Characterization of neuromuscular properties, functional mobility and fatigue in persons with Type 2 diabetes mellitus.

Lynette A. Singh-Peters
University of Windsor

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Characterization of Neuromuscular Properties, Functional Mobility and Fatigue in Persons with Type 2 Diabetes Mellitus

By Lynette A. Singh-Peters

A Thesis
Submitted to the Faculty of Graduate Studies and Research through Kinesiology
in Partial Fulfillment of the Requirements for the Degree of Master of Human Kinetics at the University of Windsor

Windsor, Ontario, Canada

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ABSTRACT

Persons with Type 2 diabetes (T2D) report fatigue, compromised strength and physical performance, yet studies utilizing objective measures are sparse. This study assessed isometric strength, contractile properties and performance in the tibialis anterior in 6 women (50 ±5 years) and 8 men (54 ±6 years) with T2D, and 6 gender-, age- and activity-matched women (50 ±7 years) and 4 men (55 ±4 years). Muscle fatigue was examined using a 75 % intermittent protocol. HbA1c and blood glucose were higher in T2D, but strength, contractile properties and physical performance did not differ. Fatigue and recovery were parallel between groups. When non-neuropathic individuals with T2D are age, gender and activity matched to controls, they are not weaker nor fatigue faster. This presents good news for persons who control glucose fairly well and suggests that neuropathy, age, gender and physical activity should be considered when assessing persons with strength and fatigue in T2D.
DEDICATION

For Cody, Joshua, Amy, Justin, Brandon. Tyler, Lauren, Adriana, Carson, Calista and Abigail. My success and hope for all of you as an aunt and mother will measure well if you grow up with respect and curiosity for the natural world, including the "apparent" ugliest of creepy crawlies. You have, and will always be, my greatest source of joy.
ACKNOWLEDGEMENTS

This study would not have occurred without the generous donation of time and patience by the volunteers who had the courage to try something new by participating in scientific research. I also acknowledge product donations and financial support from Bayer Incorporated, Canus Canada, Company's Coming Publishers, Kerr Brothers Limited, Pfizer Canada, and the University of Windsor Women's Research Grant.

This thesis is not only a record of my work as a Masters student, but it marks my academic and personal growth through a chapter in my life that was guided by a few key people. By their encouragement and constructive criticism, they have enabled me to think creatively and trust my own judgment beyond the constraints of the undergraduate "box" that I came packaged in from Queen's to Human Kinetics. You were all able to see my potential, when I could have let my feelings sell me short. After all of this, and sometimes non-stop questions – my thesis is complete and I feel confident to at least raise my hand, voice a stronger opinion or ask thoughtful questions in the company of others.

To the members of the committee, your time, assistance and criticism of the proposal and defense of my work have been invaluable.

Dr. Jakobi, you have given me so much by allowing me to venture in my own right. Thank you for introducing me to the academic world of conferences and publications. For setting such a good example of how hard work and long hours can pay off, and most importantly, that work isn't the end-all and life is allowed to happen. You have and continue to be a very positive mentor for me, and a continuous supplier of trustworthy advice. I have
higher expectations of myself now. You have given me the gift of self-demand. *Push* a little harder, even when it gets tough, and then do *a bit more*. If you fail at the second point, you got further than what you were set up for in the first place.

Dr. Kenno, my thought processes will never be the same. *Why?* was not just a single question or one word that could be so aggravating. It was one that always led me to another. Pretty soon, all I did was ask why. And in the end, I question everything I see or hear and I have realized that science can’t give us all of the answers we want, nor does it provide us with one solid, or clear cut solution.

Mr. Don Clarke, the technical wizard of HK, who could fix just about anything, or solve any problem. The machinery of this project would have been a mystery to me if you did not take extra time to teach me about your perspective on how things really work.

Miss. Sylvia Jimenez, who was the best computer translator around, showed me how to handle all of the seemingly “little” problems that would arise on a daily basis and add up to headache proportions for me.

Colin and Abigail, you were with me firsthand throughout this entire process and we will be linked forever because of this experience. This was our first true test as a family unit. In the years to come, it is my hope that this entire experience enriches my quality as a mother and wife in the decisions and actions that will carve our lives and without a doubt lead us to do good things in this world.
My parents, siblings, friends, and lab mates who have provided an endless supply of
great conversation and support throughout my education, life is too serious and
unwholesome without you.
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**TERMS**

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>4m walk</td>
<td>four-metre timed walk</td>
</tr>
<tr>
<td>ABC scale</td>
<td>Activities-specific Balance and Confidence scale</td>
</tr>
<tr>
<td>AChR</td>
<td>acetylcholine receptors</td>
</tr>
<tr>
<td>AChE</td>
<td>acetylcholinesterase</td>
</tr>
<tr>
<td>A/D</td>
<td>analog to digital</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BBS</td>
<td>Berg Balance Scale</td>
</tr>
<tr>
<td>CD</td>
<td>contraction duration (milliseconds)</td>
</tr>
<tr>
<td>CDA</td>
<td>Canadian Diabetes Association</td>
</tr>
<tr>
<td>DSES</td>
<td>Diabetes Self-Efficacy Scale</td>
</tr>
<tr>
<td>HbA1c</td>
<td>glycosylated haemoglobin (percent of all haemoglobin molecules in blood)</td>
</tr>
<tr>
<td>HRT</td>
<td>half-relaxation time (milliseconds)</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>iEMG</td>
<td>integrated electromyography</td>
</tr>
<tr>
<td>LG</td>
<td>lateral gastrocnemius</td>
</tr>
<tr>
<td>MHC</td>
<td>myosin heavy chain</td>
</tr>
<tr>
<td>MNSI</td>
<td>Michigan Neuropathy Screening Instrument</td>
</tr>
<tr>
<td>MVC</td>
<td>maximum voluntary contraction</td>
</tr>
<tr>
<td>m-wave</td>
<td>muscle compound action potential</td>
</tr>
<tr>
<td>n/a</td>
<td>not applicable</td>
</tr>
<tr>
<td>NMJ</td>
<td>neuromuscular junction</td>
</tr>
<tr>
<td>PT</td>
<td>peak torque (Newton-metre)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>sEMG</td>
<td>surface electromyography</td>
</tr>
<tr>
<td>SF-36</td>
<td>RAND 36-item Health Survey 1.0</td>
</tr>
<tr>
<td>STEP</td>
<td>Step Test Exercise Prediction of submaximal oxygen consumption</td>
</tr>
<tr>
<td>T1D</td>
<td>Type 1 Diabetes Mellitus</td>
</tr>
<tr>
<td>T2D</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>TA</td>
<td>tibialis anterior</td>
</tr>
<tr>
<td>TPT</td>
<td>time to peak torque (milliseconds)</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed “up and go” test</td>
</tr>
<tr>
<td>VO$_2$ max</td>
<td>maximal oxygen uptake (millilitres per kilogram per minute)</td>
</tr>
<tr>
<td>WFQ</td>
<td>Waterloo Footedness Questionnaire</td>
</tr>
<tr>
<td>YPAS</td>
<td>Yale Physical Activity Survey for Older Adults</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

UNITS

\( \mu s \) \hspace{1cm} \text{microsecond}

\( \text{cm} \) \hspace{1cm} \text{centimetre}

\( g \) \hspace{1cm} \text{gram}

\( \text{Hz} \) \hspace{1cm} \text{hertz}

\( \text{kg} \) \hspace{1cm} \text{kilogram}

\( m \) \hspace{1cm} \text{metre}

\( \text{min} \) \hspace{1cm} \text{minute}

\( \text{mm} \) \hspace{1cm} \text{millimetre}

\( \text{mmHg} \) \hspace{1cm} \text{millimetre of mercury}

\( \text{mmol/L} \) \hspace{1cm} \text{millimole per litre}

\( \text{mL} \) \hspace{1cm} \text{millilitre}

\( \text{mV} \) \hspace{1cm} \text{millivolt}

\( \text{Nm} \) \hspace{1cm} \text{Newton-metre}

\( \text{ms} \) \hspace{1cm} \text{millisecond}

\( s \) \hspace{1cm} \text{second}

\( V \) \hspace{1cm} \text{volt}
GLOSSARY

I. Terms relating to Diabetes Mellitus

beta-cell
Pancreatic cell occurring in the Islet of Langerhans responsible for insulin production and secretion.

cardiopathy
Disorder of the cardiovascular system; secondary disease of Type 2 diabetes where hyperglycaemia results in damages to the blood-carrying vessels and the heart.

diabetes mellitus
A group of metabolic disorders characterized by chronically elevated blood glucose.

endothelial
A single layer of cells that line blood vessels.

foot ulcer
A sore on the underside of the foot often the result of neuropathy; when a wound goes unnoticed because of lack of sensation and becomes severe.

galactitol
Used to artificially induce diabetes; is a chemical origination from plants and formed by reduction of galactose.

glucose
A monosaccharide sugar, C₆H₁₂O₆, found in plants and animals. Main energy source of the body.

glycosylated haemoglobin
Haemoglobin subunit (A1) that has irreversibly attached to glucose by a glycosylation reaction. Important tool to assess glucose control over past 120 days.

hypercholesterolemia
Excessive presence of cholesterol in blood (above 5.2 mmol/L) (Health Canada, 2007).

hyperglycaemia
High levels of glucose (beyond 3.9 – 5.8 mmol/L) in the blood; a sign of diabetes (Health Canada, 2007).

hypertension
Abnormally elevated blood pressure [normal less than 120/80 millimetres of mercury [mmHg]; Stage 1 is 140-159/90-99 mmHg; Stage 2 is 160-179/100-109 mmHg; Stage 3 greater than 180/110 mmHg (Health Canada, 2007)].

insulin
A protein that is produced by the beta-cells of the pancreas important for glucose uptake into cells (chemical ligand).
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>nephropathy</td>
<td>Degenerative disease of the kidneys; secondary disease of Type 2 diabetes where high levels of blood glucose results in impaired function of nephrons in the kidney.</td>
</tr>
<tr>
<td>polyol pathway</td>
<td>Glucose enters this cycle when aldose reductase reduces it to sorbitol forming advanced glycation end-products (these can cause damage to cells).</td>
</tr>
<tr>
<td>retinopathy</td>
<td>Degenerative disease of the retina; secondary disease of Type 2 diabetes where increased blood glucose can result in destruction of the retina over time.</td>
</tr>
<tr>
<td>secondary disorder</td>
<td>Refers to degenerative diseases of organ systems (e.g. neuropathy) that occur as the direct result of another condition (e.g. hyperglycaemia).</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Non-insulin dependent form of diabetes; where insulin recognition and receptor function is impaired resulting in high blood glucose levels.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action potential</td>
<td>Single electrical potential change occurring between the inside and outside of a nerve or muscle fibre (originating from the central nervous system or electrically induced). Successive depolarization and repolarization of cell membrane. <em>Electrical message.</em></td>
</tr>
<tr>
<td>Agonist</td>
<td>The contracting muscle in the agonist-antagonistic pair of opposing/working muscles.</td>
</tr>
<tr>
<td>Alpha motoneurone</td>
<td>Neurons originating from the central nervous system, which have axons that extend outside to control muscle (efferent).</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Opposes the agonist in the agonist-antagonistic pair; is the muscle that lengthens.</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Wasting away, or decrease in tissue size from disease, disuse or injury.</td>
</tr>
<tr>
<td>Central activation</td>
<td>Reflects the ability of the central nervous system to voluntarily initiate movement in the peripheral muscle per demand.</td>
</tr>
<tr>
<td>Central failure</td>
<td>Inability of the components of the central nervous system (above the alpha motor neuron and muscle) to demand movement from muscle.</td>
</tr>
<tr>
<td>Co-activation</td>
<td>Activation (muscle activity) of the antagonist while the agonist is engaged in activity.</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>Speed of electrical message transmission (action potential) along a nerve.</td>
</tr>
<tr>
<td>Contractile properties</td>
<td>Refers to the electrically-induced response of a muscle. The descriptors of that twitch are classified as contractile properties – relating to muscle function and fibre type.</td>
</tr>
<tr>
<td>Demyelination</td>
<td>Destruction of the myelin sheath covering nerve axons. Interrupts signal transmission.</td>
</tr>
<tr>
<td>Dorsiflexion</td>
<td>An upward turning action of the foot/hand (e.g., point toes to the sky). Important component in efficient locomotion.</td>
</tr>
<tr>
<td>Doublet discharge</td>
<td>Two action potentials that are discharged by one motor unit close in time (less than 10 ms).</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>dynamometre</td>
<td>An instrument used to quantify torque production.</td>
</tr>
<tr>
<td>electromyography</td>
<td>The task of recording electrical activity within a muscle; the result is an electromyograph.</td>
</tr>
<tr>
<td>electrophysiology</td>
<td>The study of electrical phenomena concerning bodily function.</td>
</tr>
<tr>
<td>end-plate potential</td>
<td>A potential generated on the post-synaptic membrane causing partial membrane depolarization, inducing an action potential along the sarcolemma.</td>
</tr>
<tr>
<td>fast twitch (Type IIa/IIb)</td>
<td>A type of muscle fibre that has the ability to contract fast. Involved in intense, short duration activity. Includes types IIa and IIb.</td>
</tr>
<tr>
<td>fatigue</td>
<td>Defined as a decline of the force generating capacity of muscle.</td>
</tr>
<tr>
<td>fibre type</td>
<td>Classification of muscle cells by function; slow-twitch (I) and fast-twitch (IIa/IIb/IIx).</td>
</tr>
<tr>
<td>half-relaxation time</td>
<td>Time it takes for peak torque to fall to one half of its maximum value. Timing characteristic to define the twitch.</td>
</tr>
<tr>
<td>integrated electromyography</td>
<td>Smoothed signal integrated over time to allow observation of the accumulated EMG activity over time.</td>
</tr>
<tr>
<td>inversion</td>
<td>To turn over or backward (e.g., turn foot laterally up to show foot underside).</td>
</tr>
<tr>
<td>isokinetic</td>
<td>An exercise providing variable resistance with constant speed, with special equipment.</td>
</tr>
<tr>
<td>isometric</td>
<td>Muscle contraction against resistance where muscle fibre length or joint angle does not change.</td>
</tr>
<tr>
<td>lactate</td>
<td>The end product of anaerobic glycolysis.</td>
</tr>
<tr>
<td>latency</td>
<td>Time interval between stimulus and reaction.</td>
</tr>
<tr>
<td>lateral gastrocnemius</td>
<td>A muscle on the posterior side of the lower leg. Originates from the lateral and medial condyles of the femur, inserts with the soleus muscle via the Achilles tendon into the posterior surface of the calcaneus. Innervated by the tibial nerve, to cause plantarflexion of the foot.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>maximum voluntary contraction</td>
<td>Greatest voluntary force generated for a muscle.</td>
</tr>
<tr>
<td>motoneurone</td>
<td>A neuron originating in the central nervous system or ganglion, sends impulses to a muscle.</td>
</tr>
<tr>
<td>motor end-point</td>
<td>Highly innervated region of a muscle.</td>
</tr>
<tr>
<td>motor nerve</td>
<td>Same as motoneurone.</td>
</tr>
<tr>
<td>motor unit</td>
<td>A group of muscle fibres that are controlled and innervated by a single neuron = one unit.</td>
</tr>
<tr>
<td>motor unit firing rate</td>
<td>Rate (number of impulses per unit of time) that a motor unit emits action potentials.</td>
</tr>
<tr>
<td>motor unit recruitment</td>
<td>Important in modulation of force. Motor units of different sizes are called upon in specific order to maximize force production. Smallest diameter first to largest are turned on, and largest to smallest to turn off.</td>
</tr>
<tr>
<td>motor unit remodelling</td>
<td>Adjacent nerve reinnervates muscle fibre when the commanding alpha-motoneurone dies; the muscle fibre takes on the characteristics of the adjacent nerve fibre over time.</td>
</tr>
<tr>
<td>muscle activation</td>
<td>Same as activation.</td>
</tr>
<tr>
<td>muscle fibre</td>
<td>Muscle cell. Smallest functional unit of a muscle.</td>
</tr>
<tr>
<td>m-wave</td>
<td>Compound muscle action potential; the EMG result of an electrical stimulus received in a muscle and the synchronous action potentials from varying motor units combine to give a general tracing.</td>
</tr>
<tr>
<td>myofibre</td>
<td>Muscle cell; smallest functional unit of a muscle.</td>
</tr>
<tr>
<td>myopathy</td>
<td>Disorder of muscle tissue.</td>
</tr>
<tr>
<td>myosin</td>
<td>Important contractile protein involved in cross-bridge cycling in muscle contraction.</td>
</tr>
<tr>
<td>myosin heavy chain</td>
<td>Component of myosin.</td>
</tr>
<tr>
<td>neurodegeneration</td>
<td>Deterioration of elements of the nervous system.</td>
</tr>
<tr>
<td>nerve</td>
<td>Ensheathed bundle of neurons (axons).</td>
</tr>
<tr>
<td>neuromuscular junction</td>
<td>Junction where alpha-motoneurone and sarcolemma meet.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>neuron</td>
<td>Nerve cell. Smallest functional unit of the nervous system.</td>
</tr>
<tr>
<td>neuropathy</td>
<td>Degenerative disease of the nervous system; secondary disease occurring in type 2 diabetes from prolonged exposure to high levels of glucose. Diagnosed clinically by nerve conduction studies.</td>
</tr>
<tr>
<td>oscilloscope</td>
<td>Device used to show changes in voltage or current.</td>
</tr>
<tr>
<td>peak torque</td>
<td>Characteristic of the twitch; the greatest amount of force produced from an electrical impulse elicited along a nerve to a muscle.</td>
</tr>
<tr>
<td>peroneal nerve</td>
<td>Nerve innervating the tibialis anterior; derived from the dorsal branches of the fourth and fifth lumbar and the first and second sacral nerve. Divides into the superficial and deep peroneal nerve.</td>
</tr>
<tr>
<td>rate coding</td>
<td>Refers to when the intensity of a stimulus increases the firing rate.</td>
</tr>
<tr>
<td>reinnervation</td>
<td>The subsequent process by which a muscle loses nerve stimulation and regains it, usually by adjacent nerve input.</td>
</tr>
<tr>
<td>resting membrane potential</td>
<td>Charge separation established by sodium and potassium pumps across a membrane in living cells; source of stored or potential energy. Usually measures -70 mV.</td>
</tr>
<tr>
<td>slow twitch (Type I)</td>
<td>Slow oxidative; capillary, mitochondria and myoglobin dense (red colour). More oxygen can go into it to sustain long bouts of aerobic activity. Also denoted as Type I.</td>
</tr>
<tr>
<td>supramaximal twitch</td>
<td>A twitch that is elicited by incrementally increasing voltage to obtain a maximal size twitch, then increasing the voltage a subsequent 10 %.</td>
</tr>
<tr>
<td>surface electromyography</td>
<td>Type of electromyography (EMG) where signals are collected by surface electrodes.</td>
</tr>
<tr>
<td>synaptic vesicle</td>
<td>In axon of neuron, carries neurotransmitters that are stored and released at the pre-synaptic membrane into the synaptic cleft (between pre and post membranes).</td>
</tr>
<tr>
<td>synergist</td>
<td>A muscle that aids the agonist in movement.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>tetanus</td>
<td>Completely fused twitches, elicited by continuous electrical stimulation.</td>
</tr>
<tr>
<td>tibialis anterior</td>
<td>Muscle that covers the tibia, originates in the lateral surface of the tibia, inserts into the medial cuneiform and first metatarsal of the foot; contraction will dorsiflex/invert foot.</td>
</tr>
<tr>
<td>time to peak tension</td>
<td>Characteristic of a twitch, the time it takes to generate maximal force during a twitch.</td>
</tr>
<tr>
<td>torque</td>
<td>Rotational force; equals force times perpendicular distance. Units are Nm.</td>
</tr>
<tr>
<td>twitch</td>
<td>Muscle response to single electrical impulse, causes change in the force tracing.</td>
</tr>
<tr>
<td>twitch interpolation</td>
<td>Technique that assesses whether a muscle is fully activated. Based on the premise that if muscle is completely engaged through voluntary effort, an electrical impulse (makes twitch along nerve and muscle) will not cause an increase in force.</td>
</tr>
</tbody>
</table>
III. Outcome Measures

4-metre walk
Test of functional mobility; exemplifies ability to walk/walking speed in daily living.

Activities-balance confidence scale
Questionnaire that yields information about personal confidence concerning balance in daily living.

Activities of daily living
Daily tasks and actions that a person is or may be involved in during a normal day that relates to their personal autonomy.

Berg Balance Scale
Functional balance test that assesses balance capabilities in daily living context.

Diabetes Self-Efficacy Scale
A clinical questionnaire assessing a person's perception/ability/confidence to care for his/her diabetes.

Michigan Neuropathy Screening Instrument
A set of questions relating to/defining the existence of neuropathy.

Mobility
Ability to move safely without hindrance.

Semmes-Weinstein Monofilament
A nylon filament/bristle that bends at a predetermined force (i.e. 10 g). Important in sensory testing of nerves.

Short-form 36
A subset of the Medical Outcomes Survey consisting of 36 questions. It yields information relating to health perception.

Step-test exercise prediction of submaximal VO₂
Submaximal predicted test of oxygen consumption involving stepping exercise.

Timed "up and go"
Test of functional mobility, gives information about walking speed.

VO₂ max
Maximum amount of oxygen, in millilitres [mL], that a person can use in one minute per kilogram of bodyweight.

Waterloo Footedness Questionnaire
A set of questions designed to determine leg dominance.

Yale Physical Activity Survey
A set of questions that yield information to quantify the amount of activity a person is involved in daily/weekly.
CHAPTER I
INTRODUCTION

Type 2 Diabetes Mellitus in Society

Diabetes mellitus refers to a group of metabolic disorders of the endocrine system, where hyperglycaemia (an elevation in blood glucose concentration) is a hallmark outcome. According to the Canadian Diabetes Association [CDA] (2003), more than two million Canadians are affected with some form of diabetes. It has been estimated that Type 2 diabetes [T2D] (also known as non-insulin dependent diabetes mellitus) has a 90 % prevalence rate within the general population (CDA, 2003) and traditionally the age of onset is late adulthood. It has been suggested that changes in lifestyle and nutrition patterns, particularly in developed nations, will largely contribute to an exponential rise in T2D (Said & Bril, 1999). Consequent to the onset of T2D, patients often self-report muscle weakness and reduced function (Sayer, Dennison, Syddall, Gilbody, Phillips, & Cooper, 2005). The reduction in physical function alone causes a staggering financial burden on our health care system (Katzmarzyk, Glendhill, & Shephard, 2000; O'Brien, Patrick, & Caro, 2003).

Currently, there is no cure for T2D (Pontiroli, 2004), but existing treatment involves modifications of diet, reduction of body fat, exercise prescription, pharmaceutical intervention and insulin therapy in some cases (Bailes, 2002). Although many components of the aetiology of T2D have yet to be elucidated, it is believed to result from the interaction of complex genetic and environmental factors (Östenson, 2001). Sedentary lifestyles along with a lack of exercise are environmental factors that are not only additive but also have the
potential to influence the onset and progression of this disease when combined with increases in adiposity and decreases in lean body mass (Skinner, 2005).

Chronic hyperglycaemia in T2D is suspected to result from insulin resistance in hepatic, skeletal and adipose tissues and impaired insulin secretion from the beta cells of the pancreas, or a combination of both (Silverthorn, 1998). During disease progression, catabolic enzymes are subsequently upregulated, contributing to increases in fat, carbohydrate and protein breakdown (Östenson, 2001; Silverthorn, 1998). As a direct result, an increase in glucose flux through metabolic pathways (i.e. sorbitol pathway) results in impaired homeostatic function and disease progression via the excessive formation of toxic by-products (Ivy, Zderic, & Fogt, 1999). Of particular importance to any discussion of T2D is its constellation, metabolic syndrome. The definition of metabolic syndrome has been redefined in recent literature as clinical perspectives and experimental ideas merge. Although its definition is multi-factorial, the contributing elements emerge and oftentimes contain the diagnosis of T2D. According to the International Diabetes Federation, metabolic syndrome is defined as central (referring to girth) obesity (characterized with respect to race) plus two of the following: elevated triglycerides, decreased HDL ("good") cholesterol, increased blood pressure/diagnosed hypertension, or increased fasting plasma glucose/T2D (Zimmet, Magliano, Matsuzawa, Alberti, & Shaw, 2005). Thus, when assessing T2D and control subjects of similar physical attributes, care must be taken to ensure individuals with metabolic syndrome and T2D are appropriately classified.

It is nearly impossible to tell by observation whether a person has diabetes. A person living with abnormally high levels of blood glucose may feel "healthy" and assert "no need"
to change their current lifestyle patterns because they do not experience physical signs of their disease. This is particularly hazardous because untreated chronic hyperglycaemia has the potential to manifest in numerous secondary disorders including retinopathy and nephropathy, cardiopathy, neuropathy (CDA, 2003) and myopathy (Marques & Santo Neto, 2002). Although neuropathies result from other reasons, diabetes is the most common underlying cause of disabling neuropathy (Said & Bril, 1999). Approximately 60 % of persons with T2D suffer from neuropathy-related conditions (Mišur, Žarković, Barada, Batelja, Miličević, & Turk, 2004). Diabetic neuropathy refers to neurodegeneration resulting from the effects of chronic hyperglycaemia and the subsequent formation of advanced glycation end-products (King, 2001). Diabetic neuropathies are subdivided into three categories: most commonly diagnosed are 1) distal symmetrical polyneuropathy; 2) polyneuropathy, which occurs in two distinct forms characterized by either demyelination (asymptomatic) and/or axonal loss (symptomatic); and 3) focal neuropathies (proximal motor neuropathies) that occur less frequently (Brown & Asbury, 1984; Valls-Canals, Povedano, Montero, & Pradas, 2002). In many cases, the hyperglycaemic condition that leads to irreparable bodily damage remains undetected until physical harm occurs. The point where reversible damage becomes so severe that it becomes irreversible is equivocal. Many studies have been conducted on neuropathic individuals with T2D (Simmons & Feldman, 2002). It is important to not only focus on symptomatic individuals, but also those who are asymptomatic for neuropathies in order to understand diabetic disease progression.

Type 2 diabetes is projected to place an enormous economic burden on Canadian society (O'Brien et al., 2002). Hospital and physician visits, plus drug research and
development have been estimated to pose an annual cost of 620 million Canadian dollars (Katzmarzyk et al., 2000). Alas, the global response to the rise of chronic diseases, including diabetes, is inadequate (Yach, Hawkes, Gould, & Hofman, 2004). To reverse anticipated trends in world health, Yach et al. (2004) recommend more research into diabetes as a core task, to support policy reformation and ensure higher placement in the government agenda to counteract economic impediments. For this reason, it is paramount that a thorough understanding of T2D and its associated disability be established so that appropriate interventions and treatment may be provided. Skeletal and neural tissues are central to our ability to generate force for basic movements and locomotion. In persons living with T2D, the neural and muscular systems are altered due to chronic hyperglycaemia and consequent to secondary disorders. This creates extensive constraints on performance of activities of daily living, subsequently having negative consequences on personal autonomy and overall quality of life.

Pharmaceutical agents are being developed to control and/or mitigate hyperglycaemia and these advances will aid in the delay and ultimately the prevention of diabetic neuropathies. Within the realm of controlling hyperglycaemia, non-pharmaceutical interventions such as diet and exercise adaptations are advised. Exercise has been prescribed as the first therapy in the management of T2D, as it improves overall physical and mental health, decreases stress, improves immune system function, and quality of life, as well as increasing life expectancy. When a person performs any type of exercise, glucose is utilized as an energy source, enabling the extra to get "mopped up". Moreover, post-exercise glucose handling is also more efficient as free fatty acid availability is reduced and insulin sensitivity of glucose uptake is augmented (Shojaee-Moradie, Baynes,
Pentecost, Bell, Thomas, Jackson \textit{et al.}, 2007) from increased blood flow to the muscle, increased capillarization, fibre type shifts from IIb to IIa, biochemical changes and increased muscle mass representing acute and chronic changes (Ivy \textit{et al.}, 1999). Thus, glucose control is optimized during and following bouts of physical activity. Although exercise is promoted as a prehabilitative and rehabilitative strategy, very little is understood about muscle function in persons with T2D.
CHAPTER II
REVIEW OF LITERATURE

Strength and Physical Function

Many people living with T2D often report muscle weakness (Andersen, Nielsen, Mogensen, & Jakobsen, 2004a; Andersen, Gjerstad, & Jakobsen, 2004b; Cetinus, Buyukbese, Uzel, Ekerbicer, & Karaoguz, 2005; Clarke, 2004), yet the cause of this weakness and the influence on functional activities of daily living is presently undefined. Possible sources of muscle weakness include neural and muscular adaptations due to chronic hyperglycaemia, physical inactivity and/or disuse, or combinations of these factors. The best method to study muscle function in T2D would involve longitudinal study of persons known to be at high-risk for the development and then following diagnosis of T2D. Due to the nature of longitudinal studies, such a study would be difficult to administer considering issues of poor adherence that have been previously reported (Domenech, Assad, Mazzei, Kronsbein, & Gagliardino, 1995). Given the plasticity of muscle and differences in muscle strength due to gender (Kent-Braun, Ng, Doyle, & Towse, 2002; Yerdelen, Uysal, Koc, & Sarica, 2006) the most appropriate, secondary method for study involves the investigation of a group of individuals with diagnosed T2D compared to individuals that are well matched by levels of physical activity, age and gender. This type of matching has been utilized elsewhere (Jakobi, Killinger, Wolfe, Mahon, & Rice, 2001) and enables scientific investigation when intervention (i.e. inducing diabetes) studies are difficult to administer for ethical reasons or are limited by extensive ‘on-site’ involvement of clinical staff.
The final aspect of force modulation is at the level of the motor unit, through progressive recruitment and increases in discharge rates of already active motor units (Christie & Kamen, 2006; Kernell & Sjoholm, 1975). Such neural modulation enables the neuromuscular system to adapt to a variety of tasks from gross movements such as marching on the spot to more precise or fine movements such as finger-tapping. Motor unit firing rates have been demonstrated to change during sustained isometric contractions to maintain force (De Luca, Foley, & Erim, 1996), while recruitment of additional motor units occur to maintain force during a submaximal fatiguing contraction (Conwit, Stashuk, Suzuki, Lynch, Schrager, & Metter, 2000). The neural aspect of the motor unit is typically studied with invasive indwelling EMG procedures (Connelly, Rice, Roos, & Vandervoort, 1999; Jakobi & Cafarelli, 1998), where the contractile component can be assessed via production of voluntary and involuntary force. Twitch and tetanic contractile properties reflect a muscle’s ability to generate force in time as a consequence of electrical stimulation (McComas, 1996). In the tibialis anterior [TA] of older adults contractile properties slow and voluntary force is reduced in older adults compared with younger adult men (Connelly et al., 1999). It has been suggested (Jakobi, Rice, Curtin, & Marsh, 2000) that these alterations impair functional mobility in older adults. Functional mobility has been described as the ability to move safely from one place to another by independent means (Shumway-Cook & Woollacott, 2001). If contractile properties slow and voluntary force is reduced in the TA, this would in part, explain some of the observed impairments in mobility that are directly related to muscle and nerve function. To date, no study has ascertained whether alterations in contractile properties reflect the decrease in functional mobility that is self-reported by persons with T2D in clinical histories.
Changes in contractile properties in diabetes may be independent of age, as hyperglycaemic interference in muscle activity has been reported in studies of pharmacologically induced diabetes in rodent models. In the murine model, there seems to be a decrease in twitch tension, no change in contractile speed and an increase in the synaptic delay in the flexor digitorum superficial muscle after eight weeks of induced T2D (Fahim, El-Sabban, & Davidson, 1998). In the sternohyoid muscle of streptozotocin diabetic rats, contraction duration [CD], half relaxation time [HRT], twitch tension and tetanic tension increase, with no effect on fatigue and the tension-frequency relationship (McGuire, Dumbleton, MacDermott, & Bradford, 2001), causing a net increase in the capacity for force generation. Dietary accumulation of galactitol (a polyol pathway metabolite) induced experimental diabetes resulted in loss of muscle mass, damage to the myofibres, slowed time to peak tension [TPT], an increase in peak tension with no alterations in relaxation period in the extensor digitorum longus (fast-twitch) of rats (Cameron, Cotter, Robertson, & Cox, 1992). In the soleus muscles (slow-twitch) of these rats peak tension was unaltered, but HRT and CD were prolonged for both a single twitch and tetanus. Interestingly, there was a marked reduction in the number of fast oxidative glycolytic (Type Ila) fibres (Cameron et al., 1992). Overall, the results from studies of contractile alterations in animal models are equivocal, but lend support to the notion that hyperglycaemia may alter contractile function in humans because changes occur in rodent muscle, albeit invariably, when exposed to hyperglycaemic conditions.

While animal studies provide interesting and valuable insight regarding physiological mechanisms, they may not provide the most accurate description of the phenomena involved in the development of T2D in humans. One must not only consider the biological
and species differences between animals and humans, but also the differences between
the uses of artificially induced (i.e. toxicity of drug used) versus natural diabetes (i.e. cumulative effects of hyperglycaemia and vascular dysfunction). Caution must be followed when utilizing the results of animal studies to understand human phenomena as it is apparent that two entirely separate diseases are studied. Animal studies, hence, may not completely represent the human diabetic condition due to the enormous complexity and interplay between factors that are involved in the actual pathogenesis of diabetes.

Post-mortem study of the fibre composition of the human TA was determined to be 73 % Type I fibres and 27 % Type II fibres (Johnson, Polgar, Weightman, & Appleton, 1973). It is important to note, that fibre type composition varies between muscles and species (Bicer & Reiser, 2004) for example, the TA in individuals with paraplegia ranges from 1-40 % myosin heavy chain [MHC] I with MHC Ila presenting as the dominant form (32-96 %) and MHC IIX in lesser amounts (<1-28 %) (Harridge, Andersen, Hartkopp, Zhou, Biering-Sørensen, Sandri, & Kjær, 2002), whereas the MHC composition in the TA of Fisher rats was found to be 2.4 ± 2.1 % MHC I, 12.2 ± 6.6 % MHC Ila, with dominant form MHC IIB 49.0 ± 14.8 % while muscle MHC composition varied when comparing soleus, extensor digitorum longus, superficial and deep digitorum longus muscles (Staron, Kraemer, Hikida, Fry, Murray, & Campos, 1999). It is unknown in T2D whether changes are generally muscle or species specific, or influenced by the agent used to induce artificial diabetes, presenting substantial barriers in extrapolating results from animal studies to humans. Although this study will not reveal direct fibre type composition of the TA in persons with T2D, contractile times will provide a gross measure of the general fibre type, because a relationship exists
between fibre type and electrically induced whole muscle contractile properties (Harridge, Bottinelli, Canepari, Pelligrino, Reggiani, Esbjornsson, & Saltin, 1996).

Muscle volume has been related to muscular strength. When considering neuropathic versus non-neuropathic individuals, neuropathic persons may be weaker because of muscle loss. However, muscular atrophy alone, cannot fully explain the losses in strength that are observed in diabetes (Lesniewski, Miller, & Armstrong, 2003) or healthy older adults (Narici, Reeves, Morse, & Maganaris, 2004) because force decreases more than the size of muscle (Lesniewski et al., 2003). It has been proposed that decreases in muscle strength may be related to alterations in the structure and function of α-motoneurones (Lesniewski et al., 2003) or incomplete reinnervation of muscle after axon damage in a collapsed group of persons with type 1 diabetes [T1D] and T2D (Andersen, Stålberg, Gjerstad, & Jakobsen, 1998). Following this logic, it is possible that persons with T2D who have neuropathy could be different than persons who do not have neuropathy because a pronounced loss of muscle mass in distal groups may be greater in neuropathic individuals (Andersen, Gadeberg, Brock, & Jakobsen, 1997). Accordingly, Andersen et al. (1997) suggest a length-dependent process of peripheral neurodegeneration. In individuals with neuropathic T1D, muscle volume and strength decrease compared to healthy individuals and persons without neuropathic pathology; however, data of this sort are lacking for persons with T2D (Andersen et al., 1997). Moreover, this information has been gained from isokinetic dynamometry to assess strength of the ankle dorsal and plantar flexors, knee extensor and flexors rather than isometric strength. The latter enables a direct assessment of an isolated muscle group with minimal contribution of antagonist and synergist muscles and permit quantification of isolated whole muscle contractile properties.
Isometric contractile properties have yet to be quantified in persons with T2D and compared to healthy individuals.

The purpose of skeletal muscle is to produce force and necessitate movement. Hence, muscular strength is highly related to functional ability and consequent to weakness, declines in physical function ensue (Chandler, Duncan, Kochersberger, & Studenski, 1998). In older non-diabetic adults there is a strong relationship between muscular strength in the lower limbs to gait and balance (Wolfson, Judge, Whipple, & King, 1995). As well, there is evidence to suggest that mobility, balance and endurance seem to increase as strength is increased in older individuals (Chandler et al., 1998; Krebs, Jette, & Assmann, 1998; Mulrow, Gerety, Kanten, Cornell, DeNino, Chiodo et al., 1994; Ramsbottom, Ambler, Potter, Jordan, Nevill, & Williams, 2004; Toulouette, Fabre, Dangremont, Lensel, & Thévenon, 2003). Although data on these relationships is sparse in persons with T2D, Brandon, Gaasch, Boyette, & Lloyd (2003) have suggested that as strength increases, mobility improves. While losses in mobility are common in the diabetic condition, the mechanisms contributing to the marked loss in strength and how strength may be regained remain equivocal. However, electromyography [EMG] data from gait studies provide further support for altered neuromuscular function contributing to declines in mobility in T2D. Persons with diabetic induced neuropathies required more time to develop force during walking, and had weaker force development during braking (Meier, Desrosiers, Bourassa, & Blaszczyk, 2001). Petrofsky, Lee, & Bweir (2004) studied walking characteristics of T2D patients and noticed that persons with T2D walked slower than controls. Persons with T2D also seemed to use a wider stance while walking in a linear pathway and while turning indicating differences in locomotion patterns between T2D and
controls. This seems to be translated into gait compensatory adaptations that occur in persons with neuropathy and T2D (Kwon, Minor, Maluf, & Mueller, 2003). During walking, they seem to employ more co-contractions of agonist and antagonist muscles at the knees and ankle joints during the stance phase of walking to adopt a safer and more stable pattern of gait likely due to impaired sensory feedback (Kwon et al., 2003). According to Sacco & Amadio (2003), delayed EMG responses of the thigh and leg muscles during treadmill walking suggest sensory and motor disturbances. Unfortunately, these studies did not dissociate the T2D group into those with neuropathy and those without. Thus, it could not be determined whether these findings were solely related to hyperglycaemia and the diabetic condition.

Further support for alterations in neural activity of the muscle in persons with T2D come from morphological and histological studies using rodent models. In the dorsiflexors of the mouse, there is a decrease in resting membrane potential and miniature end-plate potentials due to impaired sarcolemmal-Ca$^{2+}$ mobilization (Fahim, Hasan, & Alshuaib, 2000), and tetanic potentiation has been found to be lower, while the neuromuscular junction [NMJ] shows resistance to high-frequency stimulation (Schiller & Rahaminoff, 1989). This phenomenon is suspected to result from changes in K$^+$ gradients along the sarcolemma after high-frequency stimulation (Schiller & Rahaminoff, 1989). As well, ultrastructural disruptions such as reduction in the number of synaptic vesicles, mitochondrial degeneration (Fahim et al., 1998, 2000), decreases in electron-dense bodies and myelin-like figures (Fahim et al., 1998) with marked disarray of the microtubules and neurofilaments of the nerves have been reported in animal models and related to the reduction in contractile function (Fahim et al., 2000).
In the streptozotocin rat model, the distribution of acetylcholinesterase [AChE] molecules in fast twitch extensor digitorum fibres is altered, resulting in a shift of the AChE profile from fast-type to isoforms found in slow-type muscle (Kiss et al., 2001). Such a concentration shift was suspected to be the result of changes in neuromuscular function (reinnervation), or from dysfunctional liberation of trophic factors (Kiss, Somogyi, Csermely, Szelenyi, & Vér, 2001). In female diabetic mice, irregularities in acetylcholine receptors [AChR] at the motor end-plate resulted in patchy distribution with regular junctional folds, with co-localization of AChR and sprouts at the nerve terminal (Marques & Santo Neto, 2002). Despite the disruptions observed in the murine model, study of the rat model of diabetes indicates that the NMJ remains intact, but intracellular myofibril disarray, myelin figures, mitochondrial swelling and cristae lysis occur (Ozaki, Matsuura, & Narama, 2001). As discussed earlier, the value of the experimental animal model is great for invasive study, but the equivocal results between mouse and rat serve to highlight species differences and the requirement for human study.

The muscle compound action potential (m-wave) is utilized to assess the integrity of the NMJ and is a useful tool to study pathophysiology of nerves (Kim, Date, Park, Choi, & Lee, 2005). The m-wave is induced via supramaximal electrical stimulation and results in synchronous summation of motor unit action potentials. The amplitude of this potential is measured from start to peak and represents the temporal and spatial summation of individual action potentials from individual muscle fibres while the duration corresponds to the time required for the rising phase and lowering phase of the m-wave, and is determined by temporal dispersion (Kim et al., 2005). The overall m-wave will yield information on the
number of functional motor units and is a useful tool to study pathophysiology of nerves (Kim et al., 2005). Currently, no study has assessed m-waves in persons with T2D to determine whether the NMJ is altered in humans with T2D.

Functional mobility tests enable identification of the ability to perform functional activities including sitting and standing, but do not show the underlying mechanisms for observed impairments in mobility. Alterations in functional mobility will have serious ramifications on overall well-being and independence. In older persons with T2D marked changes in postural stability and a decrease in balance occurs (Corriveau, Prince, Hébert, Raîche, Tessier, Maheux, & Ardilouze, 2000). Such alterations in posture and balance inevitably lead to loss of mobility which has been attributed to muscle weakness in older persons with and without T2D. Yet, in younger persons with T2D, there is no information available on functional mobility and muscle strength. Leg muscles are important in maintaining balance and posture for all upright movements. In particular, the TA is important in dorsiflexion and inversion of the foot, which are integral components for locomotion (Mount & Dacko, 2006). An assessment of contractile properties of the TA in conjunction with functional mobility and balance tasks will help to understand the relationship between changes in mobility and balance with respect to muscle characteristics in persons with T2D.

It is quite possible that neuromuscular changes in diabetes do not happen until advanced stages of this disease, perhaps due to chronically elevated glucose levels that lead to secondary dysfunction (i.e. neuropathy) from ineffective disease management. Or, it might be possible that complex changes occur in diabetes in concert with cellular processes.
that are cued during aging. This would be consistent with studies performed on older persons with T2D who show functional changes different from healthy non-diabetic individuals (Resnick, Stansberry, Harris, Tirivedi, Smith, Morgan et al., 2002). Age-related alterations in the motor unit are typically evident at approximately 65 years, but do not manifest in functional loss of strength until 80 years or so (McNeil, Doherty, Stashuk, & Rice, 2005). Unequivocal within the literature concerning increasing age are the noticeable reductions in motor unit firing rates (Connelly et al., 1999, Jakobi & Cafarelli, 1998), with a decrease in the occurrence of motor unit doublet discharge during isometric force production (Christie & Kamen, 2006), and an increase in discharge variability resulting in greater fluctuations in force output in older adults (Tracy, Maluf, Stephenson, Hunter, & Enoka, 2005). To exclude the confounding effect of age-related change on physiology of the motor unit and its possible interplay with hyperglycaemia, middle-aged adults should be studied.

Muscle Fatigue

Muscular fatigue involves a progressive decrease in peak tension and power output resulting in a reduction of the overall capacity to perform muscular work (Fitts, 1996). The aetiology involves a complicated and multi-factorial set of integrated mechanisms, some of which have yet to be fully elucidated. When muscles fatigue in healthy individuals, timing of the twitch profile slows and there is a decrease in the peak twitch tension (Fitts, 1994, 1996).

Disease may influence the endurance of muscle via disruptions in cellular conditions. These changes may result in the premature development of fatigue (Westerblad &
Lannergren, 2001). It is conceivable that the onset of muscle fatigue could occur earlier because exercise in diseased conditions may begin at a point that is closer to the maximum working capacity of the muscle (Westerblad & Lannergren, 2001). This may be particularly true concerning the altered metabolic state of tissues due to hyperglycaemia. If this is a valid conjecture, an experimental fatigue protocol must ensure that all subjects work at the same relative intensity. In older adults the time to fatigue is longer than younger individuals when both groups perform at the same intensity for both isometric and dynamic tasks (Lanza, Russ, & Kent-Braun, 2004). It is unknown how persons with T2D will respond to the same work intensity.

It is important to make note of the potential influence of metabolic status on motoneurone activation state and muscle fatigue (Duchateau, Balestra, Carpentier, & Hainaut, 2002). Impaired glucose metabolism will influence aerobic fatigue, due to the altered metabolic energy supply. To minimize differences due to glucose metabolism, an anaerobic submaximal intermittent fatigue protocol would be optimal. To monitor metabolic status, blood glucose should be measured prior to and after the fatigue protocol to observe the glycaemic response to exercise. As well, lactate is a by-product of anaerobic energy production. During exhaustive exercise, lactate is produced and accumulates within the tissues leading to its subsequent diffusion into the venous supply. Measures of blood lactate and glucose would yield a gross representation of the metabolic status of the tissue, and has yet to be measured in persons with T2D.

In older persons, motor unit remodelling is believed to occur and has been related to the selective atrophy of fast-twitch fibres allowing slow twitch fibres to predominate in a
muscle (Macaluso & De Vito, 2004). Interestingly, while maximal muscle strength decreases during the aging process, muscular endurance is preserved. This “fatigue paradox” has been described as task-dependent which varies among muscle groups (Allman, Cheng, & Rice, 2004; Lanza et al., 2004) and is likely due to age-related motor unit remodelling (Lanza et al., 2004, Macaluso & De Vito, 2004). The ankle dorsiflexors in older persons for an isometric submaximal endurance test are more fatigue resistant (Lanza et al., 2004). Since time to fatigue depends on a person’s fitness level (Garland, Walton, & Ivanova, 2003) and fibre type composition (Hamada, Sale, MacDougall, & Tarnopolsky, 2003), there is reason to believe that the occurrence of fatigue may be different in persons with T2D. Furthermore, it remains unknown whether contractile properties are altered during fatigue in individuals with T2D, and whether the magnitude of change reflects the state of diabetic condition (i.e. glucose levels). To date no study has assessed muscle endurance in a controlled task in persons with T2D. Prior study of Addison’s Disease, an endocrine disorder of the adrenal gland, has suggested that patients’ self-report of muscle weakness and fatigue are not measured as changes in endurance time, or contractile function in controlled laboratory studies (Jakobi et al., 2001). Whereas, in studies of chronic fatigue syndrome (Lloyd, Gandevia, & Hales, 1991), poliomyelitis (Allen, Gandevia, Neering, Hickie, Jones, & Middleton, 1994) and fibromyalgia (Miller, Allen, & Gandevia, 1996) decreases in muscle endurance have been related to alterations in contractile function.
Objectives

The relationship between functional mobility and neuromuscular properties has yet to be determined in T2D. Also, little is known whether differences exist in muscle fatigue between non-neuropathic persons with T2D and healthy individuals. Neuromuscular studies are essential, as the design and execution of effective therapeutic intervention cannot be successful without a thorough understanding of the neuromuscular adaptations to disease.

The overall objective of this thesis is to characterize neuromuscular properties, functional mobility, balance and fatigue in middle-aged persons with T2D.

Specific Goals

Aim 1: To determine whether strength, m-wave and twitch contractile properties of the TA are different between persons with non-neuropathic T2D from age, gender and activity-matched individuals.

Aim 2: To study the relationship between neuromuscular properties, balance and functional mobility in persons with non-neuropathic T2D.

Aim 3: To investigate acute fatigue and recovery of the TA in persons with non-neuropathic T2D.
CHAPTER III
DESIGN AND METHODOLOGY

Subjects and Recruitment

Prior to participation in this study, all subjects provided written informed consent. This investigation was conducted in the Neuromuscular Laboratory at the University of Windsor in accordance with the Declaration of Helsinki (The World Medical Association General Assembly, 2004) and the guidelines established by the University of Windsor Human Research Ethics Board (Appendix A). Volunteers were recruited through advertisements in local pharmacies, the University of Windsor Cardiac Rehabilitation Program, the St. Denis Centre (fitness centre), advertisements in local newspapers, and mass campus email (Table 1; Appendix B). All procedures were thoroughly explained by the investigator prior to obtaining consent (Appendix A).

Subject Inclusion Criteria. Volunteers were able to walk independently without pain or assistive devices, free from orthopaedic, neurological or mental disorders, were not pregnant, of sound general health, and demonstrated a willingness to participate in this study to be included. Diabetes Group. All persons with diagnosed T2D completed glycosylated haemoglobin [HbA1c] testing in the lab (A1c Now Multi-test System, Metrika Inc., Sunnyvale, CA) as a screening test to indicate glucose control over the past 120 days (HbA1c less than 8 % is considered optimal) (Appendix C). HbA1c is considered a useful tool for diabetes management, and diabetes-risk screening (Edelman, Olsen, Dudley, Harris, & Oddone, 2004). Control Group. All matched individuals for control were free from a history of diabetes mellitus (according to subject reported information from their personal
physician), and also underwent HbA1c testing to ensure no chronic elevations in blood glucose over the past three months (excluded if HbA1c ≥7 %). All controls were age, gender and activity matched to persons with T2D.

**Subject Exclusion Criteria.** Volunteers were excluded if they had serious musculoskeletal disorders, injury, neurological diseases unrelated to diabetes, severe cardiovascular disease or history of heart attack, electrical implants (i.e. cardiac pacemaker), recovering from surgery, acute focal neuropathy and acute painful neuropathies (Braune, 1997), myopathies (Braune, 1997; Roos, Rice, Connelly, & Vandervoort, 1999), bilateral orthopaedic pathologies of the lower limbs (Roos et al., 1999), lower extremity dysfunctions or extreme physical activity patterns.

**Table 1.** A list of recruitment tactics showing the number of attempts made, estimated contact and the total number of persons recruited with T2D from July 2005 to June 2006.

<table>
<thead>
<tr>
<th>Recruitment Strategy</th>
<th>Attempts Made</th>
<th>Distribution Rate</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posters</td>
<td>~75</td>
<td>Not applicable [n/a]</td>
<td>5</td>
</tr>
<tr>
<td>Windsor Star Saturday Edition News</td>
<td>1</td>
<td>207,163</td>
<td>5</td>
</tr>
<tr>
<td>University of Windsor DailyNews</td>
<td>1</td>
<td>4,000</td>
<td>1</td>
</tr>
<tr>
<td>Campus mass email to Faculty/Staff</td>
<td>2</td>
<td>2,339</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes educator groups</td>
<td>~13</td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>Word of Mouth</td>
<td>n/a</td>
<td>n/a</td>
<td>6</td>
</tr>
</tbody>
</table>
Session One: Experimental Protocol and Arrangement

Laboratory Familiarization. Subject familiarization with the study and experimenters occurred on the first visit to the laboratory. During this visit, subjects were asked to complete consent forms, background questionnaires, physical performance tests and sensory testing.

Questionnaires. Subject Contact Sheet (Appendix C) and Background Questionnaire (Appendix C) were used to collect general personal and contact information. The YPAS was administered in order to assess physical activity patterns and for subject matching (DiPietro, Caspersen, Ostfeld, & Nadel, 1993) (Appendix C) and the Waterloo Footedness Questionnaire [WFQ] (Elias, Bryden, & Bulman-Fleming, 1998) (Appendix C) was used to determine leg dominance. The RAND 36-item Health Survey 1.0 [SF-36] (Appendix C) was utilized to assess physical functioning, bodily pain, role limitations from health problems, and role limitations from emotional or personal issues, emotional well-being, social functioning, energy/fatigue and perception of general health. The Diabetes Self-Efficacy Scale [DSES] (Appendix C) was employed to yield information about personal confidence with respect to living and caring for their diabetes. The Activities-specific Balance and Confidence scale [ABC scale] (Powell & Myers, 1995) (Appendix C) assessed balance confidence while performing daily activities.

Physical Performance Tests. To quantify functional mobility and balance, a series of simple physical performance tests were utilized including the Berg Balance Scale [BBS] (Appendix D) to measure balance capability, Timed “up and go” test [TUG] (Podsiadlo & Richardson, 1991) (Appendix D) and the 4-metre timed walk [4m walk] (Guralnik, Fried,

**Screening for Diabetic Neuropathy.** Screening for diabetic peripheral neuropathy was conducted by sensory testing using a 10-gram [g] Semmes–Weinstein monofilament (Neuropen, Owen Mumford Ltd., Brook Hill, Woodstock, UK) by application to the dorsum of the great toe between the interphalangeal joint and cuticle of the nail using brief (1 second [s]) vertical, even pressure. The subjects were blinded and asked to respond to whether they felt the pressure by saying “yes”. This test was repeated 10 times with a + 8/10 response as no indication of neuropathy or a 0-7 positive indication of neuropathy (Padua, Saponara, Ghirlanda, Aprile, Padua, Pauri et al., 2001) (Appendix C). The Michigan Neuropathy Screening Instrument [MNSI] (Appendix C) was used in conjunction with the aforementioned sensory testing to confirm the existence of peripheral neuropathy (Feldman, Stevens, Thomas, Brown, Canal, & Greene, 1994). Control subjects were also tested to maintain consistency between groups and to assess non-diabetic related sensory abnormalities.

**Session Two: Experimental Protocol and Arrangement**

**Experimental Arrangement.** Measures of contractile function and muscle endurance occurred during the second visit to the laboratory. To reduce the potential ergogenic effects of caffeine on the generation of peak force and muscle fatigue, the subjects were asked to
abstain from consumption of caffeine for at least 2 hours prior to the second session of the study (Kalmar & Cafarelli, 1999). All tests were performed on the TA of the non-dominant leg except in three instances where knee impairment (n=2) or previous muscle injury (n=1) prevented study of the non-dominant leg. The subject was seated in a custom-built isometric dynamometer with the ankle of the non-dominant leg positioned to 30° of plantar flexion, and the hip and knee joints positioned at 90°. To minimize hip flexion, a seat-belt was utilized to maintain seated position during dorsiflexion. A series of two straps were used to restrict movement at the region of the dynamometer footplate during isometric contractions. Force measurements were collected by a commercial load cell attached to the underside of a metal footplate (Model MLP-500-T, Transducer Techniques, Inc., Temecula, CA). Signals were amplified and filtered (60-Hertz [Hz] notch filter), sampled at 1000 Hz (Model V72-25A, Coulbourn Instruments, Allentown, PA) and displayed on an oscilloscope in real-time for the subject to observe during the study session for feedback of their movements. Signals from the load cell were subsequently converted from analog to digital format using a 12-bit analog to digital [A/D] converter (Model 1401, Cambridge Electronic Design, Ltd., Science Park, Cambridge, UK) and displayed on a computer monitor. Offline quantification was completed using Spike 2 version 5 (Cambridge Electronic Design, Ltd., Science Park, Cambridge, UK). The load cell was calibrated with known weights to confirm consistent linear recordings over trials.

**Surface Electromyography.** Surface electromyography [sEMG] signals of the TA and lateral gastrocnemius [LG] were obtained using self-adhering, disposable electrodes (4 millimetres [mm]). The TA ground electrode was positioned over the patella, while the reference electrode was placed over the distal tendon of the TA. The active electrode was
then positioned 1 centimetre [cm] distal to the motor end point of the TA. The motor end point was located using continuous single pulses (100 microsecond [μs] single square waves) by applying increasing current to the surface over the TA until an obvious response or muscle twitch was noted. To record co-activation of the antagonist LG muscle, the ground electrode was placed over the patella, while the active electrodes were placed 1 centimetre [cm] apart over the mid belly of the LG. Surface electromyography signals were amplified (1.0 Hz) and filtered (13-1000 Hz) (Model V75-04, Coulbourn Instruments, Allentown, PA) and converted from analog to digital by a 12-bit A/D converter (Model 1401, Cambridge Electronic Design, Ltd., Science Park, Cambridge, UK) and displayed on a computer monitor. Offline quantification was completed using Spike 2 version 5.

**Twitch Contractile Properties.** Contractile properties were elicited percutaneously using an electrical stimulator (Model DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) and a hand-held custom made electrode bar (4 cm length). The peroneal nerve was palpated along the lateral side of the tibial tuberosity of the non-dominant leg. Contractile properties were measured by evoking single twitches at a frequency of 1 Hz with a pulse duration of 100 μs. Stimulation intensity was determined by increasing current intensity until a plateau of m-wave was observed (Figure 1). The stimulation current was then increased 10 % to ensure supramaximal twitch responses. Force and sEMG signals were monitored on a computer screen during each session and quantified offline. Measurements of electrically-induced contractile properties consisted of: peak twitch torque [PT], TPT and HRT (Figure 2). PT, TPT, and HRT were obtained from the average of 8-12 twitch force profiles. M-wave characteristics assessed were latency, motor nerve conduction velocity, and peak to peak amplitude. Latency was measured from the end of the stimulus artefact to
the rising phase of the m-wave. Motor nerve conduction velocity was calculated using the
distance from the centre of the stimulating electrode to the active recording electrode in
metres [m] divided by the latency (in seconds) (Figure 3). M-wave latency, conduction
velocity and peak to peak amplitude data were calculated from the average of 8 - 12 muscle
compound action potentials.

Figure 1. M-wave and twitch growth following successive stimulation of the tibialis anterior.
The top portion of the graph shows the incremental growth and subsequent plateau of the
m-wave, while the bottom portion shows twitch growth and plateau.
**Figure 2.** A single twitch showing Pt (Newton-metre [Nm]), TPT (milliseconds [ms]) and HRT (ms).

**Figure 3.** A single m-wave showing latency (ms) and peak to peak amplitude (V)

*Maximum Voluntary Contraction and Twitch Interpolation.* To assess isometric voluntary strength subjects were instructed to force their toes upwards as hard and as fast as possible (dorsiflexion of the tibialis anterior) and maintain the position for 5 s while
provided with visual feedback from an oscilloscope and strong verbal encouragement (maximum voluntary contraction, [MVC]). To familiarize subjects with this effort three MVCs were performed prior to testing. Subsequently, the interpolated twitch technique was utilized to assess central drive to the TA, where the presence of a superimposed twitch on the force record indicates a lack of motivation or central failure. This technique involves application of a maximal electrical stimulus over the surface of the peroneal nerve prior to, during and after an MVC (Figure 4). This measure was calculated as the torque amplitude from the superimposed twitches ($T_s$) compared with a resting twitch ($T_r$) obtained after the MVC trial:

$$\% \text{ Muscle Activation} = [1 - (T_s/T_r)] \times 100 \quad (A)$$

Figure 4. An MVC effort showing twitch interpolation at positions 1 (reference twitch), 2 and 3 (supramaximal twitches) and 4 (resting post-twitch).
Three MVCs separated by approximately 3 minutes of rest were performed. Force and sEMG signals were monitored on a computer screen during each session and quantified offline. The peak force generated during each MVC trial, in addition to the corresponding muscle activation was calculated and the best attempt was used as the MVC.

**Fatigue Task.** Blood glucose and blood lactate were measured before and at the end of the fatigue protocol as a gross indication of metabolic activity using a blood glucose monitoring system (Appendix C) (Ascencia Contour 7152, Bayer HealthCare LLC, Mishawaka, IN) and a standard blood lactate test metre (Appendix C) (Lactate Pro, Arkray Factory, Inc., Kouka-Gun, Shiga, Japan). The 75 % submaximal intermittent fatigue test was administered via, the subject being instructed with the use of prompts from an oscilloscope to exert a given muscle force with a work to rest ratio of 6 to 4 s, respectively. The protocol involved five, 75 % MVC efforts and one MVC every minute [min] until the end task criterion was met (MVC force decreased to 75 % of muscle force). Consistent, strong verbal encouragement from the experimenter and visual feedback from an oscilloscope were provided to each subject during the fatigue task. The stimulation intensity utilized for the fatigue protocol was the level of optimal tetanic force production. Fused tetanic contractions were obtained by sequentially increasing current intensity and ensuring voltage compliance (200-300 ms) to obtain fused tetanus by delivering a burst of 16-50 μs wide pulses at a rate of one pulse every 20 ms (50-Hz). The tetanic contraction occurred once per each minute cycle. Central drive was assessed using the modified twitch interpolation technique (Connelly et al., 1999), and muscle activity was assessed with sEMG. Electrically-induced contractile properties were obtained from single and double pulses administered at pre-determined times throughout the protocol (Figure 5).
Electrice. Single pulse
Double pulse

One-Minute Cycle

Figure 5. A 75 % submaximal, modified Bigland-Ritchie fatigue protocol showing regions of
stimulation and pulse numbers over a one minute cycle. The cycle was repeated until the
target MVC (shown in black) becomes 75 % of the original force produced in the pre-fatigue
condition. Submaximal 75 % MVC target efforts are shown as grey shaded blocks.

Recovery from Fatigue. Muscle recovery was assessed with electrically-induced
contractile properties, central activation, force and sEMG at 1, 3, 5 and 10 minutes after
fatigue was declared. Each subject was instructed to perform a single 75 % contraction,
MVC and 75 % contraction for 6 s with 4 s of rest separating each contraction (Figure 6).
Figure 6. Depiction of the recovery cycle performed at 1, 3, 5, and 10 minutes post-fatigue. Solid black box represents a 100 %MVC target force, while shaded boxes represent 75 % target force.

Data Analysis. Time to fatigue was noted as the number of fatigue cycles completed until the end-task criterion was obtained (MVC reached 75 %MVC force). Force and sEMG signals were monitored on a computer screen during each session and quantified offline. The peak force generated during each MVC per cycle, in addition to the corresponding muscle activation was calculated and normalized to the first MVC (100 %). Twitch PT, HRT and TPT were normalized to the pre-fatigue values. Surface electromyography signals were full-wave rectified and integrated [iEMG] over 0.5 s intervals for the middle 2 s of the MVC and first 75 % effort after the MVC in each cycle of fatigue and recovery. The MVC and 75 % iEMG for each cycle were normalized to the first MVC performed in the fatigue task.
Statistical Methods

Independent t-tests were utilized to determine differences between persons with Type 2 diabetes and matched controls with respect to the dependent variables of anthropometry (age, weight, waist to hip ratio), activity scores (YPAS), balance confidence (ABC Scale Score, %), balance ability (BBS, out of 56), self-perceived health status, diabetic neuropathy (Monofilament test, out of 10; MNSI, out of 15), walking ability (TUG score, 4m walk score, SPWT score), exercise score (STEP score), HbA1c (%), blood glucose (millimoles per litre, [mmol/L]) and lactate (mmol/L). As well t-tests were conducted on baseline measures of twitch contractile properties at baseline (PT, TPT, HRT), MVC, central activation and m-wave measures (latency, conduction velocity, peak to peak amplitude).

Dependent variables of contractile properties, force, central drive and iEMG from the fatigue task were compared between T2D and controls with two-way (2 groups x 7 levels) analysis of variance [ANOVA] tests. Comparisons were made for the start, middle, and end of fatigue and at 1, 3, 5 and 10 minutes post fatigue.

Linear regression analysis was conducted to determine the strength of the relationship between resting blood glucose and HbA1c, HbA1c and conduction velocity, PT compared to TUG score and fast pace STEP predicted VO₂ max compared to MVC scores in persons with T2D and healthy individuals.
CHAPTER IV
ANALYSIS OF RESULTS

Physical Performance and Health Related Questionnaires

Six women (50 ± 5 years) and 8 men (54 ± 6 years) with diagnosed T2D, as well as a group of healthy age, gender and activity matched women (6; 50 ± 7 years) and men (4; 55 ± 4 years) served as control in this study. Age, weight, height and waist to hip ratio were similar between T2D and control (Table 2). Persons with T2D had significantly higher blood glucose (8.33 ± 2.21 mmol/L, P=0.001) and HbA1c (8.4 ± 1.3 %, P= 0.00002) levels compared with the control group (5.50 ± 0.95mmol/L; 6.1 ± 0.4 %). Persons participating in this study were living with diagnosed T2D ~5.2 ± 4.4 years. Only one participant (living with T2D) was a smoker. Ninety-three percent of the diabetic persons considered themselves as overweight, whereas all of the controls believed they were overweight. Physician diagnosed hypertension (43 %) and hypercholesterolemia (71 %) were prominent in T2D. However, in the controls 20 % reported hypertension and hypercholesterolemia. There were no reports or indication of foot ulceration at the time of the study, and 86 % of the T2D subjects reported a next of kin (parent, grandparent, and sibling) history of diabetes. Sixty-four percent of T2D subjects reported metformin as the primary method of glucose control while 21 % used insulin, and 14 % utilized dietary modifications (Table 2).
Table 2. Anthropometric data of subjects with T2D and control individuals. Values are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T2D</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.6 ± 6.2</td>
<td>51.7 ± 6.9</td>
<td>0.73</td>
</tr>
<tr>
<td>Weight (kilogram [kg])</td>
<td>102.0 ± 18.6</td>
<td>99.2 ± 18.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.6 ± 12.0</td>
<td>170.4 ± 6.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>0.94 ± 0.09</td>
<td>0.92 ± 0.07</td>
<td>0.47</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>8.33 ± 2.21</td>
<td>5.50 ± 0.95</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 ± 1.3</td>
<td>6.1 ± 0.4</td>
<td>0.00002</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>5.2 ± 4.4</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Smoker</td>
<td>n=1</td>
<td>n=0</td>
<td>n/a</td>
</tr>
<tr>
<td>Weight perception</td>
<td>n=13</td>
<td>n=10</td>
<td>n/a</td>
</tr>
<tr>
<td>Overweight</td>
<td>n=0</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>n=1</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Healthy Weight</td>
<td>n=0</td>
<td>n=0</td>
<td></td>
</tr>
<tr>
<td>Hypertension (physician diagnosed)</td>
<td>n=6</td>
<td>n=2</td>
<td>n/a</td>
</tr>
<tr>
<td>Hypercholesterolemia (physician diagnosed)</td>
<td>n=10</td>
<td>n=2</td>
<td>n/a</td>
</tr>
<tr>
<td>Foot Ulcers</td>
<td>n=0</td>
<td>n=0</td>
<td>n/a</td>
</tr>
<tr>
<td>Family History of T2D (next of kin)</td>
<td>n=12</td>
<td>n=1</td>
<td>n/a</td>
</tr>
<tr>
<td>Primary medications for T2D control</td>
<td>n=9</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Metformin</td>
<td>n=3</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>n=2</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Blood glucose had a weak negative relationship to conduction velocity (Figure 7), while HbA1c was not related to conduction velocity (Figure 8). Blood glucose and HbA1c showed a good positive relationship (Figure 9).

![Graph showing the relationship between conduction velocity and resting blood glucose. The line of best fit equation is provided: y = -0.0533x + 10.747 with R² = 0.1573.](image)

Figure 7. The relationship between conduction velocity and resting blood glucose.
Figure 8. Conduction velocity related to glycosylated haemoglobin.

![Graph showing the relationship between conduction velocity and glycosylated hemoglobin](image)

\[ y = -0.0083x + 7.9918 \]
\[ R^2 = 0.0089 \]

Figure 9. Glycosylated haemoglobin related to resting blood glucose levels.

![Graph showing the relationship between glycosylated hemoglobin and pre-exercise blood glucose](image)

\[ y = 0.4363x + 4.3098 \]
\[ R^2 = 0.4412 \]
The control and diabetes groups were similar in total weekly energy expenditure (P=0.37), number of hours of daily activities performed (P=0.45), number of flights of stairs climbed (P=0.43) and average walking speed (P=0.37). Stair climbing time from the STEP exercise test was similar between groups (P=0.93) and the resting heart rate and post heart rate response for the normal (P=0.73) and fast (P=0.40) stepping task did not differ (Table 3). In both groups heart rate increased significantly from rest for the normal and fast paced exercise tasks (T2D normal p=7.5 x 10^{-11}, fast p=7.5 x 10^{-10}; Control normal p=7.9 x 10^{-5}, fast p=5.4 x 10^{-4}) indicating the cardiovascular system was challenged.

Persons with diabetes had significantly lower (P=0.03) functional balance scores (53.1 ± 1.8) compared with the controls (54.6 ± 1.1), yet the perception of personal confidence in balancing (ABC scale) was similar between groups. Even though the people with T2D showed no difference in the majority of the performance tests, data from the SF-36 showed that they perceived their health to be worse than controls in terms of how their emotional and physical health have affected their social roles (family, work, friends). Overall, persons with diabetes had poorer scores reflective of their emotional and general health (Table 4). On a 10 point scale, persons with T2D scored 7.0 ± 2.4 for the DSES, which measures confidence with respect to the education they received from clinicians and educators in caring for their health (Table 4). Both T2D subjects and controls received low neuropathy screening scores, indicating an unlikely presence of neuropathy (MNSI) or neuropathy of the peroneal nerve (monofilament score) (Table 4).
Table 3. Functional mobility, balance and daily activity scores. Values are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>T2D</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Expenditure (kcal/week)</td>
<td>9098.6 ± 10101.2</td>
<td>6113.6 ± 2313.4</td>
<td>0.37</td>
</tr>
<tr>
<td>Activity Score (hours/week)</td>
<td>37.6 ± 41.2</td>
<td>27.2 ± 10.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of Flights Climbed</td>
<td>8.7 ± 6.2</td>
<td>6.7 ± 5.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Resting heart rate (BPM)</td>
<td>73.0 ± 9.3</td>
<td>72.6 ± 11.7</td>
<td>0.93</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>9.6 ± 2.1</td>
<td>8.9 ± 1.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Berg Balance Scale (/56)</td>
<td>53.1 ± 1.8</td>
<td>54.6 ± 1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Stair Time (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Pace</td>
<td>84.0 ± 14.0</td>
<td>80.4 ± 28.8</td>
<td>0.69</td>
</tr>
<tr>
<td>Fast Pace</td>
<td>59.0 ± 10.8</td>
<td>54.5 ± 12.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Post-Exercise HR (BPM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Pace</td>
<td>118.1 ± 13.7</td>
<td>120.5 ± 18.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Fast Pace</td>
<td>127.9 ± 16.6</td>
<td>135.7 ± 23.3</td>
<td>0.40</td>
</tr>
<tr>
<td>Predicted Submaximal V0₂ (mL/kg/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Pace</td>
<td>25.3 ± 4.4</td>
<td>27.3 ± 6.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Fast Pace</td>
<td>30.9 ± 5.0</td>
<td>33.2 ± 2.4</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Table 4. Health related questionnaire scores. Values are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>T2D</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC Scale Score</td>
<td>88.2 ± 15.2</td>
<td>89.5 ± 13.0</td>
<td>0.83</td>
</tr>
<tr>
<td>SF-36 (%) Role Limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional problems</td>
<td>69.0 ± 40.2</td>
<td>100 ± 0</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical Health</td>
<td>54.8 ± 41.6</td>
<td>92.5 ± 16.9</td>
<td>0.01</td>
</tr>
<tr>
<td>SF-36 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Well-being</td>
<td>74.6 ± 21.0</td>
<td>91.2 ± 5.9</td>
<td>0.02</td>
</tr>
<tr>
<td>General Health</td>
<td>53.2 ± 18.5</td>
<td>76.5 ± 16.5</td>
<td>0.004</td>
</tr>
<tr>
<td>DSES</td>
<td>7.0 ± 2.4</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>MNSI (/15)</td>
<td>4.5 ± 1.7</td>
<td>4.1 ± 2.1</td>
<td>0.62</td>
</tr>
<tr>
<td>Monofilament Score (/10)</td>
<td>9.8 ± 0.4</td>
<td>9.9 ± 0.17</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Isometric Muscle Strength: Voluntary and Involuntary Components

Twitch contractile properties and muscle strength were similar between persons with T2D and controls and both groups were equally able to activate the TA muscle (Table 5). M-wave latency, conduction velocity and peak to peak amplitude were similar between groups, indicating no change in peroneal nerve function or alterations in contractile properties as a result of hyperglycaemia for these persons with T2D compared to controls (Table 5).
Table 5. Voluntary and involuntary force results for persons with T2D compared to matched controls. Values are represented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>T2D</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Twitch Contractile Properties</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Torque (Nm)</td>
<td>4.1 ± 1.5</td>
<td>3.9 ± 1.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Time to Peak Torque (ms)</td>
<td>94.8 ± 11.3</td>
<td>100.3 ± 13.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Half-relaxation time (ms)</td>
<td>114.5 ± 22.9</td>
<td>105.8 ± 20.0</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>M-wave</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>0.003 ± 0.001</td>
<td>0.002 ± 0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Conduction Velocity (m/s)</td>
<td>63.1 ± 17.5</td>
<td>73.6 ± 14.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Peak to Peak Amplitude (V)</td>
<td>1.7 ± 2.0</td>
<td>0.85 ± 0.24</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>MVC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Torque (Nm)</td>
<td>39.6 ± 9.6</td>
<td>34.3 ± 7.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Central Activation (%)</td>
<td>98.8 ± 3.4</td>
<td>100.0 ± 0</td>
<td>0.26</td>
</tr>
<tr>
<td>Twitch: MVC ratio (Torque)</td>
<td>0.11 ± 0.03</td>
<td>0.12 ± 0.04</td>
<td>0.43</td>
</tr>
</tbody>
</table>

A series of regressions were completed between functional mobility scores (BBS, TUG, STEP) compared to MVC strength and PT. TUG scores and PT showed a positive relationship in control ($R^2=0.6964$) but not T2D ($R^2=0.011$) groups (Figure 10). As well, STEP Predicted Submaximal $V_{O2}$ (fast pace) and MVC showed a negative relationship in control ($R^2=0.6745$) but not in T2D ($R^2=0.0081$) groups (Figure 11).
Figure 10. Relationship between TUG score and twitch PT. Data for T2D shown as shaded circles and control as unfilled triangles.

Figure 11. Relationship between STEP Predicted Submaximal VO₂ (fast pace) and MVC. Data for T2D shown as shaded circles and control as unfilled triangles.
**Muscle Fatigue**

Pre-exercise glucose (8.3 ± 2.2; 5.5 ± 0.9 mmol/L) and post exercise glucose levels (7.7 ± 2.0; 5.2 ± 0.9 mmol/L) were significantly different (P=0.001; P=0.001) between T2D and controls, albeit the magnitude of the increase in blood glucose was similar between groups (P=0.72). Pre-exercise blood lactate (3.8 ± 5.1; 2.2 ± 1.1 mmol/L) and post-exercise blood lactate (4.6 ± 5.3; 2.2 ± 1.3 mmol/L) did not differ between groups (P=0.33; P=0.16), and increased in the T2D group but not in the control group after the fatigue task. The magnitude of change in blood lactate was not different between groups (P=0.72) (Table 6).

**Table 6.** Submaximal fatigue time to failure and gross estimates of metabolic change. Each value represents the mean plus standard error bars.

<table>
<thead>
<tr>
<th>Measure</th>
<th>T2D</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue Time (minutes)</td>
<td>4.9 ± 2.5</td>
<td>7.9 ± 5.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Blood Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>8.3 ± 2.2</td>
<td>5.5 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>7.7 ± 2.0</td>
<td>5.2 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Total change (decrease)</td>
<td>0.61 ± 0.88</td>
<td>0.27 ± 0.72</td>
<td>0.31</td>
</tr>
<tr>
<td>Blood Lactate (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>3.8 ± 5.1</td>
<td>2.2 ± 1.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>4.6 ± 5.3</td>
<td>2.2 ± 1.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Total change (increase)</td>
<td>0.78 ± 7.14</td>
<td>0.01 ± 1.03</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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Time to fatigue ranged 2 – 11 minutes for T2D, and 3 – 20 minutes for controls (Figure 12). The average duration of the fatigue task was slightly longer in the control group (p=0.07) (7.9 ± 5.1 minutes) compared with T2D (4.9 ± 2.5 minutes) (Table 6).

Figure 12. MVC force achieved during the fatigue exercise over time, expressed as a percentage of the pre-fatigue MVC. Performance of persons with T2D is shown as solid lines and control group as dotted lines.

Central activation did not differ between groups, and was near maximal for the duration of the fatigue protocol (Figure 13). Although force decreased significantly by the middle of the fatigue task (85 %) and slightly more by the end of the task (77 %) it was similar between groups. Force did not recover in either group to the pre-fatigue values 10
minutes after the exercise bout (Figure 13).

**Figure 13.** MVC performance and muscle activation (central drive) over time during the fatigue and recovery tasks. The MVC force (Nm), was normalized to the MVC obtained prior to fatigue and expressed on a time scale as start or pre- (0), middle (50) and end (100). The recovery phase is shown in minutes at 1 (R1), 3 (R3), 5 (R5) and 10 (R10) minutes post-fatigue declaration. Each value represents the mean plus standard error bars. The top lines represent central drive while the bottom lines represent the normalized MVC force (* represents a statistically significant difference from pre-fatigue, where P<0.05).

Peak torque was significantly different from pre-fatigue at the middle and end, and declined to approximately 58 % midway through the fatigue task (P<0.05), although it did not fall significantly between the middle to the end of the fatigue task. At 10 minutes post-
fatigue, there was a significant recovery of twitch PT to approximately 75% of the pre-fatigue value (Figure 14).

![Graph showing Twitch Peak Torque (% Pre Fatigue) over time for Diabetes and Control groups.](image)

**Figure 14.** Single twitch peak torque (Nm) performance during fatigue and recovery for the T2D and control groups during the fatigue and recovery tasks. All Pt values obtained were normalized to the pre-fatigue peak torque. Each value represents the mean plus standard error bars. *Indicates significant difference from pre-fatigue. T2D differed from controls significantly along the fatigue and recovery tasks.

Over the duration of the fatigue task contractile properties did not slow. TPT was similar between groups for the fatigue and recovery tasks. At 5 and 10 minutes post-fatigue, TPT was significantly shorter than the pre-fatigue value (approximately 88 and 85%, for 5 and 10 minutes, P>0.05) (Figure 15). HRT was similar between groups during the fatigue and recovery task (Figure 16).
Figure 15. Single twitch time to peak torque (ms) values for the T2D and control groups during the fatigue and recovery tasks. All TPT values obtained were normalized to the pre-fatigue peak torque. Each value represents the mean plus standard error bars. * Represents significant difference (P<0.05) from pre-fatigue value.
Figure 16. Single twitch half-relaxation time (ms) values for the T2D and control groups during the fatigue and recovery tasks. All HRT values obtained were normalized to the pre-fatigue peak torque. Each value represents the mean plus standard error bars.

* Represents significant difference (P<0.05) from pre-fatigue value.

Integrated electromyography was similar between the T2D and control groups. Submaximal iEMG increased significantly during the fatigue protocol and remained elevated from pre-fatigue values for the 10 minutes of recovery. Maximal iEMG was similar between groups and did not change for the fatigue task, yet there was a slight decline in both groups during recovery (Figure 17).
Figure 17. iEMG expressed as a percentage of the pre-fatigue MVC. The top lines represent the iEMG obtained for the 100 % MVC performance during the fatigue and recovery protocol and the bottom lines represent the 75 % MVC iEMG normalized to the pre-fatigue MVC iEMG. Each value represents the mean plus standard error bars. * Represents significant difference (P<0.05) from pre-fatigue value.
CHAPTER V

DISCUSSION

Subjects and Recruitment

This is the first case-control investigation to measure isometric contractile properties and relate muscle strength and contractile activity to functional mobility in persons with T2D. In addition to characterization of the above mentioned properties in persons with T2D, the specific objectives of this study were to compare these findings to a control group of non-diabetic persons who were matched for both physical attributes and physical activity levels. Age, gender, body size and physical activity are strong factors in functional mobility and strength (Kent-Braun et al., 2002; Wolfson et al., 1995; Yerdelen et al., 2006), yet very few studies match for age and gender (Corriveau et al., 2000; Meier et al., 2001) and no study of persons with T2D has considered physical activity a key factor in muscle performance or functional mobility. In conjunction with the standard series of questionnaires utilized in clinical studies, functional mobility, balance, and cardiorespiratory function were assessed with objective laboratory tests.

Initially, a proposed objective was to investigate two groups of persons with T2D; those with peripheral neuropathy and those without neuropathy. This would have enabled the independent effect of neuropathy to be assessed with respect to neuromuscular properties and functional mobility in persons with T2D. However, no persons with neuropathy volunteered for this study. It was extremely challenging to recruit T2D volunteers to participate in this study; highlighting the importance of hospital and clinic investigators in becoming involved with university research, and indicating poor community
relationship and interest with research in this particular region. Interestingly, all of the persons who volunteered to participate in this project were "healthy" diabetics with extreme interest in understanding their condition and prolonging function. Despite numerous and various tactics to "excite" potential volunteers, or evoke interest in the community, a number of attempts to recruit volunteers (Table 1) failed to attract more than twenty persons with T2D over a one year period in the Windsor-Essex region. This may be related to the lack of direct university interaction with a clinical hospital or endocrinology specialists. Most studies on contractile and neural function in persons with T2D have been conducted in clinical research hospitals (e.g. Andersen et al., 1997, 1998, 2004a, 2004b; Corriveau et al., 2000).

All volunteers of the T2D population studied were free from neuropathy (Table 4) as determined by self-report based upon physician consultation as well as standardized questionnaires and physical screening (Feldman et al., 1994; Valk, De Sonnaville, Van Houtum, Heine, Van Eijk, Bouter et al., 1997). Determination of health history, daily and physical activity, resting heart rate and predicted submaximal VO2 (Table 3) also established that the T2D and control groups did not differ and because the controls were representative of others in their general age category in terms of mobility speed (Podsiadlo & Richardson, 1991), physical activity scores, resting heart rate (King, Everett, Mainous, & Liska, 2006), and predicted submaximal VO2 (Petrella, Koval, Cunningham, & Paterson, 2003) we can infer that the T2D were also 'healthy' outside the diabetic state. Moreover, the significant difference in HbA1c and glucose between groups and the mean (8.4 ± 1.3 %; 8.33 ± 2.21 mmol/L, T2D and 6.1 ± 0.4 %; 5.50 ± 0.95 mmol/L, controls) data are similar to
standardized values for T2D diagnosis (CDA, 2007) substantiates that one group was healthy T2D and the other healthy age, gender and activity matched controls.

**Strength and Physical Function**

Although the persons with T2D had higher baseline blood glucose levels and HbA1c levels (Table 6), they performed similarly in tests of isometric strength and retain the ability to maximally activate the TA when sufficient practice is given (Jakobi *et al.*, 2001). Irrespective of the condition of diabetes, the muscle strength data in this study was similar to prior reports in the dorsiflexors (Vandervoort & McComas, 1986). As well, twitch contractile properties, peroneal nerve conduction velocity, and m-wave profiles were similar between groups and comparable to the literature. Because electrically induced contractile properties provide a strong indication of fibre type (Gorelick & Brown, 2007) and an indirect assessment of Ca²⁺ dynamics during the cross bridge cycle (McComas, 1996) it is highly unlikely that hyperglycaemia has induced fibre type or contractile function adaptations in this healthy group of T2D subjects. Neuromuscular junction activity also seems to be unaltered at this stage of diabetes, as evidenced by similar m-wave peak to peak amplitude. Since human studies on contractile function are sparse, a continuum of change due to disease progression is not possible. The data describing personal attributes of this particular group of individuals suggests that they collectively represent “active” and “healthy” people (Table 3, 4 & 5) at the beginning of the disease continuum considering the age of diagnosis, HbA1c and glucose levels (Table 2). Thus, this study is the first to quantify contractile measures in the early state of T2D. In order to clearly establish the progressive, but deleterious effect of hyperglycaemia, it is necessary to conduct a long-term
study where contractile properties are monitored from diagnosis through loss of functional independence.

Strength data from this study might differ from prior studies due to the stage of disease progression at the time of study, as strength studies have investigated individuals that are neuropathic and/or older adults. Van Schie, Vermigli, Carrington, & Boulton, (2004) observed a decrease in strength in neuropathic individuals, compared to controls and others have reported differences between neuropathic and non-neuropathic individuals (Andersen et al., 1997; Andreassen, Jakobsen, & Andersen, 2006). It also seems that many studies have included groups of older neuropathic individuals; this leads to the question of whether the natural physiological process of aging exacerbates the deleterious effect of hyperglycaemia reported in the animal literature (Cameron et al., 1992; Fahim et al., 1998; McGuire et al., 2001) and in extreme states where glucose is ill-controlled (Resnick et al., 2002). Had healthy older adults (less than 75 years) with T2D been assessed the possible interrelationship between the diabetic condition and natural aging might have been possible to clarify. Moreover, differences between this study and others might have occurred due to the isometric measures of strength. Most studies utilize manual muscle testing (Van Schie et al., 2004), grip tests (Sayer et al., 2005) or isokinetic dynamometry (Andersen et al., 1997, 1998; Andreassen et al., 2006; Park, Goodpaster, Strotmeyer, De Rekeneire, Harris, Schwartz et al., 2006) to assess muscle strength. Isometric force measures and utilization of the twitch interpolation technique facilitates the study of an isolated muscle where minimal equipment is required and the movements are readily learned and executed (Jakobi et al., 2001). Manual muscle testing, hand dynamometry and isokinetic measures of strength are subjective measures that are
dependent upon whole body extrapolation. Furthermore, it is difficult to establish when maximal performance has been learned and attained.

Physical activity was carefully monitored and matched between T2D and controls. Although a few studies have matched for age and gender (Corriveau et al., 2000; Meier et al., 2001), no study to date has matched for physical activity. This is an important task as strength and mobility are related to physical activity, and a major determinant of functional mobility differences may be accounted for by participation in daily activity or exercise (DiPietro et al., 1993). When daily physical activity is matched, muscle strength was not different between persons with T2D and non-diabetic controls, indicating that the diabetic condition does not result in muscle weakness.

The human literature is unclear with respect to the relationship between conduction velocity and hyperglycaemia. Ørskov, Worm, Schmitz, Mengel, & Sidenius (1994) observed conduction velocity slowing, whereas Cappellari, Airaghi, Capra, Ciammola, Branchi, Levi-Minzi et al. (2005) observed no remarkable changes in conduction velocity. In this study, neither blood glucose (Figure 7), nor HbA1c (Figure 8) were found to be well correlated with peroneal nerve conduction velocity. The relationship may have escaped detection in this study because the magnitude of change in peroneal nerve conduction velocity is significantly greater in individuals with HbA1c greater than 8.5 % (Huang, Chen, Weng, Lee, Tseng, & Huang, 2005). The glucose and HbA1c levels in the T2D groups were less in this study compared to others where relationships with conduction velocity have been observed. It is likely that detectable differences in peroneal nerve function occur in association with the onset of neuropathies due to chronic hyperglycaemia, because
studies that include neuropathic individuals report difference in peroneal nerve function (Resnick et al., 2002). Thus, when glucose is carefully controlled peroneal nerve activity is not altered due to hyperglycaemia; rather alterations in conduction velocity are associated with development of neuropathies secondary to the diabetic condition.

These groups were well matched for all aspects of physical performance, daily activity, and exercise participation, but functional balance was lower in T2D (53.1 ± 1.8) compared with the controls (54.6 ± 1.1). Albeit a significant difference exists between the groups, both scores are high (scored out of 56) suggesting no balance deficits (Powell & Myers, 1995). Although balance was still good, the difference noted in the diabetic group could be indicative of an early decline in neural function or blood flow prior to the outward presence of foot ulcerations or loss of sensation because perception of balance confidence did not differ between groups (Table 4). It has been found that posture, gait and balance change in both T2D and T1D (free from neuropathy) (Nicholson, King, Smith, & Darlington, 2002) possibly due to changes in the vestibulo-ocular and opto-kinetic reflex (Petrofsky et al., 2004; Petrofsky, Lee, Macnider, & Navarro, 2005a; Petrofsky, Lee, & Cuneo, 2005b). It is known that balance is modulated by musculoskeletal, visual and vestibular networks and because strength and contractile properties were similar between groups it is highly unlikely that the loss of balance in these persons with T2D was due to musculoskeletal adaptations. No finite tests were conducted on the vestibular and visual system but, a few volunteers (4 with T2D) used corrective lenses, however, it is unknown when use of corrective lenses began. It is unknown, and difficult to elucidate in most instances whether the reason for wearing corrective lenses was related to T2D, but it is known that T2D may be manifested in secondary disease of the ocular system.
Regression analysis revealed a relationship between PT and TUG walking speed for controls ($R^2=0.6964$), yet in the T2D group there was virtually no association ($R^2=0.011$). Similarly, a relationship between predicted VO$_2$ max from fast paced stepping was related to MVC in controls ($R^2=0.6745$), but was unrelated in the T2D group ($R^2=0.0081$). It is possible that knowledge of having a disease translates to performance that is impacted by self-perception or confidence (Stewart, Turner, Bacher, DeRegis, Sung, Tayback et al., 2003). The individuals with T2D reported poorer perceptions of their health compared to controls (Table 4). Because VO$_2$ max and walking speed on the TUG are subjective to each individuals effort it is possible that the T2D group did not reach peak values because of a conviction that their physical/emotional health limited performance, whereas the attainment of maximal on the subjective measure of performance resulted in a strong relationship with objective measures of contractile function (PT, isometric strength) in the non-diabetic group.

**Muscle Fatigue**

Clinical reports from patients not only suggest muscle weakness but also fatigue (Adriaanse, Dekker, Spijkerman, Twisk, Nijpels, Van der Ploeg, et al., 2005). To-date no study has assessed muscle fatigue and recovery in T2D. In this study T2D and control subjects underwent a modified isometric submaximal fatiguing exercise. This fatigue protocol which utilizes a 6:4 work to rest ratio has been employed for the study of muscle endurance in disease elsewhere (Jakobi et al., 2001). However, for this study the work level was increased to 75 %, rather than utilizing the traditional 50 % (Bigland-Ritchie, Furbush, & Woods, 1986). A higher intensity was chosen because the phosphagen and anaerobic energy systems are primarily utilized for short duration intense activity, thus the
contributions from aerobic metabolism; albeit active, were less in a 75 % work intensity protocol compared with the traditional 50 % protocol. It was necessary to minimize aerobic production of ATP because glucose levels are substantially higher in T2D compared with controls, thus the effect of the aerobic system whereby carbohydrates are the primary source of energy would have created an artificial ‘carbohydrate loaded’ condition. Pilot studies indicated time to fatigue for the 50 % work intensity was 20-30 minutes, whereas for the 75 % condition pilot data suggested time to fatigue would be 50 % less (8-12 minutes), and the intensity was of sub-maximal level that would be tolerated by volunteers. The neuromuscular components assessed during the fatigue protocol were voluntary force, twitch interpolation, twitch contractile properties and muscle activity through surface iEMG. Recovery was also studied through the utilization of identical measures to the fatigue task in order to understand the re-establishment of homeostatic set-points in the diseased versus the control group.

When exposed to an acute bout of a fatiguing exercise, the groups performed similarly with respect to time to fatigue (4.9 ± 2.5 min T2D; 7.9 ± 5.1 control) at the same relative work intensity. Maximal activation was assessed for the entire duration of the fatiguing exercise with the twitch interpolation technique and central drive was maintained in both groups. As suggested by these data, the decline in force was not due to an inability to perform an MVC in either group. Collectively, the data from this study does not support clinical reports of fatigue in persons with T2D. It is possible that due to the anaerobic nature of the fatigue protocol, the mechanism whereby fatigue occurs earlier in the diabetic group was circumvented. Furthermore, fatigue might be due to alterations in aerobic metabolism. The T2D group had higher pre- and post-exercise glucose levels compared to
controls, but the magnitude of change from pre to post fatigue was similar between groups. This suggests that the ‘carbohydrate’ contribution to aerobic metabolism was similar between groups. Because differences occur in specific enzymatic function at various steps in biochemical pathways which are influenced by glucose concentrations it is plausible that aerobic function may change in T2D (Bouché, Serdy, Kahn, & Goldfine, 2004). The magnitude of change for pre and post-exercise blood lactate did not differ between groups (P=0.72), but it seems that the change was ‘observably’ greater in T2D, possibly indicating a greater emphasis on anaerobic metabolism. Since the limiting factor in aerobic metabolism is oxygen availability, the trend to greater lactate production could be indicative of limited oxygen perfusion in muscle, while this limitation may be consequent to early systemic microvascular changes (Rask-Madsen & King, 2007). Overall, these ‘gross’ metabolic measures suggest that future studies should assess muscle fatigue in persons with T2D and compare between aerobic and anaerobic exercises. These comparisons might elucidate the mechanism to support the clinical reports of fatigue in persons with T2D.

Twitch tension decreased to ~50 % in both groups, and this rate of decline was similar between groups, and to studies of women with Addison’s Disease or older adults (Jakobi et al., 2000; 2001). Changes in contractile timing were similar between groups, but slowing did not occur during the fatigue protocol. It is likely that slowing was not present in this study because the duration of the fatigue protocol was too short to induce contractile slowing of the twitch; however, had tetanic force been studied contractile slowing might have been evident. Twitches are less reliable (ICC 0.83) and much more affected by fatigue than higher frequency responses (ICC 0.95) and thus 50 Hz contraction times are often
utilized to assess rates of whole muscle activity (Edwards, Hill, Jones, & Merton, 1977; Wiles, Young, Jones, & Edwards, 1979). An attempt to measure 50 Hz tetanic contractions was made; however due to technical difficulty in maintaining consistent electrode placement, the contractile responses were unpredictable. This was determined by monitoring of stimulus artefact and electrical EMG responses. Overall, stimulated contractile measures indicate that Ca$^{2+}$ kinetics through the cross-bridge cycle and fibre composition are unaltered in humans, as a consequence of hyperglycaemia. The animal literature is equivocal with respect to fibre type changes (Fahim et al., 1998; McGuire et al., 2001) but it seems that the more heterogeneous a muscle the less apt it is to change proportion as a result of induced diabetes (Cameron et al., 1992).

Muscle activity was characterized by surface iEMG, and did not differ between groups over the duration of the fatigue protocol. Consistent with other intermittent isometric fatigue studies (Bigland-Ritchie et al., 1986; Jakobi et al., 2000; 2001) submaximal iEMG increased and maximal iEMG remained relatively constant during the fatiguing exercise. This rise in submaximal iEMG is the result of motor unit recruitment and increases in discharge rate (Conwit et al., 2000). Although both groups of subjects demonstrated this increase in submaximal iEMG it is known that at some point during a fatigue continuum submaximal iEMG will meet maximal iEMG (Bigland-Ritchie et al., 1986; Jakobi et al., 2000; 2001) and this is the point of physiological muscle 'exhaustion'. The T2D group and control group did not reach this point; however, the increase in the submaximal iEMG corresponds to the end-point of force loss (~80%).
There are no reports in the literature with respect to recovery subsequent to a fatiguing exercise in persons with T2D. These data suggest that when force decline is similar there is no difference in rate of recovery between persons with T2D and age, gender and activity matched controls. However, in this middle-aged group of men and women voluntary force production remained significantly depressed at 10 minutes post-fatigue. It is likely that lack of recovery may be partially attributed to muscle drive. Although, central drive as assessed with the twitch interpolation technique indicated that the muscle was fully active, the maximal iEMG suggested that neural activity was slightly depressed during recovery. Overall, the diminutive disparity between the central activation data and the iEMG data can be accounted for by the twitch interpolation data reflecting a very brief moment (~0.5 s) of the MVC, whereas the EMG measures were averaged over the duration of the 6 s contraction.

Together, these results indicate that when persons with T2D are age, gender and physical activity matched to control subjects muscle strength, contractile function and fatigue is unaltered. On the other hand, these persons experience psychosocial or emotional consequences of being "diseased" as evidenced through self-report. Evidence from this study serves to highlight the importance of preventing secondary disease progression associated with chronically high levels of blood glucose. Functional deficits that have been reported previously in the literature (Dolan, Liu, Criqui, Greenland, Guralnik, Chan et al., 2002; Gregg, Mangione, Cauley, Thompson, Schwartz, Ensrud et al., 2002; Volpato, Blaum, Resnick, Ferrucci, Fried, & Guralnik, 2002) may be linked to poor glycaemic control that results in secondary diseases (i.e. neuropathies) over time, or functional decline may be exaggerated by the complex interplay of the physiological
process of aging. This study clearly measured strength and function in non-neuropathic adults prior to an age where physiological changes of aging would be of primary concern (McNeil et al., 2005). This study purports that clinical self-reports of muscle weakness, fatigue and functional decline are likely related to the psychological impact of diagnosis of a ‘disease’. In such cases, it is critical that these people receive accurate feedback on their disease from practitioners in addition to appropriate social support. The issue is not denying the condition exists, but focusing and conveying that impaired glucose control in itself does not indicate immediate functional change and that persons with T2D are as ‘able’ as non-diabetic age, gender and activity matched controls. These results are good news for those individuals who are challenged with glucose management.

Conclusions

This study represents the first attempt to incorporate measurements of isometric contractile properties, strength, functional mobility and fatigue in persons with T2D, who are age, gender and activity matched to controls. To-date there has been no attempt to utilize physical activity as a component of subject matching. Because, exercise and physical activity are an integral component of muscle strength (Dreyer, Schroeder, Hawkins, Marcell, Tarpenning, Vallejo et al., 2006) and functional mobility (Scott, Votora, Scanlan, & Close, 2007) extreme care was taken with subject matching. Unlike many other studies conducted on persons with T2D, results from this experiment indicate that when activity is accounted for muscle strength and fatigue are not reduced as a consequence of hyperglycaemia. This study provides a key example of the need to assess physical activity
when alterations in strength and physical function are being evaluated with respect to a pathological condition.

The unique aspect of this study were the combined utilization of objective physical performance and muscle function tests with subjective measures of functional mobility, performance and health perception, in a group of relatively healthy, well-controlled persons with T2D. The combination of assessment of health perception with quantitative performance tests enabled elucidation of information with respect to how individuals who perceive their health negatively, have lower scores on subjective performance tests but do not differ from age, gender and activity matched controls on objective physical function tests that control for motivation and effort (twitch interpolation, twitch contractile properties). This work serves to highlight the importance of how disease perception can negatively impact physiological function. Moreover, these data elucidate the necessity and importance of early detection, glucose regulation and exercise adherence. When these are occur persons with T2D do not differ from age, gender and activity matched non-diabetic persons. This work underlines the need for clinicians to convey to persons with T2D, that this is not a debilitating disease, as long as glucose is controlled through physical activity in conjunction with standard pharmacological and diet manipulation techniques. The impact of health-perception and emotion on subjective physical function should not be underestimated, and thus reports of fatigue and weakness should be considered in conjunction with self-perception of health.

Although there were no significant differences between T2D and controls, the overall message of these results is not only very important for clinicians but persons who live with
T2D. Both populations should not underestimate how perceptions of health and exercise, influence physiological function. While the trend of most disease related studies is to focus on the critically affected to reveal significant changes from the healthy condition, and oftentimes the outcome message is negative, yet the impact of this study from well-managed individuals is inverse, and should not be underestimated. Hence, this study enables persons with T2D with a positive message of the benefit of exercise and glucose control.

Considerations for Future Research

1. Future studies should consider evaluating physical function and strength in conjunction with perceptions of health in persons with T2D who are neuropathic and in a group who undertake regular exercise at moderate to intense levels to understand the extent that neuropathy effects strength and function before the onset of age-related changes, and whether individuals who exercise are much different from individuals who perform moderate to little exercise (exemplified in this study).

2. A questionnaire with respect to self-perception of muscle fatigue and weakness needs to be developed and evaluated in conjunction with any future tests of muscle function or strength so that a direct link between self-perceived ability and objective measures of function can be made.
3. A study to assess physical function, strength and nerve function in healthy persons without T2D who are subjected to glucose infusion to observe the acute effects of hyperglycaemia.

4. Since motor unit function is critical to force modulation, a study evaluating discharge rates and recruitment during isometric force production in middle-aged neuropathic individuals with T2D might reveal whether losses in strength reported elsewhere are due to inherent changes to the motor unit when age is not a factor.

5. The results of this study suggest that individuals who have T2D do not fatigue differently when exposed to an anaerobic fatigue task, yet a common report in T2D along with weakness is fatigue. An aerobic 50% submaximal intermittent fatigue protocol would be useful for comparison with this study and enable determination of muscle fatigue due to metabolic alterations that are inherent to T2D (i.e. glucose which is the primary substrate for aerobic metabolism).
REFERENCES


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APPENDICES

Appendix A. Research Ethics Approval, Consent and Information Forms

Today's Date: October 12, 2005
Principal Investigator: Ms. Lynette Singh
Department/School: Kinesiology
REB Number: 05-146
Research Project Title: Characterization of neuromuscular properties: functional mobility and fatigue in persons with Type 2 Diabetes mellitus
Clearance Date: October 12, 2005
Project End Date: July 31, 2006
Progress Report Due: July 31, 2006

This is to inform you that the University of Windsor Research Ethics Board (REB), which is organized and operated according to the Tri-Council Policy Statement and the University of Windsor Guidelines for Research Involving Human Subjects, has granted approval to your research project on the date noted above. This approval is valid only until the Project End Date.

A Progress Report or Final Report is due by the date noted above. The REB may ask for monitoring information at some time during the project's approval period.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the REB. Minor change(s) in ongoing studies will be considered when submitted on the Request to Revise form.

Investigators must also report promptly to the REB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

Forms for submissions, notifications, or changes are available on the REB website: www.uwindsor.ca/reb.

We wish you every success in your research.

Maureen Muldoon
Chair, Research Ethics Board

cc: Dr. Jennifer Jakobi, Kinesiology
      / Linda Bunn, Research Ethics Coordinator

This is an official document. Please retain the original in your files.
Title of study: Characterization of Neuromuscular Properties, Functional Mobility and Fatigue in Persons with Type 2 Diabetes mellitus

You are asked to participate in a research study conducted by Lynette Singh, Dr. Jennifer Jakobi and Dr. Kenji Kenno, from the Department of Kinesiology, Faculty of Human Kinetics at the University of Windsor. The results of this study will contribute to Lynette Singh's thesis project to complete the candidacy for Masters of Human Kinetics (MHK) degree.

If you have any questions or concerns about the research, please feel to contact:

Lynette Singh, BScH
Department of Kinesiology
Faculty of Human Kinetics
Neuromuscular Laboratory, rm 231
University of Windsor
Windsor, Ontario N9B 3P4
Tel. (519) 253-3000 ext. 4049
E-mail: singh3d@uwindsor.ca

PURPOSE OF THE STUDY

Skeletal and neural tissues are central to our ability to generate force for all movement. In persons living with diabetes, the neural and muscular systems may be affected by high blood glucose. This seems to create problems with performance of daily tasks, affecting personal autonomy and overall quality of life. Currently, much of the information that is known about the neuromuscular system in diabetes comes from animal models, while information gathered from human studies is sparse. The goal of this study is to quantify and compare muscle properties from the tibialis anterior of healthy middle-aged adults to persons with Type 2 diabetes. Electrophysiological data will be compared to the results of functional mobility performance indicators and questionnaires to see if any relation exists between physical performance and any changes in neuromuscular function. This information will show how persons with Type 2 diabetes differ from healthy individuals and ultimately aid in understanding mechanisms of the decline in physical function. In addition, possible neuromuscular differences found during a fatigue protocol will be utilized to highlight changes in muscle function that may result, and could offer plausible insight to the muscle weakness that is experienced by some people living with Type 2 diabetes.

PROCEDURES

Day 1 – Part A: Questionnaires and Familiarization Session

After arriving at the Neuromuscular laboratory, you will be asked to complete the Letter of Consent and receive the Letter of Information. All information gathered will be coded to ensure anonymity and will be kept confidential in a locked cabinet. You will be asked to complete a Background Questionnaire, the Yale Physical Activity Survey for Older Adults, the Waterloo Footedness Questionnaire (WFQ) and The Medical Outcomes Study (MOS) Questionnaire, the Diabetes Self-Efficacy Scale (OSES) and the Activities-specific Balance Confidence scale (ABC scale).

In the Multi-purpose room in the St. Denis Centre, you will be asked to participate in a Timed-up and go (TUG), step test (STEP), self-paced walk (SPW), Berg Balance Scale (BBS), and the 4m timed walk test with rest periods in between.

Day 1 - Part B: Sensory Tests

To distinguish neuropathic and non-neuropathic persons, initial screening will be conducted by sensory testing using a 10-g Semmes-Weinstein monofilament (nylon brush) that will be applied lightly to the back of each great toe below the cuticle on the skin 10 times in different places. You will be asked to complete the Michigan Neuropathy Screening Instrument (MNSI) in addition to the initial sensory testing.
Day 1 - Part C: Glycosylated Hemoglobin Test

All persons will receive a glycosylated hemoglobin test from a single drop of blood obtained using standard sampling techniques that are the same as finger prick testing used for blood glucose measurements.

Day 2: Electrophysiological Testing

Before the neuromuscular study, you will be asked to refrain from consuming caffeine for at least 2 hours prior. Blood glucose will be measured using a standard glucose meter. Blood lactate will be measured at the same time, using a standard lactate sampling technique.

You will be seated with your non-dominant leg in a device to measure force. Your non-dominant leg will be secured using a series of straps at the foot, and padded leg clamps to keep your leg in position. At rest, a non-adhesive electrode will be connected to a stimulator and will be placed on the surface of the skin over your shin and utilized to assess twitch contractile properties. Electrical activity will be recorded by attaching self-adhering button electrodes to the skin over your shin region. In the first part, with the muscle at rest, your lower leg muscle over the front of your lower leg (tibialis anterior) will be maximally stimulated. This stimulation begins at low and progressively increases until the muscle responds without the interference of the calf muscles. In the second part of the neuromuscular investigation, you will be asked (in same seated position) to force your toes upwards as hard and as fast as possible and hold the position for 3 seconds (maximum voluntary contraction, MVC) and will be allowed to monitor your progress. The interpolated twitch technique involves application of a maximal electrical stimulus to the nerve in your leg prior to, during and after a maximum voluntary contraction (MVC). You will be asked to perform three MVCs separated by 5 minutes of rest. One to two MVCs will be performed before testing to familiarize you with the technique. In a fatigue test, you will be asked to exert muscle force in your leg until your muscle fatigues. At the end of this test, your blood glucose and blood lactate levels will be measured again. Day 2 will take approximately 1 hour to complete.

POTENTIAL RISKS AND DISCOMFORTS

There is always a risk when performing any physical activity, but the risk associated with these tests do not exceed the risk of performing activities of daily living. With the use of surface EMG electrodes a minimal risk of minor skin irritation exists, but is similar to that of wearing a bandage. A standard minimal risk (similar to "at home tests") may be associated with blood work in the neuromuscular laboratory, but sterile precautions for use and disposal of lancets will be taken.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

There is evidence to suspect that people with Type 2 diabetes are different from healthy individuals. At present, however, there is very little information available regarding electrophysiological characteristics of muscle in Type 2 diabetes. To date, no study has combined electrophysiological tests, nor assessed fatigue in conjunction with such a variety of physical performance tests and questionnaires to gather a gradation of information concerning how the body adapts physiologically to this disease.

This study provides volunteers an opportunity to participate in research that could provide information to advance current knowledge about diabetes. Information that may help in the advancement of more suitable exercise prescriptions and treatment for Type 2 diabetes. Volunteers will gain a greater self-awareness from completion of questionnaires and mobility tests and will have an opportunity to see their glycosylated haemoglobin levels.

PAYMENT FOR PARTICIPATION

All subjects will receive a gift package containing information about general health and diabetes, sample products and a cookbook (total value approximately $30.00).

CONFIDENTIALITY

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission. All data from subjects will be collected and coded for anonymity at the beginning of the study session.
PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind. You may also refuse to answer any questions you do not want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so. Any persons with musculoskeletal disorders, injury, other neurological disorders or painful neuropathy, myopathy, severe cardiovascular disease, have a pacemaker, recovering from surgery, alcoholism, pregnancy, or extreme physical activity patterns are unsuitable candidates for this study and will be excluded.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS

You will receive information about your glycosylated haemoglobin levels. Because this experiment involves the use of non-diagnostic tests, the results of each test will not be available until cumulative group averages are found. Study results will be published on the University of Windsor ethics website at www.uwindsor.ca/reb for you to look through at the final completion of the investigation.

SUBSEQUENT USE OF DATA

This data will be used in subsequent studies.

Do you give consent for the subsequent use of the data from this study? □ Yes □ No

RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. This study has been reviewed and received ethics clearance through the University of Windsor Research Ethics Board. If you have questions regarding your rights as a research subject, contact:

Research Ethics Coordinator
University of Windsor
Windsor, Ontario N9B 3P4
Tel. (519)253-3000 ext. 3916
E-mail: lbunn@uwindsor.ca

SIGNATURE OF RESEARCH SUBJECT/LEGAL REPRESENTATIVE

I understand the information provided for the study Characterization of Neuromuscular Properties, Functional Mobility and Fatigue in Persons with Type 2 Diabetes mellitus as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

Name of Subject

Signature of Subject Date

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

Signature of Investigator Date
Researchers at the University of Windsor are looking for individuals WITH and WITHOUT Type 2 Diabetes to participate in a study to look at mobility and strength.

Volunteers between the ages of 40-65 can have a free glycoated haemoglobin test.

If you are male or female between the ages of 40-65 and would like more information

PLEASE CONTACT
Lynette Singh or Jennifer Jakobi, PhD
(519)253-3000 extension 4049
NEEDED

Individuals between 40-65 years of age with and without Type 2 Diabetes

Researchers at the University of Windsor are conducting a study to examine mobility and muscle characteristics in persons with Type 2 Diabetes.

Volunteers between the ages of 40-65 can have a free glycolated hemoglobin test.

For further Information, PLEASE CONTACT:
Lynette Singh or Jennifer Jakobi, PhD
(519)253-3000 extension 4049
Researchers at the University of Windsor are looking for individuals to participate in a study to look at mobility and strength.

If you are male or female between the ages of 40-65 and would like more information

PLEASE CONTACT
Lynette Singh or Jennifer Jakobi, PhD
(519)253-3000 extension 4049
Campus-wide Email

Volunteering Opportunity at the University of Windsor

I am a Master of Human Kinetics student who is currently working on my research project which focuses on understanding the relationship between strength and mobility. We are inviting you to participate in this project. Currently, I require participants who have been diagnosed with Type 2 diabetes as well as individuals who do not have diabetes that are between 40 to 65 years of age. This project involves general health questionnaires, mobility/walking tests and strength assessment. This study has received approval from the University of Windsor Research Ethics Board. If you would like more information I (or my supervisor) would be happy to chat with you about the specifics of my Master's project.

Thanks for your consideration,

Lynette A. Singh, BScH
Master's Candidate
University of Windsor
Faculty of Human Kinetics
Department of Kinesiology
Human Kinetics Bldg., Rm. 231
Telephone: 519-253-3000 ext. 4049
Email: singh3d@uwindsor.ca

Jennifer M. Jakobi, PhD
University of Windsor
Faculty of Human Kinetics
Department of Kinesiology
Human Kinetics Bldg., Rm. 120
Telephone: 519-253-3000 ext. 2473
Email: jjakobi@uwindsor.ca
### Appendix C. Questionnaires, Blood and Neuropathy Screening

**Session One: Familiarization Session Checklist**

<table>
<thead>
<tr>
<th>Subject Code</th>
<th>Date</th>
</tr>
</thead>
</table>

- [ ] Consent Form (in file)
- [ ] Letter of Information (to subject)
- [ ] Subject Contact Information (in confidential file)

- [ ] Background Questionnaire (subject file)
- [ ] Waterloo Footedness Questionnaire (subject file)
- [ ] The Yale Physical Activity Survey for Adults (subject file)
- [ ] SF-36 (subject file)
- [ ] The Diabetes Self-Efficacy Scale (subject file)
- [ ] The Activities-specific Balance and Confidence Scale (subject file)

- [ ] The Berg Balance Scale (subject file)
- [ ] The Timed “Up and GO” test (subject file)
- [ ] The 4-metre timed walk (subject file)
- [ ] Step Test Exercise Prediction of VO₂ max (subject file)
- [ ] The Michigan Neuropathy Screening Instrument Questionnaire (subject file)
- [ ] Neuropen Sensory Testing (subject file)
- [ ] HbA1c Test (subject file)

- [ ] Schedule second session to the lab
Day Two: Your Next Visit to the Neuromuscular Laboratory

Thank you very much for participating in the first part of the study. In order for us to complete this study, we ask that you come back to the laboratory for the second part (*) (**).

Your next visit is scheduled on:

________________________________________________________

*Please refrain from consuming any caffeine for at least 2 hours prior to this visit.  
**Bring a pair of comfortable shorts and socks along with you.

Neuromuscular Laboratory  
Room 231  
Human Kinetics Building

Please contact us if you need to reschedule this visit.

Department of Kinesiology  
University of Windsor  
Windsor, Ontario N9B 3P4

Tel. 1(519) 253-3000 ext. 4049  
E-mail: singh3d@uwindsor.ca
### Session Two. Neuromuscular Assessment

<table>
<thead>
<tr>
<th>Subject Code</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Dominant Leg Tested</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SG Excitation</th>
<th>SG Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>taEMG Amplifier</td>
<td>taEMG Gain</td>
</tr>
<tr>
<td>lgEMG Amplifier</td>
<td>lgEMG Gain</td>
</tr>
</tbody>
</table>

#### A. Conduction Velocity and Supramaximal Twitch

- 10 single twitches to analyze

<table>
<thead>
<tr>
<th>Max M-wave/Twitch</th>
<th>Pulse Duration</th>
<th>Current</th>
<th>Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance (mm)</td>
<td>Stimulator electrode to Active sEMG electrode:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>File Name</th>
<th></th>
</tr>
</thead>
</table>

#### B. MVC

- 1-3 x Practice MVC
- 3 x MVC to Analyze

<table>
<thead>
<tr>
<th>File Name</th>
<th></th>
</tr>
</thead>
</table>

#### C. Fatigue

**Blood Analysis – PART ONE**

<table>
<thead>
<tr>
<th>Time</th>
<th>Hours since last consumed food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Lactate Before</td>
<td>Blood Glucose Before</td>
</tr>
<tr>
<td>Blood Lactate After</td>
<td>Blood Glucose After</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fused Tetanus</th>
<th>Pulse Duration</th>
<th>Current</th>
<th>Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise/Recovery</td>
<td>File Name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Exercise plus 1 minute Recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Recovery after 3 minutes Recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Recovery after 5 minutes Recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Recovery after 10 minutes Recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Session One. Subject Contact Information

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Street Address</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td></td>
</tr>
<tr>
<td>Province</td>
<td></td>
</tr>
<tr>
<td>Postal Code</td>
<td></td>
</tr>
<tr>
<td>Email</td>
<td></td>
</tr>
<tr>
<td>Phone Number</td>
<td></td>
</tr>
<tr>
<td>Emergency Contact</td>
<td></td>
</tr>
<tr>
<td>Emergency Contact Number</td>
<td></td>
</tr>
<tr>
<td>Subject Code</td>
<td></td>
</tr>
</tbody>
</table>
### Session One. Background Questionnaire

<table>
<thead>
<tr>
<th>Subject Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

#### Section 1. Tell us about yourself.

<table>
<thead>
<tr>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Girth Measurement (cm)</th>
<th>W:</th>
<th>H:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Section 2. Tell us about your health

<table>
<thead>
<tr>
<th>Are you a regular smoker?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you consider yourself ...</th>
<th>At the Right Weight</th>
<th>Overweight</th>
<th>Underweight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are you a frequent dieter?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you had surgery in the past year?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you ever been diagnosed by a health professional as having any of the following? (Check all that apply, make specifications where applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart trouble</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>High Blood Pressure</td>
</tr>
<tr>
<td>High Cholesterol</td>
</tr>
<tr>
<td>Cardiac Pacemaker</td>
</tr>
<tr>
<td>Electronic Implant</td>
</tr>
<tr>
<td>Back problems</td>
</tr>
<tr>
<td>Foot Problems</td>
</tr>
<tr>
<td>Muscle Problems</td>
</tr>
<tr>
<td>Bone or Joint Disorder</td>
</tr>
<tr>
<td>Previous Injury</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
</tbody>
</table>
### Allergies (including hay fever and sinus problems)

- 

- 

- Difficulties hearing
- Difficulties seeing
- Other health problems

### Diabetes

- Diabetes
- **YES**, please complete Section 3

### Family history of diabetes?

- No
- Yes
- If so, please provide details

### Are you currently using any medications?


### Section 3. Tell us about your diabetes

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many years has it been since you were first diagnosed with Type 2 diabetes?</td>
<td></td>
</tr>
<tr>
<td>Do you receive regular medical care for your diabetes? (such as visits to a family physician, specialist etc.)</td>
<td></td>
</tr>
<tr>
<td>What level do you control your blood sugar?</td>
<td></td>
</tr>
<tr>
<td>What method(s) do you use to control Type 2 diabetes? (please check all that apply, provide details if applicable)</td>
<td>Regular exercise</td>
</tr>
<tr>
<td>Have you received educational counselling with respect to controlling Type 2 diabetes?</td>
<td>Family physician</td>
</tr>
</tbody>
</table>

**Thank you** for completing this background questionnaire. The information provided will assist in completion of this study. If you have found any of the sections unclear, please bring it to the attention of the experimenter.
**Session One. Waterloo Footedness Questionnaire – Revised**

**Instructions:** Answer each of the following questions as best you can. If you *always* use one foot to perform the described activity, circle Ra or La (for right always or left always). If you *usually* use one foot circle Ru or Lu, as appropriate. If you use both feet equally often, circle Eq. Please do not simply circle one answer for all questions, but imagine yourself performing each activity in turn, and then mark the appropriate answer. If necessary, stop and pantomime the activity.

1. Which foot would you use to kick a stationary ball at a target straight in front of you?   
2. If you had to stand on one foot, which foot would it be?   
3. Which foot would you use to smooth sand at the beach?   
4. If you had to step up onto a chair, which foot would you place on the chair first?   
5. Which foot would you use to stomp on a fast-moving bug?   
6. If you were to balance on one foot on a railway track, which foot would you use?   
7. If you wanted to pick up a marble with your toes, which foot would you use?   
8. If you had to hop on one foot, which foot would you use?   
9. Which foot would you use to help push a shovel into the ground?   
10. During relaxed standing, people initially put most of their weight on one foot, leaving the other leg slightly bent. Which foot do you put most of your weight on first?   
11. Is there any reason (i.e. injury) why you have changed your foot preference for any of the above activities? YES NO (circle one)   
12. Have you ever been given special training or encouragement to use a particular foot for certain activities? YES NO (circle one)   
13. If you have answered YES for either question 11 or 12, please explain:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Which foot would you use to kick a stationary ball at a target straight in front of you?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>2. If you had to stand on one foot, which foot would it be?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>3. Which foot would you use to smooth sand at the beach?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>4. If you had to step up onto a chair, which foot would you place on the chair first?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>5. Which foot would you use to stomp on a fast-moving bug?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>6. If you were to balance on one foot on a railway track, which foot would you use?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>7. If you wanted to pick up a marble with your toes, which foot would you use?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>8. If you had to hop on one foot, which foot would you use?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>9. Which foot would you use to help push a shovel into the ground?</td>
<td>La Lu Eq Ru Ra</td>
</tr>
<tr>
<td>10. During relaxed standing, people initially put most of their weight on one foot, leaving the other leg slightly bent. Which foot do you put most of your weight on first?</td>
<td>Yes No</td>
</tr>
<tr>
<td>11. Is there any reason (i.e. injury) why you have changed your foot preference for any of the above activities?</td>
<td>Yes No</td>
</tr>
<tr>
<td>12. Have you ever been given special training or encouragement to use a particular foot for certain activities?</td>
<td>Yes No</td>
</tr>
</tbody>
</table>
**Session One. The Yale Physical Activity Survey for Older Adults**

**INTERVIEWER:** PLEASE MARK TIME: ____ : ____ : ____

**INTERVIEWER:** (Please hand the subject the list of activities while reading this statement). Here is a list of common types of physical activities. Please tell me which of them you did during a typical week in the last month. Our interest is learning about the types of physical activities that are a part of your regular work and leisure routines.

For each activity you do, please tell me how much time (hours) you spent doing this activity during a typical week. (Hand subject card #1.)

<table>
<thead>
<tr>
<th>Work</th>
<th>Time (Hrs/Wk)</th>
<th>Intensity Code* (kcal/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shopping (e.g., grocery, clothes)</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Stair climbing while carrying a load</td>
<td></td>
<td>8.5</td>
</tr>
<tr>
<td>Laundry (time loading, unloading, hanging, folding only)</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Light housework: tidying, dusting, sweeping; collecting trash in home; polishing; indoor gardening; ironing</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Heavy housework: vacuuming, mopping; scrubbing floors and walls; moving furniture, boxes, or garbage cans</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Food preparation (10+ mins in duration): chopping stirring; moving about to get food items, pans</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Food service (10+ mins in duration): setting table; carrying food; serving food</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Dish washing (10+ mins in duration): clearing table; washing/drying dishes, putting dishes away</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Light home repair: small appliance repair; light home maintenance/repair</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Heavy home repair: painting, carpentry, washing/polishing car</td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Code (Hrs/Wk)</td>
<td>Intensity Code (kcal/min)</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Yardwork</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardening: planting, weeding, digging, hoeing</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Lawn mowing (walking only)</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Clearing walks/driveway: sweeping, shoveling, raking</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caretaking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older or disabled person (lifting, pushing wheelchair)</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Childcare (lifting, carrying, pushing stroller)</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brisk walking (10+ mins in duration)</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Pool exercises, stretching, yoga</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Vigorous calisthenics, aerobics</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Cycling, exercycle</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Swimming (laps only)</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recreational Activities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisurely walking (10+ mins in duration)</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Needlework: knitting, sewing, needlepoint, etc.</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Dancing (mod/fast): line, ballroom, tap, square, etc.</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Bowling, bocci</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Golf (walking to each hole only)</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Racquet sports: tennis, racquet ball</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Billiards</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTERVIEWER: (please read to subject). I would now like to ask you about certain types of activities that you have done during the past month. I will ask you about how much vigorous activity, leisurely walking, sitting, standing, and some other things that you usually do.

1. About how many times during the month did you participate in vigorous activities that lasted at least 10 minutes and caused large increases in breathing, heart rate, or leg fatigue or caused you to perspire? (Hand subject card #2.)

   SCORE: 0 = Not at all (go to Q3)
   1 = 1-3 times per month
   2 = 1-2 times per week
   3 = 3-4 times per week
   4 = 5+ times per week
   7 = Refused
   8 = Don’t know

   FREQUENCY SCORE = ____________

2. About how long do you do this vigorous activity(ies) each time? (Hand subject card #3.)

   SCORE: 0 = Not applicable
   1 = 10-30 minutes
   2 = 31-60 minutes
   3 = 60+ minutes
   7 = Refused
   8 = Don’t know

   DURATION SCORE = ____________

   WEIGHT = 5

   VIGOROUS ACTIVITY INDEX SCORE:

   FREQUENCY SCORE x DURATION SCORE x WEIGHT = ____________

   (Responses of 7 or 8 are scored as missing.)

3. Think about the walks you have taken during the past month. About how many times per month did you walk for at least 10 minutes or more without stopping which was not strenuous enough to cause large increases in breathing, heart rate, or leg fatigue or cause you to perspire? (Hand subject card #2.)

   SCORE: 0 = Not at all (go to Q5)
   1 = 1-3 times per month
   2 = 1-2 times per week
   3 = 3-4 times per week
   4 = 5+ times per week
   7 = Refused
   8 = Don’t know

   FREQUENCY SCORE = ____________
4. When you did this walking, for how many minutes did you do it? (Hand subject card #3.)

SCORE: 0 = Not applicable
1 = 10-30 minutes
2 = 31-60 minutes
3 = 60+ minutes
7 = Refused
8 = Don't know

DURATION SCORE = ______________________
WEIGHT = 4

LEISURELY WALKING INDEX SCORE:

FREQ SCORE ___ x DUR SCORE ___ x WEIGHT ___ = ______________
(Responses of 7 or 8 are scored as missing.)

5. About how many hours a day do you spend moving around on your feet while doing things? Please report only the time that you are actually moving. (Hand subject card #4.)

SCORE: 0 = Not at all
1 = less than 1 hr per day
2 = 1 to less than 3 hrs per day
3 = 3 to less than 5 hrs per day
4 = 5 to less than 7 hrs per day
5 = 7+ hrs per day
7 = Refused
8 = Don't know

MOVING SCORE = ______________________
WEIGHT = 3

MOVING INDEX SCORE:

MOVING SCORE ___ x WEIGHT ___ = ______________
(Responses of 7 or 8 are scored as missing.)

6. Think about how much time you spend standing or moving around on your feet on an average day during the past month. About how many hours per day do you stand? (Hand subject card #4.)

SCORE: 0 = Not at all
1 = less than 1 hr per day
2 = 1 to less than 3 hrs per day
3 = 3 to less than 5 hrs per day
4 = 5 to less than 7 hrs per day
5 = 7+ hrs per day
7 = Refused
8 = DK

STANDING SCORE = ______________________
WEIGHT = 2
STANDING INDEX SCORE:

STANDING SCORE _____ X WEIGHT ___ = ____________
(Responses of 7 or 8 are scored as missing.)

7. About how many hours did you spend sitting on an average day during the past month? (Hand subject card #5.)

SCORE: 0 = Not at all
1 = less than 3 hours
2 = 3 hours to less than 6 hours
3 = 6 hours to less than 8 hours
4 = 8+ hours
7 = Refused
8 = Don't know

SITTING SCORE = ____________

WEIGHT = 1

SITTING INDEX SCORE:

SITTING SCORE _____ X WEIGHT ___ = ____________
(Responses of 7 or 8 are scored as missing.)

8. About how many flights of stairs do you climb up each day? (Let 10 steps = 1 flight.)

9. Please compare the amount of physical activity that you do during other seasons of the year with the amount of activity you just reported for a typical week in the past month. For example, in the summer, do you do more or less activity than what you reported doing in the past month? (INTERVIEWER: PLEASE CIRCLE THE APPROPRIATE SCORE FOR EACH SEASON.)

<table>
<thead>
<tr>
<th>Season</th>
<th>Lot More</th>
<th>Little More</th>
<th>Same</th>
<th>Little Less</th>
<th>Lot Less</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring</td>
<td>1.30</td>
<td>1.15</td>
<td>1.00</td>
<td>0.85</td>
<td>0.70</td>
<td>.</td>
</tr>
<tr>
<td>Summer</td>
<td>1.30</td>
<td>1.15</td>
<td>1.00</td>
<td>0.85</td>
<td>0.70</td>
<td>.</td>
</tr>
<tr>
<td>Fall</td>
<td>1.30</td>
<td>1.15</td>
<td>1.00</td>
<td>0.85</td>
<td>0.70</td>
<td>.</td>
</tr>
<tr>
<td>Winter</td>
<td>1.30</td>
<td>1.15</td>
<td>1.00</td>
<td>0.85</td>
<td>0.70</td>
<td>.</td>
</tr>
</tbody>
</table>

SEASONAL ADJUSTMENT SCORE = SUM OVER ALL SEASONS / 4 ____________

INTERVIEWER PLEASE MARK TIME: ___:___:___
HR SEC MIN

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CARD #1

WEEKLY PHYSICAL ACTIVITIES

Work

Shopping (e.g., grocery, clothes)
Stair climbing while carrying a load

Laundry

Light Housework: tidying, dusting, sweeping, collecting garbage in home, polishing, indoor gardening, ironing

Heavy Housework: vacuuming, mopping, scrubbing floors and walls, moving furniture, moving boxes or garbage cans

Food preparation (10+ min.): chopping, stirring, moving around to get food items, pots or pans

Food service (10+ min.): setting table, carrying food, serving food

Dish washing (10+ min.): clearing table, washing and drying dishes, putting dishes away

Light home repair: small appliance repair, light household maintenance and repair tasks

Heavy home repair: painting, washing and polishing car, carpentry

Other:

Yardwork

Gardening: pruning, planting, weeding, hoeing, digging

Lawn mowing (walking only)

Clearing walks and driveway: raking, shoveling, sweeping

Other:
Caretaking

Older or disabled person:

Childcare: lifting, pushing wheelchair

lifting, pushing stroller

Exercise

**Brisk walking for exercise (10+ min.):** causes large increases in heart rate, breathing or leg fatigue

Stretching exercises, yoga, pool exercise

Vigorous calisthenics, aerobics: causes large increases in heart rate, breathing or leg fatigue

Cycling, exercycle

Lap swimming

Other:

Recreational Activities

**Leisurely walking (10+ min.)**

Hiking

Needlework: knitting, sewing, crocheting, needlepoint

Dancing (mod/fast): line dancing, ballroom, square, tap, etc.

Bowling, boccie

Golf (walking to each hole only)

Racquet sports: tennis, racquetball

Billiards

Other:
CARD #2

Not at all
1-3 times per month
1-2 times per week
3-4 times per week
5 or more times per week
Don’t know

CARD #3

10-30 minutes
31-60 minutes
60 or more minutes
Don’t know

CARD #4

Not at all
less than 1 hour per day
1 to less than 3 hours per day
3 to less than 5 hours per day
5 to less than 7 hours per day
7 or more hours per day
Don’t know

CARD #5

Not at all
less than 3 hours per day
3 hours to less than 6 hours per day
6 hours to less than 8 hours per day
8 or more hours per day
Don’t know
**Session One.** Medical Outcomes Study: 36-Item Short Form Survey Instrument

**RAND 36-Item Health Survey 1.0 Questionnaire Items**

1. In general, would you say your health is:
   - Excellent 1
   - Very good 2
   - Good 3
   - Fair 4
   - Poor 5

2. Compared to one year ago, how would you rate your health in general now?
   - Much better now than one year ago 1
   - Somewhat better now than one year ago 2
   - About the same 3
   - Somewhat worse now than one year ago 4
   - Much worse now than one year ago 5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle One Number on Each Line)

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Yes, Limited a Lot</th>
<th>Yes, Limited a Little</th>
<th>No, Not limited at All</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>[1]</td>
<td>[2]</td>
<td>[3]</td>
</tr>
<tr>
<td>4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>[1]</td>
<td>[2]</td>
<td>[3]</td>
</tr>
<tr>
<td>5. Lifting or carrying groceries</td>
<td>[1]</td>
<td>[2]</td>
<td>[3]</td>
</tr>
<tr>
<td>6. Climbing several flights of stairs</td>
<td>[1]</td>
<td>[2]</td>
<td>[3]</td>
</tr>
<tr>
<td>7. Climbing one flight of stairs</td>
<td>[1]</td>
<td>[2]</td>
<td>[3]</td>
</tr>
</tbody>
</table>
8. Bending, kneeling, or stooping [1] [2] [3]
9. Walking more than a mile [1] [2] [3]
10. Walking several blocks [1] [2] [3]
11. Walking one block [1] [2] [3]
12. Bathing or dressing yourself [1] [2] [3]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle One Number on Each Line)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Cut down the amount of time you spent on work or other activities</td>
<td>1</td>
</tr>
<tr>
<td>14. Accomplished less than you would like</td>
<td>1</td>
</tr>
<tr>
<td>15. Were limited in the kind of work or other activities</td>
<td>1</td>
</tr>
<tr>
<td>16. Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
</tr>
</tbody>
</table>

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Cut down the amount of time you spent on work or other activities</td>
<td>1</td>
</tr>
<tr>
<td>18. Accomplished less than you would like</td>
<td>1</td>
</tr>
<tr>
<td>19. Didn't do work or other activities as carefully as usual</td>
<td>1</td>
</tr>
</tbody>
</table>
20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)
Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

21. How much bodily pain have you had during the past 4 weeks?

(Circle One Number)
None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)
Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .

(Circle One Number on Each Line)

<table>
<thead>
<tr>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Did you feel full of pep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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24. Have you been a very nervous person?

25. Have you felt so down in the dumps that nothing could cheer you up?

26. Have you felt calm and peaceful?

27. Did you have a lot of energy?

28. Have you felt downhearted and blue?

29. Did you feel worn out?

30. Have you been a happy person?

31. Did you feel tired?

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1
Most of the time 2
Some of the time 3
A little of the time 4
None of the time 5

How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Don't Know</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>33. I seem to get sick a little easier than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>34. I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>35. I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>36. My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Session One. The Diabetes Self-Efficacy Scale (DSES)

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that corresponds to your confidence that you can do the tasks regularly at the present time.

1. How confident do you feel that you can eat your meals every 4 to 5 hours every day, including breakfast every day?

2. How confident do you feel that you can follow your diet when you have to prepare or share food with other people who do not have diabetes?

3. How confident do you feel that you can choose the appropriate foods to eat when you are hungry (for example, snacks)?

4. How confident do you feel that you can exercise 15 to 30 minutes, 4 to 5 times a week?

5. How confident do you feel that you can do something to prevent your blood sugar level from dropping when you exercise?

6. How confident do you feel that you know what to do when your blood sugar level goes higher or lower than it should be?

7. How confident do you feel that you can judge when the changes in your illness mean you should visit the doctor?

8. How confident do you feel that you can control your diabetes so that it does not interfere with the things you want to do?
**Session One.** The Activities-specific Balance and Confidence scale (ABC scale) (Powell & Myers, 1995)

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Confidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>walk around the house?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk up or down stairs?</td>
<td>_____ %</td>
</tr>
<tr>
<td>bend over and pick up a slipper from the front of a closet floor?</td>
<td>_____ %</td>
</tr>
<tr>
<td>reach for a small can off a shelf at eye level?</td>
<td>_____ %</td>
</tr>
<tr>
<td>stand on your tip toes and reach for something above your head?</td>
<td>_____ %</td>
</tr>
<tr>
<td>stand on a chair and reach for something?</td>
<td>_____ %</td>
</tr>
<tr>
<td>sweep the floor?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk outside the house to a car parked in the driveway?</td>
<td>_____ %</td>
</tr>
<tr>
<td>get into or out of a car?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk across a parking lot to the mall?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk up or down a ramp?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk in a crowded mall where people rapidly walk past you?</td>
<td>_____ %</td>
</tr>
<tr>
<td>are bumped into by people as you walk through the mall?</td>
<td>_____ %</td>
</tr>
<tr>
<td>step on or off an escalator while holding onto a railing?</td>
<td>_____ %</td>
</tr>
<tr>
<td>step on or off an escalator while holding parcels and cannot hold onto the railing?</td>
<td>_____ %</td>
</tr>
<tr>
<td>walk outside on icy sidewalks?</td>
<td>_____ %</td>
</tr>
</tbody>
</table>

*Note.* From Powell and Myers (1995), Myers et al. (1996), and Myers et al. (1998). Reprinted with permission of the Gerontology Society of America. Copyright by the GSA.

**Administrating the ABC.**

The ABC can be self-administered or administered via personal or telephone interview. Use a larger typeset font for self-administration, while an enlarged version of the rating scale on an index card will facilitate in-person interviews. Instruct respondents, “If you do not currently do the activity in question, try to imagine how confident you would be if you had to do the activity. If you normally use a walking aid or hold onto someone, rate your confidence as if you were using these supports. If you have any questions, please ask.”

**Instructions for Scoring.**

Total the ratings (possible range = 0 to 1,600) and divide by 16 (or the number of items completed) to get each person’s ABC score. If a person qualifies her response to items 2, 9, 11, 14, or 15, solicit separate ratings and use the lowest confidence of the two (as this will limit the entire activity, e.g., likelihood of using stairs). Total scores can be computed if at least 12 of the 16 items are answered and alpha does not decrease appreciably with the deletion of item 16—icy sidewalks—for administration in warmer climates (Myers et al. 1998).

**Psychometric Properties of the ABC Scale.**

The ABC has good test-retest reliability, high internal consistency, is able to discriminate between fallers and nonfallers and low versus high mobility groups (Powell and Myers 1995), and corresponds with balance performance measures (Myers et al. 1996). ABC scores above 50 and less than 80 are indicative of a moderate level of functioning characteristic of persons with chronic health conditions. Scores above 80 indicate higher functioning, usually active older adults and are achievable through exercise and rehabilitative therapies (Myers et al. 1998).
<table>
<thead>
<tr>
<th>Subject Code</th>
<th>Date</th>
</tr>
</thead>
</table>

- □ Put gloves on
- □ Warm hand to increase blood flow
- □ Clean skin with alcohol wipe
- □ Prepare lancing device
- □ Set up HbA1c holder and chemical, open cap
- □ Lance skin
- □ Express blood drop and wipe with cotton pad
- □ Express blood drop into capillary for HbA1c
- □ Fill HbA1c capillary tube to black line (do not squeeze)
- □ Squeeze blood into HbA1c chemical tube and squeeze rinse 2-3 times
- □ Recap tube and shake vigorously 6-8 times
- □ Wipe finger and apply dressing if needed
- □ Open Pouch 2 of HbA1c, insert cartridge into metre immediately, monitor/code match
- □ ♦ SMPL appears, fill dropper by squeezing and releasing slowly (leave dropper in tube)
- □ Liquid in overflow bubble (never out) squeeze capillary contents only x1 onto test spot
- □ Results in 5 minutes, alternating signal QCOK unless error code

<table>
<thead>
<tr>
<th>Glycosylated Hemoglobin Level (%)</th>
</tr>
</thead>
</table>

- □ Remove cartridge from HbA1c metre and dispose, remove gloves and dispose
Session One. The Michigan Neuropathy Screening Instrument Questionnaire (MNSI)

Please take a few minutes to answer the questions below about the feeling in your legs and feet. Circle YES or NO based on how you usually feel.

1. Are your legs and/or feet numb?  YES  NO
2. Do you ever have any burning pain in your legs and/or your feet?  YES  NO
3. Are your feet too sensitive to touch?  YES  NO
4. Do you get muscle cramps in your legs and/or feet?  YES  NO
5. Do you ever have any prickling feelings in your legs or feet?  YES  NO
6. Does it hurt when the bed covers touch your skin?  YES  NO
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?  YES  NO
8. Have you ever had an open sore on your foot?  YES  NO
9. Has your doctor ever told you that you have diabetic neuropathy?  YES  NO
10. Do you feel weak all over most of the time?  YES  NO
11. Are your symptoms worse at night?  YES  NO
12. Do your legs hurt when you walk?  YES  NO
13. Are you able to sense your feet when you walk?  YES  NO
14. Is the skin on your feet so dry that it cracks open?  YES  NO
15. Have you ever had an amputation?  YES  NO

Scoring: The greater the number of positive (yes) responses equals the greater the severity of neuropathy. Tabulate score out of 15, each “yes” response receives one point and “no” receives zero points (Feldman et al., 1994).
Session One. Screening for Peripheral Neuropathy – Checklist (per Neuropen Instructions)

<table>
<thead>
<tr>
<th>Subject Code</th>
</tr>
</thead>
</table>

- Rest subject’s foot on a stable and padded surface (towel on floor). Ensure they are comfortable and free from distractions.
- Wipe the tip with an alcohol pad in the presence of the subject.
- Explain testing procedure by showing them how stimulus feels on the back of their hand.
- Once testing begins, ensure the patient cannot see the test being performed, use a shield or ask them to look away.
- Press the monofilament at 90° angle to the skin surface and increase pressure until it bows – hold it for 2 seconds. Instruct the subject to say “yes” or “now” when they believe that they can detect the stimulus. Test sites at random on dorsum of great toe on the non-dominant leg. Place an x where site of compression is detected. Put an “N” where no stimulus is sensed. Repeat test a total of 10 times.
- Wipe tip of pen with alcohol after end of test. Replace a tip and discard in sharps container after ten trials (100 uses). DO NOT USE NEAR BROKEN SKIN/OPEN SORES. IF THIS CANNOT BE AVOIDED, USE A NEW TIP AND DISCARD AFTER USE IN SHARPS CONTAINER.

**LEFT**

**RIGHT**

SCORE _____/10
Appendix D. Balance, Functional Mobility and Performance Scoring

Session One. Berg Balance Scale (BBS)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>DESCRIPTION</th>
<th>SCORE (0-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sitting to standing</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Standing unsupported</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Sitting unsupported</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Standing to sitting</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Transfers</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Standing with eyes closed</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Standing with feet together</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Reaching forward with outstretched arm</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Retrieving object from floor</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Turning to look behind</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Turning 360 degrees</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Placing alternate foot on stool</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Standing with one foot in front</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Standing on one foot</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td>**         **</td>
</tr>
</tbody>
</table>

*references on page 4

GENERAL INSTRUCTIONS

Please demonstrate each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for specific time. Progressively more points are deducted if the time or distance requirements are not met, if the subject's performance warrants supervision, or if the subject touches an external support or receives assistance from the examiner. Subjects should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing are a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5 and 10 inches (5, 12.5 and 25 cm). Chairs used during testing should be of reasonable height. Either a step or a stool (of average step height) may be used for item #12.
1. **SITTING TO STANDING**
   INSTRUCTIONS: Please stand up. Try not to use your hands for support.
   - ( ) 4 able to stand without using hands and stabilize independently
   - ( ) 3 able to stand independently using hands
   - ( ) 2 able to stand using hands after several tries
   - ( ) 1 needs minimal aid to stand or to stabilize
   - ( ) 0 needs moderate or maximal assist to stand

2. **STANDING UNSUPPORTED**
   INSTRUCTIONS: Please stand for two minutes without holding.
   - ( ) 4 able to stand safely 2 minutes
   - ( ) 3 able to stand 2 minutes with supervision
   - ( ) 2 able to stand 30 seconds unsupported
   - ( ) 1 needs several tries to stand 30 seconds unsupported
   - ( ) 0 unable to stand 30 seconds unassisted

   **If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.**

3. **SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL**
   INSTRUCTIONS: Please sit with arms folded for 2 minutes.
   - ( ) 4 able to sit safely and securely 2 minutes
   - ( ) 3 able to sit 2 minutes under supervision
   - ( ) 2 able to sit 30 seconds
   - ( ) 1 able to sit 10 seconds
   - ( ) 0 unable to sit without support 10 seconds

4. **STANDING TO SITTING**
   INSTRUCTIONS: Please sit down.
   - ( ) 4 sits safely with minimal use of hands
   - ( ) 3 controls descent by using hands
   - ( ) 2 uses back of legs against chair to control descent
   - ( ) 1 sits independently but has uncontrolled descent
   - ( ) 0 needs assistance to sit

5. **TRANSFERS**
   INSTRUCTIONS: Arrange chairs(s) for a pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
   - ( ) 4 able to transfer safely with minor use of hands
   - ( ) 3 able to transfer safely definite need of hands
   - ( ) 2 able to transfer with verbal cueing and/or supervision
   - ( ) 1 needs one person to assist
   - ( ) 0 needs two people to assist or supervise to be safe
6. **STANDING UNSUPPORTED WITH EYES CLOSED**

**INSTRUCTIONS:** Please close your eyes and stand still for 10 seconds.

- () 4 able to stand 10 seconds safely
- () 3 able to stand 10 seconds with supervision
- () 2 able to stand 3 seconds
- () 1 unable to keep eyes closed 3 seconds but stays steady
- () 0 needs help to keep from falling

7. **STANDING UNSUPPORTED WITH FEET TOGETHER**

**INSTRUCTIONS:** Place your feet together and stand without holding.

- () 4 able to place feet together independently and stand 1 minute safely
- () 3 able to place feet together independently and stand for 1 minute with supervision
- () 2 able to place feet together independently and to hold for 30 seconds
- () 1 needs help to attain position but able to stand 15 seconds feet together
- () 0 needs help to attain position and unable to hold for 15 seconds

8. **REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING**

**INSTRUCTIONS:** Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the finger reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)

- () 4 can reach forward confidently >25 cm (10 inches)
- () 3 can reach forward >12.5 cm safely (5 inches)
- () 2 can reach forward >5 cm safely (2 inches)
- () 1 reaches forward but needs supervision
- () 0 loses balance while trying/ requires external support

9. **PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION**

**INSTRUCTIONS:** Pick up the shoe/ slipper which is placed in front of your feet.

- () 4 able to pick up slipper safely and easily
- () 3 able to pick up slipper but needs supervision
- () 2 unable to pick up but reaches 2-5 cm (1-2 inches) from slipper and keeps balance independently
- () 1 unable to pick up and needs supervision while trying
- () 0 unable to try/ needs assist to keep from losing balance or falling

10. **TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING**

**INSTRUCTIONS:** Turn to look directly behind you over toward left shoulder. Repeat to the right. Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.

- () 4 looks behind from both sides and weight shifts well
- () 3 looks behind one side only other side shows less weight shift
- () 2 turns sideways only but maintains balance
- () 1 needs supervision when turning
- () 0 needs assist to keep from losing balance or falling
11. TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only in 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cueing
( ) 0 needs assistance while turning

12. PLACING ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps >20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete >2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

13. STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT)
Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead of other independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

14. STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding.
( ) 4 able to lift leg independently and hold >10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold <5 or >3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently
( ) 0 unable to try or needs assist to prevent fall

( ) TOTAL SCORE (Maximum = 56)
Session One. Physical Performance Score Sheets

Subject Code

1. Timed “up and go” test (TUG)

The TUG test involves measurement of the time (seconds) that it takes for a person to stand up from an arm chair (approximately 45 cm high) after “go”, walk a straight distance of 3 m at a comfortable or regular pace, turn, walk back to the chair and sit down again (Figure 3).

Practice Trial (not timed)

Time to complete task ________________ s

* Regular footwear is worn, using any ambulatory aids that s/he normally uses, without any other sort of physical assistance. The person begins the test with her/his back against the chair with any ambulatory aids available in hand. A first try is given in order to familiarize the subject with the protocol (Podsiadlo & Richardson, 1991).

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2. The 4-metre timed walk.

The subject will be asked to walk in a 4 m pathway. At the start, each subject will be required to stand with both feet touching the start line, and commence walking at a normal, comfortable speed at the instruction “go”. The time it takes for the individual to walk 1 m from the start and 4 m from start will be recorded (Figure 6). This protocol will be repeated 3 times (2 times per usual pace and 1 time at the fastest walking pace). The speed of the faster usual pace walks will be recorded. To calculate average walking speed, 4m or 1m divided by time to complete the task (seconds). Regular footwear is worn, using any walking aids that s/he normally uses, without any other sort of physical assistance (Guralnik et al., 1995).

Usual Pace:
Time to walk 1m _______________ s  Walking Speed ___________________ m/s
Time to walk 4m _______________ s  Walking Speed ___________________ m/s

Usual Pace:
Time to walk 1m _______________ s  Walking Speed ___________________ m/s
Time to walk 4m _______________ s  Walking Speed ___________________ m/s

Fastest Pace:
Time to walk 1m _______________ s  Walking Speed ___________________ m/s
Time to walk 4m _______________ s  Walking Speed ___________________ m/s

Subject Code

| Start Line | 1 metre | 3 metres | Finish Line |

Time (s) to complete 1 m of task

Total time (s) to complete task
3. Step Test Exercise Prediction of VO₂ max (STEP)

Two 20 cm steps will be used for stepping up (both feet on top of step) and down (both feet at bottom of step) 20 times at three different paces (Figure 5). Resting heart rate will be measured before the onset of the tests. In the first part (familiarization component), the subject will be asked to step up and down 10 step cycles at a pace considered by the subject to be "slow". After 5 minutes of rest, the subject will be asked to repeat the step protocol, but using 20 step cycles instead of 10 step cycles at a "normal" pace (timed in seconds) and post-exercise heart rate will also be recorded immediately as well as their RPE (Table 2). After another 5 minute rest period or after the heart rate returns to within 5 beats per minute (BPM) of the resting heart rate, the subject will be asked to repeat the procedure (20 steps cycles) but at a "fast" pace (timed in seconds) and post-exercise heart rate will also be recorded (Table 2). Step test speed, heart rate reserve, oxygen cost of stepping and oxygen pulse will be calculated (Table 3) and VO₂ max will be estimated for males and females (Table 4) (Petrella et al., 2001).

<table>
<thead>
<tr>
<th>Step Task Rate</th>
<th>Time to Complete Task (s)</th>
<th>Post-Exercise Heart Rate (BPM)</th>
<th>RPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T1</td>
<td>SHR₁</td>
<td>6-20</td>
</tr>
<tr>
<td>Fast</td>
<td>T2</td>
<td>SHR₂</td>
<td>6-20</td>
</tr>
</tbody>
</table>

Resting Heart Rate ___________________________ BPM

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Appendix E. Scientific Journal Manuscript

Gender and Physical Activity: Necessary Measures when Assessing Strength in Persons with Type 2 Diabetes

Lynette Singh-Peters BSc¹ Gareth R. Jones PhD², Kenji A. Kenno PhD¹, Jennifer M. Jakobi PhD¹

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Word Count: 4,429 (including references)

Running Title: Gender, Activity and Strength
OBJECTIVE –
Assess the role of muscle strength on functional mobility when physical activity is matched in addition to weight, gender, and age in persons with type 2 diabetes.

METHOD –
Physical activity was assessed and (N=14) matched between persons with type 2 diabetes and non-diabetic controls. Performance tests were conducted and isometric muscle properties and strength measured.

RESULTS –
Physical activity was similar (p=0.83) but HbA1c was significantly elevated in the type 2 diabetes group (8.4 ± 1.3 %) compared with controls (6.1 ± 0.4 %). Contractile properties (p=0.66) and strength were similar between groups (p=0.19). When gender and physical activity were considered independent factors vigorous activity accounted for 25 % of muscle strength and functional mobility scores were no lower in persons with type 2 diabetes.

CONCLUSION –
Hyperglycaemia does not cause muscle weakness and subsequent declines in function in persons with type 2 diabetes. Daily activity may maintain muscle strength, but exercise is needed to lower hyperglycaemia and preserve mobility.

KEYWORDS –
Physical activity, exercise, functional mobility, strength, gender
Introduction -

Deterioration of functional mobility is estimated to be 2 to 3 times higher in persons with diabetes compared to individuals without (1-3), and this decline is exacerbated in women (4). The association between muscle weakness and decline of functional mobility in persons with type 2 diabetes is questionable because most studies do not quantify muscle strength; rather manual muscle testing or subjective questionnaire assessments have been utilized. In addition, there is substantial literature to suggest that women are generally weaker than men (5) and that exercise training increases muscle strength resulting in higher functional mobility scores (6), but this knowledge is generally not applied to studies of persons with type 2 diabetes. In order to clearly ascertain whether muscle weakness influences functional mobility in persons with type 2 diabetes, gender and physical activity (PA) must be considered independent factors, and strength quantified in individuals without co-morbidities associated with hyperglycaemia. Co-morbidities such as neuropathies, foot ulcerations, retinopathy and nephropathy are also autonomous factors that influence muscle strength and thus these conditions should be excluded from independent assessment of PA on strength and muscle function. In this study we have weight-, age-, gender- and activity-matched persons with type 2 diabetes to non-diabetic control subjects to determine whether muscle strength is altered with chronic hyperglycaemia in a manner that impairs functional mobility.

Methods -

Subjects, Diabetes and Physical Activity Assessments

Prior to participation all subjects provided written informed consent. Persons with type 2 diabetes were recruited from the local university area; all were independent community dwelling adults. A local diabetes education group, posters (~75), community newspaper
(distribution rate; 207,163), and mass campus email to staff and faculty (2,339 distribution list) were utilized for subject recruitment. The majority of respondents (n=20) were from the campus email advertisements, whereas the fewest responses came through diabetes educators (n=1). Control subjects were recruited similarly and matched with extreme care to persons with diabetes (Table 1). Initially subjects were screened with the self-report Yale Physical Activity Survey (7) and excluded based upon contraindications of the study (physician diagnosed diabetic neuropathies, bone spurs, fibromyalgia, cardiac complications). Consequent to a possible match objective physical performance tests were conducted. The sample consisted of 14 persons with type 2 diabetes (n=6 ☺, n=8 ☻) where 10 (n=6 ☺, n=4 ☻) were successfully matched to control subjects. Three male persons with type 2 diabetes were unmatched because of high weight or low activity scores (128.9 ± 8.3 kg, 3-4x less) and the fourth male subject was excluded due to extensive participation in planned exercise training (3x higher than other scores).

The RAND 36-item Health Survey 1.0 [SF-36] was utilized to assess physical functioning, bodily pain, role limitations from health problems, and role limitations from emotional or personal issues, emotional well-being, social functioning, energy/fatigue and perception of general health. The Diabetes Self-Efficacy Scale [DSES] was employed to yield information about personal confidence with respect to living and caring for diabetes (8). The Activities-specific Balance and Confidence scale [ABC] (9) assessed balance confidence performing daily activities. A series of physical performance tests were utilized to quantify functional mobility and balance, including the Berg Balance Scale [BBS] (10), and the Timed “up and go” test [TUG] (11). The Step Test Exercise Prediction (STEP) was employed to measure heart rate responses to exercise, and to estimate submaximal oxygen uptake (12).
Sensory threshold was assessed using a 10- Semmes–Weinstein monofilament (Neuropen, Owen Mumford Ltd., UK) by application of the filament to the dorsum of each great toe (13). In conjunction with this test the Michigan Neuropathy Screening Instrument [MNSI] was also utilized to assess the existence of peripheral neuropathy (14). Control subjects were also tested to maintain consistency between groups and to assess non-diabetic related sensory abnormalities.

**Muscle Properties**

Voluntary strength and electrically induced contractile properties were assessed in the tibialis anterior. This muscle is the primary dorsi-flexor (raising forefoot and toes) and is closely associated with deterioration of gait (15). All tests were performed on the non-dominant leg except in three instances where knee joint surgery (n=2) or previous muscle injury (n=1) precluded investigation. The subject was seated in a custom-built isometric dynamometer with the ankle at 30° of plantar flexion, and the hip and knee joints positioned at 90°. The commercial load cell was fixed to the underside of the metal footplate (Model MLP-500-T, Transducer Techniques, Inc., Temecula, CA). Signals from the load cell were amplified (1000x) filtered (60-Hz notch filter), and sampled at 1000 Hz (Model V72-25A, Coulbourn Instruments, Allentown, PA) and subsequently analog to digital converted with offline quantification (Spike 2, Cambridge Electronic Design Ltd., Cambridge, UK).

Contractile properties were elicited percutaneously using an electrical stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK) and a hand-held custom-made electrode bar (4 cm length). The peroneal nerve was palpated along the lateral side of the patello-femoral joint. Pulse intensity was determined by slow increases in current until a plateau in twitch force.
was obtained. Ten maximal electrical pulses (100μs) at a frequency of 1 Hz were applied and the peak torque (PT), time to peak torque (TPT) and half relaxation time (HRT) determined from an average of 8-10 responses. To assess maximal voluntary contraction (MVC) subjects were instructed to lift their forefoot upward as hard and as fast as possible and maintain the position for 5 seconds while provided with visual feedback from an oscilloscope and strong verbal encouragement. To familiarize subjects with the MVC 3-5 practise attempts were given prior to testing. Following the practice trials 3 ‘test’ contractions were performed and the highest attempt was utilized in the analysis. In order to verify that the force produced was maximal the twitch interpolation technique was utilized which involves application of a maximal electrical stimulus over the peroneal nerve during and after the MVC. The presence of a superimposed twitch on the force record indicates a lack of motivation or central failure. This measure is quantified by expressing the difference in amplitude of the interpolated twitch response to the post MVC twitch response as a percentage of the latter (16,17).

A two-way analysis of variance (gender x diabetic condition) was utilized to determine differences in muscle strength, PA, health and well-being between persons with type 2 diabetes and controls. All values are reported as the mean ± standard deviation. Significance set at p < 0.05.

**Results**

**Subjects, Diabetes and Physical Activity Assessments**

Physical activity was successfully matched between the two groups with the questionnaire, but glucose at the time of testing and HbA1c were significantly greater in persons with type 2 diabetes (Table 1). The average duration of physician diagnosed diabetes was 5.2 ± 4.4
years. As the primary means to manage hyperglycaemia 7 subjects were utilizing oral hypoglycaemic agents, two insulin and one diet manipulations. All persons with diabetes indicated that they were aware of the benefits of exercise in managing diabetes, but all subjects reported that they did little exercise and all considered themselves overweight.

The neuropathy scores, as assessed with the MNSI and monofilament scores did not differ between groups (Table 2). Results from the RAND SF-36 questionnaire indicated that persons with type 2 diabetes perceived their health to be worse compared to the non-diabetic control group, specifically how poor emotional and physical health (p=0.004 – 0.02) had affected their social life (family, work, friends) (Figure 1). This is the first study to measure muscle properties and match PA between groups, and when activity is accounted for functional performance measures did not differ for fear of falling (ABC), balance (BBS), mobility (TUG) and stair climbing time (STEP). Moreover, assessment of resting heart rate and its responses to an exercise stair challenge and the subsequent prediction of sub-maximal oxygen consumption (VO$_2$), an indicator of cardiorespiratory fitness, was also similar between groups (Table 2).

**Muscle Properties**

Electrically induced contractile properties were similar between groups (Table 3). Voluntary strength also did not differ between persons with diabetes and controls (p=0.19) and maximal activation was achieved in both the diabetes (98.8 ± 3.3 %) and control groups (99.0 ± 1.0 %) (p=0.25). However, there was an effect of gender for voluntary strength. Men were significantly stronger (40.5 ± 2.1 Nm) compared with women (30.3 ± 1.7 Nm) irrespective of the condition of diabetes. As vigorous activity increased, irrespective of gender and diabetic condition, muscle strength also increased ($r^2 = 0.25$).
Discussion

This study clearly indicates that muscle strength and functional mobility are not altered when co-morbidities are not apparent in persons with type 2 diabetes, and when age-, gender-, and PA level are matched to non-diabetic controls muscle strength and functional mobility are not altered as a result of hyperglycaemia. As well, irrespective of hyperglycaemia the higher the PA scores the greater the muscle strength. These data suggest that reductions in functional mobility in persons with type 2 diabetes do not result from muscle weakness. Rather, chronic elevation of blood glucose, indicative in this sample by elevated HbA1c (8.4 %), likely results in co-morbidities that inevitably influence muscle strength and in-turn result in declines in independent function. Results also demonstrate the necessity in delineating between genders and defining the activity characteristics of both the diabetic and non-diabetic control groups. When gender and PA are considered as independent factors women were weaker than men irrespective of the diabetic condition, and 25 % of muscle strength was accounted for by increased participation in vigorous PA. Thus, PA is a key component to maintaining strength in persons with type 2 diabetes, and must be considered when evaluating weakness and functional decline in this condition. Longitudinal studies monitoring PA, glucose control and co-morbidities associated with type 2 diabetes are warranted in order to fully ascertain additional sources that contribute to altering muscle strength and in-turn functional mobility. This study also alludes to the necessity of behaviour modification studies in determining possible ways to increase the intensity of PA or participation in exercise programs into the lifestyle patterns of persons with type 2 diabetes. It seems that persons with type 2
diabetes are aware of the importance of exercise, but do not utilize this knowledge as a method of glucose control.

PA refers to bodily movement produced by the contraction of skeletal muscle that requires energy expenditure in excess of resting energy expenditure. Whereas, exercise is identified as a subset of PA that is planned and structured and involves repetitive bodily movement to improve or maintain any of the components of physical fitness (cardiorespiratory, muscular and flexibility) (18). Thus, in this study individuals that establish and adhere to a planned exercise program were excluded, and daily PA was scored and matched between persons with type 2 diabetes and controls. There is strong and consistent evidence that exercise training is beneficial to persons with type 2 diabetes (19-21) and this study confirms that persons with type 2 diabetes are aware of the importance of exercise but do not utilize this knowledge with structured participation. The activity scores are indicative of modest levels of daily PA, and self-report revealed that walking was the primary activity of choice. It has been shown that home based training is sufficient to maintain strength gains subsequent to a structured and group based exercise program, but it was suggested that the intensity declined to a level that resulted in minimal influence on glucose control (22). In this study, PA levels where matched between persons with and without type 2 diabetes and when this is undertaken lower leg strength is similar between groups. However, light activity did not aid in controlling hyperglycaemia in persons with type 2 diabetes and it is likely that moderate to heavy intensity PA and/or structured exercise would aid in glucose management (23, 24). Thus, practitioners must acknowledge and promote that daily PA aids in maintaining strength to a level that is similar to controls, but more moderate to vigorous PA, such as participation in a structured
exercise regime is necessary to aid in glucose control and inevitably delay co-morbidities associated with type 2 diabetes.

Blood glucose and glycosylated haemoglobin were ~40 % higher in the diabetic group compared with the control. The level of glucose control in the diabetic group was within the 5.0 – 10.0 mmol/L range that is broadly advised, however the glycosylated haemoglobin score was slightly elevated (8.4 %), based upon the ≤7 % suggested by The Canadian Diabetes Association (25). Subjects should attempt to consistently lower blood glucose and for longer time periods because elevated HbA1c levels are associated with an increased risk of both microvascular and macrovascular complications, (26-29), and hyperglycaemia is strongly associated with undetected motor neuropathies (30,31). It is likely that over time neuropathies, rather than hyperglycaemia, result in muscle weakness and that the inevitable decline in function may be misattributed to a loss of strength.

The dorsi-flexors were chosen because they are functionally relevant to gait and balance ability (15, 32, 33) and typically demonstrate early signs of sensory and motor weakness relative to the thigh, arm and wrist (30,34). Very few studies have utilized isometric muscle strength as a means of determining strength; rather most studies utilize manual muscle testing or clinical grading and few studies have utilized isokinetic strength (30,31). Isokinetic measures of strength provide a quantifiable measure of dynamic muscle torque, however this type of testing requires expensive equipment and the resultant torque is dependent upon the speed of the contraction (35, 36) and training or familiarization with the contraction is necessary because of the unique nature of the movement (37). Isometric measures of force are readily quantified, require minimal equipment with negligible costs, are relatively
easy to learn and perform (17, 38) and it is well established that maximal force can be obtained and the maximal level of activation ensured with the twitch interpolation technique (17). With sufficient practice the ability to fully activate muscle and attain MVC is generally observed in a variety of conditions (17,38,39). Thus, isometric force is not only a viable means to assess muscle strength, but application of the twitch interpolation technique shows that individuals with type 2 diabetes were able to fully activate the tibialis anterior. These results indicate that the diabetic condition does not preclude maximal force production and that when maximal activation is attained muscle strength is similar to age-, gender-, PA matched controls.

Contractile properties were also similar between groups. There is substantial literature to indicate that in rodent models of streptozotocin induced diabetes there are alterations in electrically induced contractile properties (40-42), yet no information is available in persons with type 2 diabetes. There is no indication of contractile slowing in this study of middle-aged persons with type 2 diabetes, and the tension values are within the natural age-related decline for men and women (43, 44). Our human muscle data, unlike many animal models indicate that contractile alterations do not occur in the tibialis anterior of persons with type 2 diabetes who present with no diagnosed or overt neuropathies.

Women experience a greater number of years in a state of functional dependence as compared to men, and this has been associated with loss of muscle mass (45), and it seems that this relationship is exacerbated in women with type 2 diabetes (46). This study and many others indicate that women are generally weaker than men (5) and thus it is imperative to consider gender as an independent factor when assessing strength. Many
studies that utilize manual muscle testing fail to consider normal variations in strength due to this factor as well as age, weight and height (47). When force was normalized to body weight in this study women and men with type 2 diabetes did not differ from controls, suggesting that the greater decline in functional mobility in women with type 2 diabetes does not result from muscle weakness or activation failure. In order to resolve the gender issue longitudinal studies are necessary and consideration of the onset of co-morbidities in men and women and their associated alterations upon strength must also be taken into account.

These data clearly indicate that when daily PA is matched between persons with type 2 diabetes and non-diabetic controls and gender is delineated, muscle strength does not differ suggesting that it is not lower leg weakness that influences the deterioration of functional mobility in persons with type 2 diabetes but rather it is more likely associated with chronic hyperglycaemia and other associated co-morbidities. Thus, to maintain and/or improve functional mobility exercise prescription for persons with type 2 diabetes must be of sufficient intensity (moderate-vigorous) to reduce/control hyperglycaemia and other co-morbidities. This study visibly addresses the necessity of conducting a prospective population-based control study evaluating the progressive development of neuropathy in relation to participation in PA and hyperglycaemia, where gender is assessed as an independent factor in the relationship between muscle strength and functional mobility in persons with type 2 diabetes.
Acknowledgements -

Mr. Don Clarke is thanked for his contributions to the mechanical and technical design and build of the isometric dynamometer and strain gauge. We also acknowledge product donations and financial support from Bayer Incorporated, Canus Canada, Company’s Coming Publishers, Kerr Brothers Ltd., and Pfizer Canada, University of Windsor Women’s Research Grant.
References -


17. Jakobi JM, Rice CL. Voluntary muscle activation varies with age and muscle group. *J


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40. Fahim MA, el-Sabban F, Davidson N. Muscle contractility decrement and correlated


### Table 1. Anthropometric data of persons with Type 2 diabetes and control individuals. Values = mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Diabetes</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>52.6 ±6.2 (50.5 ± 5.5 ♀, 54.5 ± 6.0 ♂)</td>
<td>51.7 ±6.9 (49.5 ± 7.6 ♀, 55.0 ± 4.7 ♂)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>102.0 ±18.6 (93.3 ± 16.2 ♀, 97.8 ± 8.8 ♂)</td>
<td>99.2 ±18.7 (103.4 ± 21.9 ♀, 92.9 ± 12.7 ♂)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>172.6 ±12.0 (161.5 ± 6.9 ♀, 175.3 ± 3.8 ♂)</td>
<td>170.4 ±6.3 (167.5 ± 4.9 ♀, 174.8 ± 6.0 ♂)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>YPAS (hours/week)</strong></td>
<td>28.8 ± 20.3</td>
<td>20.3 ± 27.3</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Vigorous Activity Score</strong></td>
<td>11.5 ± 12.03</td>
<td>19.5 ± 16.7</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Leisure Index Score</strong></td>
<td>16.4 ± 15.1</td>
<td>13.2 ± 9.2</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Moving Index Score</strong></td>
<td>8.7 ± 2.9</td>
<td>9.0 ± 4.0</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Glucose (mmol/L) at time of strength test</strong></td>
<td>8.33 ±2.21</td>
<td>5.50 ±0.95</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>8.4 ±1.3</td>
<td>6.1 ±0.4</td>
<td>0.0000</td>
</tr>
<tr>
<td><strong>Foot Ulcers</strong></td>
<td>n=0</td>
<td>n=0</td>
<td>n/a</td>
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</table>
Table 2. Functional mobility, balance and daily activity scores. Values = mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Type 2 diabetes</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSES</td>
<td>6.8 ±2.3</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>MNSI (%)</td>
<td>30.3 ±12.1</td>
<td>25.2 ±13.2</td>
<td>0.62</td>
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<tr>
<td>Monofilament Score (/10)</td>
<td>9.8 ±0.4</td>
<td>9.9 ±0.17</td>
<td>0.21</td>
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<tr>
<td>Berg Balance Scale (%)</td>
<td>94.8 ±3.3</td>
<td>97.6 ±2.0</td>
<td>0.14</td>
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<tr>
<td>TUG (s)</td>
<td>9.5 ±2.2</td>
<td>8.8 ±1.3</td>
<td>0.37</td>
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<tr>
<td>Stair Time (s)</td>
<td>85.1 ±14.0</td>
<td>80.4 ±28.8</td>
<td>0.69</td>
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<tr>
<td>Resting heart rate (BPM)</td>
<td>72.2 ±9.2</td>
<td>69.9 ±9.4</td>
<td>0.93</td>
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<tr>
<td>Post-Exercise HR (BPM)</td>
<td>Normal Pace</td>
<td>117.2 ±13.9</td>
<td>120.5 ±18.8</td>
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<tr>
<td></td>
<td>Fast Pace</td>
<td>126.0 ±15.8</td>
<td>135.7 ±23.3</td>
</tr>
<tr>
<td>Predicted Submaximal V0₂ (ml/kg/min)</td>
<td>Normal Pace</td>
<td>25.3 ±4.4</td>
<td>27.4 ±6.1</td>
</tr>
<tr>
<td></td>
<td>Fast Pace</td>
<td>31.1 ±5.1</td>
<td>33.2 ±2.4</td>
</tr>
</tbody>
</table>
Table 3. Voluntary and involuntary force results for persons with T2D compared to matched controls. Values = mean ± SD.

<table>
<thead>
<tr>
<th>Twitch Contractile Properties</th>
<th>T2D</th>
<th>Control</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Peak Torque (Nm)</td>
<td>4.1 ±1.5</td>
<td>3.9 ±1.3</td>
<td>0.66</td>
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<tr>
<td>Time to Peak Torque (ms)</td>
<td>94.8 ±11.3</td>
<td>100.3 ±13.0</td>
<td>0.36</td>
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<tr>
<td></td>
<td>114.5 ±22.9</td>
<td>105.8 ±20.0</td>
<td>0.49</td>
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<tr>
<td>Half-relaxation time (ms)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MVC Peak Torque (Nm)</td>
<td>39.6 ±9.6</td>
<td>34.3 ±7.6</td>
<td>0.19</td>
</tr>
</tbody>
</table>

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Figure 1: SF-36 score (per cent) for emotional problems, physical health, emotional well-being, and general health comparing control and diabetes groups.
Figure Legends –

Figure 1: Health related questionnaire scores, as assessed with the SF-36. Persons with type 2 diabetes differed from controls (p<0.05) for all variables. Values are means ± SD.
<table>
<thead>
<tr>
<th><strong>NAME</strong></th>
<th>Lynette Alicia Singh-Peters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLACE OF BIRTH</strong></td>
<td>North York, Ontario</td>
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<tr>
<td><strong>DATE OF BIRTH</strong></td>
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</tr>
<tr>
<td><strong>EDUCATION</strong></td>
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</tr>
<tr>
<td></td>
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