

# **HHS Public Access**

J Diabetes Complications. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Author manuscript

J Diabetes Complications. 2017 June ; 31(6): 983–987. doi:10.1016/j.jdiacomp.2017.03.005.

## **Relationship of shoulder activity and skin intrinsic fluorescence with low level shoulder pain and disability in people with type 2 diabetes**

**Christopher J. Sorensen, PhD**1, **Mary K. Hastings, PT**1,2, **Catherine E. Lang, PhD**1,3,4, **Janet B. McGill, MD**5, **B. Ruth Clark, PhD**1,4, **Kathryn L. Bohnert, MS**1, and **Michael J. Mueller, PhD**1,6

<sup>1</sup>Program in Physical Therapy, Washington University School of Medicine in St. Louis, St. Louis, MO

<sup>2</sup>Orthopaedic Surgery, Washington University School of Medicine in St. Louis, St. Louis, MO

<sup>3</sup>Program in Occupational Therapy, Washington University School of Medicine in St. Louis, St. Louis, MO

<sup>4</sup>Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO

<sup>5</sup>Division of Endocrinology, Metabolism, and Lipid Research, Washington University School of Medicine in St. Louis, St. Louis, MO

<sup>6</sup>Department of Radiology, Washington University School of Medicine in St. Louis, St. Louis, MO

### **Abstract**

**Aim—**People with type 2 diabetes (T2DM) have a high incidence of musculoskeletal disorders thought to be influenced by high non-enzymatic advanced glycated end-products (AGEs). The goals of this study were to determine differences in shoulder activity level and AGEs in people with T2DM compared to matched controls, and to determine factors associated with shoulder pain and disability.

**METHODS—**Eighty-one participants, T2DM (n=52) and controls (n=29), were examined for magnitude and duration of shoulder activity (measured using accelerometers), skin intrinsic florescence (SIF) as a surrogate measure of AGE level, and the Shoulder Pain and Disability Index (SPADI) as a self-report of shoulder pain and disability.

**RESULTS—**Compared with controls, T2DM participants had 23% less shoulder activity  $(p=0.01)$ , greater SIF level  $(3.6 \pm 1.7 \text{ vs } 2.7 \pm 0.6 \text{ AU}, p=0.01)$ , less shoulder strength (p<0.05),

**Conflicts of Interest** None

**Corresponding Author:** Christopher J. Sorensen, 4444 Forest Park Avenue, Campus Box 8502, Saint Louis, MO 63108 USA, Phone: 314-286-1403, Fax: 314-286-1410, sorensenc@wustl.edu.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and the duration of their shoulder activity was moderately associated ( $r = 0.40$ ;  $p < 0.01$ ) with reported shoulder pain and disability. Shoulder pain and disability were not related to SIF level.

**CONCLUSIONS—**Persons with T2DM have higher SIF levels and shoulder symptoms and disability indices than controls. Research is needed to determine if a shoulder mobility intervention to increase strength and mobility can help decrease shoulder pain and disability.

#### **Keywords**

Type 2 diabetes; Shoulder limited joint mobility; Skin intrinsic fluorescence; Advanced Glycation End Products; Accelerometers

#### **1. Introduction**

People with diabetes have a high incidence of musculoskeletal disorders and pain compared to those without diabetes (Larkin et al., 2014; Mustafa, Khader, Bsoul, & Ajlouni, 2015). These musculoskeletal problems have been particularly well documented in the shoulders and upper extremities and have been associated with other diabetic complications including nephropathy, retinopathy, coronary heart and cerebrovascular diseases (Arkkila, Kantola, & Viikari, 1997; Balci, Balci, & Tuzuner, 1999; Rosenbloom AI, Silverstein J, Lezotte DC, Richardson K, & McCallum M, 1981). In the Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study cohort, 66% of participants with type 1 diabetes (T1DM)  $(n=1,217)$  had *cheiroarthropathy*; which was defined as having shoulder adhesive capsulitis, carpal tunnel syndrome, flexor tenosynovitis, or a positive prayer sign using a targeted medical history and standardized physical exam (Larkin et al., 2014). In another large study, 70% of patients (n=1000) with T2DM had hand disorders and 63% had limited joint mobility (Mustafa et al., 2015). These disorders are often accompanied by pain. People with T2DM are 1.7–2.1 times as likely to report musculoskeletal pain compared to those without diabetes (Molsted, Tribler, & Snorgaard, 2012). In addition, we previously reported that 63% of patients with T2DM attending a Diabetes Clinic had shoulder pain or disability as measured with the Shoulder Pain and Disability Index (SPADI) (Shah et al., 2015).

Long term exposure to hyperglycemia, which characterizes both T1DM and T2DM, may make the musculoskeletal system more susceptible to pain, stiffness, joint limitations, and tissue injury (Larkin et al., 2014; Mustafa et al., 2015). In particular, hyperglycemia promotes the formation of non-enzymatic advanced glycated end-products (AGEs) and AGE receptors (RAGEs) in collagen rich structures (Abate, Schiavone, Pelotti, & Salini, 2011; Brownlee, 1992; Ramasamy et al., 2005; Schnider & Kohn, 1980). AGEs and RAGEs tend to accumulate in all tissues, but especially in tissues with low-protein turnover such as tendons, ligaments, and skin (Brownlee, 1992; Haus, Carrithers, Trappe, & Trappe, 2007; Reddy, 2004). These tissues tend to become thicker, stiffer, weaker, and more susceptible to injury (Klaesner, Hastings, Zou, Lewis, & Mueller, 2002; Reddy, 2004; Tang & Vashishth, 2010). Given the pleotropic expression of the limited joint mobility syndrome in persons with diabetes, affecting multiple weight-bearing and non-weight bearing joints in different ways, it is reasonable to postulate that high levels of tissue AGEs may indiscriminately cause the pathogenic changes in connective tissues responsible for the syndrome. The

positive prayer sign (Al-Homood, 2013; Cagliero, Apruzzese, Perlmutter, & Nathan, 2002; Rosenbloom AI et al., 1981) in the hands is the most visible of numerous joints with limited mobility (Abate et al., 2011; Delbridge et al., 1988; Mueller, Diamond, Delitto, & Sinacore, 1989; Schulte, Roberts, Zimmerman, Ketler, & Simon, 1993; Shah, Clark, McGill, Lang, & Mueller, 2015). Decreased mobility in the shoulder joint (Abate et al., 2011; Schulte et al., 1993; Shah et al., 2015) occurs insidiously, and the relationship between skin intrinsic florescence (SIF), a surrogate AGE measure, and self-reported shoulder disability has been as high as r=.51 (p=0.009) in people with T2DM (Shah et al., 2015).

Shoulder pain and disability are inseparable and known to impact shoulder movement. Accelerometers have been used to measure upper extremity activity throughout the day in community environments in a number of patient populations with chronic movement problems (Bailey, Klaesner, & Lang, 2015; Bailey & Lang, 2013; Yang, Lin, Huang, Huang, & Chao, 2014), but not in people with diabetes. People with T2DM are known to have relatively low overall physical activity (i.e, steps per day) compared to those without diabetes (Tudor-Locke et al., 2002). High physical activity is associated with many healthrelated benefits for those with T2DM, even lower mortality rates (Gregg, Gerzoff, Caspersen, Williamson, & Narayan, 2003; Hu et al., 2005), because it helps to enhance insulin sensitivity and control blood sugar levels from a number of metabolic pathways (Di et al., 2005; Tokmakidis, Zois, Volaklis, Kotsa, & Touvra, 2004). It is unknown whether high shoulder activity is beneficial or harmful to those with diabetes and shoulder problems.

**The primary goal** of this study was to determine differences in shoulder activity and SIF (as an estimate of AGE level) in people with T2DM compared to age, sex, and BMI matched controls. We also compared shoulder range of motion, shoulder strength, and grip strength between groups to understand better which musculoskeletal impairments are related to selfreported shoulder pain and disability. **A secondary goal** was to determine the factors associated with shoulder pain and disability in those with T2DM. Specifically, we examined the relationship between shoulder activity level, SIF measure, shoulder range of motion and strength, and grip strength with self-reported shoulder pain and disability in people with T2DM. We hypothesized that people with T2DM would have lower shoulder activity, range of motion, and strength; and an increased SIF measure and self-reported shoulder pain and disability compared to the control group. Furthermore, we hypothesized that in those with T2DM, shoulder activity level, shoulder motion and strength would have an inverse relationship with shoulder pain and disability (i.e. less shoulder activity and range of motion would be related to increased shoulder pain and disability) while the SIF measure would have a positive correlation to shoulder pain and disability. Better understanding of the etiology of shoulder pain and disability in people with diabetes will help direct intervention strategies to prevent or minimize this complication.

#### **2. Materials and Methods**

#### **2.1. Participants**

Fifty two participants with T2DM and 29 control participants were recruited through the Washington University Diabetes Center and 2 community-based, university-operated, recruitment services (Characteristics in Table 1). Inclusion criteria were selected to focus on

those people with type 2 diabetes who were at high risk for developing shoulder pain and disability but did not currently have severe or acute shoulder pain or disability. Participants with T2DM had to be between 40–70 years old and meet 1 of the following criteria to be considered for the study: 1) duration of diagnosed T2DM for greater than 10 years, 2) presence of a 'positive prayer sign', or 3) shoulder flexion  $< 150^{\circ}$ . To eliminate those with severe or acute shoulder pain or disability, participants also had to have a Shoulder Pain and Disability Index (SPADI) score < 70. Control participants were recruited from a database of community dwelling volunteers who had agreed to be in research studies and matched for gender, age, and BMI; and had no history of diabetes. Control participants were screened by phone and excluded if they had shoulder pain because we wanted the group with diabetes to be compared with a control group without any shoulder impairments. Exclusion criteria for both groups included diagnosed adhesive capsulitis, rotator cuff tears, recent upper extremity injury and/or fractures, stroke with residual upper extremity involvement, rheumatic conditions, use of a cane or other mobility assistance, known connective tissue diseases, and engaging in heavy upper extremity/ overhead use (i.e., painters, tennis players). All

participants read and signed an informed consent form that was approved by the Human

Research Protection Office at Washington University School of Medicine.

#### **2.2. Equipment and Procedures**

Shoulder activity was measured using tri-axial accelerometers (GT3X+ Activity Monitor, ActiGraph, Pensacola, FL). Accelerometers were placed on both upper arms immediately proximal to the elbows. All participants wore the accelerometers for at least 24 hours. The 29 control participants wore the accelerometers for 72 hours to determine day to day variability of activity level. There was no significant difference between the shoulder activity counts of day 1 compared to day 2, day 3, or an average of 3 days taken over a 24 hour period. Therefore all shoulder activity data are reported for the first 24 hours of wear, a time consistent with previous studies (Bailey, Klaesner, & Lang, 2014; Bailey et al., 2015; Bailey & Lang, 2013) and long enough to obtain representative data, but not so long to be burdensome or reduce wearing adherence. There were no significant differences between shoulder activity for the right and left arm. Therefore, all analyses were performed for the accelerometer on the right arm only. Data, sampled at 30 Hz, were downloaded from the accelerometers at 1 second epochs using ActiLife software version 6 (ActiGraph, Pensacola, FL). All subsequent data processing was completed using custom written software in MATLAB (MathWorks Inc., Natick, MA). We used accelerometer data processing methods as described previously (Bailey & Lang, 2013). Briefly, the amount of activity that occurred per second was measured in activity counts (0.001664g/count). Data from each axis of the accelerometer was combined to create a single resultant vector representing vector magnitude (sqrt( $x^2 + y^2 + z^2$ )). Any second with a vector magnitude > 2 g was considered to be shoulder movement. For right shoulder activity duration, the number of seconds that shoulder movement occurred was summed to calculate duration of movement time. Total seconds of activity were divided by 360 to convert activity duration to hours. Right shoulder activity magnitude was calculated by integrating the activity counts of the resultant vector across the 24 hour period and are expressed in g's of activity (Bailey & Lang, 2013).

SIF measures were obtained using the SCOUT DS skin fluorescence spectrometer (VeraLight, Albuquerque, New Mexico) (Conway et al., 2011; Shah et al., 2015). Participants were seated while their left volar forearm was positioned on the SCOUT DS. SIF were excited with a light emitting diode (LED) centered at 435 nm and detected over the emission range of 470–655 nm. The skin reflectance was measured over the excitation and emission regions to compensate for absorbance caused by melanin and hemoglobin (Hull et al., 2004). Intrinsic fluorescence correction equations were used as described previously (Conway et al., 2011). The resulting SIF were integrated and reported in arbitrary units (AU) (Conway et al., 2011; Shah et al., 2015).

Shoulder range of motion was measured as the angle between the humerus and the thorax with a digital goniometer (JAMAR, Patterson Medical, Warrenville, IL). The measures obtained were active flexion while seated; and passive flexion, passive external rotation, and passive internal rotation in supine using standardized methods (Schulte et al., 1993). Shoulder flexion strength was measured using a hand held, digital strain-gauge dynamometer (Microfet, Hoggan Health Industries Inc, West Jordan, Utah) with the participant in a supine position and the shoulder in 90 degrees of flexion using standardized methods and stabilization (Bohannon, 1997). Two measures were obtained and averaged for the dominant shoulder range of motion variable and shoulder strength. Dominant hand grip strength was used as an indicator of hand function and measured using a Jamar dynamometer per published protocols with established reliability (Bohannon & Schaubert, 2005).

Participants also completed the Shoulder Pain and Disability Index (SPADI); a standardized 13 item self-report questionnaire with 5 items specific to shoulder pain and 8 items specific to shoulder disability (MacDermid, Solomon, & Prkachin, 2006; Roach, Budiman-Mak, Songsiridej, & Lertratanakul, 1991). The SPADI score can range from 0 % indicating no pain or disability, to 100 % indicating severe pain and total disability (Roach et al., 1991).

#### **2.3. Statistical Analyses**

Mann Whitney U tests were used to test differences between continuous variables that were not normally distributed while an independent t-test was used on continuous variables that were normally distributed. In order to determine that the groups were appropriately matched, chi-square analyses were conducted to test for differences in the distribution of sex and race, and Mann Whitney U tests were conducted to test for differences between age and BMI. To test our primary hypotheses, Mann Whitney U tests were conducted to test for differences between people with T2DM and controls for SIF measure, activity level, grip strength, and SPADI scores and independent group t-tests were conducted to test for differences in shoulder ROM and shoulder strength. Mann Whitney U tests were conducted to test for differences of SIF measures between groups with and without participants reporting  $\frac{30}{2}$ pack years of smoking, since smoking can elevate SIF measures. To determine what factors were associated with shoulder pain and disability in participants with diabetes, a Pearson correlation coefficient was calculated for activity level, SIF measure, shoulder ROM, shoulder strength and SPADI scores. Statistical analyses were performed in SPSS version 23.0 (IBM, Armonk, NY).

### **3. Results**

The groups were well-matched, as indicated by a lack of differences between groups for sex, race, age, and BMI ( $P > 0.05$ ; Table 1). Results of outcome measures are provided in Table 2. Compared to controls, participants with T2DM had lower measures of shoulder activity and higher SIF measures ( $p < 0.02$ ). As expected, participants with T2DM also had higher total SPADI scores, SPADI Disability and Pain scores, and less active shoulder flexion range of motion and shoulder strength compared to controls  $(p<0.04)$ . There were no differences between groups for duration of shoulder activity, passive shoulder flexion, shoulder external rotation, shoulder internal rotation, and grip strength ( $p > 0.05$ ).

Relationships between variables for participants with diabetes are provided in Table 3. There were direct relationships between shoulder activity duration and SPADI Score  $(r = 0.31 0.43$ ,  $p < 0.05$ ) and inverse relationships between passive shoulder flexion and SPADI total and disability scores (r =−0.31–0.33, p< 0.03). Stated otherwise, in people with diabetes, as duration of shoulder activity went up and passive shoulder flexion went down, reports of shoulder pain and disability went up. There were no other significant relationships between continuous variables.

#### **4. Discussion**

Consistent with our primary hypothesis, results indicate that participants with T2DM had lower shoulder activity, active shoulder flexion range of motion, and strength, and higher SIF measures and self-reported shoulder pain and disability compared to the control group (Table 2). The results of the current study are in agreement with prior studies showing high SIF levels and reduced joint mobility in participants with T2DM (Conway et al., 2011; Larkin et al., 2014; Shah et al., 2015) and documents reduced magnitude and duration of shoulder activity in those with diabetes compared to controls. In addition, we found that duration of shoulder activity was associated with reported shoulder pain and disability, but in the opposite direction that we expected. Although we anticipated higher shoulder activity would be beneficial, results indicate that longer duration of shoulder activity was associated with higher reports of shoulder pain and disability (Table 3). These results are important because they provide insight to the possible causes of shoulder pain and disability and interventions that may help to prevent or manage these shoulder complications, especially those related to shoulder movements and exercise.

This study adds to the growing body of evidence indicating that, compared to controls without diabetes, people with diabetes have higher levels (17–33%) of SIF, a surrogate measure of AGEs (Conway et al., 2011; Larkin et al., 2014; Shah et al., 2015) that likely places them at increased risk for a wide variety of complications including those involving the musculoskeletal system (Conway et al., 2011; Schulte et al., 1993). Others have indicated that prolonged exposure to hyperglycemia, which is reflected in high AGE measures, makes musculoskeletal tissues thicker, stiffer, and more susceptible to injury (Haus et al., 2007; Reddy, 2004; Tang & Vashishth, 2010). High AGE and RAGE levels may even have a direct effect on inflammatory processes (Ramasamy et al., 2005). The tissue effects of these metabolic abnormalities may contribute to the documented limited joint

mobility, weakness, pain and disability at the shoulder joint that we and others have documented (Abate et al., 2011; Larkin et al., 2014; Schulte et al., 1993; Shah et al., 2015; Shah et al., 2015; Shah, Clark, McGill, & Mueller, 2015).

Furthermore, our findings of low shoulder activity in the participants with diabetes, and the association of duration of shoulder activity to reported shoulder pain and disability adds to our understanding of how these shoulder complications develop. We suggest that, consistent with the Physical Stress Theory (Mueller & Maluf, 2002), AGEs in connective tissues makes tendons, ligaments and other articular structures thicker and stiffer (Reddy, 2004; Tang & Vashishth, 2010), and lowers the tissue's tolerance for physical stress. Therefore, at the same or even lower physical stress level, tissues with a higher saturation of glycated end-products likely will be injured more easily than comparable tissues with low AGE levels. The direct relationship between duration of shoulder activity and shoulder pain and disability (Table 3), and the high incidence of musculoskeletal complications in those with diabetes, support this line of reasoning. Consistent with other diabetic complications, these musculoskeletal complications likely develop insidiously over prolonged time periods and often go unnoticed until an acute injury (i.e., adhesive capsulitis or rotator cuff tear) occurs (Balci et al., 1999).

The results of this study also have important implications for intervention strategies to reduce shoulder and other musculoskeletal complications in diabetes. Since people with diabetes show shoulder impairments of decreased active motion, strength, (Table 2) and often general passive range of motion (Abate et al., 2011; Schulte et al., 1993; Shah et al., 2015), we hypothesize that movement and exercise strategies targeted on stretching end range of motion, and increasing shoulder muscle strength would help to prevent or treat these gradually developing shoulder complications. In addition, shoulder activity level will need to be titrated depending upon the level of inflammation, the person's usual activity level, and other structural impairments (Mueller & Maluf, 2002; Yang et al., 2014), Furthermore, since AGE levels were higher in participants with diabetes, and some have found a direct relationship between AGE level and musculoskeletal complications (Larkin et al., 2014; Shah et al., 2015), treatments directed at reducing or normalizing blood glucose levels throughout the course of diabetes should have a preventative effect on musculoskeletal complications. Additional research is needed to follow these musculoskeletal changes over time and determine if early metabolic or movement interventions can help to reduce pain and disability associated with them.

Limitations of this study should be considered in interpreting these data. Participants with T2DM were recruited to characterize those who did not have acute shoulder complications but were at high risk for developing them, so the results are not indicative of those with severe shoulder impairments. This study was exploratory using selective inclusion criteria and novel accelerometers to investigate the role of shoulder activity with shoulder impairments, and the number of participants with T2DM (n=52) was modest. In addition, we focused on the magnitude and duration of shoulder activity measured during daily activities and did not consider specific movement impairments (Sahrmann, 2002) (i.e., asynchronous gleno-humeral motion) that might affect shoulder pain and disability.

#### **5. Conclusions**

In summary, this study showed that participants with T2DM had reduced shoulder activity, strength, and active flexion, and increased skin intrinsic fluorescence in their skin (suggesting increased AGEs) compared to a matched control group without diabetes. Furthermore, the duration of shoulder motion was directly related to the magnitude of selfreported pain in the participants with T2DM. Results support the hypothesis that metabolic problems associated with diabetes, as identified with high SIF, causes the musculoskeletal tissues to have a reduced tolerance for physical stresses and hence, a lowered threshold of pain and disability. Longitudinal studies with larger samples are needed to confirm these proposed mechanisms and treatments of shoulder impairments and other musculoskeletal complications secondary to diabetes. Such investigations should lead to improved strategies (i.e., movement, metabolic) to reduce the incidence of musculoskeletal pain and disability in those with diabetes.

#### **Acknowledgments**

This work was supported by NIH Grant R21 DK100793 and the Diabetes Research Center at Washington University School of Medicine in St. Louis (NIH Grant P30 DK020579). The authors would like to thank John Maynard for helping to interpret Skin Intrinsic Fluorescence data.

#### **Reference List**

- Abate M, Schiavone C, Pelotti P, Salini V. Limited joint mobility (LJM) in elderly subjects with type II diabetes mellitus. Arch Gerontol Geriatr. 2011; 53:135–140. [PubMed: 20940076]
- Al-Homood IA. Rheumatic conditions in patients with diabetes mellitus. Clinical Rheumatology. 2013; 32:527–533. [PubMed: 23247555]
- Arkkila PE, Kantola IM, Viikari JS. Limited joint mobility in non-insulin-dependent diabetic (NIDDM) patients: correlation to control of diabetes, atherosclerotic vascular disease, and other diabetic complications. Journal of Diabetes and Its Complications. 1997; 11:208–217. [PubMed: 9201597]
- Bailey RR, Klaesner JW, Lang CE. An accelerometry-based methodology for assessment of real-world bilateral upper extremity activity. PLoS One. 2014; 9:e103135. [PubMed: 25068258]
- Bailey RR, Klaesner JW, Lang CE. Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults With Chronic Stroke. Neurorehabil Neural Repair. 2015; 29:969–978. [PubMed: 25896988]
- Bailey RR, Lang CE. Upper-limb activity in adults: referent values using accelerometry. Journal of Rehabilitation Research and Development. 2013; 50:1213–1222. [PubMed: 24458962]
- Balci N, Balci MK, Tuzuner S. Shoulder adhesive capsulitis and shoulder range of motion in type II diabetes mellitus: association with diabetic complications. Journal of Diabetes and Its Complications. 1999; 13:135–140. [PubMed: 10509873]
- Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. Archives of Physical Medicine and Rehabilitation. 1997; 78:26–32. [PubMed: 9014953]
- Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. J Hand Ther. 2005; 18:426–7. quiz. [PubMed: 16271690]
- Brownlee M. Glycation products and the pathogenesis of diabetic complications. Diabetes Care. 1992; 15:1835–1843. [PubMed: 1464241]
- Cagliero E, Apruzzese W, Perlmutter GS, Nathan DM. Musculoskeletal disorders of the hand and shoulder in patients with diabetes mellitus. American Journal of Medicine. 2002; 112:487–490. [PubMed: 11959060]

- Conway BN, Aroda VR, Maynard JD, Matter N, Fernandez S, Ratner RE, et al. Skin intrinsic fluorescence correlates with autonomic and distal symmetrical polyneuropathy in individuals with type 1 diabetes. Diabetes Care. 2011; 34:1000–1005. [PubMed: 21307380]
- Delbridge L, Perry P, Marr S, Arnold N, Yue DK, Turtle JR, et al. Limited joint mobility in the diabetic foot: relationship to neuropathic ulceration. Diabetic Medicine. 1988; 5:333–337. [PubMed: 2968881]
- Di LC, Fanelli C, Lucidi P, Murdolo G, De CA, Parlanti N, et al. Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. Diabetes Care. 2005; 28:1295–1302. [PubMed: 15920042]
- Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. Archives of Internal Medicine. 2003; 163:1440–1447. [PubMed: 12824093]
- Haus JM, Carrithers JA, Trappe SW, Trappe TA. Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. J Appl Physiol (1985). 2007; 103:2068–2076. [PubMed: 17901242]
- Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care. 2005; 28:799–805. [PubMed: 15793176]
- Hull E, Ediger M, Unione A, Deemer E, Stroman M, Baynes J. Noninvasive, optical detection of diabetes: model studies with porcine skin. Opt Express. 2004; 12:4496–4510. [PubMed: 19484001]
- Klaesner JW, Hastings MK, Zou DQ, Lewis C, Mueller MJ. Plantar tissue stiffness in patients with diabetes mellitus and peripheral neuropathy. Archives of Physical Medicine and Rehabilitation. 2002; 83:1796–1801. [PubMed: 12474190]
- Larkin ME, Barnie A, Braffett BH, Cleary PA, Diminick L, Harth J, et al. Musculoskeletal complications in type 1 diabetes. Diabetes Care. 2014; 37:1863–1869. [PubMed: 24722493]
- MacDermid JC, Solomon P, Prkachin K. The Shoulder Pain and Disability Index demonstrates factor, construct and longitudinal validity. BMC Musculoskelet Disord. 2006; 7:12. [PubMed: 16472394]
- Molsted S, Tribler J, Snorgaard O. Musculoskeletal pain in patients with type 2 diabetes. Diabetes Research and Clinical Practice. 2012; 96:135–140. [PubMed: 22244365]
- Mueller MJ, Diamond JE, Delitto A, Sinacore DR. Insensitivity, limited joint mobility, and plantar ulcers in patients with diabetes mellitus. Physical Therapy. 1989; 69:453–459. [PubMed: 2727069]
- Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "Physical Stress Theory" to guide physical therapist practice, education, and research. Physical Therapy. 2002; 82:383–403. [PubMed: 11922854]
- Mustafa KN, Khader YS, Bsoul AK, Ajlouni K. Musculoskeletal disorders of the hand in type 2 diabetes mellitus: prevalence and its associated factors. Int J Rheum Dis. 2015
- Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology. 2005; 15:16R–28R.
- Reddy GK. Cross-linking in collagen by nonenzymatic glycation increases the matrix stiffness in rabbit achilles tendon. Exp Diabesity Res. 2004; 5:143–153. [PubMed: 15203885]
- Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. Arthritis Care Res. 1991; 4:143–149. [PubMed: 11188601]
- Rosenbloom AI, Silverstein J, Lezotte DC, Richardson K, McCallum M. Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. New England Journal of Medicine. 1981; 305:191–194. [PubMed: 7242598]
- Sahrmann, SA. Diagnosis and treatment of movement impairment syndromes. St Louis: Mosby, Inc; 2002.
- Schnider SL, Kohn RR. Glucosylation of human collagen in aging and diabetes mellitus. J Clin Invest. 1980; 66:1179–1181. [PubMed: 7430347]
- Schulte L, Roberts MS, Zimmerman C, Ketler J, Simon LS. A quantitative assessment of limited joint mobility in patients with diabetes. Goniometric analysis of upper extremity passive range of motion. Arthritis and Rheumatism. 1993; 36:1429–1443. [PubMed: 8216403]

- Shah KM, Clark BR, McGill JB, Lang CE, Maynard J, Mueller MJ. Relationship Between Skin Intrinsic Fluorescence–an Indicator of Advanced Glycation End Products-and Upper Extremity Impairments in Individuals With Diabetes Mellitus. Physical Therapy. 2015; 95:1111–1119. [PubMed: 25858973]
- Shah KM, Clark BR, McGill JB, Lang CE, Mueller MJ. Shoulder limited joint mobility in people with diabetes mellitus. Clin Biomech (Bristol, Avon). 2015; 30:308–313.
- Shah KM, Clark BR, McGill JB, Mueller MJ. Upper extremity impairments, pain and disability in patients with diabetes mellitus. Physiotherapy. 2015; 101:147–154. [PubMed: 25442298]
- Tang SY, Vashishth D. Non-enzymatic glycation alters microdamage formation in human cancellous bone. Bone. 2010; 46:148–154. [PubMed: 19747573]
- Tokmakidis SP, Zois CE, Volaklis KA, Kotsa K, Touvra AM. The effects of a combined strength and aerobic exercise program on glucose control and insulin action in women with type 2 diabetes. Eur J Appl Physiol. 2004; 92:437–442. [PubMed: 15232701]
- Tudor-Locke CE, Bell RC, Myers AM, Harris SB, Lauzon N, Rodger NW. Pedometer-determined ambulatory activity in individuals with type 2 diabetes. Diabetes Research and Clinical Practice. 2002; 55:191–199. [PubMed: 11850095]
- Yang JL, Lin JJ, Huang HY, Huang TS, Chao YW. Shoulder physical activity, functional disability and task difficulties in patients with stiff shoulders: interpretation from RT3 accelerator. Man Ther. 2014; 19:349–354. [PubMed: 24650638]

#### **Highlights**

- **•** People with type 2 diabetes (T2DM) have a high incidence of musculoskeletal disorders thought to be influenced by high non-enzymatic advanced glycated end-products (AGEs)
- **•** People with T2DM reported increased shoulder pain and disability compared to matched controls
- **•** People with T2DM had higher levels of AGEs than matched controls
- **•** People with T2DM had less shoulder activity levels than matched controls
- **•** Shoulder activity was related to shoulder pain and disability in people with T2DM
- **•** Persons with T2DM have high AGE levels and are at high risk for shoulder symptoms and disability which is related to shoulder activity

# **Table 1**





Chi-squared test performed for sex and race. Mann-Whitney tests were performed for continuous variables as all continuous variables were not normally distributed in the diabetes group. Fisher's Exact \* Chi-squared test performed for sex and race. Mann-Whitney tests were performed for continuous variables as all continuous variables were not normally distributed in the diabetes group. Fisher's Exact Test performed for Participants with 30 pack years of smoking. Test performed for Participants with ≥30 pack years of smoking.

 $t_{\rm Sex}$  is number of females and males in each group Sex is number of females and males in each group

J Diabetes Complications. Author manuscript; available in PMC 2018 June 01.

 $^t\!$  kace is number of African Americans, Caucasians, and more than 1 race  $*$ Race is number of African Americans, Caucasians, and more than 1 race

 $\stackrel{\text{g}}{S}\!\text{Mean} \pm \text{standard deviation}$ Mean ± standard deviation

 $^{\prime\prime}$  Not reported for 3 participants (n=49) Not reported for 3 participants (n=49)



Comparison of Outcome Variables in Participants with T2DM and Controls Comparison of Outcome Variables in Participants with T2DM and Controls

J Diabetes Complications. Author manuscript; available in PMC 2018 June 01.

 $^{\prime}$  Missing data for 1 participant with T2DM who was unable to wear accelerometer (n = 51) Missing data for 1 participant with T2DM who was unable to wear accelerometer ( $n = 51$ )

 $t_{\rm P<0.05}$ 

 $\frac{\#}{\ }$  <br>Measured as angle between humerus and thorax Measured as angle between humerus and thorax

AU = Arbitrary Units

 $AU =$  Arbitrary Units

Author Manuscript

Author Manuscript

Author Manuscript

**Author Manuscript** 

**Table 2**

**Results**

#### **Table 3**

Relationships between shoulder activity level, SIF measure, shoulder range of motion and strength, and grip strength with self-reported shoulder pain and disability in people with T2DM mellitus. Values are Pearson Correlation coefficient  $r$  (p-value).



\* P <0.05

 $\#$  Measured as angle between humerus and thorax

AU = Arbitrary Units