Therapeutic Interventions for Managing Diabetic Shoulder

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences
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Shoulder pain is a common complaint of diabetic patients that causes motion limitations and functional disability. Adhesive capsulitis (AC) is the most common disabling shoulder disorder. There is no optimal non-surgical treatment for managing AC in patients with diabetes. Furthermore, the impact of diabetes on shoulder recovery and factors predicting shoulder function following shoulder arthroplasty is not well investigated.

**Purpose and Methods**

The main purpose of this thesis was to inform clinical practice about the best intervention for managing AC in diabetic patients, and to assess the impact of diabetes on functional outcomes after shoulder arthroplasty, with the following objectives: 1) To systematically review clinical research evaluating nonsurgical interventions for managing AC in diabetic patients; 2) To pilot test study procedures and estimating the effects of incorporating a progressive walking program as an adjunct to a regular physiotherapy program for managing AC in diabetic patients; 3) To examine the effect of diabetes on shoulder function and physical health status; And 4) To determine factors that predict shoulder functional outcomes following shoulder arthroplasty.

**Results**

Eight randomized trials (RCTs) were evaluated in a systematic review. The largest effect size (2.0) was reported for joint mobilization plus exercises. The pilot RCT (n = 8) found that regular physiotherapy (PT) group and regular physiotherapy program plus progressive walking group (PT+) may improve functional performance and other outcomes, with a mean change of PT = 38±17, and PT+ = 6±33 seconds for Functional Impairment Test-Hand and Neck/Shoulder/Arm (FIT-HaNSA) test from baseline to six weeks follow-up. A sample size of 89 participants per group is needed for future studies. Diabetic and non-diabetic patients showed significant improvements in function and physical health status following shoulder arthroplasty with no significant differences between groups. At one year after arthroplasty, residual pain significantly predicted poorer shoulder function.

**Conclusions**

We found that low-quality evidence suggested large effects of joint mobilization plus exercises on AC in people with diabetes. The pilot trial established that conducting a large-scale study to assess the effect of the physiotherapy program for managing AC is feasible. Patients with
and without diabetes may get equal surgical benefits, and residual pain may cause limitations in shoulder function one year after arthroplasty.

**Keywords**
Adhesive capsulitis, Diabetes, Physical Therapy, Pilot trial, Shoulder arthroplasty, Systematic review.
Frozen Shoulder is a common problem that occurs five times more frequently in patients with diabetes. Frozen Shoulder causes pain and disability. The usual treatments reduce shoulder pain and disability, but these treatments often fail for people with diabetes. Currently, we are not sure what is the best treatment to manage Frozen Shoulder in patients with diabetes. We do not know how diabetes can affect recovery after shoulder replacement surgery. Also, we are not sure what factors can affect function after shoulder replacement surgery.

This thesis includes five papers. The first paper aimed at reviewing the literature of diabetic shoulder. The second paper evaluated the effect of different conservative treatments that reduce pain and disability in patients who have Frozen Shoulder. The third paper tests whether adding a walking program to the usual care will result in better pain relief, motion and function. The fourth paper assesses if diabetes impacts recovery after shoulder replacement surgery. The fifth paper aimed to find factors that might affect shoulder joint function after replacement surgery. Results show that exercises and steroid injections may improve shoulder pain and function in patients with diabetes who have Frozen Shoulder. We think it is also possible to conduct a large study to assess if adding a walking program to shoulder exercises would better improve shoulder function in patients with Frozen Shoulders. We found that diabetes does not affect recovery after shoulder replacement surgery. We also found that the presence of pain at one year after surgery may cause shoulder disability.
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LIST OF ABBREVIATIONS

AC: Adhesive Capsulitis
ASES: American Shoulder and Elbow Surgeons
BMI: Body Mass Index
CSS: Constant Shoulder Score
FIT-HaNSA: Functional Impairment Test - Hand and Neck/Shoulder/Arm tests
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
HA: Hemiarthroplasty
MCS: Mental Component Summary Score
MUA: Manipulation Under Anesthesia
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
PCS: Physical Component Summary Score
PT: Physiotherapy
RAPA: Rapid Assessment of Physical Activity
RCTs: Randomized Clinical Trials
ROM: Range of Motion
SF-12: Short-Form-12
SPADI: Shoulder Pain and Disability Index
SRM: Standardized Response Mean
SST: Simple Shoulder Test
TSA: Total Shoulder Arthroplasty
VAS: Visual Analogue Scale
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CHAPTER 1

THE DIABETIC SHOULDER- A LITERATURE REVIEW

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Citation:
Abstract

Shoulder pain is one of the most common complaints of patients with diabetes that causes motion limitation, functional disability and decreased quality of life. There is a higher prevalence of shoulder disorders in patients with diabetes, with adhesive capsulitis (AC) and rotator cuff (RC) tendinopathy being the most common disabling shoulder disorders. The pathophysiology that predisposes patients with diabetes for the development of AC or RC tendinopathy is not well-understood. However, the increased glycosylation of collagen fibers of the joint capsule, tendons and ligaments, and the diabetic microangiopathy might potentially explain the pathological process. Although some therapeutic interventions have been shown to be effective in managing shoulder disorders, several studies have reported higher shoulder pain, reduced mobility, poor functional outcomes, and a diminished response to treatment in patients with diabetes than patients without diabetes. In the current literature, there is a lack of studies on the best treatment approach for managing shoulder disorders in patients with diabetes. Furthermore, the effect of diabetes on shoulder function after shoulder arthroplasty is not well investigated. Future research is required to examine the effectiveness of different surgical and non-surgical interventions on managing shoulder disorders in patients with diabetes. In addition, more research is required to investigate the impact of diabetes on shoulder recovery and factors predicting shoulder function following shoulder arthroplasty.
1.1 Introduction to the thesis

1.1.1 Functional anatomy of the shoulder complex

The shoulder complex is composed of three bony structures: the clavicle, scapula, and humerus, which are connected to form three synovial (glenohumeral, acromioclavicular, and sternoclavicular) and two functional (scapulothoracic and subacromial) joints [1]. These articulations link the upper extremity to the thorax and allow for great mobility of the arm. As a result, the hand can be placed and moved through a large volume of space [2].

The combined mechanics of the articular joints and the surrounding soft tissue structures (muscles, capsules, and ligaments) interact to provide mobility and stability of the shoulder complex. In a normally functioning shoulder complex, both static and dynamic stabilizers result in a broad range of joint movements and provide adequate stability. However, the unique design of the shoulder complex that provides mobility with reduced stability also makes it highly susceptible to dysfunction and injury [1,2].

1.1.1.1 Glenohumeral joint (shoulder joint)

The glenohumeral joint is a triaxial joint that connects the head of the humerus with the glenoid fossa of the scapula. This joint has greater mobility than any other joint in the body [1]. Only 25% to 30% of the humeral head contacts the glenoid fossa at any given time. This anatomical configuration results in an extensive joint mobility but low stability [2]. However, the interplay between the static (capsule, labrum, ligaments) and the dynamic (muscle) forces provide a precise constraint of the center of rotation through a large arc of motion [3].

The glenoid labrum deepens the fossa to provide additional stability and serves as the attachment site for the joint capsule. The joint capsule along with the glenohumeral and coracohumeral ligaments tighten to limit joint translation and provide static stability to the shoulder. Further static stability is provided through the adhesive and cohesive forces of the synovial fluid and the negative joint pressure that hold joint surfaces together [1,2].

During arm elevation, the dynamic stability of the glenohumeral joint is provided mainly by the muscular forces of the rotator cuff and the deltoid. The rotator cuff consists of the subscapularis, supraspinatus, infraspinatus and teres minor muscles. This group of muscles inserts onto the facets of the greater and lesser tuberosities and provides a continual ring shaped insertion from posterior-inferior to anterior-inferior on the proximal humerus [2]. The contraction of the supraspinatus, along with the deltoid, causes arm elevation. The contraction
of the infraspinatus and the teres minor muscles provides an external rotation force while the internal rotation force results from the contraction of the subscapularis muscle \(^1\).

The co-contraction of the rotator cuff produces a concavity-compression effect directed toward the glenoid center to promote glenohumeral joint stability, while asymmetric contraction causes humeral head rotation (steering mechanism) and depression during shoulder abduction motion. However, due to the small size of the rotator cuff and its proximity to the joint center of rotation, they generate lower muscle forces when compared to the larger and more superficial muscles (deltoid, latissimus dorsi, trapezius, and pectoralis major) \(^2\).

The long head of the biceps muscle plays a role in stabilizing the head of the humerus. Along with the rotator cuff, it functions to depress the humeral head during shoulder abduction. In addition, the contraction of the long head of biceps during the late phase of throwing reduces anterior translation and resists external rotation \(^4\). Further static stabilization is promoted by the tension placed on the static restraints and the glenohumeral ligaments that limit excessive translations of humeral head \(^1\).

1.1.1.2 Acromioclavicular and sternoclavicular joints

The acromioclavicular and the sternoclavicular joints are triaxial joints that connect the clavicle to the acromion process of the scapula and the sternum, respectively. The stability of the acromioclavicular joint is maintained through static stabilizers composed of a thick capsule, an intra-articular disc, and the coracoclavicular ligament. The acromioclavicular ligaments restrain the posterior translation of the acromioclavicular joint, while the coracoclavicular ligaments restrain the vertical displacement of the joint \(^5\).

The small sternoclavicular joint is the only joint that connects the shoulder complex to the axial skeleton. The stability of the sternoclavicular joint is provided by the surrounding ligaments composed of the intra-articular disc-ligament, costoclavicular ligament and interclavicular ligament which act as a checkrein against medial displacement, excessive upward rotation and excessive downward rotation of the clavicle, respectively \(^1,2\).

1.1.1.3 Scapulothoracic articulation and muscles

The scapulothoracic articulation is a functional joint (not a true joint) that represents a space between the thoracic cage and the anterior scapula. There is considerable soft tissue flexibility that allows a relatively smooth slide of the scapula along the underlying thorax. The scapulothoracic articulation synchronizes with the glenohumeral joint and allows for 150° to
180° of shoulder range of motion (ROM) into flexion or abduction with elevation. For every 2° of glenohumeral elevation, there is 1° of scapulothoracic elevation. However, this ratio can vary among individuals and for any part of the arc of movement [1,2].

Several muscles that originate from or insert into the scapula provide motion and dynamically stabilize the scapula. In the dependent position, the scapula is maintained in downward rotation, forward tilting, and protraction position. This position is stabilized by the balanced forces of the trapezius, serratus anterior, levator scapula, and rhomboids musculature. The dependent position of the scapula is further maintained by the static stabilization of the cohesive forces of the subscapular bursa, acromioclavicular and sternoclavicular joint ligaments, and the scapulothoracic fascia [1,2].

During active arm motion, the scapulohumeral muscles maintain an effective length-tension relationship and function to stabilize and control the position of the scapula, allowing a smooth movement of the humerus. The serratus anterior maintains the medial angle of the scapula against the chest wall and along with the upper and medial trapezius, upwardly rotates the scapula during arm elevation [1,2].

During flexion and pushing activities, the serratus anterior muscle protracts the scapula on the thorax. However, during arm extension or pulling activities, the rhomboids retract the scapula and cause downward rotation while the latissimus dorsi, teres major, and rotator cuff muscles function to exert rotational forces that cause the inferior scapula to move away from the midline (upward rotation). In addition, these muscles eccentrically contract to control the upward rotation and protraction of the scapula. The levator scapula elevates the superior angle, resulting in upward and medial rotation of the scapula, while the pectoralis minor protracts and rotates the scapula inferiorly [1,2].

1.1.2 Common musculoskeletal disorders of the shoulder joint

Musculoskeletal disorders affecting shoulder joint can either lead to hypomobility (restricted mobility) or hypermobility (excess mobility) of the joint. Common pathologies that limit shoulder movements include arthritis [rheumatoid arthritis (RA) or osteoarthritis (OA)], adhesive capsulitis (AC)/frozen shoulder, and rotator cuff tendinopathy (RC)/impingement syndrome [1].

Hypermobility of the shoulder joint causes joint instability and can be atraumatic or traumatic. Atraumatic joint hypermobility can be due to an inherent generalized connective tissue laxity
or secondary to repeated microtrauma. However, traumatic instability is usually caused by high
direct or indirect applied forces to the shoulder joint that often lead to joint dislocation
(complete separation of the articular surfaces) and soft tissue damage. Further, inherent
instability may be a pre-disposing factor to traumatic dislocation, especially with repetitive
stressful overhead activities. A secondary effect of joint hypermobility is painful shoulder
syndrome \(^1\).

1.1.2.1 Shoulder arthritis

Arthritis can be defined as joint pain or joint disease. It can affect people of all ages, genders,
and races. Overtime, arthritis can lead to impaired mobility and functional limitations. Many
types of arthritis may affect shoulder joint including:

- **Osteoarthritis**: is a chronic degenerative disorder affecting the articular cartilage of
  shoulder joint leading to pain and stiffness. With degeneration, the capsule also
  becomes thickened causing further loss of rotational movements. Shoulder OA is not
  as common as OA of the knee or hip, however, it is reported to affect 32.8% of patients
  over the age of 60 years \(^6\). The etiology of the primary shoulder OA is unknown but is
  related to age (over the age of 65), genetics and sex; women are affected more
  frequently than men. Secondary OA may occur as a result of repeated micro or high
  impact trauma, chronic dislocation, or infection \(^6,7\).

- **Rheumatoid arthritis**: is an autoimmune, chronic, progressive inflammatory,
  systematic disorder primarily affecting the synovial joint capsule and connective tissue.
  Shoulder RA results in pain, loss of ROM, stiffness, progressive deformity and
  functional disability \(^1,8\). The prevalence of shoulder RA is 1% worldwide and presents
  in about 5% of people over the age of 70 years. It affects women more frequently than
  men with a ratio of 3:1. Shoulder symptoms develop in about 91% of patients with
  long-standing RA (more than 5 years) \(^8\).

- **Post-traumatic/ immobilization arthritis** occurs in response to an injury or fracture
  to the shoulder; or from lack of movement, which causes rapid destruction of articular
cartilage. Immobilization arthritis could also occur as a secondary effect of medical
  conditions such as stroke, diabetes, or heart disease \(^1\).

1.1.2.2 Rotator cuff tendinopathy/impingement syndrome
Rotator cuff tendinopathy is a progressive disorder of the rotator cuff tendons. The condition begins with acute tendinitis of the muscle tendon (mainly the supraspinatus) and progresses to tendinosis with degeneration and partial thickness tears. The condition may result in a full thickness rupture. Rotator cuff tendinopathy causes pain in the shoulder region, leading to a restricted and painful arc of motion, sleep disturbance, and shoulder dysfunction \[1,9]\.

The etiology of RC tendinopathy is often multifactorial, and the symptoms are usually brought on by repetitive or excessive overhead activities. Both intrinsic and extrinsic mechanisms play a role in the pathology development and progression. Extrinsic factors are defined as those causing narrowing of the subacromial space during arm elevation, leading to mechanical compression/impingement and irritation of the soft tissues (rotator cuff and subacromial bursa). Extrinsic factors could be anatomical, such as the shape and angle of the acromion, or biomechanical (postural and muscular impairments) or a combination of both. The extrinsic mechanism was first described by Codman (1934) and the concept was popularized by Neer in the 1980s who coined the term subacromial impingement syndrome \[9,10]\.

On the other hand, intrinsic factors affect the structural integrity of the musculotendinous structures, leading to RC tendon degeneration. These factors include vascular changes in the RC tendons, tissue tension overload, and collagen disorientation and degeneration. The condition is observed most often in patients over 40 years old and disease prevalence increases with age and can affect more than 50% of the population greater than 60 years old \[1,9]\.

1.1.2.3 Adhesive capsulitis/ frozen shoulder

Adhesive capsulitis (AC), also known as ‘frozen shoulder’, is characterized by the development of dense adhesions and capsular thickening leading to a progressive and painful restriction of shoulder ROM and functional disability \[11]\. The condition does not cause arthritic changes in the joint cartilage and bone as seen with OA and RA. The onset is gradual and usually occurs between the ages of 40 and 65 years \[1]\. Further, it is five times more common in people with diabetes and is more frequent in women \[12]\.

Codman (1934) was the first to describe the condition, coin the term ‘frozen shoulder’ and define the common criteria shared by most frozen shoulder patients which include slow onset of pain, inability to sleep on the affected side, painful and restricted shoulder abduction and external rotation motions, and normal radiographs \[13]\.
The frozen shoulder was termed shoulder adhesive capsulitis by Neviaser (1945) who found thickening and contracture of the joint capsule and described peeling the capsule from humeral head as peeling adhesive plaster from skin. In 1969, Lundberg suggested to subdivide frozen shoulder, based on Codman criteria, into two groups: primary or idiopathic frozen shoulder, which has no clear underlying cause, and secondary frozen shoulder, in which the condition is secondary to soft tissue injury, OA, RA, trauma, or secondary to a known systemic disease such as diabetes [13].

For many years, AC has been described as a self-limiting condition that progresses through a natural history of painful, frozen and thawing phases, leading to full recovery without treatment. However, a recent systematic review assessed the quality of the evidence that describes the theory of AC phases and the theory of full recovery without treatment [14]. The authors reported a lack of evidence to support the theoretical phases of AC. In addition, this review found that moderate-quality evidence supported an early improvement in shoulder ROM and function that slows over time and leads to long-term limitations [14].

The pathophysiology of idiopathic AC was studied in a recent systematic review that included 13 observational studies. There was consistent agreement among studies that the pathological changes in the anterior shoulder joint capsule originated from the subscapularis bursa, at the base of the origin of the long head of the biceps (rotator interval) [15]. These pathological changes were described as a proliferation of fibroblasts arranged alongside layers of dense collagen tissue, leading to capsular contracture. This fibrous tissue was noted to become tight if the arm was placed in external rotation, forming a checkrein to further movement (the presence of pathological fibrous tissue prevents full joint motion). The systematic review suggested that fibrotic changes were associated with primary frozen shoulder [15].

Mechano-transduction is another potential mechanism that might trigger the development of AC. Mechano-transduction refers to the mechanism by which cells convert external mechanical stimuli or force into a set of biochemical reactions that elicit adaptive responses including positional location and adhesion, contractile activation, responsiveness to shear stress and growth [16]. Mechanical loading induces hypertrophy and strengthening of skeletal muscles, tendons, ligaments and bones and have been long been implicated in regulating many physiologic and pathologic processes. Even when forces are not externally applied, cells experience endogenous mechanical forces that are generated by their internal cytoskeletal
machinery. Such cell-generated forces appear to alter many basic cellular functions, such as cell proliferation, differentiation, sorting and migration \[^{16}\].

Tissue samples from patients with AC demonstrated a dense collagen matrix and excessive proliferation of fibroblasts and contractile myofibroblasts at the anterior part of the joint capsule \[^{15}\]. The increase in collagen cross-linking and density lead to the development of fibrous tissue which alters the mechanical properties of the extracellular matrix of articular capsule, ligaments and muscle-tendon units by making tissue stiffer and weaker \[^{16,17}\].

Research investigating the mechano-transduction mechanism demonstrated that the presence of external and internal loading might alter numerous cellular functions including migration, prefiltration and differentiation, making tissue stiffer and weaker \[^{16}\]. However, these studies were inconclusive about AC pathophysiology and no study directly linked AC to the mechano-transduction mechanism.

1.1.3 Association between diabetes and shoulder disorders

Diabetes is a metabolic condition that is characterized by persistent hyperglycemia due to insulin deficiency, impaired effectiveness of insulin action, or both. Diabetes is considered one of the most challenging health problems in the 21st century. It is one of the most disabling diseases and the fifth leading cause of death in most developed countries \[^{18,19}\].

Based on the etiology, diabetes can be classified into two main types: type 1 diabetes, which results from cell-mediated autoimmune destruction of pancreatic islet beta cells causing the loss of insulin production; and type 2 diabetes, which occurs due to insulin deficiency and/or insulin resistance. However, other types of diabetes do exist such as gestational diabetes (occurs during pregnancy), type 3 diabetes (resistance to insulin in the brain), secondary diabetes (as a consequence of other medical condition), neonatal diabetes (affects babies under 6 months old), and many others \[^{18}\].

Type 1 diabetes occurs more commonly in children, while type 2 diabetes is seen more frequently among adults and constitutes about 85% to 95% of all diabetes in developed countries. Diabetes can be found in almost every population in the world. The global burden of diabetes is estimated to be 10.4% for persons aged 20-79 years by the year 2040. In Canada, it is predicted that there will be a large increase in the number of people with diabetes from 9% in 2003 to 11.2% in 2025. In addition, the prevalence of diabetes is more than four times higher
among First Nations women than non-First Nations women and more than 2.5 times higher among First Nations men as compared to non-First Nations men [18–20].

Diabetes has many well-described complications including neuropathy, cardiovascular diseases, retinopathy, stroke, peripheral vascular disease (amputation), and renal failure that result in disability, reduced life span, and increased health cost [18]. Complications involving the musculoskeletal system are generally less well-described. Shoulder pain is one of the most common complaints of patients with diabetes that causes motion limitation, functional disability and decreased quality of life. There is higher prevalence of shoulder disorders in patients with diabetes, with AC and RC tendinopathy being the most common disabling shoulder disorders [11,12].

The association between diabetes and AC was first recognized by Bridgman (1972) who found that 10.8% of patients with diabetes had AC as compared to 2.3% patients without diabetes [21]. Subsequent studies have supported this association and reported a prevalence of AC in 10-76% type 1 and 7-30% type 2 diabetes as compared to 0-10% in the general population [22–25]. Adhesive capsulitis was also reported to be associated with age in both types of diabetes [22] and with the duration in type 1 diabetes [23,24,26].

Patients with diabetes, with or without the use of insulin, have a high risk for developing RC tendinopathy, with a hazard ratio (HR) of 2.11 as compared with those without diabetes [11]. In addition, chronic RC tendinopathy and shoulder pain have been associated with diabetes [27]. Further, patients with diabetes have been reported to have a concurrent diagnosis of AC and RC tendinopathy, leading to shoulder pain and contracture [28]. Furthermore, diabetes has been associated with postoperative stiffness after rotator cuff repair [28,29].

The pathophysiology that predisposes patients with diabetes for the development of AC or RC disease is not well-understood. However, the two diseases might share similar diabetes-related mechanisms [11]. Indeed, several potential mechanisms have been suggested that explain the pathological process including the increased glycosylation of collagen fibers of the joint capsule and the diabetic microangiopathy [11,17,30].

Collagen is the main structural protein in the extracellular matrix in the various connective tissue in the body. Normally, collagen fibers are glycosylated meaning that collagen protein molecules have sugar molecules covalently bonded to them through a specific enzymatic process. However, in diabetic tissue, hyperglycemia can cause a non-enzymatic covalent bonding of sugar molecules to the collagen fibers. Over time, the glycating sugar reacts further
leading to the abnormal biochemical formation of pathological collagen tissue known as advanced glycation end-products (AGEs). These AGEs increase crosslinking in the collagen fibers of shoulder capsule, tendons and ligaments, making making these structures stiffer and weaker [11,17,30,31]. The cross-linking collagen accumulate in the shoulder capsule leading to joint stiffness and chronic inflammatory process in the synovium [11]. In addition, an increase in cell proliferation and cellularity of fibroblasts may result in dense layers of collagen tissue, leading to capsular contracture [11,30,31].

Further, arthroscopic biopsies of joint synovium in patients with diabetes showed greater amounts of endothelial growth factors and reduced amounts of inflammatory growth factors. These findings explained the prolonged course and severity of AC in patients with diabetes [31]. However, other studies reported that AGEs interact with the receptors on the surface of tenocytes and fibroblasts, leading to chronic inflammatory changes in the joint synovium, which contribute to capsular fibrosis of the shoulder joint [11,30].

The impaired microcirculation (diabetic microangiopathy) is another pathological process that may contribute to the development of AC and RC tendinopathy in patients with diabetes. There is a consensus among studies that uncontrolled hyperglycemia leads to macrovascular and microvascular complications in patients with diabetes [11,30].

It is documented that AGEs are prevalent in the diabetic vasculature and contribute to the development of atherosclerosis. AGE cross-linking of collagen fibers in the basement membrane of the extracellular matrix leads to thickening of the basement membrane, stiffness of blood vessels and alterations in vascular contractility. As a result, tissue hypoxia occurs causing joint tissue destruction and degenerative changes [11,30]. Moreover, AGEs induce vascular endothelial growth factor which causes synovial cell proliferation in the subacromial bursa synovium, leading to the development of shoulder joint contracture in patients with diabetes who have AC and RC tendinopathy [29].

1.1.4 Assessment of shoulder joint

The assessment of the shoulder joint is essential for the diagnosis and formulation of an appropriate management for patients with shoulder disorders. The assessment usually starts with obtaining a detailed history about patient's demographics, medical history, and the onset of the condition symptoms, followed by inspection and palpation. The assessor inspects shoulders for symmetry and deformity and palpates joints for any tenderness, swelling, or
anatomic abnormalities. It is also essential to examine the neck area to rule out cervical spine pathology and referred neck pain \[^{32,33}\].

One of the next steps in diagnosing shoulder pathology is to measure shoulder active and passive ROM including forward flexion, abduction, external and internal rotation. The assessment of shoulder ROM can be performed by visual estimation or by using goniometer. Goniometric measurements are extensively used in physical therapy for measuring any joint motion in degrees. Measuring shoulder joint active and passive ROM can provide useful information in differentiating some shoulder disorders such as AC and RC tendinopathy. For example, AC is reported to be associated with limitation in both active and passive ROM, while RC tendinopathy is usually associated with limitations in only active ROM \[^{33}\].

Several clinical special and strength tests are often used to diagnose shoulder pathology. However, one test is not interpreted in isolation but is clustered with additional clinical findings when establishing a clear diagnosis for shoulder problems. Examples of these tests include Hawkins' test and Neer's sign to help in diagnosing shoulder impingement syndromes; Drop-arm test, Lift-off test and Empty Can test are strength tests that indicate a defect in the RC; Apprehension and Relocation tests to diagnose anterior shoulder instability; and Yergason's test and Speed's maneuver to assist in the diagnosis of biceps tendon instability or tendonitis \[^{32,33}\].

Several self- and examiner-reported outcome measures tools have been validated to assist in the examination of shoulder pain and function. These measures include the Visual Analogue Scale (VAS) for pain assessment, and measures of shoulder function and disability such as the Shoulder Pain and Disability Index (SPADI), Constant Shoulder Score (CSS), American Shoulder and Elbow Surgeons (ASES), Disabilities of the Arm, Shoulder, and Hand (DASH; Quick DASH), and Simple Shoulder Test (SST) questionnaires. All of these questionnaires have been shown to be valid and reliable for the assessment of shoulder function in various clinical situations \[^{34}\].

Lastly, there are several imaging tests to confirm the diagnosis of shoulder joint pathology including plain x-ray to diagnose bone abnormalities such as osteoarthritis, ultrasound which may be used to diagnose rotator cuff pathology, and magnetic resonance imaging (MRI) and computerized tomography scan (CT), which are used to diagnose bone and soft tissue abnormalities \[^{32}\].
1.1.5 Management of shoulder disorders

As mentioned earlier, obtaining a complete patient history and performing a thorough physical examination are essential in determining proper means of treatment for different shoulder disorders. Several studies have examined the effectiveness of surgical and non-surgical treatment interventions for managing shoulder disorders such as AC, RC tendinopathy, arthritis, and shoulder instability. The non-surgical interventions may include physiotherapeutic interventions, pain-control medications, and steroid injection. Examples of surgical approaches include shoulder arthroscopy and shoulder arthroplasty.

1.1.5.1 Non-surgical interventions

The most common shoulder disorders that might be treated by non-surgical interventions are AC, RC tendinopathy, mild to moderate shoulder OA, and shoulder instability. It is generally recommended to start with a non-surgical treatment for managing these disorders when pain and functional limitation are modest. Surgical interventions may be considered for patients who remain functionally disabled in spite of appropriate non-surgical treatment [33,35].

Physical therapy interventions have been shown to benefit patients with different shoulder conditions. For example, low-level laser therapy was found to reduce pain and improve function in patients with AC [36]. In addition, deep and superficial heat modalities have been reported to provide short-term pain relief and improve ROM for patients with AC; however, the use of US for reduce pain and improve function is not recommended [36]. Active ROM exercises, self-stretching and joint mobilization techniques have been reported by several systematic reviews to reduce pain and restore shoulder ROM and function in patients with AC [36–39]. Further, gentle ROM and isometric strengthening of the rotator cuff and scapulothoracic muscles are effective in reducing pain and improving shoulder ROM in patients with mild to moderate shoulder OA with no evidence of atrophy or contracture [6].

Physical therapy programs that emphasize progressive strengthening of the rotator cuff, deltoid, and scapulothoracic muscles combined with functional exercises that require coordination among multiple muscle groups have been commonly recommended for treating patients with shoulder instability. These exercises are reported to control glenohumeral joint translation, improve shoulder joint stability, and reduce anterior glenohumeral ligamentous strain especially during arm elevation [40]. In addition, for post-traumatic shoulder instability, a weak evidence supports the use of ROM and strengthening exercises [35].
The effectiveness of exercise therapy for the treatment of RC tendinopathy/impingement has been investigated in several systematic reviews \[41–44\]. Data from these reviews strongly suggest that therapeutic exercises combined with manual therapy produce statistically and clinically significant reductions in pain and improvement in shoulder ROM. In addition, exercise therapy may be effective at improving shoulder function. This effect may be augmented with acromioplasty and joint mobilization techniques \[41–44\]. However, a moderate-quality evidence (on GRADE scale) indicates that subacromial decompression provides no improvement in shoulder pain and function for the treatment of RC tendinopathy \[45\].

A typical physical therapy program may include pendulum exercise, active assisted and active ROM exercises, postural exercises, scapular stabilization exercises, stretching exercises, joint mobilization techniques, and soft tissue mobilization techniques. However, none of these systematic reviews described the specific components of the exercise protocols (type, intensity, duration and frequency) that are associated with best outcomes \[41–44\].

Intra-articular steroid injections are commonly used for patients with shoulder pain. There is moderate evidence that supports small short-term pain reduction in patients with AC following steroid injection \[36–38,46\]. Further, steroid injections provide superior improvements in shoulder pain for patients with RC impingement when compared to no injection controls, and ultrasound guided injections are superior to non-guided injections \[41\]. Furthermore, corticosteroid injections seem to relieve shoulder pain in patients with shoulder OA \[6,47\].

1.1.5.2 Surgical interventions

In patients with persistent shoulder pain and dysfunction despite conservative treatments, surgery may be indicated to relieve pain and restore joint function. A number of different surgical approaches to manage shoulder disorders have been reported in the orthopedic literature including shoulder arthroscopy and shoulder arthroplasty.

Shoulder arthroscopy is performed by inserting an arthroscope into the joint through a small incision. This minimally invasive surgical procedure allows for an examination and treatment of various joint pathologies. For patients with AC, a diagnostic arthroscopy is performed to confirm the diagnosis followed by release and excision of fibrotic structures such as the rotator interval, the middle glenohumeral ligament and the axillary pouch. Two systemic reviews have reported that this procedure improves shoulder ROM and function and is an effective treatment for AC \[46,48\]. However, confidence in these findings is a concern due to poor methodological quality of the included studies \[46,48\].
Further, arthroscopic treatment of RC tendinopathy has been shown to significantly improve shoulder symptoms and function treated using different arthroscopic approaches such as debridement of the tear with or without acromioplasty, trans-tendon repair, or conversion of the lesion to full thickness tear followed by repair [49].

Shoulder arthroplasty is a common surgical procedure in which all or part of the shoulder joint is replaced by a prosthetic implant to alleviate shoulder pain and restore joint function [50]. Shoulder arthroplasty, which was pioneered by Gluck and Péan in the 1800s to treat tuberculous arthritis of the shoulder, failed miserably, and the procedure was eventually revisited by Neer in the 1950s for the treatment of proximal humeral fractures. Recent advancements in prosthesis design have resulted in expanded indications and a concomitant increase in the rates for shoulder arthroplasty [51,52].

Currently, end-stage primary glenohumeral osteoarthritis is the primary diagnosis for 77% of shoulder arthroplasty and often occurs more frequently among adults aged 65 years or older [53]. This surgical procedure is usually indicated when conservative treatments such as therapeutic exercises and manual therapy techniques fail [53].

There are three main types of shoulder arthroplasty: total shoulder arthroplasty (TSA), hemiarthroplasty (HA), and reverse total shoulder arthroplasty (rTSA). TSA involves replacing both the humeral head and the glenoid fossa, while HA involves replacing only the humeral head with metal implants. However, in rTSA, the surgeon replaces the anatomical humeral head with a plastic socket and replaces the anatomical socket of the scapula with a metal ball. Patients with OA and an intact or reparable rotator cuff typically undergo TSA, while patients with OA and an irreparable rotator cuff tear traditionally undergo rTSA or HA [54]. However, TSA has been reported to result in greater improvement in shoulder ROM and pain, and in less need for surgery revision when compared to HA [51].

The main indication for rTSA is shoulder OA with irreparable rotator cuff tear when conventional surgery fails. However, the advancement of the prosthetic design has led to expansion of the indications to include any condition about the shoulder where rotator cuff function is deficient including RA and proximal humeral fractures [55].

Despite the improvements of shoulder function and pain after shoulder arthroplasty, shoulder arthroplasty is not without complications. Shoulder subluxation or dislocation, periprosthetic fracture, and joint infection are the most commonly reported postoperative complications [50,56].
Additional complications that are specific to rTSA may include glenoid loosening, musculocutaneous nerve palsy, and acromial fractures [55].

1.1.6 Impact of diabetes on shoulder recovery

All the above-mentioned interventions have been evaluated in generic populations and have been shown to be effective in reducing shoulder pain and improving ROM and function. However, patients with shoulder disorders and concurrent comorbidities such as diabetes have been reported to respond less favorably to these interventions. Indeed, a recent systematic review evaluated the effectiveness of non-surgical interventions for managing AC in patients with diabetes [57]. The authors reported that low quality evidence suggests large effects of joint mobilization plus exercises on AC in people with diabetes and even weaker support was available for corticosteroid and manipulation under anesthesia (MUA) [57].

Vastamaki et al. followed-up patients with and without diabetes who have AC for the duration of 10 years. Although shoulder ROM improved over time in patients with diabetes, this improvement was inferior to patients without diabetes and remained below normal ROM [58]. Further, Juel et al. and Larkin et al. have also shown that patients with type 1 diabetes develop long-lasting shoulder stiffness, functional disability and reduced ROM than patients without diabetes. These studies suggested that early shoulder assessment and treatment may be needed to reduce disability and improve quality of life of patients with diabetes [23,24].

Furthermore, in longitudinal cohort studies, Rill et al. evaluated the effect of operative and nonoperative treatments on AC using the SST questionnaire, while Cole et al. evaluated the association between diabetes and shoulder complaints using the SPADI questionnaire. Both studies reported higher shoulder pain, reduced mobility, poor functional outcomes, reduced quality of life, and a diminished response to treatment in patients with diabetes who have AC than patients without diabetes [59,60].

Studies that evaluated the impact of diabetes on shoulder recovery following arthroscopic rotator cuff repair have reported an inferior improvement in shoulder pain and function in patients with diabetes, in addition to an increased risk of anatomic failure of the repaired rotator cuff tendon especially in patients with uncontrolled hyperglycemia [61,62].

Diabetes has been shown to be an independent risk factor for increased risk of non-home discharge (Odds ratio (OR): 1.3), and longer hospital stays (OR: 1.4) following shoulder arthroplasty [63,64]. Further, diabetes, along with hypertension and obesity, are associated with
postoperative complications such as humeral fracture and joint infection \cite{65}. However, the impact of diabetes on functional outcomes and motion after shoulder arthroplasty has not yet been investigated.

1.1.7 Summary of limitations in current knowledge

Studies consistently report that patients with diabetes are more frequently affected by AC, have long lasting symptoms and a poorer prognosis than patients without diabetes \cite{11,22-25,66}. Further, although some of the therapeutic interventions have been shown to be effective in managing primary AC, several studies have reported higher shoulder pain, reduced mobility, poor functional outcomes, reduced quality of life, and a diminished response to treatment in patients with diabetes than patients without diabetes \cite{23,24,59,60}. There is lack of systematic reviews to assess the effectiveness of therapeutic interventions in managing AC in patients with diabetes and to show whether the current recommendations for treatment of AC can be equally applied to patients with diabetes.

There have been efforts to define an optimal physical therapy protocol for managing AC in patients with diabetes. The usual approach to AC includes mobilization of soft tissues and implementation of shoulder exercises to restore function. However, recovery is slow and often incomplete, especially for people with diabetes. Aerobic exercises can improve hyperglycemia and insulin sensitivity in skeletal musculature \cite{67}, which may have a greater impact on the AC pathophysiology. To the author's knowledge, an optimal physical therapy protocol for managing AC in patients with diabetes is not defined.

Given the fact that hyperglycemia has a negative impact on body tissue \cite{17}, and the adverse effect of diabetes on postoperative complications and hospital stays \cite{63,65}, there is a need to investigate whether diabetes affects functional outcomes after shoulder arthroplasty. To the author's knowledge, no study has evaluated the impact of diabetes on shoulder pain and function following shoulder arthroplasty.

There are limited studies that have addressed the factors which influence postoperative functional outcomes following shoulder arthroplasty. Identifying preoperative factors that are predictive of one-year outcomes could assist surgeons and health care providers in providing patients with more realistic expectations on outcomes and may help plan postoperative pain management and rehabilitation. To the author's knowledge, factors that predict the clinical benefits following shoulder arthroplasty have not been thoroughly investigated.
1.1.8 Future directions

There is a need to conduct systematic reviews to determine the effectiveness of non-surgical interventions (steroid injections, physiotherapeutic interventions, and MUA) and surgical interventions (arthroscopy and arthroplasty) on shoulder pain, function, and ROM for managing AC in people with diabetes. Further, clinical researchers need to run more robust randomized trials to examine the impact of these therapeutic interventions on shoulder function in patients with diabetes as compared to patients without diabetes. Furthermore, studies are required to investigate the impact of diabetes on pain, patient-reported function, and impairments in shoulder ROM and muscle strength in patients who underwent shoulder arthroplasty. Lastly, further research is recommended to investigate whether factors such as comorbidities and demographics predict patient-reported outcomes including shoulder pain and function and clinical benefits following shoulder arthroplasty.

In summary, studies to examine the effectiveness of different surgical and non-surgical interventions on managing shoulder disorders in patients with diabetes are required. In addition, more research is required to investigate the impact of diabetes on shoulder recovery, and factors predicting shoulder function following shoulder arthroplasty.
1.2 Purpose of this thesis

The two purposes of this thesis were to inform physical therapy management of 1) patients with diabetes who have AC and 2) patients with diabetes who are recovering from shoulder arthroplasty. We have the following objectives:

- To conduct a systematic review that determine the effectiveness of non-surgical interventions [steroid injections, physiotherapeutic interventions (joint mobilization, laser therapy, continuous passive motion, electrotherapy, reflexology, therapeutic exercises) and MUA] on shoulder pain, function, and ROM for managing AC in people with diabetes.
- To run a pilot randomized trial that compares the effect of a regular physiotherapy (PT) program to a regular PT combined with a progressive walking program (PT+) in patients with and without diabetes who have AC. This pilot trial will also evaluate the feasibility of recruitment, randomization, retention, assessment procedures, and implementation of the novel intervention. Data from this pilot trial will be used to calculate an accurate sample size for a full-scale RCT. The secondary objective was to determine if diabetes affects response to treatment.
- To investigate the impact of diabetes on pain, patient-reported function, and impairments in shoulder ROM and muscle strength in patients who underwent shoulder arthroplasty.
- To examine whether age, sex, diabetes, hypertension, and depression predict patient-reported outcomes including shoulder pain and function one year following shoulder arthroplasty; if these factors predict the clinical benefits following surgery as reflected in the change of outcome scores; and if residual pain (pain at one-year) is associated with poorer functional outcomes.

1.3 Overview of thesis chapters

This thesis focuses on understanding the impact of diabetes on shoulder disorders. This work addresses a gap in the literature since remarkably few studies have focused on managing AC and shoulder recovery after arthroplasty in patients with diabetes. This work is completed as a manuscript thesis where following chapter one which reviews the relevant literature, a series of inter-related manuscripts are presented in individual chapters.

In chapter 2, we have conducted a systematic review where we have reviewed the quality and content of clinical research addressing the effectiveness of non-surgical interventions including
physiotherapeutic interventions, steroid injections, and manipulation under anesthesia for managing AC in patients with diabetes.
In chapter 3, we have included a pilot study which compared the effect of a regular physiotherapy (PT) program to a regular PT combined with a progressive walking program (PT+) in patients with and without diabetes who have AC.
Chapter 4 is a cohort study that evaluated the following research question: Does diabetes affect functional outcomes after shoulder arthroplasty?
Chapter 5 is a cohort study that examined factors predicting shoulder function and clinical benefits one-year following shoulder arthroplasty.
The final chapter provides a general discussion and formulated conclusions based upon the previous research, including the most significant findings. We have also provided future research directions and recommendations.
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CHAPTER 2:

EFFECTIVENESS OF NON-SURGICAL INTERVENTIONS FOR MANAGING ADHESIVE CAPSULITIS IN PATIENTS WITH DIABETES: A SYSTEMATIC REVIEW

A form of this manuscript is published in the Archives of Physical Medicine and Rehabilitation

Citation:

Abstract

**Objective:** This systematic review evaluated the effectiveness of non-surgical interventions for managing adhesive capsulitis (AC) in patients with diabetes on pain, function and range of motion.

**Data Sources:** MEDLINE and other databases were searched for studies published in the last 20 years.

**Study Selection:** Randomized clinical trials (RCTs) that assessed adhesive capsulitis in people with diabetes and implemented one or a combination of physiotherapeutic interventions, corticosteroids, and manipulation under anesthesia (MUA) were eligible for inclusion.

**Data Extraction:** The Cochrane Risk of Bias was used by two independent raters who met to achieve consensus. The quality of trials was assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Data extracted from the eligible studies included study design, subject characteristics, duration of symptoms, type of intervention, outcome measures, follow-up intervals and research findings.

**Data Synthesis:** Due to the lack of similar interventions, a narrative synthesis was conducted, and meta-analyses were not performed. The effect sizes or between-group differences of the interventions were reported. A total of eight RCTs met the inclusion criteria: four addressed physiotherapeutic interventions, three corticosteroid injections and one MUA. The effect sizes for physiotherapeutic interventions were 0.8-2.0, 0.9-2.0, and 1.0 for ROM, function and pain respectively, with the largest effect size (2.0) being reported for joint mobilization plus exercises. The effect sizes for corticosteroids were 0.2-0.5 and 0.1 for ROM and pain. The between-group improvement for MUA was 5.6 points on Constant Shoulder Score.

**Conclusion:** Low quality evidence suggests large effects of joint mobilization plus exercises on adhesive capsulitis in people with diabetes, although confidence in this conclusion is limited due to the high risk of bias. Even weaker support was available for corticosteroid and MUA. Future high quality RCTs are needed to determine the best intervention for managing AC in patients with diabetes.

**Systematic review registration #:** CRD42018084090 on PROSPERO (https://www.crd.york.ac.uk/PROSPERO)

**Keywords:** Adhesive capsulitis, Corticosteroids, Diabetes, Physiotherapy, Systematic review
2.1 Background

2.1.1 Description of the condition

Adhesive capsulitis (AC), also known as frozen shoulder, is a common shoulder disorder that is characterized by a progressive and painful restriction of range of motion (ROM), that results in functional disability [1]. The condition is more common in people with diabetes with an estimated prevalence of 10-76% in type 1 and 7-30% in type 2 diabetes as compared to 0-10% in the general population [2-5]. Adhesive capsulitis is more frequent in women [6] and is associated with age in both types of diabetes [5] and with the duration in type 1 diabetes [2,3,7]. Further, poor glycemic control has been shown to worsen shoulder pain and function in people with type 1 diabetes [2,3].

Primary or idiopathic AC has no clear underlying cause and secondary AC is associated with a known systematic cause such as diabetes. The pathophysiology of primary AC is poorly understood but could occur as a result of inflammatory or fibrosing processes [8]. However, the glycosylation of collagen fibers of the joint capsule and the impaired circulation of the joint small capillaries have been proposed as potential mechanisms that might explain the pathological process in patients with diabetes [1].

For many years, AC has been described as a self-limited condition that progresses through a natural history of painful, frozen and thawing phases, leading to full recovery without treatment. However, a recent systematic review assessed the quality of the evidence that has characterizes AC into three phases and that supports the concept that full recovery occurs without treatment [9]. The authors reported a lack of evidence to support the theoretical phases of AC. In addition, this review found that moderate-quality evidence supported an early improvement in shoulder ROM and function that slows over time and leads to long-term limitations which questions the common perception that AC is a self-limited condition. Further, they reported that low-quality evidence suggested incomplete improvement in ROM after one to four years of follow-up [9]. The authors recommended that the theory of natural progression of AC should be removed from professional and public information sites since it is not supported and potentially misleading. They also noted the need for future research towards diagnostic processes to identify the underlying causes of stiffness and disability of patients with AC [9].

2.1.2 Description of the therapeutic interventions
The diagnostic criteria of AC such as the global loss of shoulder ROM and night pain have been proposed by several experts [10]. However, these clinical criteria were not found to be valid diagnostic signs of AC due to the lack of information about the first 3-6 months of this disorder [9,10]. Thus, there is uncertainty about AC diagnosis and natural history [9]. The lack of understanding of early AC suggests that appropriate early treatment might be needed to avoid long-term functional limitations and disability [9].

Although studies [11] evaluating the supervised-neglect approach have shown to yield better outcomes than passive mobilization and stretching in patients with AC, the improvement in the supervised-neglect group cannot strictly be considered as the natural gentle thawing of the condition because patients were instructed to do pendulum and active exercises within the painless ROM which constitutes a home exercise program that is expected to provide therapeutic benefits [11]. Furthermore, Diercks et al. excluded patients with diabetes from their study because of concerns that the disorder behaved differently in this population subset [11]. Therefore, the supervised-neglect approach may not be applicable for patients with diabetes.

Vastamaki et al. followed-up patients with and without diabetes who have AC for the duration of 10 years [12]. Although shoulder ROM improved over time in patients with diabetes, the improvement was inferior to patients without diabetes and remained below normal ROM [12]. Other studies have also shown that patients with type 1 diabetes develop long-lasting shoulder stiffness, functional disability and reduced ROM than patients without diabetes [2,3]. These studies suggested the need to start early shoulder assessment and treatment to reduce disability and improve quality of life of patients with diabetes [2,3]. Lastly, Wong et al. showed that moderate to strong evidence supports early treatment interventions to reduce pain and improve ROM and function compared to the low evidence that supports a “no treatment” approach [9].

Several systematic reviews have examined the effectiveness of different treatment approaches for AC in generic populations, i.e. not specifically people with diabetes [13–18]. Moderate evidence showed small short-term benefits of steroid injection in reducing pain [13,14,16,18], while some physiotherapeutic interventions such as exercises and joint mobilization have been shown to reduce pain, restore shoulder ROM and function in both short and long-term [13,14,16,17]. Low to moderate evidence was found for the effectiveness of acupuncture on pain and ROM [14,16]. Furthermore, a recent randomized trial reported that acupuncture relieved pain and restored shoulder function in patients with frozen shoulder [19]. Studies of MUA and surgical capsular release that report clinical benefits unfortunately have poor methodological quality [15,18].
2.1.3 Why it is important to conduct this systematic review?

Studies have consistently reported that people with diabetes are more frequently affected by AC, have long lasting symptoms and a poor prognosis [20]. Further, although some of the therapeutic interventions have been shown to be effective in managing primary AC, several studies have reported higher shoulder pain, reduced mobility, poor functional outcomes, reduced quality of life, and a diminished response to treatment in patients with diabetes than patients without diabetes [2,3,12,21,22]. In addition, none of the aforementioned systematic reviews focused on patients with diabetes, or formally tested diabetes as a source of clinical heterogeneity in response to treatment. The underlying pathophysiology of AC in patients with diabetes may differ from non-diabetics and it is unclear whether existing recommendations for the treatment of AC can be equally applied to the subset of patients with diabetes.

2.2 Objectives

To determine the effectiveness of steroid injections, physiotherapeutic interventions (joint mobilization, laser therapy, continuous passive motion, electrotherapy, reflexology, therapeutic exercises) and MUA on shoulder pain, function, and ROM for managing adhesive capsulitis in people with diabetes.

2.3 Methods

2.3.1 Study selection

2.3.1.1 Study design
Randomized controlled trials published in English or any other language were eligible for inclusion in this review.

2.3.1.2 Participants
Trials that included adult participants aged 18 years or older with a stated diagnosis of AC and diabetes (both types) were eligible to be included in this review. Due to lack of a gold standard for the diagnosis of AC, trials were included if it was stated that participants had pain and restriction in shoulder joint ROM in one or more planes [23]. Studies that included participants with other shoulder disorders such as rotator cuff tendinitis or osteoarthritis were not eligible
for inclusion. Further, studies that excluded patients with diabetes or included patients with diabetes treated in one group with patients without diabetes were also excluded from this review unless these studies' authors provided a subgroup analysis of patients with diabetes.

2.3.1.3 Types of interventions
Trials that randomly implemented one or a combination of the following non-surgical interventions were eligible for inclusion in this review: physiotherapeutic interventions, corticosteroid injection, MUA, hydrodilatation, and suprascapular nerve block. Physiotherapeutic interventions could include, but were not limited to, mobilization techniques, exercises, electrotherapy, and patient education.

2.3.1.4 Outcome measures
Studies that assessed at least one outcome measure that is validated and commonly used to examine shoulder pain or function were eligible for inclusion. These measures could include measures of shoulder pain using Visual Analogue Scale (VAS), measures of ROM using standard or electronic goniometer, and measures of shoulder function and disability such as the Shoulder Pain and Disability Index (SPADI), Constant Shoulder Score (CSS), American Shoulder and Elbow Surgeons (ASES) and Simple Shoulder Test (SST) questionnaires. All of the questionnaires are valid and reliable to assess shoulder function in different clinical situations [24]. However, only the SPADI has specifically been validated for patients with AC [25,26].

2.3.2 Search methods for identification of studies

2.3.2.1 Electronic searches
To conduct this systematic review, an electronic search of the following databases was performed: MEDLINE, Science Direct, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane library, EMBASE, Ingenta connect, Sport Discus, Physiotherapy Evidence Database (PEDro) and ProQuest. The search of these databases was conducted on a university library system during the months of October 2017-January 2018. The search was limited to human subjects and articles published within last 20 years. Diabetes and the two most common terms used to describe the shoulder condition, "adhesive capsulitis" and "frozen shoulder", were combined using the operation "AND" and were used as key terms for the search. MEDLINE was searched using a combination of the key terms and the "AND"
operation with the following terms: "physiotherapy", "exercise", "manual therapy", "joint mobilization", "modalities", electrotherapy", rehabilitation", corticosteroids", "manipulation under anesthesia", "arthroscopy", hydrodilatation", and "suprascapular nerve block". The MEDLINE search strategy is illustrated in Box 1.

2.3.2.2 Searching other resources

Reference lists of all relevant articles were scanned in an attempt to identify any further studies. We also searched common shoulder and diabetes journals' supplements to identify conference abstracts.

2.3.3 Data extraction and management

After scanning the titles and abstracts of the identified studies, duplicate articles or those not related to the topic of interest were removed. Studies deemed to be relevant to the review were retrieved and assessed for eligibility. Data extraction was performed by two authors and included study design, subject characteristics and duration of symptoms, type of intervention, outcome measures, follow-up intervals, as well as methods of data analysis and research findings (Table 1).

2.3.4 Assessment of risk of bias in included studies

A calibration review was performed by the most experienced researcher (J.M.) and two co-authors (G.N. and P.B.) performed risk of bias assessments. Pairs of authors (G.N. and P.B.) independently applied the quality assessment tool for quantitative studies (Cochrane Risk of Bias tool) [27] on the eligible studies, and any disagreement was resolved by J.M. The authors followed the usual procedures to use the six domains documented in this tool to assess the risk of bias in the eligible studies [27].

2.3.5 Measures of treatment effect

A meta-analysis was considered at the initial plan of this systematic review as described in our published protocol on PROSPERO (https://www.crd.york.ac.uk/PROSPERO) (Registration #: CRD42018084090). However, due to the wide range of physiotherapeutic interventions (lack of similar interventions) assessed across the included studies, a meta-analysis was not
To assess the effectiveness of the interventions in the included trials, (i.e. the magnitude of the effects), we calculated the between group effect sizes by reporting the Standardized Response Mean (SRM) = $\delta_x / \text{SD} \delta_x$ [28]. The $\delta_x$ is the mean between-group differences, and the SD$\delta_x$ is the pooled standard deviation reflecting the variability of change between the two groups [28]. To allow and facilitate clinical decision making, benchmark values of trivial ($< 0.20$), small ($\geq 0.20$ to $< 0.50$), moderate ($\geq 0.50$ to $< 0.80$) or large ($\geq 0.80$), proposed by Cohen, were utilized [28]. In trials where SRM calculation was not possible (due to lack of SD reporting), we calculated and reported the between group mean differences.

2.3.6 Assessing the quality of individual RCTs

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach for systematic reviews, (GRADE guidelines: 4. Rating the quality of evidence – study limitations – risk of bias; GRADE guidelines: 5. Rating the quality of evidence – publication bias; GRADE guidelines 6. Rating the quality of evidence – imprecision (how precise is the effect size?); GRADE guidelines: 8. Rating the quality of evidence – indirectness (difference between the population of interest and those who have participated in relevant studies) [29–33], to assess the quality of individual RCTs related to three outcomes; shoulder pain, shoulder ROM and measures of shoulder function and disability. The quality rating of individual RCTs for each outcome across trials was performed to provide the extent of our confidence that the estimates of the effect were correct. The GRADE approach resulted in an assessment of the quality of individual RCTs for each outcome across trials as high, moderate, low, or very low [29–33].

2.4 Results

2.4.1 Characteristics of included studies

Our search strategy generated 165 articles on MEDLINE and 650 articles in total (Figure 1). After applying the inclusion and exclusion criteria, 10 studies were eligible to be included. Of these 10 studies, two studies were excluded because the full study was not published (conference abstracts). Eight studies were evaluated and data from these studies were extracted and summarized in Table 2. Among these eight studies, two studies were translated from Chinese [34] and Persian [35] languages into English language by two native language speakers.
All these studies were RCTs that assessed the effectiveness of physiotherapeutic interventions (joint mobilization, laser therapy, continuous passive motion, electrotherapy, reflexology, therapeutic exercises) \[34,36-38\], corticosteroid injection \[39-41\], and MUA \[35\] used to manage AC in patients with diabetes. The eight eligible studies ranged in size from 30–147 patients and included a total of 340 patients with diabetes. The main diagnosis was AC, and the mean age in studies ranged from 53 to 61 years. The duration of follow up ranged from two weeks to 12 months.

2.4.2 Risk of Bias Assessment

We completed a risk of bias assessment for each study and illustrated this in Figure 2. The main potential source of bias was performance bias in all eight RCTs, as a result of inadequate blinding of study participants and personnel \[34–41\]. Furthermore, seven RCTs were rated at high risk of selection bias due to unclear or lack of adequate random sequence generation \[34–38\] and allocation concealment \[34,35,37–41\]. Six trials demonstrated inadequate blinding of assessors – detection bias \[34,35,37–39,41\]. In addition, five RCTs were rated at high risk of attrition bias \[34,35,39–41\] and four RCTs at high risk of reporting bias \[34,35,37,41\], due to incomplete outcome data and selective reporting respectively.

2.4.3 Interventions

A wide range of non-surgical interventions were evaluated in the included trials:

1. Mulligan mobilization, pendular exercise and home exercise program vs. Maitland mobilization, pendular exercise and home exercise program \[38\].
2. Low-level laser therapy plus stretching exercises vs. Reflexology (thumb walk) plus stretching exercises \[37\].
3. Intra-articular corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDS) plus home exercise program vs. NSAIDS plus home exercise program \[41\].
4. Triamcinolone acetonide (40 mg) injection and home exercise program vs triamcinolone acetonide (20 mg) injection and home exercise program \[40\].
5. Continuous passive motion plus electrotherapy vs. active exercises plus electrotherapy \[36\].
6. 500 mg Naproxen (NSAID) and home exercise program vs. 40 mg triamcinolone and home exercise program \[39\].
7. Oral medication and exercises (control) vs. Super laser plus control vs. Super laser and thermotherapy plus control [34].
8. Manipulation under anesthesia (MUA), corticosteroid plus exercises for patients with diabetes vs. MUA plus exercises for patients without diabetes [35].

2.4.4 Outcome measures

Outcomes reported in studies were classified as: patient-reported shoulder pain (VAS) [34,36,39–41], shoulder range of motion (goniometer) [34,36–41], and measures of shoulder function and disability (SPADI [36,38], CSS [35,36], ASES [40,41] and SST [40]).

2.4.5 Effects of interventions

Effects of Mulligan mobilization, pendular exercise and home exercise program vs. Maitland mobilization, pendular exercise and home exercise program:

One trial (n = 30) assessed the effectiveness of Mulligan vs. Maitland techniques (both including pendular exercise and home exercise program), on shoulder range of motions and shoulder function and disability (SPADI), at six weeks follow up [38]. Mulligan techniques including pendular exercise and home exercise program demonstrated large effects in terms of improving shoulder range of motion, when compared to Maitland techniques with pendular exercise and home exercise program, at six weeks follow up [38]. SRM of 1.30, 1.08 and 1.0 were calculated and reported for flexion, abduction and external rotation range of motions respectively (high risk of bias; GRADE: very low quality). Similarly, Mulligan techniques (plus pendular exercise and home exercise program), displayed large effects (SRM = 2.0) in terms of improving shoulder function and disability, when compared to Maitland techniques (plus pendular exercise and home exercise program), at six weeks follow up (high risk of bias; GRADE: very low quality) (Table 2) [38].

Effects of low-level laser therapy plus stretching exercises vs. reflexology (thumb walk) plus stretching exercises:

One trial (n = 44) assessed the effectiveness of low-level laser therapy vs. reflexology (both including stretching exercises), on shoulder range of motion at eight weeks follow up [37]. We calculated and reported the between-group mean differences because SRM calculation was not possible due to lack of SD reporting. Low-level laser therapy plus stretching exercises
demonstrated between-group improvements of 14.5° (shoulder flexion), 14.0° (shoulder abduction) and 13.0° (shoulder external rotation), when compared to reflexology (plus stretching exercises), at eight weeks follow up (high risk of bias; GRADE: very low quality) [37].

Effects of intra-articular corticosteroids, NSAIDs plus home exercise program vs. NSAIDs plus home exercise program:
One trial (n = 45) assessed the effectiveness of intra-articular corticosteroid plus NSAIDs and a home exercise program vs. NSAIDs plus a home exercise program on shoulder pain and range of motion at 24 weeks follow up [41]. Intra-articular corticosteroid plus NSAIDs and a home exercise program demonstrated between-group improvements of 0.4 points on VAS (0 – 10), when compared to NSAIDs plus a home exercise program, at 24 weeks follow up (GRADE: very low quality) [41]. Intra-articular corticosteroid plus NSAIDs and a home exercise program displayed significant between-group improvements of 8.0° (shoulder forward elevation) and 2.0° (shoulder external rotation), when compared to NSAIDs and a home exercise program group, at 24 weeks follow up (high risk of bias; GRADE: very low quality) [41]. Intra-articular corticosteroid plus NSAIDs and a home exercise program displayed between-group improvements of 4.0 points on ASES, when compared to NSAIDS and a home exercise program group, at 24 weeks follow up (high risk of bias; GRADE: very low quality) [41].

Effects of continuous passive motion plus electrotherapy vs. active exercises plus electrotherapy:
One trial (n = 41) assessed the effectiveness of continuous passive motion vs. active exercises (both including electrotherapy), on shoulder pain, range of motion and shoulder function and disability (SPADI and CSS), at four weeks follow up [36]. Continuous passive motion plus electrotherapy demonstrated large effects (SRM = 1.0) in terms of reducing shoulder pain levels (pain in motion), when compared to active exercises plus electrotherapy, at four weeks follow up (high risk of bias; GRADE: very low quality) [36]. Continuous passive motion plus electrotherapy demonstrated moderate to large effects in terms of improving shoulder range of motion, when compared to active exercises plus electrotherapy, at four weeks follow up (high risk of bias; GRADE: very low quality) [36]. SRM of 2.0, 1.2 and 0.8 were calculated and reported for flexion, abduction and external rotation range of motion respectively. Continuous passive motion plus electrotherapy demonstrated large effects in terms of improving shoulder
function and disability, when compared to active exercises plus electrotherapy, at four weeks follow up (high risk of bias; GRADE: very low quality) [36]. SRM of 1.3 (SPADI – pain), 0.9 (SPADI – disability) and 1.1 (CSS) were calculated and reported (Table 2) [36].

**Effects of 500 mg Naproxen (NSAIDs) and a home exercise program vs. 40 mg triamcinolone and a home exercise program:**

One trial (n = 57) assessed the effectiveness of 500 mg Naproxen vs. 40 mg triamcinolone (both including a home exercise program), on shoulder range of motion and pain levels (at rest), at 24 weeks follow up [39]. Triamcinolone plus a home exercise program demonstrated trivial to moderate effects in terms of improving shoulder range of motion, when compared to Naproxen plus a home exercise program, at 24 weeks follow up (high risk of bias; GRADE: very low quality) [39]. SRM of 0.2 and 0.5 were calculated and reported for flexion and abduction range of motions respectively. Triamcinolone plus a home exercise program displayed trivial effects (SRM = 0.1) in terms of reducing shoulder pain levels, when compared to Naproxen plus a home exercise program at 24 weeks follow up (high risk of bias; GRADE: very low quality) (Table 2) [39].

**Effects of oral medication and exercises (control) vs. laser therapy plus control vs. laser therapy, thermotherapy plus control:**

One trial (n = 84) assessed the effectiveness of control vs. laser therapy plus control vs. laser therapy and thermotherapy plus control, on shoulder pain levels, at 20 days follow up [34]. Laser therapy and thermotherapy plus control, demonstrated between-group improvements of 5.0 and 0.9 points on VAS (0 – 10), when compared to the control group, and laser therapy plus control group at 20 days follow up, respectively (high risk of bias; GRADE: very low quality) [34]. Laser therapy plus control displayed between-group improvements of 4.1 points on VAS (0 – 10), when compared to the control group alone at 20 days follow up (high risk of bias; GRADE: very low quality) [34].

**Effects of triamcinolone acetonide (40 mg) injection and home exercise program vs. triamcinolone acetonide (20 mg) injection & home exercise program:**

One trial (n = 147) assessed the effectiveness of triamcinolone acetonide (40 mg) injection vs triamcinolone acetonide (20 mg) injection (both including a home exercise program), on shoulder range of motion, pain, function and disability levels at 12 months follow up [40]. In this trial, a subgroup analysis of patients with diabetes was performed but only the analysis of
blood parameters was provided. Therefore, we were unable to calculate and report effect sizes or between-group improvements (mean differences) of ASES and shoulder ROM (high risk of bias; GRADE: very low quality) [40].

Effects of MUA, corticosteroid and exercises vs. MUA and exercises:
One trial (n = 26, a mix of patients with and without diabetes) assessed the effectiveness of MUA plus corticosteroid vs. MUA (both including shoulder exercises), on shoulder function at six months follow up [35]. The primary group analysis revealed a non-significant difference between patients who received MUA plus corticosteroids and who received only MUA regardless of diabetes status. The authors provided another subgroup analysis of patients with (n=12) and without diabetes (n=14). MUA for patients without diabetes demonstrated between-group improvements of 5.6 points on CSS, when compared to MUA for patients with diabetes (high risk of bias; GRADE: very low quality) [35].

2.5 Discussion

This review identified very low quality RCTs (all at high risk of bias) that demonstrated benefits of a variety of non-surgical treatments in managing shoulder pain, ROM and function in patients with diabetes who have AC. Therefore, we have very little confidence in the effect estimates of these individual RCTs, or which treatments might be more beneficial.

In this systematic review, joint mobilization plus exercises [38], continuous passive motion with electrotherapy [36] and low-level laser therapy [37] demonstrated larger effects (better outcomes) on pain, ROM and function than other physiotherapeutic interventions. In addition, corticosteroids plus exercise were found to reduce pain, improve shoulder function and ROM when compared to NSAIDs plus exercise [39,41]. Lastly, shoulder function was improved with MUA in patients with diabetes, however, this improvement was less pronounced when compared to patients without diabetes [35].

Previous systematic reviews that investigated the effectiveness of different interventions for managing AC have reported conflicting conclusions. A meta-analysis of three RCTs with severe heterogeneity revealed a short-term effect of corticosteroids (effect estimate= 0.5-0.8) over joint mobilization plus exercises (effect estimate = 0.1-0.7) on pain, ROM, and function [13]. Similarly, corticosteroid injection with poor evidence was found to provide small short-term benefits on pain when compared to joint mobilization [18]. Another systematic review, that did not include a formal meta-analysis or effect size calculations, found that joint mobilization
plus exercises and laser therapy reduced pain and improved function \cite{16}. Two systematic reviews with high risk RCTs recommended the use of laser therapy and corticosteroids to reduce pain and the use of joint mobilization to improve shoulder ROM and function \cite{14,17} which concur with the findings of the current review. Lastly, MUA did not show additional benefits over the use of other non-surgical or surgical interventions \cite{15,17}.

The assessment of methodological quality of individual studies varied in these systematic reviews and there was no definitive consensus of the best treatment option for treating AC. In addition, some systematic review authors have recommended a separate analysis of patients with and without diabetes to consider the effect of different etiologies on the treatment effects \cite{15,17}.

In comparison to the current systematic review, the large effects of some physiotherapeutic interventions (mobilization plus exercises and continuous passive motion) over the corticosteroids may be due to the long-lasting symptoms in patients with diabetes that permitted a longer follow-up period \cite{12}. However, the overall evidence in this systematic review is of low quality and limits our ability to make recommendations on the best intervention for managing AC in patients with diabetes.

Clinicians should be aware that the pathophysiology and natural history may not be consistent with current evidence, and that much is yet unknown. Physicians should ensure that therapists are aware of the patient's diabetic status since this may affect recovery or response to treatment. Physiotherapists should be aware of emerging evidence on AC since the potential for changes in best practice is high given the low quality of current evidence.

2.5.1 Study limitations

This systematic review does have a number of limitations. There is very limited literature on the effectiveness of physiotherapeutic interventions, corticosteroids injection, and other non-surgical interventions for the treatment of AC in patients with diabetes. While there were few RCTs that addressed the effect of physiotherapeutic interventions (joint mobilization, laser therapy, continuous passive motion, electrotherapy, reflexology, therapeutic exercises), no identical physiotherapeutic interventions or exercise programs were utilized in any of these RCTs. Similar to the physiotherapeutic intervention’s trials, RCTs that assessed corticosteroid injections did not follow an identical protocol that would permit meaningful comparisons. We found only one RCT that addressed the effect of MUA for treating AC in patients with diabetes. This was the result of only including studies that assessed outcomes in patients with diabetes.
Although we included only RCTs, the interpretation of the results is hampered by many factors which are related to the internal validity of these studies. All the RCTs were rated at high risk of bias due to the flaws in the design, conduct, analyses and reporting of the results. In regard to precision, some RCTs included relatively small number of patients with short follow-up periods. Finally, the limited number of RCTs and variability in the interventions used precluded meta-analyses. Future large-scale well designed RCTs involving patients with diabetes who have AC are required to provide an accurate estimate of treatment effects.

2.6 Conclusion

Very low-quality evidence indicated that a combination of physiotherapeutic interventions (exercises, modalities, mobilization), NSAIDs and/or corticosteroid injections, can have trivial to large effects in terms of improving shoulder function/disability, range of motion and pain levels, in managing AC in patients with diabetes. Future high quality RCTs are needed to determine the best intervention for managing AC in patients with diabetes and to improve the confidence and precision of estimated effects.
2.6 Acknowledgments

Dr. Joy MacDermid was supported by a Canadian Institutes of Health Research Chair in Gender, Work and Health and the Dr. James Roth Chair in Musculoskeletal Measurement and Knowledge Translation. We would like to thank Ms. Shirin Modarresi for translating one article from Persian language to English and Mr. Steve Lu for translating one article from Chinese language to English.

2.7 Conflict of interest

None declared
2.8 References

13. Blanchard V, Barr S, Cerisola FL. The effectiveness of corticosteroid injections


Box 1: MEDLINE search strategy

#1,"Search diabetes"
#2,"Search (adhesive capsulitis OR frozen shoulder)"
#3,"Search (physiotherapy OR exercise OR manual therapy OR joint mobilization)"
#4,"Search ((diabetes) AND ((adhesive capsulitis OR frozen shoulder))) AND ((physiotherapy OR exercise OR manual therapy OR joint mobilization))"
#5,"Search ((modalities OR electrotherapy OR rehabilitation OR corticosteroids))"
#6,"Search ((diabetes) AND ((adhesive capsulitis OR frozen shoulder))) AND (((modalities OR electrotherapy OR rehabilitation OR corticosteroids)))"
#7,"Search ((manipulation under anesthesia OR arthroscopy OR hydrodilatation OR suprascapular nerve block))"
#8,"Search ((diabetes) AND ((adhesive capsulitis OR frozen shoulder))) AND ((manipulation under anesthesia OR arthroscopy OR hydro dilatation OR suprascapular nerve block))"
Table 1: A summary of the included RCTs

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients characteristics</th>
<th>DOS (months) &amp; DOD (years)</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Follow-up periods</th>
<th>Research findings from baseline to last session (Mean±SD, p-value)</th>
</tr>
</thead>
</table>
| **Kim et al. 2017** | n = 147  
- Group 1: 40 mg triamcinolone injection (n= 76, 23M+53F, age = 57.4 (45-76), n of diabetes = 13)  
- Group 2: 20 mg triamcinolone injection (n= 71, 18M+53F, age = 56.34 (47-78), n of diabetes = 14) | DOS: at least 2 months  
DOD: N/A | - Group 1: 40 mg triamcinolone acetone injection under sonography guide  
- Group 2: 20 mg triamcinolone acetone injection under sonography guide  
- Both groups started HEP after injection (pendulum & self-stretching passive ROM exercise in every plane for 4 weeks, pulley exercise, isometric and strengthening exercises with dumbbells started 8 weeks after injection). | - Pain at rest: VAS scale (0-10)  
- ROM: flexion, ER using goniometer (degrees) & IR; ability to reach scapula with tip of the thumb (0-4 points)  
- ASES score  
- SST  
- Blood glucose, fructosamine, and HbA1c | Baseline, 3rd, 6th, 12th weeks, 6 and 12 months after injection, and again at the final follow-up | The subgroup analysis of patients with diabetes was not summarized for the clinical scores. Authors provided data for blood glucose, fructosamine, and HbA1c levels. Authors reported a significant higher blood glucose level of patients with diabetes at 6 weeks after injection in group 1 compared with patients with diabetes in group 2 (p = 0.01) |
| **Ekim et al. 2016** | n = 41  
- Group 1: CPM (n= 20, 7M+13F, age = 60.5±8.1)  
- Group 2: CPT (n= 21, 8M+13F, age = 60.4±6.7) | DOS:  
- Group 1: 10.5  
- Group 2: 8.0  
DOD:  
- Group 1: 10.6±4.8  
- Group 2: 7.95±5.4 | - Pain: VAS scale (0-10) at rest, night, & during motion  
- Active & passive ROM: flexion, abduction, ER using goniometer (degrees) and IR; ability to reach scapula with tip of thumb (degrees)  
- CSS & SPADI: shoulder pain and function | Baseline, 4th, 12th weeks | Group 1:  
- Pain at rest 5.0±1.6 - 2.6±1.1 (0.001)  
- Pain on motion 7.4±1.5 - 4.0±1.1 (0.001)  
- Pain at night 8.1±1.09 - 4.35±0.88 (0.001)  
- Active abduction 86.5±14.0 - 123.8±15.4 (0.001)  
- Passive abduction 95.5±16.2 - 130.5±16 (0.001)  
- Active flexion 103.9±15.8 - 143±11.3 (0.001)  
- Passive flexion 112±15.9 - 150.5±11 (0.001)  
- Active ER 31.5±19.6 - 58.0±15.0 (0.001)  
- Passive ER 38.3±21.7 - 65.3±15.1 (0.001)  
- Active IR 41.3±21.0 - 70.3±13.2 (0.001)  
- Passive IR 46.0±20.9 - 77.0±10.9 (0.001)  
- SPADI pain 79.1±8.2 - 50.0±9.1 (0.001)  
- SPADI disability 67.5±9.2 - 42.8±8.3 (0.001) |
<table>
<thead>
<tr>
<th></th>
<th>Group 1: Mulligan (n=15, age = 54.8±5.85)</th>
<th>Group 2: Maitland (n=15, age = 53.4±5.23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOS:</strong> at least 3 months</td>
<td>- Group 1: Mulligan joint mobilization techniques, 3 times / week for 6 weeks. Passive accessory glide combined with active arm motion in three sets of 10 repetitions in each direction</td>
<td>- Group 1: Mulligan joint mobilization techniques, 3 times / week for 6 weeks. Oscillatory end-range mobilization grade III or IV. Both groups received pendulum exercises in all directions for 5 min and HEP (pendulum exercise and ADLs)</td>
</tr>
<tr>
<td><strong>DOD:</strong> at least 5 years</td>
<td>- SPADI</td>
<td>- SPADI</td>
</tr>
<tr>
<td><strong>Baseline and 6 weeks</strong></td>
<td>- Active ROM: flexion, abduction, IR, and ER using a digital level inclinometer</td>
<td>- SPADI</td>
</tr>
</tbody>
</table>

**Group 1:**
- SPADI: 85.15±4.24 - 163.6±5.68 (p < 0.01)
- Flexion: 52.74±10.51 - 144.28±22.23 (p < 0.01)
- Abduction: 39.46±15.55 - 133.8±22.27 (p < 0.01)
- ER: 24.57±11.16 - 83.86±6.38 (p < 0.01)
- IR: 45.6±6.01 - 69.46±6.61 (p < 0.01)

**Group 2:**
- SPADI: 82.3±7.21 - 127.6±22.02 (p < 0.01)
- Flexion: 52.78±12.73 - 119.36±30.27 (p < 0.01)
- Abduction: 40.57±19.69 - 111.96±26.91 (p < 0.01)
- ER: 25.01±14.14 - 73.3±14.72 (p < 0.01)
- IR: 45.73±5.44 - 67.56±7.21 (p < 0.01)

**Youssef et al., 2015**

| n = 30 | - Pain at rest 5.9±1.4 - 3.7±1.5 (0.001) |
|        | - Pain on motion 7.8±1.3 - 5.2±1.5 (0.001) |
|        | - Pain at night 8.62±0.86 - 5.86±1.74 (0.001) |
|        | - Active abduction 90.7±11.1 - 111.9±15.4 (0.001) |
|        | - Passive abduction 97.9±12.5 - 119.5±17.4 (0.001) |
|        | - Active flexion 113.8±10.6 - 131.4±12.7 (0.001) |
|        | - Passive flexion 118.3±10.2 - 139±12.4 (0.001) |
|        | - Active ER 42.14±14.7 - 55.5±17.6 (0.001) |
|        | - Passive ER 48.8±15.5 - 61.7±17.6 (0.001) |
|        | - Active IR 46.2±12.0 - 62.6±17.9 (0.001) |
|        | - Passive IR 52.1±11.3 - 68.1±17.1 (0.001) |
|        | - SPADI pain 81.0±6.6 - 63.2±9.7 (0.001) |
|        | - SPADI disability 72.9±7.4 - 56.1±10.8 (0.001) |
|        | - CSS 32.8±7.5 - 43.4±8.3 (0.001) |

DOS: at least 3 months
DOD: at least 5 years

- Mulligan joint mobilization techniques, 3 times / week for 6 weeks.
- Oscillatory end-range mobilization grade III or IV.
- Both groups received pendulum exercises in all directions for 5 min and HEP (pendulum exercise and ADLs).
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort Details</th>
<th>Intervention Details</th>
<th>Results</th>
</tr>
</thead>
</table>
| Soliman et al. 2014 | n = 44  
- Group 1: Low-level laser therapy (LLLT) (n= 20, 6M+14F, age = 59.55±3.03)  
- Group 2: Reflexology (n= 20, 16M+4F, age = 57.7±7.98) | DOS: 2-7 months  
DOD > 4 years  
- Group 1: LLLT for 15 min, 3 times / week for 8 weeks using laser applicator  
- Group 2: reflexology in the form of thumb walk for 15 min, 3 times / week for 8 weeks in upward, downward and diagonal directions over the shoulder area on the bottom of the foot under the little toe  
- Both groups received exercise program for 15 min (ER-passive stretch, forward flexion-supine position, crossover arm stretch, pendular exercise, hand behind back exercise). Each exercise was repeated 10 times | Authors also reported more improvement in Mulligan group in SPADI and flexion, abduction and ER ROM as compared to Maitland group  
- Significant increase in abduction (p < 0.001) in both groups at 4 and 8 weeks as compared to baseline.  
- Significant increase in ER (p < 0.001) at the 4 and 8 weeks in LLLT group compared to baseline  
- Reflexology was less effective at 4 and 8 weeks compared to LLLT group  
- Significant increase in IR (p <0.05) at 8 weeks in reflexology group but it was less than LLLT group |
| Dehghan et al. 2013 | n = 57  
- Group 1: Naproxen (NSAID) (n= 28, 11M+17F, age = 52.8±6.7)  
- Group 2: CS injection (n= 29, 8M+21F, age = 55.3±7.7) | DOS < 6 months  
DOD:  
- Group 1: 500 mg Naproxen (NSAID) twice daily  
- Group 2: single injection of 40 mg triamcinolone under sonography guide  
- Oral NSAID was administered for all patients who started HEP after 1 week (shoulder flexion, abduction, IR, 3 sessions/day, 15 reps/session).  
- Pain at rest: VAS scale (0-10)  
- ROM: flexion, abduction, ER using goniometer (degrees) & IR; ability to reach scapula with hand (plus 0-4) | - Authors also reported more improvement in Mulligan group in SPADI and flexion, abduction and ER ROM as compared to Maitland group  
No ROM values were summarized in a table except for the baseline data.  
Authors reported the following:  
- Significant increase in abduction (p < 0.001) in both groups at 4 and 8 weeks as compared to baseline.  
- Significant increase in ER (p < 0.001) at the 4 and 8 weeks in LLLT group compared to baseline  
- Reflexology was less effective at 4 and 8 weeks compared to LLLT group  
- Significant increase in IR (p <0.05) at 8 weeks in reflexology group  
- Significant increase in flexion (p <0.001) at 4 and 8 weeks in LLLT group  
- Significant increase in IR (p <0.05) at 4 and 8 weeks in reflexology group but it was less than LLLT group |
### Roh et al. 2012

<table>
<thead>
<tr>
<th>Group 1: CS injection</th>
<th>Group 2: NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 23, 16M+7F, age = 54.4±10.9</td>
<td>n = 22, 14M+8F, age = 55.3±11.2</td>
</tr>
</tbody>
</table>

**DOS:**
- Group 1: 6.2±4.3
- Group 2: 6.5±4.0

**DOD:** N/A

- Group 1: intra-articular CS composed of 40 mg triamcinolone acetonide under sonography guide. Patients were also offered oral NSAIDs.
- Group 2: NSAIDs

- Both groups received HEP initiated one day after injection (4-quadrant stretching program in flexion, ER, IR, and cross-body adduction for 3 times/day).

- Pain at rest: VAS scale (0-10)
- ROM: passive flexion, ER at 0 abduction using goniometer (degrees) & IR: ability to reach scapula with tip of the thumb (0-10 points)
- ASES score

**Pain at rest**

### Liang et al. 2012

<table>
<thead>
<tr>
<th>Group 1: control</th>
<th>Group 2: Super laser</th>
<th>Group 3: Super laser + thermotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 28, 12M+16F, age = 54.36±3.87</td>
<td>n = 28, 10M+18F, age = 53.64±3.29</td>
<td>n = 28, 13M+15F, age = 53.68±4.02</td>
</tr>
</tbody>
</table>

**DOS:**
- Group 1: 6.64±2.12
- Group 2: 6.64±2.18
- Group 3: 6.57±2.02

**DOD:** N/A

- Group 1: oral medication and shoulder exercises 30 to 40 times per day for 20 days.
- Group 2: super laser using probe (intermittent followed by continuous irradiation for 7 min on each trigger point with output power of 80 to 100%, one time per day for 20 days) + Group 1 treatment.
- Group 3: including the treatment of group 1 and 2 in addition to thermotherapy (using fumigation tank, temperature between 38 to 45℃, 30 min per day for 20 days). Traditional Chinese medicine was added to the tank (medicine names and amounts are listed in the original article).

**The degree of shoulder pain (VAS) and shoulder movement (integral score) as follow:**

- Cure: VAS = 0
- Effective: 0 < VAS ≤ 2
- General: 2 < VAS ≤ 5
- Invalid: VAS > 6

Baseline, and 20 days after treatment

**Baseline, 4th, 12th, and 24th week**

### Guity et al. 2007

<table>
<thead>
<tr>
<th>Group 1: MUA + CS. Intravenous CS was provided prior to manipulation which</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 26, 12 patients with diabetes 5M+21F</td>
</tr>
</tbody>
</table>

**DOS:** N/A

**DOD:** N/A

Group 1: MUA + CS. Intravenous CS was provided prior to manipulation which

- Pain and ROM: CSS questionnaire (0-100)

Baseline, two and six weeks, then

Authors reported statistically significant improvement in both groups overtime with a non-statistically significant difference between

---

51
Age = 55.7 ± 5.1
- Group 1: MUA + CS injection (n = 13)
- Group 2: MUA (n = 13)
Another subgroup analysis for patients with diabetes (n=12) and patients without diabetes (n= 14) were provided when the effect of CS between the primary groups was non-significant

was done from supine position while the affected shoulder was flexed, and then moved into 90 degrees of abduction and then rotated outward. All patients received shoulder exercises. Group 2: MUA and shoulder exercises.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1: MUA + CS</th>
<th>Group 2: MUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>29.4 ± 7.4</td>
<td>28 ± 4.2</td>
</tr>
<tr>
<td>After</td>
<td>86.9 ± 8.5</td>
<td>82.7 ± 5.1</td>
</tr>
</tbody>
</table>

From the sub-analysis of patients with diabetes:

**Patients with diabetes:**
- Before MUA: 25.9 ± 3.2
- After MUA: 79 ± 4.9

**Patients without diabetes:**
- Before MUA: 31.1 ± 6.8
- After MUA: 89.8 ± 4.6

Authors reported a statistically significant difference between patients with and without diabetes (p = 0.01)

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: MUA + CS injection</td>
<td>29.4 ± 7.4</td>
<td>86.9 ± 8.5</td>
</tr>
<tr>
<td>Group 2: MUA</td>
<td>28 ± 4.2</td>
<td>82.7 ± 5.1</td>
</tr>
</tbody>
</table>

**Additional Abbreviations:**
- RCT: randomized clinical trial
- NSAID: non-steroidal anti-inflammatory drug
- CS: corticosteroids
- M: male, F: female
- DOS: duration of symptoms
- DOD: duration of diabetes
- HEP: home exercise program
- IR: internal rotation
- ER: external rotation
- VAS: visual analogue score
- ROM: range of motion
- CPM: continuous passive motion
- CPT: conventional physiotherapy treatment
- CSS: constant shoulder score
- SPADI: shoulder pain and disability index
- US: ultrasound
- TENS: transcutaneous electrical nerve stimulation
- ASES: American shoulder and elbow surgeons
- SST: simple shoulder test
- MUA: manipulation under anesthesia
Figure 1: Flow diagram showing study selection process
Figure 2: Risk of bias summary- review authors’ judgements about each risk of bias item for each included study
Table 2: A summary of the original outcome measures and the Standardized Response Mean

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure mean and SD</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ekim et al. 2016</strong></td>
<td>- Group 1: pain in motion 7.4±1.5 - 4.0±1.1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>- Group 2: pain in motion 7.8±1.3 - 5.2±1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: active flexion 103.9±15.8 - 143±11.3</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>- Group 2: active flexion 113.8±10.6 - 131.4±12.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: active abduction 86.5±14.0 - 123.8±15.4</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>- Group 2: active abduction 90.7±11.1 - 111.9±15.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: active ER 31.5±19.6 - 58.0±15.0</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>- Group 2: active ER 42.1±14.7 - 55.5±17.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: SPADI pain 79.1±8.2 - 50.0±9.1</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>- Group 2: SPADI pain 81.0±6.6 - 63.2±9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: SPADI disability 67.5±9.2 - 42.8±8.3</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>- Group 2: SPADI disability 72.9±7.4 - 56.1±10.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: CSS 32.1±8.5 - 50.8±5.6</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>- Group 2: CSS 32.8±7.5 - 43.4±8.3</td>
<td></td>
</tr>
<tr>
<td><strong>Youssef et al. 2015</strong></td>
<td>- Group 1: SPADI 85.15±4.24 - 16.36±5.68</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>- Group 2: SPADI 82.3±7.21 - 32.76±22.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: flexion: 52.7±10.51 - 144.28±22.23</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>- Group 2: flexion: 52.7±12.73 - 119.36±30.27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: abduction: 39.46±15.55 - 133.80±22.27</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>- Group 2: abduction: 40.57±19.69 - 111.96±26.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: ER: 24.57±11.16 - 83.86±6.38</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>- Group 2: ER: 25.01±14.14 - 73.3±14.72</td>
<td></td>
</tr>
<tr>
<td><strong>Dehghan et al. 2013</strong></td>
<td>- Group 1: pain: 5.64±2.43 - 1.99±1.98</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>- Group 2: pain 6.18±2.17 - 2.24±2.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: flexion: 107.6±15.7 - 167.6±22.0</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>- Group 2: flexion: 103.7±22.3 - 167.4±24.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Group 1: abduction: 99.2±22.6 - 170.0±22.9</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>- Group 2: abduction: 90.6±21.3 - 172.9±21.6</td>
<td></td>
</tr>
</tbody>
</table>

SRM: Standardized Response Mean, SD: standard deviation, ER: external rotation, SPADI: shoulder pain and disability index, CSS: constant shoulder score.
CHAPTER 3:

PHYSIOTHERAPY EXERCISE PROGRAM FOR MANAGING ADHESIVE CAPSULITIS IN PATIENTS WITH AND WITHOUT DIABETES: A PILOT RANDOMIZED TRIAL

The manuscript is submitted to the Archives of Orthopaedics

**Abstract**

**Study design:** Prospective randomized pilot trial

**Background:** Adhesive capsulitis (AC) occurs five times more often in people with diabetes. Exercises are usually recommended to manage AC. However, the recovery is slow and often incomplete, especially for patients with diabetes. Aerobic exercises improve hyperglycemia and insulin sensitivity. Currently, no research has formally assessed the benefits of incorporating an aerobic walking training program into the treatment plan of AC in patients with diabetes.

**Purpose:** This pilot trial compared the effect of a regular physiotherapy (PT) program (PT) to a regular PT program combined with a progressive walking program (PT+) in patients with and without diabetes who have AC.

**Methods:** Eight patients with (n = 3) and without (n = 5) diabetes (five men and three women, with mean age of 57 years) were included. Patients were randomly allocated either to PT or PT+ groups. The primary outcome of shoulder function was measured using the Functional Impairment Test-Hand and Neck/Shoulder/Arm (FIT-HaNSA) test. Secondary outcomes included shoulder pain and function; shoulder range of motion in flexion, abduction, and external rotation; muscle strength of shoulder flexors and abductors; and physical activity level. The primary outcome was evaluated at baseline and after six weeks. Secondary outcomes were evaluated at baseline, and after three, six and 12 weeks from enrollment.

**Setting:** Single centre study at a tertiary-care hospital.

**Results:** A total of 13 patients were contacted with study details, only eight patients agreed to participate, with a 62% recruitment rate. Adherence with research centre visits was 97%. Patients in both groups showed improvement in all outcome measures. The FIT-HaNSA scores had a mean improvement of 38±17 in the PT group and 6±33 in the PT+ group from baseline to six weeks follow-up. Future studies, with 80% power (α= 0.05, β= 0.20) to detect a 20% between-group difference, would require a sample size of 89 participants per group.

**Conclusion:** This pilot trial established that conducting a large-scale study to assess the effect of physiotherapy program for managing AC is feasible. The current findings suggest that physiotherapy exercises may be effective in reducing pain and improving shoulder function and ROM in patients with and without diabetes who have AC. Researchers should be aware of
the recruitment challenges and should work on minimizing performance and detection bias by blinding study personnel and outcome assessors.


**Keywords:** Adhesive capsulitis, Diabetes, Physiotherapy, Pilot trial
3.1 Background

Adhesive capsulitis (AC), also known as ‘frozen shoulder’, is characterized by the development of dense adhesions and capsular thickening leading to a progressive and painful restriction of shoulder range of motion (ROM) and functional disability [1]. The onset is gradual, usually occurs between the ages of 40 and 60 years [2] and is more common in females and patients with diabetes [3]. Adhesive capsulitis has been described as a self-limiting condition that progresses through pain, frozen and thawing phases. However, Wong et al. examined the quality of the evidence that describes the theory of AC phases and reported a lack of evidence to support these theoretical phases of AC [4].

Based on Codman’s criteria [5], the condition can be classified as primary or secondary AC. Primary or idiopathic AC has no clear underlying cause [5]. However, secondary AC might develop following soft tissue injury, joint arthritis, or secondary to known systemic disease such as diabetes [6]. The association between diabetes and AC was first reported by Bridgman (1972) who found that 10.8% of patients with diabetes had AC as compared to 2.3% for patients without diabetes [7]. Subsequent studies have supported this association and reported a prevalence of AC in 10-76% type 1 and 7-30% type 2 diabetes as compared to 0-10% in the general population [1,8–11]. Adhesive capsulitis was also reported to be associated with age in both types of diabetes [8] and with the duration in type 1 diabetes [9,10,12].

The pathophysiology that predisposes patients with diabetes for the development of AC is not well-understood. Proposed mechanisms that may lead to AC include increased glycosylation of collagen fibers of the joint capsule and diabetic microangiopathy induced fibrosis [1,13,14].

The usual approach for managing AC includes steroid injections, joint mobilization techniques and the implementation of shoulder exercises to restore function. Several systematic reviews reported that active exercises and joint mobilization can reduce pain, restore shoulder ROM and function in both short- and long-term follow up [15–18], while moderate-quality evidence showed a short-term beneficial effect of steroid injection in reducing pain during the early stage of AC [15–17,19]. Only one recent systematic review has assessed the effectiveness of non-surgical intervention for managing AC in patients with diabetes and reported that low quality evidence suggests large effects of joint mobilization plus exercises on AC in patients with diabetes with a weaker support for the use of steroid injection and manipulation under anesthesia [20].
Although some of the non-surgical interventions have been shown to be effective in managing AC, recovery is slow and often incomplete, especially for people with diabetes \[21\]. Patients with diabetes often develop long-lasting shoulder stiffness, higher shoulder pain, functional disability and reduced ROM than patients without diabetes [9,10,22,23]. Furthermore, greater shoulder pain and disability were associated with poor glycemic control and diabetic complications [24].

Aerobic exercises can improve hyperglycemia and insulin sensitivity in skeletal muscle, and induce a favorable effect on blood vessels that can reduce diabetes related complications such as hypertension, hyperlipidemia, and obesity \[25\]. These effects may have a greater impact on the AC pathophysiology. However, none of the previous research has formally assessed the benefits of incorporating an aerobic training program into the treatment plan of AC in patients with diabetes. At present, there is no optimal physical therapy protocol for managing AC in patients with diabetes.

The purpose of this pilot randomized trial was to compare the effect of a regular physiotherapy (PT) program to a regular PT combined with a progressive walking program (PT+) in patients with and without diabetes who have AC. This pilot trial also evaluated the feasibility of recruitment, randomization, retention, assessment procedures, and implementation of the novel intervention. Data from this pilot trial was used to calculate an accurate sample size for a full-scale randomized clinical trial RCT. The secondary objective was to determine if diabetes affects response to treatment.

### 3.2 Methods and materials

#### 3.2.1 Study design and setting

A prospective single-blinded parallel pilot RCT was conducted at a tertiary hospital. Local Research Ethics Board has approved the study (Project ID: 111647).

#### 3.2.2 Inclusion and exclusion criteria

**Inclusion criteria:** 1) A confirmed diagnosis of AC. A diagnosis of AC was confirmed by the consultant shoulder surgeon (KF), who was blinded to treatment allocation, based on the following diagnostic criteria: shoulder pain for at least one month; inability to sleep on the affected side; and restriction of active and passive ROM in one or more planes \[26\]; 2) Patients aged 18 years or more; 3) Ability to participate in the study and follow treatment instructions.
Exclusion criteria: Patients with previous shoulder surgery, significant shoulder injury within six-months, history of shoulder dislocation or arthritis, and patients with suspected rotator cuff disease were excluded from this study.

3.2.3 Outcome measures

3.2.3.1 Primary outcome measure

The primary outcome was the Functional Impairment Test - Hand and Neck/Shoulder/Arm (FIT-HaNSA) test. The FIT-HaNSA test measures the functional performance of the upper limb, while performing multi-level tasks. In the first task (waist-up), the patient lifts three one-kg containers one at a time, with the affected arm, between a shelf at waist level and a shelf 25 cm higher at speed of 60 beats per minute for five minutes or until patient is unable to continue. In the second task (eye-down), the patient returns the three containers back to the waist level shelf. In the third task (overhead work), using both arms, the patient repeatedly screws and unscrews bolts to simulate overhead work for five minutes or until the patient feels unable to continue. Each task was timed with a stopwatch and the rhythmic speed was controlled using an auditory metronome (Soundbrenner, Berlin). All tasks were performed from a standing position. This test has been shown to be valid and reliable [27].

3.2.3.2 Secondary outcome measures

Secondary outcomes included shoulder range of motion (ROM) in flexion, abduction, and external rotation using a standard goniometer; shoulder pain and function using Shoulder Pain and Disability Index (SPADI) questionnaire; muscle strength of shoulder flexors and abductors using a dynamometer; and physical activity level using an accelerometer (Fitbit) and the Rapid Assessment of Physical Activity (RAPA) questionnaire. Secondary outcome measures were collected by a single physiotherapist at baseline, and at three, six, and 12 weeks.

Shoulder ROM

Shoulder ROM was measured using a standard goniometer with known concurrent validity and reliability [Intraclass Correlation Coefficients (ICCs) > 0.94] [28]. Active flexion and abduction ROM were assessed by measuring the angle formed by the arm and thorax from sitting position. The axis of the goniometer was located at the acromion process; the movable bar was parallel to the humerus while keeping the stationary bar parallel to the trunk [29].
Active external rotation was assessed in sitting position with the arm adducted and the elbow at the side and flexed to 90 degrees. The axis of the goniometer was located at the olecranon process of the elbow and both the stationary and movable bars were parallel to the forearm [29].

Shoulder pain and function
Shoulder pain and function were assessed using SPADI questionnaire [30]. This self-report questionnaire consists of two subscales: pain (five items) and function (eight items). The pain subscale is rated on scale from zero (no pain) to 10 (worst pain ever). The patient is asked to circle the number that best describes their pain and/or disability. The subscale scores are calculated by adding the item scores for that subscale and dividing this number by the maximum score possible for the items that are deemed applicable by the subject. This number is then multiplied by 100. The two subscales are then added and the total out of 130 is then multiplied by 100. Higher scores indicate greater impairment or disability [30,31]. The SPADI has been shown to be a valid and reliable measure of shoulder pain and disability [32]. A SPADI score can detect change over time, accurately discriminates among patients who have improved or worsened [31] and has been used in patients with AC [33,34].

Muscle strength
Isometric muscle strength was assessed for shoulder flexors and abductors using the JTech Power Track handheld dynamometer (JTech; JTech Medical, Salt Lake City, UT, USA), with known concurrent validity [35] and reliability (ICCs 0.89-0.98) [36]. Patients were seated on a straight back chair to stabilize the trunk. Abductor strength was measured by placing the device on the lateral aspect of mid-humerus and flexor strength was measured by placing the device on the anterior aspect of the upper arm.

Assessment of physical activity level
Physical activity level was measured objectively using an accelerometer (Fitbit Zip) and subjectively use a self-reported questionnaire (RAPA). Physical activity level was objectively measured using the Fitbit Zip (Fitbit Inc, USA). This activity tracker contains a three-dimensional accelerometer and is designed to track steps, distance and calories burned. Fitbit Zip is small and discreet and can be worn in a pocket, on a belt or on a bra. Data from the Fitbit Zip syncs automatically to a computer or smartphone using free online application software. Participants were asked to wear the device during all waking hours and to sync their devices on a daily basis for six consecutive weeks. Step count and distance data were obtained from
the Fitbit Zip and summarised into an activity tracking sheet. This device has been validated and found to be comparable to other accelerometers\textsuperscript{[37,38]}. Physical activities were subjectively assessed using RAPA which consists of nine self-reported questions that assess physical activity levels with a response option of yes or no. The first seven questions assess weekly aerobic activity ranging from sedentary to vigorous levels with a total score of 1-7 points, where 1 = rarely do any physical activity, and 7 = 20 minutes of vigorous activities 3+ days/week. A respondent's physical activity score is categorized into one of five levels of physical activity: sedentary, underactive, regular underactive (light activities), regular underactive, and regular active. The other two questions assess strength and flexibility training with a total score of three points; one point for strength training and two points for flexibility training. A full description of RAPA is published\textsuperscript{[39]}. The RAPA questionnaire has been validated for use in clinical practice with older adults\textsuperscript{[39]}.

3.2.4 Procedures

Patients with and without diabetes, who have been diagnosed with AC were recruited from orthopedic clinics at our tertiary hospital via surgeon referrals. Eligible patients were then given a letter of information and were asked to sign a consent form. After signing the consent form, patients attended an orientation session and were provided with information about the study and the experimental design. Patient's weight, height, age, gender, type and treatment of diabetes, affected shoulder side (right or left; dominant or non-dominant), and the duration of AC symptoms were collected during this session. Patients were then asked to complete two outcome questionnaires (SPADI and RAPA) and a Katz comorbidity scale\textsuperscript{[40]}. Next, patients underwent blinded randomization into one of the two groups: regular PT program or regular PT with a progressive walking program (PT+). The randomization was stratified by intervention (walking program) and diabetes status using a computer-generated random number table. Patients were allocated into groups using sequentially numbered, opaque, and sealed envelopes issued by the blinded assistant research. The initial intention of this study was to refer all patients to physical therapy facilities according to their preferences. However, because some patients were recently completed their PT treatment and some others were unable to start a formal PT treatment due to the long wait list at physiotherapy clinics, those patients were provided with a home exercise program from the research team. This program included a group of shoulder exercises that are proven to improve
shoulder clinical outcomes in patients with AC. A detailed exercise program is described online [41].

In the PT+ group, patients were instructed to walk at their own pace for 30-45 min, five days per week for six consecutive weeks. They recorded their walking date/time on a diary form provided by the research team. Patients in the PT+ group were not restricted from walking more than 45 minutes a day, as long as they did not feel tired or uncomfortable. Patients in both groups were provided with a Fitbit Zip accelerometer to accurately estimate their physical activity level.

Diabetes Canada is recommending a minimum of 150 minutes per week of at least moderate-intensity cardiorespiratory exercise to improve cardiovascular risk [42]. Improvements in arterial stiffness and insulin resistance have been documented after only three weeks of aerobic exercise training. To maintain a long-term effect, longer durations are recommended [43].

Walking is type of cardiorespiratory exercise training that is affordable and easy, costs nothing, safe and gentle enough for patients with comorbidities and can be done anytime, just about anywhere. However, patients with diabetes must be checked for the presence of diabetic foot as this may prevent the ability of patients to walk due to the potential adverse effect of weightbearing exercises on foot health [44].

The primary outcome measures were evaluated by a single research team member at baseline and after six weeks. Secondary outcomes were evaluated at baseline, at three and six weeks, and again at 12 weeks after enrollment (Figure 1).

3.2.5 Statistical Analysis

Statistical analysis was performed using SPSS, version 21 (SPSS Inc., Chicago, IL, USA). The analysis of this pilot study is mainly descriptive. Estimates of means and standard deviations for continuous outcomes measures, and an estimate of the proportion for categorical outcome measures were calculated. The recruitment rate was calculated by dividing the total number of patients who consented to participate by the total number of patients contacted with study details. The attendance rate was calculated by dividing the actual number of visits by the total number of all patients’ visits.

3.3 Results
Thirteen consecutive patients with AC were referred by the orthopedic surgeon (KF) between September 2018 and November 2019. Of the 13 patients contacted with study details, only eight patients, including three patients with diabetes, agreed to participate in this study, a 62% recruitment rate (8/13). Adherence with scheduled research centre visits was excellent with a 97% attendance rate (31/32). Only one patient missed the final follow-up visit which included completing SPADI and RAPA questionnaires and measures of active ROM and muscle strength.

This study included five male and three female patients with mean age of 57 years. Table 1 presents the clinical characteristics of patients for both PT and PT+ groups. Six patients were allocated in the PT group, including three patients with diabetes, and two patients were allocated in the PT+ group. Patients in the PT group were overweight with a Body Mass Index (BMI) of 26 and reported more comorbidities (Table 1).

Three patients (two in PT+) were enrolled in a formal physiotherapy program that included ROM, stretching and strengthening exercises (two patients received one session/month; one patient received 12 sessions: two sessions/week), and five patients were provided a home exercise program by the research team (the five patients completed a formal PT program before the beginning of this study which included PT modalities and exercises).

3.3.1 Change over time in outcome measures

All patients showed improvement over the six weeks follow-up time in the FIT - HaNSA outcome measure (from 155±89 to 180±88). This improvement was more pronounced in the PT group as illustrated in Table 2. Similarly, all patients had improvements in SPADI (pain, function, total), active ROM (flexion, abduction, external rotation), and muscle strength (flexors and abductors) over the 12-week follow-up period. The improvement of these outcome measures was more pronounced in the PT group when compared to PT+ group (Table 2).

The physical activity level of both groups remained the same throughout the study (RAPA = 6) (Table 2). When comparing groups, the PT+ group was more active at the six and 12-week follow-up times (RAPA = 7, 8, respectively) and showed higher step counts and longer travelled distances over the six-week use of the Fitbit activity tracker (Table 3).

3.3.2 A comparison between patients with and without diabetes

Table 4 and 5 present a comparison between patients with and without diabetes for all outcome measures. In general, patients with diabetes were younger (53±11 years) and had AC for a
longer period of time (29±38 years). In addition, patients with diabetes had worse baseline outcome measures and their improvement at six weeks was less pronounced when compared to patients without diabetes. However, patients with diabetes showed higher improvement at 12-week follow-up period compared to patients without diabetes in response to a physiotherapy exercise program (Table 4).

The level of physical activity for patients with diabetes was less at baseline (RAPA = 5) but increased over time and became higher than patients without diabetes at week 12 (RAPA = 7). However, patients without diabetes showed a higher step count and longer travelled distances as compared to patients with diabetes over the six-week use of the Fitbit activity tracker as presented in Table 5.

### 3.3.3 Sample size:

Sample size calculations were based on the mean FIT-HaNSA scores and the pooled Standard Deviation (SD) at the six-week follow-up visit. We calculated the sample size for future studies using the following equation \[^{[45]}\]:

\[
N = 2 \times \left( \frac{z_{1-\beta} + z_{1-\alpha}}{\delta} \right)^2 \times S^2
\]

Where,

- \(N\) = size per group;
- \(1-\beta\) = the power to detect a difference if one truly exists; for 80% this is 0.84
- \(\alpha\) = the probability of making a Type I error = 0.05;
- \(z_s\) = the z-score/standard normal deviate for a two-sided x; for 5% this is 1.96
- \(S^2\) = Pooled standard deviation of both comparison groups = 88;
- \(\delta\) = a clinically acceptable margin = 36. This was determined by calculating a 20% clinically important difference in the follow-up mean score.

\[
N = 2 \times (1.96 + 0.84 / 36)^2 \times (88)^2 = 77 \text{ per group}
\]

\[
\text{Total} = 2 \times 77 = 154
\]

Considering a drop-out rate of 15%, the total sample size required is 178 (89 per group).
3.4 Discussion

This prospective randomized pilot trial determined that conducting a large-scale study to assess the effect of physiotherapy program for managing AC is feasible. However, the effect of adding a progressive walking program to PT exercises was not tested for patients with diabetes due to the stratified randomization with this small sample; all patients with diabetes (n = 3) were randomized to the regular PT program group. Participant recruitment was satisfactory and there were no dropouts. For future studies, a sample size of 178 (89 participants per group), to detect 20% difference between groups is required. Seven patients would need to be recruited each month over 26-month period to successfully complete the trial in a single Centre. A multicenter approach may be more pragmatic and efficient.

This study demonstrated that clinical outcomes including shoulder performance, shoulder pain and function, active ROM, and muscle strength improved in patients with AC over a 12-week follow-up period. The improvement was more pronounced in the PT group as compared to PT+ group; however, we consider these results unstable due to the very low sample size of PT+ group. However, patients in PT+ group were more physically active as indicated by RAPA and Fitbit results. This can be due to the nature of our study in which the research team encouraged patients in the PT+ group to perform regular walking activity. Provision of the Fitbit might in itself have acted as a motivator for improving physical activity; since this is not standard practice. Although patients with diabetes had worse outcome measures at baseline, they improved overtime and showed greater recovery at week 12 when compared to patients without diabetes. At the 12-week follow-up visit, two patients without diabetes reported severe pain and inability to move their arm after performing intensive housekeeping activities. This may explain the inferior recovery in the patient without diabetes group. However, the level of physical activity was lower in patients with diabetes at baseline as indicated by the Fitbit results although the RAPA score was higher in patients with diabetes. The sample size was too small to detect treatment differences and to make definitive conclusions. However, the preliminary findings of this study, including the excellent adherence rate to research centre visits and the acceptable recruitment rate show that the novel approach taken in this pilot trial is worthy of investigation in future randomized trials.

It was difficult to recruit the required number of patients for this pilot trial. Although our recruitment rate was acceptable (62%), not all patients agreed to take part in the trial and few
(n=13) were referred to our centre. Patients had several reasons for refusing to participate in the study including lengthy travel distances to the research centre and insufficient time to commit to the study. The low recruitment rate in this trial may be due to the fact that patients with early stages of AC are usually seen by primary care centres who prescribe patient medications and refer them to physiotherapy facilities. The variable course of AC, the variations in referral patterns as many practitioners are involved in the care of AC, the delays from referral to specialist assessment, and the diagnostic uncertainty of AC limited us from recruiting enough patients to this trial. In the future, large trials on patients with AC may be best conducted at a primary care clinical setting.

The research team leader (SA) was not part of the clinical team and this also may have affected recruitment of subjects for the study. In spite of the research leader regularly communicating with other clinical team members such as physiotherapists and administrative people, the recruitment was lower than expected. As this is a critical issue, improving communication between researchers and clinical team members may be important.

In this trial, the rate of recruitment (62%) was acceptable and the rate of adherence (97%) was excellent, with only one patient lost to a final follow-up session. Patients were required to participate in many assessment sessions, an initial assessment session and in three more assessment sessions (at three weeks, six weeks, and 12 weeks), and to attend physiotherapy treatment sessions or perform the home exercise program. Both of these programs involved time and effort from patients. This suggests that with the current methodology, a future study is feasible and performing advanced statistical analysis with larger sample sizes seems achievable. However, it is important to take into account that AC is a disabling condition and patients are usually eager to try something to get their shoulder feeling better. If it was less disabling, the adherence to the program would likely be lower.

Due to the random and concealed allocation of patients in this trial, selection bias was minimized. In addition, patients in this trial were blinded to treatment groups, PT vs. PT+, and were randomly referred to physiotherapy facilities that might minimized performance bias. However, since some patients were given a home exercise program by the research leader, there may be a source of performance bias. Further, the research leader performed all the assessments and was aware of group allocations which is considered a source of detection bias. The attrition rate was minimal during the baseline, three weeks, and six weeks assessment sessions, however, at 12-week assessment session, one patient was lost to follow-up with an attrition rate of 13%. Lastly, based on our initial registered protocol, all the mentioned primary and secondary outcomes were collected and reported in this trial which minimized reporting
bias. However, there was an intention to collect data at 24-week follow-up session, but because patients were unwilling to attend this session, no data was collected.

The main aim of all AC physiotherapy programs is to relieve pain, improve function, increase shoulder ROM and to improve the patient’s quality of life. In the current literature, there is no consensus on the most appropriate treatment for AC in patients with and without diabetes.\textsuperscript{[20,46]}

Several studies have shown that physiotherapy interventions (mainly exercises) reduce pain, restore shoulder function, and improve ROM in patients with and without diabetes who have AC\textsuperscript{[15–18,47–51]}, which concur with the results of the current trial. However, the recovery might be similar\textsuperscript{[52]} or inferior\textsuperscript{[21]} to patients without diabetes contradicting the results of this pilot trial. Because of the very low sample size of patients with diabetes in this pilot trial, comparing its results to other studies could be misleading.

The improvements in shoulder pain, function and motion of the shoulder joint following physiotherapeutic interventions may be explained by the mechano-transduction mechanism by which cells convert external mechanical stimuli or force (e.g. exercise and massage) into a set of biochemical reactions that elicit adaptive responses in the tissue. For example, controlled self-stretching exercises and vacuum massage are reported to be effective in promoting collagen remodeling and maturation by breaking down adhesions and inducing collagen realignment. These changes in turn reduce motion restriction, decrease pain and improve function\textsuperscript{[53,54]}.

Fitbit Zip was reported as a valid activity tracker for recording step count and covered distance\textsuperscript{[38]}. Our results in Table 3 showed some discrepancies between steps count and the actual covered distance. Therefore, we would question the accuracy of this type of activity trackers and recommend for the use of more accurate types of activity trackers in future trials.

Lastly, no previous research has investigated the effect of incorporating specific shoulder exercises with aerobic training program to investigate shoulder recovery in patients with diabetes who have AC. Aerobic exercises that improve hyperglycemia and insulin sensitivity in skeletal musculature may have an impact on the pathophysiology of AC. Because none of our patients with diabetes were randomized to the group that include regular walking program, examining this effect was not possible. Future studies are required to examine the effect of adding walking program to the shoulder specific exercises for managing AC and to assess if walking is the ideal aerobic exercise for this population or other aerobic programs such as swimming or biking.
3.4.1 Strengths and limitations

The strengths of this study are: (1) All assessment sessions were performed by the research leader which reduced assessment variations among patients; (2) This trial reduced selection bias by having a computerized randomization process; (3) In this trial, the surgeon and the research leader were trained and experienced in the field of shoulder rehabilitation which contributed to the successful conduct of this trial. However, there are some limitations to this pilot that need to be recognized: (1) Having a small sample size has reduced the power of this trial; (2) The inability to blind the outcome assessor has introduced detection bias to this study; (3) Since no patient with diabetes were randomized to the walking program, examining the effect of incorporating aerobic program to specific shoulder exercise for managing AC was not possible. However, future studies considering a walking program for patients with diabetes must consider the presence of diabetic foot as this may prevent the ability of patients to do walking due to the potential adverse effect of weightbearing exercises on foot health [44].

3.4.2 Clinical impacts and future research directions

- This study suggests that physiotherapeutic exercises might be effective in reducing pain and improving shoulder function in patient with and without diabetes who have AC.
- Based on the findings of the current pilot trial, we have calculated the sample size for future randomized trials; for a trial to have 80% power (\(\alpha=0.05, \beta=0.20\)), and to detect 20\% difference between-groups, it would require a minimum of 89 participants per group and 178 participants in-total.
- Rigorous randomized controlled trials are needed to define the optimal combination of physiotherapy interventions for managing AC in patients with and without diabetes.
- Future trials should be well-designed to minimize biases and should be reported using CONSORT criteria [55].
- Better reporting of standardized outcomes is needed including reliable and responsive measures of physical activity level (RAPA) and FIT-HaNSA. Standardized measurement instruments would improve the quality of existing research and contribute to the ability to conduct meta-analysis in future.
- The research team members have identified some barriers to patients’ recruitment. Future trials should be aware of the possible challenges of conducting a large-scale randomized trial.
3.5 Conclusion

This randomized pilot trial established that conducting a large-scale study to assess the effect of physiotherapy program for managing AC is feasible. However, the effect of adding progressive walking program to PT exercises was not tested for patients with diabetes due to the stratified randomization with this small sample; all patients with diabetes were randomized to the regular PT program group. The current findings suggest that physiotherapy exercises may be effective in reducing pain and improving shoulder function and ROM in patients with and without diabetes who have AC. Researchers should be aware of the recruitment challenges and should work on minimizing performance and detection bias by blinding study personnel and outcome assessors.
2.6 References

14. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products:


38. Tully MA, McBride C, Heron L, Hunter RF. The validation of Fitbit Zip™ physical...


Figure 1: Flow diagram of the pilot study
Table 1: Clinical characteristics of patients (n = 8)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group allocation</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT</td>
<td>PT+</td>
</tr>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Age: mean ± SD (range) years</td>
<td>56±8 (43 - 65)</td>
<td>61±4 (59 - 64)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>4:2</td>
<td>1:1</td>
</tr>
<tr>
<td>Affected side (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Left</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of AC (months)</td>
<td>17±27 (2 - 72)</td>
<td>6±1 (5 - 7)</td>
</tr>
<tr>
<td>Diabetes (yes / no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>5±7 (6 - 17)</td>
<td>--</td>
</tr>
<tr>
<td>Heart disease (n)</td>
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<td>1</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Stomach ulcers (n)</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Kidney disease (n)</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Depression (n)</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Osteoarthritis (n)</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Back pain (n)</td>
<td>3</td>
<td>1</td>
</tr>
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</table>

Table 2: Descriptive analysis of outcome measures for PT and PT+ groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline (Mean ± SD)</th>
<th>At three weeks (Mean ± SD)</th>
<th>At six weeks (Mean ± SD)</th>
<th>At 12 weeks (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT (n= 6)</td>
<td>PT+ (n = 2)</td>
<td>All patients</td>
<td>PT (n = 2)</td>
</tr>
<tr>
<td>FIT-HaNSA (Seconds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task 1</td>
<td>151±89</td>
<td>300±0</td>
<td>189±102</td>
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</tr>
<tr>
<td>Task 2</td>
<td>88±56</td>
<td>237±89</td>
<td>124±90</td>
<td>--</td>
</tr>
<tr>
<td>Task 3</td>
<td>125±60</td>
<td>177±4</td>
<td>151±74</td>
<td>--</td>
</tr>
<tr>
<td>Tasks average</td>
<td>121±68</td>
<td>238±47</td>
<td>155±89</td>
<td>--</td>
</tr>
<tr>
<td>SPADI (Pain %)</td>
<td>69±16</td>
<td>61±4</td>
<td>67±14</td>
<td>60±26</td>
</tr>
<tr>
<td>SPADI (Function %)</td>
<td>56±19</td>
<td>61±4</td>
<td>57±16</td>
<td>50±28</td>
</tr>
<tr>
<td>SPADI (Total %)</td>
<td>61±16</td>
<td>62±4</td>
<td>61±13</td>
<td>54±27</td>
</tr>
<tr>
<td>RAPA</td>
<td>6±2</td>
<td>5±2</td>
<td>8±1</td>
<td>6±2</td>
</tr>
<tr>
<td>AROM (Flexion- degrees)</td>
<td>102±31</td>
<td>125±14</td>
<td>107±29</td>
<td>104±19</td>
</tr>
<tr>
<td>AROM (Abduction- degrees)</td>
<td>68±10</td>
<td>95±7</td>
<td>75±15</td>
<td>78±8</td>
</tr>
<tr>
<td>AROM (External rotation-degrees)</td>
<td>24±6</td>
<td>39±13</td>
<td>28±10</td>
<td>33±14</td>
</tr>
<tr>
<td>Muscle strength (Shoulder flexors- kg)</td>
<td>10±4</td>
<td>11±3</td>
<td>10±4</td>
<td>10±5</td>
</tr>
<tr>
<td>Muscle strength (Shoulder abductors- kg)</td>
<td>8±4</td>
<td>12±1</td>
<td>9±4</td>
<td>9±6</td>
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Table 3: Description of groups physical activity level

<table>
<thead>
<tr>
<th>Week/ Variable</th>
<th>Fitbit (steps) (Mean ± SD)</th>
<th>Fitbit (distance -km) (Mean ± SD)</th>
<th>Walking program (n=2)</th>
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<tbody>
<tr>
<td></td>
<td>PT</td>
<td>PT+</td>
<td>All</td>
</tr>
<tr>
<td>Week 1 (PT: n = 6; PT+: n = 1)</td>
<td>4861±2674</td>
<td>8199</td>
<td>4670±3168</td>
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<tr>
<td>Week 2 (PT: n= 6; PT+: n = 2)</td>
<td>5476±2247</td>
<td>4919±3773</td>
<td>5337±2389</td>
</tr>
<tr>
<td>Week 3 (PT: n= 6; PT+: n = 2)</td>
<td>4208±1963</td>
<td>7302±1514</td>
<td>4981±2266</td>
</tr>
<tr>
<td>Week 4 (PT: n= 5; PT+: n = 2)</td>
<td>5695±2057</td>
<td>7854±382</td>
<td>9850±10319</td>
</tr>
<tr>
<td>Week 5 (PT: n= 5; PT+: n = 2)</td>
<td>4501±1781</td>
<td>7224±249</td>
<td>5279±1972</td>
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<tr>
<td>Week 6 (PT: n= 4; PT+: n = 2)</td>
<td>4556±3342</td>
<td>7846±53</td>
<td>5652±3096</td>
</tr>
<tr>
<td>Total</td>
<td>4883±2344</td>
<td>7224±1194</td>
<td>5962±3868</td>
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PT: regular physiotherapy group, PT+: regular physiotherapy plus walking program, SD: standard deviation.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Mean ± SD)</th>
<th>At three weeks (Mean ± SD)</th>
<th>At six weeks (Mean ± SD)</th>
<th>At 12 weeks (Mean ± SD)</th>
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</thead>
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<tr>
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<td>Diabetes (n = 3)</td>
<td>No diabetes (n = 5)</td>
<td>Diabetes (n = 3)</td>
<td>No diabetes (n = 5)</td>
</tr>
<tr>
<td>Clinical characteristics:</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>53±11</td>
<td>61±4</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>2:1</td>
<td>3:2</td>
<td>--</td>
<td>--</td>
</tr>
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<td>BMI</td>
<td>24±6</td>
<td>25±4</td>
<td>--</td>
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</tr>
<tr>
<td>AC duration</td>
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<td>--</td>
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<tr>
<td>FIT-HaNSA (seconds)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Task 1</td>
<td>112±31</td>
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<td>--</td>
<td>--</td>
</tr>
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<td>Task 2</td>
<td>79±47</td>
<td>152±103</td>
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<td>Task 3</td>
<td>97±35</td>
<td>183±74</td>
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</tr>
<tr>
<td>SPADI (Pain)</td>
<td>77±10</td>
<td>61±13</td>
<td>71±11</td>
<td>56±26</td>
</tr>
<tr>
<td>SPADI (Function)</td>
<td>67±1</td>
<td>52±19</td>
<td>61±5</td>
<td>45±29</td>
</tr>
<tr>
<td>SPADI (Total)</td>
<td>71±4</td>
<td>55±14</td>
<td>65±4</td>
<td>49±28</td>
</tr>
<tr>
<td>RAPA</td>
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<td>6±2</td>
<td>6±3</td>
<td>6±2</td>
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<td>AROM (Flexion)</td>
<td>83±38</td>
<td>122±8</td>
<td>92±20</td>
<td>122±11</td>
</tr>
<tr>
<td>AROM (Abduction)</td>
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<td>81±17</td>
<td>77±7</td>
<td>83±15</td>
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<tr>
<td>AROM (External rotation)</td>
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<td>31±11</td>
<td>27±6</td>
<td>43±14</td>
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<td>Muscle strength (Shoulder flexors)</td>
<td>10±1</td>
<td>10±5</td>
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</tr>
<tr>
<td>Muscle strength (Shoulder abductors)</td>
<td>6±2</td>
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<table>
<thead>
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<th>Week/ Variable</th>
<th>Fitbit (steps) (Mean ± SD)</th>
<th>Fitbit (distance -km) (Mean ± SD)</th>
</tr>
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<tbody>
<tr>
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<td>Diabetes</td>
<td>No-diabetes</td>
</tr>
<tr>
<td>Week 1 (diabetes: n=3; no diabetes: n=5)</td>
<td>5320±3547</td>
<td>4280±3280</td>
</tr>
<tr>
<td>Week 2 (diabetes: n=3; no diabetes: n=5)</td>
<td>5577±3191</td>
<td>5193±2198</td>
</tr>
<tr>
<td>Week 3 (diabetes: n=3; no diabetes: n=5)</td>
<td>3645±2874</td>
<td>5783±1647</td>
</tr>
<tr>
<td>Week 4 (diabetes: n=3; no diabetes: n=4)</td>
<td>4708±2267</td>
<td>6435±1825</td>
</tr>
<tr>
<td>Week 5 (diabetes: n=3; no diabetes: n=4)</td>
<td>4830±2365</td>
<td>5616±1922</td>
</tr>
<tr>
<td>Week 6 (diabetes: n=3; no diabetes: n=3)</td>
<td>4595±4092</td>
<td>6710±1967</td>
</tr>
<tr>
<td>Total</td>
<td>4779±3056</td>
<td>5670±2140</td>
</tr>
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</table>

SD: standard deviation
CHAPTER 4:

DOES DIABETES AFFECT FUNCTIONAL OUTCOMES AFTER SHOULDER ARTHROPLASTY?

A form of this manuscript is published in the Journal of Clinical Orthopaedics and Trauma

Citation:

Abstract

Objectives: The purpose of this study was to assess whether diabetes affects functional and physical outcomes following shoulder arthroplasty.

Methods: A cohort of 140 patients were tested preoperatively, at an early follow-up visit (between 3-6 months) and at late follow-up visit (between 1-3 years) following shoulder arthroplasty. The American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form measured shoulder pain and function and the Short-Form-12 (SF-12) measured physical health status. Shoulder goniometry and dynamometry were used to assess motion and strength. Diabetic status was self-reported.

Results: There were significant improvements in function and physical health status for both patients with diabetes and patients without diabetes at the late follow-up visit. For patients with diabetes, shoulder function (ASES: 0-30) improved from 5 (5) to 18 (6) scores ($p < 0.001$) and physical health status improved from 27 (6) to 38 (8) scores ($p < 0.001$). For patients without diabetes, shoulder function improved from 8 (5) to 19 (8) scores ($p < 0.001$) and physical health status improved from 31 (8) to 40 (12) scores ($p < 0.001$). No significant differences between patients with diabetes and patients without diabetes was detected at the late follow-up session.

Conclusion: Patients with diabetes achieve large clinical benefits from shoulder arthroplasty that are similar to outcomes observed in patients without diabetes. Future prospective studies with a larger sample size of patients with diabetes are needed to confirm the results of this study.

Level of evidence: III

Keywords: Diabetes, Function, Muscle strength, Physical health status, Range of motion, Shoulder arthroplasty
4.1 Introduction

Shoulder arthroplasty surgery replaces the damaged humeral head and glenoid with prosthetic implants. This surgical procedure has been shown to significantly reduce pain, restore joint function and improve shoulder range of motion (ROM) at 2 years and beyond in patients who underwent total shoulder arthroplasty (TSA) or hemiarthroplasty (HA) \cite{1-4}. Osteoarthritis is the primary diagnosis for 77\% of shoulder arthroplasty and often occurs in middle-aged or older adults. Hence, comorbid health problem can be prevalent; including hypertension and diabetes which have been reported in in 63\% and 20\%, respectively \cite{5}.

Diabetes has been shown to be an independent risk factor for increased non-home discharge and longer hospital stays following shoulder arthroplasty \cite{6,7}. Further, diabetes, along with hypertension and obesity, are reported to predict increased postoperative complications such as humeral fracture and joint infection \cite{8}. Previous research found weak associations between patient satisfaction, physical impairment and patient-reported functional outcomes in patients who have undergone arthroplasty \cite{9}. This may reflect the diversity in presentation, patient priorities and expectations. While it is known that diabetes is associated with poor outcomes in ROM and patient-reported function after total knee arthroplasty \cite{10}, it is unknown whether this is also true for shoulder arthroplasty.

The prevalence of diabetes is increasing (from 11\% in 2010 to 14\% by 2030) \cite{11} and the negative impact of hyperglycemia on body tissue \cite{12} may have an adverse effect on postoperative complications and length of hospital stays \cite{7,8}. There is a need to investigate whether diabetes affects functional outcomes and motion after shoulder arthroplasty. The purpose of this study was to investigate the impact of diabetes on pain, patient-reported function, physical health status, and impairments in shoulder ROM and muscle strength in patients who underwent shoulder arthroplasty.

4.2 Materials and Methods

4.2.1 Study design and patients

A retrospective analysis of a prospective cohort of 140 patients undergoing shoulder arthroplasty at an upper extremity surgical unit was conducted. Patients' demographic characteristics were collected and recorded into a computerized database before the surgical intervention (Baseline), and at the time of early follow-up visit (3-6 months), and again at the
time of their late follow-up visit (1-3 years). Shoulder pain, function, ROM, muscle strength, and physical health status were examined across these three time-points. In this study, patients were classified into two groups: patients with diabetes and patients without diabetes based on self-report using the Self-Administered Comorbidity Questionnaire (SCQ) which is an efficient method to classify comorbidity that corresponds with medical record abstraction \(^{13}\). This cohort included patients who were treated with a mix of surgical interventions such as TSA, HA, and reverse TSA (rTSA). The local Research Ethics Board (REB) approved the study and written consents were obtained from all patients before the study.

4.2.2 Outcome measures

4.2.2.1 Primary outcome

The primary outcome measure of shoulder was pain and function assessed using the American Shoulder and Elbow Surgery (ASES) Standardized Shoulder Assessment Form \(^{14}\). The ASES has been shown to be a valid and responsive measure of shoulder pain and function after shoulder arthroplasty \(^{15}\). A full description of this form is published \(^{14}\). The minimal clinically important difference (MCID) value for shoulder pain on the Visual Analogue Scale (VAS: 0-10) is a decrease of 1.6 points and for the 100-point ASES scale is an increase of 13.6 points \(^{16}\). In this study, information from patients' self-evaluation [pain severity (VAS: 0-10) and activities of daily living (0-30 scores per side)] was collected. ASES scores were compared to norms established in an age-matched controls \(^{17}\).

4.2.2.2 Secondary outcomes

The secondary outcomes included ROM, muscle strength and physical health status. Physical health status was assessed using the Physical Component Summary (PCS) of the Short Form-12 (SF-12) survey \(^{18}\). The SF-12 has been shown to be a valid and reliable assessment tool \(^{18}\) and has been used to assess patients after shoulder arthroplasty \(^{19}\). The MCID is 4.5 points for the PCS on the SF-12 survey \(^{20}\).

Shoulder ROM was assessed in flexion, abduction, and external and internal rotation using a standard goniometer. Shoulder ROM was measured using standardized procedures with known high reliability (Intraclass Correlation Coefficients (ICCs) > 0.97) \(^{21-23}\). The MCID values for shoulder active forward flexion is 12°, active abduction is 7°, and active external rotation is 3° \(^{16}\).
Isometric shoulder flexion, abduction, external rotation and internal rotation muscle strength was assessed with the JTech PowerTrack handheld dynamometer (JTech; JTech Medical, Salt Lake City, UT, USA) [concurrent validity \[^{24}\] and reliability (ICCs 0.89-0.98)] \[^{25}\]. Shoulder muscle strength and ROM scores were compared to norms established in an age-matched controls and with similar testing procedures \[^{26,27}\].

### 4.2.3 Inclusion and exclusion criteria

Patients were included if they completed the SCQ to identify the presence of diabetes; the ASES and/or the SF-12 questionnaires; and if their shoulder muscle strength and ROM were measured at baseline, at early follow-up and at late follow-up visits. Exclusion criteria included inability or refusal to complete tests/measures.

### 4.2.4 Statistical analysis

Statistical analyses were performed using SPSS, version 23 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were performed to evaluate normality using a Kolmogorov-Smirnov (K-S) test. Descriptive statistics were calculated for the patients’ demographics, and for each outcome measure at each time point. Continuous measures were reported as means and standard deviations and categorical measures were reported as numbers and percentages. In bivariate analysis, patients with and without diabetes groups were compared using independent sample t-test for continuous data (age and all outcomes measures at baseline) and Chi-square test for categorical data. A General Linear Model (GLM) with repeated measures was used to assess significant differences in the primary and secondary measures over time, and between patients with and without diabetes at baseline, at early follow-up and at late follow-up visits while controlling for the type of surgery (total arthroplasty, reverse total arthroplasty, and hemiarthroplasty) and the indication for surgery. Mauchly’s test was used to assess the assumption of sphericity. When sphericity was violated, degrees of freedom (df) were corrected using Huynh-Feldt estimates of sphericity \[^{28}\]. To assess the effectiveness of the surgical intervention, we calculated the between group effect sizes by reporting the Standardized Response Mean (SRM) = \( \delta_x / SD\delta_x \). The \( \delta_x \) is the mean between-group differences, and the \( SD\delta_x \) is the pooled standard deviation reflecting the variability of change between the two groups. To allow and facilitate clinical decision making, benchmark values of trivial (< 0.20), small (\( \geq 0.20 \) to < 0.50), moderate (\( \geq 0.50 \) to < 0.80) or large (\( \geq 0.80 \)), proposed by Cohen,
were utilized\textsuperscript{[29]}. An alpha level (\(\alpha\)) of 0.05 was used to indicate statistical significance. Significant interactions were followed by pairwise comparisons using a Bonferroni correction.

4.3 Results

4.3.1 Descriptive statistics

Patients who underwent shoulder arthroplasty and met the inclusion criteria were included in the analysis of ASES (n=140), SF-12 (n=103), shoulder ROM (n=140), and shoulder muscle strength (n=127). The demographic characteristics of patients who completed one or both surveys are summarized in Table 1 and the demographic characteristics of patients whose shoulder ROM and muscle strength were measured are summarized in Table 2. No significant differences between patients with and without diabetes were observed for age, sex, affected side, reason for surgery, and the type of surgical intervention. Within this cohort, 55\% of the patients were treated with total shoulder arthroplasty, 30\% of the patients were treated with reverse total shoulder arthroplasty, and 15\% of the patients were treated with hemiarthroplasty. The main reason for surgery was joint arthritis (73\%) while other reasons included shoulder fractures, dislocation and rotator cuff arthropathy (27\%). Patients were tested at baseline (pre-operative), and at two time-point post-surgery: at the early follow-up visit (3-6 months), and again at the late follow-up visit (1-3 years).

4.3.2 Effect of surgical interventions

4.3.2.1 Primary outcome

Table 3 presents the means and SD of the responses for the ASES pain and function scores at each point in time. There was significant improvement over time (from baseline to late follow-up visit) on pain scores (VAS: 0-10) for patients with diabetes [7 (3.3) to 2 (2.4), \(p < 0.001\)], and for patients without diabetes [6 (3.0) to 2 (2.3), \(p < 0.001\)].

Similarly, there were significant improvements over time on function scores (ASES: 0-30) of the affected shoulder for patients with diabetes [5 (4.6) to 18 (6.3), \(p < 0.001\)] and for patients without diabetes [7 (4.9) to 19 (7.3), \(p < 0.001\)]. Pairwise comparisons revealed a significant improvement between each time point (\(p < 0.001\)) for the function score of the affected shoulder, and between baseline and late follow-up visit for pain scores.
Despite the higher pain (non-significant) and poorer function (mean difference (MD)= 3 points, $p = 0.032$) of patients with diabetes at baseline, the differences between groups became nonsignificant at the late follow-up visit (Table 3).

When we controlled for the type of surgery and indication for surgery the improvement over time in ASES pain and function scores remained significant ($p < 0.001$) and the differences in pain and function between patients with and without diabetes remained nonsignificant. In addition, the interaction between time and type of surgery and between time and reason for surgery were nonsignificant, indicating that surgical subgroups experienced similar patterns of recovery.

4.3.2.2 Secondary outcomes

There was significant improvement over time, between baseline and early follow-up visit and between baseline and late follow-up visit on the physical health status for patients with diabetes [27 (5.7) to 38 (8.2), $p < 0.001$] and for patients without diabetes [31 (7.5) to 40 (11.5), $p < 0.001$] (Table 3). Despite the significant poorer physical health status of patients with diabetes at baseline (MD= 4 points, $p < 0.033$), both groups recovered to a similar physical health status at the late follow-up visit (Table 3). As shown in Table 3, there was a significant improvement over time of the affected shoulder ROM for both groups ($p < 0.001$). The independent sample $t$-test revealed significant differences between groups at baseline in flexion (MD = 13 degrees, $p < 0.02$), and abduction (MD = 11 degrees, $p < 0.044$). However, these differences became nonsignificant at the late follow-up visit.

Similar to shoulder ROM, muscle strength of the affected shoulder significantly improved over time for both groups ($p < 0.001$) as shown in Table 3. Despite the significantly weaker shoulder flexors (MD = 2 kg, $p < 0.013$), abductors (MD = 2 kg, $p < 0.001$), and external (MD = 1 kg, $p < 0.009$) and internal (MD = 1kg, $p < 0.006$) rotator muscle groups at baseline, patients with diabetes regain similar muscle strength as patients without diabetes at the late follow-up visit. The analysis of covariance, when the type of surgery and indication for surgery were controlled for, revealed that the improvements over time in physical health status, ROM and muscle strength remained significant ($p < 0.001$) and the differences between patients with diabetes and patients without diabetes remained nonsignificant for physical health status, ROM and for muscle strength. In addition, the interaction between time and type of surgery and between time and reason for surgery were non-significant for the secondary outcome measures.
4.4 Discussion

This study demonstrated that patients with and without diabetes have equally positive improvements in shoulder function, ROM, strength and in physical health status following shoulder arthroplasty, despite the small but significantly poorer function and physical health status that patients with self-reported diabetes present with prior to surgery. In addition, the improvements in shoulder pain, function, and ROM of the current study all reached statistical and clinical significance with large effects size (Table 3), confirming prior studies that indicate a large benefit to patients treated with shoulder arthroplasty. The overall improvements in shoulder pain, function, ROM, and strength as well as physical health status were comparable to previous studies despite the differences in sample size, outcome assessment tools, the follow up periods, and the inclusion criteria [1–4,19]. However, none of these studies have examined a subset of patients with diabetes for comparison.

Similar to previous research [3,4], different types of surgery (TSA, HA, rTSA) were not significantly different in terms of functional improvements following surgery. This may be because the indications for different surgeries successfully allocates them to the type of surgery providing the optimal outcome for that clinical presentation. However, our results differ from one study that reported a greater shoulder ROM and less pain following TSA as compared to hemiarthroplasty [1].

Despite the reported improvements in shoulder ROM and strength, patients with and without diabetes had below-normal scores when compared to age-matched people with unaffected shoulder [26,27]. The lower scores can be attributed to several factors including the quality of the surrounding musculotendinous structures, the type of implant and fixation used, the general health status of patients, and the presence of comorbidities [2,4,8,30]. Patients should be made aware that improvement, not normality, is the expected outcome of surgery.

The clinical improvements in outcomes between patients with and without diabetes was previously investigated following total knee arthroplasty (TKA) [10]. The TKA study included 20 patients with diabetes with a mean age of 72 years. Similar to our study, there were small (non-significant) differences in knee ROM, muscle strength and Knee Society Score questionnaire scores between groups at baseline. However, at one year follow-up, TKR patients with and without diabetes had similar outcomes except for knee flexion which was significantly less (10°) in patients with diabetes [10]. According to the authors, the difference in the rehabilitation program intensity explained the poorer knee flexion in patients with diabetes [10].
Overall, our findings concur with results found in TKA, that patients with diabetes achieve similar clinical benefits, as compared to their patients without diabetes counterparts.

4.4.1 Strength and limitations

This study provides new information on the impact of diabetes on shoulder pain, function, ROM, strength and physical health status after shoulder arthroplasty. The data of this study were prospectively collected using valid and reliable outcome measures; and the ASES scale and SF-12 survey have been used to assess functional outcomes and physical health status after shoulder arthroplasty. We evaluated a relatively large cohort of patients and used an independent assessor to evaluate outcomes. However, several limitations of the current cohort should be recognized. First, diabetes status was based on self-report which is subject to reporting errors. However, the Katz self-administered comorbidity scale (SCQ) has been validated to assess comorbid conditions in health services research and is equivalent to extracting this information from medical records \[13\]. Diabetes is a condition that is likely accurately self-reported because of the associated treatment requirements. Second, and potentially more limiting was the fact that we did not have data about the type, the duration, the treatments of diabetes, and the level of glycemic control. It is possible that negative of effects of diabetes would be selectively present in with longer duration or poorer control. Therefore, we cannot preclude that negative effects occur in this subgroup. Lastly, although we controlled for the type of surgery and the indication for surgery and found no effect, recovery could be affected by other uncontrolled factors such as the quality and type of implant and the post-operative complications \[1,2\].

4.5 Conclusion

Patients with and without diabetes are expected to gain similar large clinical improvements in shoulder function, motion, strength and physical health status following shoulder arthroplasty. However, these improvements are not expected to reach normal values. Future large cohort studies with larger numbers of patients with diabetes and more rigorous evaluation of diabetes duration, type, and the level of glycemic control over a longer period of time could more accurately estimate the prognosis of different subgroups of patients with diabetes; and whether a dose-response relationship between glycemic control and outcomes is present.
4.6 Declaration of conflicting interests

The authors declare that there is no conflict of interest.

4.7 Acknowledgment

Dr. Joy C MacDermid was supported by a CIHR Chair in Gender, Work and Health and the Dr. James Roth Research Chair in Musculoskeletal Measurement and Knowledge Translation during the conduct of this study. **CIHR FRN: SCA-145102.**

4.8 Approval giving authority

The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB). **Study number:** 13935E.
4.9 References


Table 1: Demographic characteristics of patients who underwent shoulder arthroplasty and completed one or both of the self-reported surveys

<table>
<thead>
<tr>
<th>Variable</th>
<th>ASES Diabetes</th>
<th>SF-12 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Total number (n)</strong></td>
<td>28  (20%)</td>
<td>112   (80%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>75  (9)</td>
<td>70    (11)</td>
</tr>
<tr>
<td><strong>Sex: Male</strong></td>
<td>10  (7%)</td>
<td>47    (34%)</td>
</tr>
<tr>
<td>Female</td>
<td>18  (13%)</td>
<td>65    (46%)</td>
</tr>
<tr>
<td><strong>Dominant side: Right</strong></td>
<td>24  (17%)</td>
<td>104   (74%)</td>
</tr>
<tr>
<td>Left</td>
<td>4   (3%)</td>
<td>8     (6%)</td>
</tr>
<tr>
<td><strong>Affected side: Right</strong></td>
<td>21  (15%)</td>
<td>66    (47%)</td>
</tr>
<tr>
<td>Left</td>
<td>7   (5%)</td>
<td>46    (33%)</td>
</tr>
<tr>
<td><strong>Medical problems:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>7   (5%)</td>
<td>22    (16%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18  (13%)*</td>
<td>36    (26%)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>6   (4%)*</td>
<td>5     (4%)</td>
</tr>
<tr>
<td>Primary osteoarthritis</td>
<td>24  (17%)</td>
<td>83    (59%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2   (1%)</td>
<td>22    (16%)</td>
</tr>
<tr>
<td>Others (cancer, depression, kidney and blood disease)</td>
<td>34  (24%)</td>
<td>116   (83%)</td>
</tr>
<tr>
<td><strong>Reason for surgery:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>16  (13%)</td>
<td>60    (47%)</td>
</tr>
<tr>
<td>Rotator cuff tear</td>
<td>3   (2%)</td>
<td>4     (3%)</td>
</tr>
<tr>
<td>Others (fracture, dislocation, revised surgery)</td>
<td>9   (6%)</td>
<td>48    (33%)</td>
</tr>
<tr>
<td><strong>Type of surgery:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total arthroplasty</td>
<td>n = 26</td>
<td></td>
</tr>
<tr>
<td>Reverse total arthroplasty</td>
<td>16  (12%)</td>
<td>63    (47%)</td>
</tr>
<tr>
<td>Hemiarthroplasty</td>
<td>8   (6%)</td>
<td>36    (26%)</td>
</tr>
<tr>
<td></td>
<td>2   (2%)</td>
<td>11    (9%)</td>
</tr>
</tbody>
</table>

Independent sample *t*-test was used to detect difference in age (mean (SD)) between groups. Chi-square test was used to detect differences between groups in all categorical data (reported as number and percentage).

*Significant difference between groups, *p* < 0.05. ASES: American Shoulder and Elbow Surgeons, SF-12: Short Form-12 survey.
Table 2: Demographic characteristics of patients who underwent shoulder arthroplasty and whose shoulder motion and/or muscle strength were measured

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROM</th>
<th></th>
<th>Muscle strength</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No (%)</td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td><strong>Total number (n)</strong></td>
<td>27</td>
<td>(19%)</td>
<td>113 (81%)</td>
<td>23 (18%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>73</td>
<td>(8)</td>
<td>71 (9)</td>
<td>74 (9)</td>
</tr>
<tr>
<td><strong>Sex: Male</strong></td>
<td>12</td>
<td>(9%)</td>
<td>54 (39%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>15</td>
<td>(11%)</td>
<td>59 (42%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td><strong>Dominant side: Right</strong></td>
<td>24</td>
<td>(17%)</td>
<td>104 (74%)</td>
<td>21 (17%)</td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td>3</td>
<td>(2%)</td>
<td>9 (6%)</td>
<td>2 (2%)</td>
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<tr>
<td><strong>Affected side: Right</strong></td>
<td>23</td>
<td>(16%)*</td>
<td>70 (50%)</td>
<td>20 (16%)*</td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td>4</td>
<td>(3%)*</td>
<td>43 (31%)</td>
<td>3 (2%)*</td>
</tr>
<tr>
<td><strong>Medical problems:</strong></td>
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<td></td>
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<tr>
<td>Heart disease</td>
<td>8</td>
<td>(6%)*</td>
<td>14 (10%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>(12%)*</td>
<td>34 (24%)</td>
<td>16 (13%)*</td>
</tr>
<tr>
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<td>5</td>
<td>(4%)*</td>
<td>3 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Primary osteoarthritis</td>
<td>23</td>
<td>(16%)*</td>
<td>62 (44%)</td>
<td>20 (16%)*</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3</td>
<td>(2%)</td>
<td>12 (9%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Others (cancer, depression,</td>
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<td>(23%)</td>
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<td>kidney and blood disease)</td>
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<td><strong>Reason for surgery:</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>16</td>
<td>(13%)</td>
<td>60 (46%)</td>
<td>14 (14%)</td>
</tr>
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<td>Rotator cuff tear</td>
<td>2</td>
<td>(2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Others (fracture, dislocation,</td>
<td>10</td>
<td>(8%)</td>
<td>46 (35%)</td>
<td>7 (6%)</td>
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<td><strong>Type of surgery:</strong></td>
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<td></td>
</tr>
<tr>
<td>Total arthroplasty</td>
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<td>(14%)</td>
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<td>Reverse total arthroplasty</td>
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<td>6 (5%)</td>
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<td>Hemiarthroplasty</td>
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<td>(1%)</td>
<td>11 (8%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Independent sample *t*-test was used to detect difference in age (mean (SD)) between groups. Chi-square test was used to detect differences between groups in all categorical data (reported as number and percentage).

*Significant difference between groups, *p* < 0.05. ROM: range of motion.
Table 3: A comparison of changes in pain, function, ROM, and muscle strength between patients with and without diabetes who underwent shoulder arthroplasty

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Early follow-up visit (3-6 months)</th>
<th>Late follow-up visit (1-3 years)</th>
<th>Effect size</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>ASES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (0-10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (3)</td>
<td>2 (1)*</td>
<td>2 (2)*</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>6 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function: Affected side (0-30)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (5)*</td>
<td>13 (5)*</td>
<td>15 (7)*</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>8 (5)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Un-affected side (0-30)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (8)</td>
<td>24 (5)*</td>
<td>24 (6)*</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-12</td>
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General linear modules-repeated measures were used to detect changes over time and between groups. Values are reported as mean (SD). *significant effect of time (p < 0.05) between baseline and early follow-up visit and between baseline and late follow-up visit. †significant mean difference between groups as detected by independent sample t-test.

ROM: Range of Motion, ASES: American Shoulder and Elbow Surgeons, SF-12: Short From-12 survey.
CHAPTER 5:

PREDICTORS OF CLINICAL BENEFITS AND ONE-YEAR FUNCTIONAL OUTCOMES FOLLOWING SHOULDER ARTHROPLASTY

A form of this manuscript is published in The Iowa Orthopedic Journal

Citation:
Abstract

**Background:** Shoulder arthroplasty has been shown to improve function in patients with advanced shoulder disease. However, the response to surgery and final outcomes are not easily predictable. This study assessed the effect of residual pain, age, sex, diabetes, hypertension, and depression on changes and status at one-year following arthroplasty with respect to shoulder function and overall physical and mental health status.

**Methods:** A retrospective analysis of a prospective cohort of 140 patients tested preoperatively and one-year following shoulder arthroplasty was conducted at our tertiary hospital. Pearson's correlations and multiple regression analyses were performed to test the impact of predictors on shoulder pain and function assessed using the American Shoulder and Elbow Surgery (ASES) questionnaire, and on physical and mental health assessed using the Short Form-12.

**Results:** Pain and female sex were significant predictors of poorer function at one-year ($R = 0.56, p = 0.001$); and with other predictors, they explained 32% of the variability in function. The explained variability of changes in function scores was 15% with pain being the only significant predictor. Physical health was lower in older patients ($r = -0.31, p < 0.05$) and was less predictable for physical health change scores (12%) and the physical status at one-year (14%).

**Conclusions:** Residual pain is associated with poorer function status and less clinical benefit. Female sex is not associated with less change in function which suggest that men and women get equal benefit from the surgery. Advanced age relates to poorer physical health and to a lesser extent physical change over the year.

**Level of evidence:** III

**Keywords:** Function, Physical health status, Shoulder arthroplasty
5.1 Introduction

Shoulder arthroplasty is widely used to treat patients with severe arthritic changes in the joint
[1]. This surgical procedure has been shown to be effective in reducing pain, improving shoulder
function and increasing range of motion (ROM) [2,3]. However, the overall improvement in
shoulder functional outcomes is not always predictable and can be influenced by several factors
[4]. These factors were examined by several studies [2,4,5]; however, the results of these studies
have conflicted with one another. Young age was associated with better shoulder function on
constant score at one-year follow-up after hemiarthroplasty performed for patients with
proximal humeral fracture [6]. Further, the improvement of shoulder clinical scores over time
was associated with young age at the time of shoulder arthroplasty surgery but not with the
later follow-up years in patients with rheumatoid arthritis [5]. In contrary, advanced age was
associated with greater improvement (change) in shoulder function as demonstrated on the
Simple Shoulder Test (SST) following total shoulder arthroplasty (TSA) [2]. However, other
studies found no correlations between age and the improvement in shoulder function [4,7].
Lastly, studies that assessed the effect of gender on the improvement in shoulder function found
that men had better post-operative function assessed using SST [4,7].

Physical health is expected to decline with age [4] and be adversely affected by comorbidities
[8]. However, factors that influence physical health following shoulder arthroplasty have rarely
been examined. Advanced age is negatively associated with physical function (r = -.23) and
the better pre-operative physical health is associated with better post-operative physical
function (r = .4) as demonstrated on the Short Form-36 (SF-36) survey following TSA [4].
The presence of comorbidities, including diabetes and hypertension, have been shown to have
no effect on post-operative shoulder function [7,9], except for internal rotation ROM (R = -.2)
which was decreased with diabetes [9]. However, depression has been associated with lower
shoulder function assessed using the American Shoulder and Elbow Surgery (ASES) in 176
patients 2-year following TSA [10].

There are few studies which addressed the factors that influence postoperative functional
outcomes following shoulder arthroplasty. In addition, a number of these studies do not report
regression coefficients or explain the effect size attributable to these predictors. This makes it
difficult to determine how much these should influence decision-making. Finally, comorbidities
such as diabetes, hypertension and depression are rarely examined although they
are present in 20-60 % of patients undergoing shoulder arthroplasty [1].
Identifying preoperative factors that are predictive of one-year outcomes could assist surgeons and health care providers in providing patients more realistic expectations on outcomes and may help plan postoperative pain management and rehabilitation. Therefore, the current study was designed to address the following questions: 1) Do age, sex, diabetes, hypertension, and depression predict patient-reported outcomes including shoulder pain and function, and physical and mental health status one-year following shoulder arthroplasty? 2) Do these factors predict the clinical benefits following surgery as reflected in the change of outcome scores? Is residual pain (pain at one-year) associated with poorer functional outcomes?

5.2 Materials and methods

5.2.1 Study design and patients

A retrospective query of prospective collected data of patients who underwent shoulder arthroplasty was conducted at a tertiary care referral hospital. Demographic data were collected and recorded into a computerized database for 477 patients with shoulder arthroplasty. All patients who completed the ASES (n = 140) and the SF-12 (n = 103) questionnaires at baseline and at one-year follow-up visits and who completed a self-reported comorbidity survey (n = 140) were included in this analysis. This cohort included all patients treated with shoulder arthroplasty regardless of the type of surgery based on a previous study [11] that showed non-significant differences in ASES and SF-12 scores between patients with different surgical intervention (TSA, reverse TSA, hemiarthroplasty). Exclusion criteria included an inability or refusal to complete tests/measures. The University Ethics board approved the protocol and written consents was obtained from all patients.

5.2.2 Outcome measures

The dependent variables included the ASES [12], which assessed shoulder pain and function, and the SF-12 which assessed physical and mental health status [13]. Both questionnaires have been shown to be valid and reliable self-reported assessment tools [13,14] and have been previously used to assess patients after shoulder arthroplasty [10]. In this study, self-reported pain severity (VAS: 0-10) and activities of daily living (maximum 30 scores) information were obtained from the ASES. The Physical Component Summary Score (PCS) and the Mental Component Summary Score (MCS) scores were obtained from the SF-12. A full description
of ASES and SF-12 questionnaires has previously been published \cite{12,13}. Both questionnaires were administered preoperatively and at one-year follow-up visit. Next, scores from both questionnaires were averaged and were compared among patients based on their age, sex, and the presence of diabetes, hypertension, and depression (Table 1). To estimate the clinical benefits of shoulder arthroplasty, we calculated the change in scores from baseline (preoperative) to the one-year follow-up visit for the ASES function and SF-12 PCS.

5.2.3 Predictors (independent variables)

The predictive variables of interest included patient demographics: age and sex, and comorbidities: diabetes, hypertension and depression. Patients with a preoperative self-report of diabetes, hypertension, and depression were identified and were designated to the study cohort. The prediction effect of these factors has been examined twice; first on the final scores at one-year for ASES pain and function and for SF-12 PCS and MCS, and second on the change of scores from baseline to one-year follow-up visit for ASES function and SF-12 PCS.

5.2.4 Statistical analysis

Statistical analyses were performed using SPSS software, version 23 (SPSS Inc., Chicago, IL, USA). A \( P \) value of <.05 was considered statistically significant. Independent sample \( t \)-test was used to detect differences in the ASES and the SF-12 scores between patients based on the predictive variables: patients demographics (age and sex) and the presence of comorbidities (diabetes, hypertension, depression). All values are reported as mean and standard deviation (SD). Pearson's correlation coefficients (\( r \)) were calculated between the dependent and predictive variables and between the predictive variables. The effect size of Pearson's correlations were classified as follow: \( r = +/- 0.1 = \) small effect, \( r = +/- 0.3 = \) medium effect, \( r = +/- 0.5 = \) large effect \cite{15}. Next, a multivariable enter regression analysis was performed to examine the effect of the predictive variables on the improvement in ASES and SF-12 one-year following shoulder arthroplasty. For ASES, pain at one-year was added to a second multivariable enter regression model as a predictive variable to examine its effect on function. To predict the clinical benefits of shoulder arthroplasty, we calculated the change in ASES function and SF-12 PCS scores by subtracting scores at one-year follow-up visit from baseline scores. Then, a multivariable enter regression analysis was performed on the change scores of ASES function and SF-12 PCS. All the assumptions of multiple regression including the test
of normality, heteroscedasticity, multicollinearity and linearity were examined prior to the regression analysis.

5.3 Results

5.3.1 Descriptive statistics

Within this cohort, 140 patients completed the ASES and 103 patients completed the SF-12 survey. The average age of patients was 71 years (range, 47-89 years). 57% of patients underwent TSA, 33% underwent reverse TSA and 10% underwent hemiarthroplasty. Table 1 represents the influence of the patients’ demographics on ASES and SF-12 scores one-year following shoulder arthroplasty. For ASES, age was significantly different between patients in all subgroups ($p < 0.05$). Males and patients with depression were younger than females and patients without depression while patients with diabetes and hypertension were older than patients without these two conditions. Males had significantly better function compared to females ($r = -0.27$, $p = 0.001$) (Table 2). For the SF-12, patients with depression were younger and had worse mental health status compared to patients without depression (Table 1).

5.3.2 Pearson's correlations

Pearson's correlation between dependent variables and predictors are summarized in Table 2. The coefficients ranged from -0.31 to 0.20. There were significant correlations ($p < 0.05$) with a small effect size between ASES pain and depression, ASES function and sex, MCS and sex, MCS and depression, and a medium effect size between PCS and age. Patients with depression reported higher pain and worse mental health status, male patients had better shoulder function and mental health status, and younger patients had better physical health status (Table 2). When pain at one-year was added as a predictor to examine its effect on function, results revealed a moderate relationship between residual pain and function ($r = -0.51$, $p < 0.001$) indicating that patients with higher pain had poorer shoulder function. In addition, there was a negative association between the change in function scores and residual pain ($r = -0.36$, $p < 0.001$) indicating that patients who reported pain at one-year follow-up visit had less improvement in shoulder function.

Pearson's correlations were performed to examine collinearity between predictors. For ASES pain and function, results revealed significant correlations between diabetes and hypertension
(r = -0.25, p < 0.002) and between age and depression (r = 0.26, p < 0.001). For SF-12 PCS and MSC, results revealed significant correlations between diabetes and hypertension (r = -0.33, p < 0.001) and between age and depression (r = -0.34, p < 0.001). However, these correlations are weak [15]. We concluded that there is no collinearity within our data.

5.3.3 Multivariable regression analysis

The regression model is summarized in Table 3. In predicting pain, depression was the only significant predictor of pain (b = 1.5, SE = 0.63, t (140) = 2.4, p = 0.02) indicating that the presence of depression increases pain by 1.5 units. Together, all predictors explained 6% of the variability in pain.

For shoulder function, sex was a significant predictor of function (b = -4.2, SE = 1.3, t (140) = -3.2, p = 0.002) indicating that being a male improves shoulder function by 4.2 scores on ASES index. All predictors explained 8% of the variability in function. When pain at one-year was added as a predictor in the final model, results revealed that both sex and pain (b = -1.6, SE = 0.24, t (140) = -6.7, p < 0.001) were significant predictors of function. This indicated that as pain increases by one unit, shoulder function decreases by 1.6 scores. The explained variability in function increased to 32% with a greater contribution of pain.

In predicting the clinical benefits of shoulder arthroplasty, only residual pain was a significant predictor of the change in function scores (b = -1.1, SE = 0.26, t (140) = -4.4, p < 0.001). This indicated that with 1 unit increase in residual pain, the improvement of shoulder function decreases by 1.1 scores. Together, all predictors explained 15% of the variability in the improvement in function.

In predicting SF-12 physical and mental health status, age was a significant predictor of physical health status (b = -0.48, SE = 0.15, t (103) = -3.3, p = 0.001). With one-year increase in age, physical health status decreases by 0.5 scores. Depression had a trend to predict mental health status (b = -6.1, SE = 3.2, t (103) = -1.9, p = 0.058). Together, all predictors explained 14% of the variance in physical health status and 10% of the variance in mental health status. In predicting the change in PCS, none of the predictors were significant. However, there was a trend for both age and hypertension to predict the change in PCS (p = 0.055). The explained variability in PCS change scores was 12%.
5.4 Discussion

This study found that residual pain at one-year after shoulder arthroplasty is associated with poorer shoulder function. In addition, residual pain is the most significant predictor of function, and with other predictors, it explains 32% of the variability in shoulder function one-year after shoulder arthroplasty. Furthermore, residual pain is found to be the only predictor of improvement in shoulder function and clinical benefits following shoulder arthroplasty.

It is well established that shoulder pain can significantly affect function and the ability to perform activities of daily living [16] and pain relief is the primary goal of patients who undergo shoulder arthroplasty [17]. However, for some patients, post-surgical pain persists 1-2 years after shoulder arthroplasty, being most problematic for patients with fractures or osteoarthritis [18]. Our study found that residual pain at one-year is reported by 61% of patients who underwent shoulder arthroplasty but is highly variable in intensity (range: 0.2 - 10, VAS scale).

In addition, higher pain is associated with worse shoulder function. Higher pain may be related to arthritis in the contralateral shoulder or in other parts of the arm since often outcome measures do not differentiate the location of the pain. However, it is also possible that closer attention to pain peri-operatively and during rehabilitation could improve these outcomes.

In our study, statistically significant poorer shoulder function is associated with female sex. In addition, although female sex is associated with lower functional scores, it is not associated with less change in function which suggest that men and women get equal benefit from the shoulder arthroplasty. Furthermore, women are more likely to have a negative change in mental health following surgery in comparison to men (Table 2). We showed that pain is highly related to poor shoulder function and, although not significant, women tend to report higher pain (Table 1). This may explain the poorer shoulder function for women. These findings are consistent with previous studies in which male patients had better improvement in function at a longer follow-up periods ranged from 2 to 6 years following TSA [2,7].

In the present study, age is not a significant factor in predicting the change in shoulder scores nor the one-year shoulder function. However, age relates significantly to physical health status, in which younger patients had better physical health status, and to a lesser extent physical change over the year but not to mental health.

These findings are consistent with the study of Donigan et al. (n = 106) who reported a non-significant correlations between age and improvement in shoulder function [7]. However, advanced age was associated with significant better change in shoulder function in one study 2-year after TSA (n = 102) [2] and with less improvement in shoulder function at the time of
surgery\textsuperscript{[5]} and at one-year follow-up\textsuperscript{[6]} after shoulder arthroplasty. Advanced age was also associated with lower physical health status in the study of Matsen et al.\textsuperscript{[4]}. In addition, Matsen et al.\textsuperscript{[4]} reported that the overall well-being of patients before TSA is strongly correlated with the quality of the outcomes\textsuperscript{[4]}. These conflicting findings might be related to the conflicting mechanisms by which age can mediate outcomes. Advanced age is associated with lower occupational and life demands for most people. Further, shoulder disorders and pathologies are common in older adults and are associated with general decline in physical health and quality of life\textsuperscript{[8,19]}. However, in our regression analysis, we showed that age is not a significant predictor of the change in physical health status. This may indicate that physical health status is expected to improve following shoulder arthroplasty regardless to age. Other reasons for the conflicting conclusions among studies may include the use of different patient-reported assessment tools, the differences in the inclusion criteria, and the various sample sizes.

In general, comorbidities including diabetes, hypertension, and depression did not affect the final outcome status nor the amount of improvement gained with surgery for shoulder function, and physical and mental health status of this cohort' patients following shoulder arthroplasty. However, depression is associated with higher levels of pain and there is a trend toward worse mental health status ($p = 0.058$). Our inability to show significant correlations between function and comorbidities is consistent with previous research\textsuperscript{[7,9]}. These results are also consistent with our previous research\textsuperscript{[11]} in which we showed that patients with and without diabetes recovered to the same functional level at one-year following shoulder arthroplasty despite significantly worse pre-operative function in patients with diabetes. We concluded that patients with diabetes achieve large clinical benefits from shoulder arthroplasty, with follow-up outcomes equally positive to those without diabetes\textsuperscript{[11]}. However, the non-significant association between depression and shoulder function may be due to our low sample size of patients with depression ($n = 17$). This lack of association differs with the study of Werner et al.\textsuperscript{[10]} who reported significant effect of depression on ASES scores and shoulder function in 88 patients with depression\textsuperscript{[10]}. Our regression model showed a significant effect of depression on ASES pain in which depression, with other predictors, explained 6\% of the variability of pain. However, the low percentage of the explained variability in pain might not have a clinical importance. Werner et al.\textsuperscript{[10]} did not include a subscale of ASES pain for comparison.

5.4.1 Strength and limitations
This study provides new information about the impact of age, sex, diabetes, hypertension and depression on shoulder pain and function, and physical and mental health status one-year following shoulder arthroplasty. The data of this study were collected prospectively from a large cohort of patients who underwent shoulder arthroplasty. Shoulder pain and function, and physical and mental health status were evaluated using valid and reliable outcomes measures which have been used previously by several studies [4,10]. However, this study has several limitations. As with all regression models, a significant statistical relationship does not imply causation. Further, in some of our models, the explained variation was small and thus the clinical importance of statistically significant correlations must be questioned. Our data was derived from a single specialty upper extremity program and may not be generalizable to other clinical practices. We cannot distinguish the location of pain and thus residual pain is not necessarily related to the operated shoulder. However, none of these limitations diminish the value of this study which presented important information in a way that allow clinicians to incorporate its findings into their decision-making when planning for this surgical procedure.

5.5 Conclusion

This study found that residual pain is associated with poorer shoulder function at one-year and less clinical benefits over time. Female sex is associated with worse shoulder function at one-year but not with less change in function over time which suggests that men and women get equal benefit from the surgery. Comorbidities do not affect the final outcomes status and the amount of improvement gained with surgery. Advanced age relates to poorer physical health status and to a lesser extent physical change over the year. Lastly, patients with depression had higher pain than patients without this condition. Identifying risk factors for poor functional outcomes following shoulder arthroplasty can assist clinicians in counselling patients on the expected outcome following shoulder arthroplasty.
5.6 Acknowledgment

Dr. Joy C MacDermid was supported by a CIHR Chair in Gender, Work and Health and the Dr. James Roth Research Chair in Musculoskeletal Measurement and Knowledge Translation during the conduct of this study. **CIHR FRN: SCA-145102**

5.7 Declaration of interest

The authors report no conflicts of interest

5.8 Approval giving authority

The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB). **Study number:** 13935E.
5.9 References


Table 1: Patient demographics and its influence on ASES and SF-12 one-year following shoulder arthroplasty

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<td>69 (12)</td>
</tr>
<tr>
<td>Depression: Yes</td>
<td>17 (12)</td>
<td>64 (8)*</td>
</tr>
<tr>
<td>No</td>
<td>123 (88)</td>
<td>72 (11)</td>
</tr>
</tbody>
</table>

Independent sample t-test was used to detect differences between groups for each predictor (mean (SD)). *Significant difference between groups at P < 0.05. ASES: American Shoulder and Elbow Surgeons, SF-12: Short Form-12 survey, PCS: physical component summary, MCS: mental component summary.
Table 2: Pearson's correlations between predictors and dependent variables one year following shoulder arthroplasty

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td>ASES: Pain at 1-year Function: Model 1</td>
<td>0.1</td>
</tr>
<tr>
<td>Function: Model 2 Demographics+ comorbidities</td>
<td>-0.02</td>
</tr>
<tr>
<td>+ residual pain Change in function scores</td>
<td>-0.02</td>
</tr>
<tr>
<td>0.03</td>
<td>-0.09</td>
</tr>
<tr>
<td>SF-12: PCS at 1-year Change in PCS scores</td>
<td>-0.31*</td>
</tr>
<tr>
<td>Change in scores was calculated by subtracting scores at one-year follow-up visit from baseline scores</td>
<td></td>
</tr>
<tr>
<td>Function Model 1 predictors: age, sex, diabetes, hypertension, and depression.</td>
<td></td>
</tr>
<tr>
<td>Function Model 2 predictors: pain at one-year, age, sex, diabetes, hypertension, and depression</td>
<td></td>
</tr>
<tr>
<td>* Significant at $P &lt; 0.05$. ASES: American Shoulder and Elbow Surgeons, SF-12: Short Form-12 survey, PCS: physical component summary, MCS: mental component summary.</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Regression model summary for dependent variables one year following shoulder arthroplasty

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>R</th>
<th>R²</th>
<th>Adj. R²</th>
<th>SE</th>
<th>F-statistics</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASES: Pain</td>
<td>0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06</td>
<td>0.03</td>
<td>2.3</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Function: Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics+ comorbidities</td>
<td>0.28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.08</td>
<td>0.05</td>
<td>7.3</td>
<td>2.3</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Function: Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics+ comorbidities + pain at one-year</td>
<td>0.56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.32</td>
<td>0.28</td>
<td>6.3</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in function</td>
<td>0.38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.15</td>
<td>0.11</td>
<td>6.8</td>
<td>3.9</td>
<td>0.001</td>
</tr>
<tr>
<td>SF-12:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>0.37&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.14</td>
<td>0.09</td>
<td>10.5</td>
<td>3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Change in PCS</td>
<td>0.34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.12</td>
<td>0.07</td>
<td>10</td>
<td>2.5</td>
<td>0.033</td>
</tr>
<tr>
<td>MCS</td>
<td>0.31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10</td>
<td>0.05</td>
<td>9.0</td>
<td>2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup>Predictors: (constant), age, sex, hypertension, diabetes, depression

<sup>b</sup>Predictors: (constant), pain at one-year, age, sex, hypertension, diabetes, depression

Change in scores was calculated by subtracting scores at one-year follow-up visit from baseline scores.

Function Model 1 predictors: age, sex, diabetes, hypertension, and depression.

Function Model 2 predictors: pain at one-year, age, sex, diabetes, hypertension, and depression.

ASES: American Shoulder and Elbow Surgeons, SF-12: Short Form-12 survey, PCS: physical component summary, MCS: mental component summary, NS: nonsignificant.
CHAPTER 6:

GENERAL DISCUSSION AND IMPLICATIONS
6.1 Overview of thesis findings

This thesis focuses on understanding the impact of diabetes on shoulder conditions leading to a pilot study on a physiotherapy (PT) intervention that considers diabetes in management. This work addresses a gap in the literature since remarkably few studies have focused on managing adhesive capsulitis (AC) and shoulder recovery after arthroplasty in patients with diabetes. This work is completed as a manuscript thesis where following chapter one which reviews the relevant literature, a series of inter-related manuscripts are presented in individual chapters.

In chapter two, a systematic review synthesizes the quality and content of clinical research addressing the effectiveness of non-surgical interventions for managing AC in patients with diabetes. The systematic review showed that low-quality evidence suggests large effects of joint mobilization plus exercises on AC in people with diabetes and weaker support was available for corticosteroid and manipulation under anesthesia (MUA). This systematic review has been published in the Archives of Physical Medicine and Rehabilitation journal.

Chapter three included a pilot study that compared the effect of a regular PT program to a regular PT combined with a progressive walking program (PT+) in patients with and without diabetes who have AC. This pilot trial established that conducting a large-scale study to assess the effect of physiotherapy program for managing AC is feasible. The current findings suggest that physiotherapy exercises may be effective in reducing pain and improving shoulder function and range of motion (ROM) in patients with and without diabetes who have AC. The sample size for future studies was also determined.

Chapter four is a cohort study that evaluated the impact of diabetes on shoulder pain, function, ROM, and muscle strength outcomes as well as on physical health status following shoulder arthroplasty. This study has been published in the Journal of Clinical Orthopedics and Trauma. There was a significant improvement in all outcome measures for both patients with diabetes and patients without diabetes with no significant differences between groups at 1-3 years after surgery. We concluded that patients with diabetes achieve substantial clinical benefits from shoulder arthroplasty, with follow-up outcomes equally positive to those without diabetes.

Chapter five is a cohort study that examined factors predicting shoulder function and clinical benefits one-year following shoulder arthroplasty. This study has been published in the Iowa Orthopedic Journal. We showed that residual pain (pain at one-year) and female sex were significant predictors of poorer function at one-year and residual pain was the only significant predictor of the explained variability of change in function scores. We concluded that residual...
pain is associated with poorer function status and fewer clinical benefits. Female sex is not associated with less change in function which suggests that men and women get equal benefits from surgery. Advanced age relates to poorer physical health at one-year following surgery. Lastly, diabetes, hypertension, and depression neither affected shoulder function, nor physical and mental health status at one-year following shoulder arthroplasty.

6.2 Key messages

6.2.1 What is already known on this subject

It has been consistently reported that people with diabetes are more frequently affected by AC with long-lasting symptoms and poor prognosis. Further, although some of the therapeutic interventions are effective in managing primary AC, several studies have reported higher shoulder pain, reduced mobility, poor functional outcomes, reduced quality of life, and a diminished response to treatment in patients with diabetes than patients without diabetes [1–3]. None of the previous systematic reviews focused on patients with diabetes or formally tested diabetes as a source of clinical heterogeneity in response to treatment. Given the potential differences in underlying mechanisms for patients with diabetes, it is unclear whether the recommendations for treatment of AC can be equally applied to the subset of patients with diabetes.

Adhesive capsulitis occurs five times more often in people with diabetes [4]. Exercises are usually recommended to manage AC. However, the recovery is slow and often incomplete, especially for patients with diabetes. Aerobic exercises improve hyperglycemia and insulin sensitivity. Currently, no research has formally assessed the benefits of incorporating an aerobic training program into the treatment plan of AC in patients with diabetes.

Shoulder arthroplasty has been shown to significantly reduce pain, restore joint function and improve shoulder ROM at two years and beyond [5]. While it is known that diabetes is associated with poor outcomes in ROM and patient-reported function after total knee arthroplasty [6], it is unknown whether this is also true for shoulder arthroplasty. Further, the response to shoulder arthroplasty surgery and the outcomes are not easily predictable. Factors such as age, gender, and the presence of comorbidities have been reported by a few studies to influence functional outcomes following shoulder arthroplasty [5].
6.2.2 What this thesis adds to the knowledge base

Low-quality evidence suggests large effects of joint mobilization plus exercises on adhesive capsulitis in people with diabetes, although confidence in this conclusion is limited due to the high risk of bias. Even weaker support was available for corticosteroid and MUA. The pilot trial established that conducting a large-scale study to assess the effect of physiotherapy program for managing AC is feasible. The current findings suggest that physiotherapy exercises may be effective in reducing pain and improving shoulder function and ROM in patients with and without diabetes who have AC. Future studies, with 80% power ($\alpha= 0.05, \beta= 0.20$) to detect a 20% between-group difference, would require a sample size of 89 participants per group. This will require a large hospital or several hospitals to manage. Patients with diabetes achieve large clinical benefits from shoulder arthroplasty, with follow-up outcomes equally positive to those without diabetes. Future prospective studies with a larger sample size of patients with diabetes are needed to confirm the results of this study. Residual pain is associated with poorer function status and fewer clinical benefits. Female sex is not associated with less change in function which suggests that men and women get equal benefits from the surgery. Advanced age relates to poorer physical health. Diabetes, hypertension, and depression neither affected shoulder function, nor physical and mental health status at one-year following shoulder arthroplasty.

6.3 Limitations

Despite providing excellent insights into clinical approaches for diabetic shoulder, this thesis, on the whole, had one inherent limitation besides specific limitations of the individual studies included in it. We had time constraints that prevented us from recruiting enough subjects for the pilot study to examine the impact of incorporating an aerobic exercise program into the specific shoulder exercises for managing AC in patients with diabetes. However, we established a groundwork for future trials to assess this effect based on the experience that we gained from the pilot study.

6.4 Implication of thesis findings

The prevalence of diabetes among Canadian adults aged 20-79 years is expected to increase by 14% in 2030 [7]. Patients with diabetes are more frequently affected by AC with long-lasting
symptoms and poor prognosis. A combination of exercises, joint mobilization techniques and steroid injection can be effective in reducing pain, improving shoulder function, and motion in patients with diabetes. 

In recent years, interest in the area of postoperative outcomes for patients following shoulder arthroplasty has increased rapidly, due to the increased volume of shoulder arthroplasty surgery and the improvement in prosthesis quality. Clinicians may expect the following:
* Patients with and without diabetes gain similar large improvements in shoulder function, motion, and strength as well as physical health status after surgery;
* The presence of pain at one-year following shoulder arthroplasty may cause limitations in shoulder function;
* The presence of comorbidities such as diabetes, hypertension, and depression may not affect postoperative shoulder function and physical health status after the surgery.

6.5 Future research directions and recommendations

Rigorous RCTs that are designed to minimize bias and reported using the Consolidated Standards of Reporting Trials (CONSORT) criteria [8] are needed to determine the best non-surgical intervention, assess the effect of surgical interventions, and examine the effect of incorporating aerobic exercise program to the traditional physiotherapy program for managing AC in patients with diabetes.

Future studies are encouraged to report the reliability and responsive measure of shoulder functional performance. The use of standardized measurements, protocols, and timing would improve the quality of existing trials and contribute to conducting meta-analysis in the future. Considering 38% of patients refused to participate in this pilot trial, future clinical trials should keep this ratio in mind before deciding on their sample size. A larger multicenter randomized clinical trial or a single-centre trial with a long period can help to recruit the required number of participants which in-turn can increase the power of any study.

6.6 Overall summary

Through this thesis, we have provided evidence-based information on the effect of different non-surgical interventions and determined the feasibility of a full-scale randomized clinical trial on managing AC in patients with diabetes. We examined the impact of diabetes on
shoulder recovery, and factors predicting shoulder function at one-year following shoulder arthroplasty. This final chapter provided a general discussion and formulated conclusions based on the previous research, including the most significant findings. We have also provided future research directions and recommendations.
6.7 References


Appendix 1

Ethics Approval Notice
Western University, London, ON.

Date: 10 May 2018
To: Dr. Joy MacDermid
Project ID: 111647

Study Title: Physiotherapy program for managing adhesive capsulitis in patients with diabetes: A pilot randomized trial

Application Type: HSREB Initial Application
Review Type: Full Board
Meeting Date: April 3, 2018
Date Approval Issued: 10/May/2018
REB Approval Expiry Date: 10/May/2019

Dear Dr. Joy MacDermid,

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above-mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Document Type</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection sheet</td>
<td>Other Data Collection Instruments</td>
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</tr>
<tr>
<td>Email Script</td>
<td>Email Script</td>
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<td>Letter of debriefing and Consent-PT_FS</td>
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<td>19/Apr/2018</td>
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<td>Written Consent/Assent</td>
<td>19/Apr/2018</td>
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<td>Phone Script</td>
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<td>19/Apr/2018</td>
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<td>Study protocol</td>
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<tr>
<td>walking program diary</td>
<td>Other Data Collection Instruments</td>
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</table>

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH-GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00009940.

Please do not hesitate to contact us if you have any questions.

Sincerely,
Karen Gospod, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Date: 29 April 2019

To: Dr. Joy MacDermid

Project ID: 111647

Study Title: Physiotherapy program for managing adhesive capsulitis in patients with diabetes: A pilot randomized trial

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 07/May/2019

Date Approval Issued: 28/Apr/2019

REB Approval Expiry Date: 10/May/2020

Dear Dr. Joy MacDermid,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000946.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wygonski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix 2

Research letter of information
Informed consent form

Research Title: Physiotherapy program for managing frozen shoulder

Principal Investigator: Joy C. MacDermid, Co-director Clinical Research Lab
Roth McFarlane Hand and Upper Limb Centre, St. Joseph’s Health Centre, Professor, Physical Therapy, University of Western Ontario, CIHR Chair in Gender, Work and Health

Co-investigator:
Dr. Tom Overend PhD
Dr. Kenneth Faber, MD
Sanaa Alsabbeh, PhD candidate

Letter of Information

Introduction
You are invited to participate in this research study which will assess the impact of physiotherapy for managing frozen shoulder. You are eligible to participate in this study if you have a frozen shoulder. This letter gives you the basic information about what you will be asked to do so that you can decide whether or not to participate in this study. Please ask questions if anything is unclear.

Purpose of this Study
The main purpose of this study is to assess the effects of two different physiotherapy approaches to managing frozen shoulder. In both cases you will be provided with exercises and instructions for what to do on your own at home. The types of activities will be different based on which group you are in, but we expect both groups to be beneficial. This study will help us know whether one group of exercises is better than another. We are looking for women and men aged 18 and over who lives in London and surrounding regions, who have frozen shoulder and are able to communicate in English.

Study Procedure
If you agree to participate, you will be assigned to one of two exercise groups using a random process. Within both groups your physiotherapist will customize treatment to your needs and you will progress your exercises according to your tolerance. The study researchers will be responsible for randomizing you into the exercise groups and assessing your outcomes. The researchers will not be involved in which clinic you go to for your physiotherapy or dictating

Page 1 of 4   PT for managing frozen shoulder  2020-03-14   Participant Initials _____
to not answer any question(s) you like and to give only as much information as you are comfortable giving during the completion of questionnaires. Data about your weight, height, age, and the presence of chronic disease will also be collected. We will then assess your shoulder movement and muscle strength. These tests will take around 30 minutes to complete. Next, you will be referred to a physiotherapy clinic you choose to start physiotherapy treatment. The treatment will be decided by your treating therapist. You will be given additional home instructions and/or activity by the research team. You will be asked to come back for additional assessment sessions after 3, and 6 weeks, and again after 3 and 6 months.

We need a total of 40 individuals (women and men) at the Hand and Upper Limb Clinic to assist us for this study.

Possible Risks and Harms

You may feel little pain and discomfort at your shoulder when doing some exercises and activities.

Possible Benefits

Your shoulder pain level may reduce, and the function may improve after physiotherapy treatment. In addition, information gathered may determine the best physiotherapy treatment for managing frozen shoulder.

Compensation

You will not be compensated for participation in this research except for parking fees.

Voluntary Participation

Participation in this study is voluntary. You have the right to refuse to participate, refuse to answer any questions or withdraw from the study or withdraw your data at any time with no effect on your future care.

Confidentiality

All data collected will remain confidential and accessible only to the research team of this study. If the results are published, your name will not be used. If you choose to withdraw from this study, your data will be removed and destroyed from our database. While we will do our best to protect your information there is no guarantee that we will be able to do so. Representatives from Western University’s Health Science Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research. Lawson’s research team may also access your study-related records. Data collected from this study will be securely stored in the office of the principle investigator of this study.

Contact for Further Information
Publication

If the results of the study are published, your name will not be used. If you would like to receive a copy of any potential study results, please provide your name and contact number on a piece of paper separate from the Consent Form.
Consent Form

Study Title: Physiotherapy program for managing frozen shoulder

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Participant’s Name (please print): __________________________________________

Participant’s Signature: _______________________________________________

Date: __________________________________________________________________

Persons Obtaining Informed Consent (please print): _________________________

Signature: _____________________________________________________________

Date: __________________________________________________________________
Appendix 3

Curriculum Vitae

Name: Sana'a Alsubheen, BSc. PT, MSc. Kinesiology (Exercise Physiology), Ph.D. PT

Faculty of Health and Rehabilitation Sciences, School of Physical Therapy
Western University • London, Ontario, Canada

Post-secondary Education and Degrees

PhD of Physical Therapy Sept. 2016–present
University of Western Ontario, London, ON (Average 86 out of 100)

Memorial University, St. John’s, NL (GPA 3.75 out of 4)

BSc. of Physical Therapy Sept. 2000–June 2004
University of Jordan, Amman, Jordan (GPA 3.38 out of 4)

Professional Experience

• Teaching Assistantship, Faculty of Health and Rehabilitation sciences, UWO
  Course: PT 9513 Functional anatomy– Fall 2016, Fall 2017.

• Teaching Assistantship, School of Human Kinetics and Recreation, Memorial University

• Physical Therapist, King Fahad Specialist Hospital, Dammam, Saudi Arabia– Sept. 2004–Aug. 2013

Publications & Presentations

Peer-reviewed publications


Peer-reviewed oral presentation and abstracts


• Alsubheen S, MacDermid J, Overend T, Faber K. Does diabetes affect functional outcomes after shoulder arthroplasty? Oral presentation at the Diabetes and Diabetic Nurse Education and Practice Conference, September 2018, Montreal, Canada


• Peer-reviewed poster presentations and abstract


**Awards and Scholarships**

• Ontario Graduate Scholarship (OGS) award, 2019-2020.
• Faculty of Health Science travel award, Western University, 2017, 2018, 2019.
• Faculty of Health and Rehabilitation Sciences travel award, Western University, 2017, 2018, 2019.