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Prolotherapy in Musculoskeletal Disorders, Guideline for Orthopedic Application

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Abstract

Purpose: Prolotherapy is a therapeutic method that involves injecting an irritant substance into injured areas of tendons, ligaments, and articular spaces. It has a wide application in orthopedic fields, including arthritis, tendinopathies, and back pain. Protocol of injection varies extensively based on the pathological condition. This review aims to discuss orthopedic applications of prolotherapy and its related outcomes, intending to introduce more specific injection protocols in each field. **Methods:** In a narrative review of literature, various musculoskeletal indications and contraindications of prolotherapy, as well as the method and location of injection, solution type, procedure intervals and frequencies, outcomes and side effects are investigated to reveal all aspects of the current knowledge about this new approach. **Results:** Chronic back pain, osteoarthritis, and tendinopathies are considered the most common indications for prolotherapy. Protocol of injection varies from one condition to another. The actual concentration of administered dextrose ranges from 12.5% to 25%. Results of the different studies indicate that prolotherapy could have a pleasing effect on improving patient's pain and functional outcomes. No severe complication has been mentioned in previous investigations. **Conclusion:** Prolotherapy is a new therapeutic option that can be suggested as an effective method in recalcitrant musculoskeletal conditions.

Keywords

Prolotherapy, Hyperosmolar Dextrose, Low Back Pain, Osteoarthritis, Tendinopathy

1. Introduction

1.1. Background and Definition

Prolotherapy is defined as a nonsurgical regenerative injection technique that involves injecting sclerosing or proliferant substances into painful tendon insertion sites (entheses), ligaments, joints and adjacent joint spaces in single or several injection sessions to induce normal tissue growth in injured areas [1] [2].

The term was first introduced by a general surgeon named George Hackett in 1956, who proposed that injecting sclerosing solutions could improve joint stability by tightening interarticular ligaments and joint capsules [1] [2]. The word "prolotherapy" consists of two following root words: The Latin "proles," which means proliferation and offspring, and the English word "therapy" [1]. Dr. George Hackett initially formalized Prolotherapy injection protocols, discussing injecting small amounts of a solution into the affected site during several treatment sessions [4].

1.2. Subtypes and Mechanism of Action

Prolotherapy has been considered an alternative treatment for a wide variety of painful musculoskeletal conditions that are usually refractory to standard therapies [4]. Protocol of injection varied from one condition to another, depending on several variables such as damage type and location, clinical severity, and practitioner preference [4] [5]. Prolotherapy is performed based on palpating tender points in affected sites [6] [7], using anatomic landmarks [8] or under ultrasound or fluoroscopic guidance [5] [9]. There are multiple solutions used in prolotherapy, categorized into three major groups. Some agents are considered irritants (including phenol or Phenol-glycerin-glucose, guaiacol, and tannic acid), some are chemoattractants (sodium morrhuate), and others are known as osmotic agents (including hypertonic glucose, glycerin, and zinc sulphate) [10]. Even a mixture of these solutions can be used in treating musculoskeletal problems [7]. Chemoattractants act as vascular sclerosants and attract inflammatory mediators to the injury site [11]. Sodium morrhuate is the one and only member of this group [10]. Osmotic solutions create a hypertonic environment, leading to dehydration, cell rupture and osmotic shock, which in turn result in granulocytes and macrophages attraction and induce collagen deposition which ultimately stimulates tissue healing process. They also upregulate the expression of platelet-derived growth factor in injured areas [2]. Hypertonic dextrose (D-glucose) has been categorized as an osmotic agent. It is the most commonly used solution in practice that is water-soluble and considered one of the normal constituents of blood chemistry [1]. The third class, Irritants, directly attack cells and kill them by presenting their antigens at cellular surface through changing cell surface proteins [10]. In many of the earlier published studies, phenol-glycerin-glucose was included as an irritant substance, but it is no longer used today [11]. *In vitro* studies indicated that human fibroblasts and chondrocytes exposure to only 0.5% concentrations of dextrose have stimulated the production

of several growth factors, which are essential to the functional and structural repair of tendinous and ligamentous tissues. These substances include platelet-derived growth factor, transforming growth factor β, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor. *In vitro* studies demonstrate that the mentioned growth factors have promoted the expression of types 1 and 3 collagens which pertain to the growth of tendon, ligament, and cartilage. Growth factors production and cellular proliferation are the critical factors of tissue repair in prolotherapy injection. While using the concentrations of 0.5% dextrose prolotherapy showed promising results in experimental studies, dextrose concentrations higher than 10% are considered as inflammatory concentrations in clinics and be utilized as irritant agents in prolotherapy. Concentrations less than 10% are non-inflammatory [2]. Although the exact mechanism of action remains unclear, it is hypothesized that prolotherapy solutions may induce a local inflammatory response at the site of injection, which leads to fibroblast proliferation and subsequent collagen synthesis, resulting in stronger and tighter ligaments and tendons, reduction in pain and dysfunction and also improved joint stability and biomechanics [4] [5].

The effect of prolotherapy in pain reduction is unclear, but investigations reported that dextrose could alleviate pain through blocking transient receptor potential vaniloid 1 (TRPV1) pain receptors and even modulate sensorineural pain receptors [1].

In vitro studies demonstrated that in the environment of highly concentrated glucose, the expression of collagen type 1 and 3 genes are increased in fibroblasts, and the matrix protein aggrecan amounts is changed in chondrocytes, which could contribute to tissue regeneration in peri-articular structures. There is an increase in cellularity and fibrous components in the cartilage tissue in the hyperosmolar conditions [1].

This review has especially focused on dextrose prolotherapy protocols, as it is the most common prolotherapy substance in practice [1].

2. Technique and Protocol

Actual concentration of hyperosmolar dextrose may vary according to condition but the usual range is 12.5% to 25%. In intra articular injections, concentrations of 25% dextrose are most often used, and in peri-articular injections, 15% dextrose is usually the choice [1]. An anesthetic agent must be applied locally or as a co-injecting solution to minimize the patient's discomfort during the procedure. Lidocaine is the most common, but procaine and pontocaine are also used [7]. The selection criteria for choosing between prolotherapy agents are not mentioned in none of studies that utilized prolotherapy as therapeutic procedure. Hyperosmolar D-glucose is the most usual agent and it also could be used in combination with sodium morrhuate. Procedure will be performed by an experienced, trained physician in several treatment sessions, dividing by weekly or

monthly intervals [4] [12]. Usual injection intervals range from 2 to 6 weeks, and treatment sessions vary from 1 to 12 sessions or more [2] [4] [6] [7]. The procedure was accomplished by making multiple insertions within or adjacent to the damaged tissue, usually in one to three points to a maximum of 10 points, at each visit [2] [13]. Usual volume of injection is 0.5 to 1 ml. maximum total of injection volume is considered 5 ml at each session [6]. Target tissue characteristics determine the size of the needle, and usually, the smallest needle that can reach the target is selected [1]. Injection techniques in each indication is pragmatically defined and number of injection, injection volume, and needle size vary case by case in each category, regardingly, there is no particular unique protocol for prolotherapy injections that practitioners could benefit as a reference technique [1]. All injection steps must be performed under sterile conditions and by an expert physician [14]. Outcome assessment is usually performed months after treatment initiation to evaluate short-term and long-term effects of injection. Prolotherapy results in pain and stiffness reduction both at rest and activity levels, functional and range of motion (ROM) improvement, and size, strength, and laxity promotion in weakened ligaments and tendons [15] [16] [17] [18] [19].

3. Prolotherapy in Orthopedics

Prolotherapy is widely used as an alternative treatment for many orthopedic indications, which can be categorized into the following groups:

- Chronic low back pain (specific and nonspecific causes), neck pain, groin pain, and fibromyalgia [2] [4] [10] [20];
- Osteoarthritis (knee osteoarthritis, fingers, and thumb osteoarthritis) [17] [19];
- Tendinopathies (lateral epicondylosis, rotator cuff tendinopathy, patellar tendinopathy, Achillestendinopathy, plantarfasciopathy, Osgood-Schlatter disease, hip adductor tendinopathy, temporomandibular joint dysfunction) [1] [2].

4. Chronic Low Back Pain

Chronic low back pain (CLBP) is defined by prolonged pain and dysfunction, which remains resistant to therapies for at least three months. CLBP is one of the most common debilitating factors in the middle-aged population. The most frequent indication for prolotherapy in musculoskeletal disorders is low back pain. Injection therapies have received interest in recent years, addressing specific and nonspecific causes of back pain. Sacroiliac joint dysfunction, refractory coccygodynia, and moderate to severe degenerative disc disease, which can lead to radiculopathy, are specific causes of CLBP, and the remaining conditions are counted as nonspecific [11]. Protocols for injection vary extensively but mostly include three to eight sessions of intra-ligamentous, intra-articular, or peri-articular injections at weekly or fortnightly intervals [10]. There is no agreement on

the total injection volume for prolotherapy agents, but in most cases, physicians inject at least 20 ml of solution at each treatment session. Some studies reported administering fewer amounts of solutions. Normal saline, lidocaine, and procaine injections are frequently used as control procedures [10]. Frequently measured outcomes are pain and disability. Prolotherapy is usually performed in association with other co-interventions. Supplementary interventions are performed prior to injections, during, or after the injections. Pre-injection procedures include triamcinolone injections into the tender points, injection of lidocaine, or spinal manipulation under intravenous sedation or analgesics application. Lumbar flexion and extension stretching exercises, spinal care guides, spine supporting braces, walking and commencing previously painful activities, paracetamol, zinc, manganese, and vitamin C can be prescribed during or after the prolotherapy session. It is hypothesized that a combination of prolotherapy with other routine treatment options can be more effective and enhances the outcomes [10]. As a result, when prolotherapy is used in combination with other treatments, reduction in pain and improvement in disability scores are more significant. However, the effectiveness of prolotherapy injection alone remains controversial, according to many studies [10] [13]. In addition to its role in treating CLBP, investigations showed that prolotherapy has more viable effects than corticosteroid injection on long-term outcomes of back pain(9). Transient increases in back pain and stiffness, diarrhea, and nausea are common side effects following injection that usually resolve in a few days. Post-injection headaches are reported only in a few cases and are considered a rare complication of therapy [10] (**Table 1**).

5. Osteoarthritis

Osteoarthritis (OA) is a chronic age-related degenerative condition affecting big weight-bearing joints [21] [22]. Knee is the most common joint affected by OA [23]. Knee Osteoarthritis (KOA) is the most frequent cause of knee pain [22], which results in functional impairment and low quality of life [24]. Conservative treatments include lifestyle modifications, stretching exercises, nonsteroidal anti-inflammatory drugs, and new regenerative injection therapies [22]. Treatments are administered to reduce symptoms and improve joint ROM [25]. If conservative therapies fail to reach therapeutic goals, operative treatments are performed to help regain joint function [24]. Regenerative therapies include injecting corticosteroids, platelet-rich plasma, hyaluronic acid, ozone, botulinum toxin, and prolotherapy agent into the joint [25]. Guidelines of Osteoarthritis Research Society International (OARSI) and American College of Rheumatology/Arthritis Foundation have recommended the conditional use of prolotherapy for the management of knee-OA in 2019 [25]. Patients receive one to five doses of dextrose prolotherapy injection, with three as the most frequent [23]. Injection intervals vary between once weekly to once every two months, and the most common is once every month [23]. The concentration depends on the injection

Table 1. Prolotherapy in chronic low back pain (Dechow, Davies *et al*., 1999, Yelland, Glasziou *et al*., 2004, Kim, Lee *et al*., 2010).

Authors/ publication year	Sample characteristics and size	Study groups	Injection protocol	Measured outcomes	Follow up intervals	Result
Kim W.M. *et al*., (2010) [9]	Patients with resistant SI joint pain (n = 48)	Intervention: dextrose 25% injection (n = 23) Control: triamcinolone acetonide injection (n = 25)	Three sessions; biweekly, under fluoroscopic guidance	1. Pain (NRS scale) 2. Disability (ODI index)	2 weeks, 6, 10, 15 months after treatment completion	Improved pain and disability in 2 Ws in both groups, more significant improvement in the prolotherapy group in long-term follow-up ($p < 0.005$)
Yellend M. *et al*., (2004) [13]	Participants with chronic non-specific low-back pain (n = 110)	Intervention: dextrose 20% injection (n = 54) Control: normal saline injection (n = 56)	6 sessions; biweekly, based on tenderness points location	1. Pain (VAS scale) 2. Disability (Roland-Morris)	2.5, 4, 6, 12, and 24 months after treatment	Significant reduction in pain and disability in both groups; the between-group difference is insignificant
Dechow E. *et al*., (1999) [12]	Patients with low back pain of more than six months' duration (n = 74)	Intervention: dextrose 25%-glycerin-phenol injection (n = 36) Control: normal saline injection (n = 38)	3 sessions; weekly	1. Pain (e.g., McGill Pain) 2. Disability (e.g., MSPQ)	1, 3, and 6 months after treatment	No significant improvement in outcomes during follow-up period in prolotherapy and control groups

site, with a 10 to 25% range for intra-articular and 12.5 to 15% for extra-articular technique [23] [25]. Most commonly administered concentration is 25% in the intra-articular approach and 15% in extra-articular ones [23]. The recommended injection protocol is applying hyperosmolar dextrose in 2 - 6 sessions at monthly intervals to reach the maximum therapeutic effect [21] [25]. Comparator could be saline injection group, lidocaine, hyaluronic acid (HA), platelet-rich plasma, erythropoietin, autologous conditioned serum, botulinum neurotoxin A, radiofrequency waves, and physical therapy [26] [27]. Measured outcomes are pain through visual analogue score (VAS), functional status (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire), satisfaction assessment (36-item Short Form Health Survey (SF-36) questionnaire), and Euro-Qol-5D and Knee Pain Scale (KPS) questionnaire [27]. The most frequent outcomes used for assessment are WOMAC in the first place and VAS score in the second place, after WOMAC [27]. Prolotherapy has a significant impact on functional status and ROM improvement and pain reduction during different periods of follow-up [23]. Prolotherapy is associated with more significant results in comparison with control groups such as saline or lidocaine group [23] [27]. It has been shown that the effects of prolotherapy are long-term and could remain after 12 months or more after injection [22] [23]. Some studies reported sustained outcomes of prolotherapy even after 3.5 years [22]. Prolotherapy injec-

tion also has indicated promising results in management of OA complications in carpometacarpal joints in fingers. Long-term follow-up shows improvement in pain scoring scales and flexion ROM in the hand joints [17] [18] [19] [28] [29] [30] (**Table 2**).

6. Tendinopathy

Tendinopathy is defined by a triad of pain, swelling, and articular dysfunction in the affected site [31]. It involves a large variety of disorders, including rotator

Table 2. Prolotherapy in osteoarthritis (Reeves and Hassanein, 2000, Rabago, Patterson *et al*., 2013, Sert, Sen *et al*., 2020, Sit, Wu *et al*., 2020).

Authors/ publication year	Sample characteristics and size	Study groups	Injection protocol	Measured outcomes	Follow up intervals	Result
Sit R.W.S. *et al*., (2020) [28]	Patients with Knee OA (n = 76)	Intervention: Intra-articular dextrose 25% injection (n = 38) Control: normal saline injection (n = 38)	Injection at 0, 1, 2, and 4 months; under ultrasound guidance	1. Pain (VAS score) 2. Knee function (WOMAC) 3. Quality of life (EuroQol-5D)	At 16, 26, and 52 weeks	Significant improvement in pain, WOMAC score, and quality of life in the prolotherapy group compared to saline injection at 52 weeks
Sert A.T. *et al*., (2020) [30]	Patients with refractory chronic knee pain grade 2 or 3 OA (n = 66)	Prolotherapy: Intra articular 25% and extra-articular 15% dextrose injection and exercise (n = 22) Saline group: normal saline injection and exercise (n = 22) Control group: only exercise (n = 22)	Three sessions in 3-week intervals, Intra and extra-articular anatomic landmark-based injection	1. Pain and stiffness (VAS score) 2. Knee function (WOMAC) 3. Quality of life (SF-36)	At 6 and 18 weeks	More significant reduction in pain and WOMAC score in the dextrose group at 18 weeks Quality of life improvement in the dextrose group
Rabago D. *et al*., (2013) [29]	Patients with knee OA of more than three months' duration (n = 90)	Prolotherapy: Intra articular 25% and extra-articular 15% dextrose injection and exercise (n = 30) Saline group: normal saline injection and exercise (n = 29) Control group: only exercise (n = 31)	Injection at 1, 5, and 9 months; intra and extra-articular injection using palpation method	1. Pain (KPS score) 2. Knee function (WOMAC) 3. Participant satisfaction	At 5, 9, 12, 26, and 52 weeks	Significant improvement in pain and WOMAC score in the prolotherapy group at 52 weeks
Reeves K.D. *et al*., (2000) [17]	Patients with active hand OA (n = 27)	Intervention: dextrose 10% injection (n = 13) Control: xylocaine injection (n = 14)	Injection at 0, 2, 4 months; medial and lateral aspects of each affected joint	1. Pain at rest, with joint movement, with grip (VAS score) 2. Flexion ROM	6 months after first session	More significant improvement in outcomes in prolotherapy group compared to control

cuff tendinopathy, lateral epicondylitis, Achilles tendinopathy, plantar fasciitis, Osgood Schlatter, and hip adductor tendinopathy. Tendinopathies are now considered non-inflammatory conditions resulting from collagen destruction, connective tissue growth, and neovascularization [32]. The strongest data supporting prolotherapy injection's efficacy in treating chronic musculoskeletal conditions is extracted from the overuse tendinopathy problem studies [2]. Injections are performed by inserting a needle directly into or alongside the damaged ligament and tendons [5] [6]. Pain reduction and functional improvement have been reported as major outcomes of prolotherapy in tendinopathies [15] (**Table 3**).

6.1. Rotator Cuff Tendinopathy

Rotator cuff tendinopathy is chronic overuse tendinopathy that is determined by pain and weakness during shoulder movements of external rotation and elevation Shoulder pain is categorized as the third common cause of musculoskeletal pain, and tendinopathy of rotator cuff is the most common generator of that pain [8]. There is no consensus on the optimal treatment utilized for rotator cuff tendinopathy. Many typical treatments have been proposed, including exercise therapies, oral anti-inflammatory drugs, interventional therapies, and surgical procedures [8] [33]. Exercise therapy is generally counted as the first treatment choice in patients with impingement symptoms [34]. However, these exercises are often supplemented by adjunct therapies such as injection of corticosteroids, platelet-rich plasma, prolotherapy solutions, and hyaluronic acid. Corticosteroid is the most common substance in injections, but its long-term application is not recommended regarding to the deleterious effects that it can has on tendon integrity and further surgical outcomes [34]. Corticosteroid adjuvant therapy can be replaced by other injection therapies, such as prolotherapy. During the past decades, there has been emerging evidence in the effectiveness of prolotherapy for treating rotator cuff tendinopathy. They include various injection protocols and techniques to strengthen rotator cuff tendons, improve shoulder function and reduce pain. Initially, a landmark-based approach was performed for injecting prolotherapy solution; however, as we move forward, more accurate injections have been performed using ultrasound as a guide [8]. Dextrose injection in Rotator cuff tendinous structures results in a short-term improvement of pain, functional status, and ROM and is associated with compelling long-term follow-up results [8]. In long-term evaluation, prolotherapy has more significant effects than placebo injection on pain reduction [34]. Although, investigations suggest prolotherapy as an effective treatment, especially when performed through multiple-site injection techniques and in higher concentrations [33]. Compared to arthroscopic surgery techniques, the rate of complications is lower in prolotherapy. The variable results in prolotherapy studies may be related to the heterogeneity of treatment protocols varying in dextrose concentration, volume of injection, number of injection sites and injection intervals for rotator cuff tendinopathy [8] [33] [34] [35].

Table 3. Prolotherapy in tendinopathies (Maxwell, Ryan *et al*., 2007, Topol, Podesta *et al*., 2011, Yelland, Sweeting *et al*., 2011, Kim and Lee, 2014, Seven, Ersen *et al*., 2017, Ersen, Koca *et al*., 2018, Ahadi, Esmaeili Jamkarani *et al*., 2019, Yelland, Rabago *et al*., 2019, Akcay, Gurel Kandemir *et al*., 2020, Mansiz-Kaplan, Nacir *et al*., 2020, Nakase, Oshima *et al*., 2020, Asheghan, Hashemi *et al*., 2021, Raissi, Arbabi *et al*., 2021, Wu, Tu *et al*., 2022).

Authors/ publication year	Sample characteristics and size	Study groups	Injection protocol	Measured outcomes	Follow up intervals	Result
Seven M.M. *et al*., (2017) [35]	Patients with chronic rotator cuff lesions and symptoms longer than six months (n = 120)	Intervention: dextrose 25% injection and exercise (n = 60) Control: only exercise (n = 60)	Three sessions weekly for 12 weeks; under ultrasound guidance	1. Pain (VAS score) 2. Function and Disability (SPADI, WORC) 3. Shoulder ROM 4. Patient satisfaction	3, 6, 12, 24 weeks	Significant improvements over baseline, as measured by the VAS, SPADI, WORC index, and shoulder range of motion in both groups, between-group difference, is significant in the dextrose group
Yellend M. *et al*., (2019) [36]	Participants with lateral epicondylalgia of at least six weeks' duration (n = 120)	Prolotherapy: dextrose 20% injection (n = 40) physiotherapy (n = 40) prolotherapy and physiotherapy combination (n = 40)	Prolotherapy: 4 sessions, monthly intervals; physiotherapy: weekly for 4 sessions Palpation method	1. Function (PRTEE and the participant's perceived Global Impression of Change (GIC))	6, 12, 26, 52 weeks	Significant improvements compared with baseline status for all outcomes and groups, but no significant differences between groups at 52 weeks
Ahadi T. *et al*., 2019 [37]	Patients with at least three months of signs and symptoms of lateral epicondilosis (n = 33)	Prolotherapy group: dextrose 20% (n = 17) Shock wave group: (n = 16)	One injection in the prolotherapy group; under ultrasound guidance, Three sessions of shock wave therapy at weekly intervals	1. Pain (VAS score) 2. Function (quick-DASH) 3. Grip strength (using a dynamometer) 4. Pressure pain threshold (PPT)	4 and 8 weeks after treatment	VAS and Quick DASH had significantly more improvement in the shock wave group after 4 and 8 weeks. both groups were similar regarding grip strength and PPT
Akcay S. *et al*., (2020) [39]	Patients with resistant pain at the lateral side of the elbow lasting minimum of 3 months (n = 60)	Intervention: dextrose 15% injection (n = 30) Control: normal saline injection (n = 30)	Injection at 0, 4, and 8th week; anatomic approach	1. Pain (VAS score) 2. Function (PRTEE, DASH) 3. Pain-free grip strength	4, 8, 12 weeks	Significant improvement in all scores during the study in both groups; more significant PRTEE-T and VAS rest improvement at dextrose group in 4th week

Continued

Yellend M. *et al*., (2011) [6]	Patients with painful mid-portion Achilles tendinosis (n = 43)	Prolotherapy group: dextrose 20% (n = 14) ELE group: Eccentric loaded exercise (n = 15) Combined ELE and prolotherapy group (n = 14)	4 to 12 sessions; weekly, Palpation method	1. Pain 2. Function (VISA-A) 3. Stiffness 4. Activity limitation	6 weeks, 3, 6, 12 months	Significant increase in VISA-A score at 6 and 12 months and earlier reduction in pain, stiffness, and activity limitation in prolotherapy and combined group;
Maxwell J.N. *et al*., (2007) [57]	Patients with Achilles tendinitis symptoms for more than 3 months (n = 34)	All patients received dextrose 25% intratendinous injection (n = 36)	Injections every 6 weeks until symptom resolution or no improvement was shown; under sonographic guidance	1. Pain at rest, during daily activity, during and after sport (VAS score) 2. Sonographic features (tendon thickness, echogenicity, neovascularity)	Before every injection session, 12 months after treatment completion	Significant reduction in pain scores after hypertonic dextrose injection
Mansiz Kaplan B. *et al*., (2020) [48]	Patients with a diagnosis of plantar fasciitis (n = 60)	Intervention: dextrose 15% injection (n = 30) Control: normal saline injection (n = 30)	2 sessions; every 3 weeks, Under palpation guidance	1. Pain (VAS score) 2. Function (FFI score) 3. Fascia thickness	5, 12 weeks	Significant improvement in pain, disability and fascia thickness in dextrose injection compared to the control group
Asheghan M. *et al*., (2020) [52]	Patients with a diagnosis of plantar fasciitis (n = 59)	Intervention: dextrose 20% injection (n = 30) Control: extracorporeal shock wave Therapy (n = 29)	2 sessions; weekly intervals, Under ultrasound guidance	1. Pain (VAS score) 2. Function (FAAM score) 3. Fascia thickness	6, 12 weeks	Significant improvement in pain, disability, and fascia thickness in both groups, no significant difference between groups
Kim E. *et al*., (2014) [49]	Patients with a diagnosis of plantar fasciitis (n = 21)	Intervention: dextrose 15% injection (n = 11) Control: autologous platelet-rich plasma (n = 10)	2 sessions biweekly, Under ultrasound guidance	1. Function (FFI score)	2 weeks, 2, 6 months	Significant improvement in FFI score and its subcategories (pain, disability, and activity limitation) in both groups with better results in PRP group, no significant difference between groups
Ersen O. *et al*., (2018) [51]	Patients with a diagnosis of plantar fasciitis (n = 50)	Intervention: dextrose 15% injection (n = 26) Control: stretching exercise (n = 24)	3 sessions; every 3 weeks, Under ultrasound guidance	1. Pain (VAS score) 2. function (FFI, FAOS score)	21, 42, 90, 360 days after injection completion	Significant improvement in pain, FFI, and FAOS scores in the prolotherapy group compared to the control group

Continued

Raissi G. *et al*., (2021) [50]	Patients with a diagnosis of plantar fasciitis (n = 44)	Intervention: dextrose 20% injection (n = 22) Control: methylprednisolone and normal saline (n = 22)	Single injection, Under ultrasound guidance	1. Pain (NRS scale) 2. Function (FAAM score) 3. Sonographic features (Fascia thickness, echogenicity)	2, 12 weeks	Significant improvement in pain, FAAM score, and fascia thickness in both groups; the difference was significant in prolotherapy groups at 2 weeks
Nakase J. *et al*., (2020) [55]	Patients of Osgood-Schlatter with recalcitrant knee pain (n = 38) 49 knees involved	Intervention: dextrose 20% injection (25 knees) Control: normal saline injection (24 knees)	Monthly for 3 months, using ultra-sonographic guidance in long-axis image	1. Function (VISA)	1, 2, 3 months	Significant improvement in VISA score; similar results in both groups
Wu Z. *et al*., (2022) [54]	Patients with Osgood-Schlatter disease OSD (n = 70)	Intervention: dextrose 12.5% injection Control: normal saline injection	3 Injections, Ultrasound guidance	1. Function (VISA-P)	3, 6, 12 months	The dextrose group outperformed the control group significantly in VISA-P improvement
Topol G.A. *et al*., (2011) [56]	Patients with Osgood-Schlatter disease having pain for at least 3 months (n = 54) 65 knees	Prolotherapy group: dextrose 12.5% injection (n = 17) Lidocaine group: lidocaine 1% injection (n = 18) No injection group: usual care (n = 19)	Monthly injections for 3 months, Starting from the most distal part of the pain approaching proximal parts	1. Sport inhibition and sport-related symptoms (NPPS; unaltered sport and asymptomatic sport)	3, 6, 12 months	After 12 months, asymptomatic sport was more common in the dextrose group than two others

6.2. Lateral Epicondylitis

Lateral epicondylitis (tennis elbow) is a painful enthesopathy at the common extensor tendon in the elbow [36]. The disorder usually develops due to repetitive and intensive use of hand extensor muscles [37]. It is commonly observed in industrial workers and tennis players [38]. The condition occurs when normal tendon repair process fails to be completed, which leads to tendon degenerative changes and micro tears. The effect of local inflammation in pathology is slight [36]. Although most cases are self-limited and resolved between 6 to 12 months, 20% of cases became chronic and resistant to usual care [38]. Treatment options include operative and non-operative therapies. Physiotherapy and exercise-based rehabilitation are the primary choices for treatment. Second-line interventions include corticosteroid injection, shock wave therapy, braces and analgesics, and biological treatments [38]. Prolotherapy is a biological therapy that has shown promising results in pain improvement and functional assessment in terms of lateral epicondylitis treatment. Prolotherapy is widely compared with

saline injection as a control group. Injection for the control groups is performed using the same technique of prolotherapy injection. It is hypothesized that the control injection can have a therapeutic effect by triggering cellular rupture and local bleeding [39]. There is no consensus on the number of treatment sessions, frequencies, concentrations, and dosages of the solution, and the injection techniques. The prolotherapy solution comprises hypertonic dextrose alone or in a mixture with other irritant substances, including sodium morrhuate, glycerin, or phenol. The concentration ranges from 10% to 25%, with 20% as the most frequent concentration. Treatment sessions widely vary in number and frequency. In most cases, one or more therapeutic sessions, with a mode of three, are accomplished for each patient every three or four weeks. In some studies, practitioners used peppering techniques for injection, while in other studies, they didn't. The injection can be appliedto the points of tenderness around the elbow or, more commonly, into the epicondyle region and adjacent areas such as supracondylar ridge, annular and radial collateral ligament, and insertion of the extensor carpal muscles [39] [40]. Frequently measured outcomes include pain (VAS score), functional status of the elbow measured through disabilities of the arm, shoulder and hand (DASH)and The Patient-Rated Tennis Elbow Evaluation (PRTEE) questionairres, and handgrip strength. Different studies indicated that prolotherapy injection could significantly improve all of the mentioned outcomes [32] [37] [39]. Some studies reported that in comparison with other interventions, prolotherapy had significant effects on pain reduction and functional improvement in medium and long-term follow-up, while in the short-term, it doesn't accompany substantial results [40].

6.3. Achilles Tendinopathy

Achilles tendinopathy is the most frequent Achilles-related disorder in athletes and the general population [41]. The condition involves increased tendon thickness, decreased vascularity, and chronic tendinitis. Patients present with local pain and swelling over a specific area of a thickened tendon. Foot range of motion may be affected by decreased plantar flexion. Mid-portion Achilles tendinopathy and insertional Achilles tendinopathy are two major types of the disorder [42]. Various therapeutic modalities for Achilles tendinopathy include immobilization with night splints, physical therapy and eccentric loading exercises, shockwave therapy, nitrate oxide, cryotherapy, physiotherapy, and injection therapy [41]. Eccentric loading exercise (ELE) is considered a standard conservative treatment with promising results [6]. Prolotherapy can be used alone or as an additive to ELE treatment. The injection is performed at each tender point, usually located in the anterolateral and anteromedial border of the tendon and on the most posterior aspect of the tendon 2 - 7 cm away from the insertion point [41]. Treatment duration will be until the pain relief is achieved. Studies demonstrated that prolotherapy injection has more significant effects than eccentric loading exercise on short-, intermediate-, and long-term pain. It

is also indicated that a combination of prolotherapy and ELE resulted in earlier stiffness reduction and activity improvement [41]. Some studies denied the beneficial therapeutic effect of prolotherapy alone when that doesn't accompany eccentric loading exercises. Improvement in Victorian Institute of Sports Assessment—Achilles score (VISA-A) score increased vascularity, and reduction in tendon thickening can be expected as a result of prolotherapy injections in Achilles tendinopathy [43].

6.4. Plantar Fasciitis

Plantar fasciitis is one of the most common causes of heel pain, associated with a high burden of disability [44]. The condition affects approximately 10% of the population and is more prevalent among runners and middle-aged people [45]. Clinical manifestation involves pain alongside the calcaneal enthesis early in the morning and during the first steps after prolonged standing or sitting [46]. Ethiopatology is characterized by collagen degeneration at the fascia attachment point due to micro tears resulting from overuse tendinopathy [47]. Diagnosis of plantar fasciitis is based on history and clinical evaluation, although ultrasonography can be used as a further diagnostic instrument in challenging cases. Plantar fascia thickness greater than 4 mm and the presence of hypoechogenic areas are sonographic features supporting the diagnosis of plantar fasciitis [48]. Common conservative therapies, including nonsteroidal anti-inflammatory drugs, stretching exercises, arch supports, dorsiflexion night splints, extracorporeal shockwave therapy (ESWT), physical therapy, and injection therapies considered first-line treatment [48]. The recovery rate is 70% - 80% in conventional therapies but nearly 10% of patients remain recalcitrant to treatment [44] [49]. Recent complementary treatment options such as ESWT and injection therapies showed compelling results in treating chronic and resistant cases. Prolotherapy is administered to improve the patient's condition. Prolotherapy could be performed in one or more sessions, frequently in three sessions. Patients receive prolotherapy agents in a regular weekly order, usually every three weeks [46] [47] [48] [50] [51]. Studies reported that repeated injections are associated with the most accurate and effective results [51]. A concentration of dextrose 15% or 20% is frequently used [48] [52]. Injection is performed under palpation guidance or ultrasound guidance. It is recommended to use the ultrasound method, regarding its functionally better outcomes. Although studies determine that the palpation method is associated with a higher rate of disease recurrence [51]. In the ultrasound method, an ultrasound probe is placed over the fascia to reveal the thickness and echogenicity of different parts. A needle is inserted medially, perpendicular to the long axis of the transducer, approaching the most thickened and hypoechogenic area under sonographicguidance [49] [51]. In the palpation method, the injection can be administered in various techniques, including needle insertion into the most tender point of the heel [47] or injection at five different points of the fascia, including the attachment point of plantar fascia at

heel (medial and lateral), at metatarsal bones (top of the first and fifth metatarsus), and at the middle part of the fascia [48] Peppering technique is considered in many injections [48] [49]. Corticosteroid injection, normal saline injection, platelet-rich plasma (PRP) injection, ESWT, and stretching exercises are common control groups used to compare prolotherapy effects with other procedures. Measured outcomes are categorized into three different classes, including pain assessment during rest and activity through VAS score, and NRS (numeric rating scale), functional assessment (foot functional index (FFI), foot and ankle ability measure (FAAM), The American Orthopedic Foot and Ankle Score (AOFAS), and sonographic features (plantar fascia thickness, echogenicity). Studies indicate that dextrose prolotherapy is associated with significant improvement in pain (at rest and activity), FFI and FAAM scores, and plantar fascia thickness and hypoechogenicity in patients with plantar fasciitis [47] [48]. Compared with non-active treatments (normal saline injection and exercises), prolotherapy is significantly better at improving short-term pain [53]. Prolotherapy has been more effective than corticosteroid injection in long-term outcomes, while corticosteroid injection demonstrated more significant improvements in short-term evaluation [44]. Results didn't significantly differ between ESWT groups and prolotherapy [52]. PRP injection is more effective than dextrose prolotherapy in FFI score improvement [49].

6.5. Osgood-Schlatter

Osgood-Schlatter disease (OSD) is a common cause of chronic knee pain associated with disabilities in daily work and sport participation [54]. Nonsteroidal anti-inflammatory drugs, knee paddling, and physical and surgical therapies are usual conservative treatments for OSD. Most patients respond to conventional therapies; however, some remain resistant [55]. Only a few studies aimed to assess the effectiveness of prolotherapy on Osgood-Schlatter, making it difficult to reach a reliable conclusion. Injections performed under sonographic guidance or based on anatomical landmarks. Deep infrapatellar bursa, infrapatellar fat pad, and superficial infrapatellar bursa are frequent injection sites when ultrasound guidance is applied [55]. Monthly injections in a total period of three months are a usual method [55] [56]. Hyperosmolar dextrose prolotherapy can result in a rapid asymptomatic sport participation, greater pain reduction during activity, and significant improvement in functional status which is measured by Victorian Institute of Sports Assessment—Patellar Tendon (VISA-P) score [2] [54] [55] [56].

7. Contraindication

Absolute contraindications are similar to any other type of injection, including the presence of Cellulitis, Septic arthritis, Local abscess, and any other sign or symptom of the skin or joint infections, suffering active rheumatologic disorders, taking immunosuppressive drugs, and being allergic to corn. Relative con-

traindications includeacute gouty arthritis, acute fracture, bleeding disorders, taking anticoagulants, and patients revealing any sign of infection. According the fact that injecting irritant substances could cause bleeding and hematomas at injected area, this is assumed that prolotherapy in patients who are taking anticoagulants could lead to major bleeding complcations and should be avoided, excessive additional studies will be needed to prove this hypothesis [1] [4].

8. Post-Injection Precautions

- Patients will be advised to use acetaminophen with or without codeine in order to relieve post-injection discomfort and flare (500 - 650 mg every 4 hours as needed) [4] [57] [58].
- Ice massage for 5 - 10 min on the injection site is recommended after the procedure, the mechanism of effect is controversial [14].
- Participants must be discouraged from taking any nonsteroidal anti-inflammatory drugs (NSAIDs) after treatment sessions, it is hypothesized that NSAIDs interfere with beneficial effects of growth factors release by inhibiting prostaglandin pathway, further studies are needed to confirm this [57].
- Painful and weight-bearing activities must be avoided for 2 - 3 days after injection, and relative rest is recommended instead [59].

9. Adverse Effects

Prolotherapy seems to be a safe procedure with limited side effects. However, some patients may experience a mild increase in pain and stiffness right after injection, as the most common side effect of prolotherapy. This could be explained by the prolotherapy mechanism of action, as stated before, the procedure can induce acute inflammation in the injured area which can lead to some undesirable effects including pain and discomfort. This mentioned inflammatory behavior does not raise concerns about whole nother serious adverse effects, as *in vivo* studies indicate a limited inflammatory response which regularly proceeds to reparatory responses instead of causing crippling problems. Headache, nausea and diarrhea are some of the other reported complications. A sense of fullness and occasional numbness, mild bleeding at the injection site, bruising, and developing post-injection flares within the first 72 hours after injection which usually subside in one or two days are other common adverse effects. Serious side effects are rare and include lightheadedness and spinal headaches, and nerve damage, allergic reactions, and infections. Neurologic impairment has been reported during perispinal injection with highly concentrated dextrose, which is linked with the methods that are no longer used in practice [1] [4] [11] [60].

10. Conclusion

Prolotherapy is a regenerative therapeutic method which is consisted of injecting irritant solutions into the injured areas. Hyperosmolar dextrose is the most common agent. Administering proliferant substances can accelerate the tissue

healing process by inducing cellular rupture and inflammatory response, leading to collagen deposition, cellular growth factor production, and regeneration. Although most of the chronic musculoskeletal conditions are considered non-inflammatory to date, resulting from collagen degeneration and connective tissue replacement. Regarding to the mentioned ethiopathology, prolotherapy has recently received notable attention in treating orthopedic musculoskeletal pain problems. There is no consensus on treatment protocol and various differences have been reported in substance dosage and concentration, injection intervals, needle size, site of injection and technique. Promising results have been shown in the term of pain and functional improvement when prolotherapy is administered for low back pain, osteoarthritis, and tendinopathies. The effectiveness is fully comparable with other treatment options. According to its reparative functions, this is suggested that dextrose prolotherapy can be utilized as an effective alternative therapy in treating chronic wounds. Although, more investigations are needed to confirm this hypothesis. In conclusion, prolotherapy is an effective, inexpensive, and available therapeutic option with limited side effects, which is associated with favorable results in different musculoskeletal conditions.

Author Contributions

All the authors have accepted responsibility for the entire content of this manuscript and approved submission.

Conflict of Interests

All the individuals who contributed to this manuscript are listed as authors. The authors have no competing interests to declare that are relevant to the content of this article.

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