REGENERATIVE MEDICINE

& PERIPHERAL NERVE ENDOSCOPY

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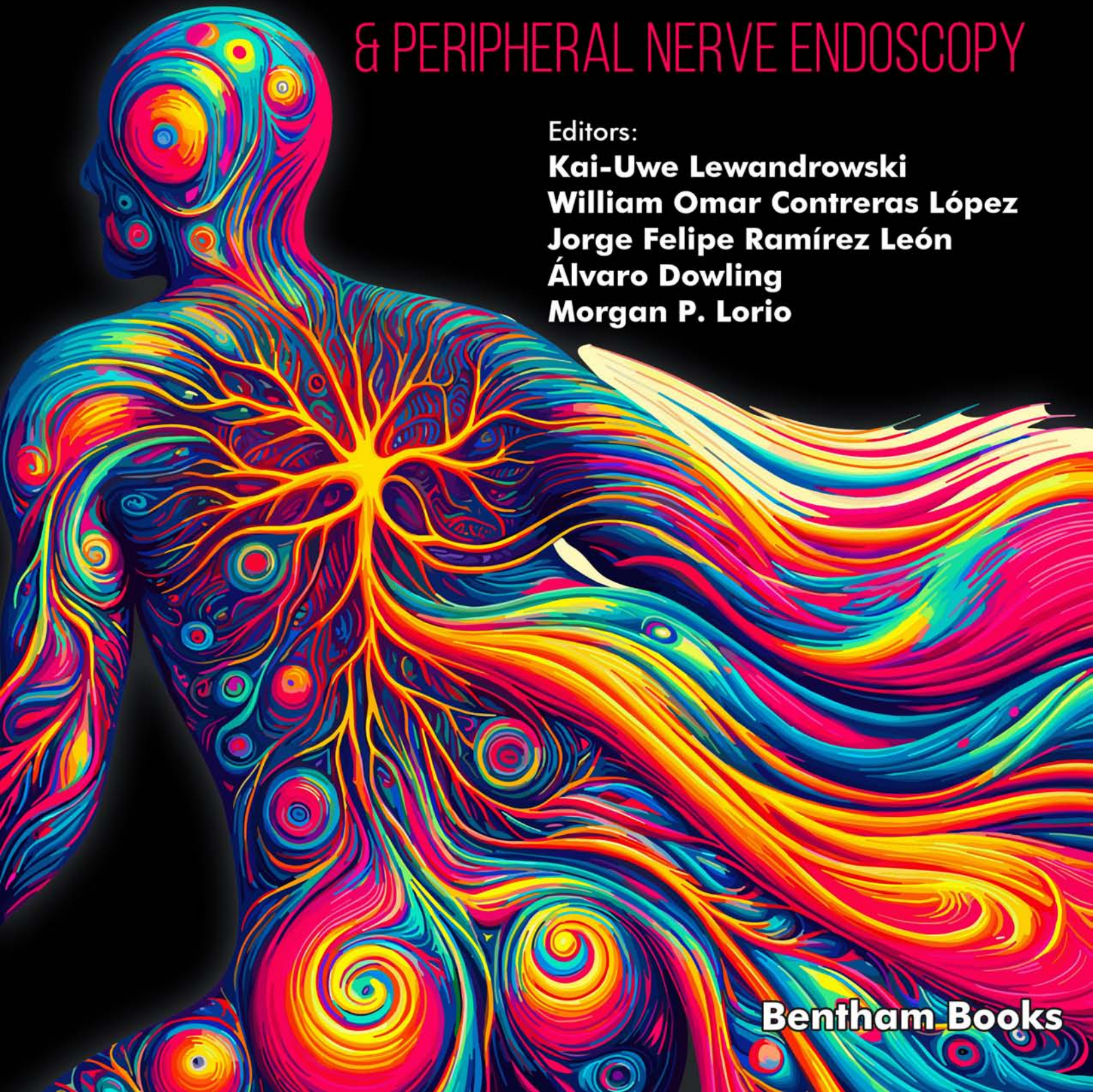

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Neuroendoscopy and Interventional Pain Medicine

(*Volume 1*)

Regenerative Medicine & Peripheral Nerve Endoscopy

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Neuroendoscopy and Interventional Pain Medicines

(Volume 1)

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PREFACE

Welcome to Neuroendoscopy and Interventional Pain Medicine, Vol. 1: Regenerative Medicine & Peripheral Nerve Endoscopy, a comprehensive volume that explores the latest advancements in regenerative medicine and minimally invasive endoscopic techniques. This book brings together the expertise of leading practitioners and researchers at the forefront of these transformative fields.

The growing impact of low back pain on individuals' health and lifespan is a significant concern, and this volume begins by addressing this issue with a focus on future care models that support healthy longevity. The book offers insights into targeted strategies for improving patient outcomes. Advancements in cell-based regeneration are crucial for treating degenerative disc disease. The current concepts and limitations of these strategies, highlighting both the potential and challenges in this evolving field, are discussed in depth. The clinical applications of regenerative strategies are further explored by providing a global perspective on the burden of low back pain and the promise of innovative treatments. Bioengineering strategies for injured or degenerative intervertebral discs are examined, and cutting-edge approaches to disc repair and regeneration are presented. Additionally, an in-depth look at current therapy strategies for vertebral endplates is provided, summarizing valuable information on treatment options for these critical structures. Stem cell therapy holds great promise for spinal cord injury, and the current concepts and advancements in this area are discussed, showcasing the potential for significant breakthroughs in patient recovery and rehabilitation. Minimally invasive and endoscopic techniques continue to revolutionize peripheral nerve decompression, as in ultrasound-guided or single portal endoscopic carpal tunnel release. These innovative approaches offer less invasive solutions for patients suffering from carpal tunnel syndrome. The use of ozone and PRP injections for symptomatic lumbar herniated discs is covered, and the respective chapter provides insights into these emerging treatment modalities and their effectiveness in alleviating pain and improving function. Lastly, the potential of allogeneic stem cell therapy for painful intermediate lumbar degenerative discs is explored, offering a glimpse into the future of regenerative medicine for spinal conditions.

Each chapter in this volume is carefully selected to reflect contemporary trends and innovations in regenerative medicine and endoscopic techniques as they apply to neuroendoscopy and interventional pain management. This book aims to meet the demands of patients, healthcare providers, and policymakers by addressing the need for safer, more efficient, and cost-effective solutions. The editors hope that Vol. 1 of Neuroendoscopy and Interventional Pain Medicine: Regenerative Medicine & Peripheral Nerve Endoscopy serves as an invaluable resource for clinicians and researchers dedicated to advancing the field and improving patient care.

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CHAPTER 1

The Implications of Low Back Pain on Prolonged Lifespan and Future Targeted Care Models to Support the Pursuit of Healthy Longevity

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Abstract: The human desire for everlasting youth and well-being has persisted throughout history. In the modern era, advancements in medicine and the emerging field of longevity have brought this age-old aspiration closer to realization. The remarkable increase in global life expectancy from a mere 30 years in 1870 to an impressive 71 years today, is a monumental healthcare achievement over the past century and a half. This achievement carries profound implications for the economy, necessitating a deeper understanding of the aging process and its influence on economic decision-making. Furthermore, it raises concerns regarding the adjustments required in behavior and lifestyle to adapt to extended lifespans while maintaining a high quality of life. The rise in life expectancy has substantial implications for managing chronic health conditions. Low back pain is nearly ubiquitous, and its global disease burden, particularly in high-socioeconomic standard countries, is high.

The youth and longevity business has carved out a niche from the traditional healthcare industry solely concerned with maintaining a high quality of life while managing the aging process. In this chapter, the authors deliver their perspective on the economic decision-making patterns of an aging population, the demographic changes associated with extended lifespans, and the adaptations in retirement planning and utilization of healthcare systems and social welfare programs. Further, the authors reflect on how aging spine patients adjust their behaviors and lifestyles to align with the demands of prolonged lifespans, prompting considerations of the economic consequences of these adjustments. The pursuit of healthy longevity raises questions about productivity, workforce participation, and the financial implications of supporting extended retire-

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Kai-Uwe Lewandrowski & William Omar Contreras López (Eds.)

ment periods. Healthy longevity refers to empowering individuals to lead longer lives while maintaining optimal physical, mental, and emotional well-being. Achieving healthy longevity entails making choices that significantly impact long-term health outcomes. The authors describe how the otherwise healthy low back pain patient over 50 should adopt a healthy lifestyle, including regular exercise, balanced nutrition, and stress management, to promote healthy aging while enhancing the quality of life during extended lifespans.

Keywords: Aging patients, Financial implications, Healthy longevity, Low back pain, Productivity, Workforce participation.

INTRODUCTION

For as long as human history has been documented, pursuing the fountain of youth has remained a steadfast endeavor driven by the desire to achieve an extended and healthier lifespan [1]. Today, fueled by remarkable advances in medical science and the exponential growth of the rejuvenation industry, this ancient dream is gradually becoming a reality. An astounding transformation in global life expectancy is a testament to the remarkable progress achieved over the past 150 years in healthcare. From a meager 30 years in 1870 (Fig. **1**), the average lifespan has reached 71 years—an unprecedented milestone [2], leaving a significant health-to-life span gap of 9.2 years [3].

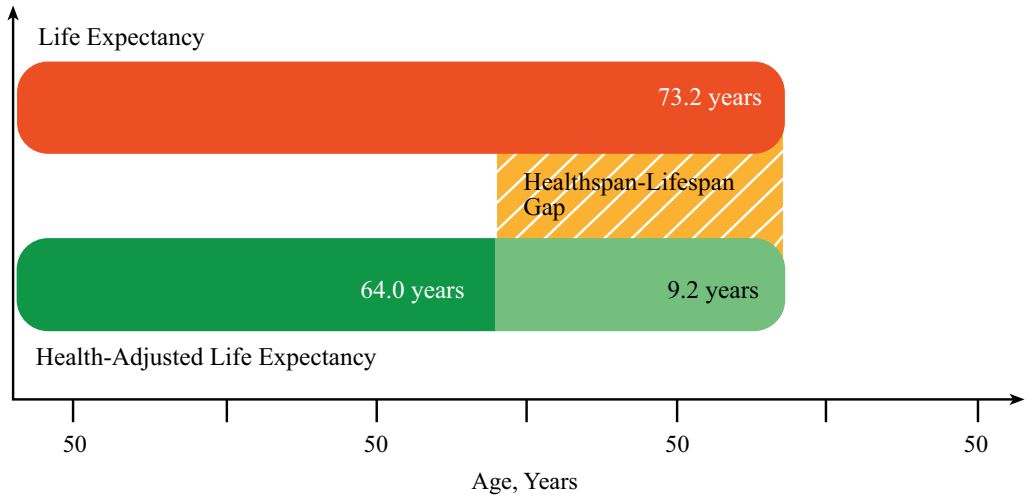

Fig. (1). Illustration of the health span to lifespan gap of 9.2 years [3].

Several considerations regarding longevity and low back pain are of concern [4]. Firstly, the substantial increase in life expectancy necessitates a deeper understanding of the aging process and its implications for economic decision-

making. With a population composed of individuals living longer, it becomes imperative to examine the complex dynamics of aging, low back pain, and its associated effects on various economic factors. Demographic shifts, such as an aging workforce and increased retirement periods, call for adaptations in retirement planning, social welfare systems, and healthcare services. Understanding the economic consequences of managing low back pain during a prolonged lifespan should enable patients, their physicians, policymakers, and economists to devise effective strategies that ensure economic stability and sustainability in the face of evolving demographic patterns [5].

Secondly, growing life expectancy raises pressing concerns about the necessary adjustments in behaviors and lifestyle habits to adapt to these long lifespans while preserving a high quality of life despite the burden of degenerative spine disease, which often manifests as low back and neurogenic claudication symptoms. From a practical point of view, it often means that patients need to reassess their choices and habits to navigate the challenges and opportunities presented by healthier longer lives. Associated factors affecting patients' life planning in their later years include financial and career management and healthcare utilization in the context of their overall well-being [1]. Such considerations are essential in enabling individuals to make informed decisions that optimize their well-being throughout their extended lifespans.

The ultimate goal of healthy longevity is to empower individuals to lead longer lives while maintaining optimal physical, mental, and emotional well-being. The key lies in making proactive and sustainable choices that positively impact long-term health outcomes. Engaging in a healthy lifestyle, encompassing regular exercise, a balanced diet, adequate sleep, stress management, and social connectedness, has been repeatedly shown to contribute to healthy aging and high quality of life significantly [1]. These lifestyle choices are fundamental pillars in the pursuit of healthy longevity, providing a robust foundation for individuals to age gracefully and enjoy enhanced well-being [6].

The authors of this chapter have become increasingly aware of a changing outlook in the healthy well-aging patient population and the need to offer treatments commensurate with the patient's goals and functional status. Low back pain is a significant concern for many of the authors' patients over age 50. These types of patients need to be better served by the spine care models running in public health care systems, where image-based criteria are often the foundation of medical necessity criteria for intervention or surgery. Frustrated, they often seek out the private practitioner for help. Hence, the need for a more structured care model for these highly functional patients - a care model that goes beyond the notion that healthy lifestyle choices profoundly impact long-term health outcomes and that

CHAPTER 2

Current Concepts and Limits of Cell-Based Regeneration Strategies for Degenerative Disc Disease

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Abstract: Degenerative disc disease stands as the predominant etiological factor behind low back pain. In recent years, the therapeutic modality of mesenchymal stem cell (MSC) infusion directly into the nucleus pulposus of the deteriorating disc has gained prominence. The intricacies of the intervertebral disc, a biomechanically robust tissue, span its components - the annulus fibrosus, nucleus pulposus, and cartilaginous endplates. Compromising the integrity of these elements can precipitate advanced disc degeneration due to biomechanical disruption. Animal models have demonstrated the therapeutic potential of MSCs. Particularly, adipose-derived stem cells (ASCs), a subset of MSCs originating from adipose tissue, possess attributes akin to their bone marrow-derived counterparts, metamorphosing into mesodermal structures, encompassing bone, cartilage, muscle, and fat. Their abundance in the human system,

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coupled with minimally invasive extraction methods, makes them appealing for regenerative medicine applications. A comprehensive literature assessment presented in this chapter delineates the therapeutic paradigm of MSCs in addressing degenerative disc disease (DDD) pain. To date, research predominantly centered on the nucleus pulposus, while neglecting the annulus fibrosus and cartilaginous endplates. Notably, clinical manifestations like annular ruptures, Modic alterations, or Schmorl's nodal formations typically hint at pathologies within these overlooked structures. The prospects of successful regenerative interventions within the annulus, endplates, or nucleus pulposus remain controversial, considering the hostile, nutrient-deprived milieu of the deteriorating intervertebral disc often culminating in the swift demise of the introduced MSCs. Singularly targeting the compromised nucleus pulposus *via* existing MSC-centric regenerative modalities may not achieve disc restoration. Therefore, MSC-based theurapeutic strategies should not just include the nucleus pulposus but also the affected annulus fibrosus and cartilaginous endplates.

Keywords: Intervertebral disc degeneration, Low back pain, Mesenchymal stem cells, Nucleus pulposus, Regenerative medicine.

INTRODUCTION

Low back pain, which plagues nearly 40% of the global populace, stands as a primary driver of muskuloskeletal disability [1]. This affliction predominantly stems from degenerative disc disease (DDD), an insidious condition marked by the degradation of the extracellular matrix and the decline in cellular viability, especially within the nucleus pulposus [2]. As a potential countermeasure, the *In vivo* reintroduction of live cells into the nucleus pulposus, sourced either from the patient or external donors, is gaining traction as a viable avenue for disc regeneration [3]. The spectrum of cellular candidates under investigation for therapeutic interventions in disc degeneration includes notochordal cells, nucleus pulposus cells, annulus fibrosus cells, chondrocytes, mesenchymal stem cells (MSCs), embryonic stem cells, and induced pluripotent stem cells, among others [4 - 18]. Of particular interest are the MSCs, residing in assorted stem tissues. These cells encapsulate a diverse cohort comprising pluripotent stem cells, progenitors, and mature cells [20]. Their prolific origin, coupled with their innate potential for self-renewal and versatile differentiation, has elevated MSCs as a favored contender for revitalizing the intervertebral disc *via* transplantation. Contemporary clinical explorations have elucidated the utility of MSCs, either autonomously or synergistically with biomaterial frameworks, to rejuvenate compromised discs [2, 3]. While these strides are commendable, the MSC-therapies are not covered by most health insurance carriers.

Normal Structures and Natural Healing

The annulus fibrosus (AF) repair mechanism is hampered, in part, due to the scant cell populations' struggle to metabolize and renew extensive collagen fiber aggregations, an obstacle further exacerbated by a constricted vascular supply [19]. The sophisticated constitution of the AF poses considerable obstacles to tissue regeneration endeavors [20]. Contemporary knowledge offers a modest understanding of the AF's foundational cellular biology, notably concerning the origins and functional capacities of specific cell clusters, and their phenotypic transformations post-trauma or in disease states. The viability of regenerative modalities that can surmount the demanding mechanical stresses and austere intra-disc milieu to realize effective AF regeneration remains unanswered [21].

Architecturally, the AF is layered into 15-25 concentric laminae, with slanting collagen fibers organized parallelly within each lamina. These fibers' angle-ply orientation (θ) diminishes progressively from ± 62° to ± 45° relative to the vertical axis, transitioning from the disc's periphery towards its center [22]. Glycosaminoglycan proportions amplify from 3% to 8% per wet weight as one traverses from the AF's external to internal sectors, concurrent with a declining type I to type II collagen ratio. The inner AF predominantly hosts spherical fibrocartilaginous cells, while its exterior is rich in elongated fibroblast-resembling cells. The AF environment also nurtures diverse cell types, including peripheral, interlamellar, and stem/progenitor cells.

The cartilaginous endplate, a svelte hyaline cartilage layer, bears resemblances with articular cartilage. Despite comprehensive studies on articular cartilage restoration, the nuances of endplate repair remain comparatively less explored [22]. Past endeavors in cartilage regeneration often culminated in the emergence of fibrocartilage as opposed to reinstating the native collagen lattice, resulting in functional inadequacy. Consequently, the rejuvenation of pristine cartilaginous endplate structures becomes paramount in addressing back pain and preserving disc nutrient supply. However, the poorly understood mechanisms of endplate restoration, compounded by gaps in comprehension regarding its cellular biology and biomechanics, have stymied the formulation of efficacious therapeutic approaches targeting cartilaginous endplates in the context of low back pain.

Normal Structure of the Intervertebral Disc

The IVD is a fibrocartilage structure that connects the vertebral bodies, contributing to spine mobility and acting as a shock absorber. It consists of three main structures: the nucleus pulposus (NP), the annulus fibrosus (AF), and the cartilaginous endplates (CEPs). The NP, located at the core of the IVD, contains NP stem/progenitor cells, notochordal cells, chondrocyte-like cells, water, and

CHAPTER 3

Current Clinical Applications of Regenerative Strategies for Lumbar Degenerative Disc Disease and Global Disease Burden Due to Low Back Pain

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Abstract: Degenerative disc disease, coupled with its consequential low back pain, presents a profound global health challenge, with efficacious clinical interventions still being subject to controversy. Cutting-edge strategies are being developed, targeting both pain mitigation and tissue regeneration. Both concentrated bone marrow aspirate and mesenchymal stem cells (MSCs) have displayed clinical potential in alleviating pain associated with degenerative disc disease. By harnessing molecular and genetic techniques, the utilization of growth factors, cytokines, and the modulation of autophagy and apoptosis processes offers hope in arresting disease progression, fostering tissue recuperation, and tempering inflammatory cascades. This chapter furnishes readers with a contemporary overview of therapeutic and regenerative modalities in clinical use and succinctly delineates the grading of the extant pinnacle clinical evidence.

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Keywords: Autologous platelet-rich plasma, Autologous mesenchymal stem cells, Low back pain.

INTRODUCTION

Defined succinctly, low back pain is characterized by discomfort in the posterior region, spanning from the twelfth rib's lower margin to the lower gluteal folds, potentially extending into one or both lower extremities, persisting for a minimum of one day [1].

As global demographics trend older, the prevalence of low back pain intensifies, becoming a ubiquitous health concern. This ailment exerts considerable morbidity and places an economic strain on numerous healthcare systems internationally. Its genesis is multifaceted; while a fraction can be attributed to genetic predispositions [2], psychological etiologies are also implicated [3]. Traumatic events may exacerbate disc degeneration [4]. Predominantly, age-induced disc degeneration is identified as the primary precursor to debilitating low back pain, commonly initiated by intervertebral disc degeneration. Consequently, afflictions of the facet joints can result in restricted mobility, often accompanied by radiculopathy, or sciatica [5 - 7]. In extreme scenarios, the compression of the cauda equina can lead to nerve root damage, intense pain, paralysis, and urinary or fecal incontinence [8 - 10]. Predominantly, surgical interventions, either decompression alone or in combination with fusion, are the foremost treatments for discogenic low back pain arising from advanced degenerative disc disease [11 - 14]. Notably, artificial disc replacements [15, 16] and other innovative interventions [17 - 24] are frequently deemed unsuitable for advanced disease stages or have not met the rigorous criteria of the FDA's approval process.

Traditional surgical interventions, like laminectomy and fusion, frequently mandate hospital stays, especially among older adults [25, 26]. They may be fraught with complications: blood loss [27], dural tears [28], postoperative pain, infections [29, 30], and a myriad of other post-surgical challenges [25, 31 - 42] often necessitating unplanned post-operative care [43]. Additionally, these procedures carry a substantial risk of reoperation [44 - 46], commonly attributable to hardware malfunctions, degeneration escalation, spinal instability, or deformities [47 - 52]. The functional deterioration ensuing from such procedures underlines the imperative for alternative methodologies. The paradigm is gradually shifting towards early-stage, minimally invasive [53], and regenerative interventions [54 - 59], opposing the historical predilection for extensive late-stage surgical reconstructions.

Recent empirical evidence underscores the efficacy of minimal interventions, employing direct visualization for patients grappling with degenerative spinal

stenosis, potentially with concomitant disc herniation [43, 60 - 62]. Preservation of the intervertebral disc's innate shock-absorbing functionality in compromised spinal movement scenarios has been advocated and tested by several experts [63]. Given the limitations intrinsic to the conventional surgical approach for spinal ailments, burgeoning research is centered on pioneering interventional modalities. The expanding research corpus substantiates this trend [64]. This chapter endeavors to encapsulate the contemporary zenith in regenerative therapies for intervertebral disc degeneration, acknowledging that the scope might not be exhaustive, and myriad validated restorative methodologies might emerge in the future.

Global Disease Burden

Globally, degenerative spinal conditions are ubiquitously observed and are an escalating concern with advancing age. Such maladies exert profound strain on both individuals and the overarching healthcare infrastructure. Specifically, intervertebral disc degeneration stands out as a noteworthy contributor to this worldwide health challenge, often culminating in prolonged disabilities among the affected.

The esteemed Global Disease Burden (GBD) study characterizes low back pain as discomfort manifesting in the posterior torso, ranging from the twelfth rib's base to the lower gluteal contours, potentially radiating into the lower extremities, and persisting for at least a day. This ailment's global impact is profound: in 2019 alone, low back pain emerged as the predominant Level 3 contributor to years lived with disability (YLDs), accounting for an estimated 63.7 million (95% UI 45.0–85.2) YLDs or approximately 7.4% (6.2–8.7) of the global total (as illustrated in Fig. **1**).

The GBD investigation encompassed a comprehensive assortment of studies on low back pain, including four centered on its incidence, 446 on prevalence, three on remission, and 15 others directly related to this ailment, with a conspicuous absence of studies focusing on its causes of death [65 - 68]. The 2019 iteration of the GBD study [67] diverged from its 2010 predecessor by omitting studies rooted in lifetime recall surveys, due to the variability in recall durations of lifelong back pain experiences exceeding the scope of a singular adjustment factor. Moreover, insurance data from Taiwan was disregarded due to its paucity. Corrections for potential biases were meticulously executed using meta-regression network analysis, specifically the Bayesian, regularized, trimmed approach (MR-BRT) [67, 69]. Adjustments accommodated studies that delineated overly extensive anatomical regions, episodes surpassing three months, varying recall periods, and constraints like pain that hampered activities. The analysis also accounted for

CHAPTER 4

Current Bioengineering Strategies for Injured or Degenerative Intervertebral Discs

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Abstract: The functionality of the intervertebral disc can be compromised due to aging and injuries. Synthetic and composite materials are investigated for disc repair to reduce pain. Synthetic materials or composite implants lack interaction with the disc's biological components and have yet to gain widespread usage or achieve desirable outcomes in treating intervertebral disc disorders. This chapter examines bioengineering approaches to disc repair, including cell-enhanced materials or biologically derived acellular materials that allow for cellular interactions and remodeling within the intervertebral disc. While still in its early stages, bioengineering techniques utilizing innovative biomaterials are showing promise as potential alternatives for the clinical treatment of intervertebral disc disorders.

Keywords: Annulus fibrosus, Disc degeneration, Degenerative disc disease, Fusion, Herniation, Intervertebral disc, Nucleus pulposus, Spine.

INTRODUCTION

The intervertebral disc (IVD) has historically been implicated in dorsalgia and has consequently undergone rigorous scientific scrutiny for the innovation of novel therapeutic modalities. The degenerative cascade within the IVD encompasses proteoglycan diminution, aberrations in extracellular matrix topography, annular fissures, formation of extruded discal fragments, and decrement in discal elevation [1 - 4]. Such morphological perturbations can culminate in radicular nerve encroachment, spinal canal stenosis, and facet joint infringement, thereby manifesting as nociceptive experiences and neurological insufficiencies [5, 6]. Additionally, the inflammatory microenvironment and neoinnervation observed within compromised discs have been postulated as etiological agents of discogenic dorsalgia [7]. Consequently, the multifaceted genesis of discogenic

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back pain involves intricate interplay amongst biomechanical attributes of the IVD, systemic inflammation, and neurophysiological systems (both peripheral and central) [8].

In light of their prospective efficacy in symptom alleviation and functional restitution, tissue engineering and regenerative medicine approaches have elicited considerable scholarly attention as pre-surgical interventions aimed at decelerating or even reversing the ongoing trajectory of IVD degradation and its concomitant nociceptive and dysfunctional symptomatology. These paradigms possess the unique merit of concurrently targeting the biomechanical, immunological, and neurophysiological dimensions implicated in IVD pathophysiology.

Contrary to the prevailing perception that the intervertebral disc (IVD) possesses a restricted regenerative aptitude following trauma (as illustrated in Fig. **1**), emergent insights into IVD ontogenesis, cellular biology, and mechanisms of degeneration portend the feasibility of cellularly-mediated rejuvenation [4]. Research has elucidated that the intrinsic cellular constituencies of the IVD exhibit a responsiveness to biomechanical provocations, such as substrate rigidity, and to an array of chemotactic and pro-inflammatory molecules, including but not limited to, chemokines and cytokines that modulate metabolic pathways and extracellular matrix assembly [9, 10]. Furthermore, aging-associated infiltration of macrophages and monocytes within the IVD has been demonstrated to modulate disc cell phenotypic expression, biosynthetic activity, and longevity. Bioengineering modalities represent a propitious avenue for directing cellular assimilation into implantable materials, representing a notable enhancement over erstwhile “inert” prosthetic devices that culminated in suboptimal clinical outcomes. There exists an escalating academic focus geared toward the refinement of both biological and bioengineering methodologies that capitalize on the endogenous cellular components resident within the IVD.

In this chapter, the authors proffer a succinct survey of clinical investigations that employ biomaterials as vectors for either cellular or pharmacological delivery. These investigations elucidate approaches for either the complete or partial restitution of the intervertebral disc (IVD) using cellularly-augmented as well as acellular, biologically-derived substrates that facilitate cellular-material interaction and architectural reorganization. Various preclinical and clinical inquiries have scrutinized the ramifications of infusing both allogeneic and autologous progenitor and stem cell lineages into the IVD milieu [11, 12]. Although the objectives aligned with cellular or drug deployment may intersect those of engineered biomaterials, such as restoring discal elevation, mitigating neural encroachments, or reversing radiological manifestations of pathology, the

complex landscape of regulatory approval coupled with the intense requirement for precise cellular introduction into the IVD has engendered work that transcends a consensus-oriented conceptualization of best practices.

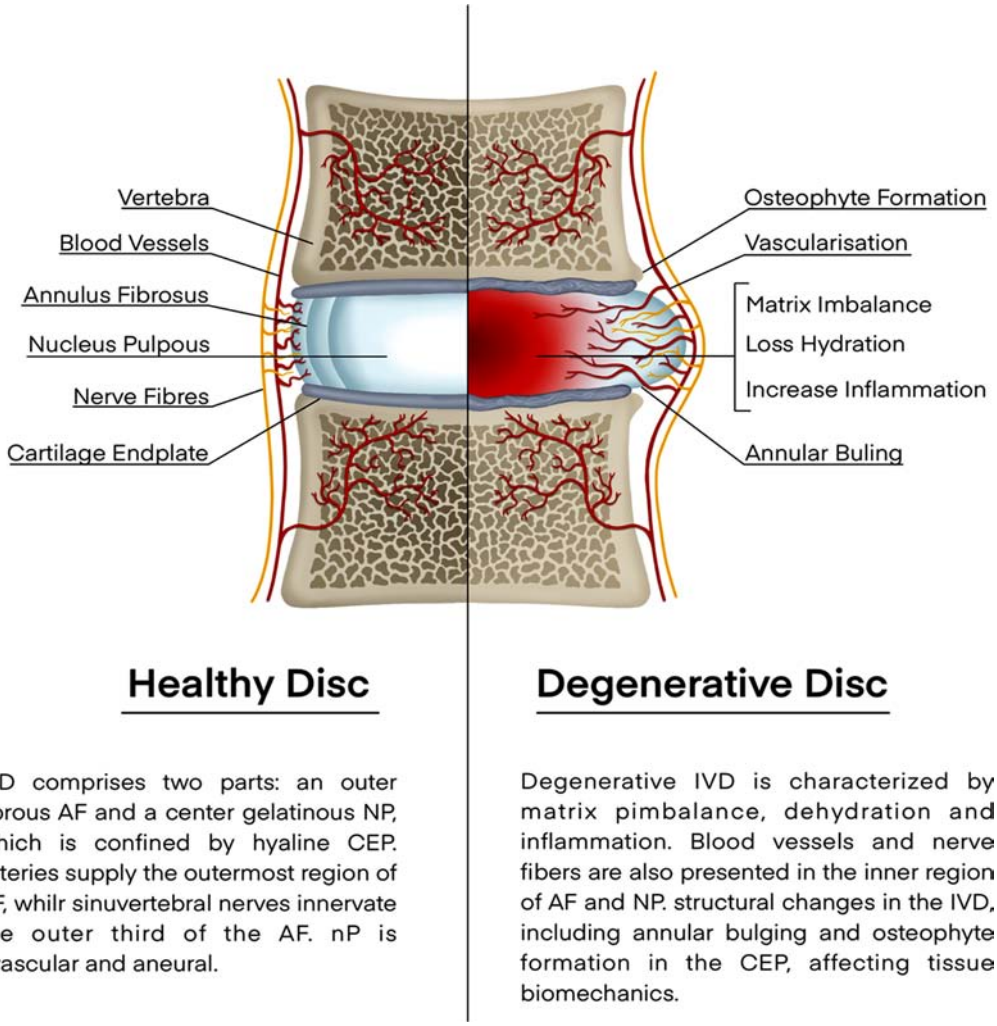

Fig. (1). In a healthy disc (left panel), the annulus fibrosus (outer layer) and nucleus pulposus (inner gel-like core) maintain their structural integrity and provide cushioning, flexibility, and shock absorption. In a degenerative lumbar intervertebral disc (right panel), the annulus fibrosus develops fissures leading to disc bulging or herniation. The nucleus pulposus may lose hydration and elasticity, becoming less capable of absorbing mechanical stresses resulting in reduced disc height and impaired disc function. Degenerative discs often are associated with osteophytes, spinal instability, nerve compression, and chronic low back pain.

In this context, the authors will delineate evolving methodologies and innovative breakthroughs involving biomaterials that are either in contemporary utilization or

CHAPTER 5

Current Therapy Strategies for Vertebral Endplates

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Abstract: The vertebral endplate is a critical component of the intervertebral disc, and its dysfunction can lead to various spinal disorders and chronic back pain. The structure and function of the vertebral endplate play an important role in disc nutrition, biomechanical support, and waste removal. Endplate-related conditions and their respective pathophysiologies may play a role in painful degeneration, fractures, and Modic changes. This chapter summarizes current concepts of therapeutic strategies with an emphasis on regenerative medicine application. It discusses using mesenchymal stem cells, platelet-rich plasma, growth factors, and tissue engineering approaches for endplate regeneration and repair. Diagnostic strategies for assessing vertebral endplate disorders and palliative as well as regenerative treatment strategies are discussed. The current evidence, ongoing research, and prospects in endplate-based therapies are highlighted.

Keywords: Annulus fibrosus, Disc degeneration, Degenerative disc disease, Fusion, Herniation, Intervertebral disc, Nucleus pulposus, Spine.

INTRODUCTION

Insufficient nutrient influx coupled with catabolic waste accrual are salient factors in the pathogenesis of intervertebral disc degeneration [1-6]. Given the disc's avascular constitution, it predominantly relies on vertebral endplates as essential conduits for nutrient facilitation [7, 8]. This solute transfer is orchestrated *via* an intricate network involving capillary beds and vascular interconnections between the osseous marrow recesses and the hyaline cartilaginous structure of the endplates [6, 9-12]. These vascular interfaces are imperative for cellular metabolic functions and the biofabrication of extracellular matrix components. Moreover, the effective expulsion of metabolic byproducts, notably lactic acid, is quintes-

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sential for averting their intradiscal accumulation [13]. Further, osmotic regulation *via* endplate-mediated water diffusion maintains intradiscal pressure equilibrium, which in turn contributes to disc height and mechanical functionality [14, 15].

Substantial empirical substantiation posits a robust correlative link between disc degenerative phenomena and concomitant alterations in adjoining endplates. Studies, exemplified by those conducted by Nachemson *et al.*, unveil a significant association between reduced endplate permeability and degenerative disc maladies [16]. Histological annotations indicate that disc degeneration is often presaged by lesions and microfractures within the endplates [17-19]. Additionally, age-associated calcification of endplate cartilage and the ensuing occlusion of nutrient conduits have been empirically observed. Radiological diagnostics, encapsulated by variations in MRI signal intensities in the vertebral marrow and morphological endplate alterations, manifest a strong linkage to degenerative disc conditions [22, 23]. Further, the aperture density within endplates has been ascertained to have a significant correlation with the degree of observed morphological deterioration [24].

Common interventional paradigms for mitigating disc degeneration encompass discectomy followed by scaffold implantation within the intradiscal environment. However, the efficacious implementation of these regenerative scaffolds is inexorably contingent upon the structural and functional integrity of the endplates. In instances where endplates exhibit sclerotic or hypertrophic characteristics, the anticipated restorative efficacy of the scaffold becomes critically compromised, owing predominantly to impeded fluidic and nutrient permeation. Thus, a compromised foundational architecture in the form of defective endplates ultimately undermines the holistic objectives oriented towards disc remediation.

Physiology

Endplates are composite structures characterized by both osseous and hyaline cartilaginous elements, discernible from embryonic developmental phases [25]. The osseous segment undergoes co-ossification with adjoining vertebral entities, while the cartilaginous component persists throughout standard ontogeny, eliciting noteworthy scientific attention. This cartilage portion is constituted by a hydrogel-like matrix replete with proteoglycan macromolecules, buttressed by a reticulum of collagen fibrils. Contrary to articular cartilage in diarthrodial joints, these collagenous fibrils refrain from direct osseous anchoring to the vertebral corpus [26]. Nevertheless, the endplate retains its proximal interface with the intervertebral disc *via* the inner annulus fibrosus lamellae [27]. During axial skeletal maturation, capillary networks transiently invade the endplates, furnishing requisite nutrients to the disc [25]. These vasculatures regress upon the

attainment ofskeletal maturity, rendering mature discs largely dependent on solute diffusion across the endplates for sustenance and metabolic reciprocity [28].

Expansive scientific exploration has interrogated the endplate's biochemical constitution under physiological homeostasis and diverse degenerative paradigms [29, 30]. Of the various collagen subtypes identified within the disc, Type X collagen accrues particular significance in endplate pathophysiology, serving as a surrogate marker for hypertrophic chondrocytes and participating in calcification cascades [31]. Intriguingly, targeted abrogation of one Collagen II gene allele in murine models precipitates diminished glycosaminoglycan content within endplates, engendering abnormally thickened and precociously calcified structures [32]. These proteoglycan moieties play pivotal roles in modulating osmotic dynamics and maintaining hydric equilibrium within endplate cartilaginous matrices [33]. Their diminution correlates with concomitant proteoglycan deficits within the nucleus pulposus, implicating proteoglycan attrition as a likely precursor to disc degenerative processes [34].

Additional biochemical alterations in the endplates during skeletogenesis may impart a contributory role in the etiopathogenesis of conditions like scoliosis [35-37]. Comprehensive metabolic and nutritional studies of the disc have employed diverse *In vitro* models, substantiating the endplate's cardinal role in metabolic orchestration [16]. Notably, lateral peripheries of the endplate adjacent to vertebral rims exhibit reduced permeability *vis-a-vis* its central or annular counterparts [9, 28]. Morphometric analyses employing post-mortem human specimens have revealed a differential distribution of microvascular networks, with central endplate regions possessing augmented capillary densities relative to peripheral disc areas [3, 38]. This circulatory infrastructure, visualized through specialized injection techniques, corroborates that primary nutrient influx into the disc is mediated by diffusional transfer of minute solutes from these microvessels [7, 39]. However, this permeability is selective, governed by molecular dimensions and ionic polarity. The nucleus pulposus' high proteoglycan content endows it with a net negative electrostatic charge, thereby facilitating the ingress of cations like sodium and calcium, in addition to neutral entities like glucose and oxygen, whilst obstructing the transit of anions such as sulfate and chloride, as well as larger macromolecules like immunoglobulins and enzymatic compounds.

Endplate and Skeletal Maturity

Upon the attainment of skeletal maturity, the cartilaginous architecture of the endplate undergoes pronounced metamorphosis, culminating in substantive mineralization—a process subsequently reversed through osteoclastic resorption and osseous substitution [20, 40]. This emergent tissue composition impinges

CHAPTER 6

The Current Concept for Stem Cell Therapy in Spinal Cord Injury

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Abstract: Spinal cord injury with neurological deficits is devastating to patients and their families. After the immediate treatment that may involve spinal decompression and stabilization surgeries, patients are typically left with long-term disability. Intense research has focused on spinal cord regeneration, tissue repair, and reinnervation to improve function. Stem cell-based therapies are at the center of this effort. This chapter summarizes common spinal cord injury (SCI) patterns, including complete and incomplete SCIs, and their classification-based prognosis and treatments. They review the types of stem cells used in preclinical and clinical trials in the treatment of SCI and the associated ethical concerns and summarize the current state of the art of stem cell-based SCI treatments.

Keywords: Classification, Prognosis, Spinal cord injury, Stem cells, Treatment.

INTRODUCTION

Spinal cord injuries (SCIs) represent a formidable public health problem, manifesting an incidence range of 40 to 80 cases per million individuals annually, according to existing epidemiological data [1]. Predominantly afflicting a younger demographic, these injuries occasion irremediable neurological deficits that exert an onerous toll on patients, healthcare providers, and medical infrastructures alike. While prophylactic measures targeting vehicular mishaps, unlawful conduct, and secondary etiological factors such as neoplastic or degenerative pathologies are indisputably vital, the true challenge confronting the scientific community lies in the domain of therapeutic intervention, especially in the absence of a universally recognized, efficacious treatment modality.

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Recent years have witnessed salient advancements in specialized, multidisciplinary methodologies for addressing SCI. Noteworthy among emerging organizational entities committed to this specialized sector of neurological injury is the International Association of Neurorestoratology (IANR). Such professional assemblies underscore the efforts to surmount a yet unresolved clinical impasse.

Within the scope of contemporary neurological practice, the re-establishment of functional capabilities post-SCI remains a daunting enterprise. This necessitates the employment of a spectrum of neurorestorative tactics throughout the acute, subacute, and chronic temporal stages of SCI, aimed at the reversing functional losses.

Primary Injury

The spinal cord of mammals is organized into ten laminae of neurons, named dorsoventrally, according to the Rexed description [2]. The neurons are mostly multipolar and vary in size. In the dorsal laminae, sensory neurons receive inputs from the dorsal root ganglion cells and project them to other spinal levels or the upper centers of the sensory pathways.

Within the dorsal laminae, sensory neurons act as afferent conduits for dorsal root ganglion cells, directing somatosensory information to alternate spinal echelons or more rostral sensorimotor processing centers. Conversely, the ventral laminae house substantial populations of cholinergic motor neurons, which orchestrate myogenic contractions *via* efferent axonal pathways. An intermediary locus is occupied by morphologically diverse interneurons, recipients of both descending corticospinal projections and recurrent axonal fibers from spinal motoneurons, thereby modulating motoneuronal discharge patterns [3, 4]. Neuronal constituents within the spinal cord forge intricate intraspinal circuitries under the governance of descending neural pathways, with the reflex arc representing the most rudimentary of such closed-loop systems.

During the acute temporal phase of SCI, the underlying traumatic etiology may encompass a variety of mechanical insults, such as contusions, lacerations, tensile forces, compressional impacts, or outright cellular obliteration. These initial traumatic events culminate in the primary injury phase, characterized by disintegration of neural circuitries [5]. In the immediate post-injury interval, typically within the first two hours [6], cellular constituents, including both neurons and glial entities at the lesion nexus, succumb to either necrotic or apoptotic fates [7]. Ergo, therapeutic objectives in post-SCI management should prioritize the restitution of native intraspinal circuitry, followed by the facilitation of regenerative growth in descending pathways, to re-establish volitional governance over these circuits. It is unequivocally acknowledged that the most

pivotal juncture in the pathophysiological trajectory of SCI pertains to the secondary injury phase. This latter phase is typified by an unchecked, maladaptive cascade involving aberrant molecular signaling pathways, inflammatory cascades, vascular aberrations, and consequent cellular dysregulations, further exacerbating the initial insult [8-11].

Secondary Injury

Within the context of an injured spinal cord, a spectrum of destructive mechanisms disturbs the local microenvironment, the severity of which is contingent upon the characteristics of the primary injury. In terms of vascular pathology, there occurs a widespread attenuation of blood perfusion attributable to phenomena such as vasospasms, focal microhemorrhagic events, and thrombotic incidents, collectively leading to a comprehensive compromise of the blood-spinal cord barrier integrity [8, 12]. Concurrently, a dysregulation in ionic equilibrium manifests around cellular membranes and associated ion transport machinery. Specifically, an efflux of potassium ions (K+) is observed in the extracellular milieu, concomitant with an intracellular accrual of sodium (Na+) and calcium ions (Ca2+) [8, 13]. These perturbations result in the attenuation of neuronal signal transduction capabilities.

An acidotic milieu further exacerbates this dysfunctional state by facilitating the ingress of water molecules into the cellular compartment, culminating in cytotoxic edema and subsequent cellular demise [14-16]. The injurious cascade also precipitates the release of multiple biochemical entities, including reactive oxygen species and various neurotransmitters. Immunologically, the breach in the blood-brain barrier inaugurates the recruitment and infiltration of immune cells—such as T lymphocytes, macrophages, microglia, and neutrophils—into the neuronal matrix, thereby adopting a proinflammatory phenotype. The ensuing milieu is further enriched by the secretion of a cadre of proinflammatory cytokines, including but not limited to, Interleukin-1 beta (IL-1β), Interleukin-1 alpha (IL-1α), Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-6 (IL-6). These factors collectively contribute to a localized cellular assembly that fosters neurodegenerative processes [17-19].

Chronic Phase and Neurodegeneration

In the chronic phase of spinal cord injury (SCI), a hallmark feature is the fibrotic encapsulation engendered by gliotic processes and the accretion of extracellular matrix components, thereby attenuating functional capacity. Bioactive molecules harboring anti-proliferative properties are liberated, targeting specific neuronal receptor complexes. The demise of oligodendrocytes during the primary injury event is of particular importance, given that the resulting myelin detritus harbors

CHAPTER 7

Ultrasound-Guided and Single Portal Endoscopic Carpal Tunnel Release

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Abstract: As surgeons evolve to minimize morbidity and maximize outcomes or return-to-work (RTW) in the treatment of carpal tunnel syndrome (CTS), so have both single portal neuro-endoscopy and ultrasound-guided (US) technical applications procedurally in the safe, effective, and complete release/transection of the transverse carpal ligament (TCL). The chapter is intended as an independent complete go-to content-repository for surgeons desiring to revisit/review a relevant topic or area of thought without needing to reread the entirety of the same prior to a surgical case as a quick refresher. For those surgeons who have either mastered neuro-endoscopy or remain a novice, US techniques may offer patients new possibilities through the simple overlay of novel instruments and instructions over one's accumulated past experience.

Keywords: Carpal tunnel syndrome, Carpal tunnel release, Endoscopy, Ultrasound.

INTRODUCTION

Learmonth described the first open surgical release of the TCL in 1933 [1]. Brain and Phalen, respectively, defined idiopathic CTS from both clinical and anatomopathological points of view [2, 3]. SPECTR (Single Portal Endoscopic Carpal Tunnel Release) and USCTR (Ultrasound Guided Carpal Tunnel Release) are two modern surgical techniques that have emerged as advancements in the treatment of CTS. While they share the common goal of alleviating pressure on the median nerve, their historical origins and overlap in development have distinctive characteristics. Open procedures utilize extensile exposure to protect vital structures during surgery. However, open-approach techniques create surgical morbidity in normal tissues. Over time, surgeons have sought to minimize morbidity, leveraging technological advances to create minimally inva-

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sive solutions without sacrificing safety or efficacy. The result has been to reduce patient recovery times and complications inherent in open techniques. The origins of SPECTR can be traced back to the introduction of endoscopic techniques in the late 1980s. Until recently, surgeons have been traditionally divided into three main camps: standard open/extensile (34%), mini-open (46%), and endoscopic (20%) (See Fig. **1**) [4]. In 1989, Chow *et al.* technically reported a dual-portal endoscopic carpal tunnel release (ECTR) [5]. After that, in 1992, Agee *et al.* detailed his SPECTR technique in a prospective randomized control trial (PRCT) using a transverse incision in the area of the proximal wrist crease [6]. This pistol-shaped 3M® Agee device evolution led to the birth of SPECTR, with the primary objective of providing enhanced visualization and reduced tissue trauma. MicroAire® Surgical Instruments later purchased the 3M® Agee device. A subsequent PRCT in 2002 by Trumble and Diao *et al.*demonstrated an equally safe and faster recovery (faster RTW) with SPECTR compared to open release [7]. Both co-authors of this book chapter were blessed to have been orthopedic residents in training within SUNY-Buffalo, a Beta-site for Agee's Hand Biomechanics Lab; both have 30 years of experience with SPECTR. The development of specialized instrumentation and improved surgical techniques have contributed to the refinement of SPECTR over the years with a proliferation of devices, including the Arthrex® Centerline ECTR, which shares a very similar ergonomic profile with USCTR paralleling the longitudinal axis of the forearm and wrist while using direct neuro-endoscopic visualization in the former and ultrasound visualization in the latter. In 2010, Arthrex® settled a patent infringement spat with MicroAire®, and now MicroAire® licenses its patented ECTR technology to Arthrex® with both companies agreeing to "maintain Microaire's practice of requiring surgeon training for the procedure" [8].

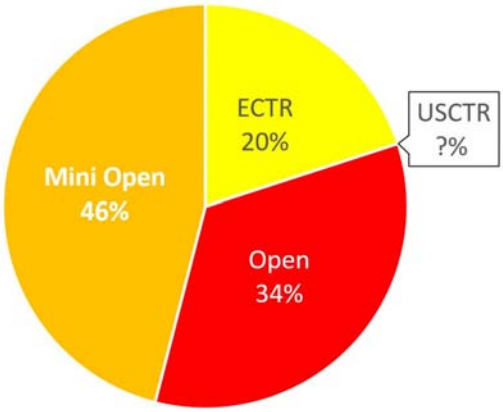

Fig. (1). Treatment of CTS (adapted from a 2012 survey of the American Association of Hand Surgery).

Although SPECTR and USCTR have distinct historical origins, there is an overlap in their evolution and technological advancements. Both techniques aim to minimize invasiveness and improve outcomes in the surgical treatment of CTS. They demonstrate the ongoing efforts within the surgical community to refine and optimize procedures to benefit patients. The development of specialized instrumentation, improved imaging modalities, and the integration of minimally invasive principles have contributed to the evolution and overlap of SPECTR and USCTR as valuable personalized precision treatment options for CTS. This chapter will attempt to describe both techniques simultaneously to avoid redundancy and expound where it is necessary to differentiate the distinctly different characteristics and nuances of each when appropriate.

Expectations

Two prominent techniques have gained recognition in the realm of minimally invasive surgical options for CTS: SPECTR and USCTR. With the increasing demand for less invasive approaches, patients and surgeons alike are eager to understand the expectations associated with the procedures. SPECTR offers the advantage of enhanced direct and familiar visualization with precise surgical intervention within the carpal tunnel, leading to potentially improved outcomes with Level I Evidence [9]. On the other hand, USCTR provides a guided and controlled release of the TCL, with minimal incision and potential for faster recovery. This chapter explores the innovations associated with these innovative techniques, highlighting their respective benefits, limitations, and anticipated outcomes, ultimately aiding clinicians and patients in making informed decisions regarding the optimal approach for CTR.

The anatomic expectation of either procedure is a complete release of the TCL, thereby releasing compression on the carpal tunnel contents, specifically the median nerve. In 1994, using advanced MRI techniques, Ablove *et al.* at SUNY-Buffalo validated that both SPECTR and a dual-portal subcutaneous CTR morphologically produced a marked increase in canal volume and median nerve cross-sectional area, suggesting equivalence to open release [10]. After that, in 1996, Ablove *et al.* found that pressures decreased in both the carpal tunnel and Guyon's canal (GC) after both endoscopic and open release, suggesting that CTR alone may be sufficient to relieve symptomatic carpal and ulnar tunnel syndromes [11]. Recently, Peters *et al.*, in 2021, using an MRI protocol, confirmed no significant morphologic differences between Agee SPECTR and open release, with both resulting in a significant increase in the AP dimensions of the carpal tunnel and GC, respectively [12]. Likewise, Occam's razor or the 'law of parsimony' would suggest that a successful USCTR would have similar results.

CHAPTER 8

Ozone and PRP Injections for Symptomatic Lumbar Herniated Disc

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Abstract: Low back pain from arthritic lumbar facet joints and painful degenerative lumbar discs is widespread and one of the world's most disabling diseases, consuming significant health care resources. In this chapter, the authors report using autologous platelet-rich plasma (PRP) and ozone spinal injections into arthritic lumbar facet joints and painful lumbar degenerative discs to treat inflammatory pain. A prospective observational cohort study from January 2016 to March 2020 was performed at an outpatient clinic of a single academic medical center to assess these injections' safety and therapeutic effectiveness in conjunction with epidural transforaminal epidural steroid injections. Results indicated functional improvements measured by Oswestry Disability Index (ODI) and modified MacNab criteria and pain measured by visual analog scale leg pain (VAS) at rest and during flexion. Although our study was limited in scope, and by the observational nature of our research and the lack of randomized

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and double-blinding, our work suggests that rapid pain reduction and functional gains may materialize in patients with low back pain due to herniated disc after spinal injections with ozone and activated PRP.

Keywords: Low back pain, Ozone, Autologous platelet-rich plasma, Spinal injection.

INTRODUCTION

Chronic lumbar pain predominantly arises from intervertebral disc degeneration. In contrast, acute episodes of severe pain in the lower back and leg, resembling sciatica, usually result from herniated lumbar discs, adversely impacting patients' daily life and productivity. Such conditions pose a significant medical challenge. Lumbar degenerative disc disease has emerged as a pressing global concern, particularly prevalent among the aging population [1, 2]. Current treatments encompass conservative methods: anti-inflammatory medication, physical therapy, and microdiscectomy. Yet, the surgical route might expedite degeneration, potentially demanding further interventions [3 - 7].

In the 1980s, chymopapain, a cysteine protease from papaya latex, was a popular choice for chemical nucleolysis in patients with persistent herniated disc symptoms. Due to complications, its use was discontinued [8]. In the same decade, intradiscal oxygen/ozone injections for symptomatic lumbar herniations were introduced [9]. Numerous studies [9 - 22] and select randomized trials [12, 13, 23 - 26] have since underscored the efficacy of ozone therapy, either standalone or combined with steroids and other inflammation-reducing agents. Techniques, such as periradicular and intraforaminal injections, have proven beneficial in managing lumbar herniated disc pain [21, 23, 25, 27 - 32].

Ozone's primary modus operandi is believed to be chemonucleolysis, as it interacts with proteoglycan GAGs that help retain intradiscal osmotic balance, causing them to decompose. This leads to the nucleus pulposus dehydrating, thereby reducing disc volume. Moreover, ozone's inherent antimicrobial properties negate the need for preventive antibiotics [33]. Interactions with intradiscal cytokines may further produce an anti-inflammatory effect, diminishing pain levels, as supported by animal studies [34, 35]. Imaging analyses, including CT and MRI scans, have confirmed the reduced size of ozone-treated herniated lumbar discs [26, 36 - 39].

Platelet Rich Plasma (PRP)

Platelet Rich Plasma (PRP), derived from autologous sources, has shown promise in alleviating pain associated with symptomatic lumbar herniated and

degenerative black discs [40]. PRP is essentially a concentrated blend of platelets suspended in a minimal volume of plasma. Its therapeutic potential arises from its capacity to promote extracellular matrix synthesis, which in turn may catalyze wound repair and intradiscal regeneration [41]. On a molecular front, PRP appears to modulate cytokine secretion, promoting the release of anti-inflammatory agents while suppressing pro-inflammatory cytokines. This modulation doesn't trigger immune reactions due to the autologous origin of the PRP [42].

Mirroring ozone's properties, PRP possesses anti-inflammatory and anti-microbial characteristics, thus potentially minimizing infection risks post-spinal injections [4, 5]. Several in vitro studies have confirmed the multifaceted advantages of PRP on degenerative disc tissues [6]. Notably, PRP has been associated with the rejuvenation of denatured discs by enhancing glycosaminoglycan concentrations [43]. Contemporary clinical findings indicate PRP's efficacy in pain mitigation related to lumbar disc conditions. However, concrete evidence verifying structural and functional enhancements remains elusive [44].

In the referenced prospective observational cohort study, the authors delve into the synergistic effects of ozone combined with activated PRP, aiming to optimize therapeutic outcomes for patients suffering from painful lumbar herniated discs.

Ozone Therapy

Ozone [$O_{(2)}$-$O_{(3)}$] has been applied in the treatment of herniated discs. It also is believed to have therapeutic effects. Chemically, ozone is a highly reactive form of oxygen. It has been employed in the treatment of painful lumbar disc herniations. In addition to anti-inflammatory effects, it has been proposed to have analgesic properties [22]. The latter property was attributed to alleviating pain stemming from acute lumbar disc herniations by modulating the pain signaling pathways, reducing inflammation, and inhibiting the release of pain-inducing substances in the affected area. Ozone therapy may promote also cause shrinkage or dissolution of the herniated disc material by inducing oxidation. The resulting breakdown of diseased disc material [16, 17, 24] has been instrumental in patients with sciatica-type back and leg symptoms from extruded herniated discs. The resultant volumetric reduction in disc volume and subsequent indirect decompression of lumbar nerve roots [35] are therapeutically beneficial when managing patients with this painful and disabling disease.

Ozone also enhances oxygenation and blood flow [33] to the damaged areas in the annulus and nucleus. It may support the metabolic needs of the disc cells, improve tissue healing, and stimulate tissue regeneration. Additional benefits are its antimicrobial properties, lowering the risk of discitis and infection of the surrounding structures, particularly when surgical or interventional treatment is

CHAPTER 9

Allogeneic Stem Cell Therapy for Painful Intermediate Lumbar Degenerative Discs

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Abstract: The management of mid-stage degenerative disc disease presenting with pain remains contentious, attributed in part to the scarcity of conclusive clinical trials. Allogeneic mesenchymal stem cells (MSCs), procured from donors, emerge as a viable alternative to autologous stem cell therapy. These MSCs are characterized by their accessibility and the streamlined administration process suitable for procedure-room settings, particularly for addressing discogenic lumbar pain. Within this manuscript, the authors delineate their proprietary protocol involving allogeneic MSC application, detailing the efficacy, safety, and clinical implications post-infusion into symptomatic lumbar intervertebral discs. Their clinical series encompassed 32 subjects, 14 females and 18 males, averaging 47.6 years of age, with a mean follow-up duration of 26.88 months. Two-year post-treatment evaluations revealed notable decrements in both ODI and VAS scores for lumbar pain. Evaluating Macnab outcomes, 11 participants (33.3%) showcased excellent results, 19 (57.6%) reported good outcomes, and a mere 3 (9.1%) indicated fair results. Notably, none necessitated supplementary interventions at

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the MSC-treated disc level. Despite the study's constraints, such as its observational nature, potential selection and hindsight biases, and modest participant count, the authors' findings substantiate the potential of intradiscal allogeneic MSC injections in managing mid-stage painful degenerative disc afflictions. To fortify these preliminary insights, future research endeavors should encompass a more regimented structure, potentially incorporating a placebo cohort or a natural progression study group.

Keywords: Allogeneic, Mesenchymal stem cells, Low back pain, Degenerative intervertebral disc disease.

INTRODUCTION

The dawn of the 21st century heralded significant strides in biotechnology, ushering in transformative therapeutic modalities that have markedly elevated patient care and outcomes. Predominantly, regenerative medicine has spearheaded this metamorphosis, encompassing novel techniques like cell therapy, gene therapy, and tissue engineering [1 - 4]. Forefront interventions in this arena include the deployment of platelet-enriched plasma [5 - 8], stem cells [3, 9], and the derivatives procured from their culture. These interventions, in many cases, have not only ameliorated symptoms but also proffered potential cures [10 - 12].

A meticulous review by Sanapati *et al.* probed into the therapeutic efficacy of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) for conditions including discogenic low back pain, radicular pain, and sacroiliac joint pain, among others [13]. The outcomes showcased a spectrum of evidentiary support for the therapeutic promise of MSCs and PRP for these pain manifestations.

In contemporary research, allogeneic stem cell transplantation has surfaced as a compelling counterpart to autologous bone marrow transplants [14 - 17]. Its preeminence is accentuated by its capacity to curtail functional discrepancies through the employment of multi-donor cell aggregates housed in a central repository. Notably, MSCs exhibit an inherent aptitude for allogeneic transplantation with a negligibly low rejection proclivity [18]. Within this discourse, the authors delineate their modus operandi for deploying allogeneic stem cell interventions for degenerative disc disease (DDD)-induced pain. The overarching endeavor is to interrogate the therapeutic safety profile of MSCs and their potential to mitigate chronic low back pain (CLBP) symptoms, thereby optimizing patient functionality. This exploration aims to set the stage for ensuing inquiries into the merits and safety considerations of allogeneic stem cell interventions for back pain and varying stages of DDD.

This chapter's focus is the safety appraisal of a solitary allogeneic MSC injection in a clinical setting, targeting a symptomatic lumbar disc, and concurrently

gauging the ensuing therapeutic ramifications in patients grappling with CLBP linked to moderate DDD.

Allogeneic Mesenchymal Stem Cells (MSCs)

The increase of allogeneic mesenchymal stem cells (MSCs) in regenerative medicine positions them as an attractive counterpart to autologous transplants. Sourced from external donors, these cells stand out due to their simplified procurement process, stellar safety record, and demonstrated efficacy in addressing myriad medical and musculoskeletal maladies. Typically extracted from bone marrow, peripheral blood, or umbilical cord blood, allogeneic MSCs present diminished risks associated with contamination, mutation, and graft rejection compared to their autologous counterparts. These multipotent cells, endowed with the ability for differentiation into diverse cell types and self-renewal, also exhibit pronounced immunomodulatory attributes, making them compelling candidates for managing inflammatory and autoimmune disorders. Advantages encompass expedited transplantation timelines, diminished infection risks, procedural complications, and lessened reliance on intensive immunosuppression.

One realm where the therapeutic potential of allogeneic stem cells shines is in addressing degenerative disc disease (DDD), a predominant contributor to chronic low back pain. DDD's etiology involves intervertebral disc degradation, precipitating disc herniation, spinal stenosis, and nerve entrapment. Conventional DDD interventions span medications, physical rehabilitative therapies, and surgical approaches, but their efficacy is oftentimes transient and fraught with potential risks. Research, such as the study by Pettine *et al.*, underscores the substantial efficacy and safety of MSCs in ameliorating discogenic pain and restoring function. Multiple investigations [19 - 24] corroborate the well-tolerated nature of these cells, with an absence of grave adverse outcomes, reinforcing their therapeutic promise in offering sustained respite from chronic lumbar discomfort.

Yet, navigating the therapeutic deployment of allogeneic stem cells is not devoid of challenges. Immune rejection [25], stemming from the recipient's immune defenses perceiving the introduced cells as alien, remains a concern [26]. Strategies to curb this include meticulous cell matching to the recipient's tissue. Notably, heavy immunosuppressive regimens are generally unnecessary. Nonetheless, an in-depth exploration into their clinical viability, safety contours, and economic competitiveness in juxtaposition to other regenerative modalities is imperative.

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