathways and mediators, including neurotrophic factors, inflammatory cytokines, chondroitin sulfate proteoglycans, and cyclic AMP, are considered in relation to neural survival and regeneration.

Conclusion: SCI care requires coordinated acute treatment and sustained rehabilitation. Biomaterial scaffolds, cellular therapies, and molecular interventions offer routes to tissue repair, but most remain experimental and require further evaluation of efficacy, safety, and outcomes.

Keywords: spinal cord injury; emergency management; rehabilitation; pharmacotherapy; tissue engineering; stem cell therapy; neuroregeneration.

Introduction

Spinal cord injury (SCI) is less common than several other traumatic conditions, including whiplash injuries, traumatic amputations, crush injuries, and traumatic brain injuries. Nevertheless, its consequences can be devastating, producing long-term physical disability, psychological distress, and substantial social and healthcare burdens. The spinal cord is a central component of the central nervous system responsible for transmitting nerve impulses between the brain and the rest of the body. Damage to this structure can disrupt motor, sensory, and autonomic pathways. Because the central nervous system has a limited intrinsic capacity for regeneration, spinal cord damage may result in persistent or irreversible neurological impairment below the level of injury. Most SCIs arise from traumatic events. Road traffic accidents account for approximately 31.5% of reported cases, while falls represent 25.3%. Other reported causes include gunshot injuries (10.4%), motor vehicle crashes (6.8%), diving accidents (4.7%), and complications associated with surgical or medical procedures (4.3%). Collectively, these causes account for

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approximately 83.1% of reported SCIs since 2005 [1]. The distribution of these causes varies according to age, sex, and environmental circumstances. Motor vehicle crashes are the leading cause among individuals younger than 45 years, whereas falls are more common among older adults. Men experience SCI more frequently than women, particularly following diving incidents, motorcycle accidents, and gunshot injuries. Differences between racial groups have also been reported, particularly in cases resulting from gunshot injuries. In addition, SCI incidence tends to increase during warmer months and weekends, potentially reflecting greater participation in outdoor activities and high-risk recreational behaviors [1].

The clinical consequences of SCI depend largely on the mechanism of injury, neurological level, and completeness of the damage. Injuries may produce varying degrees of motor and sensory impairment, ranging from partial functional limitations to complete loss of movement and sensation below the affected spinal level. Autonomic dysfunction is also common and may interfere with bladder and bowel control, sexual function, and other physiological processes. These impairments can substantially reduce independence, limit participation in daily activities, and create long-term rehabilitation and care requirements. Therefore, SCI management extends beyond the initial treatment of the traumatic injury and requires coordinated medical, nursing, rehabilitation, and psychosocial support. Research into SCI has increasingly focused on developing therapeutic strategies that can protect surviving neural tissue, support regeneration, and improve functional recovery. Investigated approaches include pharmacological interventions, gene therapy, stem cell transplantation, and tissue engineering. Among these approaches, tissue engineering represents an interdisciplinary field that combines engineering principles, materials science, and biological techniques to develop structures capable of supporting the repair or replacement of damaged tissues. This approach is particularly relevant to SCI because of the limited regenerative capacity of the central nervous system.

Tissue-engineered constructs aim to provide a supportive microenvironment that encourages cellular survival, axonal growth, and neural tissue repair while potentially reducing inhibitory processes associated with glial scar formation. These constructs may combine biomaterial scaffolds, stem or progenitor cells, and bioactive molecules to support tissue regeneration and improve functional outcomes. Synthetic polymers, including poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), offer adjustable mechanical properties and degradation rates. Natural polymers, such as collagen and chitosan, provide favorable characteristics for cellular adhesion and can resemble aspects of the natural extracellular matrix [2,3]. Combining living cells with biomimetic scaffolds may therefore help recreate aspects of the spinal cord microenvironment and provide new opportunities for neurological repair. This review discusses spinal cord injury from a multidisciplinary perspective, addressing its clinical assessment, emergency management, pharmacological treatment, nursing care, rehabilitation, and long-term support. It also considers emerging regenerative approaches, particularly tissue engineering, as potential strategies for improving neurological recovery and quality of life among individuals affected by SCI.

Anatomy and Morphology

The spinal cord is an elongated cylindrical structure located within the vertebral canal on the dorsal aspect of the body. In adults, it measures approximately 45 cm in length and forms an essential component of the central nervous system. It extends inferiorly from the medulla oblongata and typically terminates at the level of the first lumbar vertebra. The spinal cord is surrounded by three protective connective tissue membranes known as the meninges, which include the dura mater, arachnoid mater, and pia mater. These membranes provide structural protection and support for the spinal cord. The vertebral column, which protects and supports the spinal cord, is divided into cervical, thoracic, lumbar, and sacrococcygeal regions [8,9]. The spinal cord receives its blood supply through three main longitudinal arteries that run along its length and provide oxygen and nutrients to the neural tissues. An adequate blood supply is essential for maintaining neuronal function and tissue integrity. Another important protective component is the blood–spinal cord barrier (BSCB), which regulates the movement of substances between the bloodstream and spinal cord tissue. This barrier helps maintain the specialized environment required for normal neural activity and protects the spinal cord parenchyma from potentially harmful circulating substances [7–9].

Structurally, the spinal cord consists primarily of two distinct tissue components: gray matter and white matter. Gray matter occupies the central region and has a characteristic H-shaped or butterfly-shaped appearance when viewed in cross-section. It contains the cell bodies of motor neurons and interneurons, together with glial cells and blood vessels. This region plays an essential role in processing and integrating neural information and coordinating spinal reflexes. White matter surrounds the gray matter and consists mainly of myelinated nerve fibers organized into ascending and descending pathways. Ascending tracts transmit sensory information toward the brain, whereas descending tracts carry motor commands from the brain to the spinal cord and peripheral structures [8,9]. The spinal cord also contains several types of glial cells, including astrocytes, microglia, ependymal cells, and oligodendrocytes. These cells support neuronal function, maintain tissue homeostasis, and contribute

to the structural organization of neural tissue. Astrocytes are particularly important because their specialized end-feet contribute to the formation and maintenance of blood barriers and help protect the central nervous system from external insults. Understanding these anatomical and cellular components is essential for explaining the mechanisms of spinal cord injury and the challenges associated with neurological repair [7–9].

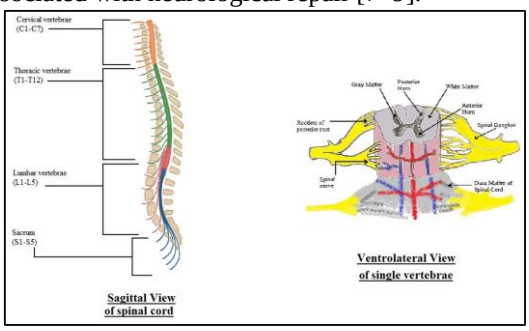


Figure-1: Spinal Cord Anatomy.

Spinal Cord Injury and Its Pathophysiology

Spinal cord injury (SCI) results from damage to the spinal cord following an external mechanical force or, less frequently, other traumatic mechanisms. The initial injury, commonly referred to as the primary injury, occurs at the moment of trauma and may involve direct compression, stretching, tearing, or disruption of spinal cord tissue. The nature and severity of the damage depend on the magnitude, direction, and duration of the applied force, as well as the anatomical level involved. Compression injuries represent a common mechanism of primary spinal cord damage. They may occur when fractured or dislocated vertebral structures exert pressure on the spinal cord, resulting in persistent mechanical compression. Hyperextension injuries can also produce temporary spinal cord compression, even in the absence of visible vertebral fractures or dislocations. Another mechanism is distraction injury, in which excessive stretching forces cause the spinal cord and its supporting structures to elongate, potentially resulting in tearing of neural tissues. More severe injuries may involve direct laceration or complete transection of the spinal cord, particularly following penetrating trauma caused by sharp objects or extensive vertebral displacement. These mechanisms can produce varying degrees of neurological dysfunction depending on the extent of therapeutic strategies aimed at limiting further tissue injury, preserving surviving neural pathways, and improving neurological recovery.

Phases of Spinal Cord Injury

Spinal cord injury (SCI) involves a series of overlapping pathological processes that develop over time following the initial traumatic event. These processes are commonly classified into four phases: acute, subacute, intermediate, and chronic.tissue disruption.

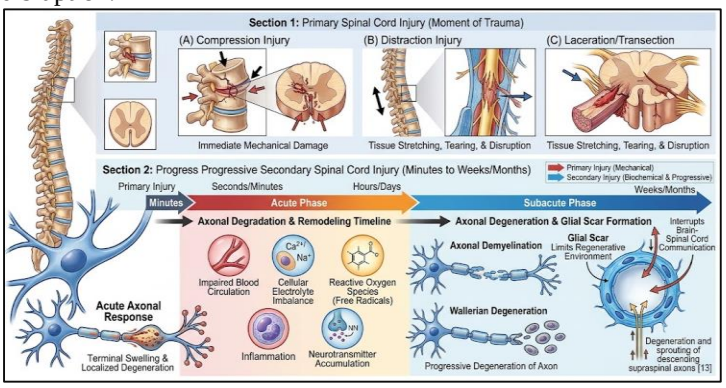


Figure-2: Pathophysiology of spinal cord injury.

In addition to the immediate mechanical damage, SCI initiates a complex sequence of biological and cellular events known as secondary injury. Unlike primary injury, which occurs at the time of trauma, secondary injury develops progressively and may continue for several weeks or months. This process contributes substantially to the extension of tissue damage beyond the initial injury site and may worsen neurological outcomes. Secondary injury begins within minutes following the traumatic event and involves several interconnected pathological mechanisms, including impaired blood circulation, disturbances in cellular electrolyte balance, excessive production of harmful free radicals, inflammatory responses, and accumulation of neurotransmitters. These changes create an unfavorable environment for surviving neurons and may contribute to additional cellular damage and neuronal dysfunction. The progression of secondary injury involves overlapping acute and subacute phases. During the acute phase, vascular disturbances and biochemical imbalances contribute to cellular stress and tissue deterioration. These processes may compromise the survival of neurons and other cells surrounding the primary injury site. The subsequent subacute phase is characterized by further structural and cellular changes. Surviving nerve fibers may undergo demyelination, resulting in the loss of the protective myelin sheath required for efficient nerve impulse conduction. Wallerian degeneration also occurs, involving the progressive degeneration of damaged axons and their associated structures. These changes can interrupt neural communication between the brain and spinal cord regions below the injury. Furthermore, tissue remodeling and glial scar formation occur during the subacute response. Although these processes are part of the tissue response to injury, the resulting environment can restrict axonal regeneration and limit functional recovery. Degeneration and subsequent sprouting of descending supraspinal axons have also been investigated following experimental spinal cord injury [13]. Understanding the relationship between primary mechanical damage and secondary pathological mechanisms is essential for developing

Each phase is characterized by specific cellular, vascular, and inflammatory changes that contribute to tissue damage, neurological dysfunction, and subsequent recovery.

Acute Phase

The acute phase occurs within the first 48 hours following injury. It is characterized by disturbances in ionic balance, excitotoxicity, lipid peroxidation, vascular dysfunction, and necrotic cell death. Damage to blood vessels compromises endothelial integrity and increases the permeability of the blood–spinal cord barrier (BSCB). Consequently, leukocytes, fluid, and plasma proteins enter the injured tissue, contributing to inflammation and edema [2]. One of the earliest pathological changes is the appearance of damage in the gray matter, which can become evident within approximately 30 minutes after injury. The damage may subsequently extend into the surrounding white matter, impairing blood circulation and causing ischemia and neuronal cell death [3,4]. Increased intracellular calcium also activates destructive enzymes, including protein kinases, cysteine proteases, and phospholipases. Furthermore, calcium accumulation disrupts mitochondrial function and promotes the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These molecules damage cellular proteins, lipids, and genetic material, contributing to progressive tissue destruction and cell death [12].

Subacute Phase

The subacute phase generally occurs between 48 hours and 14 days after injury. It is characterized by increased macrophage infiltration, phagocytic activity, and astrocyte proliferation [3]. Macrophages participate in the removal of damaged cellular components, while astrocytes become reactive and contribute to tissue responses following injury. Reactive astrocytes have different functions depending on the stage of the pathological process. During early injury, they may provide neuroprotective and reparative effects. However, their later responses may contribute to an inhibitory environment that restricts axonal regeneration [5,11]. Another important feature is the accumulation of excitatory neurotransmitters, particularly glutamate and aspartate, in the extracellular space. Excessive stimulation of their receptors can initiate excitotoxic pathways, further damaging neurons and surrounding neural structures [11].

Intermediate Phase

The intermediate phase extends from approximately 14 days to three months after injury. During this period, astrocytic scars undergo further maturation, while axonal sprouting may contribute to the re-establishment of neural connections and reinnervation [6]. However, secondary pathological processes may continue, including electrolyte disturbances, delayed cell death, oxidative stress, and persistent inflammation. Reactive oxygen species promote lipid peroxidation, damaging cellular membranes and increasing injury to surrounding tissues. Delayed calcium influx can further activate destructive enzymes and increase free radical production, prolonging tissue damage.

Chronic Phase

The chronic phase usually begins approximately six months after SCI and may continue throughout the patient's lifetime. Neurological function may become relatively stable, although motor and sensory impairments often persist. Structural changes, including cyst formation and nerve degeneration, may develop. Oxidative stress, inflammation, cell death, and demyelination can also contribute to ongoing neurological dysfunction [7]. Despite these changes, some functional improvement may occur through neural adaptation, compensatory activity, and changes in supporting cell populations. Rehabilitation during this phase focuses on maximizing independence, maintaining mobility, and preventing complications such as pressure injuries and infections. Assistive devices, physical therapy, nursing care, and psychosocial support are important components of long-term management. Psychological adjustment and effective coping strategies are also essential for maintaining quality of life.

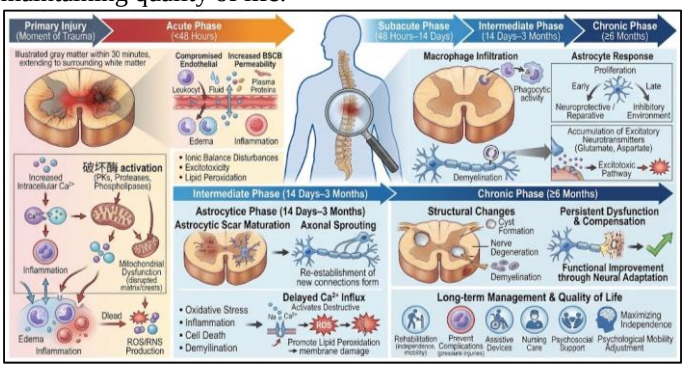


Figure-3: Phases of spinal cord injury.

Conventional Treatments for Spinal Cord Injury

The primary objective of conventional treatment for spinal cord injury (SCI) is to limit secondary tissue damage, preserve the remaining neural structures, prevent complications, and promote functional recovery. Although the initial mechanical injury cannot usually be reversed, appropriate early management may reduce the progression of neuronal damage and improve the patient's clinical outcome. Effective treatment therefore requires a comprehensive approach that addresses both the underlying neurological injury and its consequences. Several biological processes are considered important therapeutic targets in SCI. These include reducing neuronal death, limiting the development of inhibitory glial scars, and providing a supportive environment for axonal regeneration. Preventing excessive inflammatory and immune responses may also help protect surviving neural tissue from further

damage. In addition, successful neurological recovery requires the formation of functional synaptic connections and the restoration of neurotransmitter conduction through regenerating axons. Supporting axonal growth within the injured region is particularly important because newly regenerated axons must extend through the damaged tissue and establish connections with appropriate target neurons. Biomaterial matrices may provide structural support and a suitable microenvironment for axonal growth by supplying a framework and supporting the delivery of nutrients and other biological factors. Pharmacological treatment represents one component of conventional SCI management. Methylprednisolone has been investigated as an early intervention because of its potential to reduce secondary injury following acute trauma. Administration of high-dose methylprednisolone shortly after injury may provide some neuroprotective effects. However, its clinical benefit remains limited, and it does not reverse the initial mechanical damage or restore normal spinal cord function. Evidence has indicated that this treatment may produce only modest improvements in overall patient outcomes [14,15]. Consequently, pharmacological management should be considered within a broader treatment strategy rather than as an independent solution.

Surgical intervention is another important component of SCI management, particularly when spinal instability, vertebral fractures, dislocations, or persistent spinal cord compression are present. Surgical procedures may aim to relieve pressure on neural structures, restore spinal alignment, and stabilize the injured vertebral column. Appropriate stabilization can also facilitate patient mobilization and subsequent rehabilitation. The selection of a surgical approach depends on the injury characteristics, neurological status, and overall clinical condition of the patient. In addition to medications and surgery, conventional management involves supportive care and therapeutic interventions directed toward reducing disability and preventing secondary complications. These measures may include nursing care, physical therapy, occupational therapy, and rehabilitation programs designed to improve mobility, muscle function, independence, and participation in daily activities. Prevention and management of complications, including pressure injuries, infections, respiratory problems, and bladder and bowel dysfunction, are also essential components of long-term care. Overall, conventional SCI treatment combines pharmacological interventions, surgical procedures, supportive management, and rehabilitation. Although these approaches can reduce complications, improve functional capacity, and enhance quality of life, complete neurological recovery remains difficult to achieve. Current management therefore focuses on preserving neurological function, maximizing patient independence, and supporting long-term physical and psychosocial well-being [16–18].

Medication Management

Medication management is an essential component of spinal cord injury (SCI) care. Patients may experience several complications resulting from neurological damage, including neuropathic pain, musculoskeletal pain, muscle spasticity, bladder dysfunction, bowel disturbances, and mood disorders. Pharmacological interventions aim to control these symptoms, prevent complications, improve functional capacity, and support participation in rehabilitation. The choice of medication depends on the type and severity of symptoms, the level and completeness of the injury, the patient's general health, and the presence of other medical conditions. Appropriate selection and dosage adjustment require careful clinical assessment and regular monitoring. Pain management represents one of the main indications for medication use in patients with SCI. Neuropathic pain may develop because of damage to sensory pathways and can present as burning, shooting, tingling, or electric shock-like sensations. Conventional analgesics may be considered for musculoskeletal and nociceptive pain, whereas medications with specific effects on neuropathic pain pathways may be required for persistent neurological pain. Muscle relaxants and antispasticity medications are also used to manage increased muscle tone, involuntary muscle contractions, and painful spasms. Controlling spasticity can improve comfort, facilitate positioning, and support physical therapy and daily activities. However, treatment should be individualized because excessive reduction in muscle tone may interfere with transfers, standing, or other activities in patients who rely on residual muscle activity.

Bladder dysfunction is another frequent consequence of SCI and may require pharmacological treatment. Depending on the pattern of dysfunction, medications may be prescribed to reduce involuntary bladder contractions, improve urinary storage, or facilitate bladder emptying. Appropriate management is important because inadequate bladder control can contribute to urinary retention, incontinence, recurrent infections, and impaired quality of life. Antidepressants may also have a role in SCI management. In addition to treating depression and other mood disturbances, certain antidepressant medications are used to manage neuropathic pain. Their selection should consider the patient's psychological condition, pain characteristics, concurrent medications, and potential adverse effects. Beyond symptomatic treatment, several pharmacological agents have been investigated for their potential neuroprotective and regenerative effects. Gangliosides, particularly GM1 (monosialotetrahexosylganglioside), have attracted

attention because of their proposed effects on neuronal membrane function, neuroplasticity, and neurological recovery. GM1 has been investigated as an adjunct to physical therapy, with the aim of improving motor and sensory outcomes. However, the evidence supporting its clinical effectiveness remains insufficient to establish it as a routine treatment for SCI. The cited study [19] should also be interpreted in the context of its focus on lumbar spinal stenosis rather than traumatic SCI.

Other investigated approaches have targeted oxidative stress, membrane damage, and disturbances in intracellular calcium regulation. Antioxidants have been explored for their ability to reduce oxidative injury, while calcium channel blockers, including nimodipine, have been investigated for their potential neuroprotective effects. Nevertheless, clinical findings have been inconsistent, and these agents have not established a standard role in routine SCI treatment. Tirilazad and naloxone have also been investigated as potential therapeutic agents. These experimental approaches provide insight into alternative pharmacological strategies, but further evidence is required before their clinical benefits can be established. Overall, medication management in SCI requires an individualized and multidisciplinary approach. Treatment should address the patient's symptoms while considering drug interactions, adverse effects, treatment response, and functional goals. Although existing medications can improve symptom control and quality of life, their ability to restore damaged spinal cord tissue remains limited. Further clinical research is therefore needed to identify safe and effective pharmacological interventions that combine symptom management with neuroprotection and neurological recovery [20].

Surgical Interventions

Surgical intervention is an important component of spinal cord injury (SCI) management, particularly when vertebral fractures, spinal instability, dislocations, or persistent compression threaten the spinal cord and surrounding neural structures. The main objectives of surgery are to restore anatomical alignment, relieve pressure on the spinal cord and nerve roots, and stabilize the injured vertebral column. Early and appropriate surgical management may help prevent additional neurological damage, facilitate mobilization, and create better conditions for subsequent rehabilitation. Spinal decompression involves removing bone, thickened ligaments, intervertebral disc material, or other structures that compress the spinal cord or nerve roots. The procedure may be performed at different spinal levels, depending on the location and extent of the injury. Laminectomy is a commonly used decompression procedure in which the lamina is removed to increase the available space within the spinal canal and relieve pressure on neural structures. In selected cases, spinal fusion is performed alongside decompression to maintain vertebral stability and prevent abnormal movement. Fusion involves connecting adjacent vertebrae using bone grafts and, when necessary, fixation devices such as screws and rods [28]. Several surgical techniques may be selected according to the underlying pathology and anatomical location. Foraminotomy involves widening the neural foramen through which spinal nerves exit, thereby reducing pressure on compressed nerve roots. Laminoplasty is primarily used in selected cervical spine conditions and involves expanding the spinal canal while preserving or reconstructing part of the posterior vertebral structures. Diskectomy involves removing part or all of a damaged intervertebral disc when disc material contributes to neural compression. These procedures have different indications and may be performed independently or in combination with other surgical techniques, depending on the patient's clinical condition [29].

Despite their potential benefits, spinal procedures are associated with several complications. These include postoperative infection, bleeding, neurological deterioration, deep vein thrombosis, and complications related to bone grafts or fixation devices. Bone graft migration, hardware fracture, and failure of fusion may compromise surgical outcomes. Adjacent segment disease may also develop when increased mechanical stress affects spinal levels next to a fused segment. The likelihood of complications depends on factors such as the patient's general health, injury severity, surgical technique, and postoperative management. Postoperative care is therefore essential for achieving satisfactory outcomes. Patients may require intensive monitoring of neurological function, respiratory status, hemodynamic stability, and surgical wound condition. Pain control, prevention of thromboembolic events, infection prevention, and appropriate positioning are important elements of postoperative management. Once the patient's condition permits, rehabilitation should begin to improve mobility, muscle function, and independence. Overall, surgical intervention aims to protect remaining neurological function, restore spinal stability, and support the patient's participation in long-term rehabilitation.

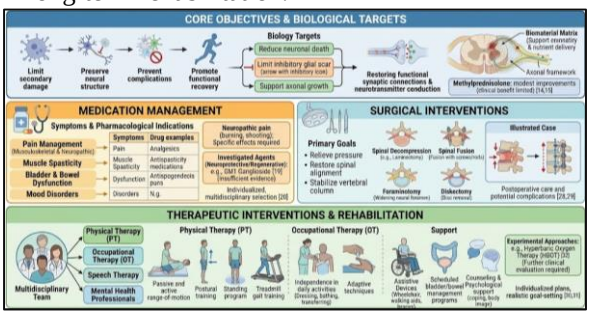


Figure-4: Management of spinal cord injury.

Therapeutic Interventions

Therapeutic interventions are essential components of spinal cord injury (SCI) management.

They aim to improve functional recovery, reduce disability, prevent secondary complications, and enhance patients' independence and quality of life. Because SCI can affect motor, sensory, autonomic, and psychological functions, effective rehabilitation requires a multidisciplinary approach involving physical therapists, occupational therapists, speech therapists, nurses, physicians, and mental health professionals. The selection of therapeutic interventions depends on the neurological level, severity, and completeness of the injury, as well as the patient's functional abilities and rehabilitation goals. Physical therapy is a central component of SCI rehabilitation. It focuses on maintaining joint mobility, improving muscle strength, preventing muscle contractures, and developing balance and coordination. Depending on the patient's remaining neurological function, rehabilitation may include passive and active range-of-motion exercises, strengthening activities, postural training, standing programs, and gait training. Repeated movement-based exercises may also help patients improve their ability to perform functional activities and maximize the use of preserved neural pathways. Treadmill-based training is one approach used in gait rehabilitation. It provides repeated stepping movements that may activate intrinsic spinal neuronal circuits and support improvements in gait mechanics and movement coordination.

Occupational therapy complements physical therapy by helping patients regain independence in daily activities. Interventions may include training in dressing, bathing, feeding, personal hygiene, transferring, and using adaptive techniques to perform household and work-related tasks. Speech therapy may also be required in selected patients, particularly when associated injuries or neurological complications affect communication or swallowing. Assistive devices, including wheelchairs, walking aids, braces, and customized seating systems, are used according to individual functional needs. These devices improve mobility, support posture, reduce physical strain, and facilitate participation in daily and social activities. Bladder and bowel management programs are also important because spinal cord damage may disrupt normal autonomic control. Individualized programs may include scheduled bladder emptying, appropriate catheterization techniques, bowel routines, and dietary or fluid-management strategies. Their objectives are to improve continence, reduce the risk of complications, and support patient independence. Pain management should similarly combine pharmacological and non-pharmacological approaches. Physical therapy, positioning, relaxation techniques, and other supportive interventions may complement medication-based treatment. Psychological support is equally important because SCI can lead to emotional distress, depression, anxiety, changes in body image, and difficulties adapting to new functional limitations. Counseling and psychological rehabilitation can help patients develop coping strategies and maintain social relationships.

Additional therapeutic approaches have also been investigated. Hyperbaric oxygen therapy (HBOT) involves breathing oxygen at concentrations approaching 100% inside a pressurized chamber. This approach increases oxygen availability in blood and tissues and has been investigated for its potential effects on tissue oxygenation and recovery following SCI. However, its effectiveness as a routine treatment for SCI requires further clinical evaluation. Similarly, combining physical exercise with other therapeutic strategies may offer additional benefits. Although exercise-based rehabilitation has an established role in improving physical function, evidence regarding its combined use with other experimental interventions remains limited [32]. The outcomes of therapeutic interventions vary according to injury severity, anatomical location, completeness, associated complications, and the patient's response to rehabilitation. Therefore, treatment should follow an individualized plan developed and regularly reviewed by the multidisciplinary healthcare team. Setting realistic goals and adjusting interventions according to functional progress are essential for maximizing rehabilitation outcomes and supporting long-term independence [30,31].

Tissue-Engineered Treatments for Spinal Cord Injury

Tissue engineering represents an emerging therapeutic approach for spinal cord injury (SCI), focusing on the regeneration of damaged neural tissue and the restoration of connections between surviving spinal cord regions. This field integrates tissue engineering techniques, stem cell technologies, and cell transplantation to develop biological constructs capable of supporting tissue repair. Over recent decades, considerable research has investigated the engineering of different human tissues and organs, including strategies for repairing injured nervous tissue. The development of tissue-engineered constructs generally depends on three essential components, collectively known as the tissue engineering triad. These components include an appropriate cell source, a biomaterial scaffold that provides three-dimensional structural support, and biological signals that regulate cellular activities. Such signals may include growth factors, chemical mediators, and biophysical cues that influence cell survival, proliferation, differentiation, and tissue organization. In SCI, the integration of these components aims to protect surviving neurons, support axonal regeneration, and reconstruct the damaged environment to facilitate communication between the injured and non-injured regions of the spinal cord.

Collagen-based scaffolds have received considerable attention in neural tissue engineering because of their biocompatibility and structural similarity to components of the natural extracellular matrix. Their architecture can provide a supportive environment for cell attachment, migration, and axonal extension. Collagen scaffolds have also been investigated as delivery systems for neurotrophic factors, including neurotrophin-3 (NT-3), which supports neuronal survival and axonal growth. Experimental studies using spinal cord transection models have demonstrated that collagen bridges containing neurotrophic factors can promote axonal regeneration and partial recovery of motor function. Linearly organized collagen scaffolds have shown potential for improving neural adhesion and guiding regenerating axons in animal models. Furthermore, combining collagen scaffolds with human placental mesenchymal stem cells has been associated with improved tissue repair and locomotor outcomes in experimental studies involving beagle dogs. However, the relatively low mechanical strength of collagen limits its independent application in some tissue engineering constructs. Consequently, researchers have investigated chemical modifications and combinations with synthetic polymers to improve scaffold stability, structural integrity, and biological activity [33].

Gelatin, a hydrolyzed derivative of collagen, represents another natural biomaterial investigated for SCI repair. Its favorable cellular compatibility and ability to support cell adhesion make it suitable for developing tissue-engineered constructs. Gelatin methacryloyl (GelMA) is a chemically modified gelatin derivative that can undergo photocrosslinking, allowing the fabrication of hydrogels with controlled structures. GelMA-based scaffolds can also be manufactured using three-dimensional printing, providing opportunities to reproduce the architecture required for neural tissue repair. Experimental studies have investigated their application in supporting bone marrow stromal cells (BMSCs) and neural stem cells (NSCs), with the aim of improving cell survival, proliferation, and differentiation. In animal models of SCI, GelMA-based constructs have demonstrated potential to improve hindlimb motor function and reduce cavity formation. Their ability to provide a hydrated, cell-compatible environment makes them promising materials for delivering therapeutic cells and supporting tissue reconstruction [34].

Fibrin is another natural biomaterial with potential applications in spinal cord tissue engineering. Derived from blood proteins, fibrin forms a biodegradable matrix that can support cellular attachment and provide a delivery platform for therapeutic agents. Fibrin scaffolds have been investigated for transporting stem cells, exosomes, microRNAs, and growth factors into injured spinal cord tissue. Their structural properties can be modified to influence cellular infiltration and tissue organization. Hierarchically arranged fibrin hydrogels have demonstrated potential to facilitate host cell infiltration, promote neovascularization, and support axonal regeneration in experimental SCI models. In addition, fibrin matrices incorporating adipose-derived mesenchymal stem cells have been associated with reduced astrocyte activation and glial scar formation. These effects may improve the local microenvironment and create more favorable conditions for neural repair and functional recovery [35]. Synthetic biodegradable polymers, particularly polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA), offer additional advantages for scaffold development. These materials allow researchers to modify mechanical properties, degradation rates, porosity, and structural organization according to the requirements of the injured spinal cord. PLGA scaffolds have been investigated as delivery systems for therapeutic agents and stem cells, with experimental findings suggesting potential benefits for neuronal survival and the reduction of secondary tissue damage. PCL is particularly useful for producing aligned and electrospun structures that can guide cellular organization and axonal growth. Such scaffolds may support the organization of regenerating neural fibers and provide a framework for interactions between neurons and supporting cells. Combinations of synthetic scaffolds with Schwann cells or oligodendrocyte progenitor cells have also been investigated to promote remyelination and improve the environment for axonal regeneration [36].

Hybrid scaffolds combine natural and synthetic biomaterials to integrate their complementary properties. Examples include collagen-GelMA and fibrin-PLGA composites. Natural components provide biological compatibility and support cell interactions, whereas synthetic polymers contribute mechanical strength, structural stability, and control over degradation. These composite systems may also accommodate multiple therapeutic components, including stem cells, cytokines, neurotrophic factors, and other biological mediators. Experimental studies have reported improvements in cell retention, axonal bridging across injured regions, and behavioral outcomes following the application of different hybrid scaffold systems. Their ability to incorporate several therapeutic components makes them relevant to combination strategies targeting multiple mechanisms of SCI pathology [37,38]. Despite these promising findings, successful clinical application requires careful consideration of scaffold characteristics and host tissue responses. An ideal tissue-engineered construct should demonstrate biocompatibility and an appropriate biodegradation rate, allowing gradual replacement by newly formed physiological tissue without premature structural collapse. Its mechanical properties should be compatible with the spinal cord environment, while

its internal architecture should support cellular migration, nutrient diffusion, vascularization, and waste removal. The scaffold should also minimize undesirable immune responses and maintain sufficient structural integrity throughout the tissue repair process. In addition, manufacturing methods should be reproducible, efficient, and cost-effective to facilitate future clinical translation [39]. Overall, tissue engineering offers a potential strategy for addressing the limited regenerative capacity of the injured spinal cord. Combining biomaterial scaffolds with therapeutic cells and biological signals may provide an environment that supports neuroprotection, axonal regeneration, remyelination, and tissue reconstruction. However, most approaches remain at the experimental stage. Further studies are required to establish their long-term safety, optimal composition, degradation characteristics, and effectiveness in human patients.

Cell-Based Therapies

Cell-based therapies represent an emerging approach to spinal cord injury (SCI) treatment, with the potential to promote neural tissue repair and improve neurological function. Unlike conventional treatments, which primarily focus on preventing secondary damage, controlling symptoms, and improving functional independence, cell transplantation aims to support biological repair within the injured spinal cord. Several cell populations have been investigated in preclinical studies, particularly neural stem cells (NSCs), mesenchymal stem cells (MSCs), and olfactory ensheathing cells (OECs). These cell types have demonstrated potential to promote neurogenesis, support axonal regeneration, and facilitate remyelination, suggesting possible applications in restoring damaged neural pathways. Neural stem cells are of particular interest because of their capacity for self-renewal and differentiation into different neural cell types. Following transplantation, these cells may contribute to tissue repair by generating neurons and supporting glial cells. They may also provide a favorable environment for neuronal survival and axonal growth through the release of biological mediators. Their potential to replace damaged neural cells and support the formation of functional connections makes them an important area of investigation in SCI research. However, successful application requires appropriate control of cell differentiation, survival, and integration within the injured spinal cord.

Mesenchymal stem cells have received considerable attention because of their immunomodulatory and trophic properties. These cells can release various growth factors and cytokines that influence inflammation, cellular survival, and tissue repair. Their therapeutic effects may therefore extend beyond direct replacement of damaged cells. By modifying the local inflammatory environment and supporting surviving neurons, MSCs may create conditions that facilitate axonal growth and functional recovery. Their potential availability from different tissue sources and their ability to interact with surrounding cells have further increased research interest in their application for SCI. Preliminary clinical investigations have reported improvements in motor and sensory outcomes following MSC-based interventions. Nevertheless, the clinical effectiveness of these treatments remains under investigation, and further controlled studies are required to establish their benefits. Olfactory ensheathing cells are another promising cell population because of their association with the natural regeneration of olfactory nerve fibers. These cells have supportive properties that may facilitate axonal growth across damaged neural regions. Experimental studies have investigated their ability to provide a permissive environment for regenerating axons and support neural reconnection following spinal cord injury. Their potential role in promoting axonal regeneration makes them relevant to strategies intended to restore communication between injured and preserved spinal cord regions.

Despite the potential benefits of cell-based therapies, several challenges must be addressed before their widespread clinical application. These include selecting the most appropriate cell type, optimizing transplantation techniques, improving cell survival after implantation, and ensuring adequate integration with host neural tissue. The long-term behavior of transplanted cells also requires investigation, particularly regarding their differentiation, functional stability, and possible adverse effects. Ethical considerations related to cell sourcing, processing, and transplantation must also be addressed. Overall, cell-based therapies offer potential opportunities for improving neurological recovery following SCI. Combining stem cell transplantation with biomaterial scaffolds, growth factors, and rehabilitation may provide additional therapeutic benefits. However, further experimental and clinical research is necessary to standardize treatment protocols, establish long-term safety, and determine the effectiveness of these approaches in different categories of spinal cord injury.

Stem Cell Therapies and Signaling Factors in Spinal Cord Injury

Neural Stem/Progenitor Cells

Neural stem/progenitor cells (NSPCs) are considered promising candidates for spinal cord injury (SCI) treatment because of their ability to self-renew and differentiate into different neural cell types. These undifferentiated cells are found within the central nervous system and may contribute to tissue repair by replacing lost neurons, supporting damaged neural cells, promoting axonal regeneration, and protecting surviving tissue. Their transplantation may also facilitate the formation of new neural

connections within the injured spinal cord, potentially restoring communication between disrupted nerve pathways. Preclinical studies have demonstrated improvements in neural regeneration and functional recovery following NSPC transplantation, particularly in models of chronic SCI. Despite these promising findings, several challenges remain before NSPC-based treatments can become established clinical interventions. These include optimizing transplantation procedures, improving cell survival and integration, and ensuring that regenerated connections become functionally effective. Research organizations, including the National Institutes of Health, have supported efforts to independently validate experimental findings. Greater attention to research quality, reproducibility, and standardized experimental methods is necessary to establish the reliability of preclinical results and support the safe development of clinical applications [40–42].

Mesenchymal Stem/Stromal Cells

Mesenchymal stem/stromal cells (MSCs) have attracted considerable attention because of their immunomodulatory, regenerative, and trophic properties. Their therapeutic effects are associated with their ability to communicate with surrounding tissues through the secretion of growth factors, cytokines, and extracellular vesicles (EVs). These biological mediators may regulate inflammation, support cell survival, and promote tissue repair. Consequently, the therapeutic potential of MSCs may extend beyond their direct differentiation into other cell types, with paracrine signaling representing an important mechanism of action. An important characteristic of MSCs is their ability to migrate toward injured tissues, a process known as homing. This process is influenced by inflammatory signals and chemotactic pathways, particularly the stromal cell-derived factor-1 alpha (SDF-1α) and C-X-C chemokine receptor type 4 (CXCR4) pathway. These signaling mechanisms help direct MSCs toward damaged regions, where they may contribute to tissue repair and modulate the local inflammatory environment [43–45]. However, the clinical application of MSCs requires improvements in cell manufacturing, quality control, and therapeutic potency. Standardized production protocols and bioengineering approaches may improve treatment consistency and provide more predictable therapeutic outcomes.

Dental Pulp Stem Cells

Dental pulp stem cells (DPSCs) represent another potential source of cells for regenerative medicine. These cells are obtained from the dental pulp and originate from neural crest-associated cell populations. They demonstrate self-renewal and multipotent differentiation characteristics and express both neural-associated markers, including βIII-tubulin, nestin, glial fibrillary acidic protein, and neuronal nuclei, and mesenchymal markers such as CD73, CD90, and CD105 [46–48]. The potential of DPSCs in neurological repair has been investigated, particularly in experimental models of ischemic stroke. Clinical studies have evaluated the safety and feasibility of allogeneic DPSCs in acute stroke and autologous transplantation in patients with chronic post-stroke disability. These investigations provide a foundation for exploring their therapeutic potential in other neurological conditions. However, comparable clinical studies are needed to determine whether DPSC transplantation can safely improve tissue repair and functional recovery in patients with SCI [49].

Oral Mucosa Stem Cells

Oral mucosa stem cells (OMSCs) are derived from the lamina propria of the oral mucosa, a tissue recognized for its capacity to heal with limited scar formation. These cells exhibit characteristics of primitive multipotent progenitors and can differentiate into several cell types. Experimental research has investigated their neuroprotective and regenerative properties in different neurological injury models. In animal studies, OMSC transplantation has demonstrated potential to protect neural tissue and improve bladder dysfunction associated with SCI. Their incorporation into three-dimensional scaffolds has also been associated with functional recovery in rats following complete spinal cord transection. These findings suggest that OMSCs may support neural repair through interactions with the injured tissue and by providing a favorable environment for regeneration. Nevertheless, further investigations, particularly well-designed clinical trials, are required to establish their safety and effectiveness in human SCI [50–55].

Olfactory Ensheathing Cells

Olfactory ensheathing cells (OECs), obtained from olfactory tissues, have been investigated for their natural capacity to support nerve fiber regeneration. They contribute to the removal of cellular debris, regulation of inflammation, and promotion of axonal growth, making them potential candidates for spinal cord repair [56,57]. OECs can be obtained from the olfactory mucosa or olfactory bulb. Harvesting cells from the nasal lining is generally more accessible and less invasive than obtaining them from the olfactory bulb, which requires neurosurgical intervention. However, clinical outcomes following OEC transplantation have been inconsistent. One major challenge is the difficulty of isolating pure OEC populations from other cell types present in olfactory tissue. The use of unpurified cell mixtures may contribute to variable therapeutic outcomes and increase safety concerns. Complications, including cyst formation at transplantation sites, have been reported following procedures involving unrefined olfactory tissue preparations [58–62]. Therefore, improving cell isolation, purification, characterization, and transplantation techniques is

essential before OEC therapy can be reliably applied in clinical practice.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) have introduced new possibilities for regenerative medicine. They are generated by reprogramming adult cells into a pluripotent state, allowing them to differentiate into multiple cell types. Unlike embryonic stem cells, iPSCs do not require the destruction of embryos, reducing some ethical concerns associated with stem cell research. Their potential for patient-specific production also provides opportunities for developing personalized regenerative therapies. In experimental SCI models, neural progenitor cells derived from iPSCs have demonstrated the ability to replace lost neural cells, support axonal regeneration, promote angiogenesis, and improve functional recovery. Studies involving rodents and common marmosets have reported neuronal differentiation and the establishment of connections with existing neural pathways following transplantation. However, uncontrolled proliferation and inappropriate differentiation remain major concerns because of the potential for tumor formation. Although some experimental studies reported no tumor development during the observation period, longer follow-up is necessary to establish long-term safety [63–65].

Signaling Factors Involved in Spinal Cord Repair

Signaling molecules, including neurotrophic factors, cytokines, and chemokines, regulate several processes following SCI. These mediators influence inflammation, neuronal survival, apoptosis, axonal regeneration, and scar formation. Their modulation represents an important therapeutic strategy for improving the biological environment of injured spinal cord tissue. Neurotrophic factors support neuronal survival, development, differentiation, and function. Important examples include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3). These molecules have demonstrated potential to improve neuronal survival and promote axonal regeneration in experimental SCI models. Localized BDNF delivery, in particular, has been associated with improved functional outcomes and regeneration of corticospinal tract fibers [66,67]. Neurotrophins interact with high-affinity tropomyosin receptor kinase (Trk) receptors and the low-affinity p75 neurotrophin receptor (p75NTR), activating signaling pathways involved in neuronal survival and growth [68]. Their expression varies according to developmental stage and anatomical location. NGF, BDNF, and NT-3 are generally expressed at higher levels during early development than in the adult nervous system. However, their continued regulation in adulthood remains important for neural plasticity and tissue maintenance [69].

Inflammation following SCI has both protective and harmful effects. Although immune responses contribute to debris removal and tissue repair, excessive inflammatory activity can increase secondary neuronal damage, apoptosis, and glial scar formation. Pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), contribute to these pathological processes. Consequently, inhibiting excessive inflammatory signaling has been investigated as a strategy to reduce secondary tissue damage [70,71]. Other mediators, including erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), have been investigated for their neuroprotective and regenerative properties. Anti-inflammatory cytokines such as IL-4, IL-10, and IL-33 may also regulate microglial and macrophage activity and reduce excessive pro-inflammatory responses. These pathways may support neuronal survival, remyelination, angiogenesis, and functional recovery [72].

Chondroitin sulfate proteoglycans (CSPGs) are major components of the glial scar that develops following SCI. Although scar formation may initially help contain tissue damage, CSPGs create an inhibitory environment that restricts axonal regeneration, cellular migration, and neural differentiation. They interact with neuronal receptors, including protein tyrosine phosphatase sigma (PTPσ), leukocyte common antigen-related phosphatase (LAR), and Nogo receptors, activating downstream pathways such as Rho-associated kinase (ROCK). These mechanisms contribute to growth cone collapse and impaired axonal regeneration [73,74]. CSPGs also influence inflammatory cell activity and inhibit the migration and differentiation of neural stem cells and oligodendrocyte precursor cells. Therapeutic strategies targeting CSPGs, particularly enzymatic degradation or receptor blockade, may therefore improve axonal regeneration, remyelination, and tissue repair.

Cyclic adenosine monophosphate (cAMP) is an intracellular signaling molecule involved in neuronal and glial cell function. Reduced cAMP levels following SCI may contribute to the failure of axonal regeneration. Increasing intracellular cAMP through pharmacological or genetic approaches has demonstrated potential to overcome certain inhibitory effects of myelin-associated molecules and promote axonal growth [75]. cAMP is produced from ATP by adenylate cyclases and degraded by phosphodiesterases. Its main downstream effectors include protein kinase A (PKA), exchange proteins directly activated by cAMP (Epac), and cyclic nucleotide-gated channels. These signaling components regulate neuronal survival, axonal development, dendritic stability, excitability, and synaptic plasticity. Modulation of cAMP signaling

may therefore represent another potential approach to improving neural regeneration and functional recovery after SCI [76].

Conclusion:

Spinal cord injury produces neurological and functional consequences that require coordinated care from the emergency phase through follow-up. Early assessment, spinal stabilization when indicated, and management of secondary injury are central to preserving neurological function and reducing complications. Pharmacological treatment can address pain, spasticity, bladder dysfunction, and associated symptoms, while nursing care and rehabilitation help prevent secondary complications and improve independence. Physical and occupational therapy, assistive technologies, and psychosocial support remain essential components of recovery. Tissue engineering and cell-based approaches offer strategies to support neural protection, axonal growth, remyelination, and tissue reconstruction. Biomaterial scaffolds, stem and progenitor cells, and molecular signaling interventions have shown promise in experimental studies. However, their clinical application remains limited by uncertainties regarding efficacy, optimal delivery, safety, integration, and durability. Future research should establish standardized protocols and evaluate functional outcomes. Progress will depend on integrating advances in regenerative science with individualized, multidisciplinary clinical care.

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