Diabetes Mellitus and Limited Joint Mobility in the Upper Extremity

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Diabetes Mellitus and Limited Joint Mobility in the Upper Extremity

by

Kshamata Mukul Shah

A dissertation presented to the
Graduate School of Arts and Sciences
Of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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ABSTRACT OF THE DISSERTATION

Diabetes Mellitus and Limited Joint Mobility in the Upper Extremity

by

Kshamata Mukul Shah

Doctor of Philosophy in Movement Science

Washington University in St. Louis, 2014

Dr. Michael J. Mueller, Chairperson

Diabetes mellitus (DM) affects about 25 million people in the United States. Musculoskeletal complications, especially those related to the upper extremity, are common and understudied in people with DM. Limited joint mobility (LJM) is a systemic complication of DM believed to be caused by thickening and stiffness of periarticular connective tissue due to non-enzymatic accumulation of advanced glycation end-products (AGEs), and resultant cross-link formation in the collagen. Specific implications of these structural changes on movement in people with DM are not known. The objectives of this research were to characterize the upper extremity movement impairments and limited joint mobility in people with diabetes mellitus and to understand the relationships between AGEs, structural changes and movement impairments on pain and disability in people with DM.

In Chapter 2, we examine the severity of upper extremity pain/disability, weakness and limited joint mobility in a group of people diagnosed with DM attending an outpatient clinic. We report that a striking majority of the patients with DM complained of shoulder pain and/or disability, and that they had significant reductions in their shoulder range of motion, strength and hand function measures as compared to non-DM controls. Further, these measures were related
to the pain and/or disability. In Chapter 3, we examine the differences in shoulder movement using 3-dimensional kinematics. We report substantial loss of humerus relative to scapula motion, in particular, external rotation motion during elevation and rotation movements. In Chapter 4, we examine the differences and relationships between a marker for AGEs, shoulder structural changes, movement, and pain and/or disability. We report that the proxy measure for skin AGEs, tendon thickness, movement impairments were higher in the DM group as compared to controls and these measures were related to complaints of pain and disability.

In summary, our data indicate that shoulder and hand impairments are frequent, severe and often associated with pain and disability. Shoulder LJM, in particular humerus relative to scapula external rotation ROM, and strength deficits are significantly large in these individuals with DM as compared to matched control participants. These studies, for the first time, examine the relationship between an AGEs marker and functional measures as they relate to upper extremity impairments and LJM in people with DM.
CHAPTER 1:

Background and Significance
Diabetes Mellitus (DM) affects about 25 million people in the United States (1). Musculoskeletal complications, especially those related to the upper extremity, are common and understudied in people with DM (2-6). These musculoskeletal complications often lead to pain and disability and may influence quality of life in individuals with DM (5-7). Therefore, studies which focus on understanding musculoskeletal complaints and its relationship to physical performance are necessary in these individuals. Some of the common impairments seen in the upper extremity are limited joint mobility (LJM) at the shoulder and hand, frozen shoulder (also referred as adhesive capsulitis), carpal tunnel syndrome and Dupuytren’s contracture. Several of these abnormalities are related to connective tissue alterations in periarticular and skeletal systems seen in people with DM.

LJM in people with DM is thought to be caused by thickening and increased stiffness in the periarticular structures (8). Aging is also characterized by limitation in joint motion (9). However, DM has been shown to have an additive negative effect on the joint stiffness seen with advancing age (9,10). LJM is a systemic problem and has been documented at several joints in the body including hand, shoulder, ankle and foot. Lower extremity LJM and associated tendon pathologies have been associated with increased stresses on the plantar foot surface and is thought to contribute to the development of foot ulcers (11,12). In the upper extremity, LJM has been well documented at the hand but not at the shoulder (10,13-15). In its beginning stage, LJM at the shoulder and hand may often be painless and go unnoticed. However, LJM may be a precursor to severe upper extremity impairments associated with pain and/or disability (9,16,17). In this introductory chapter, I will briefly overview upper extremity impairments in people with DM and discuss contributing factors that may lead to these impairments (Fig.1).
Prevalence of shoulder and hand impairments.

Studies have reported a higher prevalence of shoulder and hand impairments in people with DM compared to those without DM (2,6,10,15-21). Prevalence of shoulder impairments and pain in people with DM is about 11-50% compared to those without diabetes, 2 - 20% (2,6,7,15-21). Milgrom et al. reported that individuals with DM had a much higher risk, 5.0 – 5.9 (95% CI = 3.3, 8.4, P<0.001), for developing idiopathic frozen shoulder as compared to those without DM (22). Additionally, frozen shoulder does not respond as well to treatment and symptoms tend to last longer in individuals with DM (23). The prevalence of hand impairments is reported to be 8-75% in people with DM compared to about 0-26% in those without DM (15,19,21,24). Presence of upper extremity impairments has also been linked with poor glycemic control and presence of other diabetes related complications (2). A significant relationship has been found between the prevalence of shoulder and hand impairments, indicating that they often co-exist (2,19,25).

Ramchurn et al. examined the prevalence of shoulder and hand problems in a group of people with DM (N = 96; Mean Age = 55) compared to a group without DM (N = 100; Mean Age = 63) (2). They found significant differences between groups, with higher prevalence of shoulder (25% vs. 2%) and hand problems (63% vs. 12%) in people with DM. Another important finding was that the glycemic control was poorer in individuals who had combined shoulder and hand impairments (mean HbA1c 9.1%) versus those who had no impairments (mean HbA1c 8.0%).

Laslett et al. examined shoulder pain and disability [(measured via Shoulder Pain and Disability Index (SPADI)] in people with DM and found that 45% reported shoulder pain and/or disability. In a 12 month follow-up, 25% of individuals who reported no pain and/or disability at baseline developed clinically significant pain or disability (10% points change on the SPADI). 50% of the patients with pre-existing pain and/or disability, developed clinically significant worsening of
pain and/or disability (6). Little is known about how self reported pain and disability relates to upper extremity function measures. Therefore, there is a need for studies that examine the upper extremity impairments and factors that contribute to these functional deficits.

**Pathophysiologic factors.**

One of the main mechanisms for LJM in diabetes is believed to be the formation of non-enzymatic advanced glycation end-products (AGEs) (8,26,27). Aging has also been associated with AGEs accumulation. AGEs accumulate at a much higher rate in patients with DM as compared to healthy adults (28). It is believed that the collagen changes lead to premature aging in people with DM (28). The excessive glucose condenses with metabolic intermediates to form AGEs. These AGEs are broken down only when the metabolic intermediates degrade. Thus, AGEs tend to accumulate in tissues with low-protein turnover like the tendons, skin, ligaments etc leading to increased cross-links (29,30). Additionally, specific AGE receptors (RAGE) have been identified on the membrane of chondrocytes, tenocytes and fibroblasts (31,32) which when activated, lead to accelerated AGE cross link formation in the collagen fibers of these tissues (33,34). The cross-links in the tissues tend to make these structures thick, stiff, weak and susceptible to injury (29,30).

AGEs also accumulate in body fluids such as serum and urine (28). Some of the methods to measure AGEs in serum include high-performance liquid chromatography, enzyme-linked immunosorbent assay and immunohistochemistry (28). However, these methods require blood draws and expensive laboratory equipment to measure the level of AGEs. Skin AGEs provide a good estimate of long term hyperglycemia. The half life of AGEs in the skin is about 15-20 years.
and therefore, are a better indicator of this chronic hyperglycemia as compared to a single measure of glycated hemoglobin which provides the glycemic exposure over 2-3 months (35,36).

Results from a study by Yian et al. provide further evidence for using biomarkers other than HbA1c (37). They found that the HbA1c measure was not related to the prevalence of frozen shoulder in a large sample of 1150 patients with diabetes and a diagnosis of frozen shoulder. The skin AGEs can be measured non-invasively using the SCOUT DS device (VeraLight Inc., Albuquerque, NM), which uses ultraviolet light to excite and measure the fluorescence produced by AGEs (38-40). In a validation study, the in-vitro AGEs levels in porcine skin biopsy samples were related to the SIF (Skin Intrinsic Fluorescence) measured using spectrometry (41).

Additionally, research has shown that this in-vivo, non-invasive measure of the Skin Intrinsic Fluorescence (SIF) has been related to various diabetes related complications like neuropathy, increased arterial stiffness, nephropathy (38,42,43). However, the relationship between SIF and shoulder structural changes, LJM and upper extremity function is unknown.

**Structural Changes**

Influence of AGEs accumulation can be seen on a variety of tissues, such as muscles, bones and tendons. Haus et al. have shown that the accumulation of AGEs and resultant collagen cross-links is significantly higher, approximately 200%, in muscle from healthy older individuals as compared to younger individuals (44). DM has an additive negative effect on the accumulation of AGEs and formation of cross-links. Higher concentrations of AGEs in the intramuscular connective tissue may contribute to decreases in function. Changes associated with AGEs accumulation are also seen in the bone. In a cadaver study, Tang and his colleagues
showed that physical properties of cancellous bone, i.e. decreased energy, loss of stiffness etc., were impaired in ribosylated bone tissue samples with high AGEs as compared to control samples, thus increasing its susceptibility of fracture (45). Odetti et al. found that the cortical bone AGE level correlated negatively (P<0.01) with the degree of mass density loss (46). Accumulation of AGEs in DM has been associated with impaired bone healing and osteoporosis (47,48). Thus AGEs measurement may be a good indicator of bone strength and quality. High AGEs concentrations have also been reported in cartilage tissues, possibly making the tissue stiffer (35).

Upper extremity tendon changes have been studied using ultrasound. It is an easy and relatively inexpensive method to evaluate tendon properties, particularly tendon thickness. Studies have found increased thickness of long head of the biceps tendon and supraspinatus tendon along with an increased incidence of tears in the supraspinatus tendon in people with DM (9,49,50). The biceps and supraspinatus tendon changes are commonly studied because of their important impact on movement, and because they can be measured easily using ultrasonography. Further, the supraspinatus tendon is an abductor of the arm and contributes to external rotation motion in an abducted position (50). Akturk et al. evaluated supraspinatus and biceps tendon thickness in 150 individuals with DM (Mean age 50.2 (15)) and 94 without DM (Mean age 47.5 (14)) (50). They determined that individuals with DM had thicker supraspinatus and biceps (long head) tendons compared to the control group (Supraspinatus tendon, 6.60 (6.58) mm vs. 4.91 (0.41) mm, P<0.01; Biceps tendon, 4.00 (1.05) mm vs. 2.95 (0.40) mm, P<0.01). Similarly, Abate et al., measured supraspinatus and biceps (long head) tendon thickness changes in asymptomatic elderly people with DM and compared to older people without DM (49). Tendon thickness was significantly greater in people with DM compared to those without DM for the
supraspinatus (6.20 (0.09) mm vs. 5.20 (0.70) mm, P<0.01) and biceps tendon (4.00 (0.80) mm vs. 3.20 (0.40) mm, P<0.01). Other changes observed in these tendons in people with DM compared to those without are higher incidence of tears, increased degenerative changes and calcifying tendinopathy (9,49,52,53). In addition to the structural properties, the physical properties of the tendons in DM are also impaired. Tendon fiber sliding is decreased due to the AGEs accumulation and collagen cross-links (54). AGE cross-link formation impacts the synthesis of the extracellular matrix (55), further making the tissues stiff.

Other structural changes seen at the shoulder include fibrous contractures and dense collagen matrix in the joint capsule and its adherence to the head of the humerus, rotator interval area, and coracohumeral ligament at the shoulder joint in people with DM (52,56,57). Cystic and sclerotic changes have been observed on the bony margins of the humeral head, glenoid and acromion (53). These changes are twice as frequent in people with DM as compared controls. However, the impact of these structural changes on movement and function is not understood.

**Upper extremity movement and functional impairments.**

Several studies have examined hand (24,25,58-61) or shoulder (9,16,17,62) impairments in people with DM. But the combined influence of shoulder and hand impairments on function is not clearly understood. Hand impairments in people with DM have been attributed to decreases in grip strength and reduced sensation (25,58). Some studies have also shown that elderly individuals with diabetes perform less well on a task of hand dexterity as compared to a group of subjects without diabetes (25,61). Grip strength changes are frequently examined in people with DM (25,58-61). High level AGEs accumulation in older women has been associated with low
grip strength values (63). Studies that examine shoulder muscles strength are lacking. A few studies have examined LJM at the shoulder (glenohumeral joint) using goniometry and have found differences in range of motion between people with diabetes and those without (9,16,17,62). Abate et al. measured shoulder range of motion for flexion and abduction movements in elderly people with DM and without DM. They found 20 degrees (P<0.01) decrease in ROM for both motions in people with DM compared to those without DM (9).
Schulte et al. observed a significant decrease (6%, P<0.01) in composite shoulder ROM in people with DM compared to the control group without DM (16). Similarly, Shinabarger reports 20 degrees decrease in abduction, and 6 degrees loss of lateral rotation ROM in people with DM compared to those without DM (62). This study was conducted on small sample (10 with DM and 9 without DM) and hence, significant differences in ROM were not observed for all movements in the two groups. All these studies have used goniometry to detect ROM differences at the glenohumeral joint between the two groups. However, with the use of goniometry only 2-dimensional motion of the humerus relative to the thorax is quantified.

Combined scapulothoracic and glenohumeral motion is necessary to achieve full humerus-to-trunk scapular plane elevation (40° anterior to the frontal plane) and perform daily activities like personal hygiene and overhead reaching. In addition, the humerus-to-scapula external rotation motion is critical for reaching overhead and daily activities like washing ones’ back and hair, dressing etc. With the use of three dimensional movement assessment, the motion at the scapulothoracic and glenohumeral can be measured (64,65). Ludewig et al. assessed these three dimensional motions using rigidly fixed electromagnetic sensors via transcortical bone pin placement in the scapula and humerus (65) During relaxed standing, the scapula relative to the trunk is internally rotated (~41° (2)), upwardly rotated (~6° (1)) and anteriorly tilted (~13.5° (2));
and the humerus relative to the scapula is externally rotated (~14° (4)) (65). During arm elevation in the scapular plane, normal scapulothoracic movements, i.e. scapula relative to the thorax, include – scapular internal rotation, upward rotation and posterior tilting; and normal glenohumeral motions, i.e. humerus relative to scapula, include – humeral elevation and external rotation. At maximum arm elevation in the scapular plane, compared to the relaxed position, the scapula relative to the trunk will be less internally rotated (~35°), upwardly rotated (~51°) and posteriorly tilted (~8°); and the humerus relative to the scapula will be elevated (~86°) and externally rotated (~64°) (65).

Some studies have examined 3D kinematics in the shoulder joint in a heterogenic group of people with frozen shoulder (66-71). These measures were compared to the uninvolved side in the same individual or compared to measures in people without frozen shoulder. Overall, a decrease in glenohumeral motion, especially elevation and external rotation has been observed (66-71). Additionally, increased scapular upward rotation and reduced internal rotation have been observed presumably to compensate for the glenohumeral hypomobility (68,70,71). These studies examined movement deficits in people with diagnosed adhesive capsulitis, but no mention of the diabetes status of the participants has been provided. To the best of our knowledge, no study has examined the 3-dimensional shoulder movement in people with DM. The accumulation of AGEs may also have a role to play in the increased evidence of musculoskeletal pain in people with DM (28,72). Formation of AGEs and cross links induces free radical formation and leads to oxidative stress. We hypothesize that glenohumeral and scapulothoracic movement will be reduced in people with DM which will be related to complaints of pain and/or disability in people with DM.
Purpose

The overall purpose of this study is to characterize upper extremity movement impairments and LJM in people with DM, and to understand the relations between advanced glycation end products (estimated using Skin Intrinsic Fluorescence (SIF)), structural changes, movement impairments, and function in people with diabetes (DM). The hypothesized progression of these complications is illustrated in Figure 1.

Specific Aim 1: (Chapter 2)
Establish the severity of upper extremity pain/disability, weakness and limited joint mobility in a group of people diagnosed with DM attending an outpatient diabetes clinic.

Hypothesis 1: In a survey sample of individuals with DM, more than 20% of individuals with DM will report pain and/or disability (operationally defined as total Shoulder Pain and Disability Index (SPADI) score of more than 30%) in the upper extremity.

Hypothesis 2: The SPADI score will correlate inversely to shoulder range of motion (ROM), strength and hand function measures.

Hypothesis 3: External rotation and abduction ROM and strength at the shoulder, and hand function will be more impaired in people with DM than those without DM.

Specific Aim 2: (Chapter 3)
Determine differences in movement impairments in individuals with DM and those without DM.

Hypothesis 1: The group with DM will have reduced peak humerothoracic elevation, scapulothoracic upward rotation, and glenohumeral rotations, especially external rotation as compared to the group without DM.
Specific Aim 3: (Chapter 4)

Determine differences and relationships in Skin Intrinsic Fluorescence (SIF), an indicator of advanced glycation end–products, tendon thickness, movement impairments and upper extremity function in people with DM versus non-DM controls.

**Hypothesis 1**: The SIF measure will be higher, the biceps and supraspinatus tendons will be thicker, and upper extremity movement will be reduced in the DM group as compared to the control group.

**Hypothesis 2**: SIF measure will be correlated to the tendon thickness and upper extremity pain and/or disability, and negatively correlated to shoulder movement.

**Hypothesis 3**: Significant amount of the variance of the upper extremity pain and/or disability will be explained by the SIF, biceps tendon thickness, movement impairments and shoulder flexor muscle strength.
Figure 1: Theoretical model of upper extremity impairments in diabetes mellitus

Diabetes Mellitus $\rightarrow$ Accumulation of Advanced Glycation End-Products (AGEs) $\rightarrow$ Structural changes $\rightarrow$ UE movement impairments $\rightarrow$ UE pain and/or disability

UE = Upper extremity
REFERENCES


CHAPTER 2:

Upper Extremity Impairments, Pain and Disability in Patients with Diabetes Mellitus

This chapter is in review:

Shah KM, Clark BR, McGill JB, Mueller MJ. Upper Extremity Impairments, Pain and Disability in Patients with Diabetes Mellitus. *Physiotherapy*
ABSTRACT

OBJECTIVE: Determine the severity and relationships of Upper Extremity (UE) impairments, pain and disability in persons with diabetes mellitus (DM); and compare UE impairments in persons with DM to non-DM controls.

DESIGN: Case-control, and cross-sectional design.

SETTING: University-based, outpatient diabetes center and physical therapy research clinic.

PARTICIPANTS: Two hundred and thirty-six individuals with DM attending an outpatient diabetes clinic completed the Shoulder Pain and Disability Index (SPADI) questionnaire. A detailed shoulder and hand examination was conducted on a sub-group of 29 Type 2 DM volunteers, and 27 age, sex and BMI matched non-DM controls.

INTERVENTIONS: None

MAIN OUTCOME MEASURES: Measures included the SPADI scores; passive shoulder range of motion (ROM) and strength; grip strength; hand sensation; dexterity and hand limited joint mobility (LJM).

RESULTS: Sixty-three % of persons with DM reported shoulder pain and/or disability [mean SPADI score 21.7% (25.7)]. Compared to the non-DM controls, the DM sub-group had reductions (P<0.05) in shoulder ROM (-9–15%); shoulder muscle strength (-11–25%); grip (-14.8%) and key pinch strength (-12%). Persons with DM had a greater prevalence of decreased sensation (26/27 vs.14/27) and hand LJM (17/27 vs.4/27) compared to the non-DM controls. Total SPADI scores were negatively correlated (P<0.05) with shoulder ROM (r= -0.42 to -0.74) and strength measures (r= -0.44 to -0.63) in the DM sub-group.
CONCLUSIONS: UE impairments in this sample of patients with DM were common, severe, and related to complaints of pain and disability. Additional research is needed to understand the unique reasons for UE problems in people with DM and identify treatments to prevent them.

KEYWORDS: Diabetes Mellitus, Upper extremity, shoulder, hand
Upper extremity (UE) musculoskeletal disorders are a common and understudied problem in persons with diabetes mellitus (DM) (1-3). Clinical syndromes previously described in patients with DM [2,3] include but are not limited to shoulder adhesive capsulitis or frozen shoulder, limited joint mobility (LJM) at the hand, Dupuytren’s contracture and carpal tunnel syndrome. Prior reports place the prevalence of shoulder impairments in people with DM significantly higher at 11-50% (4-8) compared to those without diabetes, 2 - 20% (4,6-8). Similarly, the prevalence of hand impairments is variably reported to be 8-75% (6,9-10) in people with DM compared to about 0-26% (6,10) in those without DM. A significant relationship has been found between the prevalence of shoulder and hand impairments, suggesting that they often co-exist and may have a common mechanism [1,6,11].

LJM in DM is thought to be caused by non-inflammatory thickening and increased stiffness in the periarticular structures (12). First observed at the hand, LJM may also occur at the shoulder (4,9,13). In its beginning stage, LJM of the shoulder and hand may be painless and therefore unnoticed. However, LJM may precede severe UE impairments associated with pain and/or disability. The presence of LJM and associated impairments at the shoulder and hand may have a significant impact on UE function in people with DM.

Studies have examined shoulder (7,14-16) or hand (11,17-20) impairments in patients with DM, but the combined influence of shoulder and hand impairments on UE pain and disability has not been studied. A few studies have examined LJM at the shoulder and report differences in range of motion (ROM) between persons with DM and those without DM (7,14-16) but studies of shoulder strength and UE function are lacking. The overall aim of this study was to:

- Determine the severity of UE pain and disability in individuals with DM attending an outpatient diabetes clinic. Pain and disability were estimated using the Shoulder Pain
and Disability Index (SPADI) (21,22), a self-report questionnaire which has been previously used in patients with DM (5,7).

- Compare shoulder ROM, strength and hand function measures on a subgroup of people with DM and those without DM (matched for age, sex, body mass index (BMI)).
- Determine the relationship between the shoulder and hand strength and joint mobility, and UE pain and disability in a subgroup of people with DM.

Understanding these outcomes and relationships should help to focus future rehabilitation research and interventions to reduce the severity of UE impairments and disability in people with DM.

METHODS

Participants:

We mailed a flyer containing the SPADI questionnaire, demographic information sheet, cover letter, and consent to 336 individuals with DM enrolled in the Diabetes and Research Training Center Prevention and Control Core patient database. The flyer also had a section for the participants to indicate if they wished to be contacted for an UE examination. The cover letter encouraged the participants to respond even if they did not have pain and/or disability. We also obtained consent and distributed 103 questionnaires at the Diabetes Center to unselected DM patients willing to complete the flyer. A total of 236 patients completed the flyer (Table 1). The SPADI, a self-report questionnaire, contains a total of 13 items, divided into two sub-groups
i.e. pain (5 items) and disability (8 items) (21,22). Each item is scored from 0-10 and scores for each sub-group are averaged and converted to a percentage (22). The total SPADI scores are an average of the two sub-scores and range from 0% to 100%; higher score indicates more pain and disability. The SPADI has excellent reliability, includes questions on shoulder and hand function, and is easy (<5 minutes) to administer (23).

A detailed shoulder and hand evaluation was completed on 1) a sub-group of the first 29 individuals with type 2 DM who agreed to participate when contacted by the research team and 2) 27 individuals without DM and current shoulder pain/disability, and were well matched for age, sex, weight, height, BMI and handedness (P>0.05, Table 2). We anticipated a high effect size (Cohen’s d= 0.8) for all key outcome variables (shoulder ROM and strength, and hand function). A sample size of 27 in each group was predicted to find statistical differences between the groups [Statistical power level = 0.8 and alpha = 0.05 (two tailed)]. Data from all participants in the DM group were used to examine the relationship between the SPADI and the UE clinical measures. The control subjects were recruited from a university database of healthy volunteers. Participants in both groups were above 35 years of age and did not have recent (past six months) shoulder injuries, known rotator cuff tears, or neck pain. All participants read and signed the consent form approved by the institutional review board.

Clinical examination on both upper extremities on all participants was completed by the same physical therapist (KMS). For all evaluation measures, an average of two trials was used for data analyses with adequate rest pauses between trials.

Shoulder Evaluation:
Shoulder ROM was measured using a 12” plastic goniometer (Baseline®, Elmsford, NY) and standardized methods with established reliability (24-27). Active ROM was measured for flexion, abduction and external rotation ROM with the subject seated on a stool without a backrest (24,25). External rotation movement was measured with the arm close to the body and elbow bent at 90° (27). Maximal passive ROM in the pain free range was measured for shoulder flexion, abduction, internal rotation and external rotation with the subject in supine position (24,26). The arm rotations were measured with arm abducted to 90°, and elbow in 90° flexion and neutral rotation (25,26). The active ROM helped ‘loosen up’ the joint prior to the passive movement and the passive ROM measurement helped clarify joint limitations that may not be due to active movements.

We measured the isometric strength (in kilograms) of the shoulder flexor, abductor and rotator muscles using a hand-held, digital strain-gauge dynamometer (Microfet™, Hoggan Health, UT). The patient was in supine position and standard stabilization (provided by the tester) and test positions were used (28-30). A “make” test procedure was used, where the subject was asked to ramp up the contraction for about 2 seconds and hold the maximum effort against the resistance applied by the therapist for 4-5 seconds. Rest periods were provided between the trials. Each muscle action was measured in a gravity-neutralized position while holding the dynamometer perpendicular to the limb.

Hand Evaluation:

The grip and pinch strength (key pinch and palmar) were measured in kilograms using a Jamar dynamometer (J. A. Preston, Grand Rapids, MI) and a pinch gauge (B&L Engineering,
Santa Ana, CA) respectively. The subject was seated with their shoulder adducted and in neutral rotation, elbow flexed at 90° and forearm in neutral position (31).

The Nine-Hole Peg (Sammons Preston, Cedarburg, WI) test was used to measure dexterity using standardized methods (11). The participant placed pegs in nine holes using one hand at a time and removed them as quickly as possible one at a time. The total time to complete each test was noted.

Hand LJM was quantified via the ‘Prayer Sign’. Subjects’ inability to press their palms together completely without a gap remaining between opposed palms and fingers was termed ‘Positive Prayer Sign’ (Figure 1) (9).

Light touch perception was measured in the peripheral nerve supply of the hand using Semmes Weinstein monofilaments (Tactile™ sensory evaluator, Baseline ®, Elmsford, NY) (20,32,33). Filaments ranging from 2.83 - 6.65 (0.07g - 330g force) were applied until they bent and #6.65 was applied just to bending. The smallest perceivable monofilament was noted. The grading for the monofilaments was as follows: intact (2.83), diminished light touch (3.61), diminished protective sensation (4.31), loss of protective sensation (4.56– 6.65) (32,33).

Statistical Analyses:

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Software (SPSS Inc, Chicago, IL) for Windows (19.0); alpha level was set at $P < 0.05$. Descriptive statistics (percentages, means, standard deviations and percent changes) were used to describe outcome measures. There were no significant differences between right and left UE
evaluation measures in persons with DM, therefore only data from the right UE were included in statistical analyses. The active and passive ROM for flexion and abduction motions were not statistically different, therefore only passive ROM was included in further analysis. The data for the active external rotation ROM has been reported in the results. All data were analyzed using the Shapiro-Wilk test for normality and non-parametric tests were used when necessary. Student’s t-tests and chi-square test (for hand LJM) were used to examine group differences in the UE clinical measures; and Pearson’s correlation co-efficient was used to examine the relationship between the total SPADI score and UE measures. Further, a hierarchical multiple regression analysis was performed using the total SPADI scores as the dependent variable and the shoulder abduction ROM and hand grip strength as predictors. We chose these measures a priori because 1) abduction ROM measure provides an indication of one’s ability to perform a variety of shoulder movements, and 2) grip strength measure is often used as a surrogate measure for decreased UE strength and as a predictor of disability (19,34).

RESULTS:

Flyer:

236 flyers, containing the SPADI and demographic information were collected on persons with DM. 133 flyers were collected via mailing and 103 flyers were collected at the Diabetes Clinic. The overall response rate to the flyer was 53.8 % (236/439). Subject characteristics from the flyer are listed in Table 1. Overall, 63% (149/236) reported shoulder pain and/or disability (mean total SPADI score 21.7% (25.7). 30% (72/236) reported substantial pain and/or disability,
operationally defined as a SPADI score of more than 30% (mean total SPADI score 56.14% (16.55)) (Appendix, Figure 1).

Upper Extremity Evaluation:

Subject characteristics of the DM and control groups matched for age, weight, height, and sex are represented in Table 2.

Shoulder Measures: Shoulder flexion, abduction, external rotation passive ROM were reduced by -9 % to -15.4 % ($P<0.01$, Table 2, Fig. 2) in the DM group compared to those without DM. Active external rotation ROM was also reduced in the DM group ($59.8^\circ (10.7)$ vs. $66.8^\circ (8.7)$; $P=0.01$). Mean shoulder flexors, external and internal rotators strength were reduced by -10.9 % to -25.5 % ($P<0.05$, Table 2, Fig. 2) in the DM group compared to the control group.

Hand Measures: Grip strength and key pinch strength were decreased by -14.8% and -12.1% ($P<0.05$), respectively, in the DM group compared to the non-DM cohort (Table 3, Fig. 2). Hand LJM, indicated by ‘positive’ prayer sign, was more prevalent in those with DM compared to those without (17/27 vs. 4/27, $P=0.006$, Table 3). Peripheral sensation was more frequently impaired in those with DM compared to those without DM (26/27 vs. 14/27, Table 3).

Relationship between SPADI scores and upper extremity evaluation measures:

There was a strong negative correlation between the total SPADI scores and shoulder ROM measures ($r = -0.42$ to -0.74, $P<0.05$), and shoulder muscles strength ($r = -0.44$ to -0.63, $P<0.05$, Table 2) in the DM subgroup. 68% ($P<0.01$) of the variance of the total SPADI scores was explained by the shoulder abduction ROM ($R^2$ change = 0.55, $P\leq0.001$) and grip strength ($R^2$ change = 0.13, $P=0.003$).
DISCUSSION:

Sixty-three% of individuals with DM reported shoulder pain and/or disability. 31% of the DM patients had substantial pain and/or disability, defined in this study as a total SPADI score of more than 30%. Upper extremity impairments in this sample of patients with DM attending an outpatient Diabetes Center were common, severe, and related to complaints of pain and disability (Tables 1, 2, 3 and Fig. 2). Shoulder ROM, especially external rotation and abduction, and strength were reduced (8-25%) and negatively correlated (r = -0.42 to -0.68) to SPADI scores, indicating the close relationship between shoulder LJM and strength, and UE function.

This is the first study to comprehensively report shoulder and hand impairments, and their relationship with UE function in people with DM. Shinabarger (14) measured shoulder active ROM in a small group of people with Type 2 DM (N=9) and Abate M et al (16) measured passive ROM for flexion and abduction ROM, and report a 2-14% reduction in ROM compared to those without DM. Adequate shoulder ROM, especially external rotation and abduction, and strength are particularly important for completing tasks of daily living like reaching an overhead shelf, grooming, and self care. Interestingly, in a subgroup of individuals with DM who had a SPADI score of 0% (N=5), we found that shoulder ROM and strength were reduced by 8-10% and 5-13%, respectively, compared to individuals without DM and similar SPADI scores suggesting that early losses may not be recognized by the patient.

Hand strength, mobility and sensation were decreased in people with DM compared to those without DM, contributing to the global UE dysfunction in people with DM. Savas et al noted similar decreases in grip (16%) and key pinch (9%) strength in individuals with DM compared to those without DM (17). Significant differences in grip strength and sensation in the hand also
have been recorded by other studies (11,18-20,35). Individuals with diminished protective sensation may have decreased hand function, leading to difficulty in manipulation of small objects and a tendency to drop objects (11,32). Hand dexterity, although reduced, was not significantly different between the two groups in this study. Redmond et al reported significant association between Disability of Arm Shoulder and Hand (DASH) scores and grip strength, dexterity and BMI measures (R² = 0.38) (11). In our study, 68% (P<0.01) of the variance in the total SPADI scores was explained by abduction ROM and grip strength verifying that measurable UE impairments are related to complaints of pain and/or disability. Previous studies have failed to report the combined influence of shoulder and hand impairments on overall UE function. The results from this study support our hypothesis that shoulder and hand impairments impact UE function. Future studies in people with DM should focus on studying the shoulder and hand as one functional unit.

This study characterizes insidious UE impairments in people with DM, and these results may further help develop appropriate treatment strategies for these individuals. If impairments are identified early, simple exercises that focus on improving UE ROM, especially external rotation and elevation, and strength may be administered to minimize or prevent further detrimental changes in patients with DM. In one of the few prospective studies of shoulder disorders in DM, Laslett et al reported that 45% of people with DM had shoulder pain and/or disability, as measured via the SPADI (5). In a 12 month follow-up, 25% of individuals who reported no pain and/ or disability at baseline developed clinically significant pain or disability (10% points change on the SPADI). Additionally, of the patients with pre-existing pain and/or disability, 50% developed clinically significant worsening of pain and/or disability. We postulate that DM causes loss of ROM and strength that may hit a “threshold” leading to severe UE limitations and
disability. Further research is necessary to understand the factors that may be associated with the progression of UE impairments in people with DM and if exercise can be used to help prevent the problems.

This study adds to the growing body of research describing LJM in the upper and lower extremities of people with DM (16,36). The underlying mechanisms that lead to these systemic musculoskeletal changes need further investigation. The primary mechanism for LJM is believed to be the condensation of glucose and metabolic intermediates to form advanced glycation end-products (AGE) (12,37). AGEs accumulate in tissues with low protein turnover such as skin and tendons, and lead to cross-links making the tissues thicker, stiffer, weaker and therefore, more prone to injury (38). These structural changes may affect joint movement. Although detailed kinematic studies have been performed on the shoulders of people with adhesive capsulitis (39), additional research is needed to understand the 3D glenohumeral and scapulothoracic ROM deficits unique to diabetes and LJM. Investigating the relationships between AGEs, structural changes and UE movement impairments will provide insights to the UE musculoskeletal problems in people with DM. A better understanding of the physiological and movement related factors associated with diabetic musculoskeletal problems may lead to enhanced treatment strategies (i.e., exercise or pharmalogical) to manage or even prevent the problems.

Study Limitations

We purposed to collect data from a representative sample of patients with DM attending an outpatient clinic but there may have been a sampling bias between the respondents and non-respondents in the questionnaires. To minimize this bias, we 1) mailed a cover letter that encouraged the participant to respond even if they did not have pain/disability, and 2) collected
the SPADI information at the diabetes clinic from DM patients, not selected by their pain/disability levels. While UE impairments were evaluated in individuals with DM, who had varying levels of pain and/or disability, there is also the possibility of sampling bias. We matched the diabetes and control groups for age, weight, height, BMI, sex and handedness which allowed us to examine group differences (DM vs. no DM) in UE function with greater confidence. Lastly, we cannot comment on the temporal relationship of the development and progression of UE problems as this was a cross-sectional study. Additional research is needed to determine more clearly if the insidious loss of shoulder ROM is a precursor to severe shoulder disability.

CONCLUSIONS:

A substantial majority (63%) of individuals with DM in this study report shoulder pain and/or disability. Compared to individuals without DM, persons with DM had considerable LJM and strength deficits at the shoulder and hand, and decreased sensation. Complaints of UE functional deficits, and pain and/or disability were highly correlated with shoulder and hand ROM, especially shoulder external rotation and abduction, and strength deficits. These impairments, which may be overlooked in the rehabilitation clinic setting, are related to functional deficits and may lead to difficulty in performing daily life activities. Further studies are needed to better characterize UE movement impairments in DM, and the pathologic mechanisms and methods for prevention and treatment.

Acknowledgements: The authors thank Dr. Catherine E. Lang for contributing to the study design and methods, and Ms. Lori Buechler for helping with data collection.
Table 1. Demographic and SPADI information from the survey flyers.

<table>
<thead>
<tr>
<th>Total survey flyers</th>
<th>236</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailed-in</td>
<td>133</td>
</tr>
<tr>
<td>Completed at Diabetes Clinic</td>
<td>103</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.4 (11.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.7 (6.9)</td>
</tr>
<tr>
<td>Male</td>
<td>47.4 % (112)</td>
</tr>
<tr>
<td>Diabetes Type 2</td>
<td>72.9 % (172)</td>
</tr>
<tr>
<td>Duration of diagnosed diabetes (yrs)</td>
<td>16.4 (12.1)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.37 (1.3)</td>
</tr>
<tr>
<td>SPADI Pain score (0-100%)</td>
<td>26.3 (29.7) (Range: 0 – 100 %)</td>
</tr>
<tr>
<td>SPADI Disability score (0-100%)</td>
<td>17.2 (23.7) (Range: 0 – 90 %)</td>
</tr>
<tr>
<td>Total SPADI score (0-100%)</td>
<td>21.7 (25.7) (Range: 0 – 93.2 %)</td>
</tr>
<tr>
<td>SPADI equal to 0%</td>
<td>36.8 % (87)</td>
</tr>
<tr>
<td>SPADI not equal to 0%</td>
<td>63.2 % (149)</td>
</tr>
<tr>
<td>SPADI over 30%</td>
<td>30.5 % (72)</td>
</tr>
</tbody>
</table>

Data represented as means (SD) or % (N) unless otherwise indicated; SPADI = Shoulder Pain and Disability Index
<table>
<thead>
<tr>
<th>Measure (units)</th>
<th>Diabetes group</th>
<th>Control group</th>
<th>Significance $^a$</th>
<th>Correlation with total SPADI scores $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>27</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65.7 (8.9)</td>
<td>64.4 (8.7)</td>
<td>$P = 0.64$</td>
<td></td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>101.1 (21.2)</td>
<td>98.1 (16.4)</td>
<td>$P = 0.99$</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 (0.09)</td>
<td>1.7 (0.10)</td>
<td>$P = 0.93$</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>33.2 (5.5)</td>
<td>33.3 (6.0)</td>
<td>$P = 0.93$</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/10</td>
<td>17/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominance (R/L)</td>
<td>26/1</td>
<td>26/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPADI score (%)</td>
<td>37.1 (27.9)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive ROM (deg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>154.4 (24.6)</td>
<td>169.9 (5.7)</td>
<td>$P \leq 0.001^#$</td>
<td>-0.68$^#$</td>
</tr>
<tr>
<td>L</td>
<td>149.2 (29.7)</td>
<td>170.2 (4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>147.4 (25.8)</td>
<td>170.4 (5.2)</td>
<td>$P \leq 0.001^#$</td>
<td>-0.74$^#$</td>
</tr>
<tr>
<td>L</td>
<td>141.3 (29.4)</td>
<td>169.6 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External Rotation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>66.5 (12.8)</td>
<td>78.5 (4.5)</td>
<td>$P \leq 0.001^#$</td>
<td>-0.51$^#$</td>
</tr>
<tr>
<td>L</td>
<td>60.9 (20.3)</td>
<td>75.8 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Rotation $^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>74.6 (10.7)</td>
<td>79.0 (7.5)</td>
<td>$P = 0.10$</td>
<td>-0.42$^*$</td>
</tr>
<tr>
<td>L</td>
<td>72.9 (15.5)</td>
<td>81.5 (4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength (kgs):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>10.9 (3.9)</td>
<td>14.7 (4.2)</td>
<td>$P \leq 0.001^#$</td>
<td>-0.44$^*$</td>
</tr>
<tr>
<td>L</td>
<td>9.8 (3.8)</td>
<td>13.9 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abductors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>9.1 (3.8)</td>
<td>10.5 (2.4)</td>
<td>$P = 0.15$</td>
<td>-0.56$^#$</td>
</tr>
<tr>
<td>L</td>
<td>8.5 (2.8)</td>
<td>9.7 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External Rotators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>10.8 (3.3)</td>
<td>13.1 (3.7)</td>
<td>$P = 0.02^*$</td>
<td>-0.51$^#$</td>
</tr>
<tr>
<td>L</td>
<td>9.5 (3.8)</td>
<td>11.1 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Rotators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>12.1 (3.8)</td>
<td>13.6 (3.5)</td>
<td>$P = 0.048^*$</td>
<td>-0.63$^#$</td>
</tr>
<tr>
<td>L</td>
<td>11.3 (4.8)</td>
<td>14.5 (3.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data represented as means (SD) unless otherwise indicated.

\( a \) = \( P \) values were determined by using Independent Sample Student’s t-test; * indicates \( P < 0.05 \); # indicates \( P < 0.01 \).

\( b \) = Correlation between the total SPADI scores and shoulder ROM and strength measures was determined using Pearson’s correlation coefficient (N=29); * indicates \( P < 0.05 \); # indicates \( P < 0.01 \).

\( c \) = Non-parametric tests were used - Mann Whitney U test and Spearman’s Correlation.

R = Right; L = Left; ROM = Range of Motion; SPADI = Shoulder Pain and Disability Index
Table 3. Hand evaluation measures

<table>
<thead>
<tr>
<th>Measure (units)</th>
<th>Diabetes group</th>
<th>Control group</th>
<th>Significance a</th>
<th>Correlation with total SPADI scores b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip Strength (kgs):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>28.4 (9.7)</td>
<td>33.4 (10.3)</td>
<td>( P = 0.045^* )</td>
<td>-0.28</td>
</tr>
<tr>
<td>L</td>
<td>27.1 (10.0)</td>
<td>32.3 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key Pinch Strength (kgs):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>9.2 (5.4)</td>
<td>10.5 (2.3)</td>
<td>( P = 0.04^* )</td>
<td>-0.28</td>
</tr>
<tr>
<td>L</td>
<td>7.7 (2.5)</td>
<td>8.6 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar Pinch Strength (kgs):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>6.7 (2.2)</td>
<td>7.3 (1.9)</td>
<td>( P = 0.32 )</td>
<td>0.10</td>
</tr>
<tr>
<td>L</td>
<td>6.7 (2.6)</td>
<td>7.3 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Hole Peg Test (sec) c:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>23.8 (3.7)</td>
<td>22.4 (3.4)</td>
<td>( P = 0.056 )</td>
<td>0.14</td>
</tr>
<tr>
<td>L</td>
<td>25.0 (4.7)</td>
<td>22.9 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand sensation (N):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>1</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished Light Touch</td>
<td>17</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished Protective Sensation</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of protective sensation</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prayer sign (N):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>23</td>
<td>( P = 0.006^d )</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data represented as means (SD) unless otherwise indicated.

\( a = P \) values were determined by using Independent Sample Student’s t-test; \( * \) indicates \( P < 0.05 \);
\# indicates \( P < 0.01 \)

\( b = \) Correlation between the total SPADI scores and shoulder ROM and strength measures was determined using Pearson’s correlation coefficient (N=29).

\( c = \) Non-parametric tests were used - Mann Whitney U test and Spearman’s Correlation.
d = Significance determined by Chi-Square test

R = Right; L = Left; SPADI = Shoulder Pain and Disability Index
‘Positive Prayer Sign’ is the subjects’ inability to press their palms together completely without a gap remaining between opposed palms and fingers.
Figure 2: Shoulder and Hand evaluation measures in DM group as compared to control group

Data represented as mean percent difference (SD)

* indicates $P < 0.05$; # indicates $P < 0.01$; $P$ values were determined by using Independent Sample Student’s t-test and Mann-Whitney test (for IR ROM); Flx = Flexion; Abd = Abduction; ER = External rotation; IR = Internal rotation; ROM = Range of motion; Str = Strength; DM = Diabetes Mellitus
REFERENCES


CHAPTER 3:

Shoulder Limited Joint Mobility in People with Diabetes Mellitus

ABSTRACT

Background: Limited joint mobility (LJM) at the shoulder has not been examined using 3-dimensional kinematics in individuals with diabetes mellitus (DM). The purpose of this study was to determine the differences in shoulder kinematics between a group with DM and those without DM.

Methods: Fifty-two participants were recruited, 26 with DM and 26 non-DM controls (matched for age, BMI and sex). Three-dimensional position of the trunk, scapula and humerus were collected using electromagnetic tracking sensors during scapular plane elevation and rotation movements.

Findings: Glenohumeral external rotation was reduced by 11.1° - 16.3° (P<0.05) throughout the elevation motion in individuals with DM as compared to controls. Peak humerothoracic elevation was decreased by 10-14°, peak external rotation, with the arm adducted and abducted, was decreased, by16°- 22°, respectively in the DM group compared to controls (P<0.05). The scapulothoracic motion and glenohumeral internal rotation, with arm at the side and arm abducted, was not different between the two groups.

Interpretation: Shoulder LJM, in particular decreased external rotation, was seen in individuals with DM as compared to control participants. Future research should investigate causes of diabetic LJM and strategies to prevent or improve shoulder LJM and additional detrimental changes in movement and function.

Keywords: shoulder, limited joint mobility, kinematics, diabetes mellitus
Musculoskeletal complications, especially those related to the upper extremity, are a fairly common and yet understudied problem in people with DM (1,2). Some of the common shoulder problems include limited joint mobility (LJM) and frozen shoulder. LJM is a systemic problem which has been studied at the relatively small joints of the hands, feet and ankles (3,4); however, the specific joint motion limitations at the shoulder are not well documented. Milgrom et al. reported that individuals with DM had a much higher risk, 5.0 – 5.9 (95% CI = 3.3-8.4, P<0.001), for developing idiopathic frozen shoulder as compared to those without DM (5). Frozen shoulder is characterized by presence of severe limitation of range of motion, pain and a slow recovery process. LJM at the shoulder is often painless but may be the precursor to more severe upper extremity impairments and functional limitations (6-8). It is believed to result from metabolic abnormalities effecting connective tissues in periarticular and skeletal structures (3,9,10).

Shoulder range of motion (ROM) has been studied by conventional goniometry in persons with diabetes and compared to non-diabetic controls, with findings that abduction and ER ROM was decreased, 138 (20)° versus 158 (21)°, and 83 (8)° versus 89 (4)°, respectively (6,11). Goniometry measures 2-dimensional motion of the humerus relative to the thorax, ignoring the glenohumeral and scapulothoracic joints, which are assessed using 3-dimesional kinematic measures. In studies of persons with heterogeneous causes of frozen shoulder, 3D kinematics has demonstrated a decrease in glenohumeral motion, especially elevation and external rotation when compared to the uninvolved side in the same individual or unaffected controls (12-15). Overall, a decrease in glenohumeral motion, especially elevation and external rotation has been observed. Additionally, increased scapulothoracic upward rotation and internal rotation has been
observed. No study has examined the insidious shoulder LJM at the glenohumeral and scapulothoracic joints that occurs in asymptomatic or minimally symptomatic people with DM.

The purpose of this study was to determine the differences in shoulder kinematics in individuals with DM as compared to non-DM controls. We hypothesized that scapulothoracic upward rotation, and glenohumeral motion external rotation would be reduced during scapula plane elevation in people with DM as compared to the non-DM controls. The glenohumeral rotational movements, especially external rotations, would be reduced during rotation motion with arm at the side of the body and with the arm in an abducted position. We chose to evaluate these motions because the scapulothoracic upward rotation is the most dominant scapula motion during elevation, and glenohumeral external rotation is important to clear the greater tuberosity of the humerus from the subacromial space during overhead reaching motions (16,17). For rotation movements, we focused on the humerus relative to scapula motion, as this represents actual glenohumeral motion and these motions are important for completing activities of daily living (18).

METHODS:

We recruited 26 participants with Type 2 DM and 26 control participants matched for age, body mass index and sex and who did not have shoulder pain. Subjects were recruited from the Washington University Diabetes Center and the Volunteers for Health database at Washington University School of Medicine. The main focus of this study was to examine the kinematic differences between individuals with DM who were at risk for systemic LJM versus those without DM. Characteristics associated with LJM include duration of DM (1,2) and a positive
prayer sign, described as the inability to press their palms together completely without a gap remaining between opposed palms and fingers (19). Therefore, inclusion criteria for the DM group were: duration of diagnosed DM over 10 years or a ‘positive prayer sign’, and age between 40-70 years. We did not include or exclude individuals in the DM group based on their pain levels, and 13 study subjects with DM complained of some shoulder pain and 13 did not have shoulder pain. Participants in the control group were matched for age, body mass index and sex, did not have DM and did not have significant shoulder pain. Four participants in the control group reported very low levels of pain and disability during their laboratory visit. Demographic information is included in Table 1. The groups were well matched for age, body mass index, sex and handedness.

Exclusion criteria for both groups were: history of/or current frozen shoulder, major rotator cuff tears, recent upper extremity injuries, fractures, surgery in the thorax or arm, cervical pain, thoracic outlet syndrome, rheumatic conditions, known connective tissue disorders, stroke, severe skin allergies in areas to be tested, and allergy to adhesive tapes. In addition, participants with body mass index higher than 35 kg/m² were excluded because kinematic measurement errors are known to be large in people with high body mass indices (20).

Eligible participants in both groups provided written informed consent. Participants completed the Shoulder Pain and Disability Index (SPADI) and Disability of the Arm, Shoulder and Hand (DASH) questionnaires to characterize the upper extremity pain and functional limitations for descriptive purposes (21,22).

Shoulder 3D Kinematic measurements:
The 3-dimensional position and orientation of the subjects’ bilateral humerus, scapula, and thorax were tracked using the Flock of Birds™ 3D electromagnetic tracking device (Ascension Technology Inc., Burlington, VT, USA) and the MotionMonitor software (The Motion Monitor, Innovative Sports Training Inc, Chicago IL, USA). Five Flock of Birds sensors were used. The sensors were attached to the 1) thorax: mid sternum 2) right and left scapula: distal posterolateral flat aspect of the acromion and 3) right and left arm: distal end of the humerus, via a thermoplastic cuff secured with Coban (3M, St. Paul MN, USA) (20). Sensors and trailing wires were taped down and secured with Coban to prevent slippage and motion artifact. Previous studies for 3D scapular kinematics have demonstrated that the motion pattern obtained using surface sensors was similar to acromion-fixed sensors, especially below 120° of elevation (23). For humeral motion, the average error ranged from 0-4° for elevation angle and 1.7-2.3° for axial rotation movements during scapular plane elevation movements when the motion was compared for humerus bone fixed sensor and a sensor mounted on a thermoplastic cuff around the humerus (20,24). The average error was larger for axial rotation movement by the side of the body than with arm at 90° abduction (9.7-14.6°). To evaluate the reliability of these measures in individuals with DM (N=7) in this study, we reattached the sensors at the end of the testing session. The intra-class coefficient (ICC) (2,k) for glenohumeral rotation, scapulothoracic upward rotation, and humerothoracic elevation during scapula plane elevation was between 0.84 – 0.97. The ICCs for the rotation movements were between 0.71 – 0.97. For humeral motion, the average error ranged from 1.0-2.1° and axial rotation error ranged from 1.7 -3.0° during scapular plane elevation. The average error for axial rotation with arm adducted was 8.1-13.3° and with abducted at 90 degree the error was 2.3-7.0°. An additional sensor attached to a stylus was used for digitizing the anatomic coordinates. With arms relaxed, bony landmarks were digitized on the
thorax, scapula and humerus to transform sensor data into local segment coordinates according to the protocol recommended by the International Society of Biomechanics, Shoulder group (25).

Kinematic data was collected on both arms at 100 Hz for subjects’ full active range of motion in scapular plane (40° anterior to the frontal plane) elevation, internal rotation (IR) and external rotation (ER). The order of the movements was randomized. IR and ER data was collected in two positions – elbow flexed at 90° with arm adducted (IR-AD and ER-AD) and elbow flexed at 90° with arm abducted to 90° and forearm parallel to ground (IR-AB and ER-AB). The subjects were instructed to bring the arm back to the starting positions during all the movements and to move the arm as far as possible at a slow, steady self-selected speed. Five trials were performed on one arm at a time for each movement with rest periods between trials. Averages of available ROMs during two peak trials were used for data analysis.

**Kinematic Data analysis:**

Data were analyzed using the MotionMonitor software. Angles extracted during scapular plane elevation were humerothoracic elevation, scapulothoracic upward rotation, and glenohumeral external rotation. During the IR and ER movements, angles for glenohumeral axial rotation were extracted. During scapular plane elevation, scapula position relative to the thorax was defined as, internal/external rotation about a superior axis, upward/downward rotation about the axis perpendicular to the plane of the scapula and anterior/posterior tilting about a laterally directed axis (Euler angle sequence) (25,26). During scapular plane elevation and ER/IR movements, the humerus position relative to the scapula was defined as, angle of elevation about an anteriorly directed axis perpendicular to the medial to lateral epicondylar line, angle of horizontal adduction/abduction (or flexion/extension) about a laterally directed axis parallel with
the epicondylar line, and axial rotation about a superior axis directed towards the humeral head center (Cardan angle sequence) (13,27). For all planar motions, results were analyzed at neutral, 30°, 60°, 90°, 120° and maximum humerothoracic elevation consistent with other methods (15,26). For axial rotation with arm adducted and with arm abducted at 90°, the results were analyzed at maximum ROM for external and internal rotation (20). Data for scapular plane elevation, external rotation and scapulothoracic upward rotation were multiplied by -1 for easier interpretation of the ROM data.

Statistical analyses

Statistical analyses of the data were performed using IBM SPSS (SPSS Inc, Chicago, IL) for Windows (22.0). Descriptive statistics (means, standard deviations and percent changes) were used to describe the variables. Student’s t-test and chi-square analysis were used to examine the differences in the demographic variables. All variables were tested for their distribution and appropriate statistics were used. We collected kinematic data on both shoulders. The ROM was different for the left and right shoulders; therefore, data are represented for both upper extremities (Table 2). We chose to represent the data as right/left versus involved/uninvolved because complaints of shoulder pain were distributed equally in the DM group, and the groups were matched for handedness. For scapular plane elevation motion, data were analyzed using a two-way repeated measures analysis of variance (ANOVA), with the group (DM vs. control) and angle (neutral, 30°, 60°, 90°, 120° and maximum humerothoracic elevation) as factors. The outcome variables for scapular plane elevation motion included scapulothoracic upward rotation and glenohumeral external rotation. Protected independent sample student’s t-test was used post-
hoc to compare data if the ANOVA was significant. Peak humerothoracic elevation angle, IR-AD, IR-AB, ER-AD and ER-AB data were compared between the two groups using independent sample student’s t-test. Since we had 13 individuals with DM who had no pain, we conducted an additional post-hoc analysis (t-test) to examine the movement differences between the non-painful DM subgroup and the control group. Statistical significance was set at $P<0.05$.

RESULTS:

Demographic information is included in Table 1 for 26 participants in the DM group and 26 control participants. The groups were well matched for age, body mass index, sex and handedness. The mean SPADI and DASH scores in individuals with DM were 21.4 (27.4) % and 19.4 (22.4) %, respectively, and in those without DM were 1.9 (3.5) and 2.6 (5.1) ($P<0.01$).

Scapular plane elevation: The peak humerothoracic elevation was decreased in individuals with DM as compared to the controls on the right, 139 (12)$^\circ$ versus 150 (11)$^\circ$ and left shoulders, 122 (16)$^\circ$ versus 136.4 (11)$^\circ$ ($P<0.05$) (Fig 1). Glenohumeral ER increased with increasing humerothoracic elevation angles for the right and left sides in both groups, as expected (main effect of angle for right, $F= 68.7$, $P<0.01$; left, $F= 37.1$, $P<0.01$). The glenohumeral external rotation angle was decreased in the DM groups as compared to the control group at 120$^\circ$ and peak humerothoracic angle for the right side, and at 30$^\circ$, 60$^\circ$, 90$^\circ$ and peak humerothoracic elevation for the left side (Table 2, Fig. 1), as indicated by the post-hoc t-tests performed under the significant main effect of different angles between the two groups on the left and right side (main effect for group for right, $F= 4.2$, $P=0.045$; left, $F= 11.3$, $P<0.01$). The groups started at similar degrees of glenohumeral external rotation; however, the DM group had reduced ER for
every 30 deg of increasing elevation angle, as indicated by the significant interaction effect between angles and group for the right shoulder (F=5.1, \(P<0.01\)), but not significant for the left glenohumeral ER (F=2.2, \(P=0.12\)). The scapulothoracic upward rotation increases with increasing humerothoracic elevation angles for the right and left sides in both groups, as expected (main effect of angle for right, F=429.4, \(P<0.01\); left, F= 310.5, \(P<0.01\)) (Fig. 3). The scapula upward rotation was not different between the DM and control group on the right and left shoulder, as indicated by the interaction effect (right, F=3.1, \(P=0.052\); left, F= 0.1, \(P=0.99\)) and group effect (main effect for group for right, F= 4.2, \(P=0.63\); left, F= 0.14, \(P=0.71\)).

Glenohumeral ER during scapular plane elevation was very similar in the DM sub groups with and without pain (Fig 2). The DM sub-group with no pain (N=13) had decreased glenohumeral external rotation angle at 60°, 90°, 120° and peak humerothoracic angle for the right side (Fig. 2), and at 30°, 60°, 90° and peak humerothoracic elevation for the left side as compared to the control group (\(P<0.05\)). The scapulothoracic upward rotation was not different between the DM sub-group without pain and control group.

Rotation: External rotation with arm adducted, ER-AD, was decreased on the right, 34.8 (17.4)° versus 52.2 (27.7)° and left, 33.9 (18.7)° versus 49.5 (23.6)° shoulders in individuals with DM as compared to the control group (\(P<0.05\)) (Table 3). External rotation with arm abducted at 90°, ER-AB, was decreased on the right, 51.7 (16.4)° versus 71.1 (27.6)° and left, 48.3 (17.6)° versus 70.7 (21.3)° shoulders respectively, in individuals with DM as compared to the control group (\(P<0.05\)) (Table 3). IR-AD and IR-AB was not different between the two groups for both sides. In the DM sub-group without pain, the ER-AD (right, 34.8 (13.1)°; left 33.3 (14.6)°) and ER-AB (right, 51.2 (8.0)°; left 54.0 (16.6)°) were substantially reduced as compared to the control group (\(P<0.05\)) but not different compared to the DM subgroup with pain.
DISCUSSION:

The results of this study indicate that the glenohumeral external rotation and peak humerothoracic elevation during scapular plane elevation were decreased by 11º - 16º and 10º-14º, respectively in both shoulders in individuals with DM as compared to the control group. The scapulothoracic upward rotation was not different between the two groups during scapular plane elevation. Glenohumeral rotations, especially external rotation with arm adducted and abducted, were reduced by 16-22º in people with DM as compared to controls. Surprisingly, similar LJM changes were also seen in the DM subgroup that did not have complaints of shoulder pain (Fig. 2).

This is the first study to examine the three-dimensional kinematic differences in shoulder movement in people with DM compared to controls. Shoulder LJM, as evidenced in this study, may be a precursor to severe shoulder motion limitation, pain and disability. Previous research has examined LJM at the shoulder in people with DM using traditional goniometric methods (6-8,11) and reported approximately 20 degrees of decrease in shoulder abduction motion and about 8 degrees of loss of external rotation motion. Results (unpublished) from a study in our lab also found similar decreases in shoulder ROM, especially elevation (148º vs. 170º) and external rotation motion (67º vs. 77º) in people with DM as compared to controls. The peak humerus relative to thorax elevation was reduced by 10-14º in individuals with DM as compared to the controls. Goniometric measurements are limited in scope to humerothoracic movements. Further, the contributions of the humerus and scapula to the different movements are not known with goniometry alone. The 3D analysis provides new understanding of shoulder LJM which has not
been studied previously. With the use of 3D kinematics we were able to track glenohumeral external rotation throughout the elevation range and not just at the end ranges. One of the main findings of this study was the reduced glenohumeral external rotation observed throughout increasing angles of humerothoracic elevation. Better understanding of specific movement deficits can help in the development of exercise programs that target movements where ROM loss is the greatest. Specific exercises to improve shoulder elevation and external rotation throughout the ROM may help prevent future problems of severe LJM, pain and disability.

There was substantial loss of glenohumeral ER during the rotation movement in individuals with DM as compared to the control participants (Table 3); internal rotation motion was not different between the two groups. Surprisingly, reductions in external rotation of similar magnitude have been reported in patients with idiopathic frozen shoulder, with humerus-to-scapula external rotation. The ER with arm adducted (ER-AD) and abducted (ER-AB), limited to 34.7º and 45.3º, respectively, in patients with frozen shoulder as compared to the control group (50.8º and 65.4º, respectively) (13). In another study, Rundquist et al. reported 14-16% decrease in ER ROM in the involved shoulder of the patient as compared to the non-involved shoulder of the same patient (14). While pain and shoulder disability characterize idiopathic frozen shoulder, this study shows similar large deficits in the ER ROM in patients with DM, who did not have a history of or current frozen shoulder and had not sought treatment for shoulder conditions.

Surprisingly, the glenohumeral ER ROM during elevation and rotation movements was reduced even in individuals with DM who did not complain of pain (N=13) (Fig. 2). The glenohumeral ER was reduced at almost all elevation angles, and ER-AD and ER-AB was reduced in the DM sub-group with no pain as compared to the control group. The reductions in ROM of the humerus relative to the scapula are observed before individuals with DM have
symptoms of pain and/or disability. This finding strengthens our hypothesis that LJM of the shoulder is an insidious process that is variably associated with pain.

One of the mechanisms for LJM is believed to be the excessive accumulation of advanced glycation end-products (AGEs), formed by the non-enzymatic condensation of the metabolic intermediates and glucose (3,9,10). The glycosylation process occurs in a variety of tissues, but particularly those with high protein and collagen content like the tendons, skin, ligaments etc., and leads to collagen cross links in these tissues (28,29). The multi-step glycosylation process is irreversible in the later stages, and causes changes in the structural properties of tissues. This is supported by clinical studies that have shown thicker biceps and supraspinatus tendons (30,31) and thick fibrous capsule in the rotator interval area and thicker coracohumeral ligament in people with DM compared to controls (32,33). We postulate that the reduction in ER ROM observed in this cohort of patients with diabetes is due to the structural changes in the anterior structures of the shoulder e.g. increased tendon thickness, anterior capsule changes, and ligament changes. The supraspinatus assists in ER when the shoulder is abducted (34); therefore, we speculate that the structural changes of the tendon may affect external rotation movement. The coracohumeral ligament and rotator interval provide passive constraints to the ER ROM in the adducted and abducted humerus position, respectively (35,36).

Contrary to our hypothesis, there were no differences in the scapulothoracic upward rotation between the two groups. Previous studies have reported excessive scapulothoracic upward rotation in individuals with frozen shoulder as a mechanism to compensate for glenohumeral hypomobility. The peak scapulothoracic upward rotation was higher in the involved arm in patients with idiopathic frozen shoulder as compared to the non-involved arm in these patients (52.9° vs. 45.2°, P=0.006) (12,15,37). In this study, the peak scapula upward rotation was not
different between the DM group and control group (Fig. 3, Table 2). The scapula is connected to the thorax via muscular attachments and is highly mobile. We speculate the scapula upward rotation was not decreased because of the lack of multiple tendon and ligament attachments between the scapula and thorax, and therefore, not affected by systemic LJM in the same way that the glenohumeral joint is affected.

This study provides unique insights about LJM at the shoulder joint in people with DM. If these changes are identified and addressed early, appropriate interventions may help to prevent severe upper extremity impairments, including limitation of ROM, pain and disability. In a study by Diercks et al., outcomes were compared in two groups of patients with idiopathic frozen shoulder, a group that received intensive physical therapy treatment and another group that received general instruction for shoulder movement and patient education. At the end of the study, pain, ROM and functional status were better for the group that received minimal instruction (38). Decreased physical activity and use of arms may also be one the reasons for LJM and movement impairments in individuals with DM. We speculate that an upper extremity exercise program that incorporates simple ROM exercises and focuses on increasing overall use of the arm may help reduce LJM in individuals with DM.

The examination of 3D shoulder kinematics is a powerful tool to examine LJM in individuals with DM. However, some limitations must be acknowledged. Firstly, we excluded subjects with body mass index greater than 35 kg/m² to minimize shoulder kinematic measurement error. Therefore, our results may not be generalized to all individuals with DM. We attached the humerus sensors to thermoplastic cuffs versus directly on the skin to reduce errors due to movement artifacts. However, this set-up may under represent the IR and ER motions because the cuff may not fully track the humeral motion at end ROM. Lastly, the main focus of this study
was to examine the differences between people with DM versus controls; however, the ROMs were different between the right and left shoulders. We compared the right and left shoulder ROMs in the DM group to right and left side of the control group. Preferential use of the dominant arm may be one of the reasons for the higher ROMs on the right side, which was the dominant arm for 84% of the individuals who participated in this study.

In conclusion, shoulder ROM was decreased in individuals with DM, even those without pain. The glenohumeral external rotation was reduced by 11º - 16º throughout the elevation motion in individuals with DM as compared to controls. The peak humerothoracic elevation was decreased by 10º - 14º, and the external rotation, with arms adducted and abducted, was decreased by 16º - 22º in the DM group compared to the controls. Movement impairments in persons with diabetes are similar to those with idiopathic frozen shoulder, but with fewer symptoms. Future research should focus on strategies to identify LJM in persons with diabetes earlier and to develop prevention and treatment modalities to limit the associated disability.

**Acknowledgements:** The authors thank Victor Cheuy, Emily Martin, Lisa Simone and Molly Burns for helping with data collection and analysis.
<table>
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<tr>
<th></th>
<th>DM</th>
<th>Control</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.5 (5.6)</td>
<td>64.2 (5.8)</td>
<td>P = 0.8</td>
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<td>Sex (M/F)</td>
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<td>13/13</td>
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</tr>
<tr>
<td>Height (m)</td>
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<td>1.7 (1.0)</td>
<td>P = 1.0</td>
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<tr>
<td>Weight (kgs)</td>
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<td>86.6 (12.7)</td>
<td>P = 0.8</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
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<td>30.0 (4.0)</td>
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<td>Diabetes duration (y)</td>
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<td>-</td>
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<td>Dominance (R/L)</td>
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<td>22/4</td>
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<tr>
<td>Shoulder Problems (N)</td>
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<td>R = 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L = 6</td>
<td>L = 2</td>
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</tr>
<tr>
<td></td>
<td>Both = 2</td>
<td></td>
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<tr>
<td></td>
<td>No pain = 13</td>
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<td>SPADI (%)</td>
<td>21.4 (27.4)</td>
<td>1.9 (3.5)</td>
<td>P&lt;0.01</td>
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<td>DASH (%)</td>
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<td>2.6 (5.1)</td>
<td>P&lt;0.01</td>
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<tr>
<td>Prayer Sign (positive/negative)</td>
<td>15/11</td>
<td>9/17</td>
<td>P = 0.164&lt;sup&gt;b&lt;/sup&gt;</td>
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All data represented as means (SD) or N.

<sup>a</sup> Significance was determined using independent sample t-test student’s t-test

<sup>b</sup> Significance was determined using chi-square analysis
Table 2. Kinematic differences during scapular plane elevation motion

<table>
<thead>
<tr>
<th>Humerothoracic Elevation (deg)</th>
<th>Shoulder</th>
<th>Scapulothoracic Upward Rotation (deg)</th>
<th>Glenohumeral External Rotation (deg)</th>
<th>DM</th>
<th>Control</th>
<th>DM</th>
<th>Control</th>
<th>P value $^a$</th>
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<td>Neutral</td>
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<tr>
<td>R</td>
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<td>14.2 (12.6)</td>
<td>16.0 (6.1)</td>
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<tr>
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<tr>
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<tr>
<td>L</td>
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<td>35.3 (12.3)</td>
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<td>0.003</td>
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</table>

All data represented as means (SD).

$^a$Significance determined for glenohumeral external rotation using protected independent sample student’s t-test since two-way repeated measures analysis of variance was significant.

*P<0.01; #P<0.05; R=Right; L=Left
Table 3. Glenohumeral rotations

<table>
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<th>DM</th>
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<th>P value $^a$</th>
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<tr>
<td>ER-AD (deg)</td>
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</tbody>
</table>

All data represented as means (SD).

$^a$Significance determined using independent sample student’s t-test.

ER=external rotation; IR=internal rotation; IR-AD, ER-AD= internal rotation and external rotation with arm adducted; IR-AB, ER-AB= internal rotation and external rotation with arm abducted at 90°
Figure 1. Right glenohumeral external rotation during scapular plane elevation

*P<0.05, Significance determined for glenohumeral external rotation using protected independent sample student’s t-test since two-way repeated measures analysis of variance was significant.

DM = Diabetes Mellitus
Figure 2. Right glenohumeral external rotation (DM sub-group without pain) during scapular plane elevation

*P<0.05, Significance based on post-hoc independent sample student’s t-tests to examine difference between DM no-pain sub-group and control group

DM = Diabetes Mellitus
Figure 3. Right scapulothoracic rotation during scapular plane elevation

DM = Diabetes Mellitus
REFERENCES


CHAPTER 4:

Relationship between Advanced Glycation End Products and Upper Extremity Impairments in Individuals with Diabetes Mellitus

Shah KM, Clark BR, McGill JB, Lang CE, Maynard JD, Mueller MJ. Relationship between advanced glycation end products and upper extremity impairments in individuals with diabetes mellitus.
ABSTRACT
OBJECTIVE Determine the differences and relationships between the Skin Intrinsic Fluorescence (SIF), a proxy measure of advanced glycation end-products, biceps and supraspinatus tendon thickness, upper extremity movement and disability in groups with and without diabetes mellitus (DM).

RESEARCH DESIGN AND METHODS Fifty-two subjects participated; 26 with Type 2 DM (13F/13M; Age 64.5 (5.6) yrs; BMI 30.1 (4.1) kg/m²) and 26 sex, age and BMI matched controls. The main outcome measures were: SIF; biceps and supraspinatus tendon thickness; three- dimensional peak humerothoracic and peak glenohumeral external elevation; and Disability of the Arm, Shoulder and Hand (DASH) questionnaires.

RESULTS Mean SIF measures were higher in the DM group as compared to the control group, 3.1 (1.4) AU versus 2.6 (0.6) AU (P<0.05). Biceps (4.7 (0.7) mm vs. 3.2 (0.8) mm) and supraspinatus (6.4 (1.1) mm vs. 4.9 (1.2) mm) tendons were thicker, and peak humerothoracic elevation and glenohumeral external rotation were reduced by 11° and 16°, respectively in the DM group as compared to the control group (P<0.05). The SIF was correlated to biceps tendon thickness, and DASH (r = 0.44-0.51, P<0.05), and negatively correlated to the peak humerothoracic elevation (r = -0.44, P<0.05). The SIF score and shoulder strength explained 65% of the DASH scores (P<0.01).

CONCLUSIONS SIF, an indicator of advanced glycation end products, was related to tendon thickness, shoulder movement impairments and disability. Clinicians should be aware that accumulation of AGEs in individuals with DM may have deleterious effects on structural changes, joint mobility and function of the upper extremity.
Keywords: Diabetes, Advanced Glycation End-products, shoulder, limited joint mobility, upper extremity impairments, tendon thickness
Musculoskeletal complications associated with Diabetes Mellitus (DM) are frequent (1-3) and often lead to pain and disability (4). Limited joint mobility (LJM) at the hand and shoulder are common impairments observed in the upper extremity (5-9). Prevalence of shoulder impairments is reported to be about 11-50% in people with DM (4,10-13). However, the underlying mechanism for this upper extremity LJM is not completely understood. It is speculated that LJM is caused by the excessive accumulation of advanced glycation end products (AGEs), formed by non-enzymatic condensation of excessive glucose and proteins (14-16). These AGEs lead to collagen cross-links and structural changes in the tissues, of particular interest is the cross linking in the collagen-rich musculoskeletal tissues i.e. tendons, ligaments, skin, muscle etc (17-19). We speculate that this further leads to upper extremity movement impairments and pain and disability. (Fig 1)

The AGEs that accumulate in the skin have an estimated half life of 15-20 years, and therefore, are a better indicator of chronic hyperglycemia as compared to a single measure of glycated hemoglobin which provides the glycemic exposure over 2-3 months (20,21). The skin AGEs can be measured non-invasively using the SCOUT DS device (VeraLight Inc., Albuquerque, NM), which uses ultraviolet light to excite and measure the fluorescence produced by AGEs (22-24). Previous research has shown that this in vivo, non-invasive measure of the Skin Intrinsic Fluorescence (SIF) is correlated with the severity of tissue-specific diabetes related complications such as neuropathy, increased arterial stiffness, and nephropathy (22,25,26). However, the relationship between SIF and shoulder structural changes, LJM and upper extremity function is unknown.

Some of the structural changes previously identified in diabetes include increased thickness in the biceps and supraspinatus tendons (8,27,28). Additionally, fibrous contractures and dense
collagen matrix have been observed in the shoulder joint capsule and adherence to the head of
the humerus, rotator interval area, and coracohumeral ligament (29,30). Studies that have
examined upper extremity joint mobility, especially using 3-dimensional (3D) kinematics are
lacking. Combined scapulothoracic and glenohumeral motion is necessary to complete overhead
reaching and tasks of daily living like grooming. These movements can be accurately quantified
and analyzed using 3D motion capture devices. However, no study, to the best of our knowledge,
has examined the relationships between these diverse metabolic and functional measures as they
relate to upper extremity musculoskeletal impairments.

The purpose of this study was to determine the differences and relationships between SIF (an
indicator of the AGEs accumulation in the skin), structural changes, and upper extremity
movement impairments and disability (Fig. 1). We hypothesize 1) the SIF measure will be
higher; the biceps and supraspinatus tendons will be thicker, and upper extremity movement will
be reduced in the DM group as compared to the control group; 2) the SIF measure will be
correlated to the tendon thickness and upper extremity disability, and negatively correlated to
shoulder movement; 3) a significant amount of the variance of the upper extremity disability will
be explained by the SIF, biceps tendon thickness, movement impairments and shoulder strength.
These variables were selected based upon the sequence of events illustrated in Fig 1.

RESEARCH DESIGN AND METHODS

We recruited a total of 52 subjects, 26 participants with Type 2 diabetes and 26 age, BMI and
sex matched controls, who agreed to participate in this study. Both groups were recruited from
the Washington University Diabetes Center and the Volunteers for Health database.
The intent of this study was to recruit individuals attending an outpatient diabetes clinic without acute or severe shoulder problems who were at high risk of developing shoulder LJM and subsequent shoulder impairments. Characteristics associated with systemic LJM include duration of diabetes (6,9-13) and the positive prayer sign; an inability to approximate the interphalangeal joints of the fingers (6). Therefore, inclusion criteria for the DM group were: duration of diagnosed diabetes over 10 years or a ‘positive prayer sign’, and age between 40-70 years. We wanted to include the insidious development of shoulder impairments; therefore we did not exclude individuals in the DM group based solely on their pain levels. To eliminate other potential confounders, participants in the control group were matched for age, body mass index, side of hand dominance, and sex.

Individuals in both groups were excluded if they had acute or severe shoulder problems including a history of and/or current adhesive capsulitis, rotator cuff tears, recent upper extremity injury and/or fractures, surgery in the upper extremity or thorax, neck pain, stroke with residual upper extremity involvement, rheumatic conditions, hypothyroid malfunctions, angina and/or other symptoms of myocardial ischaemia, severe skin allergies in area to be tested, known, or at risk for, photosensitivity reactions and known connective tissue diseases. In addition, participants with BMI over 35 kg/m² were excluded as the kinematic measurement errors are known to be large in people with high BMI (31).

All measurements were made by a single examiner during a single session on the right arm of the individuals in the DM and control groups.

Skin Intrinsic Fluorescence (SIF): The SCOUT DS® device (VeraLight Inc., Albuquerque, NM) was used to measure SIF non-invasively in the skin on the volar side of the forearm. Based on
previous studies, the SIF was excited with an LED centered at 405 nm and detected over the emission range of 441-482 nm. The skin reflectance was measured over the excitation and emission range to accommodate for absorbance caused by melanin and hemoglobin (22-24). The correction equations were used as described by Conway et al. (22). The resulting SIF was integrated over the 441-496 nm spectral regions to give the SIF sum. The intra subject skin variation in SIF assessed by the SCOUT has been previously documented in 2,589 participants at risk of developing type 2 DM (24). A mean of two consecutive measurements was used.

**Tendon thickness:** Ultrasound examination (US) (Acuson XP 128/10, Siemens medical Solutions, Inc., Mountain View, CA, USA) for tendon thickness of the long head of the biceps and supraspinatus was performed using a high resolution, multi-frequency (7-10 MHz) linear transducer by a single examiner. Images of the transverse view and longitudinal view were obtained for the biceps and supraspinatus, respectively, as described previously (27,28). The tendon thickness was measured using ImageJ [version 1.45s (NIH, Bethesda, MD)] computerized image analysis program. The maximum thickness of the biceps tendon in the transverse view was measured within the bicipital groove of the humerus (Appendix, Figure 2). In the longitudinal view, the maximum supraspinatus thickness was measured just in front of the lateral part of the humeral head close to its insertion (anatomical neck) on the lesser tubercle. We took an additional measurement at the midpoint of the anatomical footprint (greater tubercle of the humerus) of the supraspinatus tendon to account for differences in the anatomy of the tendon in between individuals (Appendix, Figure 3). The longitudinal thickness was an average of these two measures. The intra-rater reliability for tendon thickness measurements taken a week apart was 0.86 – 0.96. An average of three tendon thickness measurements for each tendon was used for data analyses.
Upper extremity movement: 3D humerothoracic (humerus relative to thorax) and glenohumeral (humerus relative to scapula) joint motion was measured using Flock of Birds Electromagnetic tracking device (Ascension Technology Inc., Burlington, VT, USA) and MotionMonitor software (The Motion Monitor, Innovative Sports Training Inc, Chicago IL, USA). The humerus sensor was attached to a thermoplastic cuff to reduce rotation errors and attached to the humerus using tapes. Standard methods were used to build the anatomic segments and define the motion. (32,33). Three trials were collected during full, pain-free active range of motion during scapular plane elevation, defined as elevation in a plane 40° anterior to the frontal plane. The angles extracted for this study were the peak humerothoracic elevation and peak glenohumeral external rotation.

Shoulder flexor muscle strength: The isometric strength of the shoulder flexor muscles was measured using a hand-held, digital strain-gauge dynamometer (Microfet™, Hoggan Health, UT). The patient was in supine position and standard stabilization and test positions were used (34). An average of two trials was used for the data analysis.

Measure of upper extremity disability: We used the Disability of the Arm, Shoulder and Hand (DASH) (35) self report questionnaire that has been used previously in the diabetes population and has reported excellent reliability (4,12). The DASH has 30 questions, including questions on disability as well as pain. The scores were calculated for a range between 0-100%, where a higher number indicated more impairments. This self report questionnaire provides a comprehensive assessment of the upper extremity pain and disability.

Statistical analyses:
Statistical analyses of the data were performed using IBM SPSS (SPSS Inc, Chicago, IL) for Windows (22.0). Descriptive statistics (means, standard deviations and percent changes) were used to describe the variables. Differences in the demographic variables were analyzed using independent sample student’s t-test and chi-square analysis. The mean peak humerothoracic elevation and peak glenohumeral external rotation angles were converted to positive values for ease of understanding. All variables were tested for their distribution and appropriate statistics were used. For all variables included in the a-priori hypotheses, independent sample one-tailed student’s t-tests were used to examine the differences between the two groups. Pearson’s correlation coefficient was used to examine relationships between SIF and tendon thickness, peak humerothoracic elevation and glenohumeral external rotation, and upper extremity pain and disability. We further conducted a hierarchical multiple regression analysis to explain the variance of the DASH scores. The variables of interest were the SIF scores, biceps tendon thickness, peak glenohumeral external rotation and shoulder flexor muscle strength. These variables were selected a - priori from the sequence of events described in Fig. 1. Shoulder flexor muscle strength was added to the model because a combination of shoulder mobility and strength is necessary for adequate upper extremity function. Statistical significance was set at $P<0.05$.

RESULTS:

Demographic information is listed in Table 1. Data were collected on 26 participants with Type 2 DM (mean age 64.6 (5.6) y, BMI 30.1 (4.1) kg/m², 13M/13F) and 26 age, BMI and sex matched control participants. The mean DM duration was 13.0 (4.3) yrs and HbA1c was 6.9 (1.0) % or 52
mmol/mol. Hand LJM, as indicated by the positive prayer sign was positive in 15 individuals with DM and 9 individuals without DM ($P=0.164$) (Table 1).

Differences between groups (Table 2):

The mean SIF measure was higher in individuals with DM as compared to control participants, 3.1 (1.4) Arbitrary Units versus 2.6 (0.6) Arbitrary Units. The biceps tendon and supraspinatus tendon were 46.9% and 30.6% thicker, respectively, in the DM cohort as compared to the non-DM controls. Peak external rotation and humerothoracic elevation were decreased by 16° and 11°, respectively, and the shoulder flexors strength was reduced by 27% in the DM as compared to the controls. The mean DASH score was 19.4 (22.4) % in people with DM, indicating that these individuals had some complaints of upper extremity disability and pain. Four control participants reported very low levels of pain and disability during their laboratory visit (Table 2).

Relationships between SIF and tendon thickness, upper extremity movement, and pain and/or disability:

The SIF measure was moderately correlated to the biceps tendon thickness ($r = 0.44, P<0.05$; Fig 2a) but not correlated to the supraspinatus tendon thickness ($r = 0.28, P=0.2$). The SIF measure was negatively correlated to the humerothoracic elevation ($r = -0.44, P<0.05$; Fig 2b) but not correlated to the glenohumeral external rotation ($r = -0.32, P=0.13$). The SIF measure was not related to shoulder flexor muscle strength ($r = 0.07, P=0.7$). The SIF measure was correlated to the DASH scores, a measure of upper extremity disability ($r = 0.51, P<0.05$, Fig. 2c).
The SIF (R^2 change = 0.26; P<0.01) and shoulder flexor muscle strength (R^2 change = 0.39; P<0.01) explained 65% of the variance of the DASH scores. The biceps tendon thickness and peak glenohumeral external rotation were not included in the final model because the individual contributions of these predictors were not significant.

CONCLUSIONS:

The results of this study demonstrate that the biceps and supraspinatus tendons were thicker, and shoulder movements, especially humerus relative to scapula external rotation and muscle strength, were substantially reduced in the DM group as compared to the age matched group without DM. The skin intrinsic fluorescence (SIF), an indicator of advanced glycation end-products (AGEs) accumulation was related to the biceps tendon thickness and upper extremity disability, and negatively correlated to the peak humerothoracic elevation. This is the first study to examine relationships between a proxy measure of AGEs, structural changes, and upper extremity limited joint mobility and disability in people with DM.

The SIF measure was higher in individuals with DM as compared to controls in this study. Reports place the SIF values about 17 – 33% higher in patients with DM as compared to the control population (22,25,26). Previous studies have used SIF to understand the relationship between accumulation of AGEs and diabetes related complications such as coronary artery disease (25, 26) and polyneuropathy (22) in individuals with Type 1 and Type 2 DM. Further, the non-invasive dermal SIF may be a better marker for understanding the musculoskeletal complications in individuals with DM than blood or serum markers. The SIF has been reported to be more strongly associated with the presence of neuropathy than the mean 18-year average of
the HbA1c (22). In our study, the mean HbA1c values (single measure) were not related to any of the key variables, including the SIF measure \((r = 0.14, P = 0.5)\). In contrast, and as we had predicted, the SIF measures were related to the tendon thickness, upper extremity movement and pain and disability.

The biceps and supraspinatus tendons were considerably thicker in the DM group as compared to the age, BMI and sex matched control group (Table 2). Previous work in this area has shown similar results with biceps and supraspinatus tendons thicker in DM groups compared to control groups \((4.0 \text{ mm vs. } 3.0-3.2 \text{ mm, and } 6.2-6.6 \text{ mm vs. } 4.9-5.2 \text{ mm, respectively})\) (27,28). A unique contribution of our study is that the SIF measure was related to the biceps tendon thickness, indicating that as the skin accumulation of AGEs increases the tendons tend to be thicker. Although not measured in this study, the physical properties of the tendons are also altered in individuals with DM. Tendon fiber sliding is decreased due to the AGEs accumulation and collagen cross-links (36). AGE cross-link formation impacts the synthesis of the extracellular matrix (37), further making the tissues stiff. Some of the other structural changes include fibrous contractures in the capsule and coracohumeral ligament in the shoulders of individuals with DM (29,30). This study provides unique insights in the relationship between the in-vivo skin fluorescence and the tendon thickness which have not been examined previously. We hypothesize that the changes in tendon thickness and other structures (i.e., shoulder capsule) are a result of the accumulation of AGEs that leads to limited joint mobility and movement impairments in the upper extremity (Fig 1).

There was substantial loss of peak glenohumeral external rotation (humerus relative to scapula), humerothoracic (humerus relative to thorax), and shoulder flexor muscle strength in the DM group as compared to the control group. Decreased elevation motion (about 20°) has been
reported in people with DM using traditional goniometric methods of assessing range of motion 
(7,8). A previous study in our laboratory (unpublished data) found similar decreases of about 22° and 10° in the humerothoracic elevation and external rotation movement. We also observed decreased flexor muscle strength in these individuals (10.9 kgs versus 14.7 kgs) in the DM group and age, body mass index matched control group. High levels of AGE accumulation in older adults has been associated with low grip strength values (38,39). Higher concentrations of AGES in the intramuscular connective tissue may contribute to decreases in muscle function and increased disability. The SIF measure was negatively related to the peak humerothoracic elevation, indicating that as the skin AGES accumulation increases the movement decreases. We hypothesized that a significant portion of the upper extremity disability would be explained by the SIF, biceps tendon thickness, peak glenohumeral external rotation movement, and flexor muscle strength. 65% of the variance in the DASH scores was explained by the SIF and shoulder flexor muscle strength. Therefore, accumulation of AGES and a decrease in shoulder flexor muscle strength are important predictors of adverse outcomes of upper extremity disability. Further exploration of these relationships, especially the relationship between self reported pain and disability and AGES, is warranted in future studies.

Specific AGES receptors (RAGE) have been identified on the surface of chondrocytes, tenocytes and fibroblasts (40) which when activated, lead to accelerated AGES cross link formation in the collagen fibers of these tissues (17,18). The AGES-RAGE mechanism leads to increased production of reactive oxygen species which further leads to increased inflammation (41). This elevated inflammatory status in individuals with DM may manifest in complaints of pain. Results from this study showing a strong relationship between SIF and upper extremity disability and pain further strengthen this hypothesis. If impairments related to functional
limitations are detected early, rehabilitation and pharmaceutical (AGE inhibiting and cross-link breaking agents) therapies may be developed to help prevent additional detrimental changes.

Some limitations for this study are acknowledged. The SIF is a proxy measure of the skin AGEs. Although not a direct measure of AGEs, in-vitro AGEs levels in porcine skin biopsy samples have been related to the SIF measured using spectrometry (42). In this study, we only assessed tendon thickness and not the intrinsic tendon quality such as histology, stiffness and strength. Although, we evaluated tendon thickness in individuals with DM to see how it relates to movement impairments, there are other factors (e.g. bone spurs, muscle stiffness, capsule stiffness etc.) that may influence shoulder LJM. Kinematic measures are useful to examine 3D shoulder movement; however, it does have a few limitations. Use of the humerus surface marker mounted on a thermoplastic cuff may under estimate humerus motion, especially at end-range. However, the difference between the surface marker versus bone pin marker for humerus motion was only 0-4º for elevation angle and 1.7-2.3º for axial rotation movements (31). Since this was a cross-sectional study design, we were not able to establish a cause-effect relationship. Also, we do not have information about the temporal relationship of the risk of diabetes and development of shoulder problems. Longitudinal studies are needed to clarify the causal relationship of these variables. The groups were powered to examine differences between individuals with DM and those without DM, but additional prospective studies with larger sample sizes are necessary to confirm the findings of these relationships.

This study uniquely evaluated and determined differences and relationships between a proxy measure of AGEs, upper extremity LJM and disability in individuals with DM as compared to those without DM. In particular, the biceps and supraspinatus tendons were thicker by 46.9% and 30.6%, respectively and shoulder movement, especially humerus relative to scapula external
rotation was reduced by 16° in individuals with DM as compared to the non-DM controls. The other key finding of this study was that as the skin intrinsic fluorescence, a measure for AGEs accumulation, increases, the tendons tend to be thicker, shoulder movement is reduced and complaints of upper extremity disability and pain increase. It is crucial to understand the role of AGEs on different tissues and their contributions to musculoskeletal impairments in DM. These insights can help focus future interventions on the mechanisms of upper extremity musculoskeletal problems in people with DM and develop targeted strategies to manage them.

Acknowledgements: The authors thank Victor Cheuy, Emily Martin, Lisa Simone and Molly Burns for helping with data collection and analysis.
Table 1 Demographic information

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<td>Weight (kgs)</td>
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<td>86.6 (12.7)</td>
<td>P = 0.8</td>
</tr>
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<td>30.0(4.0)</td>
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<tr>
<td></td>
<td>mmol/mol</td>
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<td>9/17</td>
<td>P = 0.164&lt;sup&gt;b&lt;/sup&gt;</td>
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All data presented as means (SD) or N

<sup>a</sup> Significance determined using independent sample student’s t-tests

<sup>b</sup> Significance determined using chi-square analysis
Table 2 Differences and relationships between the metabolic, structural and upper extremity movement and function in groups with DM and without DM

<table>
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<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>4.9 (1.2)</td>
<td>$P &lt; 0.01$</td>
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<td>Peak Humerothoracic Elevation (deg)</td>
<td>139 (12)</td>
<td>150 (11)</td>
<td>$P &lt; 0.01$</td>
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<td>Peak Glenohumeral External Rotation (deg)</td>
<td>35 (21)</td>
<td>51 (22)</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Flexors Strength (kgs)</td>
<td>13.0 (3.9)</td>
<td>16.6 (4.7)</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>DASH (%)</td>
<td>19.4 (22.4)</td>
<td>2.6 (5.1)</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

All data presented as means (SD)

<sup>a</sup> Significance determined using independent sample student’s t-test (one tailed) to examine group differences

*P < 0.05

DM = Diabetes Mellitus; SIF = Skin Intrinsic Fluorescence; DASH = Disability of the Arm, Shoulder and Hand
Figure 1. Theoretical framework for upper extremity impairments

Diabetes Mellitus → Accumulation of Advanced Glycation End-Products → Structural changes → UE movement impairments → UE pain and/or disability

UE = Upper extremity
Figure 2. Correlations between SIF and Biceps Tendon thickness, peak humerothoracic elevation and SPADI

a)
Peak Humerothoracic Elevation (deg) vs. Skin Intrinsic Fluorescence (AU) for DM and Control groups.
Correlations between Skin Intrinsic Fluorescence and a) Biceps tendon thickness, measured in the bicipital groove (DM group, $r = 0.44$, $P<0.05$) b) peak humerothoracic elevation (DM group, $r = -0.44$, $P<0.05$) c) DASH (DM group, $r = 0.51$, $P<0.05$).

Data analyzed using Pearson’s correlation coefficient.

DM = Diabetes mellitus; DASH = Disability of the Arm, Shoulder and Hand
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CHAPTER 5:

Summary of major findings
Summary of Key Findings

The objectives of this research were to characterize the upper extremity movement impairments and limited joint mobility (LJM) in people with diabetes mellitus (DM) and to understand the relationships between advanced glycation end products, structural changes and movement impairments on pain and disability in people with DM.

Chapter 2 asked the question: What is the severity of upper extremity pain/disability in a group of people diagnosed with DM attending an outpatient diabetes clinic? What are the specific impairments (shoulder and hand impairments) that may be associated with the upper extremity pain/disability in people with DM? Our results indicate that a striking majority of the patients with DM complained of shoulder pain and/or disability, and overall, a third of the individuals with DM complained of moderate to high pain and/or disability. Goniometric measurements of shoulder range of motion (ROM) indicate a decrease in all shoulder movements, in particular external rotation and abduction as compared to age, body mass index and sex matched control participants. Shoulder muscle strength and hand grip strength were reduced in the DM group as compared to the non-DM controls. Hand limited joint mobility (LJM) and decreased sensation were more severe and frequently present in the individuals with DM as compared to the control cohort. Upper extremity LJM and strength deficits were related to complaints of self reported pain and/or disability.

Chapter 3 asked the question: What are the differences in the shoulder kinematics, humerothoracic, glenohumeral and scapulothoracic between people with DM and those without DM? Our results show that the peak humerothoracic elevation was reduced in the DM group as compared to the age, BMI and sex matched non-DM control group. We observed substantial loss
of glenohumeral motion; in particular, external rotation during elevation and rotation movements. Contrary to our hypothesis, scapulothoracic motion was not reduced in the DM group as compared to the non-DM group. We speculate that LJM related changes are much higher at the glenohumeral joint owing to the extensive tendon and ligament attachments between scapula and humerus as compared to the scapulothoracic joint which is formed by muscle attachments.

Chapter 4 asked the question: What are the differences and relationships in the Skin Intrinsic Fluorescence, a marker of advanced glycation end-product accumulation, biceps and supraspinatus tendon thickness, shoulder LJM and strength, and upper extremity function in people with DM versus non-DM controls? The skin intrinsic fluorescence was higher, biceps and supraspinatus tendons were thicker, shoulder movement and strength were reduced, and the upper extremity disability was higher in individuals with DM as compared to the control group. The SIF measure was related to the biceps tendon thickness, peak elevation movement and upper extremity disability and pain, measured via the Disability of the Arm, Shoulder and Hand questionnaire. We had predicted that the SIF, biceps tendon thickness, peak external rotation movement and flexor muscle strength would explain significant amount of variance in the Disability of the Arm, Shoulder and Hand questionnaire scores (Figure 1, Chapter 1). However, only the skin intrinsic fluorescence and flexor muscle strength added significant independent variance to the model.

This strong association between the SIF measure and upper extremity disability and pain, and strength, led us to rethink the *a-priori* linear relationship among the variables. Based on this observation, we propose a revised model of shoulder impairments in individuals with DM (Figure 1). We hypothesize that the AGEs accumulation in people with DM has a direct role to
play in the pathogenesis of pain as opposed to our previous model. Advanced glycation end products (AGEs) play an important role in the inflammatory pathways in DM. The AGE-specific receptor (RAGE) leads to generation of reactive oxygen species, and attract inflammatory cells, such as interleukin-2 (IL-2), polymorphonuclear leukocytes, lymphocytes and mononuclear phagocytes. This in turn triggers the inflammatory pathways, and may contribute to the propagation of a chronic inflammatory process (1,2). Previous research has shown the importance of this pathway in diabetes complications like nephropathy, atherosclerosis etc. Similarly, this AGE-RAGE interaction may contribute to the pathogenesis of diabetic musculoskeletal complications as well. Increase in systemic inflammatory markers has implications on joint pain (3); however, these mechanisms need to be explored further. Existing information about the role of AGEs in inflammation, and results from this study further strengthen our hypothesis about the possible role AGEs in patient reported complaints of pain and disability.

In summary, our data indicate that shoulder and hand impairments are frequent, severe and often associated with pain and disability. Shoulder LJM, in particular humerus relative to scapula external rotation ROM, and strength deficits are significantly large in these individuals with DM as compared to matched control participants. The SIF is an important biomarker for AGEs and is related to structural changes, movement impairments and upper extremity function.

Limitations

There are several limitations to these studies including 1) sample size, 2) potential selection bias of the groups, and the 3) cross-sectional nature of this study. First, studies with
larger sample sizes are necessary to confirm the relationships between the clinical measures and pain and/or disability in Chapter 2, and the SIF, upper extremity structure, and function measures in Chapter 3. Secondly, we may have some selection bias in recruiting subjects for these studies. In all these studies, we purposed to collect data from a representative sample of patients with DM attending an outpatient diabetes clinic and who were at-risk for developing shoulder problems. Therefore, the DM groups included participants with and without pain but did not have any major shoulder pathology, such as rotator cuff tears and frozen shoulder. Interestingly, the deficits in humerothoracic (measured using goniometry) and glenohumeral (measured via 3-dimensional kinematics) movement, strength and hand function were seen regardless of their pain status. Further, we had excluded individuals with high BMI (over 35 kg/m²) to reduce the errors associated to the kinematic measures (Chapters 3 and 4). Therefore, these results may not be generalizable to all individuals with DM. We believe that shoulder impairments will be greater in individuals with DM and high BMI because of greater detrimental effects of circulating AGEs and inflammatory markers which are associated with obesity. Lastly, our studies used correlational analyses to examine the relationships between SIF, structural changes, upper extremity clinical measures, and pain and/or disability. We did not have data on the temporal relationship between the risk of diabetes and development of shoulder problems. Prospective studies our needed to examine the causal relationships.

**Clinical Implications**

Our research has shown that upper extremity impairments are prevalent in people with diabetes. These studies, for the first time, show the relationship between an AGEs marker and
functional measures as they relate to upper extremity impairments and LJM in people with DM. Musculoskeletal conditions, in particular upper extremity impairments, are understudied. Health care providers should focus on examination of these impairments as they are related to complaints of pain and/or disability and may further lead to decreases in the quality of life. If impairments related to functional limitations are detected early, rehabilitation and pharmaceutical (AGE cross-link breaking agents) therapies may be developed to help prevent additional detrimental changes (4-7).

Future Directions

Studies need to further explore the mechanisms related to musculoskeletal impairments in people with diabetes and methods to prevent these impairments. The relationship between the AGEs accumulation and structural changes needs additional examination. In this study, we only explored the thickness of the shoulder tendons using ultrasound. Changes are seen in other structures in the shoulder as well, including ligaments, capsule, muscle and bone (7-10). The impact of these structural changes on movement needs to be examined. Use of imaging tools can help identify the quality of the shoulder structures and muscles, in-vivo. Examination of fatty infiltration in the lower extremity muscles has been linked to decreased physical performance (11). Similarly, we speculate that fat infiltration in the shoulder muscles may be linked to poor performance of these muscles and functional deficits in the upper extremity. DM has been linked to higher proportion of rotator cuff tears and poor outcomes after surgery (12-15). The knowledge about tissue level mechanics and its influence on movement and healing may help improve recovery post-surgery. Few studies have examined the physical and mechanical
properties of the tissues, in-vitro (16-18). Examination of tendon, muscle and bone properties at the microscopic level has shown evidence of increased stiffness and decrease in the toughness. Emphasis must be placed on relating these tissue level mechanics to joint function in people with DM.

The effect of joint movement and exercise in the early stage of LJM in DM is not known. Our results show that shoulder LJM changes start early and may not be related to complaints of pain at the early stage. We postulate that the insidious loss of ROM and strength may hit a “threshold” and manifest into severe symptoms of pain and/or disability. An exercise program that focuses on improving the upper extremity ROM and overall use of the arm may be useful in reducing LJM, strength deficits and pain/disability. The risk of developing frozen shoulder is substantially higher in people with DM. Further, limited joint mobility may eventually manifest in symptoms of frozen shoulder for some individuals with DM. Therefore, identifying these LJM changes early may help prevent the sequelae of extreme pain, disability and joint limitation. A number of non-operative treatment options have been suggested such as patient education, modalities, exercises, joint mobilization and intra-articular corticosteroid injections (19,20). However, results from a systematic review on the effectiveness of treatments for frozen shoulder have shown that there is very limited clinical evidence about the best treatment option based on the stage of the disease (21). In a study by Diercks et al., outcomes were compared in two groups of patients with idiopathic frozen shoulder, a group that received intensive physical therapy treatment and another group that received general instruction for shoulder movement and patient education. At the end of the study, pain, ROM and functional status were better for the group that received minimal instruction (22). Decreased physical activity and use of arms may also be one the reasons for LJM and movement impairments in individuals with DM. We speculate that
simple home based exercises in the early stages of LJM will not only reduce the limitations but also prevent the onset of severe frozen shoulder like symptoms in people with DM. Results from our study also suggest that emphasis must be placed on exercises that improve shoulder external rotation and elevation motion.

Longitudinal studies are necessary to examine the course of DM and its impact on accumulation of AGEs and shoulder joint mobility. In one of the few prospective studies of shoulder disorders in DM, Laslett et al. reported that 45%, 81 of 179 individuals with DM had shoulder pain and/or disability, as measured via the SPADI. In a 12 month follow-up, 25% of individuals who reported no pain and/or disability at baseline developed clinically significant pain or disability (10% points change on the SPADI) (23). Additionally, of the patients with pre-existing pain and/or disability, 50% developed clinically significant worsening of pain and/or disability. However, it is unknown if including an exercise program will help reduce LJM and pain/disability, and prevent additional detrimental deficits in people with DM.

Pharmaceutical agents that are AGE-inhibitors or AGE-breakers such as aminoguanidine, ALT-711, pyridoxamine and glucosamine have shown some promise in animal studies. These have been useful in delaying the onset of the diabetic complications in animal models (24-26). Some of these drugs have been included in clinical trials; however, none have been approved yet. Clinical trials that used aminoguanidine in types 1 and 2 DM in examining nephropathy outcomes showed reductions in proteinuria and decrease in progression of retinopathy; however, no significant beneficial effects were seen on the progression of nephropathy (27,28). Alagebrium or ALT-711, which is an AGE breaker showed increased collagen solubility and decreased RAGE in diabetic rats as compared to placebo treatment (29). In older humans, there have been reports of improved vascular function (30). Further, pharmacological compounds that
reverse or inhibit the effects of RAGE may help in reducing the effects of inflammation in the pathogenesis of diabetes complications. Therapeutic treatments which counteract the detrimental negative effects of the AGEs may become a part of clinical trials with subsequent transition to clinical practice to control musculoskeletal changes in patients with DM.

Overall, these studies have highlighted the important issue of upper extremity musculoskeletal complications in people with DM. LJM, decreases in shoulder and hand strength, pain and disability are severe in individuals with DM. Strikingly, LJM changes were also observed in people with diabetes who did not have complaints of pain. These studies provided insight into the possible mechanism and relationships between a marker of AGEs and musculoskeletal complications. Increase in the accumulation of skin AGEs was related to increased tendon thickness, decreased shoulder motion, and complains of disability. We speculate that increasing levels of AGEs are a key cause of these musculoskeletal complications, such as LJM, perhaps even directly contributing to inflammation and pain. The high correlation between SIF and Disability of the Arm, Shoulder and Hand questionnaire scores (r = 0.51) supports this speculation. The findings from these studies can help focus future interventions on the mechanisms of upper extremity musculoskeletal problems in people with DM and help develop targeted, exercise and pharmacological, strategies to manage them.
There was a strong association between the skin intrinsic fluorescence (SIF) measure (an indicator of advanced glycation end-products) and upper extremity disability and pain, and strength, which led us to rethink the *a-priori* linear relationship among the variables. Further, advanced glycation end products play an important role in the inflammatory pathways in DM. Based on these observations, we propose a revised model of shoulder impairments in individuals with DM.
REFERENCES


Appendix:

Supplementary data
Figure 1 Frequency distribution of SPADI scores

Mean (SD) SPADI Score = 34.7 (24.8)
**Figure 2** – Biceps Tendon Ultrasound Image

Transverse view of the long head of biceps tendon. Solid yellow line indicates the maximum tendon thickness measured within the bicipital groove of the humerus a) DM participant b) Control participant.

DM = Diabetes Mellitus
Figure 3 – Supraspinatus Tendon Ultrasound Image

Longitudinal view of supraspinatus tendon thickness. Solid yellow line indicates measurement at the anatomical neck of the humerus, dotted yellow line indicates measurement at the midpoint of the anatomical footprint of the supraspinatus tendon a) DM participant b) Control participant.

DM = Diabetes Mellitus