Outcomes of Prolotherapy in Chondromalacia Patella Patients: Improvements in Pain Level and Function

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ABSTRACT: We retrospectively evaluated the effectiveness of prolotherapy in resolving pain, stiffness, and crepitus, and improving physical activity in consecutive chondromalacia patients from February 2008 to September 2009. Sixty-nine knees that received prolotherapy in 61 patients (33 female and 36 male) who were 18–82 years old (average, 47.2 years) were enrolled. Patients received 24 prolotherapy injections (15% dextrose, 0.1% procaine, and 10% sarapin) with a total of 40 cc in the anterior knee. At least 6 weeks after their last prolotherapy session, patients provided self-evaluation of knee pain upon rest, activities of daily living (ADL) and exercise, range of motion (ROM), stiffness, and crepitus. Symptom severity, sustained improvement of symptoms, number of pain pills needed, and patient satisfaction before treatment and improvement after treatment were recorded. Following prolotherapy, patients experienced statistically significant decreases in pain at rest, during ADL, and exercise. Stiffness and crepitus decreased after prolotherapy, and ROM increased. Patients reported improved walking ability and exercise ability after prolotherapy. For daily pain level, ROM, daily stiffness, crepitus, and walking and exercise ability, sustained improvement of over 75% was reported by 85% of patients. Fewer patients required pain medication. No side effects of prolotherapy were noted. The average length of time from last prolotherapy session was 14.7 months (range, 6 months to 8 years). Only 3 of 16 knees were still recommended for surgery after prolotherapy. Prolotherapy ameliorates chondromalacia patella symptoms and improves physical ability. Patients experience long-term improvement without requiring pain medications. Prolotherapy should be considered a first-line, conservative therapy for chondromalacia patella.

KEYWORDS: cartilage, chondromalacia patella, osteoarthritis, knee, pain, prolotherapy

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Introduction

Chondromalacia patella is defined as the softening, thinning, and degradation of cartilage underneath the patella. It is also defined by patellofemoral pain syndrome, a condition that affects both younger and older patients. In adolescents and young adults, the condition is primarily due to injury leading to the breakdown of intraarticular cartilage and resultant osteoarthritis.[1] In older adults, chondromalacia patella is primarily the result of age-related osteoarthritis of the knee. Conservative, first line therapy for chondromalacia patella includes exercise, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections.[2] While temporary pain relief is associated with chondromalacia patella,

both treatments also lead to cartilage degeneration and knee replacement is ultimately required. As a result, in the number of knee replacements has increased dramatically. From 2000 to 2004, the number of knee replacements increased by 53%, from 281,534 to 431,485.[3] It has been projected that in 2015, the number of knee replacements will reach nearly 1.4 million.[3] We propose that prolotherapy, a technique first pioneered by George Hackett in the 1950s,[4] can obviate patellofemoral pain syndrome resulting from chondromalacia patella and lead to cartilage synthesis in the knee.

Anatomy and physiology. The movement of the patella, also known as the knee cap, in a distal to caudal motion occurs through the quadriceps tendon, which is connected

to the quadriceps muscle caudally, and the patellar tendon, which connects the patella to the tibia distally. As part of a more intricate anatomy of tendons and vasculature, the patella overlies the joint consisting of the junction of the femur and the tibia. The space between these two bones is where cartilage and an extracellular matrix exist. Additionally, the surface under the patella is covered with articular cartilage that is smooth and slippery. When the knee flexes and extends, this smooth surface allows the patella to slide easily into the groove of the femur. This cartilage becomes rough and wears away in chondromalacia patella.

Causes of chondromalacia patella. In adolescents and active adults, chondromalacia patella can be due to sports injury with participation in athletics, such as running, soccer, cycling, skiing, and gymnastics, which are high-impact sports, involve abrupt stopping, and apply repetitive torsion, stress, and force to the joint. Overuse or injury can lead to the degradation of intraarticular cartilage under the knee cap. This osteoarthritis can result from ligament injury, excess laxity, joint hypermobility, and clinical instability with osteoarthritis appearing in the synovial joint.[1] Other sources that can lead to patellofemoral pain syndrome in teens and young adults include injury due to car accidents (dislocation and fracture) and congenital flat feet. When the patella does not fit properly into the femoral groove upon movement or is dislocated to one side due to anomaly of the ligaments or musculature, chondromalacia patella can result.

In older adults, the hallmark condition associated with chondromalacia patella is osteoarthritis. Although the pathogenesis of osteoarthritis involves both the degradation and synthesis of articular cartilage, cytokines cause greater breakdown than repair.[5–27]

Chondromalacia patella is differentiated from the diagnoses of anterior cruciate ligament tear and tendon injuries, although these conditions contribute to the development of patellofemoral pain syndrome. In chondromalacia patella, the occurrence of degeneration of cartilage is hidden behind the hard bony, floating structure of the patella.

Signs and symptoms. In addition to acute or chronic pain, other symptoms of chondromalacia patella include popping and cracking sounds. These symptoms are worse upon climbing stairs, running, kneeling, squatting, or other physical activity involving the knee. Typically, the symptoms of chondromalacia patella worsen over time.

Upon physical examination, crepitation or dysfunction of the patella may be noted. Palpation of the patellofemoral articulation during active and passive range of motion of the knee will determine if there is crepitation of the joint or abnormal tracking of the patella within the femoral trochlea. Compression of the patella against the femur at varying degrees of knee flexion may elicit articular pain. An alternative method involves manually resisting the upward movement of the patella as the patient actively contracts the quadriceps. Manipulating the patella with simultaneous compression of the patellofemoral

joint may elicit pain, but, more importantly, may identify areas of significant cartilage wear on the joint surfaces.

The examination is completed by thorough evaluation of the knee ligaments. This includes examination of the medial and lateral collateral ligaments as well as examination of the anterior and posterior cruciate ligaments. Joint line tenderness and crepitation of the joint may identify medial and lateral meniscus tears with provocative maneuvers such as McMurray testing.

Treatment. Upon diagnosis, initial treatment for osteomalacia patella includes rest and vitamin D, but these therapies do not regenerate cartilage. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also be prescribed, but studies show further degradation of cartilage with this therapy in both animals and humans.[6] In addition to molecular changes in the cartilage by NSAIDs, the cartilage break down also may be due to increased joint use and load upon the knee following pain amelioration.[28–30] Muscle strengthening exercises may improve the relative location of the patella upon movement, but do not improve the tendons, ligaments, or cartilage. As chondromalacia patella worsens, corticosteroid injections may be provided in an attempt to relieve pain symptoms. However, a comprehensive review of the literature documents significant necrosis of cartilage from even just one injection.[31] The known effects of intraarticular corticosteroids on articular cartilage have been documented in a study by Hauser. As it worsens, arthroscopy may be recommended to remove the degraded cartilage. Finally, due to the resultant osteoarthritis, knee replacement may ultimately be recommended.

To ameliorate the resultant pain of chondromalacia patella and reverse the process of cartilage degeneration, we recommend prolotherapy consisting of dextrose injections over a series of 4 visits.

Patients and Procedures

Patients. We examined a population of 117 patients recruited for prolotherapy for chondromalacia patella from February 2008 to September 2009. Of these, 69 knees in 61 patients were enrolled in this retrospective study. (Eight patients underwent prolotherapy on bilateral knees).

Inclusion criteria for the study included chondromalacia patella; age of at least 18 years; duration of pain greater than 3 months; completion of a series of prolotherapy injections, consisting of 24–40 injections per treated knee at each session; no other prior or concomitant therapy for the condition, including other physician visits for chondromalacia, no NSAID use, no corticosteroid injections, no physical therapy, or other treatments specifically designed to treat chondromalacia; completion of follow-up visits; and completion of written and verbal questionnaire by patient as provided by study administrator (DG) regarding prolotherapy results.

Exclusion criteria included other conditions affecting the patella or knee, age younger than 18 years, incomplete series of prolotherapy injections, concomitant therapy,

incomplete follow up, and inability to complete questionnaire of prolotherapy results. Use of NSAID medications, over-the-counter or prescription, or steroid preparations resulted in exclusion from the study.

Injection protocol and post-procedure regimen. Each patient reviewed and signed a procedure consent form, which described the inherent benefits and risks associated with the prolotherapy procedure. Each patient verbalized the understanding and desire to undergo the procedure. After recording the patient's vital signs and obtaining patient history, the patient was placed on the treatment table in a supine position. The treatment area was cleaned with hydrogen peroxide and then with ChloraPrep® (2% chlorhexidine gluconate/70% isopropyl alcohol) (CareFusion Corporation, San Diego, CA, USA). Lidocaine cream 5% was applied to the area 10–15 min prior to treatment. The area was cleaned again using 3% hydrogen peroxide and ChloraPrep®, 15 min after application of the lidocaine.

The patient was administered a solution of 15% dextrose, 0.1% procaine, and 10% sarapin solution at the bony attachments in and around the anterior knee, including the medial and lateral collateral ligaments, patellar ligament, vastus medialis and iliotibial tract, and pes anserinus. An intraarticular injection with 8 cc of solution was also provided.

A total of 40 cc of solution was utilized for 24 separate injections. In addition to the active agents in each injection, the following additives were used as needed: human growth hormone (2 IU, intraarticular), as well as 0.5–1 cc/knee per syringe of manganese (0.1 mg/mL), morrhuate sodium, 5% (American Regent, Shirley, NY, USA), and procaine 1%. The type and amount of these additives were determined by the physician as indicated by the patient condition.

Following the injection series, the patient rested with moist heat covering the knee for 10–15 min following the procedure. After the compress was removed, the area was cleaned with 3% hydrogen peroxide before ambulation.

Patients received follow-up phone calls by a clinician the first day following treatment, and then at 1 month and 3 months. Treatment intervals were provided every 4–6 weeks. This duration between injections allows production of fibrous collagen.

Patient questionnaire. At least 6 weeks following completion of the series of prolotherapy injections, each patient's condition was self-evaluated utilizing a 32-point questionnaire. Patients were asked about the severity of their conditions at baseline and after prolotherapy. The outcomes measured included level of pain and function. Twelve questions involved patient assessment of severity of condition on a scale of 0–10, where 0 was no pain and 10 was crippling or severe pain. These questions included average daily pain level at rest, during normal activity (or activities of daily living), and during exercise before and after prolotherapy. After prolotherapy, patients were asked to assess the lasting improvement

in daily pain level as a percentage. Range of motion was also assessed on the scale of 0–10.

Levels of stiffness and crepitus were evaluated with another set of questions that ranked these symptoms on a scale of 0–10. Additionally, stiffness and crunching were ranked according to percentage of improvement. Walking ability in terms of distance was ranked before and after prolotherapy, as was exercise ability.

Each patient's total number of medications, with a breakout of number of pain medications, was accounted for in the questionnaire. Each patient was asked about the length of time prior to prolotherapy treatment, length of time since last prolotherapy treatment, any surgery recommendations prior to prolotherapy, and patient expectations about prolotherapy. Finally, patients were assessed about their reason for discontinuation of prolotherapy.

Data analysis. Data from outcomes were analyzed against baseline utilized a paired Student t test. The level of significance was set at $P < 0.0001$.

Results

Of the 117 patients recruited for this study, 61 patients with 69 knees (8 patients with bilateral knee prolotherapy) were included in this study. Of the 69 knees, 36 (52%) were from female patients and 33 (48%) were from male patients. The average age of patients was 47.2 years with a range of 18–82 years. Three patients who experienced re-injury and were currently undergoing prolotherapy treatment were excluded from the study. Forty-five patients were unavailable for phone or email follow up. Eight patients did not receive the recommended number of sessions and were excluded from the study.

Patients were administered a survey of 32 questions via phone to evaluate the effects of prolotherapy. A self-assessment of pain at rest was ranked on a 10-point scale, which aligns with the Visual Analog Pain Scale.[32] No pain to minimal pain was calculated as scores 0 through 3. Moderate pain was considered as 4–6 points on the questionnaire, and severe pain was scores from 7–10. The following data was reported by patients before prolotherapy: 45 knees had no pain to minimal pain (65.2%), 13 knees produced moderate pain (18.8%), and 11 had moderately worse to severe pain (15.9%). Following prolotherapy, 67 knees (97.1%) were reported to have no pain to minimal pain. Only 2 knees (2.9%) had moderate pain after prolotherapy with no patients (0%) citing severe pain at rest. At rest, pain amelioration after prolotherapy was statistically significant as compared to level of pain before prolotherapy ($P < 0.0001$) (Table 1).

Upon assessment of pain in patients during normal activities of daily living before prolotherapy, 22 knees (31.9%) were pain-free or had minimal pain, 24 knees (34.8%) sustained moderate pain, and 23 (33.3%) had severe pain. Following prolotherapy, 65 knees (94.2%) were reported to have no pain to minimal pain, and only 4 knees (5.8%) retained moderate pain. No patients (0%) experienced severe pain. Alleviation of pain upon normal activity was statistically significant

Table 1. Symptom assessment in chondromalacia patella patients* before and after prolotherapy.

PAIN LEVEL^	PAIN (AT REST)		PAIN (ADL†)		PAIN (EXERCISE)‡		ROM**		STIFFNESS‡		CREPITUS	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE‡‡	AFTER
0–3 (minimal)	45 (65.2%)	67 (97.1%)	22 (31.9%)	65 (94.2%)	10 (14.7%)	57 (83.8%)	53 (76.8%)	67 (97.1%)	40 (58.8%)	65 (94.2%)	31 (44.9%)	59 (85.5%)
4–6 (moderate)	13 (18.8%)	2 (2.9%)	24 (34.8%)	4 (5.8%)	16 (23.5%)	9 (13.2%)	8 (11.6%)	1 (1.4%)	17 (25.0%)	3 (4.3%)	19 (27.5%)	8 (11.6%)
7–10 (severe)	11 (15.9%)	0 (0%)	23 (33.3%)	0 (0%)	42 (61.8%)	2 (2.9%)	8 (11.6%)	1 (1.4%)	11 (16.1%)	0 (0%)	14 (20.3%)	2 (2.9%)
	$P < 0.0001$		$P < 0.0001$		$P < 0.0001$		$P < 0.0001$		$P < 0.0001$		$P < 0.0001$	

Notes: *N = 69 knees in 61 patients, ^Pain level as rated by Visual Analog Pain Scale (VAS), †ADL = activities of daily living, ‡n = 68 responders, **ROM = range of motion, ‡‡n = 64 responders.

in patients after prolotherapy as compared to baseline ($P < 0.0001$) (Table 1).

Finally, pain during exercise before prolotherapy was absent or minimal in 10 knees (14.7%) of patients. Sixteen knees (23.5%) had moderate pain. Severe pain was experienced in 42 knees (61.8%) of patients during exercise. After prolotherapy, 57 knees (83.8%) of patients experienced no pain or minimal pain. Nine knees (13.2%) sustained moderate pain with exercise, and 2 knees (2.9%) developed severe pain with exercise despite prolotherapy. One patient was excluded from answering this question due to overall health condition. The reduction in pain during exercise was statistically significant as compared to pain before prolotherapy ($P < 0.0001$) (Table 1).

At least 6 weeks since their last prolotherapy treatment, patients ranked their continued improvement in daily pain level. Of those receiving prolotherapy, 43 knees (62.3%) of patients had 100% sustained improvement. Seventy-five percent to 99% of improvement in pain relief from the last prolotherapy session was sustained in 19 knees (28.8%). Two knees (2.9%) of patients experienced 50% to 74% improvement in their relief following the last prolotherapy session. One knee (1.4%) of a patient had less than 25% continuation of pain relief achieved through prolotherapy. Finally, one patient (1.4%) stated that prolotherapy did not produce lasting pain relief. Three patients were non-responders.

Range of motion was not affected or was affected minimally in 53 knees (76.8%) of patients prior to prolotherapy. Eight knees (11.6%) had moderate impairment and 8 (11.6%) experienced severely impaired range of motion. After prolotherapy, 67 knees (97.1%) showed improvement in range of motion with an absence of or minimal pain. One patient (1.4%) reported moderately affected range of motion in his knee, and 1 patient (1.4%) said he had continued to experience a severely affected range of motion. The improvement in range of motion is shown in Table 1.

Stiffness severely affected 11 knees (16.2%) of patients and moderately affected 17 knees (25.0%) before prolotherapy. Forty knees (58.8%) had no stiffness or minimal stiffness.

After prolotherapy, 65 knees (95.6%) of patients experienced no stiffness or minimal stiffness. Three knees (4.4%) continued to experience moderate stiffness, but no patients (0%) reported severe stiffness after prolotherapy. One patient was a non-responder. Improvement in stiffness following prolotherapy is shown in Table 1.

Severe crepitus, or crunching, affected 14 knees (20.3%) prior to prolotherapy. Nineteen knees (27.5%) had moderate crunching, and 31 knees (44.9%) had no crunching or minimal crunching. Sixty-four patients rated their crepitus before prolotherapy. After prolotherapy, patients reported an absence of or minimal crepitus in 59 knees (85.5%). Eight knees (11.6%) sustained moderate crunching, and 2 knees (2.9%) had severe crunching after prolotherapy. Improvement in crepitus is shown in Table 1.

Walking ability was completely affected with an inability to ambulate in 6 knees (8.8%) in 68 responders. Before prolotherapy, walking ability was severely compromised with an inability to walk one block in 8 knees (11.8%). Four knees (5.9%) were moderately affected with an ability to walk only one to two blocks. Twenty-six knees (38.2%) were mildly affected, with an ability to walk more than three blocks, but not as far as desired. Before receiving prolotherapy 24 knees (35.3%) were not compromised. One patient was a non-responder on ability before prolotherapy. After prolotherapy 56 knees (82.3%) had no distance restrictions and were able to walk over three blocks. Eleven knees (16.2%) were mildly compromised and could walk over three blocks, but not as far as desired. Only 1 patient (1.5%) stated moderate compromise with an ability to walk one to two blocks (Table 2).

Exercise and walking ability before and after prolotherapy was determined, and is shown in Table 2. Before prolotherapy 17 knees (25.0%) were completely compromised and patients were unable to exercise. Nineteen knees (27.3%) were severely compromised, and patients were only able to exercise 0–30 min. Seventeen knees (25.0%) were moderately comprised, and patients were unable to exercise for longer than 30–60 min. Nine knees (13.2%) were mildly compromised, meaning patients were able to exercise longer than 60 min, but

Table 2. Movement assessment of knees* of chondromalacia patella patients before and after prolotherapy.

WALKING ABILITY	BEFORE PROLOTHERAPY†	AFTER PROLOTHERAPY
No distance restriction for walking	24 (35.3%)	56 (82.3%)
Mild: > 3 blocks but not as far as desired	26 (38.2%)	11 (16.2%)
Moderate: 1−2 blocks	4 (5.9%)	1 (1.5%)
Severe: < 1 block	8 (11.8%)	0
Total disability: requires wheelchair or aid	6 (8.8%)	0
EXERCISE ABILITY	BEFORE PROLOTHERAPY‡	AFTER PROLOTHERAPY†
None: exercise ability not affected	6 (8.8%)	38 (55.9%)
Mild: no restrictions; can exercise >60 min, but not as long as desired	9 (13.2%)	23 (33.8%)
Moderate: can exercise 30−60 min maximum	17 (25.0%)	5 (7.3%)
Severe: can exercise 0−30 min maximum	18 (27.3%)	1 (1.5%)
Total disability	17 (25.0%)	1 (1.5%)

Notes: *N = 69, †1 non-responder, ‡2 non-responders.

not as long as desired before prolotherapy. In 6 knees (8.8%), patients said their exercise ability was not affected. One patient did not respond to the question.

After prolotherapy, 38 knees (55.9%) showed no compromised exercise ability. Twenty-three knees (33.8%) were mildly compromised. These patients were able to exercise longer than 60 min, but not for the length of time desired. Five knees (7.3%) had moderately comprised exercise ability, and patients were unable to exercise longer than 30−60 min despite prolotherapy. One patient (1.5%) said he was still severely compromised, and only able to exercise 0−30 min. One patient (1.5%) stated he was completely compromised and unable to exercise. One patient did not reply to this question.

Patients were surveyed regarding the total number of pain medications as well as number of pills of each that they needed prior to prolotherapy. No pain medication was needed in 40 study knees (58.0%) before prolotherapy, but 24 knees (34.8%) needed at least 1 pain medication and 5 knees (7.2%) needed 2 pain medications. After prolotherapy, 66 knees (95.6%) of patients in the study required no pain medication and only 3 patients (4.3%) required 1 medication for pain relief.

Of the 24 knees of patients who required 1 pain medication before prolotherapy, 6 knees (25.0%) required at least 1 pill per day and 13 knees (54.2%) required 2 pills per day. Four knees (16.7%) of patients required 4−6 pills per day of one medication. One knee (4.2%) required 8 pills. After

prolotherapy, in patients who required only 1 medication per day, 3 knees required 1 pill (33.3%) or 2 pills (66.6%) per day. Sixty-six of 69 knees (95.6%) of patients required no pain medication.

Of the 5 knees of patients who required 2 pain medications before prolotherapy, 2 knees (40.0%) required 2 pills. One knee (20.0%) required 4 pills of 2 pain medications. Finally, 1 knee (20.0%) required 12 pills total and 1 knee (20.0%) required 16 pills total of 2 pain medications. Of the patients who required 2 pain medications, following prolotherapy only 1 knee required 1 pain medication consisting of 1 pill; this was in the patient who originally required 12 pills of 2 pain medications. The remaining knees that required 2 medications initially did not require any pain medication following prolotherapy (Table 3).

Patients were asked how long they had waited from their pain complaint to prolotherapy treatment. For 22 knees in the study, patients had waited less than 6 months before seeking treatment with prolotherapy. For 10 knees, patients waited longer than 6 months, but less than 12 months. Twelve knees were enrolled in prolotherapy after waiting 1 year, but less than 2 years. Fifteen knees of patients had symptoms for 2–3 years before treatment. Five knees had pain related to chondromalacia patella for almost 4–6 years before treatment. Finally, 2 patients waited 10 years before prolotherapy and another patient did not undergo prolotherapy for 12 years following onset of pain related to chondromalacia patella. The average duration of pain onset to prolotherapy was 21.6 months.

Time from last prolotherapy varied among patients. Fifteen knees (22.0%) had undergone prolotherapy within the last 6 months. Twenty-seven knees (39.7%) had undergone prolotherapy in the last 7–12 months. There were 18 knees (26.5%) that received prolotherapy in the last 13–24 months. Six knees (8.8%) received treatment with prolotherapy in

Table 3. Pain medication in chondromalacia patella patients before and after prolotherapy.

PAIN MEDICATIONS	NUMBER OF PILLS PER DAY	BEFORE PROLOTHERAPY	AFTER PROLOTHERAPY
0 Prescriptions		40 (58.0%)	66 (95.6%)
1 Prescription		24 (34.8%)	3 (4.3%)
	1	6 (25.0%)	1 (33.3%)
	2	13 (54.2%)	2 (66.6%)
	4–6	4 (16.7%)	0
	8	1 (4.2%)	0
2 Prescriptions		5 (7.2%)	0
	1	0	0
	2	2 (40.0%)	0
	4–6	1 (20.0%)	0
	12	1 (20.0%)	0
	16	1 (20.0%)	0

the last 25–36 months. Finally, 1 patient (1.5%) underwent prolotherapy 8 years prior. Information on 1 knee was unavailable. The average time from last prolotherapy was 14.7 months.

Of the 16 knees (23.2%) that were recommended for surgery prior to receiving prolotherapy, only 3 knees (4.3%) were recommended for surgery after prolotherapy.

Fifty-eight of 61 patients (95.1%) enrolled in this study said prolotherapy met or exceeded their expectations. No side effects of prolotherapy were reported by the study patients.

Prolotherapy was discontinued for 15 study knees (21.7%) due to financial constraints. Distance to the clinic was a factor for discontinuation of treatment of 1 knee (1.4%) in 1 patient. The patients of 5 knees in the study (7.2%) were happy with the results of prolotherapy, although not 100%, and discontinued prolotherapy. Patients of 38 knees (55.1%) discontinued prolotherapy because they were pain-free. Finally, prolotherapy was discontinued in 10 knees (14.5%) for unknown reasons.

Discussion

In the United States, approximately one third of adults between the ages of 25 and 74 years have radiological evidence of osteoarthritis in a major joint. The knee is the most commonly affected joint in those greater than 45 years old.[2] Chondromalacia patella, the result of osteoarthritis in the knee, can be age-related or due to trauma. Prolotherapy in this cohort of 69 knees showed statistically significant improvements in pain at rest and with activity. Functionality was improved by evidence of increased range of motion, walking ability, and exercise ability. Previous prolotherapy studies show the improvement of pain in human patients in various locations of the body, including the knee.[33–44]

Prolotherapy improved the pain and associated symptoms of chondromalacia patella in nearly all knees in this study despite the fact that patients waited an average of nearly 2 years (21.6 months) before prolotherapy. Improvements in pain, range of motion, stiffness, and crepitus were sustained in over 92% of patients. Pain medication usage also was decreased following prolotherapy.

Specifically, with prolotherapy, there was a substantial decrease in the number of knees with modestly worse to severe pain at rest from 11 knees (15.9%) to 0 knees (0%) and in those knees with modest pain at rest from 13 knees (18.8%) to 2 knees (2.9%). More knees had no pain or minimal pain at rest following prolotherapy compared to before treatment ($P < 0.0001$).

Prolotherapy had a notable effect on the potential for pain-free activity and exercise. After prolotherapy there was a substantial increase in the number of knees reported to have no pain or little pain upon activity from 22 knees (31.9%) to 67 knees (97.1%). A decrease in the number of knees experiencing moderate pain was also observed from 24 knees (34.8%) to 4 knees (5.8%). Initially, 23 knees (33.3%) produced severe pain during activity, but no patient experienced severe pain after

prolotherapy. Overall, this reduction in pain during activity was statistically significant ($P < 0.0001$).

Similarly, upon exercise and before prolotherapy, 42 knees (61.8%) of patients developed severe pain and 16 knees (23.5%) produced moderate pain. After prolotherapy, only 2 knees had severe pain upon exercise and 9 knees sustained moderate pain. Fifty-nine knees (86.8%) had no pain or minimal pain during exercise after prolotherapy compared to 10 knees (14.7%) without pain before prolotherapy. The alleviation of pain upon exercise compared to the pain before prolotherapy was also statistically significant ($P < 0.0001$).

At least 75% of prolotherapy effect on pain relief lasted in 62 knees (89.9%) following treatment. Only 1 patient stated that pain relief from prolotherapy did not last.

Knee stiffness was also ameliorated with prolotherapy. Eleven knees experienced severe stiffness before prolotherapy, but no knees were reported to have this extreme stiffness following treatment. Of the 17 knees (25.0%) with initial moderate stiffness, only 3 knees (4.4%) continued to have this degree of stiffness. The number of knees that sustained no stiffness or minimal stiffness increased from 40 knees to 65 knees (95.6%).

The associated symptom of crepitus was also alleviated with prolotherapy. Severe crunching was originally reported in 14 knees (20.3%), which decreased to 2 knees (2.9%) after prolotherapy. Moderate crunching only affected 8 knees (11.6%) after prolotherapy. Fifty-nine knees (85.5%) had no crunching or a slight degree of crepitus after prolotherapy.

Range of motion, walking ability, and exercise ability all were improved with prolotherapy. Of 8 knees (11.6%) with a severely limited range of motion and 8 knees (11.6%) with moderate limitation, 14 knees showed improvement following prolotherapy. Before prolotherapy, 5 patients with 6 knees (8.8%) were completely unable to walk. Of these patients, 4 achieved the ability to walk with no distance restrictions and 1 patient could walk farther than 3 blocks, but not as far as desired. In the remainder of patients whose walking ability was mildly to severely affected, 82.3% (56 knees) had no distance restrictions during walking after prolotherapy. Of 17 knees (25.8%) that could not tolerate exercise before prolotherapy, only 1 knee continued to be completely compromised. Although 18 knees (27.3%) could not tolerate exercise beyond 30 min, only 1 knee was affected to this extent after prolotherapy. Seventeen knees before prolotherapy with 5 patients stating moderate compromise after prolotherapy, meaning patients could not exercise the knee beyond 60 min. Initially, only 9 knees (13.6%) reported mild compromise and 6 knees (9.1%) were not affected by exercise. After prolotherapy, the condition of 23 patients (33.8%) had improved to mildly compromised, and 38 knees (55.9%) experienced no degree of compromise during exercise. Fifty-eight of 64 knees (90.6%) had sustained this improvement at rates $\geq$ 75% of the effect achieved at their last prolotherapy session.

The total number of pain medications and their frequency were decreased after prolotherapy. Before prolotherapy, 29 knees (42.0%) of patients required 2 or fewer medications. The number of pain pills needed ranged from 1 pill per day (in 4 knees) to 16 pills per day (in 1 knee). Sixty-six of 69 study knees (95.6%) no longer required medication.

Twenty-nine knees needed pain medication prior to prolotherapy, but only 3 knees required pain medication after treatment. Only 3 knees of the 69 knees in our study were later recommended for surgery by an orthopedist. The length of time from last prolotherapy was also notable with an average length of time of 14.7 months (range, 6 months to 8 years).

The limitations of our study include the limited number of patients. We also did not include control subjects. Additionally, there is some inherent bias of self-reporting questionnaires. Although diagnostic equipment was available, no objective data, such as X-rays, magnetic resonance imaging, or other data from physical examinations, were used for these study patients. These tests were not conducted so that the cost to the patient remained low as prolotherapy is typically not covered by medical insurance. However, we believe future studies involving imaging studies will document successful cartilage regeneration in joints following prolotherapy, as already shown in a preliminary case series of prolotherapy patients who underwent high-resolution ultrasound and magnetic resonance imaging.[45]

The strengths of our study include the numerous parameters of activities of daily living that were evaluated in the study patients. No other treatment was provided so that the effects of the prolotherapy regimen could be clearly examined.

The results of this study confirm the findings of our previous study of 119 knees in 80 patients, in which more than 82% of patients showed improvements in walking ability, medication usage, athletic ability, anxiety, depression, and overall disability following prolotherapy injections for unresolved knee pain. In that study, patients were provided prolotherapy of 20–40 injections every 3 months and then evaluated at 15 months. As in this study, 96% of patients felt that prolotherapy had improved life overall.[33]

Changes in the current treatment modalities for chondromalacia patella resultant from osteoarthritis are needed and are evolving. In fact, the International Cartilage Repair Society and Osteoarthritis Research Society International has stated that of NSAIDs should only be used short-term.[46]

The results of this study suggest that prolotherapy in the treatment of chondromalacia patella is associated with substantial gains in pain relief and functionality. As prolotherapy is a simple, rapid, and a low-morbidity option for use in the outpatient setting, it can be considered a first-line conservative therapy for chondromalacia patella. The application of prolotherapy to chondromalacia patella, a rheumatological disease in need of definitive therapy, warrants further investigation.

Author Contributions

Conceived and designed the experiments: RH. Analyzed the data: RH, IS. Wrote the first draft of the manuscript: RH, IS. Contributed to the writing of the manuscript: RH, IS. Agree with manuscript results and conclusions: RH, IS. Jointly developed the structure and arguments for the paper: RH, IS. Made critical revisions and approved final version: RH, IS. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Wheaton MT, Jensen N. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2(1):294–304.
2. Hauser RA, Cukla JJ. Standard clinical x-ray studies document cartilage regeneration in five degenerated knees after prolotherapy. *Journal of Prolotherapy*. 2009;1:22–8.
3. Kim S. Changes in surgical loads and economic burden of hip and knee replacements in the US: 1997–2004. *Arthritis Rheum*. 2008;59(4):481–8.
4. Hackett GS, Hemwall GA, Montgomery GA. Ligament and Tendon Relaxation Treated by Prolotherapy. 5th edition. Oak Park (IL): Gustav A. Hemwall; 1993.
5. Hauser RA. The regeneration of articular cartilage with prolotherapy. *Journal of Prolotherapy*. 2009;1(1):39–44.
6. Hauser RA. The acceleration of articular cartilage degeneration in osteoarthritis by nonsteroidal anti-inflammatory drugs. *Journal of Prolotherapy*. 2010;2(1):305–22.
7. Palmoski MJ, Colyer RA, Brandt KD. Marked suppression by salicylate of the augmented proteoglycan synthesis in osteoarthritis cartilage. *Arthritis Rheum*. 1980;23(1):83–91.
8. Palmoski MJ, Brandt KD. Effects of some nonsteroidal anti-inflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. *Arthritis Rheum*. 1980;23(9):1010–20.
9. Brandt KD, Slowman-Kovacs S. Nonsteroidal antiinflammatory drugs in the treatment of osteoarthritis. *Clin Orthop Related Res*. 1986;213:84–91.
10. Palmoski MJ, Brandt KD. Relationship between matrix proteoglycan content and the effect of salicylate and indomethacin on articular cartilage. *Arthritis Rheum*. 1983;26(4):528–31.
11. McKenzie LS, Horsburgh BA, Ghosh P, Taylor TK. Letter: Osteoarthrosis: uncertain rationale for anti-inflammatory drug therapy. *Lancet*. 1976;1(7965):908–9.
12. Dekel S, Falconer J, Francis MJ. The effect of anti-inflammatory drugs on glycosaminoglycan sulphation in pig cartilage. *Prostaglandins Med*. 1980;4(3):133–40.
13. Mitrovic D, McCall E, Front P, Aprile F, Darmon N, Dray F. Anti-inflammatory drugs, prostanoid and proteoglycan production by cultured bovine articular chondrocytes. *Prostaglandins*. 1984;28(3):417–34.
14. Serni U, Mannoni A, Benucci M. Is there preliminary in-vivo evidence for an influence of nonsteroidal anti-inflammatory drugs on progression in osteoarthritis? Part II-evidence from animal models. *Osteoarthritis Cartilage*. 1999;7(3):351–2.
15. Kalbhen DA. The inhibitory effects of steroidal and non-steroidal antirheumatic drugs on articular cartilage of osteoarthrosis and its counteraction by a biological GAG-peptide complex (Rumalon). *Z Rheumatol*. 1982;41(5):202–11.
16. Chang JK, Wu SC, Wang GJ, Ho ML. Effects of non-steroidal anti-inflammatory drugs on cell proliferation and death in cultured epiphyseal-articular chondrocytes of fetal rats. *Toxicology*. 2006;228(2–3):111–23.
17. Matsuda K, Nakamura S, Matsushita T. Celecoxib inhibits nitric oxide production in chondrocytes of ligament-damaged osteoarthritis rat joints. *Rheumatol Int*. 2006;26(11):991–5.

18. Schwartz Z, Gilley RM, Sylvia VL, Dean DD, Boyan BD. The effect of prostaglandin E2 on costochondral chondrocytes differentiation is mediated by clinic adenosine 3', 5'-monophosphate and protein kinase C. *Endocrinology*. 1998;139(4):1825–34.

19. O'Keefe RJ, Crabb ID, Puzas JE, Rosier RN. Influence of prostaglandins on DNA and matrix synthesis in growth plate chondrocytes. *J Bone Miner Res*. 1992;7(4):397–404.

20. Miyamoto M, Ito H, Mukai S, et al. Simultaneous stimulation of EP2 and EP4 is essential to the effect of prostaglandin E2 in chondrocytes differentiation. *Osteoarthritis Cartilage*. 2003;11(9):644–52.

21. Clark CA, Schwarz EM, Zhang X, et al. Differential regulation of EP receptor during chondrogenesis and chondrocytes maturation. *Biochem Biophy Res Commun*. 2005;328(3):764–76.

22. Brochhausen C, Neuland P, Kirkpatrick CJ, Nüsing RM, Klaus G. Cyclooxygenases and prostaglandin E2 in growth plate chondrocytes in vitro and in situ–Prostaglandin E2 dependent proliferation on growth plate chondrocytes. *Arthritis Res Ther*. 2006;8(3):1–21.

23. Maroudas A, Evans H, Almeida L. Cartilage of the hip joint. Topographical variation of glycosaminoglycan content in normal and fibrillated tissue. *Ann Rheumatologic Dis*. 1973;32(1):1–9.

24. Mankin HJ, Lippiello L. Biochemical and metabolic abnormalities in articular cartilage from osteoarthritic human hips. *J Bone Joint Surg Am*. 1970;52(3):424–31.

25. McKenzie LS, Horsburgh BA, Ghosh P, Taylor TK. Effect of anti-inflammatory drugs on sulphated glycosaminoglycan synthesis in aged human articular cartilage. *Ann Rheumatologic Dis*. 1976;35(6):487–97.

26. Dingle JT. Prostaglandins in human cartilage metabolism. *J Lipid Mediators*. 1993;6(1–3):303–12.

27. Reijman M, Bierma-Zeinstra SM, Pols HA, Koes BW, Stricker BH, Hazes JM. Is there an association between the use of different types of nonsteroidal anti-inflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. *Arthritis Rheum*. 2005;52(10):3137–42.

28. Lane NE, Wallace DJ. All About Osteoarthritis: The Definitive Resource for Arthritis Patients and Their Families. Oxford University Press, Oxford, England; 2002:19.

29. Andriacchi TP, Lang PL, Alexander EJ, Hurwitz DE. Methods for evaluating the progression of osteoarthritis. *J Rehab Res Dev*. 2000;37(2):163–70.

30. Schnitzer T, Popovich JM, Andersson GB, Andriacchi TP. Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis Rheum*. 1990;36(9):1207–13.

31. Hauser RA. The deterioration of articular cartilage in osteoarthritis by corticosteroid injections. *Journal of Prolotherapy*. 2009;2:107–23.

32. Scott J, Huskisson EC. Accuracy of subjective measurements made with or without previous scores: an important source of error in serial measurement of subjective states. *Ann Rheum Dis*. 1979;38(6):558–9.

33. Hauser RA, Hauser MA. A retrospective study on dextrose prolotherapy for unresolved knee pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1:11–21.

34. Lennard T. Pain Procedures in Clinical Practice. Second edition. Philadelphia: Hanley and Belfus, Inc. 2000.

35. Lennard T. Physiatric Procedures in Clinical Practice. Philadelphia: Hanley and Belfus, Inc.; 1995.

36. Hauser R, Hauser M. Prolo Your Pain Away! Second edition. Oak Park, IL: Beulah Land Press; 2004.

37. Dorman T. Prolotherapy in the Lumbar Spine and Pelvis. Philadelphia: Hanley and Belfus, Inc.; 1995.

38. Hackett GS. Ligament and Tendon Relaxation Treated by Prolotherapy. Fifth edition. Oak Park, IL: Gustav A. Hemwall; 1992.

39. Reeves KD. Prolotherapy: present and future applications in soft tissue pain and disability. *Physical Medicine & Rehabilitation Clinics of North America*. 1995;6:917–26.

40. Ongley M, Dorman TA, Bjorn CE, Lundgren D, Klein RG. Ligament instability of knees: a new approach to treatment. *Manual Medicine*. 1988;3:152–4.

41. Hackett GS. Prolotherapy in whiplash and low back pain. *Postgrad Med*. 1960;27:214–9.

42. Kayfetz D. Occipital-cervical (whiplash) injuries treated by prolotherapy. *Med Trial Tech*. 1963;9–29.

43. Reeves K, Hassanein K. Randomized, prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med*. 2000;6(2):68–74, 77–80.

44. Ongley M. Ligament instability of knees: A new approach to treatment. *Manual Medicine*. 1988;3:152–4.

45. Fullerton BD. High-resolution ultrasound and magnetic resonance imaging to document tissue repair after prolotherapy: a report of 3 cases. *Arch Phys Med Rehabil*. 2008;89(2):377–85.

46. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137–62.