

# Regenerative Injection Therapy (Prolotherapy) for Hip Labrum Lesions: Rationale and Retrospective Study

Ross. A. Hauser<sup>\*,1</sup> and Amos Orlofsky<sup>2</sup>

<sup>1</sup>Caring Medical Rehabilitation Services, 715 Lake Street, Suite 600, Oak Park, IL 60301, USA

<sup>2</sup>Albert Einstein College of Medicine, 1300 Morris Park Avenue, F717ND, Bronx, NY 10461, USA

**Abstract:** *Background:* Acetabular labral tear is a debilitating condition for which there are few effective non-surgical treatment options. A number of studies in humans and in animal models suggest that the labrum may have a capacity for spontaneous healing, and that therapies that seek to exploit and facilitate this process may be beneficial. Regenerative injection therapies have shown promise in the treatment of several musculoskeletal disorders, but have not previously been applied to labral tear.

*Methods:* We present an initial case series of 19 patients with labral tear that were treated in our clinic with intra-articular injections of hypertonic dextrose. Patient-reported assessments were collected by questionnaire between 1 and 60 months post-treatment (mean = 12 months).

*Results:* All patients reported improvements in pain relief and functionality. Patients reported complete relief of 54% of recorded symptoms. Improvements did not show dependence on the time between treatment and follow-up. No adverse events were reported.

*Conclusions:* Regenerative injection therapy (prolotherapy) for acetabular labral tear appears to be a safe and potentially efficacious procedure that merits further investigation as a non-surgical option.

**Keywords:** Acetabular labral tear, chronic pain, regenerative injection therapy, prolotherapy, self report.

## BACKGROUND

Chronic pain of the hip or groin is a common complaint in sports medicine. Hip and groin injuries account for 2 to 9 percent of sports-related injuries [1-7]. In a prospective cohort study, 14 percent of all injuries to European soccer players were to the hip or groin [8]. The time to functional recovery for athletes with these injuries is highly dependent on the injury type. For players in the National Football League, the mean time lost to all hip injuries was 12 days; however, for intra-articular hip injuries, including fracture, subluxation/dislocation and labral tear, the time lost was 94 days [7].

The awareness of labral tears as a potential source of hip and groin pain has grown in recent years due to advances in diagnostic imaging. In a study of 18 sports patients with groin pain, 22 percent had tears of the labrum [9]. In a study of 436 patients with mechanical hip pain, arising in most cases from trauma, 55 percent had labral tears [10]. In a series of 412 arthroscopies in patients with disabling hip pain, labral tear was the major diagnosis in 18 percent [11]. Notably, 74 percent of the labral tears in this study were associated with a non-traumatic etiology, including a degenerative etiology in 45 percent [11], suggesting a

potential causative role for labral tear in a broad spectrum of hip pain conditions. Cadaveric studies indicate that acetabular labral tears may accumulate to a high frequency in the general population: 52 percent of 54 cadaveric acetabula, with a mean age of 78 years, contained one or more labral tears [10]. In spite of the high frequency of labral tears, specificity of tears for hip pain has been detected: in a study of 176 patients with unilateral hip pain, 158 had labral tears in the symptomatic hip, and of these only 20 had a contralateral tear in the asymptomatic hip [12].

In addition to the symptomatic complaints of pain and functional impairment, labral tears may be important for degenerative changes in the hip joint. McCarthy *et al.* detected chondral damage in 73 percent of patients with labral lesions, and observed that chondral damage was more severe in these patients [10]. In 94 percent of these cases, the chondral damage and labral lesion occurred in the same acetabular region. These authors also observed that full-thickness erosion of articular cartilage often occurred in direct continuity with a labral tear, leading them to propose that labral tears represented an early stage of degenerative processes culminating in osteoarthritis [13].

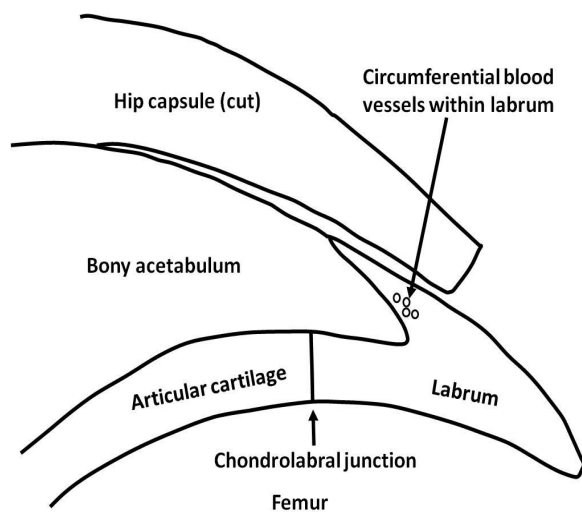
The potential impact of labral pathology on the long-term health of the hip joint, coupled with a growing appreciation of the contributions of the labrum to joint function, has led to increased emphasis on management approaches that maximize labral preservation. Patients are often initially treated conservatively, followed if necessary by surgical treatment. Surgical approaches based on labral resection

\*Address correspondence to this author at the Caring Medical Rehabilitation Services, 715 Lake Street, Suite 600, Oak Park, IL 60301, USA;  
Tel: 708-848-7789; Fax: 708-848-7763;  
E-mail: [JonesM@caringmedical.com](mailto:JonesM@caringmedical.com)

have in recent years been supplemented by more preservative options that involve labral repair or reconstruction [14]. Preservative surgery is not optimal for many patients, however, and it would be valuable to develop preservative non-surgical options that enhance conservative treatment to provide satisfactory outcomes. Regenerative injection therapies have shown promise for functional restoration in a number of musculoskeletal complaints [15], but have not been explored for acetabular labral tears. Here we review and discuss this issue and present initial observations in a group of patients treated with regenerative injection (prolotherapy) for labral tears.

### ACETABULAR LABRUM: ANATOMY AND FUNCTION

The labrum is a ring of tissue that runs circumferentially around the bony rim of the acetabulum. The articular margin of the labrum is directly apposed to the articular cartilage lining the acetabular surface (Fig. 1).



**Fig. (1).** Anatomic features of the acetabular labrum (adapted from Seldes *et al.* [16]).

The labrum is not a well vascularized tissue [16-19]. The external third of the labrum, adjacent to the capsular surface, contains clusters of blood vessels that travel circumferentially [16, 17, 19] (Fig. 1). No vessels are observed in the internal two thirds of the tissue. These studies were carried out, however, in cadavers aged > 40 years, with a mean age much greater. The fetal acetabular labrum has been shown to be abundantly vascularized [20], similar to the perinatal meniscus [21]. The meniscus displays a gradual age-dependent loss of vascularity, progressing from the internal to the external surface [21]. By analogy, it is possible that the acetabular labrum of younger subjects, including many patients with traumatic labral pathology, is more completely vascularized than the cadaveric subjects that have been reported.

The mechanical function of the labrum is not completely understood. Since the labrum increases acetabular coverage by 28 percent [22] and has biomechanical properties comparable to the meniscus [23], it may serve to enhance joint stability. A stabilizing role is supported by cadaveric studies [24,25]. The labrum may also contribute to joint stability by sealing the joint to maintain intra-articular hydrostatic pressure [26]. This sealing function may also be

important to maintain adequate joint lubrication and minimize the friction generated by movement of the femoral head [27]. In addition to its biomechanical functions, the detection of several kinds of proprioceptive nerve endings in the labrum suggests a potential role in proprioception [28].

### DIAGNOSIS AND CLINICAL PRESENTATION OF LABRAL TEARS

Radiographic imaging has come to play a central role in the diagnosis of acetabular labral tears, although arthroscopy remains the gold standard. Plain radiographic images of hips with labral tears are typically normal, while plain MRI can detect labral tear, but with only 30 percent sensitivity and 36 percent accuracy, when compared to arthroscopy [29]. Magnetic resonance arthrography (MRA), in which MRI is enhanced by the intra-articular injection of gadolinium, has become the modality of choice for evaluation. The most recent studies find that MRA has a sensitivity of 93 - 100 percent and an accuracy of 93- 96 percent [30-32]. Meta-analysis supports the superior reliability of MRA to plain MRI, although variability and the use of small datasets were noted [33]. The accuracy of MRA may be dependent on training: for both MRA and plain MRI, the accuracy of labral tear diagnosis was 85 percent for musculoskeletal radiologists and 70 percent for general radiologists [34]. The need to distinguish between labral tears and normal variants of sublabral recesses represents a potential pitfall that may limit the accuracy of MRA [35]. Disadvantages of MRA include limited availability and morbidity due to postprocedural pain [36]. CT arthrography provides an alternative [37], although it may be inferior to MRA [38].

While radiographic evaluation is valuable for differential diagnosis of labral tear against other potential sources of hip pain, diagnostic injection of the hip with local anesthetic is sufficient for discrimination of referred pain from pain generated by hip pathology. Pain relief following anesthetic injection is diagnostic for the hip as pain generator with a sensitivity of 88 - 100 percent and a specificity of 81 - 100 percent [39-41], implying high sensitivity for labral tear, though with likely lower specificity than MRI or MRA. The availability of this simple and inexpensive procedure suggests a potential advantage of non-surgical treatments, such as regenerative injection therapies. For these low-morbidity therapies, which potentially target both the labrum and other intra-articular lesions, specific diagnosis of labral tear, requiring imaging, may be less critical than accurate diagnosis of the hip generator.

Significant functional limitations are associated with labral tears. In a retrospective review by Burnett *et al.* of 66 consecutive cases of arthroscopically confirmed labral tear, patients reported limitation of walking distance to 6 blocks or less (36 percent), inability to sit for more than 30 minutes (31 percent) and difficulty in donning shoes and socks (37 percent) [42].

Misdiagnosis is frequent. In the study of Burnett *et al.*, the mean interval from onset of symptoms to definitive diagnosis was 21 months [42]. Thirty-three percent of the patients had been given a total of 18 different diagnoses other than labral tear. Thirty-nine percent had received recommendations for narcotic medication, and surgical intervention at sites other than the hip had been

recommended to 17 percent. Six percent had actually received these surgeries, without obtaining relief. It is conceivable that the lack of cost-effective, non-invasive options for the management of labral tear is an exacerbating factor in the misdiagnosis of these patients.

## TREATMENT

Regimens of conservative management unfortunately do not provide lasting relief in most cases [43]. These treatments incorporate the concept of facilitating the spontaneous healing of the labral lesion. The failure of conservative approaches is therefore likely related to the limited healing capability of this poorly vascularized tissue, which is further discussed below. It has been proposed that manual procedures, including hip joint tractional maneuvers, may facilitate healing [44]. Studies in support of such approaches are lacking. In theory, treatments that enhance the vascularity or the healing activities within labral tissue, as well as in adjacent involved cartilage, hold promise for the improvement of conservative therapy and the avoidance of surgery. We will later discuss regenerative injection therapy as an approach of this kind.

Patients who fail conservative treatment may be offered arthroscopy, which has become the cornerstone of interventional therapy for labral tear. Initially, surgical treatment, whether open or arthroscopic, focused on simple excision (debridement) of torn labrum. Growing appreciation for the functional importance of the labrum, coupled with concern over the potential contribution of labral defects to eventual osteoarthritic progression, has led to a new emphasis on labral preservation and the development of techniques for arthroscopic repair of labral tears [45, 46]. Typically, detachment of the labrum is followed by acetabular resection to correct femoroacetabular impingement (FAI) and subsequent refixation of the labrum to the rim [47]. A limitation of the repair/refixation procedures is that many labral tears are not eligible for this procedure: these include tears with cleavage planes perpendicular to the margin (radial flaps), which are very frequent [48], as well as tears with degeneration, calcification or ossification of the tissue [45, 46, 49]. In addition, the efficacy of repair for maintaining the sealing function of the labrum may be dependent on the suturing procedure chosen by the surgeon [14]. A recent systematic review of studies comparing labral resection and labral repair [50] concludes that labral preservation appears to produce slightly better outcomes, and one of these studies has been updated to 3.5 years of follow-up with similar outcome [51].

A systematic review of studies of patient satisfaction following arthroscopy for labral tear found that good-to-excellent results were observed in 68 – 93 percent of cases [52]. Positive outcome was strongly dependent on the degree of cartilage degeneration observed intraoperatively: fewer than half of patients with arthritic changes or chondromalacia obtained good results [13, 53]. None of these studies contained controls or a cohort design, and none had a mean follow-up period greater than three years. A more recent study of 97 patients treated for FAI with labral tear had a mean follow-up of 58 months and reported an

increase in Christensen nonarthritic hip score from 55 to 84 [54].

Major complications from hip arthroscopy were uncommon in a recent prospective study [55]. However, the authors noted that the extent of iatrogenic damage to chondral or labral tissue was difficult to ascertain. They suggested that the 18 percent of cases in which access was considered difficult might represent an upper limit for iatrogenic damage. Although described by many authors, labral puncture or chondral scuffing during arthroscopy are not usually included among complications and are likely to be underreported [56, 57]. Badylak *et al.* reported that iatrogenic labral puncture occurred in 20 percent of cases in a consecutive series of 250 hip arthroscopies [58]. Ilizaliturri *et al.* observed 68 cases of iatrogenic cartilage lesions and one labral puncture in a consecutive series of 100 arthroscopies [59]. While neither of these two studies observed any effect of the iatrogenic injuries on short-term outcome [58, 59], the long-term consequences with respect to potential iatrogenic osteoarthritis or other pathologies are unknown. Labral resection is also a potential source of iatrogenic illness, since cadaveric studies indicate that resection, in contrast to labral repair, results in cartilage consolidation and increased cartilage strain, perhaps due to compromise of joint sealing and pressurization [26].

## NEW DIRECTIONS IN LABRAL TEAR TREATMENT

The development of arthroscopic procedures has been beneficial to large numbers of patients suffering from hip pain. The limitations of these procedures, however, are a stimulus to the exploration of alternative modalities. In spite of its benefits, arthroscopy remains an expensive, invasive procedure whose long-term efficacy and potential iatrogenic effects are not well understood. Many patients with labral tear are not considered eligible for labrum-preserving repair, and labral resection in these patients may result in long-term compromise of labral functionality and health of the hip joint. Finally, patients with cartilage degeneration derive limited benefit from arthroscopy.

A potential alternative to surgery is to exploit and amplify spontaneous healing and repair processes in the hip joint. Current trends in arthroscopy already point in this direction. Labral repair embodies the concept that approximation of cleaved labral fragments may lead to healing and restoration of an intact structure. Labral refixation to the external acetabular surface is founded on the expectation that at least the external third of the labrum is sufficiently vascularized to support a process of healing and bonding to the acetabulum. This expectation is supported by observation of partial healing of an incised and repaired labrum in an ovine model [60]. The authors observed two kinds of healing: 1) a proliferation of fibrovascular scar tissue originating at the capsular labral surface, and 2) formation of new bone at regions of exposed acetabulum. The scar tissue progressed toward the articular labral surface, leaving only a shallow unhealed cleft at the articular side. The authors note that incomplete healing may have been related to the immediate and full weight-bearing permitted to the animals post-surgery. They did not examine spontaneous healing in the absence of arthroscopic repair. These findings

suggest a potential for labral healing that may extend beyond the vascularized region of normal labrum.

These developments raise the question as to whether it is possible to generate beneficial healing responses in the hip joint without recourse to surgical intervention. The rationale for this approach is built on observations of spontaneous healing in disrupted labrum, both in an animal model and in patients. In the sheep model, resection of the superior one third of the labrum, without repair, induced a regenerative process that led to the replacement of the defect with dense fibrous tissue, of similar triangular shape to normal labrum, in 16 of 18 animals, including 5 of 6 animals at 6 weeks, the earliest timepoint examined [61]. The regenerative process included remodeling of subchondral bone, ingrowth of new blood vessels, and apparent penetration of remodeled bone by scar tissue fibers. The new tissue was approximately 130 percent larger in cross-sectional area than control, sham-operated labrum. Healing occurred in spite of the limitation imposed by full weight-bearing post-surgery. The ovine labrum is notable for its histologic resemblance to human labrum, including restriction of vascularity to the capsular layer [60, 61].

Evidence of healing in human labrum was obtained by Seldes *et al.*, who examined labral histology in 55 cadaveric human hips from individuals of unknown symptomatic history [16]. Labral tears were detected in 53 specimens, the majority of which occurred at the chondrolabral junction. Notably, all tears were associated with hypervascularity within the labral substance at the base of the tear adjacent to bone. This was observed even for tears in the internal articular region of the labrum, far from the external capsular layer in which vascularity is normally present. The authors also noted chondrocyte proliferation, as well as hyalinization of labral fibrocartilage along the edges of the defects. These observations strongly suggest the potential for vascular growth and healing responses throughout the human labrum.

The high frequency of labral tear in asymptomatic individuals, implied by the cadaveric studies, has recently been confirmed in a prospective study of 45 volunteers (average age 38 years) [62]. Labral tears were identified in 69 percent of hips by MRI scan. Coupled with the observation of vascular healing responses in cadaveric tears [16], these findings suggest that symptomatic labral tears may represent a subset of tears in which healing responses are suboptimal, perhaps comparable to the two of 18 sheep in which regeneration was not observed [61]. This interpretation provides a plausible conceptual framework for the exploration of regenerative therapy for the diseased hip. The goal of regenerative therapy, in this view, is to enhance the regenerative potential of the labral microenvironment and convert suboptimal responses to the adequate healing that may occur in the asymptomatic population.

## **PROLOTHERAPY FOR MUSCULOSKELETAL REPAIR**

Regenerative injection therapy may be broadly defined as “the injection of growth factors or growth factor production stimulants to promote regeneration of normal cells and tissue.” [15] Within this group of therapies, the term “prolotherapy” (i.e. proliferative therapy) is applied to the administration of irritant or sclerosant substances with the

potential to provoke inflammatory and healing responses. The most common injectants for this purpose are hypertonic dextrose (12 – 25 percent) and sodium morrhuate (0.1 – 1 percent). Anesthetics such as lidocaine are often included in the injectant. The mechanistic basis for the action of these agents is not well defined. In cell culture studies, hypertonic dextrose, the most frequently used injectant, has been shown to enhance the growth factor responsiveness of multiple cell types, including fibroblasts, vascular smooth muscle cells and ligament cells [63-65]. Preclinical studies with sodium morrhuate have demonstrated the anabolic potential of prolotherapy in tendons and ligaments [66-68].

Clinical trials have shown efficacy of hypertonic dextrose for multiple musculoskeletal conditions [69]. Two recent studies, including a randomized controlled trial comparing dextrose injection, saline injection and exercise, have shown efficacy of prolotherapy for improvement of pain and function in knee osteoarthritis [70, 71]. In an RCT of prolotherapy (dextrose + sodium morrhuate) for lateral epicondylitis, Scarpone *et al.* showed significant gains in pain score and grip strength that persisted for at least one year [72]. An RCT carried out by Yelland *et al.* compared dextrose prolotherapy, eccentric loading exercise, or combined therapy for Achilles tendinosis. Prolotherapy as monotherapy, and particularly in combined treatment, provided more rapid reductions of pain, stiffness, and functional limitations [73]. The evidence for efficacy of prolotherapy in low back pain is less consistent: a Cochrane review found five high-quality RCTs [74], two of which had positive findings for prolotherapy in combination with other treatments.

In addition to prolotherapy, the injection of platelet-rich plasma, another form of regenerative therapy, has also shown efficacy in the treatment of musculoskeletal disorders, including knee osteoarthritis and lateral epicondylitis [75, 76].

## **HYPERTONIC DEXTROSE TREATMENT OF LABRAL TEAR: A CASE SERIES**

The evidence that regenerative injection therapy can support connective tissue growth responses and provide clinical benefit with low morbidity in musculoskeletal conditions has encouraged us to explore this therapeutic approach as a cost-effective alternative to surgery for patients with hip pain and labral tear. We describe here our experience with a consecutive series of 19 patients (21 hips) diagnosed with labral tear of traumatic etiology.

## **METHODS**

### **Patients**

This study concerns 19 patients (7 men and 12 women) out of 22 consecutive patients who presented at our chronic pain clinic with pain in the anterior groin, greater trochanter or buttock region. Three of the 22 patients could not be contacted for final interview. The 22 patients represent all the qualifying patients treated with prolotherapy for hip pain at our clinic from mid-2008 through February 2012. Patients were retrospectively excluded from the study if they had other chronic pain or systemic conditions, were taking anti-inflammatory medication, had a history of narcotic use or were under 18 years of age. Patients reported having pain for

a mean of 26 months prior to visit. All had failed conservative management with physical therapy and exercise. At physical exam, all patients had a positive McCarthy sign and/or a positive internal rotation load/grind test. Labral tear was confirmed by MRI or MRA in 15 out of 21 hips. Six patients chose to forego imaging due to financial concerns. The average age of the patients was 50.9 (19 – 84) years. Patient characteristics are summarized in Table 1. This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

**Table 1. Patient Characteristics**

Variable	Mean ± SD
Age (years)	50.9 ± 17.1
Female (%)	63
Duration of pain (months)	25.7 ± 29.1
MRI/MRA performed (%)	71
Surgery previously recommended (%)	63
Number of treatments	4.7 ± 1.9
Duration of treatments (months)	11.9 ± 7.0
Time since last treatment (months)	9.9 ± 8.9

### Intervention

For dextrose prolotherapy, the area to be treated was anesthetized with 5% lidocaine cream and cleaned with hydrogen peroxide and Chloraprep. In all cases, the injectant contained 15% Dextrose, 0.1% Procaine, 10% Sarapin and 2 IU human growth hormone (hGH). Sarapin, a pitcher plant extract, is included in almost all prolotherapy injectants in our clinic due to its long history of reported favorable effects for chronic pain [77, 78]. hGH has reported stimulatory effects on chondrocytes that may facilitate joint healing [79-81], and we routinely include it in prolotherapy injectants for conditions involving cartilaginous or fibrocartilaginous tissue. Hip joints were injected with a total of 50 cc at 38 locations around the hip, including the greater trochanter, intertrochanteric crest, neck of femur, and dorsal ischium. Injected areas included the bony attachments of the ischiofemoral and iliofemoral ligaments, tensor fascia lata, gluteus medius, piriformis, gemellus superior, quadratus femoris, obturator internus, gemellus inferior, and vastus lateralis. The mean number of prolotherapy sessions was 4.8 (1 – 8). The duration of the treatment period was 3 - 24 months (mean 11.9).

### Clinical Outcomes

At final interview, a questionnaire was administered in which patients used a 0 – 10 rating scale (0 = no pain; 10 = crippling/severe pain) to assess pre-treatment and post-treatment pain intensity (at rest, during normal activity and during exercise). Patients also used 0 – 10 rating scales to assess stiffness (0 = no stiffness; 10 = extremely stiff), range of motion (0 = normal motion; 10 = no motion), and crunching (0 = no crunching; 10 = extreme crunching with even slight movement). Multiple choice questions were used to assess pre- and post-treatment ability to walk distances

and ability to exercise. For walking distance, patients chose between the following intervals: < 50 ft; 50 ft - 1 block; 1 block - 0.5 mi; 0.5 mi - 1 mi; no restriction. For exercise ability, patients selected one of five options: no compromise ('able to exercise as much as I want'); mild compromise ('able to exercise greater than 60 minutes, but not as much as desired'); moderate compromise ('able to exercise 30 - 60 minutes'); severe compromise ('able to exercise 0 - 30 minutes'); total compromise ('unable to exercise'). Patients were also asked how many pills they took for their condition pre- and post-treatment.

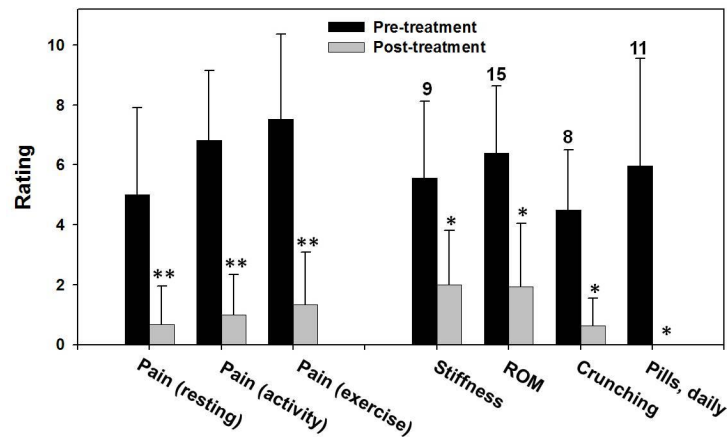
### Statistical Analysis

The distributions for baseline values were non-normal by Shapiro-Wilk test. Post-treatment and pre-treatment values were compared by Wilcoxon two-tailed signed rank test. Differences with *p* values < 0.05 were considered significant.

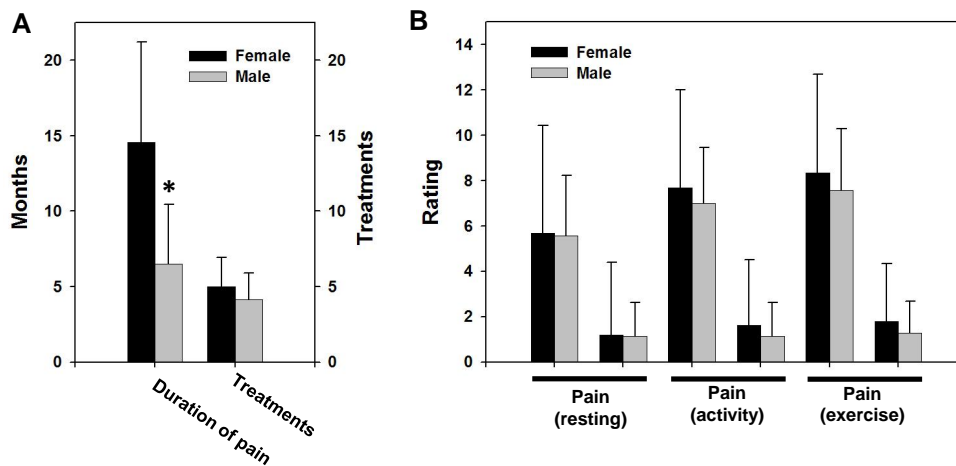
### RESULTS

Patient-reported outcomes were obtained at a mean of 12 months after completion of treatment (range 0 – 60 months). Significant reductions (*p* < 0.001) were observed in pain ratings for pain at rest (mean ± SD of 5.0 ± 2.9 at baseline vs 0.7 ± 1.3 post-treatment), pain during normal activity (6.8 ± 2.3 vs 1.0 ± 1.3), and pain during exercise (7.5 ± 2.8 vs 1.3 ± 1.7) (Fig. 2). Pain ratings in these three categories were reduced to 13%, 15% and 18% of their baseline values, respectively. All patients had reduced pain during normal activity and exercise, and 18 patients had reduced pain at rest. Although female patients presented with a significantly longer history of pain (Fig. 3A), no significant gender difference was observed for the response of pain to treatment (Fig. 3B). Pain reduction did not show any dependence on the interval between treatment completion and patient report (Fig. 4). For stiffness, range of motion, crunching and pill consumption, only patients with non-zero baseline values were analyzed. All patients had non-zero baseline for at least one of these categories, and all but six had non-zero baseline for at least two categories. With the exception of two patients who reported no gain for range of motion, all patients with non-zero baseline for these categories experienced gain. For stiffness, range of motion and crunching, baseline vs post-treatment ratings were, respectively, 5.6 ± 2.6 vs 2.0 ± 1.8 (*p* = 0.01); 6.4 ± 2.2 vs 1.9 ± 2.1 (*p* = 0.0016); 4.5 ± 2.0 vs 0.63 ± 0.92 (*p* = 0.01) (Fig. 2). Notably, daily pill consumption for alleviation of symptoms, the most objective of our patient-reported outcomes, was completely eliminated: none of the 11 patients who reported pill use before treatment reported any pill use post-treatment (*p* = 0.0036) (Fig. 2). No patient reported an adverse result (increased rating) for any outcome. Patient-reported scores are summarized in Table 2.

Patients reported gains in functionality following treatment. All patients who reported walking limitations at baseline experienced improved walking distance. Six of 19 patients (32%) reported inability to walk more than 1 block pre-treatment, while after treatment all patients could walk 0.5 miles and 16 of 19 (84%) reported no limit to walking (Fig. 5). Eighteen of 19 patients with compromised ability to exercise at baseline reported improved ability to exercise post-treatment. Six of 19 patients (32%) reported a complete



**Fig. (2).** Patient-reported quantitative outcomes. Patients reported pain, stiffness, range of motion (ROM) and crunching on a 0 – 10 rating scale. For consumption of medications, the ordinate represents the number of daily pills taken. For pain reports,  $n = 21$  hips (19 patients). For stiffness, ROM, crunching and medications, only reports with non-zero baseline values were analyzed, the numbers of which are indicated above the bars. \*  $p \leq 0.01$ , \*\*  $p \leq 0.0001$  by Wilcoxon signed-rank test.



**Fig. (3).** Gender differences in pain experience and treatment. (A) Gender comparison for duration of pain prior to treatment and number of treatments. \*  $p = 0.016$ . (B) Gender comparison for response of pain to treatment. For each of the three pain categories, the left two bars represent baseline values for patient rating of pain, and the right two bars represent corresponding values after treatment.

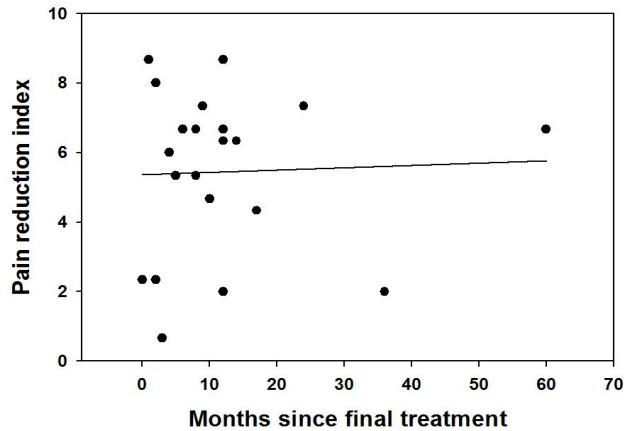
inability to exercise before treatment, and none were capable of unrestricted exercise. After treatment, no patient reported complete compromise and 8 of 19 (42%) regained capacity for unlimited exercise (Fig. 5). No adverse outcomes were reported for functionality.

To estimate the frequency with which patients experienced complete relief from a symptom, we combined all the categories on the questionnaire and observed a total of 136 patient reports of a symptom (i.e. a non-zero value or a degree of functional limitation) at baseline. In 73 of these 136 instances (54%), patients reported complete relief (i.e. the best possible score) post-treatment. Eighteen of 19 patients (95%) reported complete relief of at least one symptom, and the mean number of such reports per patient was 3.8. Eleven out of 19 patients (58%) reported that they discontinued treatment because they were pain-free (Fig. 6).

## DISCUSSION

This case series represents the first report of a prolotherapeutic approach to the treatment of labral pathology. The results of the study were encouraging, as all 19 patients reported pain reduction and all reported improvement in at least one of two functional categories. All patients expressed a positive view of their treatment on the questionnaire. Although we did not follow individual patients at multiple time points, improvements appeared to be stable during at least the first two years post-treatment, as judged by the lack of time dependence for pain reduction. The treatment was well tolerated and no adverse events were observed.

This pilot study has several limitations. In the absence of controls, we cannot conclude that therapy was effective. In addition, we cannot distinguish among the potential effects



**Fig. (4).** Time-dependence of pain relief after treatment. A pain reduction index was calculated for each patient by subtracting the post-treatment from the pre-treatment value for each of the three pain categories, and then obtaining the mean of the three differences. The line on the scatter plot represents a least-squares linear regression.

**Table 2. Patient-Reported Symptom Scores at Baseline and Post-Treatment (1 - 10 Rating Scale).**

	Baseline (Mean ± SD)	Post-Treatment (Mean ± SD)	p Value (Wilcoxon Test)
Pain at rest	5.0 ± 2.9	0.7 ± 1.3	0.0001
Pain during activity	6.8 ± 2.3	1.0 ± 1.3	0.0001
Pain during exercise	7.5 ± 2.8	1.3 ± 1.7	0.0001
Stiffness <sup>a</sup>	5.6 ± 2.6	2.0 ± 1.8	0.01 <sup>b</sup>
Range of motion <sup>a</sup>	6.4 ± 2.2	1.9 ± 2.1	0.0016
Crunching <sup>a</sup>	4.5 ± 2.0	0.63 ± 0.92	0.01 <sup>b</sup>

<sup>a</sup>Only patients with non-zero baseline values included.

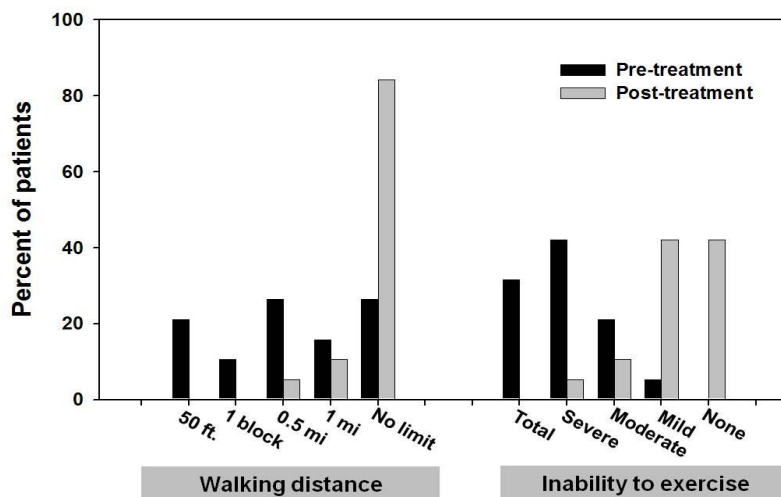
<sup>b</sup>Estimated from tables due to n < 12.

of the several agents injected (dextrose, sarapin, hGH), as well as the potential effects due to needling and fluid injection. It is also possible that some patient gains represent spontaneous improvement. However, the mean duration of symptoms prior to treatment was 24 months, and we observed no time dependence in symptomatic improvement, which for eight patients occurred in 0 – 6 months post-treatment. These findings suggest that much of the gain observed is the result of treatment. Additional limitations include the reliance on post-hoc questionnaires and the paucity of objective outcome measures. The complete absence of pain medication use after treatment provides a degree of objective confirmation of patient benefit. In addition, the expected confounding effect of post-hoc reporting is the exaggeration of gain by inflation of baseline values. However, our data are notable for the high frequency of post-treatment reports of complete symptomatic relief, rather than partial relief from high baseline values, suggesting that post-hoc reporting is not a major confounding factor in the study.

Hypertonic dextrose potentially has multiple effects that may enhance labral healing, including the induction of growth factor production and proliferative responses [63-65], as well as the possible elicitation of inflammatory changes [82] that may promote angiogenic and healing responses. The nature of healing responses in the labrum is still poorly understood, but earlier studies suggest that considerable spontaneous healing occurs [16, 61], and that therapies that focus on amplifying and optimizing this spontaneous process may have merit. Given the poor efficacy of current conservative treatment of labral tear, and the risks, failure rate and expense associated with arthroscopy, regenerative therapy may be viewed as a potential adjunct to conservative management that deserves investigation, both in animal models of labral tear and in expanded and controlled clinical studies.

**CONCLUSIONS**

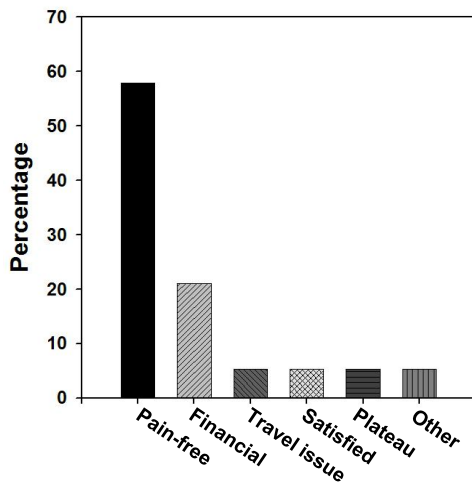
Earlier studies of the acetabular labrum indicate a potential for healing responses and provide a rationale for the investigation of regenerative injection therapy for labral



**Fig. (5).** Patient-reported functional outcomes. Patients chose from five possibilities to describe their maximum walking distance and the degree of compromise in their ability to exercise. n = 19.



tear. Our initial experience with hypertonic dextrose in patients with labral tear suggests that the procedure is safe and potentially efficacious. We observed substantial gains in pain relief and functionality in a large majority of patients.



**Fig. (6).** Reasons for discontinuing treatment. Results are reported as a percentage of total patients (n = 19). 'Satisfied' patients reported satisfaction with treatment despite not achieving a pain-free state.

#### AUTHORS' CONTRIBUTIONS

RAH conceived and executed the study, contributed data and edited the manuscript. AO contributed to analysis and interpretation of the data and wrote the manuscript.

#### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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