ADVANCEMENTS IN REGENERATIVE THERAPIES FOR LUMBAR DISCOGENIC PAIN : THEORETICAL REVIEW OF STEM CELL THERAPY AND GENE THERAPY

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ABSTRAK

Nyeri diskogenik lumbal yang diakibatkan oleh degenerasi diskus intervertebralis merupakan kondisi yang umum dan melemahkan yang berdampak signifikan pada kualitas hidup pasien dan membebani sistem perawatan kesehatan. Perawatan tradisional sering kali gagal mengatasi patologi yang mendasarinya, sehingga mendorong peningkatan minat pada terapi regeneratif seperti terapi sel punca, biologik, dan terapi gen, yang bertujuan untuk memulihkan fungsi diskus dan memberikan kelegaan yang bertahan lama. Tinjauan pustaka dilakukan menggunakan PubMed, MEDLINE, dan Embase, dengan fokus pada studi dari 10 tahun terakhir. Kata kunci meliputi "regenerasi diskus intervertebralis," "terapi sel punca," dan "terapi gen." Studi dipilih berdasarkan relevansi dan kualitas metodologis. Hasil penelitian menunjukkan bahwa terapi sel punca menunjukkan hasil yang menjanjikan dalam meningkatkan regenerasi diskus melalui diferensiasi seluler dan sekresi faktor pertumbuhan. Terapi gen menawarkan perbaikan diskus yang terarah tetapi menghadapi kendala terkait sistem pemberian dan keamanan. Terapi regeneratif berpotensi mengubah manajemen nyeri diskogenik lumbal dengan mengatasi akar penyebabnya daripada gejalanya. Namun, tantangan etika, regulasi, dan teknis harus diatasi. Penelitian lebih lanjut, termasuk uji coba jangka panjang dan multipusat, sangat penting untuk memvalidasi manfaat klinisnya.

Kata kunci : nyeri diskogenik lumbar, pengobatan regeneratif, terapi gen, terapi sel punca

ABSTRACT

Lumbar discogenic pain resulting from intervertebral disc degeneration is a prevalent and debilitating condition that significantly impacts patients' quality of life and burdens healthcare systems. Traditional treatments often fail to address the underlying pathology, prompting increased interest in regenerative therapies such as stem cell therapy, biologics, and gene therapy, which aim to restore disc function and provide lasting relief. Literature review was conducted using PubMed, MEDLINE, and Embase, focusing on studies from the last 10 years. Keywords included "intervertebral disc regeneration," "stem cell therapy," and "gene therapy." Studies were selected based on relevance and methodological quality. Results indicated that stem cell therapy shows promise in promoting disc regeneration through cellular differentiation and growth factor secretion. Gene therapy offers targeted disc repair but faces hurdles related to delivery systems and safety. Regenerative therapies have the potential to change lumbar discogenic pain management by addressing root causes rather than symptoms. However, ethical, regulatory, and technical challenges must be overcome. Further research, including long-term and multi-center trials, is essential to validate their clinical benefits.

Keywords *: lumbar discogenic pain, regenerative medicine, stem cell therapy, gene therapy*

INTRODUCTION

Lumbar discogenic pain is a prevalent and debilitating condition that significantly impacts patients' quality of life and imposes a heavy burden on healthcare systems. Originating from a degenerated intervertebral disc in the lumbar spine, this type of pain often exacerbates with activities that increase intradiscal pressure, such as sitting, bending, or lifting, making it particularly common among working-age adults. As a leading cause of chronic lower back pain, discogenic pain accounts for approximately 40% of cases, surpassing other causes like

disc herniation and zygapophysial joint pain (Zhang, et al., 2009) (Cooper & Cooper, 2015) (Masuda, et al., 2023).

Discogenic pain accounts for 21.8% of chronic low back pain cases, with its prevalence increasing among patients who undergo diagnostic procedures like discography Internal disc disruption is implicated in 26% to 42% of chronic low back pain cases, highlighting its significant clinical prevalence. Diagnosing discogenic pain is complex, with only about 20% of low back pain cases definitively linked to specific anatomical sources. Discography has shown a 74% positive identification rate in symptomatic discs, while the ultrasound-guided disc pain induction test offers a promising, simpler diagnostic alternative with significant improvements in pain scores (Masuda, et al., 2023) (Verrils, et al., 2015) (Ip & Fu, 2015)

The current therapeutic landscape for lumbar discogenic pain primarily includes conservative management strategies such as physical therapy, pharmacological interventions (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], muscle relaxants), and epidural steroid injections. These approaches are aimed at managing symptoms and improving functional outcomes. However, they often fail to address the underlying pathology of disc degeneration and, consequently, provide only temporary relief. For patients with persistent or severe symptoms, surgical interventions such as spinal fusion or total disc replacement may be indicated. While these procedures can provide significant pain relief and stabilization, they are not without limitations, including the risk of adjacent segment degeneration, pseudarthrosis, and the inherent morbidity associated with major spinal surgery (Ju, et al., 2020) (Zhang, et al., 2023) (Ju, et al., 2022).

Given the limitations of both conservative and surgical treatments, there is a growing interest in regenerative approaches that aim to restore the structure and function of the intervertebral disc. These innovative therapies seek to address the fundamental causes of discogenic pain by promoting disc repair and regeneration, rather than merely alleviating symptoms. This paradigm shift towards regenerative medicine is driven by the potential to offer more durable and effective solutions for patients suffering from lumbar discogenic pain, particularly those who are not ideal candidates for surgery or have failed conventional treatments (Cooper & Cooper, 2015) (Ju, et al., 2020) (Mannchikanti, et al., 2015) (Sevgili & Sari, 2020).

The purpose of this review is to critically assess and synthesize recent advancements in regenerative therapies aimed at intervertebral disc repair. By analyzing the latest research and clinical trials, the review seeks to provide a comprehensive understanding of how these innovative treatments, such as stem cell therapy, biologics, and gene therapy, can restore disc function and potentially reverse degeneration. Additionally, the review evaluates the practical application of these therapies in clinical settings, particularly their effectiveness in alleviating lumbar discogenic pain, with the goal of identifying promising approaches that could improve patient outcomes and reduce the need for invasive surgery.

METHOD

The literature search was conducted to identify relevant studies on regenerative therapies for intervertebral disc repair, a structured literature search was conducted across several major biomedical databases, including PubMed, MEDLINE, and Embase. The search strategy employed a combination of specific keywords and Medical Subject Headings (MeSH) terms to ensure thorough coverage of the relevant research. These included terms such as "intervertebral disc regeneration," "stem cell therapy," "lumbar discogenic pain," "biologics," "gene therapy," "disc degeneration," "nucleus pulposus repair," "extracellular matrix," "mesenchymal stem cells," "growth factors," "cell-based therapy," "spinal tissue engineering," "discogenic low back pain," "autologous disc cell transplantation," "platelet-rich plasma," "disc

repair," and "inflammatory cytokines." This diverse set of search terms was used to capture studies that explore various aspects of regenerative therapies for the intervertebral disc, ranging from basic science research to clinical applications.

The inclusion criteria were set to capture human studies published within the last 10 years, focusing on peer-reviewed articles, clinical trials, and systematic reviews of high quality. Studies involving animal models or those not directly addressing regenerative therapies for intervertebral disc degeneration were excluded from consideration. Only articles published in English were included in the final analysis. The study selection process followed a multi-step approach. Initially, titles and abstracts of all identified studies were screened to exclude irrelevant articles. Subsequently, full-text reviews of the remaining articles were conducted to assess their relevance and quality. The evaluation criteria for quality included study design, sample size, methodological rigor, and clarity of outcome measures. Articles that did not meet these standards were excluded. For the studies that were included, data extraction was conducted systematically, focusing on patient demographics, treatment modalities, and clinical outcomes. The extracted data were then analyzed using thematic synthesis to identify commonalities, patterns, and discrepancies across the studies. This analysis facilitated a comparative evaluation of the effectiveness of various regenerative therapies, providing a comprehensive understanding of their potential in the clinical management of lumbar discogenic pain.

DISCUSSION

The theoretical foundations of disc regeneration are grounded in understanding the biological processes of disc degeneration and repair. Disc degeneration involves the breakdown of the extracellular matrix, loss of proteoglycans, and reduced cell viability within the nucleus pulposus. Regeneration focuses on reversing these processes through the use of stem cells, which can differentiate into necessary disc cells, and growth factors that stimulate cell proliferation and matrix production. The extracellular matrix plays a critical role in providing structural support and regulating cellular activities, making it a key target in regenerative strategies aimed at restoring disc integrity and function (Miyagi, et al., 2018) (Pettine, et al., 2018) (Ni, et al., 2015).

Growth factors like TGF-β and BMPs stimulate cell proliferation, enhance extracellular matrix production, and promote the differentiation of cells necessary for disc repair. Cytokines can help modulate inflammation, which is a critical factor in disc degeneration. While biologic therapies have shown potential in enhancing disc regeneration, their effectiveness is often limited by challenges such as the precise delivery to target tissues, potential side effects, and variability in patient response. Addressing these challenges is essential for optimizing biologic-based treatments (Zhang, et al., 2023) (Pettine, et al., 2018) (Ni, et al., 2015).

Gene therapy in disc regeneration operates on the theoretical framework of introducing or modifying specific genes within disc cells to promote repair and reverse degeneration. Targeted genes often include those that regulate extracellular matrix production, such as genes encoding for collagen or proteoglycans, and anti-inflammatory cytokines to reduce chronic inflammation. Delivery systems for gene therapy range from viral vectors, which offer high efficiency, to non-viral methods like nanoparticles, which may reduce immune responses. While current research shows promise, challenges such as ensuring targeted delivery, long-term expression, and avoiding off-target effects present significant hurdles for clinical application (Padda, et al., 2021) (Silverman, et al., 2020) (Singh, et al.,2021).

In addition to surgical interventions, minimally invasive procedures such as Percutaneous Laser Disc Decompression (PLDD) and DISC FX have gained popularity as alternative interventional approaches. These techniques aim to achieve three primary objectives: the

reduction of disc volume, denervation of the pain fibers in the disc's outer wall, and the induction of an autoimmune response within the disc. The reduction of disc volume, primarily achieved through PLDD, involves using laser energy to vaporize part of the nucleus pulposus, subsequently decreasing intradiscal pressure and relieving nerve compression. Denervation is attained by ablating the nociceptive nerve fibers in the outer annulus, thereby reducing pain transmission. Furthermore, these interventions may initiate an autoimmune response by attracting anti-inflammatory agents to the disc, thereby reducing inflammation and potentially promoting a more conducive environment for healing. PLDD and DISC FX are increasingly utilized for patients who either do not qualify for or wish to avoid more invasive surgical procedures, offering shorter recovery times and targeted symptom relief (Terai, et al., 2021) (Beyaz, et al., 2020) (Yam, et al., 2021).

The integration of regenerative therapies into existing treatment paradigms for lumbar discogenic pain involves a theoretical discussion on how these innovative approaches could complement or replace current practices. Regenerative therapies, such as stem cell therapy, biologics, and gene therapy, offer the potential to address the root causes of disc degeneration rather than merely alleviating symptoms, as many conventional treatments do. By targeting the underlying pathology, these therapies could reduce the need for more invasive procedures like spinal fusion or disc replacement.

The potential for regenerative therapies to change the clinical approach to lumbar discogenic pain lies in their ability to provide long-term relief and possibly restore normal disc function. This shift could lead to earlier intervention, focusing on repairing disc damage before it progresses to severe degeneration. If successfully integrated, these therapies could redefine the standard of care, making regenerative treatments a first-line option for patients with early to moderate disc degeneration. However, their successful adoption will require rigorous clinical trials to establish efficacy, safety, and cost-effectiveness, along with the development of standardized protocols for their use in clinical settings (Soufi, et al., 2023) (Buckley, et al., 2018) (Her, et al., 2022).

The development and implementation of regenerative therapies for discogenic pain face several theoretical challenges, including ethical considerations and regulatory issues. Ethical concerns primarily revolve around the use of stem cells, particularly those derived from embryonic sources, and the long-term effects of gene therapy, which may have unpredictable consequences. Regulatory challenges include the rigorous approval processes required to ensure the safety and efficacy of these novel treatments. These processes can be lengthy and complex, potentially delaying the availability of therapies that could benefit patients (Buckley, et al., 2018) (Navani, et al., 2016) (Asipp, 2013).

Future research directions in regenerative spine care will likely focus on improving the precision and effectiveness of these therapies. This includes refining delivery methods to ensure that regenerative agents reach their target tissues with minimal side effects, as well as developing more robust clinical trials to validate the long-term benefits and safety of these treatments. Additionally, there is potential for the evolution of personalized regenerative medicine, where treatments are tailored to the specific genetic and cellular profiles of individual patients, enhancing outcomes and reducing risks. As research progresses, regenerative therapies may become integral to spine care, offering innovative solutions for patients with discogenic pain that were previously unmanageable with conventional treatments (Haldeman, et al., 2016) (Levi, et al., 2018)

CONCLUSION

Regenerative therapies such as stem cell therapy, and gene therapy offer promising strategies for treating lumbar discogenic pain by directly addressing the root causes of disc

degeneration through enhancing cell growth, extracellular matrix repair, and controlling inflammation. These innovative treatments have the potential to transform clinical practice by providing effective, less invasive alternatives to traditional surgical procedures and enabling earlier intervention. To fully realize their benefits, comprehensive long-term and multi-center research is necessary to establish efficacy and safety, optimize delivery techniques, and develop personalized approaches suitable for diverse patient populations.

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