




# A Case Series: Effect of Comorbidities on the Outcomes of Prolotherapy Injection for Frozen Shoulder Patients

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**Abstract:** Frozen shoulder (FS) is a disease caused by an inflammatory condition that causes severe pain and decreased range of motion by loss of glenohumeral mobility. Frozen Shoulder restricts daily life's functional aspect, increasing morbidity. Hypertension and diabetes mellitus are risk factors that make an FS poor prognosis during treatment because of the diabetes glycation process and hypertension-enhanced vascularization. Prolotherapy injects an irritant solution into the tendon, joints, ligaments, and joint spaces to release growth factors and collagen deposition, reducing pain, restoring joint stability, and increasing the quality of life. We report 3 cases of patients with confirmed FS. Patient A with no comorbidity, patient B with diabetes mellitus, and patient C with hypertension, with all patient's chief complaints of shoulder pain and limited ROM, and symptoms affected the general quality of daily life. This patient was provided injection with Prolotherapy treatment combined with physical therapy intervention. Patient A had significantly improved ROM to maximum after 6 weeks with relieved pain and improved shoulder function. Patients B and C showed increased ROM, still tiny, decreased pain, and improved shoulder function. In conclusion, prolotherapy demonstrated a beneficial effect in a patient with FS with comorbidities, although not to the maximum extent in patients without comorbidity.

**Keywords:** protherapy, frozen shoulder, comorbidity, range of motion, quality of life

## Introduction

One in three people will experience shoulder pain at some point in their lifetime because the shoulder is frequently a “primary mover” for daily movement; shoulder diseases severely limit one's ability to do daily activities.<sup>1</sup> Frozen shoulder is a common condition that causes pain and a progressive loss of glenohumeral mobility.<sup>2,3</sup> It is characterized by clinical signs of shoulder discomfort with progressively limited active and passive motion in addition to normal radiographic glenohumeral joint imaging caused by an inflammatory condition with the molecular mechanism that causes fibroproliferative tissue fibrosis.<sup>4,5</sup> FS is the condition that has been restricted to clinical and functional aspects, such assessments do not allow considering all the implications that the disease can cause to the patient's life.<sup>6</sup> The Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) is a regional questionnaire consisting of 30 questions, rather specific to evaluate the functional capacity of the affected upper limb, also being self-administered.<sup>7</sup>

Frozen shoulder is subdivided into primary and secondary, primary also called idiopathic, and occurs without any specific trauma. Secondary can be categorized into systemic.<sup>8</sup> Comorbidities occur in 85% of patients with FS, and 37.5% have more than three comorbidities.<sup>9</sup> Diabetes, hypertension, shoulder injury, stroke, thyroid disease, and neck surgery are some known risk factors for its development.<sup>10</sup> Contrary to the current opinion of many medical experts, FS

does not resolve spontaneously in a significant portion of individuals, and FS can be quite disabling.<sup>11</sup> The most common comorbidity in people with FS is diabetes and hypertension that increase the inflammatory processes leading capsular fibrosis and subsequent contracture.<sup>12–14</sup>

The development of numerous therapy approaches for FS is now underway.<sup>15</sup> Dextrose prolotherapy injection is one of the therapeutic techniques developed and put into practice in FS<sup>8</sup> to address the issues with conventional modalities. During treatment sessions, prolotherapy injects tiny volumes of an irritating solution into sore and deteriorated tendon insertions (entheses), joints, ligaments, and nearby joint spaces to encourage the formation of healthy cells and tissues.<sup>16,17</sup> The therapeutic principle of prolotherapy initiates a local inflammatory cascade, which releases growth factors and collagen deposition. Induced cytokine’s role in mediating chemo-modulation, which promotes to proliferation and strengthening of new connective tissue, joint stability, and a reduction in pain and dysfunction.<sup>16–18</sup> A major goal of prolotherapy in chronic musculoskeletal conditions is stimulating regenerative processes in the joint that restore joint stability by increasing the tensile strength of stabilizing components such as ligaments, tendons, joint capsules, menisci, and labral tissue.<sup>16</sup>

In this article, we present a report on four patients in which FS was diagnosed along with various comorbidities. This case report aims to describe the functional outcome of the patient treated with prolotherapy combined with physical therapy using Visual Analog Scale (VAS), The Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH), and Range of Motion (ROM) in order to assess the efficacy of prolotherapy in maintaining and improving the quality of life and to reduce morbidity in a patient with comorbid conditions.

Case Description

Patient A

A fifty-eight-year-old female, entrepreneur presented with right shoulder pain during 3 months ago. With a limited range of motion at the initial evaluation and no visible crepitus on movement, the pain had slowly started in the shoulder and spread insidiously to the neck and elbow. Shoulder discomfort while exercising. There is no comorbidity from patient. The diagnosis of frozen shoulder was determined following normal photos of radiographs, mechanism of injury, past medical history and physical therapy examination and evaluation.

Upon palpation, the physical examination determined that the patient had tenderness along the deltoid region and right biceps tendon. His pain was measured based on the VAS, which was 6 out of 10. The patient’s shoulder ROM flexion 90°, extension 45°, abduction 90°, adduction 35°, internal rotation 50°, and external rotation 15° (Table 1). All the shoulder ROM was limited, consistent with the typical presentation of FS.

Table 1 Data Before Intervention of the Patients

	Patient A	Patient B	Patient C
Age	58 years old	60 years old	59 years old
Sex	Female	Male	Female
Job	Entrepreneur	Entrepreneur	Teacher
Comorbidity	No comorbid	Diabetes mellitus	Hypertension
Chief complaint	Right shoulder pain	Right and left shoulder pain	Right shoulder pain
Onset of symptoms	3 months ago	4 months ago	3 months ago
VAS	6 out of 10	6 out of 10	7 out of 10
DASH Score	44%	50%	45,7%

(Continued)

**Table 1** (Continued).

	Patient A	Patient B	Patient C
ROM			
Flexion (0–180°)	90°	100°	115°
Extension (0–90°)	45°	55°	50°
Abduction (0–180°)	90°	90°	75°
Adduction (30–75°)	35°	40°	60°
Internal Rotation (0–90°)	50°	35°	45°
External Rotation (0–45°)	15°	20°	15°
Blood Pressure	130/90 mmHg	130/80 mmHg	165/110 mmHg
Laboratory Finding			
Plasma Glucose Level	136 mg/dl	143 mg/dl	120 mg/dl
Intervention	Prolotherapy injection combined with physical therapy intervention	Prolotherapy injection combined with physical therapy intervention	Prolotherapy injection combined with physical therapy intervention

## Patient B

A sixty-one-year-old male, entrepreneur presented with right and left shoulder pain during 4 months ago. The pain had slowly started in the shoulder and spread insidiously to the neck with cramping of the fingertip at the time of the initial evaluation, which showed a limited range of motion and no visible crepitus on movement. The patient complained of difficulty doing everyday tasks and nighttime pain awakening. The patient was previously diagnosed with type II diabetes mellitus (DM). Following the evaluation of normal radiographs, the mechanism of the injury, prior medical history, and physical therapy examination and testing, the diagnosis of a frozen shoulder was made.

Upon palpation, the physical examination determined that the patient had tenderness along the rotator cuff muscle and long head biceps tendons. His pain was measured based on the VAS, which was 6 out of 10. The patient's shoulder ROM flexion 100°, extension 55°, abduction 90°, adduction 40°, internal rotation 35°, and external rotation 20° (Table 1). The main limitations in ROM included flexion and internal rotation, consistent with the typical presentation of FS. On laboratory findings, the plasma glucose level was 143, and after injection, prolotherapy was 160. The patient regularly takes diabetes medications.

## Patient C

Right shoulder pain first appeared in a teacher who was 59 years old 3 months ago. The symptoms of these issues started gradually, but with time, they started to impact his general quality of life. The patient's range of motion was restricted, and there was no palpable crepitus when the shoulder moved. Her pain increased while working and cooking, interfering with her nighttime sleep. Hypertension was previously identified as the patient's condition. The diagnosis of a frozen shoulder was made after reviewing normal radiographs, the mechanism of the injury, prior medical history, and physical therapy examination and testing.

According to the physical examination, the patient felt soreness along the biceps tendons, glenohumeral joint, and deltoid region. His VAS score of 7 out of 10 was used to assess his pain level. The patient's shoulder has a range of motion (ROM) of 115° flexion, 50° extension, 75° abduction, 60° adduction, 45° internal rotation, and 15° external rotation (Table 1). Extension, internal, and external rotation were the main ROM restrictions, consistent with how FS is typically presented. After prolotherapy injections, the tension measure was 165/110 mmHg compared to 150/110 mmHg before intervention. The patient takes hypertension medication regularly.

## Treatment and Intervention

All the patients were provided with the same treatment and intervention with a prolotherapy injection containing 15% dextrose, with a disposable syringe of 10 mL containing 4 mL of 15% dextrose, 1 mL of lidocaine, and 5 mL of distilled water. The injection point on the rotator cuff includes the supraspinatus, infraspinatus, teres minor, and subscapularis. Intraarticular injection of the glenohumeral joint, subacromial bursa, long head biceps tendon, and acromioclavicular joint performed by a qualified physician. Injections were administered four times in week 0, week 2, week four, and week 6. Injection combined with a physical intervention consisted of shoulder strengthening exercise, gentle stretching, and ultrasound diathermy with frequency 3 MHz, duty cycle 50%, pulsed mode, 3W/cm<sup>2</sup> for five minutes of the shoulder region. In performing frozen shoulder exercise, stretch to the point of tension but not pain. There are seven stretches and strengthening exercises for building muscle; 1) Swing the arm in a short circle to perform the pendulum stretch, 2) The towel stretch, which involves holding one end of a three-foot towel behind the back and grabbing the other end with the other hand while holding it horizontally, 3) Finger walk by facing a wall from a distance of three-quarters of an arm, 4) Cross-body reach, in which the afflicted arm is raised at the elbow and brought up and across the body using the good arm, 5) Armpit stretch, using the good arm, lift the affected arm onto a shelf about breast high, gently bend your knees, opening up the armpit, the deep knee being slight, 6) Outward rotation, which involves holding a rubber exercise band between hands and rotating the affected arm's lower portion outward two to three inches while holding the position for five to ten seconds, 7) To perform an inward rotation, stand next to a closed door, wrap one end of a rubber exercise band around the doorknob, hold the other end in the affected arm's hand while maintaining a 90-degree angle at the elbow, and pull the band two to three inches toward body while holding for five to ten seconds. The patient also provides a home exercise program with muscle stretching and shoulder strengthening by ROM exercise.

Progress notes were completed every two weeks, which consisted of goniometric measurements with the following prime mover muscle of the shoulder joint, shoulder flexion starting position bony landmarks for goniometer alignment by the lateral aspect of the acromion process, lateral midline of thorax, lateral humeral epicondyle, shoulder extension with the lateral aspect of the acromion process, lateral midline of thorax, lateral humeral epicondyle, shoulder abduction with the anterior aspect of the acromion process, midline of sternum, medial humeral epicondyle, shoulder adduction with the anterior aspect of the acromion process, midline of sternum, medial humeral epicondyle, shoulder internal and external rotation with olecranon and styloid processes of the ulna. Reassessment of goals and patient-reported pain. DASH score was given to measure the functional improvements at the initial and final evaluation (Tables 2–4).

**Table 2** Data After Intervention of the Patients in Weeks 2

	Patient A	Patient B	Patient C
Comorbidity	No comorbid	Diabetes mellitus	Hypertension
VAS Week	4 out of 10	4 out of 10	6 out of 10
DASH Score	35,8%	41,7%	31,7%
Blood Pressure	120/80 mmHg	120/60 mmHg	145/100 mmHg
Laboratory Finding			
Plasma Glucose Level	124 mg/dl	151 mg/dl	113 mg/dl
ROM Week 2			
Flexion (0–180°)	120°	105°	120°
Extension (0–90°)	55°	60°	60°
Abduction (0–180°)	120°	100°	95°
Adduction (30–75°)	40°	60°	50°
Internal Rotation (0–90°)	70°	35°	55°
External Rotation (0–45°)	25°	20°	20°

**Table 3** Data After Intervention of the Patients in Weeks 4

	Patient A	Patient B	Patient C
Comorbidity	No comorbid	Diabetes mellitus	Hypertension
VAS Week	0 out of 10	3 out of 10	4 out of 10
DASH Score	10%	28.3%	15%
Blood Pressure	120/70 mmHg	130/90 mmHg	145/100 mmHg
Laboratory Finding			
Plasma Glucose Level	98 mg/dl	152 mg/dl	120 mg/dl
ROM Week 4			
Flexion (0–180°)	165°	130°	145°
Extension (0–90°)	70°	70°	65°
Abduction (0–180°)	150°	120°	105°
Adduction (30–75°)	55°	65°	55°
Internal Rotation (0–90°)	75°	50°	60°
External Rotation (0–45°)	40°	35°	35°

**Table 4** Data After Intervention of the Patients in Weeks 6

	Patient A	Patient B	Patient C
Comorbidity	No comorbid	Diabetes mellitus	Hypertension
VAS Week	0 out of 10	0 out of 10	2 out of 10
DASH Score	0%	10%	8,3%
Blood Pressure	110/60 mmHg	120/80 mmHg	140/90 mmHg
Laboratory Finding			
Plasma Glucose Level	105 mg/dl	140 mg/dl	115 mg/dl
ROM Week 6			
Flexion (0–180°)	180°	145°	160°
Extension (0–90°)	90°	75°	75°
Abduction (0–180°)	180°	150°	125°
Adduction (30–75°)	75°	75°	65°
Internal Rotation (0–90°)	90°	65°	80°
External Rotation (0–45°)	45°	40°	40°

## Discussion

Both patients were diagnosed with frozen shoulders, as indicated in Table 1, characterized by pain and a limited range of motion, particularly in external rotation.<sup>19</sup> FS is generally divided into three stages, freezing (pain and reduced ROM) for

10–36 weeks, frozen (stiffness predominates) for 4–12 months and thawing (symptoms resolve) for 5–24 months or more.<sup>20</sup> Both individuals were approaching the point of freezing.

Diabetes mellitus is a disease that typically coexists with FS. Patients with diabetes may get FS at an incidence of 10.8% to 30%, with a tendency toward more severe symptoms and treatment resistance.<sup>21</sup> According to a systematic review in 2021, it provides that people with diabetes experience worse outcomes from frozen shoulders than those without diabetes. Diabetes' prognostic significance in FS was demonstrated by poor ROM outcomes, low pain outcomes, and moderate multidimensional clinical scores.<sup>22</sup> Diabetes associated with a frozen shoulder is that glycation processes may cause changes in capsule tissue and consequently lead to the development of a frozen shoulder.<sup>21,22</sup> Tables 2–4 show the detailed that patient with diabetes takes a longer time to increase ROM than non-comorbid patient.

A risk factor for developing a frozen shoulder is hypertension.<sup>23</sup> Univariate analysis of the Cao, 2022 study revealed a strong connection between hypertension and the start of a frozen shoulder ( $p = 0.009$ ).<sup>24</sup> The mechanism arising from inflammation, with cytokine proliferation leading to an increase in fibroblast proliferation, blood flow increasing in patients with hypertension, and enhanced vascularization, may explain the patient's pain.<sup>25</sup> In our case, patients with hypertension showed more painful than non-comorbid patients.

The presence of comorbidities in the frozen shoulder causes a worsening prognosis in the treatment process. Using prolotherapy in a patient with comorbidities has been shown to reduce pain and increase the quality of life, which is almost the same as in patients without comorbidities. Prolotherapy injections cause local tissue irritation that triggers an immediate inflammatory response, enhances fibroblast proliferation and promotes the production of collagen, which promotes tissue renewal and repair.<sup>26</sup> After prolotherapy, Jensen et al<sup>27,28</sup> revealed increased inflammatory agents at the injection sites and considerable ligament or cartilage structure growth. High glucose levels activate platelet-derived growth factor (PDGF), which boosts TGF-beta gene expression and triggers DNA synthesis in human mesangial cells. High glucose levels stimulate human mesangial cells to express connective tissue growth factors and other genes.<sup>26–28</sup> Our report showed that the patient injected with prolotherapy with comorbid diabetes and hypertension did affect the healing process in the patient.

## Conclusion

In a patient with a comorbid frozen shoulder, prolotherapy, and physical therapy exhibited the same potential benefits for improved range of motion, dramatically reduced discomfort, and improved quality of life. A patient with a comorbid frozen shoulder may benefit from prolotherapy, which has effects that last till full recovery. However, it takes longer to complete recovery compared to non-comorbid patients.

## Data Sharing Statement

The data used to support the findings of this study will be available from the corresponding author upon reasonable request.

## Ethical Review

After receiving permission from Hasanuddin University with protocol number UH219070463 obtained ethics approval.

## Consent for Publication

The patients provided written informed consent for the publication of this case series. The consent included case-specific information and any accompanying images.

## Disclosure

The authors declare no conflicts of interest for this work.

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