REVIEW ARTICLE

https://doi.org/10.5125/jkaoms.2025.51.6.354
pISSN 2234-7550 · eISSN 2234-5930

Prolotherapy for temporomandibular joint disorders: an updated comprehensive review

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Abstract (J Korean Assoc Oral Maxillofac Surg 2025;51:354-361)

Temporomandibular joint disorders (TMDs) comprise multifactorial conditions involving pain, joint noises, and restricted mandibular motion. Prolotherapy, involving intra-articular or periarticular injection of proliferative agents such as hypertonic dextrose or polydeoxyribonucleotide (PDRN), has recently gained attention as a regenerative therapy for refractory TMDs. This review summarizes current evidence and biological mechanisms underlying prolotherapy in temporomandibular joint (TMJ) disorders. Literature searches identified clinical and experimental studies evaluating efficacy, safety, and treatment protocols. Prolotherapy promotes fibroblast activation, collagen synthesis, and ligamentous stabilization. Dextrose remains the most validated proliferant, while PDRN provides comparable efficacy with less discomfort and shorter treatment intervals. Clinical data consistently show reduced pain and improved maximum mouth opening across chronic and degenerative TMJ cases, with preliminary imaging evidence of subchondral bone remodeling. Reported adverse events are minimal and transient. Prolotherapy appears to be a regenerative approach that may be regarded as one of the conservative treatment modalities for TMDs. Further controlled studies are needed to validate its long-term clinical and structural outcomes.

Key words: Temporomandibular joint disorders, Prolotherapy, Dextrose, Polydeoxyribonucleotides, Biological therapy

[paper submitted 2025. 10. 13 / revised 2025. 12. 2 / accepted 2025. 12. 9]

I. Introduction

Temporomandibular joint disorders (TMDs) represent a broad spectrum of musculoskeletal and articular conditions involving the temporomandibular joint (TMJ) and its associated structures, typically characterized by pain, joint sounds, and limited mandibular motion[1]. The etiology of TMDs is multifactorial, incorporating structural, functional, and psychosocial components such as occlusal disharmony, trauma, parafunctional habits, systemic inflammation, and psychological stress[2]. Conventional management primarily aims at symptom control and restoration of mandibular function. First-line therapy typically consists of self-care education, splint therapy, physiotherapy, and pharmacologic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or muscle relaxants[3]. In refractory cases, minimally to moderately invasive procedures—including arthrocentesis and intra-articular corticosteroid or hyaluronic acid injections—may be considered, while surgical interventions such as arthroplasty, condylectomy, discoplasty, or total joint replacement are typically reserved for severe, unresponsive cases[4,5]. However, these approaches are largely palliative rather than regenerative, often providing only transient relief without addressing the underlying degenerative pathology.

Prolotherapy therefore emerged as a regenerative alternative for refractory TMDs. This minimally invasive technique involves the injection of hyperosmolar or biologically active proliferants—most commonly hypertonic dextrose—into ligamentous, tendinous, or intra-articular tissues to initiate a controlled reparative response[6-8]. The injected agents induces mild cellular stress and localized inflammation, which subsequently activates fibroblasts, promotes collagen turnover,

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and enhances the mechanical integrity of capsular and ligamentous tissues. Recent researches have demonstrated that prolotherapy can significantly reduce TMJ pain and improve mandibular range of motion compared with placebo or standard conservative therapies[9-11]. Nevertheless, the available evidence is constrained by methodological heterogeneity and limited sample sizes. This comprehensive review provides an updated overview of prolotherapy for TMJ disorders, incorporating new evidence from the latest studies, and summarizes current understanding to provide an updated understanding of the biological basis, indications, and therapeutic outcomes of prolotherapy in TMD management.

II. Mechanisms of Action and Proliferant Agents of Prolotherapy in the TMJ

Prolotherapy aims to enhance the body's intrinsic reparative capacity in chronically injured tissues[12]. The therapeutic concept is to provoke a controlled, localized inflammatory or proliferative response that activates fibroblasts, stimulates collagen synthesis, and ultimately restores the tensile integrity of weakened connective structures[8]. Originally developed for orthopedic indications such as knee osteoarthritis and spinal ligament instability, prolotherapy has repeatedly demonstrated pain reduction and improved function in musculoskeletal disorders[7]. Within the TMJ, injections are directed at peri-articular soft tissues—including the capsular and lateral ligaments, disc attachments, and adjacent tendon insertions—with the purpose of tightening lax fibers, repairing microtears, and reducing excessive joint mobility[13,14]. Different proliferant agents may achieve this goal through distinct biological pathways—either inflammatory (e.g., hypertonic dextrose) or non-inflammatory (e.g., polydeoxyribonucleotide [PDRN])[13,15]. The regenerative cascade initiated by prolotherapy involves up-regulation of growth factors such as PDGF, TGF-β, connective-tissue growth factor, and epidermal growth factor, which together promote angiogenesis, fibroblast proliferation, and extracellular-matrix remodeling[16].

Classical dextrose-based prolotherapy relies on osmotic stimulation: injection of a hypertonic dextrose solution induces transient cellular dehydration and metabolic stress, leading to release of pro-healing cytokines and initiation of the wound-healing sequence. Conversely, newer agents such as PDRN promote regeneration through predominantly non-inflammatory pharmacologic signaling[17]. A number of clinical studies of controlled trials and systematic reviews has evaluated prolotherapy for TMDs, generally demonstrating meaningful improvements in pain and mandibular function, although the methodological quality of available studies remains variable[2,9-11,13-15,18]. Consequently, prolotherapy is increasingly regarded as a reasonable adjunct or alternative for patients unresponsive to conventional TMD management.

1. Hypertonic dextrose

Among the various proliferants, hypertonic dextrose (typically 10%-25%) remains the most established and widely studied agent[8]. Dextrose is inexpensive, readily available, and has an extensive clinical history across multiple joints[6]. It exerts its therapeutic action by inducing mild osmotic stress, which triggers a transient inflammatory cascade characterized by the release of PDGF and TGF-β and subsequent stimulation of fibroblast activity and collagen deposition[8,11,18]. In TMJ applications, 10% dextrose is usually prepared by diluting 50% dextrose with anesthetic and saline to achieve a mildly hyperosmolar solution that elicits a targeted regenerative response[19,20]. Over several weeks, fibrovascular tissue develops within the ligamentous framework, enhancing capsular stability and reducing aberrant motion.

Although a universally standardized regimen has not yet been established, most studies recommend three to five sessions administered at 4 to 6-week intervals to allow collagen maturation between treatments[14]. Clinical protocols generally employ small injection volumes (0.5-2 mL per site) distributed across multiple peri-articular regions[15,17,18]. A typical TMJ prolotherapy session with dextrose consists of injections to the posterior disc attachment (around 2 mL), anterior disc attachment (1 mL), and the superior and inferior aspects of the lateral joint capsule (0.5 mL each), performed under temporo-auricular nerve block. These injections target the key ligamentous support areas of the joint. Patients commonly experience mild post-injection pain for 24-48 hours, as the inflammatory phase, followed by progressive pain relief and improved joint stability. For optimal tissue recovery, a 2 to 3-week interval between sessions is generally recommended for the inflammatory reaction to subside and new collagen to mature. In 2024, Park et al.[18] administered four-site 10% dextrose prolotherapy at 2-3 week intervals to 19 patients with chronic TMJ pain unresponsive to conventional treatments. They observed that pain on the numerical rating scale (NRS) gradually improved, and although maximum mouth opening (MMO) slightly decreased after the first prolotherapy session, it gradually increased in subsequent sessions. In 2025, the same group confirmed these findings in a larger cohort

of 66 patients, showing sustained improvement in both NRS pain scores and MMO after a single injection, maintained through follow-up[17]. Most patients require two to four sessions depending on clinical response, and special caution is warranted in individuals with diabetes mellitus or heightened pain sensitivity[18,21].

2. Polydeoxyribonucleotide (PDRN)

PDRN is a mixture of DNA fragments (50-2,000 base pairs) usually derived from salmon sperm, and promotes healing through pharmacologic rather than purely irritant mechanisms[22]. Its regenerative actions are primarily mediated by the activation of adenosine A_2A receptors (ADORA2A), which play a central role in modulating inflammation, angiogenesis, and tissue regeneration[23]. Upon receptor activation, PDRN downregulates pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-1β, IL-6, and high mobility group box 1 (HMGB1), while upregulating the anti-inflammatory cytokine IL-10 and vascular endothelial growth factor (VEGF)[24]. As a result, PDRN injections tend to cause less post-injection flare than dextrose and allow shorter intervals between treatments. In orthopedic applications, PDRN has demonstrated robust regenerative and anti-inflammatory activity in multiple tissues. In vitro studies show that PDRN enhances fibroblast migration and collagen synthesis, while in chondrocyte cultures it exerts chondroprotective effects and preserves extracellular matrix integrity[25]. Recent TMJ studies demonstrate that PDRN achieves clinical outcomes comparable to dextrose prolotherapy but with improved tolerability and patient compliance[17,26]. Because its biological half-life is approximately 3-4 hours, repeated intra-articular administration as frequently as 1-2 times per week, compared to dextrose prolotherapy[27]. In 2025, Jang et al.[26] evaluated 111 patients with TMJ osteoarthritis treated with 1-3 PDRN injections at 2 to 6-week intervals. They observed improvements in both MMO and pain NRS scores, with particularly favorable outcomes in patients with acute TMD (symptom duration ≤3 months), and noted that the clicking sound resolved in some cases. Similarly, Choi et al.[17] found that administering PDRN injections at shorter 2-week intervals (compared to the typical dextrose injection interval) resulted in similar efficacy to dextrose prolotherapy, with both treatments yielding significant improvements in MMO and visual analogue scale (VAS) scores. Notably, among patients who initially presented with joint sounds, a complete resolution of the sounds was observed in most cases, accompanied by significant reductions in jaw displacement (from 69.6% to 13.0%) and deflection (from 52.2% to 8.7%). This suggests that PDRN can achieve comparable clinical efficacy to the well-established dextrose prolotherapy while offering advantages in comfort and treatment frequency.

3. Other proliferants and adjuncts

Platelet-rich plasma (PRP) has been explored as a biologic analog of prolotherapy, leveraging autologous growth factors to enhance angiogenesis and tissue repair, capitalizing on its angiogenic and anti-inflammatory cytokines[28]. PRP injections—often combined with arthrocentesis—have demonstrated short-term pain reduction and improved mandibular mobility, though variability in preparation methods hinders cross-study comparisons[29]. However, PRP is costly, operator-dependent (blood processing), and lacks standardized protocols in TMJ prolotherapy; strictly speaking, PRP is often considered separate from classic "prolotherapy". Other agents, including polidocanol, morrhuate sodium, and phenol–glycerin–glucose (P2G), have historical use in ligament prolotherapy but only limited application in TMJ disorders[30].

Injectable platelet-rich fibrin (i-PRF), a second-generation platelet concentrate, has recently gained attention as a promising orthobiologic adjunct for TMJ disorders. In contrast to PRP, i-PRF is produced without anticoagulants using low-speed centrifugation, which yields a three-dimensional fibrin network that entraps platelets and leukocytes and allows a more gradual release of growth factors over time. In a prospective study, intra-articular i-PRF provided greater reductions in pain scores and better recovery of mandibular function than PRP or hyaluronic acid in patients with TMJ internal derangement[31]. Similarly, a randomized clinical trial reported that i-PRF administered after arthrocentesis yielded larger improvements in pain and MMO compared with hyaluronic acid[32]. In TMJ osteoarthritis, another randomized trial found that i-PRF led to significant decreases in pain and joint crepitation, together with improved mandibular mobility, suggesting a possible benefit for cartilage and subchondral bone support[33].

In summary, hypertonic dextrose remains the most widely used proliferant for TMJ prolotherapy due to its extensive validation and accessibility. PDRN has recently emerged as an effective, well-tolerated alternative supported by early clinical evidence. PRP and other orthobiologic injections represent a parallel avenue of regenerative therapy for TMJ disorders. Ongoing research is likely to clarify which injec-

tate, or perhaps which combination of injectates, yields the best long-term results for different TMD subsets. In 2025, Ku et al.[15] treated TMJ degenerative joint disease (DJD) by alternating PDRN and dextrose injections, and noted not only symptomatic relief (improvements in MMO and NRS) but also radiographic evidence of new bone formation along eroded condylar surfaces after prolotherapy, suggesting potential for structural regeneration in degenerative joints. Thus, there is interest in whether combining agents (such as using dextrose plus PRP, i-PRF, or sequencing PDRN after a round of dextrose) might harness both inflammatory and non-inflammatory pathways for maximal benefit–though no clinical studies have directly tested combined approaches yet. Clinicians should choose the proliferant based on patient-specific factors—pain threshold, metabolic status, cost, and accessibility—while adhering to precise injection techniques and strict asepsis to ensure safety.

III. Clinical Evidence and Suggested Indications for TMJ Prolotherapy

TMDs comprise a heterogeneous group of conditions affecting both the structural and functional components of the jaw[34]. Their etiology is multifactorial and may arise from muscular dysfunction, intra-articular pathology, degenerative change, or a complex interplay of these factors. Conservative physiotherapeutic modalities—such as manual therapy, exercise-based programs, and electrotherapy—are strongly supported by current evidence as first-line management for most TMD cases[35]. Surgical interventions, including arthrocentesis as well as arthroscopic or open joint surgery, are generally reserved for cases where non-surgical treatments have failed or where there are obvious structural changes[36,37]. Intracapsular injections (e.g., corticosteroids, hyaluronic acid, PRP, PRF) have demonstrated significant pain reduction and functional improvement in TMJ arthralgia, but none has shown consistent long-term superiority[34,38]. Within this continuum of care, prolotherapy has attracted growing interest as a biologically driven injectable therapy aimed not only at symptom reduction but also at promoting connective-tissue repair and joint stabilization[17,18]. Although standardized protocols and definitive efficacy thresholds have not yet been established, current mechanistic understanding suggests that relevant therapeutic targets include periarticular muscles (e.g., lateral pterygoid, temporalis, masseter), capsular and stylomandibular ligaments, retrodiscal tissues, and the synovial membrane. Appropriate patient selection remains essential for achieving predictable outcomes. By integrating findings from recent clinical studies, the present review aims to clarify the biological rationale, therapeutic indications, and emerging clinical potential of prolotherapy in the management of TMDs.

1. Pain and joint function

Prolotherapy was first introduced in the 1950s as a regenerative treatment for chronic musculoskeletal pain[30,39]. In the TMJ region, although the exact mechanism of action remains incompletely defined, several studies have demonstrated significant improvements in both pain and mandibular function following treatment[40]. A 2025 systematic review confirmed that prolotherapy produced greater reductions in reducing pain and greater increases in jaw opening compared with placebo, autologous blood products, or occlusal splint therapy[11]. The mechanism underlying pain reduction is not yet fully understood. Proposed explanations include controlled immune-mediated amplification of the inflammatory cascade and the potential role of dextrose or PDRN as substrates for cartilage-matrix biosynthesis[41]. In addition, prolotherapy may exert neuromodulatory effects on the periarticular neural network of the TMJ[42]. Activation of potassium channels—similar to that observed in glucose-mediated inhibition of orexin/hypocretin neurons—can induce neuronal hyperpolarization and attenuate nociceptive signal transmission, thereby contributing to analgesia[43-46]. This reduction in pain facilitates greater mandibular excursion, whereas improved range of motion may further relieve pain through enhanced synovial lubrication and normalization of joint movement[47]. However, excessive mechanical loading or intensive exercise during the acute inflammatory phase may aggravate osteoarthritic degeneration[48], while controlled, low-intensity activity has been shown to exert anti-inflammatory and chondroprotective effects[49]. Choi et al.[17] revealed a statistically significant correlation between improvements in MMO and pain reduction. They suggested that patients who actively engaged in rehabilitation exercises following prolotherapy tended to achieve better treatment outcomes.

1) Disc displacement and joint sounds

The TMJ is prone to internal derangements of the articular disc, leading to deviations during mouth opening, such as deflection or clicking sounds[50,51]. Magnetic resonance imaging (MRI) findings show that clicking sounds are associated with disc displacement (with or without reduction) and disc deformities[52]. It is known that when a clicking sound is caused

by disc displacement with reduction. Despite the availability of numerous surgical and non-surgical interventions, current evidence indicates that no modality can consistently reposition a displaced disc into a stable, physiologic alignment[53-55]. Prolotherapy appears to enhance the stiffness of the capsular and ligamentous apparatus, thereby limiting excessive condylar translation and improving disc-condyle coordination. This mechanism plausibly accounts for the observed reduction in joint clicking and intermittent locking after treatment. Recent clinical reports have documented improvements in disc-related TMD symptoms such as clicking and deflection[15,17,26]. Mechanistically, prolotherapy may reinforce the peri-discal ligaments and surrounding musculature. Although direct imaging evidence of disc remodeling is limited, these functional improvements suggest a stabilizing influence on TMJ biomechanics and expand the therapeutic scope of prolotherapy beyond pain relief alone.

2. TMJ osteoarthritis (DJD)

TMJ osteoarthritis represents one of the more challenging indications for prolotherapy. It is characterized by condylar flattening, osteophyte formation, medullary sclerosis, synovitis, cartilage destruction, and subchondral bone remodeling[56]. Osteoarthritis develops through the interplay of mechanical overload and chronic low-grade inflammation, ultimately involving the entire joint complex—including the subchondral bone, articular cartilage, ligaments, capsule, synovial membrane, and peri-articular musculature[57]. Conventional management has largely been supportive, relying on splint therapy and NSAIDs, given the limited intrinsic capacity for cartilage regeneration. In orthopedics, however, prolotherapy for osteoarthritis has been associated with meaningful pain reduction and functional improvement, and may even stimulate chondrogenesis, as evidenced by favorable radiographic and histologic findings[7]. Accordingly, prolotherapy offers a biologically based approach that not only alleviates pain but also possibly slow or reverse degenerative changes by promoting endogenous repair. Regardless of whether dextrose or PDRN, prolotherapy yielded improvements in MMO and VAS in patients with DJD (osteoarthritis or osteoarthrosis), comparable to outcomes observed in TMD patients with primarily soft-tissue involvement[17,18]. A recent case series described four patients with radiographically confirmed TMJ-DJD treated with combined dextrose and PDRN prolotherapy[15]. All four experienced marked symptomatic relief and mandibular deviation on opening was corrected. Remarkably, follow-up cone-beam computed tomography (CBCT) imaging showed new cortical bone formation and smoother condylar contours in these joints. Similarly, in a cohort of 111 patients with TMJ osteoarthritis, an approximately 50% reduction in joint crepitation was observed with no significant difference between acute and chronic subgroups[26]. Collectively, these preliminary data suggest that prolotherapy may not only relieve pain but also contribute to structural restoration in degenerative TMJ disease, supporting its potential role as an early-stage or adjunctive therapy.

3. TMJ hypermobility disorders

Beyond osteoarthritis, prolotherapy is also indicated when TMD symptoms arise from ligamentous laxity or subtle soft-tissue derangements that are not amenable to other treatments. Patients with TMJ hypermobility disorders—such as recurrent subluxation or chronic dislocation caused by ligamentous insufficiency—constitute a classic target population[9,10]. In these cases, prolotherapy's collagen-stimulating and ligament-tightening effects restore functional stability and reduce symptomatic clicking. Likewise, by similar rationale, prolotherapy may serve as an adjunct to botulinum-toxin therapy for neuromuscular disorders such as oromandibular dystonia or dyskinesia, helping to reinforce peri-articular soft-tissue tone[58,59].

In summary, the ideal candidates for TMJ prolotherapy are those with chronic, refractory TMD symptoms—pain, limited motion, or instability—related to ligament, tendon, or mild osseous pathology who seek a minimally invasive treatment option. This includes cases of TMJ hypermobility, disc or capsular dysfunction, and mild-to-moderate DJD. Conventional conservative treatments should be continued in parallel, and contributory factors (e.g., parafunctional habits like bruxism) addressed simultaneously. Contraindications are few but include systemic conditions that impair healing (e.g., uncontrolled diabetes, which may complicate dextrose therapy due to hyperglycemic risk) and the use of immunosuppressive or anti-inflammatory agents that might blunt the desired reparative response—although, notably, PDRN appears less affected by NSAIDs. Future controlled studies using MRI or CT could help determine whether prolotherapy can slow disease progression or promote partial regeneration of joint structures, including open bite from degenerative condylar resorption.

IV. Limitations and Future Direction

The current evidence for TMJ prolotherapy is promising but remains limited by study design constraints. Most published data come from small randomized controlled trials, single-arm cohort studies, and case series, with very few trials having adequate sample sizes or blinding[11]. Furthermore, injection protocols are not standardized; studies vary in proliferant type (dextrose concentration vs. PDRN), dose, and injection sites, complicating comparisons and meta-analyses[60]. Despite these limitations, prolotherapy appears generally safe when properly performed. It has shown significant reductions in TMJ pain and improved jaw function, with some evidence of bone tissue regeneration. Thus, prolotherapy has progressed from an experimental concept to a clinically applied adjunct for certain TMJ disorders. Current data support its role in TMD management, but high-quality research is needed to optimize treatment protocols and confirm long-term efficacy and safety. Until more evidence is available, clinicians should be judicious but open-minded with prolotherapy, and researchers should continue to validate and refine this regenerative approach.

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Authors' Contributions

Y.K. participated in writing the manuscript. Y.K., M.J.K., J.K.K. participated in the reference search. P.Y.Y. supervised the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Funding

No funding to declare.

Conflict of Interest

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

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How to cite this article: Kim Y, Kim MJ, Yun PY, Ku JK. Prolotherapy for temporomandibular joint disorders: an updated comprehensive review. J Korean Assoc Oral Maxillofac Surg 2025;51:354-361. https://doi.org/10.5125/jkaoms.2025.51.6.354