Low back pain (LBP) is one of the most common pain conditions experienced by approximately 266 million individuals annually, imposing substantial costs and efforts [1]. According to Hoy et al. [2], LBP is a leading cause of disability-adjusted life years lost, with a lifetime prevalence exceeding 40%, indicating a substantial disease burden. This burden is particularly pronounced among the older population with facet joint syndrome, a representative degenerative spinal disease, reported to exhibit a prevalence of 10–15% among individuals with LBP, escalating to 45% in older adults [3,4]. Moreover, LBP has been documented to affect up to 75% of older individuals [5], underscoring its pervasive nature and highlighting the need for increased attention to this condition among the aging population.

Epidural steroid injections (ESIs) are one of the most commonly performed interventional treatments aimed at reducing pain in patients with LBP [6]. Although short-term pain relief from ESIs is relatively well-established [7], their frequent administration in older patients is often burdensome because of potential side effects, such as hyperglycemia and hypertension [8]. Furthermore, a recent study in South Korea has identified multiple ESIs and advanced age (65 years and older) as risk factors for deep spinal infection [9], a potentially fatal complication. Consequently, performing ESIs for pain relief in the older population warrants greater caution compared with younger patients.

Low back pain (LBP) is a prevalent and debilitating condition, particularly among older adults, with degenerative spinal disease being a major contributor. Regenerative therapy, which aims to repair and regenerate damaged spinal structures, has shown promise in providing long-term pain relief and functional improvement. This review focuses on the application and efficacy of regenerative therapies such as mesenchymal stem cells, platelet-rich plasma, and atelocollagen in older patients with LBP. Despite the potential benefits, there is a notable scarcity of studies specifically targeting the older population, and those available often have small sample sizes and limited age-related analyses. Our findings underscore the need for more comprehensive and well-designed clinical trials to evaluate the effectiveness of these therapies in older patients. Future research should prioritize larger age-specific studies to establish regenerative therapy as a viable and effective treatment option for LBP in the aging population.

Keywords: Intervertebral disc degeneration; Low back pain; Older adults; Platelet-rich plasma; Regenerative medicine; Stem cells.
Regenerative therapy, an interventional treatment that promotes the regeneration of damaged structures to alleviate pain, has garnered increasing interest in the field of pain medicine [10]. This form of therapy is widely utilized in LBP and other pain conditions, such as osteoarthritis and tendinopathy [11-13]. In the context of LBP, regenerative therapy primarily targets degenerative structures such as the intervertebral disc, facet joint, and sacroiliac joint [14]. Commonly employed regenerative agents include mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), and substances containing growth factors [15]. However, clinical evidence regarding the efficacy of regenerative therapy for LBP is lacking, particularly in the older population, where degenerative changes are more prevalent.

Therefore, we aim to review the current academic status of regenerative therapy applications for LBP, a common condition in the older population. Through this study, we seek to elucidate the efficacy of regenerative therapy in the older population and identify areas of deficiency. Additionally, our objective is to provide insights for pain physicians on the future directions of regenerative therapy, so it becomes a beneficial treatment option for LBP in this demographic.

DEGENERATIVE CHANGE OF THE SPINE

Among the various causes of LBP, pain originating from the intervertebral disc (IVD) accounts for the highest proportion, followed by the sacroiliac and facet joints [16]. Lumbar spine degenerative changes typically initiate from IVD degeneration [17], which is considered a fundamental component of age-related spinal pathology. The process of IVD degeneration is intrinsically linked to the physiological aging changes that primarily manifest in the endplates, nucleus pulposus (NP), and annulus fibrosus (AF) [18]. IVD degeneration is a complex process influenced by various factors, including genetic predisposition, mechanical stress, and biochemical changes. Degeneration begins with alterations in the composition and structure of the disc components, primarily the NP, AF, and endplates [19].

During physiological aging, the IVD undergoes progressive changes characterized by decreased cell density, particularly in the NP [17]. This decline leads to reduced proteoglycan content and an increase in collagen cross-linking, diminishing the ability of the disc to retain water and maintain its structural integrity [20,21]. Consequently, the NP loses its cushioning effect, and the ability of the disc to absorb mechanical stress diminishes. Biochemical changes further contribute to IVD degeneration by decreasing the synthesis rate of extracellular matrix (ECM) molecules, such as collagen and aggrecan [22]. The imbalance between matrix synthesis and degradation disrupts disc homeostasis, leading to further deterioration. Additionally, endplate alterations, such as calcification and sclerosis, compromise the nutrient exchange between the disc and surrounding tissues, exacerbating the degenerative process [23,24].

Structural failure, including tears and fissures in the AF, further accelerates IVD degeneration [19]. These abnormalities, along with endplate changes and osteophyte formation, contribute to disc height loss and intervertebral space collapse. Ultimately, IVD degeneration results in the development of conditions such as disc herniation, spinal stenosis, and facet joint arthritis, all of which contribute to LBP and functional impairment [22,25].

REGENERATIVE THERAPY

Mesenchymal stem cells

MSCs hold considerable promise in regenerative medicine and the treatment of musculoskeletal disorders, including IVD degeneration associated with LBP [26,27]. Derived from adult bone marrow, MSCs possess multipotent capabilities, enabling them to differentiate into various cell types, including those in the IVD, such as NP cells [28]. MSCs play a crucial role in IVD regeneration by replenishing NP cells and core ECM components, thereby promoting tissue repair and regeneration [28]. Through their regenerative properties, which include differentiation into target cell types, activation of resident cell proliferation, and paracrine effects to improve nutrient supply, MSCs offer a promising avenue for restoring degenerated IVDS [29]. Clinical studies evaluating the effectiveness of MSC-based therapies such as bone marrow concentrate injections and intradiscal injections of MSCs combined with hyaluronic acid derivatives have demonstrated significant improvements in pain relief and functional outcomes in patients with chronic LBP and severe lumbar spinal degeneration, highlighting the therapeutic potential of MSCs for IVD regeneration [30-32]. Furthermore, tissue engineering approaches involving the cultivation of MSCs under specific conditions, such as growth factor supplementation and hypoxic environments, have shown promise for generating NP cell-like phenotypes for IVD regeneration [33]. Scaffold-based strategies that provide structural support for cell attachment, proliferation, and
ECM accumulation facilitate the delivery of MSCs to damaged IVDs, leading to positive outcomes in in vitro and in vivo studies [34].

Platelet-rich plasma

PRP therapy harnesses the regenerative potential of platelets and plasma found in blood to promote tissue healing and repair [35]. By centrifuging whole blood to concentrate platelets 3-5 times higher than baseline levels, PRP is rich in growth factors essential for tissue regeneration [36]. These activated platelets release growth factors such as transforming growth factor-beta, basic fibroblast growth factor, and epidermal growth factor, which play pivotal roles in cell proliferation, migration, differentiation, and angiogenesis [37,38]. The process involves drawing blood from the patient, centrifuging it to concentrate the platelets, activating the platelets to release growth factors, and reintroducing the activated PRP into the target site. PRP therapy has shown promise in managing LBP associated with IVD pathology, with studies demonstrating its safety and efficacy in clinical trials [39]. Intradiscal PRP injections have led to significant reductions in pain scores and improvements in functional outcomes in patients with chronic LBP [39]. Additionally, PRP injections have shown comparable or superior efficacy to traditional treatments such as lidocaine injections, offering longer-lasting analgesic effects and improved functional status in patients with axial LBP [40].

Growth factors

Growth factors play a crucial role in modulating cellular functions and have garnered great interest in the field of IVD regeneration [41]. These polypeptides activate intercellular signaling pathways by binding to specific cell membrane receptors, leading to processes such as cell proliferation, differentiation, and migration [42]. In IVD degeneration, growth factors are promising therapeutic agents because they stimulate ECM synthesis, reduce inflammation, and slow the degenerative process [43]. Various growth factors, including members of the growth differentiation factor family, have shown the potential to promote disc regeneration in both in vitro and in vivo models of IVD degeneration [44]. Studies have explored the safety and efficacy of growth factor bone morphogenetic proteins in mildly degenerated IVDs and have demonstrated increased ECM expression and synthesis in human IVD cells [45]. However, the short half-life and instability of individual growth factors may limit their therapeutic efficacy, necessitating combined treatment approaches with multiple growth factors to enhance their gradual release at target sites and optimize therapeutic outcomes for IVD degeneration [46,47].

Prolotherapy

Prolotherapy involves the injection of biological substances such as dextrose into ligamentous tissues to stimulate the inflammatory healing response of the body and promote tissue repair [48]. This process triggers a cascade of events, including the influx of granulocytes, macrophages, and fibroblasts, as well as growth factor release, ultimately leading to collagen deposition and strengthening of ligaments [48]. Prolotherapy has been utilized in treating chronic LBP to reduce pain and disability by enhancing tissue integrity. While some clinical trials have reported no significant difference in pain relief between prolotherapy and control treatments for chronic LBP [49,50], others have demonstrated its efficacy in reducing pain and improving functional outcomes [51,52]. Studies have shown that prolotherapy injections combined with spinal manipulation lead to greater reductions in pain scores and disability compared with control treatments [51]. Additionally, ultrasound-guided combined prolotherapy and PRP injections have been successful in decreasing pain levels, reducing analgesic use, and improving function in patients with chronic LBP [52]. This suggests the potential effectiveness of prolotherapy as a therapeutic option for LBP management.

Current status of research on regenerative therapy for older patients with LBP

Source of data, search strategy, and data collection

We conducted a search in the Web of Science Core Collection (WoSCC) database to investigate the utility of regenerative therapy in older patients, focusing on original articles published until 2023 and indexed in the Science Citation Index Expanded (SCIE) and Emerging Sources Citation Index (ESCI). The WoSCC database is widely used in pain medicine-related research [53,54]. Our search strategy included topic searches for terms related to aging (aging or aged or elderly or old*) and title searches for terms related to LBP (low back pain or low back ache or lower back pain or lower back
ache or low backache or backache or back pain or intervertebral disc or IVD or facet* or discogenic* or sacroiliac*) and regenerative therapies (PRP or platelet rich plasma or platelet-rich plasma or stem cell or mesenchymal stem cell or MSC or prolotherapy or regenerative medicine or regenerative therapy or growth factor) [13,55]. Titles and abstracts were screened, and relevant articles were selected for further review. We specifically focused on articles written in English and excluded studies involving animal subjects, experimental research without human participants, and studies involving healthy volunteers rather than patients. Articles lacking full-text availability were excluded from the analysis.

**Previous studies of regenerative therapy for older patients with LBP**

The studies on regenerative therapy in older patients with LBP are presented in Table 1 [32,56-62]. The studies encompassed various regenerative therapies, including PRP injections (N = 6) and MSCs treatments (N = 2), and were conducted using diverse study designs, such as prospective studies (N = 4), randomized controlled trials (RCTs, N = 2), and retrospective analyses (N = 2). Three studies focused on facetogenic pain, three on discogenic pain, and two on facetogenic and discogenic pain. In facet joint injections, the volume ranged from 0.5 to 1 ml, while intradiscal injections involved injecting 1 to 3 ml.

A prospective observational study using fluoroscopy-guided PRP injections at the facet joints reported significant reductions in the visual analog scale (VAS) and Roland-Morris disability questionnaire (RMQ) scores for LBP over 3 months post-procedure [56]. In contrast, an RCT comparing PRP injections with saline found no significant difference in the Oswestry Disability Index (ODI) and numerical rating scale (NRS) scores between the groups at the 8-week evaluation [59].

A retrospective study using leukocyte-free PRP injections significantly improved the NRS and ODI scores over a follow-up period of 1 to 24 months, particularly in older patients [58]. Another prospective non-randomized study evaluating bone marrow-derived MSCs reported significant improvements in VAS and ODI scores over 1 to 12 months post-treatment [32]. Additionally, a prospective observational study using adipose-derived MSCs showed significant decreases in VAS and ODI scores compared with baseline up to 5 years post-procedure [61].

A retrospective study using PRP injections reported significant improvements in the VAS, ODI, and RMQ scores up to 12 months post-procedure. However, certain variables, such as the number of targeted discs and the presence of high-intensity zones, were associated with poorer outcomes [60]. Another prospective observational study using PRP injections showed decreases in NRS and ODI scores at 3 and 6 months compared with baseline, with a positive correlation observed between platelet concentration in PRP and improvement in NRS and ODI scores [57].

Furthermore, an RCT combining medial branch radiofrequency ablation (RFA) with facet joint injections found that the VAS score was significantly lower at 3 and 6 months post-procedure in the group combining RFA with PRP injection than in the groups combining steroids with RFA and saline with RFA [62]. Among these studies, two were related to age. One study found effectiveness specifically in older patients [58], whereas another found no correlation with age [32].

**Expected future studies**

In patients with LBP, the primary targets for regenerative therapy have been the IVD and facet joint. This approach addresses degenerative changes in the spine, specifically, the decrease in NP cell density within the IVD, which subsequently leads to facet joint osteoarthritis. Recent studies have highlighted that spinal degeneration and muscle loss, known as sarcopenia, are associated with LBP in older patients [63]. Thus, maintaining and enhancing muscle mass is crucial for managing LBP in this demographic.

Atelocollagen differs from typical collagen because it removes specific telopeptides through the action of pepsin, which reduces collagen cross-linking and antigenicity, thereby improving biocompatibility [64]. Reports have indicated that atelocollagen injections can effectively treat LBP [65] and maintain muscle mass post-surgery [66]. Moreover, a recent study by Kim and Gil [67] found that combining intramuscular atelocollagen injections with ESIs resulted in significantly better pain relief in patients with LBP compared with ESIs alone. Research has also shown that atelocollagen can serve as a scaffold for muscle tissue regeneration in a rabbit study [68] and a promising material for gingival tissue regeneration in a human study [69], suggesting its potential as a regenerative therapy option for LBP. Although the evidence remains limited, atelocollagen therapy can be particularly beneficial for older patients with LBP, offering an encouraging avenue for future clinical applications.
### Table 1. Previous Studies on Regenerative Therapy for Older Patients with LBP

<table>
<thead>
<tr>
<th>Author</th>
<th>Regenerative therapy</th>
<th>Study design</th>
<th>Groups (N)</th>
<th>Age (yr)</th>
<th>Technique</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al. [56]</td>
<td>PRP</td>
<td>Prospective</td>
<td>G1: PRP (18)</td>
<td>25–71</td>
<td>0.5 ml at each IVD</td>
<td>PRP: 0.5 ml at each FJ</td>
<td>VAS and RMQ scores for LBP significantly decreased (P &lt; 0.05) from baseline (7.05, resting VAS score) to 1 wk post-injection (4.89, resting VAS score) and continued to decline until 3 mo post-procedure (2.63, resting VAS score). At the 8 wk evaluation, no significant difference was observed between the two groups in ODI and NRS scores. However, it is essential to consider the study's premature termination, originally planned to recruit 60 patients in a 2 to 1 ratio. Patients received leukocyte-free PRP injections at intervals of 1 mo or more, with a minimum of two injections administered. Throughout the follow-up period (1–24 mo, mean 5 mo), significant improvements (P &lt; 0.05) were observed in all patients, as evidenced by outcomes including NRS and ODI scores. Notably, subgroup analysis revealed that older patients (aged 61–76 yr) exhibited the most substantial improvements.</td>
</tr>
<tr>
<td>Zielinski et al. [59]</td>
<td>PRP</td>
<td>RCT</td>
<td>G1: PRP (18)</td>
<td>51 (19–76)</td>
<td>0.5 ml at each IVD</td>
<td>G1: 2 ml PRP at each IVD</td>
<td><strong>G2: 2 ml saline at each IVD</strong></td>
</tr>
<tr>
<td>Kirchner et al. [58]</td>
<td>Leukocyte-free PRP</td>
<td>Retro-spective</td>
<td>N = 47 (51)</td>
<td>51 (19–76)</td>
<td>0.5 ml at each IVD</td>
<td>G1: 2 ml PRP at each IVD</td>
<td><strong>G2: 2 ml saline at each IVD</strong></td>
</tr>
<tr>
<td>Atluri et al. [32]</td>
<td>BM-MSCs</td>
<td>Prospective</td>
<td>G1: intervention (40)</td>
<td>61.08/59.05</td>
<td>G1: intervention (40)</td>
<td>BM-MSCs: 2 ml at each IVD, epidural space and 1 ml at each SIJ and 0.5 ml at each FJ</td>
<td>From 1 to 12 mo post-treatment, all indicators including VAS and ODI showed significant improvement in the intervention group treated with BM-MSCs compared with the conventional group receiving medication or physical therapy. Particularly noteworthy, in the intervention group, 56% of patients maintained a reduction of at least 2 points on the NRS scale up to 12 mo post-procedure. However, there was no significant correlation with age.</td>
</tr>
<tr>
<td>Rotheroi et al. [61]</td>
<td>A-MSCs</td>
<td>Prospective</td>
<td>N = 37</td>
<td>62.5 (31–78)</td>
<td>G1: intervention (40)</td>
<td>A-MSCs: 1 ml at each IVD</td>
<td>VAS and ODI scores showed a significant decrease compared with baseline (6.8 and 71.05, respectively) up to 5 yr post-procedure (1.4 and 18.7, respectively).</td>
</tr>
<tr>
<td>Akeda et al. [60]</td>
<td>PRP</td>
<td>Retro-spective</td>
<td>N = 15</td>
<td>33.9 ± 9.5</td>
<td>G1: intervention (40)</td>
<td>PRP: 2 ml at each IVD</td>
<td>Following PRP treatment, VAS, ODI, and RMQ scores showed significant improvements up to 12 mo post-procedure. However, variables such as the number of targeted discs and the presence of HIZs were associated with poorer outcomes.</td>
</tr>
<tr>
<td>Jain et al. [57]</td>
<td>PRP</td>
<td>Prospective</td>
<td>N = 20</td>
<td>34.75 ± 10.15</td>
<td>G1: intervention (40)</td>
<td>PRP: 1–2 ml at each IVD</td>
<td>The NRS and ODI scores decreased at 3 mo (4.55 and 24.8, respectively) and 6 mo (3.1 and 18.6, respectively) compared with baseline (5.85 and 35.7, respectively). A positive correlation was observed between the platelet concentration in PRP and the improvement in NRS and ODI.</td>
</tr>
<tr>
<td>Singh et al. [62]</td>
<td>PRP</td>
<td>RCT</td>
<td>G1: steroid + RFA (15)</td>
<td>45.33 ± 11.29/45.00 ± 14.10/46.87 ± 15.96</td>
<td>G1: steroid + RFA (15)</td>
<td>G1: 0.25 ml Triamcinolone acetate + 0.25 ml 0.5% Bupivacaine</td>
<td>Compared with pre-procedure, VAS and ODI scores improved in all three groups. At 3 and 6 mo post-treatment, G2 demonstrated significantly lower VAS scores (0.47 ± 0.51 and 0.07 ± 0.25, respectively) compared with G1 (2.53 ± 0.51 and 3.07 ± 0.25, respectively) and G3 (2.60 ± 0.50 and 3.20 ± 0.41, respectively).</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, mean (range), or number only. LBP: low back pain, PRP: platelet-rich plasma, BM-MSCs: bone marrow-derived mesenchymal stem cells, A-MSCs: adipose-derived mesenchymal stem cells, RCT: randomized controlled trial, RFA: radiofrequency ablation, FJ: facet joint, FS: fluoroscopy, IVD: intervertebral disc, VB: vertebral body; SIJ: sacroiliac joint, VAS: visual analog scale, RMQ: Roland-Morris Disability Questionnaire, ODI: Oswestry Disability Index, NRS: numerical rating scale, HIZ: high-intensity zone.
LIMITATIONS

Our search strategy might have been insufficient in including all studies on regenerative therapy in older patients with LBP. Despite adopting search strategies from existing research, the terms “elderly” and “LBP” encompass broad fields. Consequently, not all the relevant studies were included in the analysis. Additionally, while the WoSCC database encompasses important indexes, such as SCIE and ESCI, it is possible that not all pertinent studies were captured. Studies not written in English or those that were inaccessible were excluded, further limiting the inclusion of relevant studies.

Only two of the eight studies identified through our search were RCTs, and the number of patients included was relatively small (N < 20). Despite targeting the older population, the mean age in most studies was not significantly high, and only two studies examined the relationship between age and treatment efficacy. Therefore, rather than drawing definitive conclusions, our study aimed to assess the current state of research and identify future directions in this field.

CONCLUSION

Regenerative therapy is a promising option for treating LBP in older patients, as degenerative spinal disease is prevalent among this population. Preventing degeneration and promoting regeneration offer a fundamental treatment approach that transcends merely alleviating pain. Given the multiple comorbidities often present in older patients, traditional treatments such as medication or epidural injections can pose limitations compared with younger patients. Consequently, regenerative therapy, which may provide long-term pain relief, can emerge as a promising option for managing LBP in the aging population. However, studies specifically targeting older patients are scarce, and research on the correlation between treatment efficacy and age is lacking. To establish regenerative therapy as a viable therapeutic option for LBP in older patients, future research should focus on well-designed studies with sufficient sample sizes, particularly those that include older participants.

FUNDING

None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Writing - original draft: Jeongsoo Kim. Writing - review & editing: Jeongsoo Kim, Kunjin Bae, Jeong Hwa Seo. Conceptualization: Jeongsoo Kim. Data curation: Jeongsoo Kim, Kunjin Bae. Methodology: Jeongsoo Kim. Investigation: Jeongsoo Kim, Kunjin Bae, Jeong Hwa Seo. Supervision: Jeong Hwa Seo.

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