Review

TREATMENT OF HERNIATED DISC WITH IMMUNO-REGENERATIVE MEDICINE: PRESENT AND FUTURE

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ABSTRACT

Herniated discs, particularly lumbar disc herniation (LDH), are a significant cause of morbidity worldwide. The incidence of LDH varies based on age, gender, occupation, and genetic predisposition, with middle-aged individuals (30-50 years), smokers, and those with higher body mass index being at higher risk. The prevalence of symptomatic LDH is notably high, especially in individuals with low back pain accompanied by lower limb symptoms. The pathophysiology of LDH involves the extrusion of the nucleus pulposus through the annulus fibrosus, leading to nerve root compression and inflammation. Macrophages play a crucial role in the immune response to herniated discs. M1 macrophages are pro-inflammatory and contribute to extracellular matrix degradation, while M2 macrophages are anti-inflammatory and promote tissue repair. Recent studies have investigated the application of regenerative therapies, including platelet-rich plasma (PRP) and ozone, to modulate the immune response and promote the transition from M1 to M2 macrophages. Ozone therapy has been shown to activate macrophages, promoting the phagocytosis of the extruded nucleus pulposus and facilitating the shift from an inflammatory to a reparative phase. PRP, rich in growth factors, enhances tissue regeneration and repair, further supporting the transition to M2 macrophages. The combination of PRP and ozone therapy offers a promising approach to treating herniated discs by enhancing the body's natural healing processes. These therapies have demonstrated significant pain relief and functional improvement in clinical studies, with a favorable safety profile. Future research should focus on large-scale randomized controlled trials to validate these findings and establish standardized treatment protocols.

KEYWORDS: *hernial disc, ozone, platelet-rich plasma, macrophages M1, macrophages M2*

INTRODUCTION

The epidemiology of herniated discs, particularly lumbar disc herniation (LDH), varies globally and is influenced by multiple factors, including age, gender, occupation, and genetic predisposition. The incidence of LDH with radiculopathy in adults ranges widely depending on the case definition used. For surgical case definitions, the annual incidence ranges from 0.3 to 2.7 per 1,000 persons, while hospital-based case definitions range from 0.04 to 1.5 per 1,000 persons, and clinical case definitions range from 0.1 to 298.3 per 1,000 persons (1). Risk factors for LDH include middle age (30-50 years), smoking, higher body mass index (BMI), cardiovascular risk factors (particularly in women), and

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occupational factors such as cumulative lumbar load from forward bending postures and manual material handling (1). Genetic factors also play a significant role, with heritability estimates for lumbar disc degeneration ranging from 34% to 74% (2, 3).

The prevalence of LDH also varies by symptomatology. In a study of symptomatic populations, the prevalence of LDH was found to be 55.1%, with higher rates in those presenting with low back pain accompanied by lower limb symptoms (82.1%) compared to those with only low back pain (51.6%) or lower limb symptoms alone (54.5%) (4). Occupational factors are significant, with sedentary occupations and those requiring prolonged driving being associated with higher risks of LDH (5). Additionally, the incidence of symptomatic cervical and lumbar disc herniation increases with age and is higher in women than in men (6).

Spontaneous regression of herniated discs is well documented. However, spontaneous reabsorption of herniated discs in less than 12 months only occurs in 67% of cases. This percentage, in the case of protrusions, is even lower, at less than 50% (7). Understanding the resorption process and increasing the healing rate are, therefore, priority objectives.

A herniated disc, also known as a slipped or ruptured disc, occurs when the nucleus pulposus protrudes through a tear in the annulus fibrosus of an intervertebral disc. This condition can lead to nerve root inflammation, causing pain, numbness, or weakness in the affected area. The resorption of herniated discs has been observed and validated through clinical and imaging studies. The process involves several mechanisms, including dehydration, retraction, and an inflammatory response mediated by macrophages and neovascularization. Macrophages infiltrate the herniated disc tissue, releasing enzymes such as matrix metalloproteinases (MMPs) that degrade the extracellular matrix, facilitating the resorption of the herniated material (Fig. 1) (8-10). In fact, one of the key factors to understand this mechanism is the response mediated by macrophages, which play a crucial role in the resorption of the extruded nucleus pulposus through phagocytosis of the extruded material and the repair of the damaged annulus.

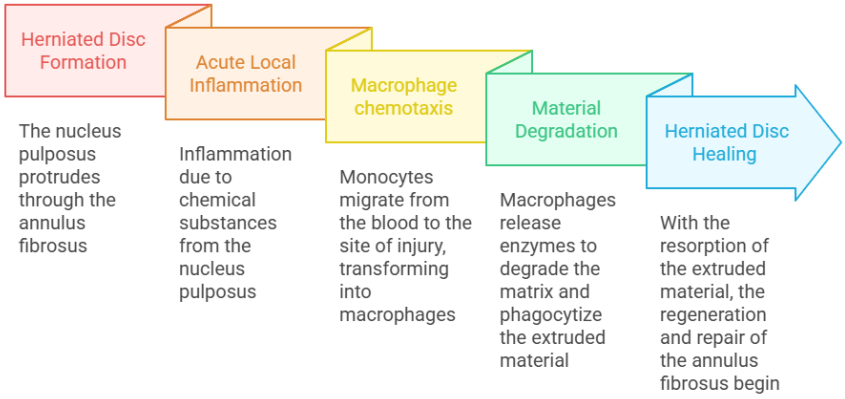

Fig. 1. *Dynamics of reabsorption of herniated discs.*

The rate of spontaneous resorption varies. Factors that predict faster resorption include larger herniations, sequestrated discs, and higher degrees of initial displacement (8, 11). The mean time for spontaneous resorption can range from a few months to over a year. For instance, one study reported a mean resorption time of approximately 8.7 months, with clinical recovery occurring in about 5.7 weeks (8). Another study found that early resorption (within 3 months) occurred in about 24.7% of patients, with factors such as greater herniated volume and specific anatomical features being predictive (12).

Macrophages play a crucial role in the wound healing process (Fig. 2) through their ability to adopt different phenotypic states, primarily categorized as M1 and M2 macrophages. M1 macrophages, also known as pro-inflammatory macrophages, are typically present in the early stages of wound healing. They are involved in the initial inflammatory response, producing pro-inflammatory cytokines such as TNF-α and nitric oxide (NO), which help in pathogen clearance and debris removal (13, 14). This inflammatory phase is essential for setting the stage for subsequent healing processes.

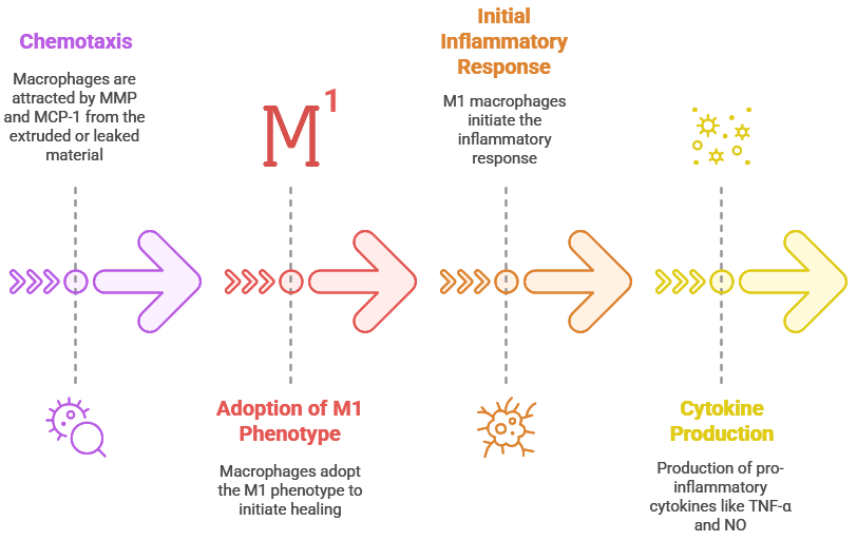

Fig. 2. *Role of macrophage in wound healing. Macrophage-mediated initial inflammatory response in herniated disc healing. MMP: matrix metalloproteinases; MCP-1: monocyte chemoattractant protein-1; NO: nitric oxide.*

As the wound healing progresses, there is a phenotypic switch from M1 to M2 macrophages. M2 macrophages, or anti-inflammatory macrophages, are associated with the resolution of inflammation and tissue repair. They secrete anti-inflammatory cytokines and growth factors such as TGF-β and VEGF, which promote tissue remodeling, angiogenesis, and extracellular matrix deposition (13, 15). This transition is critical for the proliferation and remodeling phases of wound healing, facilitating the repair and regeneration of damaged tissues.

Dysregulation in the balance between M1 and M2 macrophages can lead to impaired wound healing. Chronic wounds, for instance, often exhibit a prolonged M1 macrophage presence, resulting in sustained inflammation and delayed healing (15, 16). Therapeutic strategies aimed at modulating macrophage polarization, such as promoting the M1 to M2 transition, have shown promise in enhancing wound healing outcomes (13, 15).

The aim of this paper is to review recent articles on the use of regenerative therapies with platelet-rich plasma (PRP) and ozone in the modulation of this immune response, facilitating the transition from M1 to M2, and the healing of a herniated disc.

The Evidence Acquisition terms included in the information search were: hernial disc, ozone, platelet-rich plasma, M1 Macrophages, M2 Macrophages. Bibliographic databases consulted: MEDLINE/PubMed, SciELO, LILACS, PAHO, EMBASE, ZOTERO Ozone Health Care, WHO International Clinical Trials Registry Platform, and NIH. U.S. National Library of Medicine. The type of documents reviewed was published between 1980 and 2025, in English, Russian, or Spanish, and included: original articles, published theses, clinical reports, ongoing clinical trials, and bibliographic reviews. The exclusion criteria were the lack of free access to complete text due to financial constraints and/or studies presenting inadequate scientific evidence.

The hernial discs conflict pathogenesis

The pathogenesis of herniated discs from a molecular perspective involves a complex interplay of genetic, biochemical, and cellular mechanisms. Intervertebral disc (IVD) degeneration, a precursor to herniation, is characterized by the disruption of homeostatic balance within the disc's extracellular matrix (ECM), leading to a catabolic environment. Key molecular pathways implicated in LDH include ribosome activity, oxidative phosphorylation, and extracellular matrix response. Differentially expressed genes such as UBA52, RPLP0, RPL3, RPLP2, and RPL27 play significant regulatory roles in these pathways. Additionally, DNA methylation modification sites, such as cg12556991 (RPL27) and cg06852319 (RPLP0), have been identified as potential regulators in LDH (17).

Inflammatory cytokines, particularly interleukin-1 beta (IL-1β), play a crucial role in the pathogenesis of disc herniation. IL-1β stimulates the production of NO, interleukin-6 (IL-6), prostaglandin E2 (PGE2), and MMPs, which contribute to the degradation of the ECM and promote inflammation (18). This inflammatory milieu further exacerbates

disc degeneration and herniation. Mechanical stress also induces changes in the IVD microenvironment, leading to cell death, oxidative stress, and ECM degradation. These processes are mediated by various signaling pathways, including those involving matrix metalloproteinases (MMPs) and inflammatory responses (19). Genetic factors significantly influence susceptibility to IVD degeneration, with up to 75% of individual variability attributed to genetic predisposition. This includes variations in genes related to ECM production, degradative enzymes, and inflammatory cytokines (20).

The immune response in disc herniation

Recent studies have underscored the pivotal role of macrophages in disc herniation, emphasizing their dual functionality based on their polarization state. On one hand, macrophages play a beneficial role in the resorption of herniated discs: experimental studies in animal models have demonstrated that their administration significantly reduces hernia size, while their depletion results in an increase in volume (21). On the other hand, in cases of chronic LDH, macrophages infiltrate both the herniated nucleus pulposus (NP) tissue and the dorsal root ganglia (DRG), actively promoting the development and persistence of sciatica. This dual role highlights the complex and context-dependent nature of macrophage activity in disc herniation pathology (22).

Macrophage polarization in LDH is influenced by the microenvironment. Higher levels of M1 markers (e.g., CCR7, TNF-α) are associated with more severe pain and higher visual analog scale (VAS) scores, while M2 markers (e.g., CD206, IL-4) are linked to tissue repair and lower pain scores (23, 24). The interaction between macrophages and NP cells under inflammatory conditions leads to increased production of pro-inflammatory cytokines, such as IL-6, which further drives the degenerative process (25, 26).

When the annulus fibrosus ruptures, macrophages are recruited to the hernia site via chemotaxis mechanisms, where they play a central role in the phagocytosis of the herniated material (27). However, if the annular ring is not restored or the damage remains unrepaired, macrophage infiltration into the dorsal root ganglion (DRG) can trigger a hyperalgesia mechanism, potentially leading to the development of chronic pain (Fig. 3) (22).

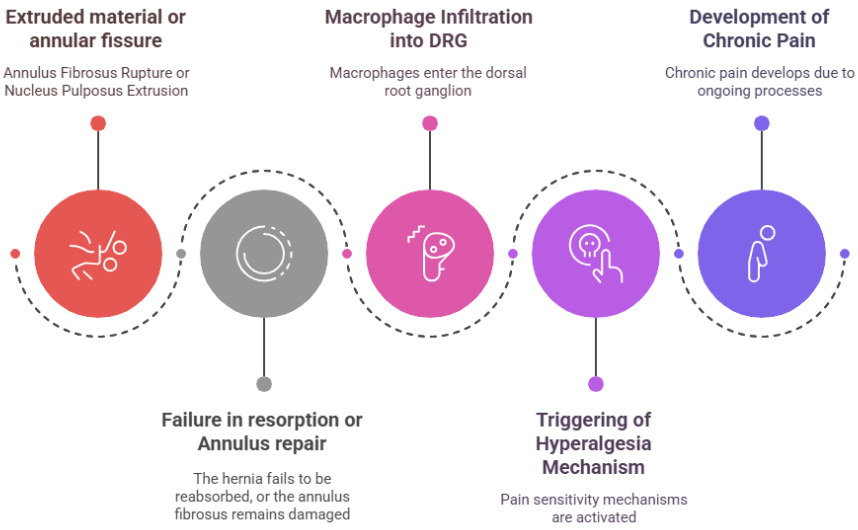

Fig. 3. *Chronic pain development in disc herniation. Dorsal root ganglion (DRG).*

M1 to M2 macrophages transition in herniated disc

M1 Macrophages are known for their role in inflammation, secreting proinflammatory cytokines that can aggravate patient symptoms such as inflammatory radiculopathy and discogenic pain (Table I). However, for effective healing to occur, it is essential that macrophages switch their phenotype to M2, a subtype that promotes inflammation resolution and tissue repair (24). This change is key to the resorption of the herniated disc, and its deficiency can contribute to the chronicity of pain.

The transition from M1 to M2 macrophages in the context of herniated discs is a critical aspect of the inflammatory response and subsequent healing process. M1 macrophages are typically associated with pro-inflammatory responses, characterized by the secretion of cytokines such as TNF-α, IL-6, and IL-8, which can exacerbate pain and

inflammation. Conversely, M2 macrophages are involved in anti-inflammatory processes and tissue repair, secreting cytokines such as IL-4 and IL-10, which help alleviate pain and promote healing.

A systematic review by Djuric et al. highlights the role of these macrophage subtypes in lumbar disc herniations. The review found that high levels of M1-related cytokines (e.g., TNF-α, IL-6) were associated with higher pain scores, while high levels of M2-related cytokines (e.g., IL-4, IL-10) were associated with lower pain scores (24). This suggests that the transition from M1 to M2 macrophages could be beneficial in reducing inflammation and pain in patients with herniated discs.

Histological studies, such as the one by Ito et al., provide further evidence of macrophage involvement in the resorption of herniated disc material. The presence of macrophages, particularly those expressing CD68, was noted in areas of neovascularization around sequestrated disc fragments, indicating an active role in the absorption process (28).

Table I. *Role of immunity in persistent sciatica. Main characteristics of the involved macrophages (M1 and M2).*

	M1 Macrophages (Pro-inflammatory)	M2 Macrophages (Anti-inflammatory)
Stimulated by	L-1, IFN-γ, TNF-α, LPS	IL-4, IL-13, IL-14
Function	Defense against pathogens, inflammation	Tissue repair, inflammation resolution
Release cytokines	IL-18, IL-6, IL-12, IL-23, TNF-α	IL-10, TGF-β
Role in immunity	Activation of Th1 responses, antigen presentation	Promotion of Th2 responses, modulation of immune reaction
Activities	Phagocytosis, cytotoxicity, acute inflammation	Healing, fibrosis, immunoregulation
Metabolism	Anaerobic glycolysis	Fatty acid oxidation, aerobic energy metabolism
Secreted products	Nitric oxide, reactive oxygen species	Growth factors, anti-inflammatory enzymes. Arginase-1
Surface markers	CD80, CD86	CD163, CD206

Platelet Rich Plasma in the Healing of Herniated Disc

PRP has emerged as a promising therapy to accelerate the healing of herniated discs. PRP has been shown to not only promote phagocytosis (29) but also favor its polarization towards the M2 phenotype (30), which improves long-term healing. Growth factors released by platelets stimulate collagen synthesis and the recruitment of circulating monocytes and stem cells (31), which contributes to the repair of the fibrous ring and the regeneration of the disc tissue (32).

In vitro studies have also supported the regenerative potential of PRP. For example, PRP has been shown to stimulate extracellular matrix metabolism, including the synthesis of proteoglycans and collagen, which are essential for disc repair (33). Furthermore, the TGF-β1/Smad2/3 pathway has been identified as a critical mechanism through which PRP exerts its regenerative effects on intervertebral discs (34).

A study has shown significant improvements in disc height and a reduction in pain in patients undergoing microsurgery who received PRP treatment in the annulus during the same procedure (35). Clinical evidence suggests that epidural administration of PRP can enhance healing, likely due to its effects on the DRG and the annulus fibrosus. In patients with sciatica, epidural PRP has demonstrated superior effectiveness compared to corticosteroids, while also being associated with fewer side effects (36-39). Unlike corticosteroids, whose therapeutic effects typically decline after 4-6 weeks, PRP maintains its efficacy at both 3- and 6-month post-treatment. Moreover, certain studies have reported sustained clinical improvement for at least one year, indicating the potential for a long-term or even curative mechanism underlying PRP's action (39). This positions PRP as a promising therapeutic option for managing sciatica and related conditions.

Clinical studies have shown promising results for the use of PRP in treating discogenic low back pain. For instance, a clinical trial demonstrated that intradiscal PRP injections significantly improved pain and lumbar function over a 48-week follow-up period in patients with discogenic low back pain (40). Additionally, the American Society of Pain and Neuroscience (ASPN) guidelines indicate that PRP injections can maintain significant improvements in functional rating index (FRI) scores for up to one year and potentially longer (41) (Fig. 4).

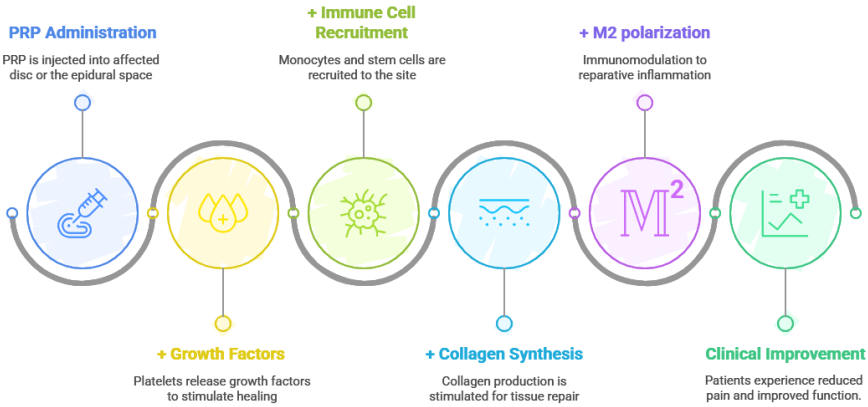

Fig. 4. *Role of PRP in disc herniation treatment.*

The activation of PRP with ozone

The activation of PRP using medical ozone has been investigated in several studies. One study demonstrated that ozonation of heparinized PRP samples significantly increased the release of platelet-derived growth factor (PDGF), transforming growth factor beta1 (TGF-beta1), and interleukin-8 (IL-8) in a dose-dependent manner (42). This suggests that ozone can enhance the release of growth factors from platelets, potentially improving the therapeutic efficacy of PRP.

In addition, it has been demonstrated that the ozonisation of heparinised plasma promotes platelet aggregation by enhancing the release of growth factors (43). A significant difference was observed when comparing the use of citrate as an anticoagulant versus heparin. Dr. Bocci's study was carried out using various ozone concentrations: 20 µg/mL, 40 µg/mL, and 80 µg/mL, following several hours (2, 4, or 8 hours) of incubation to measure the release of growth factors. It was found that the use of heparin increased platelet aggregation by 20% at an ozone concentration of 40 µg/mL and by 68% at a concentration of 80 µg/mL (42).

Heparin binds to VEGF (vascular endothelial growth factor), enhancing its stability and bioavailability, thereby preventing its premature degradation and prolonging its activity on target cells. Furthermore, heparin facilitates the binding of VEGF to its specific receptors (VEGFR), amplifying intracellular signaling pathways that stimulate cell proliferation and migration, essential processes for angiogenesis (44).

Studies conducted on endothelial cells have demonstrated that the inclusion of heparin in culture media significantly enhances the mitogenic response triggered by growth factors such as VEGF and FGF (fibroblast growth factor). This effect is attributed to heparin's ability to stabilize receptor-ligand interactions, thereby promoting the activation of signaling pathways that drive cell proliferation (45). These findings highlight heparin's critical role in modulating growth factor activity and supporting cellular processes involved in tissue repair and angiogenesis.

The platelet-derived growth factors studied included PDGF AB, particularly when heparinised blood was treated with ozone at 40 µg/mL, where the release of factors was more than double compared to when blood was treated with citrate. The highest concentrations of released factors were achieved after 2 h of incubation. TGF beta1 was consistently released between the first and fourth hours, with peak expression observed at 4 h in the group where blood was heparinised and treated with 80 µg of O_3. IL-8 was released after 4 h, which is presumed to be the time required for synthesis. TBX2 was released from the first hour of incubation, with similar values observed at 2 and 4 h. The differences in its release depended on the anticoagulant used, with variations recorded only at 2 h of incubation (42). Additionally, the presence of FGF was independent of the anticoagulant and was similarly activated by either calcium chloride or ozone (43).

A recent study found that ozone treatment of PRP induces significant morpho-functional modifications in platelets. Ozone at 16 µg/mL increases surface protrusions and dilates the open canalicular system, which is suggestive of a marked α-granule release. This leads to an increased release of platelet-derived factors, enhancing the regenerative potential of PRP without causing platelet damage (46).

Evidence of the use of ozone in hernial disc

The use of ozone therapy for the treatment of disc herniation has been evaluated in numerous studies. A meta-analysis conducted in 2021 reviewed 45 studies on percutaneous O_2/O_3 injections for discogenic low back pain and sciatica from 1980 to 2020. The findings indicated that image-guided O_2/O_3 injections were more effective for pain reduction, with an effect size of 4.48 (47). Kelekis et al. conducted a non-inferiority randomized control trial comparing intradiscal O_2/O_3 chemonucleolysis with microdiscectomy. The study found that O_2/O_3 therapy was non-inferior to microdiscectomy in terms of leg pain improvement at 6 months, with both treatments showing significant clinical improvements (48).

Kharrat et al. demonstrated that ozone nucleolysis significantly alleviated pain and enhanced function in patients with lumbar sciatica due to disc herniation. The study highlighted the cost-effectiveness and safety of this minimally invasive approach (49).

Ezeldin et al. evaluated the efficacy of ozone nucleolysis in 52 patients with symptomatic herniated lumbar discs. The study reported significant reductions in pain and disability at 2- and 6-month post-treatment, with no complications (50). A systematic review by Sconza et al. analyzed randomized controlled trials on oxygen-ozone therapy for low back pain. The review concluded that ozone therapy is a safe treatment with beneficial effects on pain control and functional recovery, although the overall quality of the studies was variable (51). Murphy et al. investigated the mechanisms of action of intradiscal O_2/O_3 therapy. The study found that ozone therapy reduces disc volume through dehydration and fragmentation of proteoglycans, which alleviates nerve root compression and reduces inflammation (52).

Erario et al. further explained that ozone therapy activates macrophages, facilitating the transition from an inflammatory to a reparative phase (53). In summary, the evidence supports the use of O_2/O_3 therapy as a safe and effective treatment for disc herniation, providing significant pain relief and functional improvement. This therapy offers a minimally invasive alternative to surgical interventions, with a lower complication rate and shorter recovery time.

Evidence of the use of ozone activated PRP in hernial disc

The combination of PRP and O_2/O_3 has been explored as a treatment for herniated discs, with promising results. A prospective non-randomized study conducted in 2016 evaluated 60 patients with severe lumbosciatica (VAS: 7–8) who underwent foraminal and facet injections of ozone (10 μg/mL, 10 mL) combined with Concentrated Growth Factors (CGF), 2 mL, and sacro-hiatal injections of ozone (15 μg/mL, 15 mL) plus CGF (1 mL). The outcomes were assessed using clinical monitoring, VAS scores, and MRI imaging. The study reported that 90% of patients achieved complete pain resolution (VAS: 0) (54). The combination of PRP and ozone leverages the regenerative properties of PRP and the anti-inflammatory and volume-reducing effects of ozone. Grangeat and Erario highlighted that ozone therapy can modulate oxidative stress and inflammation, potentially enhancing the reparative effects of PRP (55).

A study conducted in 2012 analyzed 50 clinical cases from 2010 to 2011, focusing on the use of PRP activated with ozone (PRP-O_3) for treating lumbar and cervical spine conditions. The findings revealed that the PRP-O3 technique not only promoted early pain relief but also supported joint regeneration by combining the biological benefits of PRP with the antimicrobial and anti-inflammatory properties of ozone. This outpatient, minimally invasive procedure yielded satisfactory results in 85% of cases, offering the added flexibility of allowing repeated treatments or the integration of additional therapeutic options as needed. The study concluded that PRP-O3 is a promising, low-risk intervention with both regenerative and analgesic effects, making it a viable option for managing lumbar and cervical spine disorders (56).

In summary, both ozone combined with PRP and ozone-activated PRP demonstrate potential for synergistic effects, including enhanced tissue regeneration, pain reduction, and improvements observed in imaging-based disc recovery. The safety profile of these therapies is excellent, with rare and minor adverse events, reinforcing their minimally invasive and safe nature. High success rates were reported, with up to 90% improvement in pain scores and MRI-based recovery indicators. These findings highlight the need for larger-scale, randomized controlled trials (RCTs) to validate these preliminary results and establish standardized treatment protocols. Overall, these therapies represent innovative advancements in regenerative medicine, offering less invasive alternatives to traditional surgical interventions for spine-related pathologies.

M1 TO M2 TRANSITION INDUCED BY OZONE OR PLATELET-RICH PLASMA

Platelet-rich plasma

The transition of macrophages from the M1 to M2 phenotype can be influenced by PRP. A study by Uchiyama et al. demonstrated that PRP can suppress M1 macrophage polarization and promote M2 macrophage polarization. This effect was observed with PRP prepared using different commercial kits, indicating that PRP's composition, including its humoral factors, plays a significant role in modulating macrophage phenotypes (57).

Another study by Uchiyama et al. found that both untreated PRP (utPRP) and freeze-thawed PRP (fPRP) inhibited M1 polarization while promoting M2 polarization, suggesting that PRP's anti-inflammatory properties are consistent across different preparation methods (58).

PRP-derived exosomes play a crucial role in the transition of macrophages from the M1 to M2 phenotype by regulating key signaling pathways. They inhibit M1 macrophage polarization by downregulating the NF-κB and MAPK pathways, which are associated with pro-inflammatory responses. This inhibition reduces the production of pro-inflammatory cytokines such as IL-1β and TNF-α, which are markers of M1 macrophages (59).

Simultaneously, PRP promotes M2 macrophage polarization by enhancing the phosphorylation of STAT6, a critical transcription factor for M2 differentiation. This shift increases the expression of anti-inflammatory markers such as IL-10, TGF-β, and arginase-1, which are characteristic of M2 macrophages (59, 60). Additionally, PRP-derived exosomes facilitate the autophagic degradation of the NLRP3 inflammasome, further reducing the inflammatory response. This process involves the ubiquitination of NLRP3, leading to its degradation and a subsequent decrease in IL-1β and caspase-1 production (59).

In vitro studies have shown that PRP treatment significantly decreases the expression of M1 markers (CD80, CD86) and increases the expression of M2 markers (CD163, CD206) in macrophages. This shift is associated with reduced NO production and enhanced tissue repair capabilities (57, 60).

Ozone

The impact of ozone on macrophage polarization is less well-documented compared to PRP. However, studies have shown that ozone can influence the release of various factors from platelets, which may indirectly affect the behavior of macrophages. For instance, Valacchi and Bocci reported that ozonated human platelets release higher amounts of PDGF, transforming growth factor beta1 (TGF-β1), and interleukin-8 (IL-8), which are known to play roles in inflammation and tissue repair (42).

The fact that O_2/O_3 has also been shown to be effective in the treatment of herniated discs (61-64). Studies have shown that ozone can not only reduce disc pressure (53). It is proposed that O_2/O_3 therapy exerts a modulating effect on the immune system, specifically by promoting the polarization of macrophages towards the M2 phenotype. This shift in macrophage polarization could enhance anti-inflammatory and tissue-repair mechanisms, potentially contributing to the therapeutic benefits observed in conditions characterized by chronic inflammation or impaired healing (53). Further experimental studies are needed to validate this hypothesis and elucidate the underlying molecular pathways involved in this immunomodulatory process. It appears that the mechanism by which ozone is able to decrease the concentration of proinflammatory cytokines such as TNF-alpha, IL-1β (65), and IL-6 (66) are closely connected with its modulating the activation of the NrF2 pathway (67, 68) and the activation of heme oxygenase-1 synthesis (69). Based on the available data, it appears that the combination of PRP and O_2/O_3 therapy may yield promising results in alleviating pain and enhancing the healing process for herniated discs, as both modalities share similar mechanisms of action.

The transition from M1 to M2 macrophages plays a pivotal role in the healing of herniated discs, as it mediates the resorption of the extruded nucleus pulposus and promotes the repair of damaged tissue. Supportive therapies, such as PRP and ozone, have been shown to enhance this immunologic shift, contributing to pain relief and long-term functional improvement in patients. As ongoing research continues to validate these findings, combination therapies like PRP and ozone may emerge as the standard of care for herniated disc treatment, offering a less invasive and more effective alternative to conventional surgical interventions (Fig. 5).

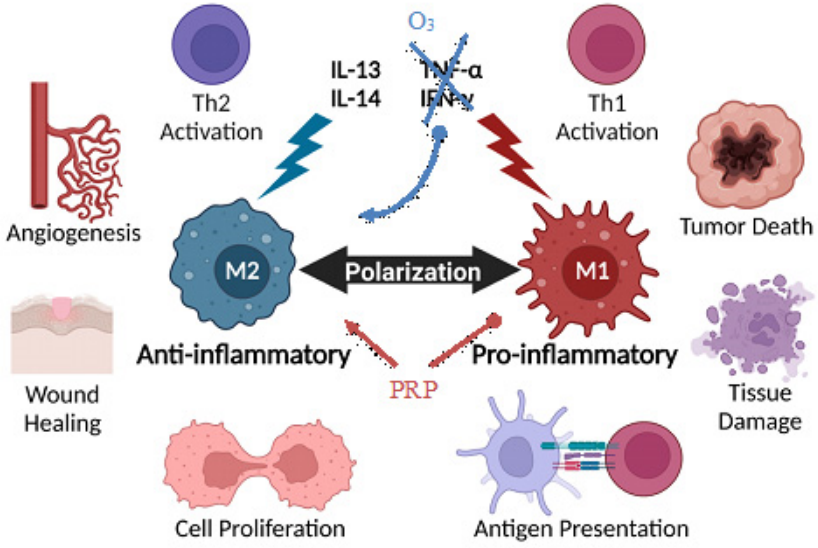

Fig. 5. *Potential role of Platelet Rich Plasma (PRP) and Ozone (O_3) on macrophages polarization. Ozone may induce macrophage polarization from M1 to M2 by modulating the NrF2 pathway and enhancing heme oxygenase-1 synthesis, thereby reducing proinflammatory cytokines like TNF-α, IL-1β, and IL-6. PRP inhibits M1 macrophage polarization while promoting M2 macrophage polarization through several mechanisms. PRP contains a high concentration of growth factors and cytokines that modulate the immune response and promote tissue repair. Modified from Morris et al. 2022 (70).*

CONCLUSIONS

Modulation of the inflammatory microenvironment through the transition from M1 to M2 macrophages emerges as a fundamental mechanism in resolving inflammation and promoting tissue repair in patients with disc herniation. In this context, the application of PRP has been established as a therapeutic strategy capable of stimulating collagen synthesis and enhancing the recruitment of reparative cells, resulting in a significant reduction in lumbar and radicular pain. On the other hand, ozone therapy not only contributes to the dehydration and reduction of disc volume through its action on proteoglycans but also exerts a potent modulatory effect on the inflammatory response.

Current evidence suggests that both treatments, PRP and ozone, act synergistically by enhancing the transition of macrophages from M1 to M2, an effect reinforced by ozone's ability to increase the release of growth factors such as PDGF, TGF-β1, and IL-8. These findings open the possibility of establishing a combined therapy that offers a less invasive and more effective approach for managing disc herniation. Nonetheless, despite the promising results observed in preliminary studies, it is imperative to conduct large-scale controlled trials to standardize treatment protocols and consolidate the scientific evidence supporting this therapeutic strategy.

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