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Characterization of Quadriceps Neuromuscular Function in Knee Osteoarthritis

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Kinesiology

CHARACTERIZATION OF QUADRICEPS NEUROMUSCULAR FUNCTION IN KNEE OSTEOARTHRITIS

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SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

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Characterization of Quadriceps Neuromuscular Function in Knee Osteoarthritis

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ABSTRACT

PURPOSE: The purpose of this thesis was to characterize quadriceps neuromuscular dysfunction in patients with knee osteoarthritis (OA). Concerns pertaining to study design in this patient population (e.g. disease severity criteria and muscle imaging outcome measures) were also addressed.

METHODS: Five studies were undertaken using data acquired from volunteers recruited at the local institution and from participants in the public source dataset of the Osteoarthritis Initiative (http://oai.epi-ucsf.org/datarelease/). Clinical disease severity was evaluated with the Western Ontario and McMaster Osteoarthritis Index (WOMAC). Radiographic severity was evaluated with Kellgren-Lawrence Grading (KLG). Quadriceps muscle isometric strength and isotonic power were measured with dynamometry. Voluntary activation (VA) of the quadriceps was determined with the interpolated twitch technique. Information about intrinsic properties of the neuromuscular system were assessed with magnetic resonance imaging (MRI) derived measures of muscle volume, intramuscular and surface electromyography and measurement of evoked contractile properties.

RESULTS: Radiographic definition of disease severity displayed a ceiling effect and led to underestimation of quadriceps muscle weakness in patients with knee OA (Chapter 2). Quadriceps muscle isometric strength, velocity and isotonic power were reduced across a clinical spectrum of knee OA, however muscle quality (i.e. specific torque and specific power were unaffected, Chapter 3). Quadriceps whole muscle volume, measured with MRI can be reliably measured and was strongly associated with isometric strength (Chapter 4). VA deficits were minimal in knee OA

patients, even in those with severe knee pain and disability (Chapter 5). No changes in evoked contractile properties were observed across a clinical spectrum of knee OA, however average motor unit size was larger and firing rates slightly lower in patients with knee OA compared to healthy controls during submaximal contractions (Chapter 6).

CONCLUSION: This thesis provided information about the magnitude and mechanisms of quadriceps neuromuscular dysfunction in patients with knee OA, which have consequences with regard to the treatment and prognosis of this disorder. Furthermore, the information provided about the validity of commonly used predictor variables and outcome measures has implications for future study design in this disease population.

KEYWORDS: knee osteoarthritis, quadriceps strength, quadriceps power, interpolated twitch technique, magnetic resonance imaging, Kellgren-Lawrence grading, motor unit

CO-AUTHORSHIP

This thesis contains material from submitted manuscripts (Chapters 2, 3, 4, 5 and 6). On all manuscripts Michael J. Berger was the first author and Timothy J. Doherty was a co-author. Crystal O. Kean and Aashish Goela were co-authors on Chapter 2. Charlie A. McKenzie was a co-author on Chapters 3, 4 and 5. David G. Chess was a co-author on Chapters 3, 4, 5 and 6.

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LIST OF ABBREVIATIONS

AAR – area-to-amplitude ratio

ACSA – anatomical cross sectional area

ADLs – activities of daily living

BMI – body mass index

DESTA – decomposition-enhanced spike triggered averaging

DQEMG – decomposition-enhanced quantitative electromyography

EMG - electromyography

FOV - field-of-view

HRT – half-relaxation time

ICC – intraclass correlation coefficient

IDEAL - iterative decomposition of water and fat with echo asymmetry and least squares estimation

KLG – Kellgren-Lawrence grading

MHC – myosin heavy chain

MRI – magnetic resonance imaging

MU – motor unit

MUP – motor unit potential

MVC – maximal voluntary contraction

N-MUP – needle motor unit potential

OA – osteoarthritis

OAI – Osteoarthritis Initiative

PF – patellofemoral compartment

P_T – peak twitch tension

ROI – region-of-interest

S-MUP – surface motor unit potential

SPGR – spoiled gradient echo

TE – echo time

TF- tibiofemoral compartment

TPT – time-to-peak twitch

TR – repetition time

VA – voluntary activation

WOMAC – Western Ontario and McMaster Osteoarthritis Index

Zero Load - Isotonic power measured at the minimum programmable load of the Biodex dynamometer

CHAPTER 1

QUADRICEPS MUSCLE WEAKNESS IN KNEE OSTEOARTHRITIS

1.0 GENERAL INTRODUCTION

1.0.1 Knee Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis, affecting over 10% of adults in Canada.[1] The prevalence of OA increases with age and the burden on health care systems will increase exponentially as older adults continue to comprise a larger proportion of the population. By age 65, up to 80% of people have radiographic features of OA in at least one joint.[45] The knee is a frequently affected joint in the lower limb with up to 65% of people over age 65 years of age demonstrating radiographic evidence of knee OA.[6]

The characteristic structural features of knee OA are articular hyaline cartilage degradation (seen as non-uniform joint space narrowing on X-ray), osteophytosis, bony sclerosis and subchondral cyst formation (Figure 1.1). The knee is a tri-compartmental joint (patellofemoral, medial tibiofemoral and lateral tibiofemoral compartments) and OA can be isolated or multi-compartmental. The hallmark symptoms of knee OA are pain on most days, morning stiffness (usually lasting less than 30 minutes), the absence of systemic features and instability leading to a reduction in the capacity to perform activities of daily living (ADLs). Data from the Framingham study reveal that disability caused by knee OA equals heart disease and is greater than other common diseases of aging such as diabetes

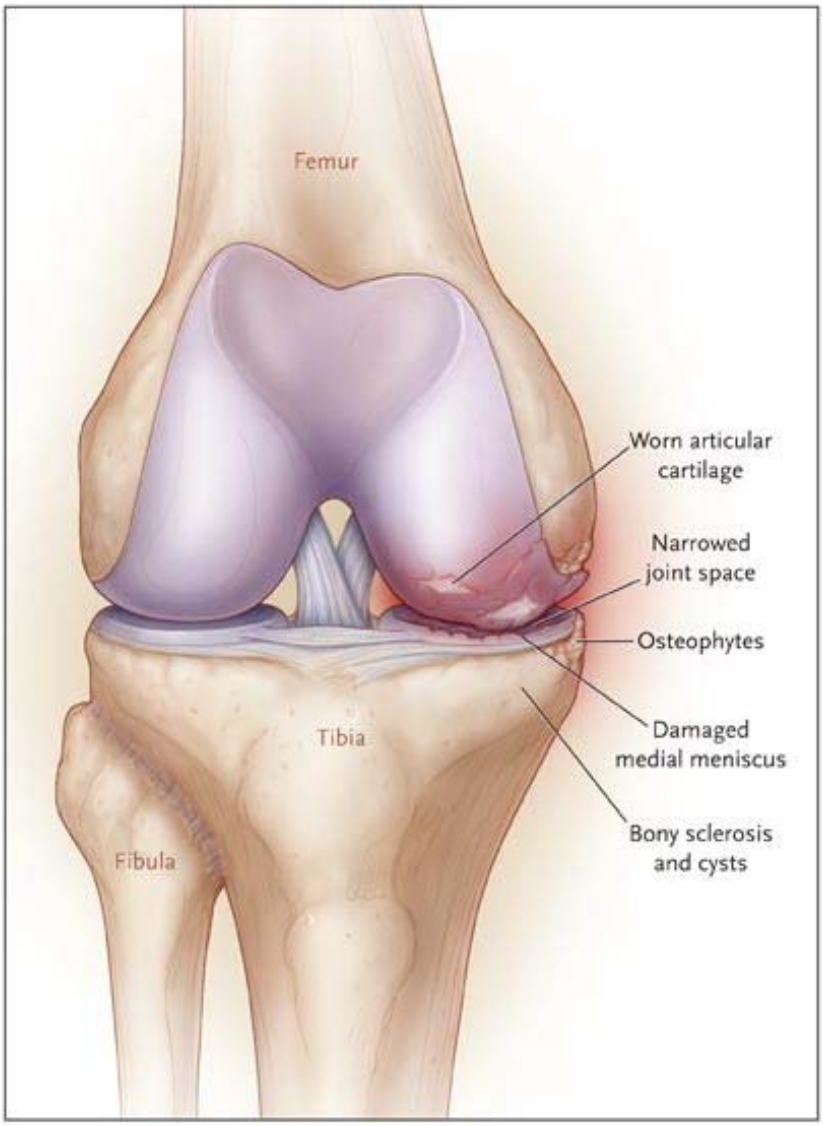

Figure 1.1 Osteoarthritis of the medial side of the knee (From Felson DT. Clinical Practice. Osteoarthritis of the knee. N Engl J Med 2006; 354(8): p 841-8).[22] Used with permission from the Massachusetts Medical Society.

and chronic obstructive pulmonary disorder.[31] Consequently, an understanding of the etiology, pathophysiology and natural history of knee OA is paramount. Traditionally, knee OA has been defined as a disease of articular cartilage and accordingly, a large proportion of the literature is devoted to understanding the molecular mechanisms of cartilage degradation in order to develop treatments aimed at preventing cartilage loss (i.e. chondroprotection). However, chondroprotection strategies have proven unsuccessful thus far and may not adequately address the symptom of knee pain as cartilage itself is aneural.[23] A more recent approach asserts that knee OA constitutes "whole organ failure" as all joint structures including cartilage, bone, ligaments, synovium, menisci and muscle are affected.[37] In particular quadriceps muscle weakness is associated with pain and loss of function and has been suggested as a risk factor for disease incidence and progression.[21] Quadriceps muscle strengthening has long been an accepted part of the continuum of strategies designed to reduce symptoms of knee OA (Figure 1.2).[71, 72] However, the effect sizes of knee extensor strengthening on quality of life outcome measures are small[25] and some clinical trials using quadriceps exercise as an intervention have not shown positive results.[5] Also, a single clinical trial failed to report any benefit for quadriceps strengthening on structural knee OA progression[53] and there is evidence that decreased quadriceps strength is even a risk factor for disease progression in malaligned and lax knee joints.[64] An incomplete understanding of the magnitude, mechanisms and natural history of quadriceps weakness, leading to inappropriate and poorly timed interventions could be

1.0.2 Quadriceps Muscle Weakness in Aging and Knee Osteoarthritis

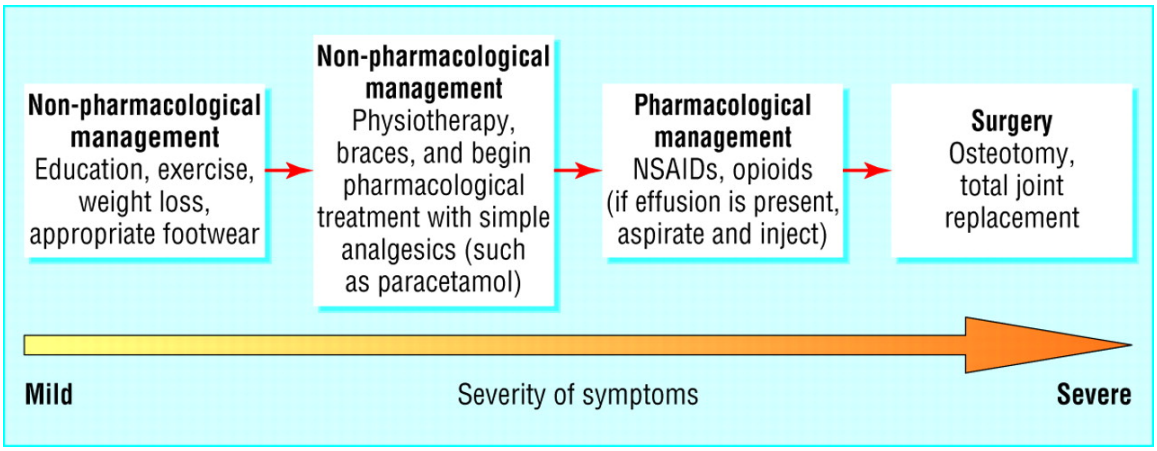

Figure 1.2 Stepwise algorithm for the management of patients with osteoarthritis. This is an example of a treatment algorithm that is modified according to a patient's response and clinician's preference. It highlights the encompassing need to consider non-pharmacological management as first line for all patients (From Hunter DJ and Felson DT. Clinical Practice. Osteoarthritis. BMJ 2006; 332(7542): p 639-42).[37] Used with permission from BMJ Publishing Group Ltd.

Both OA and normal biological aging are associated with a decline in skeletal muscle function and mobility that can be attributed in part to a loss of muscle strength. It has been reported that such deficits are magnified in older subjects with chronic knee pain or radiographic evidence of knee OA. For healthy older subjects between 60-80 years, knee extensor strength appears to be 20-40% lower than healthy young subjects for isometric, isokinetic and isotonic contractions.[19, 69, 70] It is important to note that quadriceps weakness in knee OA is not simply a result of aging as knee extensor strength is reduced an additional 20-40% for isometric [33, 38, 40, 47, 48] and isokinetic [24, 32, 35, 65] contractions, compared to healthy older subjects.

In healthy older adults, cross-sectional and longitudinal observations have shown that strength loss begins in the 6th decade but its progression is highly variable depending on the individual and muscle group studied.[43] With respect to studies of the knee extensors, Frontera et al. showed decrements in isokinetic knee extensor strength of 23% for slower velocities (60°/s) and 30% for higher velocities (240°/s), along with a significant decrease in muscle cross-sectional area (CSA), during a 12-year follow-up of male subjects from a previous study.[26] Interestingly, cross-sectional data from this group estimated the rate of strength loss to be 1.5 $N \cdot m^{-1} \cdot yr^{-1}$, compared to 3.2 $N \cdot m^{-1} \cdot yr^{-1}$ in the follow-up study, suggesting that cross-sectional studies underestimate the rate of strength decline in this population.[27] Similarly, Aniansson and colleagues found a reduction in isokinetic knee extensor strength (30°/s) of 18% for males and 13% for females between 70 and 75 years.[4] Hughes et al. found a decline of 14%/decade between 46 and 78 years, with the rate of strength loss higher in the older subjects of the study group, while testing for

isokinetic strength at a velocity of 60°/s.[36] Information about the rate and magnitude of decline in knee OA is limited to a single study. Messier et al. documented changes in physical function and balance over a 30-month period in 480 subjects aged 65-85 years with chronic knee pain and knee OA.[52] The results showed significant decrements in lower-extremity isokinetic strength (concentric knee extension declined by 12.1%). It should be noted that subjects in the upper quartile of strength at baseline experienced the lowest rate of decline, whereas those in the lowest baseline strength quartile experienced the highest, suggesting a protective effect for lower-extremity muscle strength in OA. This longitudinal study provides evidence of progressive muscle dysfunction in knee OA, however it is not conclusive for a more rapid rate of decline compared to a healthy cohort. Taken altogether, the results of the aforementioned studies indicate that the rate of isokinetic knee extensor strength decline in healthy subjects is between 1.5-3%/year, in comparison to the study by Messier et al. (in OA subjects) reporting a decrement in isokinetic strength of 4.8%/year. This tangential comparison is of limited utility in that it doesn't consider differences in age, sex and methodology, but it does highlight the need for further research into the possibility that the rate of strength decline is more rapid in knee OA. The consequences of reduced quadriceps strength are twofold; 1) the quadriceps may act to protect the knee joint from harmful loading forces, thereby preventing disease incidence and progression; and 2) quadriceps muscle impairment leads to disability.

1.0.3 Quadriceps Muscle Weakness as a Risk Factor For Incident and Progressive Knee Osteoarthritis

Risk factors for development and progression of knee OA are divided broadly into systemic versus local.[21] There is evidence to suggest the breakdown of neuromuscular protective mechanisms around the knee joint (e.g. quadriceps muscle weakness) is a local and modifiable risk factor that increases the risk for knee OA. In two cross-sectional studies, quadriceps weakness was significantly correlated with radiographic knee OA even in those who did not describe symptoms of knee pain.[6, 65] In a longitudinal prospective cohort study, Slemenda et al. followed healthy women for a mean of 31.3 months and reported that quadriceps muscle strength in women who developed radiographic knee OA was 18% lower than those who did not.[66] Further evidence comes from Becker et al. who reported reduced quadriceps strength in a group of patients who had undergone medial meniscectomy (presumably a "preosteoarthritic" state), compared to healthy controls.[10]

Biomechanical analysis of gait may provide a plausible mechanism to explain how quadriceps muscle weakness causes incident and progressive disease. Eccentric contraction of the quadriceps muscle prior to and during heel strike provides deceleration of the lower limb and shock absorption from the loading impulses generated at heel-strike during the gait cycle.[16] A few studies report increases in loading forces in models of weak quadriceps, but these findings have not been extended to models of knee OA.[42, 58] A more likely scenario involves a complex interplay of neural gait strategy, knee joint alignment and quadriceps function causing abnormal loading forces on a susceptible knee joint.[60, 62] In animal models, quadriceps weakness induced by botulinum injection actually caused

reduced loading forces across the knee joint, but led to degenerative changes in patellofemoral cartilage.[50, 59] Despite conflicting evidence as to the exact mechanism, altered quadriceps muscle function is implicated in disease initiation.

Studies of disease progression and quadriceps function are more limited and less consistent than studies of disease incidence. One longitudinal study reported no protective effect for quadriceps muscle strength on structural disease progression.[15] Furthermore, a clinical trial for quadriceps strength training reported no benefit on structural OA outcome measures.[53] It could be that the effect of quadriceps strength is dependent on the stability and alignment of the knee joint affected,[64] although more experimental evidence is needed to substantiate this theory.

1.0.4 Mechanisms of Quadriceps Muscle Weakness in Knee Osteoarthritis

The traditional model of muscle weakness in knee OA is one whereby chronic disuse due to knee pain precipitates muscle atrophy, resulting in further disuse. There are a few studies providing direct evidence that muscle atrophy (presumably from disuse) is a primary mechanism of quadriceps muscle weakness. Ikeda et al. reported a 12% reduction in quadriceps muscle mass in women who displayed evidence of incident radiographic knee OA compared to those who did not.[41] Subsequently, Peterson et al. reported that patients with end-stage (KLG = IV) radiographic knee OA displayed a 12% reduction in muscle cross-sectional area compared to a healthy contralateral leg.[57] It is possible that quadriceps muscle weakness in knee OA represents a process of "accelerated aging" whereby the mechanisms of sarcopenia (e.g. muscle fibre loss, increased proportion of the type I

muscle fibres and selective type II fibre atrophy) are occurring at a faster rate.[19] In support of this theory, a recent study by Ling et al. assessed motor unit (MU) properties during voluntary contractions in patients with radiographic knee OA.[48] During low-intensity contractions, the mean amplitude of the surface motor unit action potential (S-MUP) sampled with needle electromyography was higher for knee OA patients than for controls. This finding is consistent with the MU denervation-collateral reinnervation process documented in healthy aging, which accounts for larger MUs being recruited at low-intensity contractions.[68] Further study of muscle contractile and MU properties as well as analysis of individual muscle fibre properties is required to determine if atrophy is occurring and identify potential mechanisms.

Beyond disuse atrophy, there is ample evidence supporting impairment in neuromuscular function as a cause of reduced strength. Numerous studies report a reduction in the ability of the central nervous system to recruit and maximally rate code all available MUs during maximal voluntary contraction (i.e. voluntary activation (VA) deficits).[10, 14, 33, 38, 40, 57, 67] Afferent excitation from pain, effusion or joint damage, may lead to increased alpha-motor neuron inhibition during voluntary contractions, a mechanism termed "arthrogenous muscle inhibition".[38] Other studies have shown no difference in VA between knee OA and healthy subjects, in particular in younger subjects with less severe disease.[34, 47] It is possible that disease severity determines the ability to maximally activate the quadriceps, although this has yet to be examined.

Another proposed neuromuscular mechanism for reduced strength is an increase in co-contraction of the antagonist muscles, perhaps in an attempt to stabilize an abnormal knee joint.[46] At this point, only one study has investigated co-contraction as a mechanism for reduced quadriceps muscle strength in knee OA with no changes in co-contraction reported.[34] Until the mechanisms of muscle weakness in knee OA are accurately characterized, the design of mechanism-appropriate rehabilitation strategies is challenging.

1.0.5 Relationship with disability

Research highlighting the causes of disability and pain in knee OA is essential to the process of developing rehabilitation programs to combat the burden of disease. It has been documented that the severity of radiographic change alone is a poor predictor of clinical symptoms of OA,[18, 51, 54, 56] but a large proportion of research is still aimed at establishing causation between risk factors and radiographic onset and progression. Lower extremity muscle strength is a critical predictor of functional performance and dynamic stability during ADLs, and disability is common as strength declines with age. Although less attention has been devoted to these principles by OA researchers, available data suggest that the reduction in quadriceps muscle strength creates a significant disability burden in this population. Two large studies of community dwelling subjects reported that muscle weakness is a stronger predictor of disability and pain than structural radiographic OA. McAlindon et al. assessed disability with the Stanford Health Assessment Questionnaire[44] in 155 subjects and found a significant protective association with isometric quadriceps strength (OR=0.84).[51] There was no

association between Kellgren-Lawrence grade (KLG) and disability. O'Reilly et al, measured similar variables in 300 subjects and found that muscle strength was a significantly stronger predictor of knee pain than radiographic score.[55] In addition, the authors analyzed a subgroup of those with knee pain independently and found that muscle strength, but not radiographic score was strongly predictive of disability in this subgroup. Both of these studies stratified strength into quartiles, with those in the lowest quartile experiencing a threefold or more increase in disability and pain.

The results of large prospective population studies confirm cross-sectional data and also establish the temporality of the relationship, with muscle weakness preceding disability. In the Women's Health and Aging Study II, Ling et al. found that knee extensor strength was an independent predictor of the transition from normal function to both mobility and ADL limitations over 72 months, in women aged 70-79 with knee OA.[49] Furthermore, longitudinal studies have shown that lower knee extensor strength increases the risk of poor function in previously disabled adults with OA. Messier et al, found that the greatest declines in isokinetic strength over thirty months in those aged 65 years and older with chronic knee pain were associated with the worst balance scores (measured as the excursion of the centre of pressure in the anterioposterior plane on a force platform).[52] Over three years, Sharma et al. found that performance during a chair-stand test was strongly influenced by maximal isometric quadriceps strength and proprioception, in those with radiographic knee OA at baseline.[63] However, the relationship between strength and performance was lost after adjustment for knee pain and scores on a

self-efficacy scale, highlighting the close relationship between muscle strength, pain and psychological factors.

Thus it is evident that in order to reduce the disability burden in those with knee OA, quadriceps muscle weakness must be attenuated. It is the objective of this thesis to characterize the magnitude, natural history and mechanisms of quadriceps muscle dysfunction in knee OA. A comprehensive understanding of quadriceps muscle function in this disease population will provide a scientific basis for the interventions and outcomes used in clinical trials designed to attenuate weakness, disability and perhaps the disease process itself.

1.1 OVERVIEW OF THESIS CHAPTERS

The objectives of this thesis are 1) to determine how variability in study methodology influences the measurement of quadriceps muscle parameters in knee osteoarthritis (OA) and 2) to gain insight into the natural history and mechanisms of quadriceps muscle dysfunction across a clinical spectrum of knee OA. To address the first objective, data obtained from patients recruited locally was analyzed in conjunction with data obtained from the public use datasets of the Osteoarthritis Initiative (OAI, version 0.2.2 clinical dataset, version 0.E.1 imaging dataset; online at www.oai.ucsf.edu). The influence of disease severity definition (i.e. radiographic vs. clinical) on isometric quadriceps muscle weakness was assessed (experiment 1), along with the effect of muscle size definitions, clinical disease severity and segmentation procedures on the quadriceps muscle size-strength relationship (experiment 3). To address the second objective, locally recruited volunteers stratified into clinically defined mild, moderate and severe knee OA subgroups,

underwent comprehensive neuromuscular evaluation. Quadriceps muscle strength and power (experiment 2), muscle volume and voluntary activation (VA, experiment 4) and muscle contractile and motor unit (MU) properties (experiment 5) were assessed across a clinical spectrum of disease, to gain further insight into the natural history and mechanisms of neuromuscular dysfunction in knee OA.

1.1.1 Experiment 1

Objectives: To determine 1) the influence of disease severity definition (i.e. clinical versus radiographic) on outcome measurement in knee OA research, 2) the natural history and magnitude of quadriceps muscle weakness in patients with knee OA and 3) the relationship between two commonly used measurement tools in knee OA research; The Western Ontario and McMaster Osteoarthritis Index (WOMAC)[12] and Kellgren-Lawrence Grading (KLG) for radiographic knee OA.

Rationale: Assessment of the relationship between clinical and radiographic knee OA is necessary because 1) the definition of disease severity status using a composite index of pain, structural and functional features has been identified as a means of developing valid outcome measures for clinical trials,[30] 2) stratification of patients in descriptive and randomized studies is commonly performed using radiographic criteria in isolation or combined with clinical criteria[61] and 3) X-rays are perceived to be helpful in making management decisions by clinicians.[11] Any discrepancy between clinical and radiographic features has potential negative consequences, including heterogeneity in the severity of study groups (e.g. severe clinical but mild radiographic disease) and a confounding influence on OA

management. WOMAC and KLG are routinely used in knee OA research (both as predictor variables and outcome measures) and the nature of their relationship remains unclear.[7, 17, 20]

1.1.2. Experiment 2

Objective: To determine whether deficits in quadriceps isotonic power exist across a clinical spectrum of knee OA and whether these deficits predict loss of function.

Rationale: Many studies have documented deficits in isometric and isokinetic knee extensor strength in patients with knee OA compared to healthy controls and/or a healthy contralateral limb.[13] No study to date has investigated whether a similar deficit in muscle power (the product of torque and velocity) exists or whether the torque-velocity relationship is affected. Reports from the literature on aging suggest that power deficits are more robust than isometric strength measures in predicting reduced ability to perform the activities of daily living.[8, 9]

1.1.3. Experiment 3

Objective: To describe the quadriceps muscle size-strength relationship in patients with knee OA and to determine the influence of variation in 1) muscle size measures derived from magnetic resonance imaging (MRI; e.g. whole muscle volume vs. single slice anatomical cross-sectional area; ACSA), 2) disease severity and 3) MRI protocol, on this relationship.

Rationale: Despite the evidence that the number and size of muscle fibres is a primary determinant of strength,[29] between-study variation in the size-strength

relationship has been reported, with some studies observing weak-to-moderate correlations[2, 70] and others observing stronger relationships.[28] In particular, one study of patients with severe structural knee OA observed that mid-thigh quadriceps ACSA predicted only 27% of the variance in isometric quadriceps strength.[57] It has been suggested that variation in the size-strength relationship is due to differences in the definition of muscle size.[3]

1.1.4. Experiment 4

Objective: To determine the mechanisms underlying quadriceps muscle weakness in knee OA.

Rationale: It is commonly proposed that quadriceps weakness in knee OA is due to atrophy from pain, disuse or both.[13] Few studies however, have attempted to document and quantify the extent of muscle atrophy. Furthermore, there is evidence from some studies, that deficits in VA (presumably from joint pain causing afferent inhibition of motor neurons) are responsible for strength deficits,[14, 33, 38, 39] though not all studies have observed this phenomenon.[47] Additionally, no study to date has investigated whether the mechanisms of muscle weakness are altered throughout the natural history of disease.

1.1.5. Experiment 5

Objective: To determine whether evoked quadriceps muscle contractile properties and MU properties are altered in knee OA.

Rationale: It was observed that quadriceps muscle strength is strongly associated with quadriceps muscle volume (experiment 3) and that volume is less in those with severe knee OA (experiment 4). This confirms that preserving muscle size is critical to attenuation of strength deficits in knee OA, however it does not confirm that atrophy is occurring or that a disuse scenario is responsible for weakness. Assessment of evoked contractile properties (e.g. twitch properties and modeling of the torque-frequency relationship) can provide information about muscle fibre properties. Decomposition-enhanced quantitative electromyography (DQEMG) provides information concerning MU size, recruitment patterns and firing characteristics. If disuse atrophy is occurring, characteristic changes in evoked contractile and MU properties should also be observed.

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CHAPTER 2

DEFINITION OF DISEASE SEVERITY INFLUENCES OUTCOME MEASUREMENT IN PATIENTS WITH KNEE OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INTITIATIVE

2.0 INTRODUCTION

The relationship between radiographic and clinical features of knee osteoarthritis (OA) is difficult to define and the literature in this area is equivocal. Some studies report discordance between the degree of severity of radiographic and clinical features,[15, 26] while others have observed modest-to-strong associations.[11, 24, 36] The continued examination of the relationship between clinical and radiographic knee OA is necessary because 1) the definition of disease severity status using a composite index of pain, structural and functional features has been identified as a means of developing valid outcome measures for clinical trials,[14] 2) stratification of patients in descriptive and randomized studies is commonly performed using radiographic criteria in isolation or combined with clinical criteria[31] and 3) X-rays are perceived to be helpful in making management decisions by clinicians.[5, 6]

Discrepancy between clinical and radiographic categorization of severity for knee OA has potential negative consequences including adding inappropriate heterogeneity in the severity of study groups (e.g. severe clinical but mild radiographic disease) and serving as a confounding variable when considering clinical management of OA. Duncan et al. reported a moderate relationship between radiographic disease severity defined by Kellgren-Lawrence grade (KLG) and clinical severity measured with the Western Ontario and McMaster Osteoarthritis Index (WOMAC).[11] This suggests that the use of either of these tools to define

disease severity states should affect an outcome measure similarly (i.e. the value of an outcome measure should be similar regardless of disease definition). Others have reported that KLG is a poor predictor of clinically relevant outcomes, including WOMAC.[4, 10] Therefore, it remains unclear how the definition of disease (i.e. radiographic vs. clinical) affects the measurement of common outcomes in knee OA research.

Quadriceps muscle strength is a clinically relevant outcome measure in knee OA, which has been shown to have a protective effect against pain and loss of function.[23, 25] Furthermore, the likelihood of experiencing quadriceps weakness is increased in the presence of radiographic disease, although this relationship is not as consistent as the relationship between weakness, pain and function.[3] It is well known that the quadriceps muscles are weaker in OA compared to healthy-contralateral limbs or age-matched controls.[8] For example, quadriceps muscle weakness was observed across a radiographic spectrum of knee OA, however no difference in strength was noted between those with KLG =2 and those with KLG >2, suggesting a possible ceiling effect for this method of disease stratification.[27] The extent of muscle weakness across a clinical spectrum of knee OA has yet to be assessed. The purpose of this study was to determine whether muscle weakness occurs across a clinical spectrum of knee OA and whether the definition of knee OA (clinical vs. radiographic) has an impact on the magnitude of measured weakness. A secondary purpose was to further examine the relationship between WOMAC and KLG.

2.1 METHODS

Data for the analysis of tibiofemoral (TF) knee OA was obtained from the public use datasets (version 0.2.2 clinical dataset) of the Osteoarthritis Initiative (OAI; online at www.oai.ucsf.edu), a multicentre, longitudinal cohort study designed to identify biomarkers for the development and progression of symptomatic knee OA. The OAI dataset comprises demographic, clinical and imaging data on 4796 patients (age 45-79) from four centres. Only baseline data from tibiofemoral (TF) compartment of native (i.e. non-replaced) right knees of the progression sub-cohort were analyzed in this study. Eligibility for the progression sub-cohort was based on the presence of pain, aching or stiffness in or around the knee for at least one month during the last 12 months and the presence of TF osteophytes (Osteoarthritis Research Society International atlas, grade ≥ 1),[1] on a posterio-anterior fixed-flexion knee x-ray. A description of the rationale for these criteria and a full list of exclusion criteria can be found on the OAI website (www.oai.ucsf.edu/datarelease/OperationsManuals.asp). Other inclusion criteria were the availability of baseline KLG and completion of three trials of isometric knee extension testing. After excluding patients failing to meet the inclusion criteria, the analysis was conducted on 659 participants. Institutional review board approval was obtained at the participating sites (Baltimore, MD; Columbus, OH; Pittsburgh, PA, and Pawtucket, RI) and written informed consent was obtained from each participating subject.

2.1.1 Measurement of clinical severity

WOMAC is a validated questionnaire that is widely used to quantify clinical severity of knee OA.[7] The WOMAC Likert version 3.1 has 24 items and is divided

into pain, stiffness and function domains. Each item has 5 response options (none, mild, moderate, severe, extreme) corresponding to scores 0-4, with higher scores indicating increasing severity (see Appendix A). In order to compare muscle strength across a clinical spectrum of OA, WOMAC was used as an independent variable whereby total score (24 items, total score 0-96) was used to stratify study participants into tertiles with the lowest, middle and highest groups representing mild, moderate and severe knee OA, respectively. In order to compare the relationship between WOMAC and KLG, WOMAC total score and pain and function subscale scores (pain: 5 items, total score 0-20, function: 17 items, total score 0-68) were used as dependent variables across a radiographic spectrum of knee OA.

2.1.2 Measurement of radiographic disease severity

KLG was used to assess radiographic severity semi-quantitatively.[13] KLG is performed using a 5 point scale where 0=no changes, 1=doubtful narrowing of joint space and possible osteophytic lipping, 2=definite osteophytes, definite joint space narrowing, 3=moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour and 4=large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.[19] KL<2 was designated mild OA, KL=2 as moderate OA and KL>2 as severe OA.[12] For the TF analysis, standing PA radiographs were acquired using the fixed-flexion protocol, described previously.[28] Briefly, bilateral x-rays were acquired with the patient standing with knees flexed 20-30 degrees and feet internally rotated 10 degrees. Patient positioning was fixed using a plexiglass positioning frame (SyanFlexer, Synarc). Further details can be downloaded at

www.oai.ucsf.edu/datarelease/OperationsManuals.asp. Reliability of KLG was assessed (2 blinded readers) on a subset of the progression cohort with a weighted kappa=0.88 (95%CI 0.82-0.94).

2.1.3 Measurement of isometric muscle strength

Participants completed brief isometric knee extension maximal voluntary contractions (MVC) to measure maximal quadriceps strength. Quadriceps strength was normalized to body mass to control for sex and body size differences between groups. The best trial was used to represent maximal strength. Knee extensor strength in the OAI dataset was assessed with the Good Strength apparatus (Metitur, Jyväskylä, Finland). Briefly, patients were positioned upright in a chair with test leg at 60 degrees from full extension. Two submaximal practice trials were completed, followed by 3 MVCs, each separated by 30 s. A complete description of the protocol and data collection process can be downloaded at www.oai.ucsf.edu/datarelease/OperationsManuals.asp.

2.1.4 Statistical analysis

One-way ANOVA with Tukey's honestly significant differences test was used to assess between-group differences for muscle strength for both clinical and radiographic disease definitions. The relationship between muscle strength and WOMAC score was described by the Spearman rank correlation coefficient. The Kruskal-Wallis test with post-hoc Dunn's multiple comparisons test was used to determine between group differences for WOMAC total and subscale scores (excluding stiffness subscale) for radiographic severity. The relationship between the dependent variable (strength) and possible covariates was determined with

Pearson correlation coefficient for both datasets. For the OAI dataset, both sex ($r=0.40$, $p<0.01$) and age ($r=-0.21$, $p<0.01$) were significantly correlated with strength and were therefore tested for their covariate effects. A one-way randomized ANCOVA was performed to rule out the possibility that observed differences in strength between disease severity states were due to covariate effects. Level of significance was set at $p<0.05$. All descriptive data are reported using means ± standard deviation. Statistics were performed with Graphpad Prism Version 5.0b (La Jolla, CA), except for ANCOVA, which was performed using SPSS Version 17.0 (Chicago, IL).

2.2 RESULTS

Basic demographic information for all participants is listed in Table 2.1. The relationship between normalized isometric muscle strength (N/kg) and total WOMAC score is depicted in Figure 2.1. A significant negative correlation was observed ($r=-0.31$, $p<0.05$). Mean strength values for clinical and radiographic predictor variables are listed in Table 2.2. When comparing muscle strength across a clinical disease spectrum, a significant difference was observed ($p<0.05$). With post-hoc testing, all differences between groups were significant, where strength differences were; moderate 10.9% lower than mild, severe 11.2% lower than moderate and 20.9% lower than mild. When KLG of the TF compartment was used as the predictor variable, a significant difference in strength was observed ($p<0.05$). Both moderate (11.2% lower) and severe (8.7% lower) groups were significantly different than the mild group with post-hoc testing. After controlling sex and age covariates, all differences between groups remained significant ($p<0.05$).

The values for pain subscale, function subscale and total WOMAC score across a spectrum of radiographic severity are listed in Table 2.3. A significant difference for total WOMAC score, and pain and function subscale score was observed. Although differences were significant there was variability in WOMAC score across radiographic severity. Coefficients of variation for total WOMAC scores for mild, moderate and severe OA were 79.3%, 74.6% and 61.6%, respectively.

2.3 DISCUSSION

The results of this study suggest that definition of disease severity influences the measurement of quadriceps muscle strength and may similarly affect other clinically relevant outcomes in knee OA research. Furthermore, it appears that there is a ceiling effect to using KLG as a severity stratification tool, such that differences in strength between clinically moderate and severe patients were not observed between radiographically moderate and severe patients. Finally, with increasing KLG, an increase in WOMAC score (both total and subscale scores) was observed, although there was substantial variability in WOMAC scores within radiographic subgroups. This suggests that in a large sample, using KLG should not result in clinically heterogeneous subgroups although the large variability has implications for the management of individual patients.

Quadriceps muscle weakness is a common and early finding in patients with knee OA and its relationship with disability and pain is well established.[2, 22, 23, 25] McAlindon et al. reported reduced likelihood of disability in knee OA patients with better quadriceps strength.[23] Subsequently, O'Reilly et al. observed that quadriceps weakness was independently associated with pain and that there was an increased

Table 2.1 Patient characteristics.

n	659
Age	61.4±9.0 (45:79)
Height (m)	1.69±0.09 (1.48:1.90)
Weight (kg)	85.5±16.4 (48.8:131.4)
Body Mass Index (kg/m^2)	29.9±5.0 (19.5:48.7)
Sex (male/female)	289/370

Data are presented as mean ± standard deviation. Data in parentheses indicate range.

Table 2.2 Normalized isometric quadriceps muscle strength across clinical and radiographic spectra of tibiofemoral knee OA. Values for strength are in N/Kg.

Predictor Variable	Mild	Moderate	Severe	p-value
WOMAC	4.49±1.51	4.00±1.44*	3.55±1.35*†	<0.05
KLG	4.38±1.59	3.89±1.59*	4.00±1.34*	<0.05

WOMAC: Western Ontario and McMaster Osteoarthritis Index; KLG: Kellgren-Lawrence grading of the tibiofemoral joint. For the WOMAC predictor variable, participants were stratified into severity groups based on tertiles of WOMAC score. For KLG predictor variables KLG<2, KLG=2 and KLG>2 represented mild, moderate and severe radiographic disease respectively. Data are presented as mean ± standard deviation.

*Significantly different than mild OA ($p<0.05$)

†Significantly different than moderate OA ($p<0.05$)

Table 2.3 WOMAC scores across tibiofemoral osteoarthritis disease severity measured by Kellgren-Lawrence grade.

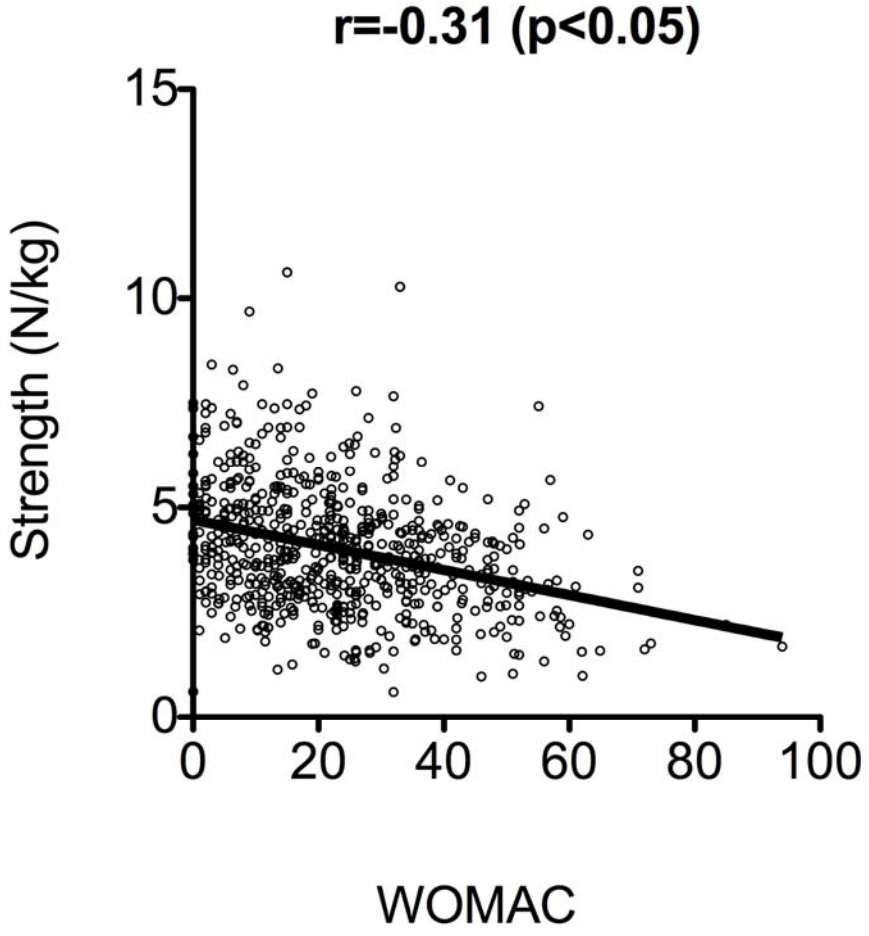
Predictor Variable	**KLG<2**	**KLG = 2**	**KLG>2**	**p-value**
Pain	3.97±3.47	4.70±3.87	5.20±3.56*	<0.05
Function	12.25±10.87	15.50±12.76	16.40±11.20*	<0.05
Total	18.4±14.6	23.1±17.2*	24.7±15.2*	<0.05

WOMAC: Western Ontario and McMaster Osteoarthritis Index; KLG: Kellgren-Lawrence grade.

Data are presented as mean±standard deviation.

*Significantly different than mild OA ($p<0.05$)

Figure 2.1 The relationship between total WOMAC score and quadriceps muscle strength (N/kg) for 659 patients. A significant ($p<0.05$) negative linear correlation was observed with $r=-0.31$. WOMAC: Western Ontario and McMaster Osteoarthritis Index.


r=-0.31 (p<0.05)
Strength (N/kg)
15
10
5
0
0
20
40
60
80
100
WOMAC

likelihood of disability if weakness was present in a pain positive OA group.[25] In both of these studies, weakness was a stronger predictor of pain and/or disability than the presence of radiographic knee OA. Our observations add to previous literature given that prior studies defined disease and weakness dichotomously (e.g. pain present or absent). We observed an association between quadriceps strength and a continuous measure of disease severity (Figure 2.1). Moreover, WOMAC represents three separate domains of knee OA allowing for greater construct validity than measuring associations between strength and disability or knee pain in isolation.

Stratification of a knee OA study sample using WOMAC scores allowed for clinically homogeneous subgroups. Thus, it was apparent that quadriceps muscle weakness occurs across a clinical spectrum of knee OA. While it is well established that quadriceps muscles in knee OA are weaker than healthy controls or contralateral knees,[8, 16-18, 21] the progression of quadriceps weakness in knee OA had not previously been examined from a clinical perspective. From our observations, it is clear that weakness occurs across a disease spectrum. Conversely, we observed that although weakness occurred across a radiographic spectrum, there was no difference in strength between moderate and severe radiographic knee OA. Palmieri-Smith reported similarly that the knee extensors of those with KLG ≥ 2 were approximately 20% weaker than a group with KLG <2, however there was no difference between those with KLG=2 and KLG >2.[27] Along with our results, this implies that there is a ceiling effect to KLG. Consequently, important changes in the

natural history of knee OA may be obscured when using radiographic disease definitions. Brandt et al. reported no difference in quadriceps strength between those with stable versus progressive radiographic knee OA over 2.5 years, however it is possible that differences were masked by the ceiling effect for radiographic severity.[9] Furthermore, assessing OA clinically may provide information about optimal type and timing of intervention. Previous research has illustrated that quadriceps weakness occurs early in the natural history of knee OA and strength training interventions implemented early may be of benefit.[20, 35] Our results suggest that interventions targeting those with already significant clinical OA could also be effective. Moreover, the optimal type of intervention may change as the disease progresses. There is evidence to suggest that muscle weakness in early knee OA may be from disuse atrophy, while deficits in voluntary activation have been reported in more severe disease.[29, 32] It is unclear if employing different treatment strategies depending on disease severity may alter relevant outcomes, such as time to joint replacement.

We also observed that deficits in strength were of a higher magnitude when patients were stratified clinically. Specifically strength deficits in severe OA compared to mild were twofold higher when stratifying clinically. This finding is not surprising considering the tenuous relationship that has been reported between radiographic findings and quadriceps muscle weakness. Recent reports have illustrated that quadriceps weakness is not associated with isolated patellofemoral and tibiofemoral OA in men,[3] does not predict incident radiographic OA[34] and is not a risk factor for cartilage loss measured semi-quantitatively with MRI.[2] Therefore, it

is clear that disease definition influences the measurement of quadriceps strength deficits in knee OA, such that quadriceps muscle weakness was underestimated when stratifying with KLG.

Similar to Duncan et al. we observed WOMAC score (both total and subscale scores) of increasing severity for worsening of KLG.[12] An association between these two commonly used measurement tools supports their utility for disease severity stratification in large population studies. However, to our knowledge we are the first to report on the variability of WOMAC scores for individual participants in the KLG groups. The high coefficients of variation for total WOMAC score (>60% variation in total WOMAC score for each group) have implications not only for outcome measurement, but also for individual patient care. Bedson et al. reported that primary care physicians were less likely to refer patients with knee pain to a physiotherapist and more likely to refer to an orthopedic surgeon when X-rays were positive for knee OA, regardless of clinical severity.[6] As the relevance of radiographic findings to the individual patient is variable, this has the potential to impact on patient management.

A limitation of this study was the use of ordinal measurement tools for clinical and radiographic disease severity. In particular, KLG has been criticized because the magnitude of difference between the grades may not be equal.[13] Furthermore, Schipof et al. reported that there is a discrepancy between studies on how KLG is implemented (e.g. 5/11 studies reviewed in their article defined KLG = 2 as having definite osteophytes), making inter-study comparison difficult.[31] The use of novel quantitative and semi-quantitative scoring systems based on MRI of the

knee joint is becoming increasingly popular and is more sensitive to structural progression than plain films.[37] It may be that WOMAC is better correlated with MRI measures of disease incidence and progression, although some studies have reported weak or no associations.[30, 38] Moreover, many of these measurement tools have yet to be validated in clinical studies, and the use of radiographs for disease stratification and as an outcome measure is still widespread.

A further limitation is that data in this study are limited to the TF compartment. Associations have also been observed between KLG for the patellofemoral (PF) compartment and WOMAC[12] and it is possible that quadriceps muscle strength is affected to a greater degree in PF disease. Large population studies have observed significant associations between quadriceps muscle weakness and progression[2, 33] of PF OA, particularly of the lateral PF compartment. A potential mechanism has also been postulated whereby weak quadriceps (particularly the vastus medialis) allows for lateral tracking of the patella during activity.[33] The relationships between clinical and radiographic measures observed in our study may have been stronger and less variable if PF OA was incorporated into the analysis.

In conclusion, we observed that clinical, as opposed to radiographic measures for disease severity stratification may be more valid when measuring clinically relevant outcomes, such as quadriceps muscle weakness in patients with knee OA. Furthermore, using radiographic criteria in isolation may distort the natural history of quadriceps weakness in knee OA. Additionally, the variability in clinical severity in those with mild, moderate and severe radiographic knee OA

brings into question the utility in making treatment decisions based on radiographic findings alone.

2.4 REFERENCES

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CHAPTER 3

QUADRICEPS STRENGTH, POWER AND MUSCLE QUALITY ACROSS A CLINICAL SPECTRUM OF KNEE OA

3.0 INTRODUCTION

The quadriceps muscles of patients with knee osteoarthritis (OA) are weak in comparison with the less affected contralateral limb or age-matched control limbs.[6] Weak quadriceps muscles show a higher degree of association with mobility impairments than radiographic evidence of cartilage degeneration[21, 26] and may be a risk factor for disease incidence and progression.[29, 32, 35] Despite its clinical relevance, the magnitude and mechanisms of quadriceps muscle weakness in knee OA have not been fully characterized.

Studies of muscle function report a 20-40% reduction in quadriceps muscle strength in knee OA for isometric and isokinetic contractions.[6, 13, 14, 16, 18, 19, 23, 34] The type of design utilized in these studies does not provide information about the severity of muscle weakness across a clinical spectrum of disease. Commonly, knee OA is defined dichotomously (i.e. present or absent) using radiographic scoring such as Kellgren-Lawrence grading (KLG), with KLG $\geq$ II representing presence of OA. The validity of using radiographic features is limited when considering the discrepancy that exists between clinical and radiographic features of knee OA.[4] Consequently, if radiographic criteria alone are used to define knee OA, a clinically heterogeneous study sample will be produced that may lead to underestimation of muscle weakness, particularly in those with clinically severe disease.

The way in which strength is measured may also impact studies aimed at determining the extent of weakness in knee OA. Quadriceps muscle power, the product of torque and velocity of movement, has yet to be assessed in patients with knee OA. Recent evidence suggests that power declines more precipitously than strength and is a more robust predictor of functional outcomes in healthy older compared to younger adults, presumably because most activities of daily living require a combination of adequate torque and velocity.[2, 9, 11, 27, 31] Additionally, rehabilitation of muscle power deficits may be optimized with power or velocity specific resistance training.[3, 7] It is unknown whether quadriceps power deficits exist in those with knee OA and if function could be improved with power specific rehabilitation. Therefore, the purpose of this study was to determine whether quadriceps muscle strength and power differ across a clinical spectrum of severity in knee OA. In order to elucidate the mechanism of muscle weakness, strength and power were normalized to MRI-derived measures of quadriceps volume to provide an index of muscle quality (i.e. specific torque and specific power).[36]

3.1 METHODS

3.1.1 Study participants

Forty-one community dwelling men and women, recruited from local orthopedic outpatient clinics, volunteered to participate in the study. Participants were included if they had persistent knee pain that resulted in referral to an orthopedic surgeon and/or X-ray findings consistent with knee OA in at least one compartment (e.g. presence of osteophytes, apparent joint space narrowing, subchondral sclerosis and areas of cyst formations) confirmed by an experienced

musculoskeletal radiologist or orthopedic surgeon. All participants met the American College of Rheumatology criteria for knee OA.[1] Exclusion criteria included musculoskeletal, neurological or rheumatological impairment of the lower limbs other than knee OA, prior high tibial osteotomy, unicondylar or total knee arthroplasty or cardiopulmonary impairment that precluded performing vigorous muscle contractions. If a patient had bilateral knee OA, the limb with the more severe symptoms (as reported by the patient), was selected as the test limb. Ethical approval for the study was obtained from the Human Research Ethics Board at the University of Western Ontario and written consent was obtained from each participant prior to study commencement.

Participants were stratified into tertiles of disease severity based on their responses to the Western Ontario and McMaster Osteoarthritis Index (WOMAC). WOMAC is a validated, widely used tool to quantify clinical severity in knee OA patients.[5] The lowest, middle and highest tertiles were designated mild, moderate and severe knee OA respectively.

3.1.2 Experimental setup and test protocol

Participants were seated upright in a multi-joint dynamometer (Biodex System 3, Shirley, NY), with knee and hip angles of 90° and 100° respectively. The centre of rotation of the knee was aligned with the axis of rotation of the dynamometer's lever arm. The force transducer was positioned with its bottom edge two fingerbreadths proximal to the medial malleolus of the test leg and fixed with a Velcro strap. A seat-belt strap was positioned across the lap in order to avoid unwanted movement of synergist hip flexors during quadriceps contractions. The

test protocol commenced with a series of submaximal isometric contractions (approximately 50-75% of maximal intensity) for the purposes of warm-up and familiarization. Participants then performed repeated, brief (~5 s) isometric maximal voluntary contractions (MVCs) of the quadriceps (3-5 repetitions), each separated by a minimum of 90 s of rest. Maximal contraction intensity was determined when two consecutive MVCs differed by less than 5%. The highest MVC torque was utilized as the value for maximal isometric strength and to normalize submaximal torque during subsequent isotonic power testing.

To investigate torque-velocity and torque-power relationships, participants performed a series of submaximal isotonic concentric quadriceps contractions through a 90° range of motion, at maximum speed. Range of motion was tailored to each individual participant such that 90° from their full extension range was used as the starting point for contraction. Submaximal loads set at 10, 20, 30, 40 and 50% of isometric MVC were programmed in a random order using the Biodex Isotonic Mode. An additional intensity level with a load of 1 N•m (the minimum load added to the resistance of the force transducer) was performed to determine power and velocity at the lowest possible load (i.e. Zero Load). For each contractile intensity, participants were instructed to move through the concentric phase as quickly as possible and allow for passive return to the initial position. Immediately thereafter a second contraction was performed at that same load. Peak velocity and the load programmed into the dynamometer at each intensity level were used to calculate isotonic power. Multiple practice contractions were performed at Zero Load for familiarization prior to the test. A 1 min. rest period separated each load. Loud

verbal encouragement and visual feedback using the real-time digital torque and velocity tracings were used during all contractions to ensure maximal intensity and velocity. At least 10 min. rest separated the protocols for measuring isometric strength and power to allow for appropriate recovery.

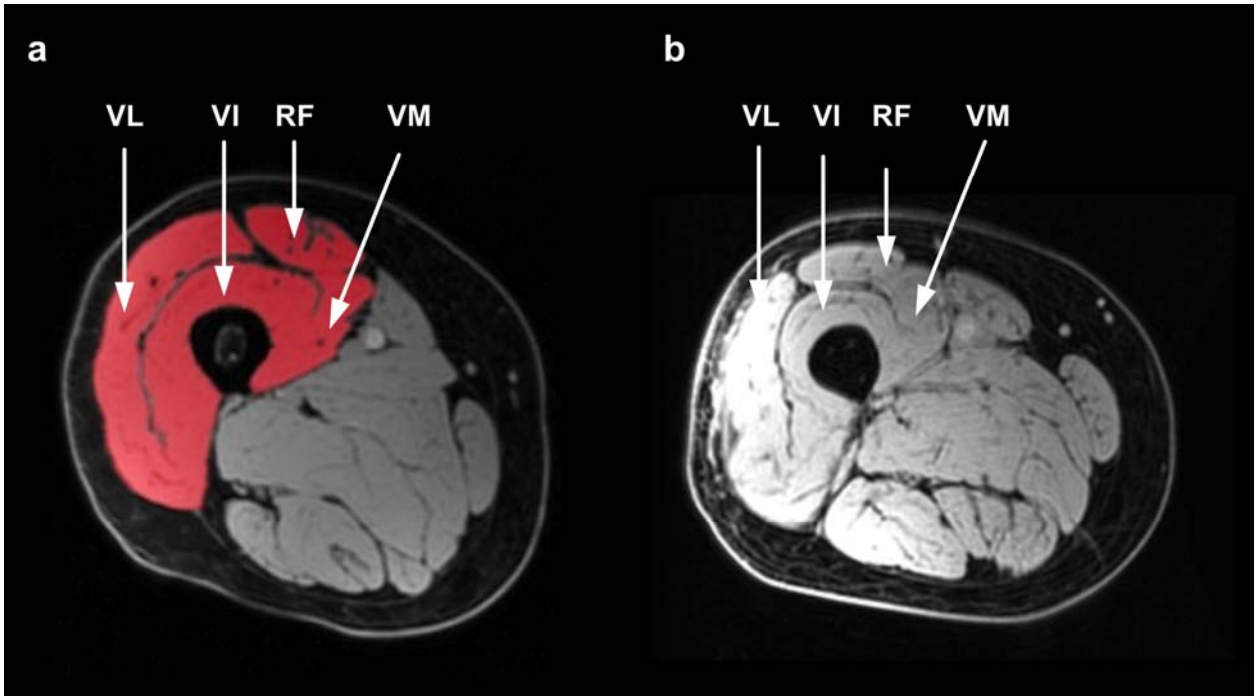
3.1.3 Magnetic resonance imaging of quadriceps muscle volume

MRI scans of the thigh were acquired using a 3.0T MR system (GE Discovery MR750, GE Healthcare, Waukesha, Wisc.) with an 8-coil torso phased array. The patient was positioned supine in the scanner bore. A 3-plane localizing scan and calibration scan were performed to ensure the anatomy of interest was contained in the field-of-view (FOV). Three-dimensional axial images were acquired from proximal (femoral head) to distal (femoral condyles) with a proton density weighted multiecho-spoiled gradient echo (SPGR) imaging sequence (FOV: 42-46x21-23 cm, slice thickness: 4 mm, matrix: 320x160x120, TR: 7.4 ms, echoes: 6, TE, 1.4, 2.1, 2.9, 3.6, 4.4, 5.1 ms, flip angle 5°, bandwidth: ± 142.86 kHz). An investigational version of the IDEAL (iterative decomposition of water and fat with echo asymmetry and least squares estimation) multipoint water-fat separation method that is T1 independent, T2* corrected and employs accurate spectral modeling of fat, was used to reconstruct both water-only and fat-only images from the multiecho SPGR source images.[28, 38] Fat-water separation also ensured that non-muscle tissue (in particular fat) was not included in analysis of the thigh images. Image analysis was performed on the water only images produced by the IDEAL reconstruction for assessment of muscle volume.

A combination of manual and semi-automated techniques using open-source OsiriX image processing software (version 3.7, Geneva, Switzerland) was used to analyze images and calculate muscle volume. Analysis began proximally from the first slice not containing the gluteal muscle to the last distal slice containing the rectus femoris, as this region is thought to represent maximal thigh muscle mass[37] and because it is difficult to differentiate between thigh muscles at the most proximal and distal slices.[8] Quadriceps muscle volume was calculated from the water-only images by manually outlining the most proximal and distal slices with the brush tool to create regions of interest (ROI). This process was repeated for every tenth slice in-between and missing ROIs were generated automatically. Once the quadriceps had been roughly outlined, all pixel values outside the ROIs were set to zero. Subsequently, a 3D threshold-growing tool was used to grow ROIs for the quadriceps muscle tissue only from a defined seedpoint within the muscle. This was done to ensure exclusion of non-muscular tissue in the septal spaces. Any errors produced by the automatic tool were corrected manually. The software automatically calculated volume for the series of ROIs. The reliability of this method defined by the intraclass correlation coefficient (ICC; 2,1) and 95% confidence intervals was high (intra-rater: ICC=0.997, 0.991-0.999 and inter-rater: ICC=0.997, 0.988-0.999 based on 16 and 11 cases, respectively). Thigh images from representative male subject in the mild and severe group are presented in Figure 3.1.

3.1.4 Data reduction and statistics

Figure 3.1 Axial view of the mid-region of the right thigh for representative male subjects from the mild (a) and severe (b) disease subgroups. The four bellies of the quadriceps are labeled VM (vastus intermedius), RF (rectus femoris), VI (vastus intermedius) and VL (vastus lateralis).


a
VL
VI
RF
VM
b
VL
VI
RF
VM

Torque and position were sampled at 100 Hz, AD converted with a 12-bit converter (CED micro1401 mk II, Cambridge Electronic Design Limited, Cambridge, UK) and displayed in real-time on an online digital system using commercially available software (Spike2 ver. 5, Cambridge Electronic Design). During offline analysis, power for each submaximal load was calculated as the product of torque (N•m) and peak velocity generated during the contraction (rad/s). Torque and power were normalized to body mass to account for body size differences among participants.

A one-way ANOVA with a post-hoc Tukey's test was used to compare participant characteristics and strength measures between severity states. A two-way ANOVA with a post-hoc Bonferonni Correction was used to compare velocity, power and specific power across loads (main effect 1) and disease severity (main effect 2). MRI-derived measures of muscle volume were not available for 4 participants in the moderate group (1 female, 3 male) and one participant in the severe group (1 male) due to contraindication to MRI (e.g. claustrophobia, presence of metallic objects). In order to account for these missing values, the software program converts the ANOVA problem to a multiple regression problem and then displays the results as ANOVA. The data were collapsed across disease subgroups and univariate linear regression models were used to determine the predictive value of strength, velocity and power measures to self-reported function (WOMAC function subscale). Multivariate regression was not employed as all of the independent variables were collinear. All descriptive statistics are presented as

mean ± standard deviation. Level of significance was set at $p<0.05$. All statistical tests were performed with Graphpad Prism Version 5.0b (La Jolla, CA).

3.2 RESULTS

Participant characteristics, including WOMAC score, maximal isometric torque and muscle volume are presented in Table 3.1. No significant difference was observed for age and body mass index (BMI) between groups ($p>0.05$). Significant differences were observed for height and body mass ($p<0.05$). After post hoc testing, patients in the moderate group were taller and had greater body mass than those in the severe group and patients in the mild group had significantly less body mass than those in the moderate group. Significant differences were observed for WOMAC score, absolute isometric torque, normalized isometric torque and muscle volume (Table 3.1, $p<0.05$). Post hoc testing revealed that all subgroups differed significantly from each other with respect of WOMAC score ($p<0.05$). Post hoc significant differences in normalized isometric strength between mild and severe groups were also observed, with mean strength ~36% lower in the severe group. No significant difference was observed between mild and moderate and moderate and severe groups for normalized isometric strength ($p>0.05$) .

A significant main effect for disease severity was observed for both torque-velocity and torque-power (normalized to body mass) relationships (Fig. 3.2, $p<0.05$). Post hoc testing revealed that velocity at Zero Load, 10% and 20% MVC was lower in the severe group compared to both mild and moderate groups (Fig. 3.2a). Additionally, velocity at 30% MVC was lower in the severe compared to mild group. The largest difference between mild and severe groups occurred at 20%

Table 3.1 Participant characteristics (n = 41).

	Mild	**Moderate**	**Severe**	**p-value**
Sex (M/F)	8/5	8/6	6/8	
Age	61.1±8.2	58.6±5.3	61.8±4.3	0.37
Height (m)	1.67±0.10	1.74±0.09*	1.66±0.05	<0.05
Weight (kg)	78.8±11.2†	99.1±7.4*	84.9±15.4	<0.05
BMI (kg/m^2)	28.2±3.9	32.7±5.6	30.8±5.4	0.08
Total WOMAC score	17.5±8.5*†	40.1±6.5*	61.2±7.7	<0.05
Isometric torque (N•m)	177±76*	189±80*	120±52	<0.05
Normalized isometric torque (N•m/kg)	2.19±0.83*	1.94±0.74	1.42±0.49	<0.05
Muscle volume (cm^3)	909±334	1019±324*	670±214	<0.05

Data are presented as means ± standard deviations. BMI: body mass index.
*Significantly different than severe with post-hoc testing ($p<0.05$).
†Significantly different than moderate with post-hoc testing ($p<0.05$).

Table 3.2 Coefficients of determination (r^2) for univariate regression models using WOMAC function subscale as the dependent variable.

	Coefficient of Determination (r^2)	**P-value**
Isometric Strength (N•m/kg)	0.14	0.01
Power (N•m•rad/s/kg):		
Zero Load	0.27	<0.001
10% MVC	0.16	0.009
20% MVC	0.19	0.005
30% MVC	0.17	0.007
40% MVC	0.12	0.03
50% MVC	0.12	0.03

MVC: maximal voluntary contraction.

Figure 3.2 Velocity (a) and power normalized to body mass (b) at Zero Load, 10%, 20%, 30%, 40% and 50% MVC. Participants were stratified by WOMAC score into mild (triangle), moderate (square) and severe (circle) subgroups. Zero Load: load equal to 1 N•m combined with the mass of the dynamometer foot-plate; WOMAC: Western Ontario and McMaster Osteoarthritis Index; MVC: maximal voluntary contraction.

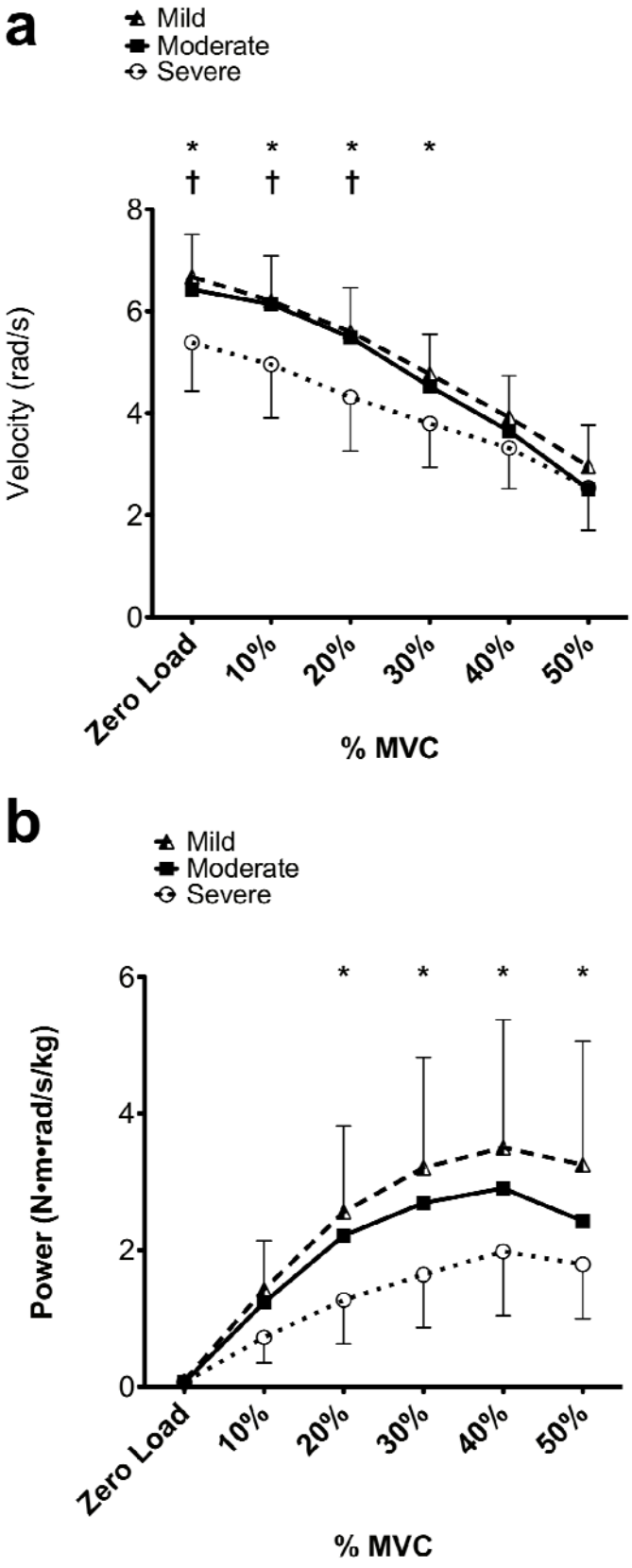
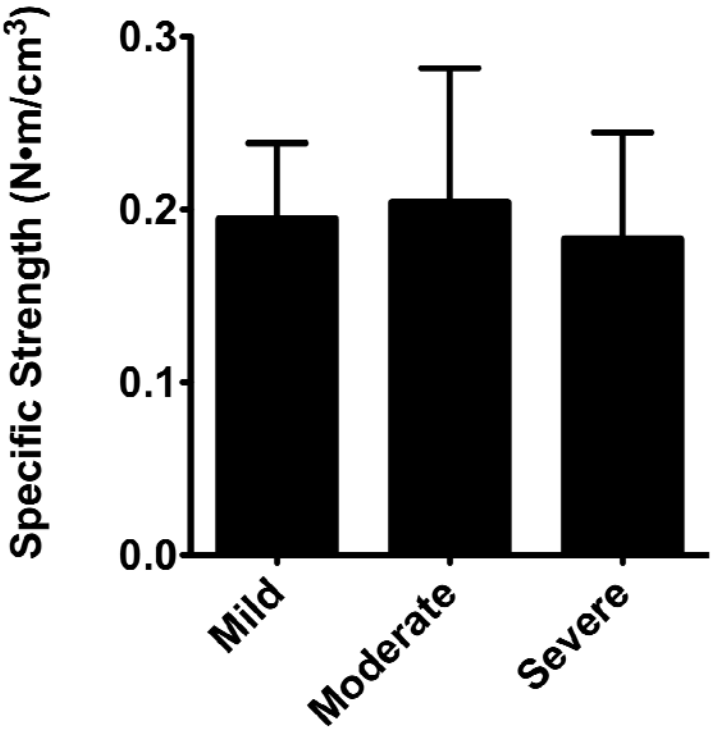
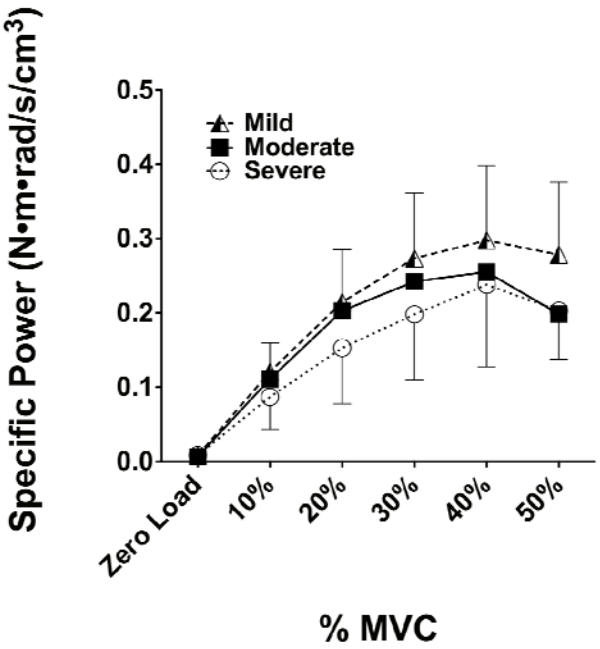

a
Mild
Moderate
Severe
* * * *
† † †
8
6
4
2
0
Velocity (rad/s)
Zero Load
10%
20%
30%
40%
50%
% MVC
b
Mild
Moderate
Severe
* * * *
6
4
2
0
Power (N•m•rad/s/kg)
Zero Load
10%
20%
30%
40%
50%
% MVC

Figure 3.3 Quadriceps torque (a) and power (b) for mild (triangle), moderate (square) and severe (circle) knee OA, normalized to MRI-derived measures of muscle volume (i.e. specific torque and specific power). Zero Load: load equal to 1 N•m combined with the mass of the dynamometer foot-plate; MVC: maximal voluntary contraction.

a


Specific Strength (N•m/cm3)
0.3
0.2
0.1
0.0
Mild
Moderate
Severe

b


Specific Power (N•m•rad/s/cm3)
0.5
0.4
0.3
0.2
0.1
0.0
Mild
Moderate
Severe
Zero Load
10%
20%
30%
40%
50%
% MVC

MVC where velocity was 23% lower in the severe group. Differences in isotonic power were also observed between the mild and severe groups only, after post hoctesting (Fig. 3.2b). Power was lower at 20%-50% MVC (45-50% lower with the greatest difference occurring at 20% MVC). It should be noted that peak power (contractile intensity at which velocity and torque are optimized) in this study occurred at 40% MVC. Muscle quality as determined by specific torque was not significantly different between groups (Fig. 3.3a), nor was specific power at any contractile intensity level (Fig. 3.3b, $p>0.05$).

WOMAC function subscale was used as the measure of self-reported disability in this study. Individual, univariate linear regression models yielded coefficients of regression for the relationship between function and measures of muscle strength and power (Table 3.2). Power measured at Zero Load explained the largest proportion of the variance in function compared to power measured at 40 % and 50% MVC, which explained the lowest proportion of variance.

3.3 DISCUSSION

The results of this study have implications for future study design, rehabilitation and further understanding of the mechanisms of neuromuscular dysfunction in knee OA. By defining disease severity using clinical criteria, we observed a reduction in normalized quadriceps strength in severe compared to mild knee OA. Furthermore in this first investigation of isotonic muscle power, it was observed that normalized quadriceps power across a range of contractile intensities was reduced in severe knee OA. Additionally, the deficits in power were greater than those observed for strength. As the reduction in power was not accompanied

by a change in whole muscle quality (measured with specific torque and specific power) it is reasonable to suggest that power deficits may be due to differences in muscle fibre size, particularly of the type II, fast twitch muscle fibres. Finally, power deficits (in particular power measured at the lower loads) explained more of the variance in self-reported function than isometric strength, suggesting that these deficits should be addressed in order to attenuate disability in knee OA patients.

The observation that isometric strength in the severe group was ~36% lower than the mild group is similar to the magnitude of strength deficits reported by others in this patient population (for a review see reference [6]). However, knee OA is usually defined dichotomously (i.e. presence or absence) based on radiographic criteria such as KLG and this could lead to heterogeneous disease subgroups and an underestimation of muscle weakness. There are currently no universally accepted criteria encompassing the clinical, radiological and pathological features of knee OA available to designate disease severity states.[12] Furthermore, the tenuous relationship between radiographic disease markers and symptoms has been well documented.[4] Consequently, in our study patients were stratified into tertiles of disease severity based on WOMAC scores. While this method certainly has its limitations (see below), it revealed that muscle weakness is not homogeneous in all patients with knee OA. Furthermore, the strength deficit in those with severe knee OA has implications for rehabilitation, as it has been reported that quadriceps weakness predicts poor function after total knee arthroplasty.[25] It should also be noted that the strength deficits observed in this study were likely not attributable to patient characteristics (Table 3.1). Subgroups were reasonably well matched for

sex, age and body size and strength was normalized to body mass.[36] Those in the moderate group were taller and heavier than those in the other groups, however this did not affect the observed strength differences (i.e. moderate group did not display differences in normalized strength and power compared to mild or severe groups).

To our knowledge this is the first study to report reductions in quadriceps isotonic velocity and power at a range of contractile intensities in those with severe knee OA. Isotonic rather than isokinetic contractions were used because they are more functionally relevant[22] and because severely impaired participants may not be able to achieve the velocities required during high velocity contractions.[17] While this is a novel finding in participants with knee OA, certain parallels can be drawn to similar observations in healthy older adults. Studies of healthy elders report that power deficits compared to young subjects occur more precipitously and are of greater magnitude than strength deficits.[24, 33] In our study, deficits in power at 20-50% MVC contractile intensities (~45-50% reduction in power) in the severe versus mild group were of greater magnitude than deficits in isometric strength. Furthermore, the greatest deficit occurred at 20% MVC. This is of significance because activities of daily living (e.g. walking, ascending/descending stairs etc.) are rarely performed at or near maximal contractile intensities, but require adequate power at these lower contractile intensities. Therefore, impaired quadriceps function at submaximal intensities may have greater implication for functionality. In addition to deficits in speed and power, deficits have also been reported in proprioception and the ability to control force output at submaximal contractile

intensities,[13] indicating the possibility of widespread neuromuscular dysfunction in this population. These deficits have implications for rehabilitation. Specifically, it is unknown if interventions targeting power deficits would have a greater effect on attenuating disability. Specific power or velocity training has been shown to result in greater improvements in muscle outcomes in some,[3, 7] but not all[30] studies of healthy older participants.

Based on our results we can also make inferences about the mechanisms of strength and power deficits in the quadriceps in knee OA. The traditional paradigm of weakness in knee OA is one of muscle fibre atrophy due to disuse induced by a painful knee joint.[15] Normalization of quadriceps torque and power to MRI-derived measures of muscle volume allowed for measurement of differences in muscle quality independent of muscle size. We observed no differences in specific torque or specific power across groups, suggesting that muscle mass is predominantly responsible for reduced muscle strength and power in the severe compared to mild group, thus substantiating the model of disuse atrophy. This is in contrast to whole muscle and individual fibre studies of healthy older compared to younger participants showing that specific torque and power are reduced.[36] Reduced number of sarcomeres in series, changes in the function of myosin heavy chain ATPase enzyme and reductions in neural activation may explain the reductions in muscle quality observed in these studies of healthy elders, however similar muscle quality across groups in our study suggests no such changes are occurring across a clinical spectrum of knee OA. It is interesting to note that reductions in velocity were only significant at the lowest contractile intensities and reductions in power

significant only at the highest contractile intensities. Based on these results, it is possible that the type II, fast twitch muscle fibres are preferentially involved in the atrophy process. Type II muscle fibres are usually recruited for fastest and or highest intensity contractions. This notion is supported in a study by Fink et al. in which the vastus medialis muscles of knee OA patients were biopsied peri-operatively (during total knee arthroplasty) and preferential type II fibre atrophy was observed in conjunction with evidence of fibre type grouping (indicative of a collateral reinnervation process).[10] This hypothesis requires confirmation in longitudinal studies.

In univariate linear regression models, power measured at the lowest contractile intensities was a stronger predictor of the variance in self-reported function than isometric strength (Table 3.2). In particular, power measured at Zero Load explained almost double the variance explained by MVC strength. Similarly, there is evidence to suggest that power is a more robust predictor of function than strength in healthy elderly subjects. Bean et al. reported that leg extensor peak power measured in older adults with mobility limitations explained a greater degree of variance in performance on the Short Physical Performance Battery than strength.[2] It is interesting that power at zero load and not peak power (i.e. the point where both velocity and torque are optimized) was the strongest predictor of subjective function. A reduction in the velocity component of power may be an independent predictor of function. Mayson et al. reported that maximal leg extensor velocity was a stronger predictor of balance than strength.[20] Intuitively, reductions in power at the lowest contraction intensities should be more detrimental to

function, since many activities of daily living are performed at higher contraction velocities with low-to-moderate loads (e.g. gait velocity, prevention of falling etc.).

There are limitations to the interpretation of these results. First, no differences in strength and power were observed between the moderate group and other disease subgroups. Stratifying participants into cross-sectional severity states using an ordinal scale is not without limitations. As the WOMAC cutoffs used to define the disease subgroups were arbitrary, it is conceivable that many participants in the moderate group with borderline WOMAC scores would have been in either the mild or severe groups. This limitation in study design may have masked clinically relevant differences between mild and moderate knee OA. Another limitation is that measures of function in this study were self-reported. It is unknown if the relationships between strength, power and function would persist or be more robust with objective functional outcome measures.

In conclusion, strength, velocity and power were lower in those with clinically defined severe, compared to mild knee OA. The deficits in strength and power were not accompanied by changes in muscle quality, suggesting that muscle atrophy, particularly of the type II muscle fibres is predominantly responsible for quadriceps muscle weakness. Furthermore, deficits in power, especially at low contraction intensities may be more robust predictors of disability in this patient population. Further investigation into the impact of improving quadriceps velocity and power on functional outcomes is warranted.

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CHAPTER 4

QUADRICEPS SIZE-STRENGTH RELATIONSHIPS IN PATIENTS WITH KNEE OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

4.0 INTRODUCTION

Quadriceps muscle weakness in patients with knee osteoarthritis (OA) has been attributed to atrophy secondary to joint pain and/or disuse.[4] Accordingly, a relationship should exist between quadriceps muscle strength and size in this clinical population, as muscle size has been shown to be the primary determinant of strength in studies of aging,[8] resistance training[27] and sex differences.[21] However, in a study of patients with severe unilateral knee OA (Kellgren-Lawrence Grade, KLG=IV), quadriceps muscle size was only weakly correlated with isometric maximal voluntary contraction (MVC, r^2=0.27).[22] Furthermore, the relationship between quadriceps muscle strength and size (i.e. the size-strength relationship) has been shown to vary in studies of healthy young and older individuals.[1, 10, 28]

Inter-study variability could arise for a number of reasons. First, the quadriceps size-strength relationship in knee OA may be affected by the definition of disease severity. Knee OA is usually defined dichotomously (i.e. presence vs. absence) using radiographic criteria, resulting in OA groups comprising patients with both mild and severe disease. Furthermore, the relationship between symptom severity and radiographic change is tenuous.[2] Consequently, those with severe radiographic disease may have variable clinical presentation. It is unknown whether the size-strength relationship is altered across a clinical spectrum of knee OA. Second, methodological differences in the measurement of muscle size may

affect the size-strength relationship. Muscle size can be measured with a variety of imaging or anthropometric techniques, although magnetic resonance imaging (MRI) is the gold standard as contrast allows for non-muscle tissue to be excluded from the image analysis and unlike computed tomography, there is no exposure to ionizing radiation.[6] The parameter used to represent muscle size may also be variable and can range from whole muscle volume to single slice anatomical or physiological cross-sectional area. For example, it is common to image a small section of the thigh or to report the anatomical cross sectional areas (ACSA) of a single slice from MRI scanning in order to estimate thigh volume, as MRI acquisition time for the entire thigh may be long and segmentation of the whole muscle can be time consuming.[20] However, muscle volume estimation from single slice ACSA is associated with a certain degree of error, depending on the region of the thigh the slice is acquired from.[7, 19, 25] Muscle volume may be a more appropriate index of muscle size when evaluating size-strength relationships,[1, 5] however volume error is inversely proportional to the number of slices used in the analysis; therefore imaging only a small section of the thigh may result in inaccurate muscle size measurement.[18, 20, 25] The quadriceps muscle size-strength relationship has yet to be thoroughly examined in knee OA and it is unknown if the relationship is affected by the method of muscle size estimation.

The primary objective of this study was to examine the nature of the quadriceps size-strength relationship in patients with knee OA and to determine if this relationship is influenced by clinical disease severity or by different indices of muscle size. Because the validity of muscle size measurements may also be

influenced by the MRI protocol and segmentation methods, a secondary objective was to determine the effect of inter-study differences in MRI protocol and segmentation parameters on the quadriceps size-strength relationship.

4.1 METHODS

Two separate datasets were used in this study. The primary objective was addressed using thigh images acquired as part of a comprehensive study of neuromuscular function in knee OA (herein referred to as local participants). The secondary objective was addressed using additional thigh images from the public use datasets of the Osteoarthritis Initiative (OAI, version 0.2.2 clinical dataset, version 0.E.1 imaging dataset; online at www.oai.ucsf.edu).

4.1.1 Study participants

Thirty-six community-dwelling male and female individuals (ages 46-74), recruited from local orthopedic outpatient clinics, volunteered to participate in the study and comprised the local patient population. Participants were included if they had persistent knee pain that required referral to an orthopedic surgeon and/or X-ray findings consistent with knee OA in at least one compartment (e.g. presence of osteophytes, apparent joint space narrowing, subchondral sclerosis and areas of cyst formations). Exclusion criteria were musculoskeletal, neurological or rheumatological impairment of the lower limbs other than knee OA, prior high tibial osteotomy, unicondylar or total knee arthroplasty, contraindication to MRI or cardiopulmonary impairment that precluded performing vigorous muscle contractions. Strength testing and image segmentation were performed on the symptomatic limb only. If a patient had bilateral knee OA, the limb with the most

severe symptoms (as reported by the patient), was selected as the test limb. Ethical approval for the study was obtained from the local institutional ethics review board and written consent was obtained from each participant prior to study commencement.

To address the secondary objective, thigh images from a sample of 31 male and female participants selected at random from both the incident (5 patients) and progression (26 patients) subcohorts of the OAI were analyzed. Participants in the incident subcohort did not have symptomatic knee OA at baseline but did have 2 or more risk factors for knee OA as previously defined. Participants in the progression subcohort had symptomatic and radiographic OA in the right knee. A description of the rationale for inclusion in these subcohorts and a full list of exclusion criteria is available on the OAI website (www.oai.ucsf.edu/datarelease/OperationsManuals.asp).

4.1.2 MRI of the thigh

MRI scans of the thigh were acquired in the local participants using a 3.0T MR system (GE Discovery MR750, GE Healthcare, Waukesha, Wisc.) with an 8-coil torso phased array. The patient was positioned supine and feet first in the scanner bore. A 3-plane localizing scan and calibration scan were performed to ensure the anatomy of interest was contained in the field-of-view. Three-dimensional axial images were acquired from proximal (femoral head) to distal (femoral condyles) with a proton density weighted multiecho-spoiled gradient echo (SPGR) imaging sequence (FOV: 42-46x21-23 cm, slice thickness: 4 mm, matrix: 320x160x120, TR: 7.4 ms, echoes: 6, TE, 1.4, 2.1, 2.9, 3.6, 4.4, 5.1 ms, flip angle 5°, bandwidth: ± 142.86

kHz). An investigational version of the IDEAL (iterative decomposition of water and fat with echo asymmetry and least squares estimation) multipoint water-fat separation method that is T1 independent, T2* corrected and employs accurate spectral modeling of fat, was used to reconstruct both water and fat images from the multiecho SPGR source images.[24] A fat-water separation was used to ensure that non-muscle tissue (in particular fat) was not included in analysis of the thigh images. Image analysis was performed on the water only images produced by the IDEAL reconstruction for assessment of muscle size parameters.

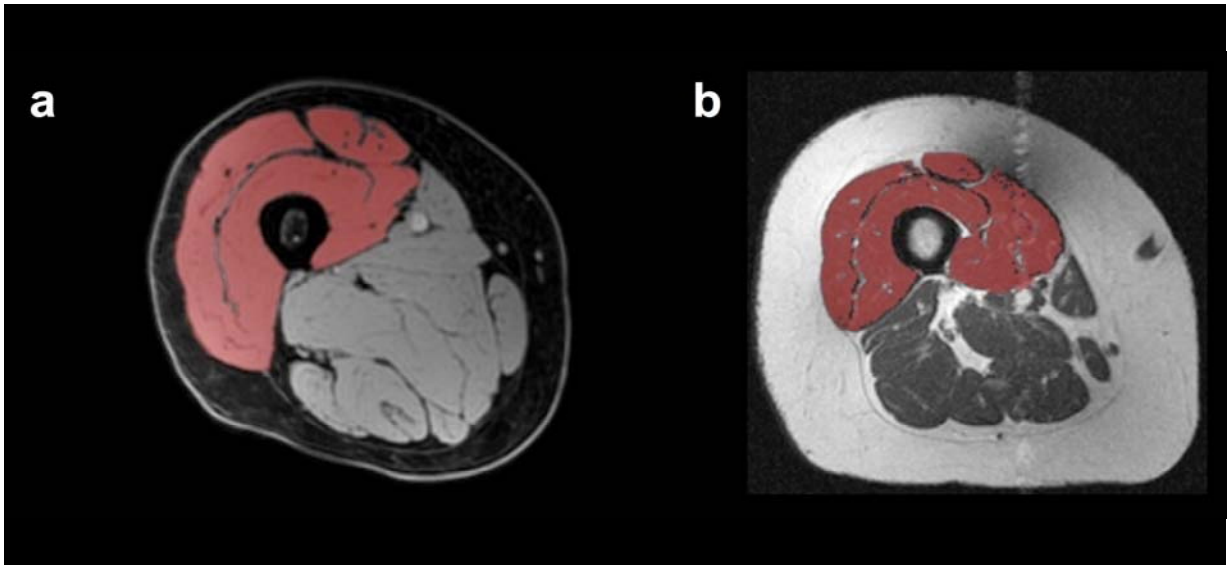
For the OAI dataset, axial T1-weighted scans of the thigh were acquired at 3.0T (Siemens 3.0T Trio Systems). A full description of the rationale and protocols for thigh MRI for the OAI is available at www.oai.ucsf.edu/datarelease/OperationsManuals.asp. Briefly, participants were positioned in a supine position with legs aligned neutrally. The apex of the right patella was palpated and the mid-thigh region was defined by measuring to a point 15 cm proximal. A biplanar (coronal-axial) T1-weighted, localizing scan was performed. From the localizer, the distal femoral epiphyseal line was visualized and the first axial T1-weighted slice was acquired 10 cm proximal from this point. A 7.5 cm region of 15 contiguous axial slices of the thigh was acquired with the following sequence parameters: FOV: 500 mm, slice thickness: 5 mm, matrix: 384 x 512, TR: 600 ms, TE/TI: 13 ms, flip angle: 180°, bandwidth: ±199 Hz/pixel.

4.1.3 Segmentation methods

Segmentation of quadriceps muscle for calculation of muscle volume and ACSA was performed with two different segmentation methods. A combination of

manual and semi-automated techniques using open-source OsiriX image processing software (version 3.7, Geneva, Switzerland) was used to analyze images from both datasets (local and OAI). Analyses of the images from the local participants began proximally from the first slice not containing the gluteal muscle to the last distal slice containing the rectus femoris, as this region is thought to represent maximal thigh muscle mass[26] and because it is difficult to differentiate between thigh muscle at the most proximal and distal slices.[7] Quadriceps muscle volume was calculated from the water-only images by manually outlining the most proximal and distal slices with the brush tool to create regions of interest (ROI). This process was repeated for every tenth slice in-between and missing ROIs were generated automatically. Once the quadriceps had been roughly outlined, all pixel values outside the ROIs were set to zero. Subsequently, a 3D threshold-growing tool was used to grow ROIs for the quadriceps muscle tissue only from a defined seedpoint within the muscle. This was done to ensure exclusion of non-muscular tissue in the septal spaces. Any errors produced by the automatic tool were corrected manually by one trained segmenter. The software automatically calculated volume for the series of ROIs and ACSA for each slice analyzed. Two parameters were used from images in the local participant dataset to estimate muscle size; 1) total muscle volume and 2) mid-thigh ACSA (defined as the middle slice between the first slice including the femoral head and the last slice containing the lateral femoral condyle). This corresponded to a mean of 39.9±6.0 slices/patient included in measures of muscle volume (range: 30-51). In the OAI dataset, muscle volume estimates were

Figure 4.1 Axial thigh slices of representative subjects from the local participant dataset (a) and the OAI dataset (b).


a
b

based on the segmentation of all 15 available slices. Segmented thigh images from representative subjects for each imaging sequence are presented in Figure 4.1.

To compare the effect of segmentation technique, a separate operator analyzed the OAI images using a different commercially available software program (SliceOmatic 4.3, Tomovision, Magog, Quebec) which divides images into small regions based on the boundaries created by a watershed technique with thresholds set at 1 pixel surface and 0.01% mean difference. On each slice, quadriceps muscles were identified and tagged a specific colour. Fat within the muscle (intramuscular fat) was included in the segmentation of the muscle as the software program was not sensitive enough to separate it from muscle tissue. The morphological segmentation of the first analyzed slice was propagated forward to the next 14 slices. Single slice cross-sectional area was multiplied by slice thickness to obtain a volume measurement.

4.1.4 Measurement of isometric strength

For analyses of the primary objective, isometric knee extensor strength for the local participants was measured using a multi-joint dynamometer (Biodex System 3, Shirley, NY). Participants were seated upright with knee and hip angles of 90° and 100°, respectively. The centre of rotation of the knee was aligned with the axis of rotation of the dynamometer's lever arm. The force transducer was positioned with its bottom edge two fingerbreadths proximal to the medial malleolus of the test leg and fixed with a Velcro strap. A seat-belt strap was positioned across the lap in order to avoid unwanted movement of synergist hip flexors during quadriceps contractions. Additionally, during all contractions,

participants were instructed to fold their arms across the chest and to avoid multi-joint movement.

The test protocol commenced with a series of submaximal isometric contractions (approximately 50-75% of maximal isometric voluntary contraction; MVC) for the purposes of warm-up and familiarization. Participants then performed repeated, brief (~5 seconds) MVCs of the quadriceps (3-5 repetitions), each separated by a minimum of 90 seconds of rest. Maximal contraction intensity was attained when two consecutive MVCs differed by less than 5%. Torque was sampled at 100 Hz, AD converted with a 12-bit converter (CED micro1401 mk II, Cambridge Electronic Design Limited, Cambridge, UK) and displayed in real-time on an online digital system using commercially available software (Spike2 ver. 5, Cambridge Electronic Design). Loud verbal encouragement and visual feedback using the real-time digital torque was provided during all contractions in an attempt to obtain maximal effort.

For the OAI analysis, all participants were required to complete 3 trials for isometric knee extension testing. Knee extensor strength was assessed with the Good Strength apparatus (Metitur, Jyväskylä, Finland). Briefly, participants were positioned upright in a chair with test leg at 60 degrees from full extension. Two practice trials were completed at 50% MVC, followed by 3 MVCs, each separated by 30 seconds. A complete description of the protocol and data collection process can is available www.oai.ucsf.edu/datarelease/OperationsManuals.asp. To compare the strength measure to quadriceps muscle volume, knee extensor torque was

calculated as the product of force and moment arm (length measured from the force transducer to the joint line).[1]

4.1.5 Measurement of disease severity

Self-reported disease severity was measured with the Western Ontario and McMaster Osteoarthritis Index (WOMAC). WOMAC is a validated questionnaire that is widely used to quantify clinical severity of knee OA.[3] The WOMAC Likert version 3.1 has 24 items and is divided into pain, stiffness and function domains. Each item has 5 response options (none, mild, moderate, severe, extreme) corresponding to scores 0-4, with higher scores indicating increasing severity. In order to compare the size-strength relationship across a clinical spectrum of OA, WOMAC was used as an independent variable whereby total score (24 items, total score 0-96) was used to stratify study participants into tertiles with the lowest, middle and highest groups representing mild, moderate and severe knee OA, respectively.

4.1.6 Statistics

The relationships between measures of muscle size and isometric muscle strength were analyzed with univariate linear regression models and described with the coefficient of determination (r^2). Inter and intra-rater reliability of each quadriceps segmentation method was determined using a two-way random, single measure intraclass correlation coefficients (ICC 2,1) with 95% confidence intervals (ICC; SPSS v.17.0, Chicago, IL). Differences in demographic characteristics between disease severity subgroups were analyzed with a one-way ANOVA with post hoc Tukey's honestly significant differences test. The relationship between two methods of segmentation was plotted and described with the Pearson correlation

coefficient (r). Differences in muscle volume measured between the two segmentation methods were compared with a paired t-test (for 18 cases). Level of significance was set at $p<0.05$. All statistical tests except ICCs were performed with Graphpad Prism Version 5.0b (La Jolla, CA).

4.2 RESULTS

Using the OsiriX software, intra-rater (ICC=0.997, 0.991-0.999) and inter-rater (ICC=0.997, 0.988-0.999) reliability were high, based on 16 and 11 cases, respectively. The same was found for the SliceOmatic software for intra-rater reliability (ICC=0.994, 0.989-0.997) and inter-rater reliability (ICC=0.998, 0.997-1.00) where 43 and 17 cases were analyzed, respectively.

Participant characteristics for each dataset are presented in Table 4.1. Figure 4.2 illustrates the relationships between measures of quadriceps muscle size and isometric knee extension MVC strength for both datasets. The magnitude of the relationship between muscle volume and strength ($r^2=0.73$, $p<0.05$, Fig. 4.2a) was larger than that for mid-thigh CSA and strength ($r^2=0.62$, $p<0.05$, Fig. 4.2b) for the local participants. The relationship between mid-thigh ACSA and whole muscle volume was strong ($r^2=0.73$, $p<0.05$). For the OAI dataset (Fig. 4.2c), the relationship between quadriceps muscle volume and strength ($r^2=0.42$) was lower than for the local participants, but still significant ($p<0.05$). With regard to the relationship between segmentation methods, a significant difference ($p<0.0001$) was observed between measures of muscle volume for each segmentation method (253.9 ± 64.4 cm^3 for OsiriX analysis vs. 316.8 ± 73.3 cm^3 for SliceOmatic analysis), but

Table 4.1 Participant Characteristics.

	Local Participants (n=36)	**OAI Participants (n=31)**
Age	60.6±6.5	64.5±5.6
Height (m)	1.67±0.09	1.69±0.09
Weight (kg)	87.0±16.0	82.0±16.3
BMI (kg/m^2)	30.6±5.4	28.3±4.1
Isometric MVC (N•m)	157.7±72.7	109.6±47.0
Total WOMAC Score	38.2±19.6	14.7±12.6

MVC: maximal voluntary contraction; WOMAC: Western Ontario and McMaster Osteoarthritis Index.
Data are presented as means±standard deviations.

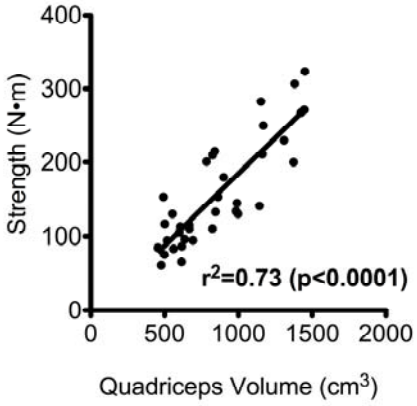
Table 4.2 Participant Characteristics by Disease Severity Subgroup.

	Mild	**Moderate**	**Severe**	**p-value**
Age	60.8±8.5	59.1±6.2	61.8±4.5	0.59
Height (m)	1.69±0.10	1.71±0.12	1.67±0.05	0.61
Weight (kg)	78.5±11.6	97.0±14.7*	85.4±16.7	0.01
BMI (kg/m^2)	27.5±3.3	33.5±5.2*	30.8±5.9	0.02

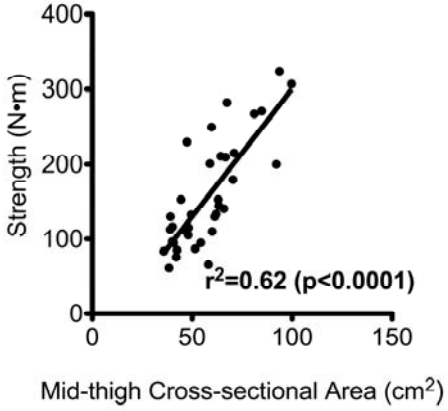
Data are presented as means±SD. BMI: body mass index.
*Significantly different than mild OA after post hoc testing ($p<0.05$)

Figure 4.2 Univariate linear regression models with strength as the dependent variable. Predictor variables were whole muscle volume from the local dataset (a), mid-thigh anatomical cross-sectional area from the local dataset (b) and volume from the OAI dataset (c).

a


400
300
200
100
0
Strength (N•m)
r²=0.73 (p<0.0001)
0
500
1000
1500
2000
Quadriceps Volume (cm³)

b


400
300
200
100
0
Strength (N•m)
r²=0.62 (p<0.0001)
0
50
100
150
Mid-thigh Cross-sectional Area (cm²)

c

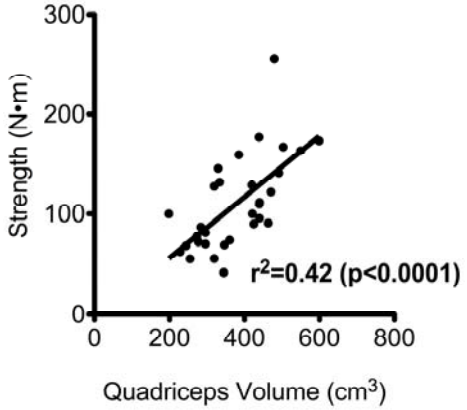
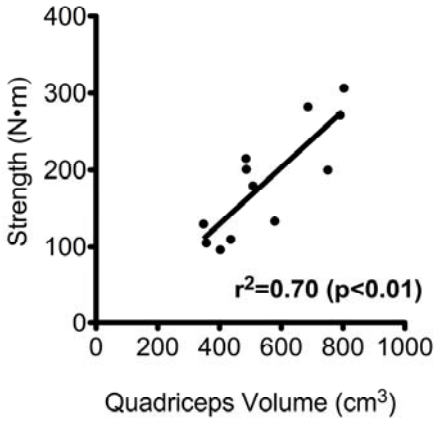
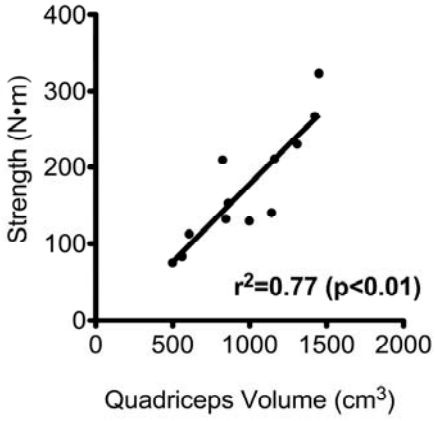

300
200
100
0
Strength (N•m)
r²=0.42 (p<0.0001)
0
200
400
600
800
Quadriceps Volume (cm³)

Figure 4.3 Univariate linear regression models for the relationship between muscle volume and strength for mild (a), moderate (b) and severe (c) knee OA.

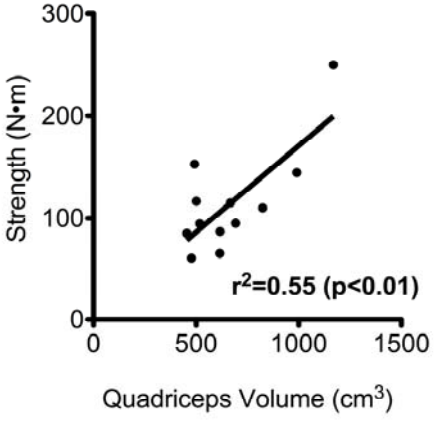
a


400
300
200
100
0
Strength (N•m)
r²=0.70 (p<0.01)
0 200 400 600 800 1000
Quadriceps Volume (cm³)

b


400
300
200
100
0
Strength (N•m)
r²=0.77 (p<0.01)
0 500 1000 1500 2000
Quadriceps Volume (cm³)

c


300
200
100
0
Strength (N•m)
r²=0.55 (p<0.01)
0 500 1000 1500
Quadriceps Volume (cm³)

there was a significant correlation for muscle volume measures between segmentation methods ($r=0.97$, $p<0.05$).

Participants in each disease subgroup were similarly matched for age, height, weight and BMI (Table 4.2), except for participants in the moderate group who had more body mass and larger BMI than those in the mild group. Plots of the relationships between quadriceps volume and isometric muscle strength are shown in Figure 4.3 for each disease subgroup. The r^2 values for mild, moderate and severe OA were 0.70, 0.78 and 0.55, respectively ($p<0.05$).

4.3 DISCUSSION

We observed that whole muscle volume accounts for a substantial proportion of the variability in muscle strength in patients with knee OA, which is much higher than previously reported for this population.[22] Furthermore, we report that the magnitude of association between quadriceps muscle size and strength may be dependent on clinical disease severity, muscle size index and MRI protocol. These observations extend the validity of using muscle size as an outcome measure in interventional studies in this population and also provide preliminary data for further investigation into whether the mechanisms of muscle weakness are altered over the severity spectrum of knee OA. Additionally, the use of different segmentation methods for the same patient resulted in large differences in absolute muscle volume (253.9 ± 64.4 cm^3 for OsiriX analysis vs. 316.8 ± 73.3 cm^3 for sliceOmatic analysis), but the same relative volume (i.e. there was a strong, significant correlation between measures derived from each technique, $r=0.97$),

suggesting that relative muscle volume can be measured reliably independent of operator or manual segmentation technique.

Quadriceps muscle weakness in patients with knee OA compared to both healthy controls and healthy contralateral limbs has been widely reported.[4] It has often been suggested that weakness is primarily due to muscle atrophy in response to disuse in a painful knee joint.[4] However, the direct evidence in support of a disuse atrophy model is actually quite limited. Peterson et al. reported that patients with severe unilateral knee OA had 12% smaller mid-thigh quadriceps ACSA in the affected vs. contralateral limb.[22] Additionally muscle fibre composition changes analogous to those observed in age-associated muscle atrophy (i.e. sarcopenia), such as fibre type group and selective type II fibre atrophy have also been observed in a study of end-stage knee OA patients undergoing joint replacement.[9] Our results lend support to the disuse atrophy paradigm by showing the muscle volume is a primary predictor of the variance muscle strength. While this cross-sectional study is limited by its inability to document atrophy or show that atrophy is the primary mechanism of muscle weakness, it does establish a scientific basis with which to test the temporal aspects of the relationship between muscle size, strength and disease severity.

Calculation of muscle volume from contiguous axial slices is the current gold standard for *in vivo* measurement of muscle size, however it is a time consuming process.[13] Accordingly, a number of studies have advocated for the use of single slice, mid-thigh ACSA as a proxy for muscle volume, citing strong correlations between the two parameters.[7, 19] Similarly, we also found a strong association

between mid-thigh CSA and muscle volume (r^2=0.73). However, despite the strength of association between these size indices, single-slice mid-thigh ACSA did not display as strong an association with muscle strength. A recent study by Hudelmaier et al. reported that proximal thigh, as opposed to mid-thigh was the region most sensitive to change in muscle mass during an exercise intervention.[13] It is possible that the mid-thigh size in patients with knee OA is not a strong determinant of strength and that other regions of the thigh play a more vital role in strength and the development of weakness, although there is little experimental evidence to substantiate this. It is unknown whether specific regions of muscle are susceptible to atrophy in patients with knee OA (e.g. distal quadriceps in patellofemoral OA).[12]

Our observation of a strong association between muscle volume and strength in knee OA is in contrast to that of Peterson et al. who reported that neural activation (i.e. the ability of the central nervous system to activate the entire population of motor units during MVC) is of greater importance than muscle size in determining muscle strength in these patients.[22] We report that muscle size explains 73% of the variance in muscle strength in knee OA versus 27% in Peterson's group.

There are several possible reasons for this discrepancy. First, the issue of using single slice ACSA as a proxy for muscle volume has been described above. Second, we tested knee OA patients with a range of clinical disease severities, isometric strength values and muscle volumes. Testing a severe group only, as in the study by Peterson et al. may have resulted in clustering of size and strength

measures, making it difficult to demonstrate covariance, even though the true correlation may be quite high.[23] Third, the magnitude of the size-strength relationship may be influenced by disease severity. Upon stratification of knee OA patients into homogeneous clinical severity subgroups, we observed that the size-strength relationship was variable (i.e. stronger for mild/moderate OA than severe OA).

The determinants of muscle strength may change as the disease progresses. To our knowledge, no other study has differentiated between severities of knee OA to determine if the mechanism of muscle weakness is altered over the natural history of disease. It has been shown in many studies that deficits in neural activation occur in OA.[11, 14, 15] However, one study using individuals with mild OA did not show neural activation differences compared to healthy controls.[17] Deficits in neural activation are thought to arise from an inhibitory effect of pain afferents on motor unit excitability.[14] It is possible that factors such as neural activation assume a greater role in predicting strength as joint pain becomes more severe (i.e. in the later stages of disease).

Other factors that could influence strength independent of muscle size in clinically severe knee OA patients include; reduced force producing capacity of individual fibres/cross-sectional area (i.e. reduced specific strength), changes in muscle fibre composition and increased antagonist co-contraction. For example, antagonist co-contraction has been observed in gait analysis as a potential compensatory mechanism to provide stability to a lax knee joint.[16] It is unknown

whether co-contraction of the agonist hamstring muscle contributes to reduced maximal knee extensor strength during isometric contractions.

The relatively small association between size and strength observed in the OAI dataset is surprising, despite the segmentation of a series of slices in order to estimate whole muscle volume. It has been observed that single slice ACSA loses its strength of prediction as the representative slice moves more proximal/distal to the mid-thigh region.[7] While the intention of the OAI protocol was to encompass a section of the leg containing the mid-thigh region, an absolute criterion measure (i.e. 10 cm proximal to the epiphyseal line) was used to landmark the most distal slice in the MRI acquisitions. As participant height and leg length are variable, image acquisition would have been performed at a different section of the thigh for each patient, with more distal regions acquired in taller subjects and more proximal regions acquired in shorter subjects. Therefore the regions acquired may not have been representative of whole muscle volume in some subjects and thus, the size-strength relationship was smaller than that observed for the local participant dataset. Additionally, measurement error has been shown to increase when the number of slices used to estimate muscle volume decrease.[20] As only a small number of slices were used (n=15), the error associated with this volume estimate may have been large. Based on these results, it is recommended that relative measurements (e.g. percentage of femur length) be used to identify anatomical landmarks if only partial thigh scans are to be used in analysis, to ensure accurate scanning for all study participants.

It should be noted that the quadriceps size-strength relationship could also have been affected by the different methods for measuring isometric strength. In the OAI participants, the joint angle used for isometric strength measurement was different than that used in the local participants. In the OAI participants, the joint angle selected was 60° from full knee-extension, while in the local participants a standard joint angle of 90° (measured as the angle between the thigh and lower-limb) was selected. It is possible that some OAI participants with reduced range of motion were not able to achieve the same degree of knee extension and thus the measured joint angle could be variable for these participants. Consequently, isometric strength testing could have been performed at different muscle lengths, which would have an effect on the length-tension relationship and the resulting strength outcomes.[27] The size-strength relationship may also be affected by the type of muscle contraction used to represent strength. Blazevich et al. reported that muscle volume was the most robust predictor of isometric and slow (30°/s), concentric isokinetic contractions, but the product of physiological cross-sectional area and fascicle length explained a greater proportion of the variance for fast (300°/s) concentric isokinetic contractions.[5] The effect of variation in joint angles and type of muscle contraction used to represent muscle strength on the size-strength relationship requires further investigation.

Despite evidence that automated segmentation methods accurately predict whole quadriceps muscle volume,[20] the majority of studies evaluating size-strength relationships use manual segmentation methods. Few studies have evaluated the reliability of manual segmentation methods even though they may be operator,

software and image sequence dependent. Our study showed that segmentation methods using different software programs have excellent intra- and inter-rater reliability. Furthermore, there was an excellent correlation (r=0.97) between absolute muscle volume measures calculated using the two different techniques, although absolute agreement between the two techniques was poor (i.e. significant difference observed between the two absolute measures). One potential cause of the poor agreement between techniques was the differences in segmentation techniques in the OsiriX software compared to SliceOmatic (i.e. region growing from a defined seed-point based on pixel intensity, automatic generation of missing ROIs compared to watershed technique). This could have eliminated operator error by automatically excluding non-muscular tissue above/below certain intensity thresholds so as not to include non-muscular tissue in the analysis. It was evident that a greater proportion of non-muscular tissue was eliminated using the first method, as absolute muscle volume estimates were consistently smaller. Despite poor absolute agreement our results suggest that relative measures of muscle volume can be acquired reliably, regardless of segmentation method or operator.

In conclusion, the results of our study indicate that muscle volume is strongly associated with isometric muscle strength in patients with knee OA, although this relationship may change as clinical disease severity changes or if proxy measures are used to estimate muscle volume. These results provide support for the use of muscle volume as an outcome measure in interventional trials designed to improve strength and also provide a preliminary investigation into the mechanisms of muscle weakness across a clinical spectrum of knee OA.

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CHAPTER 5

QUADRICEPS MUSCLE MASS AND VOLUNTARY ACTIVATION ACROSS A CLINICAL SPECTRUM OF KNEE OSTEOARTHRITIS

5.0 INTRODUCTION

Quadriceps muscle weakness in knee osteoarthritis (OA) has been widely reported,[6] is associated with pain and disability,[24, 30] is an important predictor of disability following joint replacement[26] and may be linked with disease incidence and progression.[21, 34, 38] Accordingly, conservative, non-surgical management of OA includes interventions designed specifically to attenuate reductions in muscle strength.[42] However, meta-analysis of clinical trials shows only small improvements for pain and function (i.e. comparable to non-steroidal anti-inflammatories) following quadriceps strengthening exercise[12] and trials assessing the efficacy of exercise using quadriceps strength as a primary outcome measure are equivocal.[2, 22] An incomplete understanding of the mechanisms of quadriceps weakness could explain the negative outcomes for some clinical trials involving quadriceps strengthening exercise.

A widely accepted model for muscle weakness purports that pain from OA leads to a perpetuating cycle of disuse, followed by muscle atrophy. However, the evidence that this is actually occurring and that atrophy is a significant contributor to weakness and subsequent disability is limited. Peterson et al. reported reductions in muscle mass of 12% between a thigh with severe radiographic knee OA and a contralateral control thigh, although muscle mass was a weak predictor of

strength.[31] In another study, quadriceps cross-sectional area had only a small positive correlation with muscle strength in those with moderate radiographic OA.[14] Few studies at the muscle fibre level are able to substantiate the disuse model. Fink et al. performed muscle biopsy of OA patients at the time of arthroplasty and reported predominantly type II atrophy with some type I atrophy and fibre type grouping in the vastus lateralis muscle.[11] These observations are consistent with disuse but without a control group, are difficult to distinguish from changes in muscle fiber composition associated with normal aging.

With limited evidence in favour of a simple disuse model, some attention has shifted to other potential mechanisms, principally a reduction in voluntary activation (VA) of the quadriceps. The term "arthrogenous muscle inhibition" was coined by Hurley and Newham to describe the apparent inhibition of high threshold motor units by pain afferents, during maximal voluntary contractions (MVC), leading to a reduction in VA.[19] There is evidence that VA is reduced in OA up to 20% compared to a non-diseased limb or healthy control.[16] However, there is considerable variability in the magnitude of VA deficits between studies, including one recent study in patients with mild OA showing no reduction in VA compared to healthy controls.[23]

It is possible that the degree of disease severity predicts the magnitude of muscle atrophy or VA deficit, although this has yet to be investigated. In many studies assessing quadriceps muscle function in knee OA, disease is defined dichotomously (i.e. presence or absence). This does not allow for analysis of how quadriceps muscle function progresses across a disease spectrum. Consequently, the

optimal type and time for intervention remains unknown. Furthermore, disease cohorts are often stratified based on radiographic disease severity, which is known to have a tenuous relationship with clinical severity and thus OA subgroups may be clinically heterogeneous in composition.[3] Therefore, the purpose of this study was to evaluate strength, muscle volume and VA across a clinical spectrum of knee OA.

5.1 METHODS

5.1.1 Patient characteristics and stratification for disease severity

Thirty-six community dwelling men and women participated in the study. Participants were included if they had persistent knee pain that required referral to an orthopedic surgeon and/or X-ray findings consistent with knee OA in at least one compartment (e.g. presence of osteophytes, apparent joint space narrowing, subchondral sclerosis and areas of cyst formations) confirmed by an experienced musculoskeletal radiologist or orthopedic surgeon. Participants also met the American College of Rheumatology definition of knee OA.[1] Exclusion criteria included musculoskeletal, neurological or rheumatological impairment of the lower limbs other than knee OA, prior high tibial osteotomy, unicondylar or total knee arthroplasty or cardiopulmonary impairment that precluded performing vigorous muscle contractions. If a patient had bilateral knee OA, the limb with the most severe symptoms (as reported by the patient), was selected as the test limb. Ethical approval for the study was obtained from the local institutional ethics review board and written consent was obtained from each participant prior to study commencement. Measurement of quadriceps muscle strength, VA and muscle volume was undertaken as part of a comprehensive assessment of neuromuscular

function that also included procedures for measurement of muscle power and muscle contractile properties. The entire test protocol was completed in a single visit to the Neuromuscular Assessment Laboratory. The order of all testing procedure was randomized and a minimum of 10 minutes rest was allotted between testing sessions, in order to minimize fatigue and learning effects.

The Western Ontario and McMaster Osteoarthritis Index (WOMAC) was used to stratify subjects into study groups based on clinical disease severity. WOMAC is a validated questionnaire that is widely used to quantify clinical severity of knee OA.[5] The WOMAC Likert version 3.0 has 24 items and is divided into pain, stiffness and function domains. Each item has 5 response options (none, mild, moderate, severe, extreme) corresponding to scores 0-4, with higher scores indicating increasing severity. WOMAC scores were used as the independent variable in this study whereby total score (24 items, total score 0-96) was used stratify study participants into tertiles, with the lowest, middle and highest groups representing mild, moderate and severe clinical knee OA, respectively.

5.1.2 Measurement of isometric muscle strength and voluntary activation

For both strength and VA measurements, participants were seated upright in multi-joint dynamometer (Biodex System 3, Shirley, NY), with knee and hip angles of 90° and 100° respectively. The centre of rotation of the knee was aligned with the axis of rotation of the dynamometer's lever arm. The force transducer was positioned with its bottom edge two fingerbreadths proximal to the medial malleolus of the test leg and fixed with a Velcro strap. A seat-belt strap was positioned across the lap in order to avoid unwanted movement. Furthermore,

during all contractions, the participants were instructed to fold their arms across the chest and to avoid hip flexion, so that the contribution of synergist muscles to torque could be attenuated.

The highest torque output achieved during repeated (3-5 repetitions) isometric quadriceps maximal voluntary contractions (MVCs) was used to represent muscle strength. Torque was normalized to body mass (N•m/kg) in order to control for sex and body mass differences between participants. The test protocol commenced with a series of submaximal isometric contractions (approximately 50-75% of maximal intensity) for the purposes of warm-up and familiarization. Participants then performed repeated, brief (~5 s) isometric MVCs of the quadriceps (3-5 repetitions), each separated by a minimum of 90 s of rest. Maximal contraction intensity was attained when two consecutive MVCs differed by less than 5%.

The interpolated twitch technique was used to measure VA. The premise of the technique is that additional twitch torque resulting from a supramaximal stimulus superimposed on a MVC is indicative of reduced central drive to the muscle resulting in incomplete activation. Normalizing the superimposed twitch to a resting, potentiated control twitch provides an index of VA:

$$VA = [1 - (\text{Superimposed Twitch} / \text{Potentiated Resting Twitch})] \times 100\%^{4} \qquad \textbf{equ. 1}$$

The intramuscular fibres of the femoral nerve supplying the quadriceps were stimulated supramaximally with a constant current stimulator (Digitimer DS7AH, Digitimer Ltd., Hertfordshire, UK). Aluminum foil electrodes, wrapped in paper

towel, soaked in water and conducting gel were cut into 6 cm strips (lengthwise) and placed over the belly of the quadriceps. Before application of the electrodes, patients were asked to perform submaximal isometric knee extension contractions, so that the bellies of the quadriceps could be visualized and palpated, to avoid erroneous electrode placement over antagonist muscle fibres. Electrodes were then cut widthwise so that no conducting material was placed over antagonist muscle fibres. The cathode was placed with its proximal edge at a point just distal to the inguinal crease and the distal edge of the anode was placed three fingerbreadths proximal to the base of the patella. In order to improve sensitivity of the technique for detecting superimposed twitches, doublets were used to stimulate the quadriceps at rest and MVC (pulse width=100 μs, interpulse interval=10 μs, 400 V).[37] To ensure that the stimulus was supramaximal prior to study onset, a series of incremental stimuli of increasing intensity were delivered to the resting muscle. Once the torque output reached a plateau, the stimulus was deemed maximal (this usually occurred at an intensity of 300-600 mA). The stimulus intensity was then increased an additional ~10% to achieve supramaximality. Patients were then instructed to perform an MVC in an identical fashion to the description above. When a plateau in the torque tracing was perceived during MVC (~3s into the contraction), the stimulator was triggered manually by the study examiner. The MVC lasted for ~5s and was followed ~3 s later by the resting stimulus. This procedure was repeated 3-4 times for each subject with a minimum of 90 s rest between trials. VA was calculated as the median for all acceptable trials.

For both MVC and VA testing, torque was sampled at 100 Hz, AD converted with a 12-bit converter (CED micro1401 mk II, Cambridge Electronic Design Limited, Cambridge, UK) and displayed in real-time on an online digital system using commercially available software (Spike2 ver. 5, Cambridge Electronic Design). Loud verbal encouragement and visual feedback using the real-time digital torque was used during all contractions to ensure maximal intensity.

5.1.3 Magnetic resonance imaging methods and volume estimation

MRI scans of the thigh were acquired using a 3.0T MR system (GE Discovery MR750, GE Healthcare, Waukesha, Wisc.) with an 8-coil torso phased array. The patient was positioned supine in the scanner bore. A 3-plane localizing scan and calibration scan were performed to ensure the anatomy of interest was contained in the field-of-view (FOV). Three-dimensional axial images were acquired from proximal (femoral head) to distal (femoral condyles) with a proton density weighted multiecho-spoiled gradient echo (SPGR) imaging sequence (FOV: 42-46x21-23 cm, slice thickness: 4 mm, matrix: 320x160x120, TR: 7.4 ms, echoes: 6, TE, 1.4, 2.1, 2.9, 3.6, 4.4, 5.1 ms, flip angle 5°, bandwidth: ± 142.86 kHz). An investigational version of the IDEAL (iterative decomposition of water and fat with echo asymmetry and least squares estimation) multipoint water-fat separation method that is T1 independent, T2* corrected and employs accurate spectral modeling of fat, was used to reconstruct both water-only and fat-only images from the multiecho SPGR source images.[33, 41] Fat-water separation also ensured that non-muscle tissue (in particular fat) was not included in analysis of the thigh images. Image analysis was performed

on the water only images produced by the IDEAL reconstruction for assessment of muscle volume.

A combination of manual and semi-automated techniques using open-source OsiriX image processing software (version 3.7, Geneva, Switzerland) was used to analyze images and calculate muscle volume. Analysis began proximally from the first slice not containing the gluteal muscle to the last distal slice containing the rectus femoris, as this region is thought to represent maximal thigh muscle mass[40] and because it is difficult to differentiate between thigh muscles at the most proximal and distal slices.[9] Quadriceps muscle volume was calculated from the water-only images by manually outlining the most proximal and distal slices with the brush tool to create regions of interest (ROI). This process was repeated for every tenth slice in-between and missing ROIs were generated automatically. Once the quadriceps had been roughly outlined, all pixel values outside the ROIs were set to zero. Subsequently, a 3D threshold-growing tool was used to grow ROIs for the quadriceps muscle tissue only from a defined seedpoint within the muscle. This was done to ensure exclusion of non-muscular tissue in the septal spaces. Any errors produced by the automatic tool were corrected manually. The software automatically calculated volume for the series of ROIs. The reliability of this method defined by the intraclass correlation coefficient (ICC; 2,1) and 95% confidence intervals was high (intra-rater: ICC=0.997, 0.991-0.999 and inter-rater: ICC=0.997, 0.988-0.999 based on 16 and 11 cases, respectively). Axial single-slices taken from the mid-thigh region for representative subjects from the mild and severe groups

are presented in Figure 5.1. Quadriceps muscle volume was normalized to number of slices used in the analysis to control for differences in thigh length.

5.1.4 Statistics

One-way ANOVA with post-hoc Tukey's honestly significant differences testing was used to compare quadriceps muscular strength and volume across the different severity groups. A Kruskal-Wallis with post-hoc Dunn's test was used to compare differences in VA. A stepwise multiple regression model was used to determine the relative contributions of muscle volume and VA to the variance in isometric strength. Univariate linear regression models were used to determine the relationships between VA and pain and function scores on the WOMAC. Differences in absolute torque values between isometric strength testing and the interpolated twitch technique were compared with a paired t-test. Level of significance was set at $p<0.05$. All normally distributed data are described with mean±standard deviation (SD). VA is non-Gaussian and central tendency is described with median and 95% confidence intervals. All statistical analyses were performed with Graphpad Prism Version 5.0b (La Jolla, CA).

5.2 RESULTS

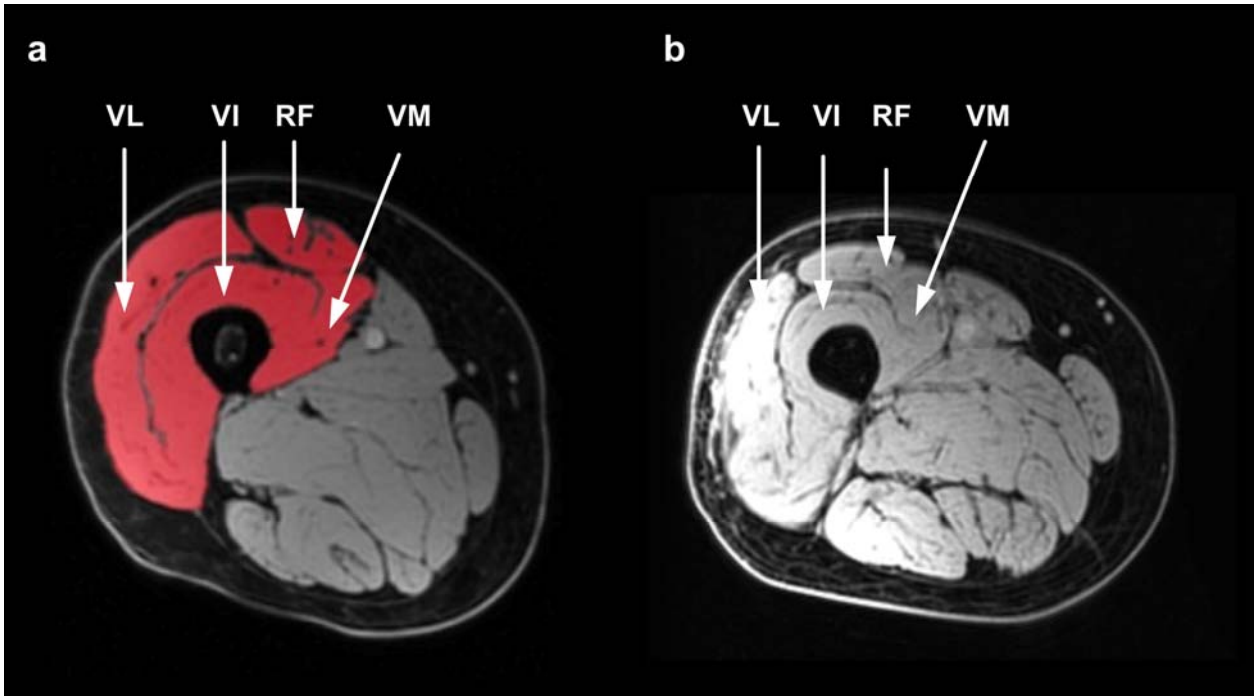
Participant characteristics, including normalized strength, muscle volume and VA measures for each disease subgroup are presented in Table 5.1. Participants in each group were relatively similar for age, height and body size, although those in the moderate group were slightly heavier and had greater body mass index than those in the mild group ($p<0.05$). Sex differences were noted between groups with the mild group having double the number of men and the severe group having

Table 5.1 Participant characteristics (n = 36).

	Mild	**Moderate**	**Severe**	**p-value**
Sex (Male/Female)	8/4	5/7	4/8	
Age	60.8±8.5	59.1±6.2	61.8±4.5	0.59
Height (m)	1.69±0.10	1.71±0.12	1.67±0.05	0.61
Weight (kg)	78.5±11.6	97.0±14.7*	85.4±16.7	<0.05
BMI (kg/m^2)	27.5±3.3	33.5±5.2*	30.8±5.9	<0.05
WOMAC total score	16.6±8.1	37.5±6.5*	60.5±7.4*†	<0.05
WOMAC pain score	4.5±2.4	6.9±2.2	11.9±1.9*†	<0.05
Strength (N•m/kg)	2.30±0.77	1.78±0.74	1.29±0.51*	<0.05
Muscle volume (cm^3/# slices)	23.68±6.84	22.47±6.30	17.7±3.95*	<0.05
% VA	95.3 (91.8-98.8)	95.7 (93.7-97.6)	89.9 (85.3-94.4)	0.06

Data are presented as means±SD, except for %VA, which has 95% confidence intervals in parentheses). BMI: body mass index; %VA: percent voluntary activation.
*Significantly different from mild OA after post hoc testing ($p<0.05$).
†Significantly different from moderate OA after post hoc testing ($p<0.05$).

Figure 5.1 Axial view of the mid-region of the right thigh for representative male subjects from the mild (a) and severe (b) disease subgroups. The four bellies of the quadriceps are labeled VM (vastus intermedius), RF (rectus femoris), VI (vastus intermedius) and VL (vastus lateralis).

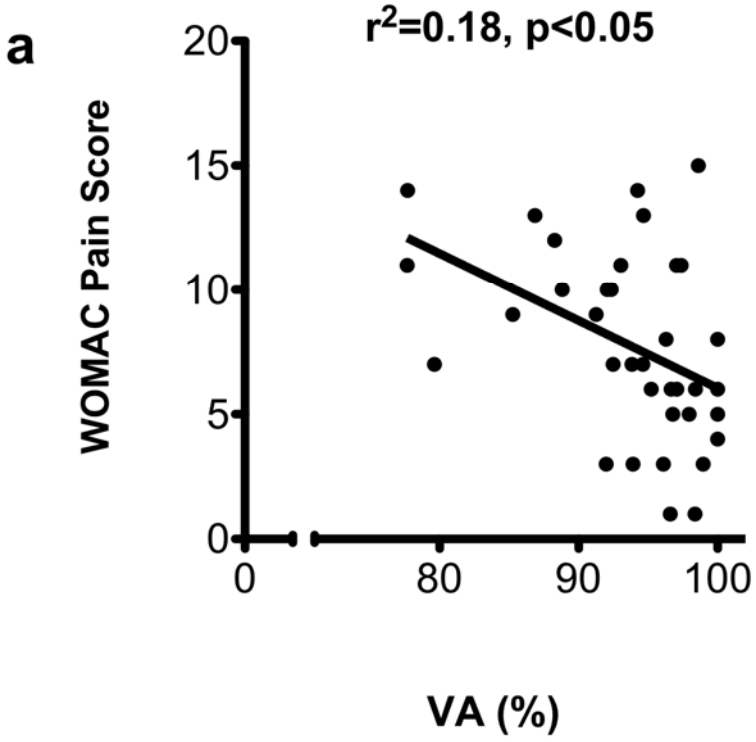

a
VL
VI
RF
VM
b
VL
VI
RF
VM

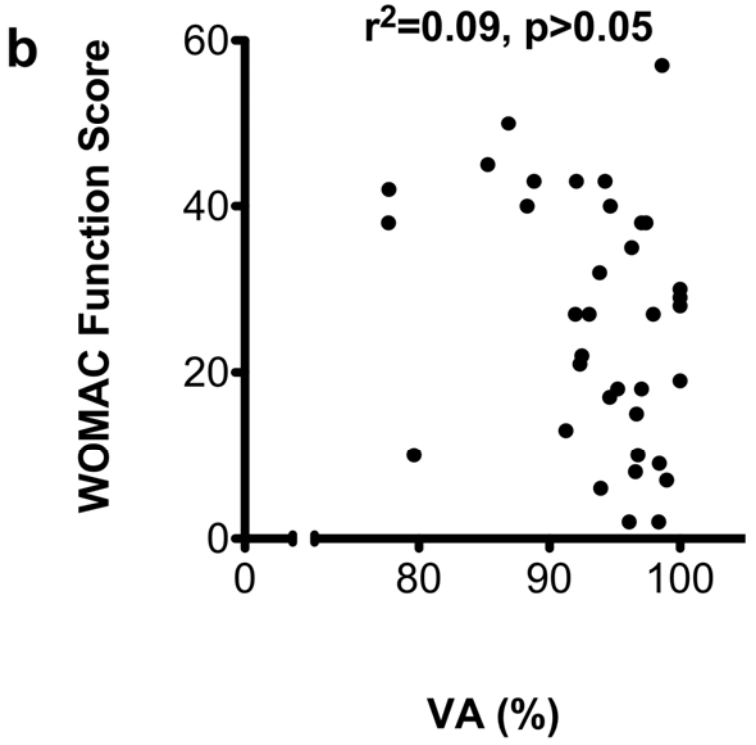
double the number of women, however an attempt was made to control for these differences by normalizing muscle parameters. Significant differences were observed for WOMAC total and pain sub-scale scores ($p<0.05$). Post hoc testing revealed that each group differed significantly for total WOMAC score, while the severe group was significantly different from both mild and moderate groups for pain sub-scale score. A significant difference was observed for normalized strength ($p<0.05$). With post hoc testing, the difference between mild and severe groups remained significant with those in the severe group having ~44% lower strength. Similarly, normalized muscle volume was significantly reduced in the severe compared to mild group (~25% reduction, $p<0.05$). No significant difference across groups for VA was evident ($p>0.05$).

A non-significant ~5-6% difference in VA was observed in the severe compared to mild and moderate groups. Five subjects in the mild group, and 4 subjects in the moderate group achieved 100% activation in at least one trial compared to only two subjects in the severe group. Intersubject variability in VA was similar across clinical severity of OA, although slightly higher in the severe group. Coefficients of variation were 5.8, 3.2 and 8.0% in the mild, moderate and severe groups, respectively.

Participants were able to produce ~10 N•m more torque during simple isometric strength testing than during testing with the interpolated twitch technique (MVC during isometric strength testing = 157±72 N•m vs. MVC during interpolated twitch = 147±72 N•m, $p<0.05$).

Figure 5.2 Linear regression models depicting the relationship between % voluntary activation (VA, x-axis) and self-reported pain (a) and function (b).


a
r^2=0.18, p<0.05
WOMAC Pain Score
20
15
10
5
0
0
80
90
100
VA (%)


b
r^2=0.09, p>0.05
WOMAC Function Score
60
40
20
0
0
80
90
100
VA (%)

From the multiple regression analysis, the combination of muscle volume and VA predicted 75% of the variance in isometric strength (adjusted R^2=0.75, $p<0.05$). When VA was removed from the analysis, muscle volume alone explained 72% of the variance in isometric strength ($\beta = 0.85$). Thus, VA only accounted for an additional 3% of the variance in strength ($\beta = 0.20$). Individual univariate linear regression models with VA as the dependent variable are illustrated in Figure 5.2. A small, but significant association was observed between VA and self-reported pain on the WOMAC questionnaire (r^2=0.18, $p<0.05$, Fig. 5.2a), but no association was observed between VA and self-reported function (r^2=0.09, $p>0.05$, Fig. 5.2b).

5.3 DISCUSSION

The results of this study suggest that quadriceps muscle volume is a primary determinant of knee extensor strength and those with clinically severe knee OA have reduced muscle mass relative to those with mild disease. Furthermore, VA deficits reported in previous studies may have been overestimated. With ample practice and motivation, no significant differences in VA were observed across a clinical spectrum of knee OA. The small VA deficits in some subjects observed in this study may be related to knee pain, however the clinical significance of these deficits is questionable. These results have implications for the rehabilitation of quadriceps muscle weakness in knee OA.

Knee OA as a model of quadriceps disuse atrophy has been suggested previously.[18] The results of this study highlight the strong relationship between muscle mass and strength. However due to the cross-sectional design, these results

do not provide direct evidence for disuse atrophy *per se* because it is difficult to determine the temporality of the relationship between changes in muscle mass and clinical disease severity. Indeed, reduced muscle mass may predispose a patient to more severe knee OA. Reductions in muscle strength have been shown to predict both radiographic[21, 39] and symptomatic disease incidence[35] in large population studies. This has also been substantiated in an animal model of botulinum toxin induced quadriceps muscle weakness.[34] However, a similar association between strength and disease progression has not been reported.[8] Studies incorporating a measure of muscle mass have been conflicting, with one reporting a protective effect for increased muscle mass on radiographic disease incidence[21] and one reporting that women with muscle weakness who developed incident radiographic knee OA had increased muscle mass compared to those who did not.[39] The relationship between strength and disease incidence and progression becomes more complex when one considers the recent study by Sharma et al. reporting a negative effect of quadriceps strength in malaligned and lax knees.[36]

Regardless of the temporality of the relationship between muscle mass and disease severity and the mechanism of atrophy, this study illustrates the importance of muscle mass to quadriceps strength, a finding that has not been supported by previous research. From the multiple regression analysis, it was clear that muscle volume alone accounted for large proportion of the variance in isometric strength (73%), while VA explained only an additional 4%. Conversely, Peterson et al. reported that VA was more predictive of variance in strength than quadriceps cross-sectional area [31]. Also, Gur and Cakin reported only a moderate relationship

between concentric strength and mid-thigh quadriceps cross-sectional area, measured by computed-tomography.[14] A strength of our study was the use of novel imaging and segmentation techniques to quantify muscle volume to eliminate the possibility of confusing bright water signal for fat. Any such misidentification would introduce error into the measurements of both compartments since a misidentified pixel would be removed from the volume of the correct compartment and added to the volume of the incorrect compartment. Furthermore, we segmented a large volume of the quadriceps as opposed to estimating volume using a single mid-thigh slice of the quadriceps, which has been shown to have error of 10% or greater depending on the slice used.[28] The observation that muscle mass is the greatest predictor of strength in knee OA is consistent with the aging literature.[10] Thus, preservation of muscle mass should be an important outcome of intervention (see below).

Contrary to previous studies in this area, we did not observe a significant difference in VA across a spectrum of disease severity. Our results can likely be attributed to a combination of factors related to study design and to technical issues related to the interpolated twitch technique. VA values observed in this study are similar to those reported previously in the quadriceps of healthy participants.[29, 32] Participants in this study had ample warm-up and practice prior to undergoing testing with the interpolated twitch technique. Furthermore, participants also completed other tests within a single session for measurement of muscle power and muscle contractile properties involving a large number of maximal and submaximal contractions (data not reported). Therefore, participants were well familiarized

prior to VA assessment. From a technical perspective, many studies of activation in knee OA have used the central activation ratio as an index of VA.[27, 31] This technique employs high frequency trains to stimulate the quadriceps during MVC, which may cause pain and subsequent inhibition of motor units leading to apparent decreases in activation. In other studies, VA has been calculated by normalizing the superimposed twitch to an unpotentiated resting twitch,[15, 20] which would cause an overestimation of VA deficit, since the superimposed twitch itself is potentiated by the MVC. We controlled for many methodological errors that may occur when using the interpolated twitch technique including 1) the use of a superimposed doublet for improved sensitivity, 2) verification of supramaximality of the stimulus and 3) normalization the superimposed twitch to a potentiated control twitch.[37]

It should be noted that one subject in the mild group had a median VA of 79.6%, the second lowest score in the study. This score was also greater than two standard deviations below mean VA for the mild group and could be considered an outlier. Removing this subject from the analysis led to a significant difference in VA between mild and severe knee OA ($p<0.05$). It could be that VA is dependent to a certain extent on disease severity. Pain afferent inhibition of high threshold motor units during high intensity contractions (i.e. "arthrogenous muscle inhibition") has been postulated as the mechanism of reduced VA in knee OA.[19] Correspondingly, we showed a small but significant relationship between self-reported pain and VA (Fig 5.3a). However, self-reported pain (Table 5.1) was significantly greater in the severe group, with only a small, non-significant reduction in VA.

The relevance of a 5-6% deficit in VA in the severe group compared to mild or moderate knee OA is questionable. First, no relationship was observed between VA and self-reported function in this study (Fig. 5.3b). Second, we have recently reported on the validity of the interpolated twitch technique and have questioned its utility as an absolute measure of neural activation due to lack of responsiveness of the motor neuron pool to external stimulation because of the hyperpolarizing effects of voluntary activity during the MVC.[7] Third, small deficits in VA during maximal isometric contractions intuitively have little functional relevance as the activities of daily living are usually performed dynamically and at submaximal contractile intensities. There is indirect evidence to suggest that submaximal contractions are impaired in patients with knee OA,[17] however no study has measured intrinsic muscle and motor unit properties at lower intensities in this population.

There are several limitations to this study. The limitation of the cross-sectional design in establishing temporality of association has been described above. A second limitation is the use of a continuous measure of disease severity to stratify patients into tertiles. There is currently no optimal measurement tool that can be used to stratify knee OA patients based on severity.[13] WOMAC was chosen in this study over commonly used radiographic scoring of knee OA (e.g. Kellgren-Lawrence scale), due to questionable relationship between radiographic and clinical severity.[3] While WOMAC is a widely accepted research tool, the use of a continuous measure implies arbitrary cutoff points, which may have produced variability within the study groups. Another limitation in interpreting the results arises from the sex

differences between study subgroups. While participants were relatively similar for age and body size (Table 5.1), the severe group had a higher proportion of women. We attempted to control for this discrepancy by normalizing strength to body mass and muscle volume to number of slices (i.e. a measure of thigh length), however it is unknown if the magnitude of the deficits reported in the severe category would be the same if either men or women were assessed in isolation. We did not possess the necessary study power to analyze subgroups based on sex.

In summary, this study found that quadriceps muscle volume was the primary determinant of knee extensor strength across a clinical spectrum of knee OA. Reduced muscle mass in severe knee OA should be targeted with interventions specifically designed to preserve and increase muscle mass. For example, it is well established that the benefits of short-term resistance training exercise (e.g. 1-2 weeks in duration) are primarily neural, (i.e. improvements in VA).[25] Thus short term resistance training programs may not appropriately target the mechanism of muscle weakness in patients with knee OA. Furthermore, the clinical significance of the small non-significant deficits in VA observed in this study is questionable. Therefore, we propose that future studies investigate the efficacy of longer duration, hypertrophy-inducing resistance training programs on improving strength, pain and functional outcomes.

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CHAPTER 6

QUADRICEPS CONTRACTILE AND MOTOR UNIT PROPERTIES IN KNEE OSTEOARTHRITIS

6.0 INTRODUCTION

Quadriceps muscle weakness is commonly associated with knee osteoarthritis (OA). The relationship between weakness and disability has been well documented[22, 23] and quadriceps weakness may be a risk factor for disease incidence and progression.[2, 28] An understanding of the mechanisms and natural history of quadriceps weakness in knee OA is critical in order to optimize the type and timing of both rehabilitative and surgical interventions. Furthermore, knowledge of the how the neuromuscular system is affected in knee OA may provide information about disease prognosis and the ability of the quadriceps to recover after interventions such as joint replacement.

Weakness in knee OA is usually attributed to a progressive pattern of disuse from knee pain, resulting in muscle atrophy and associated loss of strength.[7] Characteristic deficits related to disuse including reduced muscle size and increased neural inhibition[12] have been reported in cross-sectional studies of knee OA.[16, 18, 24] Experimentally controlled studies of disuse employing immobilization, bed rest or microgravity have reported alterations in single fibre protein expression (i.e. increased expression of myosin heavy chain (MHC) IIa and IIx proteins), frequently leading to a speeding of whole muscle contractile properties.[12] It is possible that knee OA constitutes a clinically applicable model of chronic disuse, however no

study to date has measured quadriceps muscle contractile properties in this patient population.

There is also evidence to suggest that the individual motor units (MUs) supplying the quadriceps may be affected by knee OA. Neural inhibition, presumably due to pain preventing maximal MU recruitment and/or rate coding during maximal isometric contractions has been widely reported.[17] Measures of neural inhibition during maximal contractions do not provide information about individual MUs. Studies of individual MU behaviour at low intensity contractions may be more clinically relevant as most activities of daily living require low-to-moderate intensity quadriceps contractions. There is also evidence of MU remodeling from one study of patients with radiographically severe knee OA.[20] However, this observation requires confirmation as radiographic definition of disease severity may not be appropriate when investigating neuromuscular outcomes.[23] In order to further understand the mechanisms of muscle weakness in knee OA, the purpose of this study was to investigate whether *in vivo* contractile and MU properties (e.g. motor unit potential size and firing rates) are altered in knee OA.

6.1 METHODS

6.1.1 Study participants

6.1.1.1 Study participants for measurement of contractile properties

Thirty-nine community dwelling men and women underwent testing of quadriceps evoked contractile properties. Participants were included if they had persistent knee pain that required referral to an orthopedic surgeon and/or X-ray findings consistent with knee OA in at least one compartment (e.g. presence of

osteophytes, apparent joint space narrowing, subchondral sclerosis and areas of cyst formations) confirmed by an experienced musculoskeletal radiologist or orthopedic surgeon. Participants also met the American College of Rheumatology definition of knee OA.[1] Exclusion criteria included: prior high tibial osteotomy, unicondylar or total knee arthroplasty, musculoskeletal, neurological or rheumatological impairment of the lower limbs other than knee OA, or cardiopulmonary impairment that precluded the performance of vigorous muscle contractions. If a patient had bilateral knee OA, the limb with the more severe symptoms (as reported by the patient), was selected as the test limb. Ethical approval for the study was obtained from the local institutional ethics review board and written consent was obtained from each participant prior to study commencement.

Quadriceps muscle contractile properties were compared across a clinical spectrum of knee OA. In order to facilitate comparison, participants were stratified into tertiles of disease severity based on their responses to the Western Ontario and McMaster Osteoarthritis Index (WOMAC). WOMAC is a validated, widely used tool used to quantify clinical severity in knee OA patients.[5] The lowest, middle and highest tertiles were designated mild, moderate and severe knee OA respectively.

6.1.1.2 Study participants for measurement of vastus medialis motor unit properties

Measurement of vastus medialis MU properties was undertaken in a separate study sample. Eight participants with knee OA and eight healthy, age-matched control subjects participated in this part of the study. Participant recruitment

strategy and inclusion/exclusion criteria were identical to that described above for the OA participants. Control subjects were recruited from the local university community and had no self-reported history of knee pain.

6.1.2 Measurement of isometric muscle strength

Isometric MVCs were performed in both parts of the study in order to measure maximal strength and to use as a reference for normalization of submaximal contractions and stimulus intensity levels. Participants were seated upright in a multi-joint dynamometer (Biodex System 3, Shirley, NY), with knee and hip angles of 90° and 100° respectively. The centre of rotation of the knee was aligned with the axis of rotation of the dynamometer's lever arm. The force transducer was positioned with its bottom edge two fingerbreadths proximal to the medial malleolus of the test leg and fixed with a Velcro strap. A seat-belt strap was positioned across the lap in order to avoid unwanted movement. The test protocol commenced with a series of submaximal isometric contractions (approximately 50-75% of maximal intensity) for the purposes of warm-up and familiarization. Participants then performed repeated, brief (~5 s) isometric MVCs of the quadriceps (3-5 repetitions), each separated by a minimum of 90 s of rest. Maximal contraction intensity was attained when two consecutive MVCs differed by less than 5%. Visual feedback in the form of the real-time torque tracing and verbal encouragement were provided as motivation. Torque was sampled at 100 Hz, AD converted with a 12-bit converter (CED micro1401 mk II, Cambridge Electronic Design Limited, Cambridge, UK) and displayed in real-time on an online digital system using commercially available software (Spike2 ver. 5, Cambridge Electronic Design). Torque was

normalized to body mass to control for sex and body size differences between participants. The same force measurement procedure was used during the submaximal contractions performed during the recording of MU properties (see below).

6.1.3 Electrically evoked contractile properties

The intramuscular branches of the femoral nerve were stimulated with a constant current stimulator (Digitimer DS7AH, Digitimer Ltd., Hertfordshire, UK) to evoke quadriceps muscle twitches and to measure the torque-frequency relationship. Aluminum foil electrodes soaked in water and conducting gel were cut into 6 cm wide strips and placed over the belly of the quadriceps. Before application of the electrodes, patients were asked to perform submaximal isometric knee extension contractions, so that the bellies of the quadriceps could be visualized and palpated in an attempt to avoid erroneous electrode placement over antagonist muscle fibres. Electrodes were then cut lengthwise so that no conducting material was placed over antagonist muscle fibres. The cathode was placed with its proximal edge at a point just distal to the inguinal crease and the anode was placed three fingerbreadths proximal to the base of the patella.

Resting twitches were elicited using single pulses of 100 μs duration (1 Hz, 400 V). Stimulus intensity was increased incrementally until a plateau in twitch torque was observed. Stimulus intensity was then increased an additional 10% in order to ensure that the stimulus was maximal. Three maximal twitches were recorded separated by 30 s rest, in order to avoid potentiation effects. Twitch parameters assessed during offline analysis were the mean of peak twitch tension

(P_T), time to peak tension (TPT) and half-relaxation time (HRT), for the three twitches.

Resting torque-frequency characteristics were measured using trains of 500 μs pulses delivered at 1, 5, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 75 and 100 Hz. The stimulus intensity selected was that required to elicit a contraction equivalent to 20% MVC torque, using the 100 Hz train. Trains were separated by 10s and were delivered in a random order to control for potentiation effects. Torque values were normalized to torque at 100 Hz and the torque-frequency curve for each subject was modeled.

6.1.4 Motor unit properties

Decomposition-enhanced spike-triggered averaging (DE-STA) was used to extract information about individual MUs from both the intramuscular concentric needle signal and the surface electromyography (EMG) interference pattern. The DE-STA method and algorithms have been described in detail previously.[14, 31] Briefly, both intramuscular concentric needle and surface EMG signals are acquired simultaneously during a sustained isometric contraction. A series of algorithms decomposes the concentric needle detected EMG signal into its constituent motor unit potential (MUP) trains using information related to both MU shape and firing times. The firing times of the detected and classified needle MUPs (N-MUP) from each train are then used as triggers for locating time-locked 100 ms epochs in the surface signal. These surface signal epochs are then averaged to extract a surface MUP (S-MUP) template for a particular MUP train. The concentric N-MUP template is based on a median filtered average of 51 isolated MUPs.

Needle and surface EMG signals were acquired from the vastus medialis muscle using custom DE-STA software on the Neuroscan Comperio system (Neuroscan Medical Systems, El Paso, TX). N-MUPs were detected with a commercially available disposable concentric needle electrode (model no. N53153; Teca Corp., Hawthorne, NY). Self-adhesive silver/silver chloride electrodes were cut into 1 cm x 3 cm strips and applied over the area of interest, after abrasion of the skin with isopropyl alcohol pads. The active electrode was applied to the belly of the vastus medialis (3 fingerbreadths superiolateral to the base of the patella), approximately over the motor point. The reference and ground electrodes were applied to the patella and the lateral thigh, respectively. Surgical tape was used to reinforce the electrode position to limit movement during the study. The needle and surface signals were amplified and filtered with a bandpass of 10 Hz to 10 kHz and 5 Hz to 5kHz, respectively.

Subjects were positioned in the dynamometer and completed the protocol for determination of isometric MVC as described above. Subsequently, the needle was inserted into the muscle belly ~1 cm distal to the active surface electrode at a depth of ~0.5-1cm and held in place manually. Participants were asked to contract minimally while the needle position was adjusted to minimize the rise times of the N-MUPs from the first 2-3 recruited MUs. Participants performed repeated contractions at two intensity levels; 10% and 20% MVC. Two levels were selected in order to sample MUs of increasing size that are recruited at progressively higher contraction intensities. These particular intensities were selected because participants had difficulty maintaining higher intensity levels for the required 30 s

and because the complex interference pattern generated at higher intensities is difficult to accurately decompose and may under represent smaller MUs.[9] A target line was placed across the real-time torque tracing and auditory feedback of the firing pattern was used to ensure maintenance of a steady contraction. Each contraction lasted 30 s, which was the time necessary to allow for an adequate number of averages to adequately extract the S-MUPs. Successive contractions for a particular intensity level were separated by at least 30 s and approximately 2 min. rest was allotted between intensity levels. The order of the contraction intensities was randomized for each participant. Three to nine contractions were required for each intensity level in order to acquire a sample of at least 20 distinct N-MUPs and S-MUPs for analysis. For each contraction, the needle position and depth were altered to increase the possibility of detecting different N-MUP trains. A new needle insertion site was also used between intensities to decrease the likelihood of sampling the same MU repeatedly.

Offline analysis of each N-MUP train and S-MUP was performed to determine acceptability. Rejection criteria for an N-MUP train or S-MUP included a template with less than 51 individual contributions, a non-gaussian MU interdischarge interval (IDI) histogram, a coefficient of variation greater than 0.3 for the IDI and a non-physiological or inconsistent firing rate. Subsequently, all N-MUP trains and their respective N-MUPs and S-MUPS were visualized and markers for onset, negative-peak, positive-peak and endpoint were readjusted manually when necessary (see Appendix D for decomposition results from a typical 30-s contraction from the vastus medialis of a representative control participant). Reliability of the

analysis has been previously established in healthy and diseased populations[8]. The firing pattern of each MUP was characterized by a histogram and estimation of the mean interdischarge interval (IDI). Each MU's average firing rate was calculated as the inverse of its mean IDI.

6.1.5 Statistics

Mean ± standard deviation was used as the measure of central tendency for all descriptive statistics. One-way ANOVAs with post hoc Tukey's Honestly Significant differences test were used to compare parametric data across disease severity groups. Differences in non-parametric data were assessed with Kruskal-Wallis and Dunn's multiple comparisons post hoc test. A two-way ANOVA with a post-hoc Bonferonni correction was used to compare torque across disease severity (main effect 1) and frequencies (main effect 2). A one-way ANOVA with post hoc Tukey's honestly significant differences test was used to compare MUP properties between OA and control subjects and between contractile intensities. Level of significance was set at $p<0.05$. All statistical tests were performed with Graphpad Prism Version 5.0b (La Jolla, CA).

6.2 RESULTS

6.2.1 Evoked contractile properties of the quadriceps

Total WOMAC score was significantly different between all groups with post-hoc testing ($p<0.05$, Table 6.1). There was a significant difference for isometric knee extensor torque across groups ($p<0.05$, Table 6.1). Post hoc testing revealed a significant difference in normalized knee extensor torque between mild and severe OA, with those in the severe group producing ~38% less torque. A significant

difference was observed between moderate and severe groups with regard to height and weight with post hoc testing ($p<0.05$), however, due to the lack of statistical difference in strength between these groups, height and weight were not controlled for with covariate analysis. The normalized torque-frequency curves for mild, moderate and severe knee OA are shown in Figure 6.1. Significant main effects were observed for both frequency and disease severity ($p<0.05$). No interaction effect was observed ($p = 0.99$). Post hoc Bonferroni correction did not reveal any significant differences between disease severity groups at any of the 14 frequencies tested. Similarly, no differences in evoked resting twitch properties were observed between groups for P_T, TPT or HRT ($p>0.05$, Table 6.2), although the between-group differences for P_T did approach significance ($p=0.06$).

6.2.2 Needle and surface detected quadriceps motor unit potentials

Disease severity measured by WOMAC score was significantly lower in the control versus OA group ($p<0.05$, Table 6.3). No significant differences were observed for age, height, weight, BMI or normalized knee extensor torque ($p>0.05$, Table 6.3). Due to the finding that no differences in normalized strength existed between groups, a second analysis on strength was performed comparing the mild OA participants from the contractile properties study and the healthy controls from the MU properties study. No significant difference was observed between these groups ($p<0.05$). Size-related parameters of the N-MUPs and S-MUPs, as well as mean MU firing rates were determined (Table 6.4). The final analysis was conducted on 27±2 (control 10% MVC), 28±5 (control 20% MVC), 24±3 (OA 10% MVC) and 25±6 (OA-20% MVC) N-MUPs per participant. No significant differences

Table 6.1 Participant characteristics by disease severity subgroup.

	Mild	**Moderate**	**Severe**	**p-value**
Sex (male/female)	8/5	8/5	5/8	
Age	60.8±8.1	58.5±5.5	61.6±4.4	0.41
Height (m)	1.68±0.10	1.75±0.10	1.66±0.05*	<0.05
Weight (kg)	79.7±9.8*	101.2±16.1	85.0±16.0*	<0.05
BMI (kg/m^2)	28.2±3.9	33.2±5.5	30.8±5.6	0.057
Total WOMAC score	19.4±8.4	40.9±6.0†	60.3±7.2*†	<0.05
Knee Extensor MVC (N•m/kg)	2.17±0.84	1.97±0.76	1.35±0.55†	<0.05

Data are presented as means±standard deviations. BMI: Body mass index; WOMAC: Western Ontario and McMaster Osteoarthritis Index; MVC: maximal voluntary contraction.

*Significantly different than moderate OA ($p<0.05$)

†Significantly different than mild OA ($p<0.05$)

Table 6.2 Resting evoked twitch properties of the quadriceps by disease severity group.

	Mild	**Moderate**	**Severe**	**p-value**
P_T (N•m)	26.9±7.3	29.6±9.7	22.4±4.7	0.06
TPT (ms)	112±11	111±18	114±7	0.85
HRT (ms)	100±35	84±37	111±43	0.22

Data are presented as means±standard deviations. P_T: Peak twitch tension; TPT: Time to peak twitch tension; HRT: Half-relaxation time.

Table 6.3 Participant characteristics for OA and control groups.

	Control	**OA**	**p-value**
Male/Female	4/4	4/4	
Age	61.8±5.9	61.3±3.8	0.84
Height (m)	1.69±0.07	1.72±0.09	0.46
Weight (kg)	77.9±24.0	99.9±20.3	0.069
BMI (kg/m^2)	27.0±27.3	33.4±4.6	0.054
WOMAC Score	0.75±0.76	42.4±14.8	<0.05*
Knee Extensor MVC (N•m/kg)	1.87±0.49	1.47±0.43	0.11

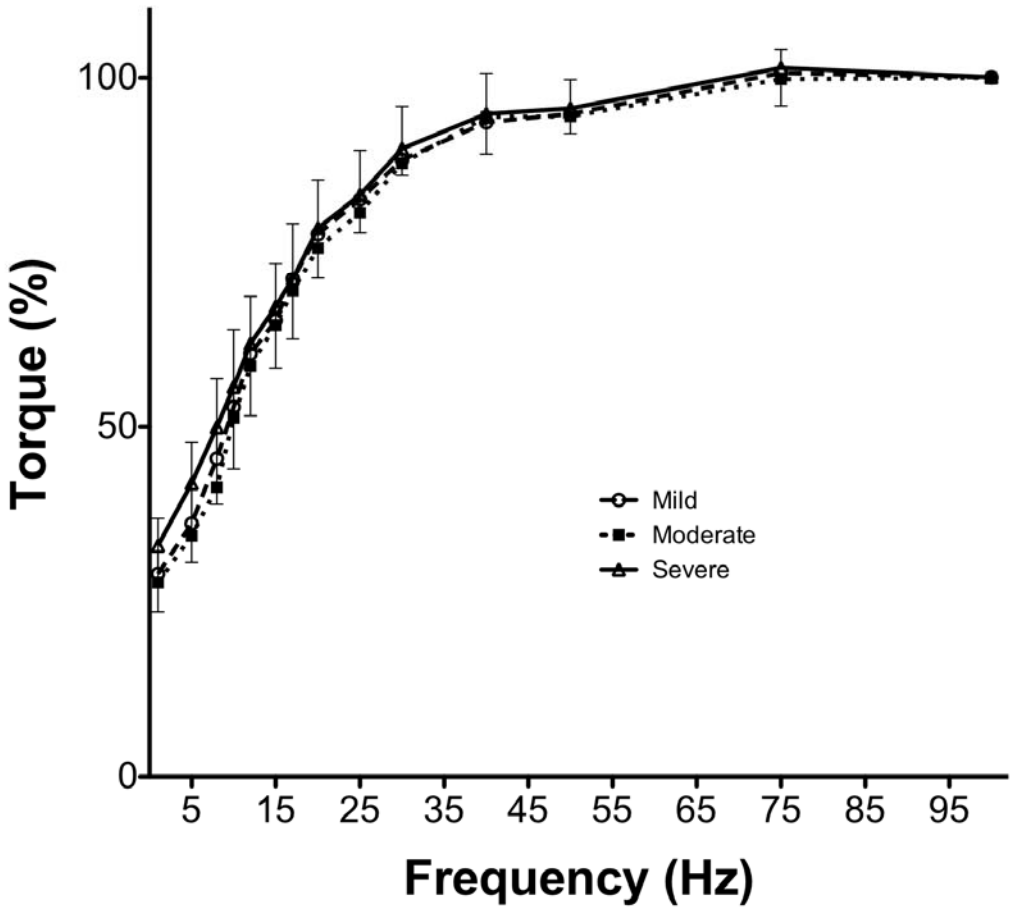
Data are presented as means±standard deviations.
*Significant difference between groups ($p<0.05$)

Table 6.4 Needle and surface motor unit potential parameters at two different contraction intensities for OA and control participants.

	10% MVC		**20% MVC**	
	Control	*OA*	*Control*	*OA*
N-MUP Parameters				
Peak-to-peak voltage (μV)	505±318	437±216	548±295	505±318
Duration (ms)	12.1±4.9	12.2±4.9	10.5±5.1	12.0±4.9*
AAR	1.7±0.5	1.9±0.6*	1.7±0.5	1.9±0.5*
S-MUP Parameters				
Negative peak amplitude (μV)	32±24.0	35.0±51.8	41.2±29.2	41.7±29.2
Negative peak duration (ms)	9.6±2.4	9.7±3.9	8.9±2.6	9.0±2.4
Negative peak area (μV•ms)	142.8±101.5	152.4±172.9	180.4±122.4	173.2±98.7
Firing rate (Hz)	8.6±1.8	8.0±1.7*	9.1±1.9	8.4±1.8*

Data are presented as means±standard deviations. N-MUP: needle motor unit potential; AAR: area-to-amplitude ratio, S-MUP: surface motor unit action potential. *Significant difference between Control and OA groups ($p<0.05$).

Figure 6.1 Torque-frequency curves for mild (open circle), moderate (solid square) and severe (open triangle) for 500 ms pulse trains of differing frequency. No significant difference was observed across disease severity group for any frequency of stimulation ($p>0.05$).


100
50
0
Torque (%)
5
15
25
35
45
55
65
75
85
95
Frequency (Hz)
Mild
Moderate
Severe

between groups in the number of N-MUPs per participant were noted, thus no single subject was more representative of group statistics than any other ($p>0.05$). Mean N-MUP peak-to-peak voltage was not significantly different between groups at either contraction intensity ($p>0.05$, Table 6.4). A significant increase in N-MUP duration was observed in the OA group at 20% MVC, but not at 10% MVC ($p<0.05$, Table 6.4). The area-to-amplitude ratio (ARR), also known as N-MUP "thickness" was significantly greater in OA versus control subjects at both contraction intensities ($p<0.05$, Table 6.4). N-MUP complexity as measured by the number of turns (10% MVC: OA=3.2±1.3, control=3.5±1.8; 20% MVC: OA=3.0±1.1, control=2.9±1.2) and phases (10% MVC: OA=2.7±0.9, control=2.9±0.9; 20% MVC: OA=2.6±0.7, control=2.6±0.7) was not significantly different between groups ($p>0.05$). No differences were observed in S-MUP size parameters (negative peak amplitude, duration and area) between groups at either contraction intensity ($p>0.05$, Table 6.4). Firing rates were slightly, but significantly lower in the OA group at both contraction intensities ($p<0.05$, Table 6.4).

6.3 DISCUSSION

We observed that quadriceps muscle contractile properties remain unaltered across a clinical spectrum of knee OA, despite lower quadriceps muscle strength in those with severe knee OA. As quadriceps contractile properties provide information about the relative proportion of type I and type II muscle fibres within a given muscle, this observation indicates that muscle fibre composition is similar between disease severity subgroups. Experimental models of chronic disuse have observed speeding of muscle contractile properties reflecting a switch to the

expression of faster type II muscle fibres.[12] Thus, muscle weakness in severe knee OA is likely not accompanied by large changes in muscle fibre phenotype. Interestingly, even in the absence of muscle weakness, MU behaviour and possibly morphology was altered at low contraction intensities in those with knee OA compared to healthy controls in the second part of this study. Although preliminary, these results suggest that if progressive changes are occurring to the neuromuscular system in knee OA, they are subtle. It remains to be determined whether these changes are due to permanent MU remodeling or reflect a compensatory recruitment strategy in response to OA symptoms or structural changes.

6.3.1 Reduced isometric quadriceps strength across a clinical spectrum of knee OA

Quadriceps muscle weakness in patients with knee OA compared to healthy controls or a healthy contralateral limb, have been documented for both isometric and isokinetic muscle contractions [6]. However, in these studies, radiographic criteria such as KLG are commonly used to define knee OA. Furthermore, OA is usually defined dichotomously as present or absent, which does not provide information about OA severity. Palmieri-Smith et al. stratified OA patients using KLG and reported no difference in strength between those with moderate versus severe radiographic OA. Conversely, we observed that isometric knee extensor strength normalized to body mass was ~38% lower in severe versus mild clinical knee OA. Using a clinically relevant predictor variable may be more appropriate when measuring clinically relevant outcomes, in particular quadriceps muscle strength. Quadriceps muscle weakness is associated with pain and disability,[2, 22, 23]

while the relationship between radiographic disease and strength is weak or non-existent.[2, 3, 27] Furthermore, the tenuous relationship noted between clinical and radiographic features of knee OA adds to the complexity of using predictor variables that are not clinically-oriented.[4]

It is surprising then that no difference in normalized strength between healthy controls and OA subjects was observed in the study of MU properties (Table 6.3). As the goal of this experiment was obtain information about MU properties, only a small number of participants were recruited due to the ability to sample large numbers of MUs within each participant. It is possible that low sample size led to type II error in this portion of the study as there was a non-significant ~22% difference between groups. Alternatively, unlike the first part of the study, the participants in the OA group were not stratified for clinical disease severity and some of the participants had WOMAC scores consistent with those in the mild and moderate groups may have caused increased variability in strength in the OA group.

6.3.2 Evoked contractile properties across a clinical spectrum

Quadriceps muscle weakness has traditionally been attributed to disuse atrophy in a painful knee joint.[6] Chronic disuse atrophy, such as disuse associated with muscle paralysis following spinal cord injury is associated with a rightward shift in the torque-frequency relationship and a speeding of TPT and HRT, which are all indicative of a relative increase in the proportion of type II, fast twitch muscle fibres.[26] To our knowledge, this is the first study to examine evoked contractile properties in patients with knee OA. The results of our study do not substantiate knee OA as a model of chronic disuse as we observed no differences in the

quadriceps torque-frequency relationship or twitch properties across a clinical spectrum of knee OA. It is possible that the effects of disuse associated with knee OA are not so severe as to initiate alterations in fibre type, but do cause reductions in muscle fibre size. Peterson et al. reported small but significant differences (~12%) in mid-thigh quadriceps cross-sectional area between an ipsilateral limb with severe radiographic knee OA and a contralateral healthy limb.[24] In our study, P_T was ~17-25% lower in the severe compared to the mild and moderate OA groups, a result that approached, but did not reach statistical significance ($p = 0.06$). Reduced P_T without concomitant changes in speed-related twitch properties and the torque-frequency relationship would indicate that only muscle fibre size is affected in knee OA. In models of disuse where EMG activity is minimized (e.g. immobilization) atrophic changes are much more pronounced than in disuse models where only weight bearing is minimized (e.g. space flight, bedrest).[12] Additionally, the effect of disuse on muscle fibre phenotype is time dependent, such that longer studies allowing for less electromyographic activity may have a greater effect on MHC gene expression.[12] While activity levels were not controlled in this study, all participants were mobile and community dwelling and thus their activity levels were much higher than those in experimental disuse studies. Also, we did not control for duration of symptoms in this study. Mannion et al. reported that duration of symptoms in patients with chronic back pain predicted the greatest proportion in variance of fast-fatigable type IIX fibres in the paraspinal muscles.[21] It is possible that duration of symptoms rather than symptom severity would exert a greater influence on MHC expression. Due to the lack of stimulation frequency

related contractile changes and the relatively high activity levels of the participants in the study, we speculate that the reduction in muscle strength observed across a clinical spectrum of muscle weakness was predominantly due to reduced muscle fibre size.

6.3.3 Differences in needle and surface motor unit parameters between OA and control participants

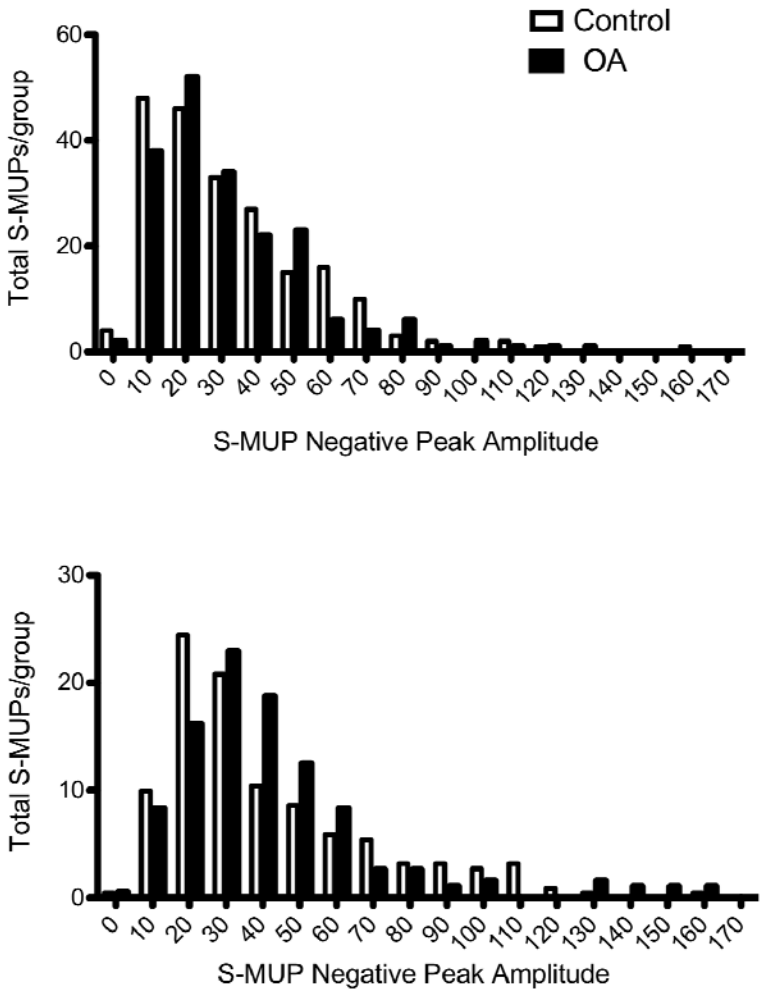
DQEMG is a fast, valid and reliable method of deriving quantitative information from needle and surface EMG signals.[8, 10] MUPs, in turn provide information about MU morphology and physiology that is sensitive to pathological processes affecting the motor unit.[30] In particular, both N-MUPs and S-MUPs can provide complementary information about MU size. In this study, there was no difference in N-MUP peak-to-peak voltage between OA and control groups. It is well known that N-MUP amplitude represents the contribution of only those muscle fibres activated within close proximity of the recording electrode and is affected by principles such as temporal dispersion and variation in terminal axon conduction velocity.[30] Other N-MUP parameters such as duration and AAR, or "thickness" are not as affected by electrode position and likely provide supplementary information about MU size.[30] Increases in duration and thickness suggest that more muscle fibres are contributing to the resultant MUP. We observed that thickness (at both contraction intensities) and duration (at 20% MVC only) were significantly larger in the OA group. These observations are usually interpreted as evidence that collateral reinnervation has taken place whereby denervation leads to collateral sprouting and a subsequent increase in the number of muscle fibres per MU.[30]

Interestingly, S-MUP amplitudes were not significantly different between groups. S-MUP amplitude is thought to be the parameter that best represents MU size, since the surface electrode detection area is much larger, thereby encompassing a greater proportion of muscle fibres for a given MU.[11, 29] No between-group difference in S-MUP negative peak amplitude could indicate similarly sized MUs, however there was large variability in S-MUP negative peak amplitude between groups (Table 6.4). Electrophysiological studies from studies of healthy older adults suggest that MU remodeling is a chronic process, often requiring decades to manifest [6]. In this regard, it is possible that MU remodeling is occurring in OA patients, but the process is not chronic enough to induce widespread alterations in MU size. In support of this hypothesis, we present the frequency distributions of S-MUP amplitudes at both contraction intensities for OA and control participants for the present study as shown in Figure 6.2. In a previous study we speculated that a qualitative rightward shift in the frequency distribution of S-MUP amplitudes indicates that only select MUs had increased in size through collateral reinnervation.[11] Particularly at the 20% contractile intensity, the OA participants had greater numbers of larger amplitude S-MUPs. In keeping with the evidence for mild-to-moderate as opposed to chronic disuse atrophy described above, it is possible that only early MU remodeling is apparent in the vastus medialis in knee OA.

6.3.4. Reduced motor unit firing rates in OA participants

This is the first study to report reduced MU firing rates at submaximal contraction intensities in the vastus medialis muscles of patients with knee OA.

Figure 6.2 Distribution of S-MUP amplitudes expressed as total number per bin at the 10% (upper panel) and 20% (lower panel) contractile intensities for control (open bars) and OA (solid bars) participants. Particularly at the 20% intensity, it appears that the OA participants had a greater number of relatively large S-MUPs, signifying a tendency towards increased motor unit size. S-MUP: surface motor unit action potential.


Control
OA
Total S-MUPs/group
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
S-MUP Negative Peak Amplitude
Total S-MUPs/group
30
20
10
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
S-MUP Negative Peak Amplitude

Reduced MU firing rates may be a compensatory response to increased MU size. It has been proposed that increases in MU size due to accumulation of increased number of muscle fibres results in increased torque output per MU.[25] As a result, the discharge rate required to maintain a given torque output is less than for a smaller MU. Thus small reductions in MU firing rate could be complementary to the small increases in MU size observed in this study. Alternatively, it has been shown in experimental pain models that MU firing rate and MU recruitment strategy are altered. Tucker et al. injected the infrapatellar fat pad with hypertonic saline to induce pain and reported reduced MU firing rates and a greater contribution from more MUs to maintain submaximal force.[32] In our study, OA participants had significant knee pain compared to healthy controls. It is unknown whether increases in recruitment were responsible for maintenance of torque output to compensate for reductions in firing rate.

The significance of such small reductions in MU firing rate between OA and control participants (< 1Hz) is questionable, however larger muscles such as the vastus medialis have been shown to grade force through recruitment as opposed to rate coding strategies, such that step increases in contractile intensity are accomplished predominantly through increases in recruitment.[25] Accordingly, MUs in this muscle have been shown to have a narrow range of firing rates (approximately 8-26 Hz).[25] In such a narrow window, it's possible that even small changes in firing rates may indicate significant changes in motor control.

6.3.5. Limitations

There are a few caveats to interpretation of the data. First, testing of evoked contractile properties may be an insensitive method for measuring change at the muscle fibre level. Roos et al. measured contractile properties of the quadriceps in young and old participants and found only very modest changes in speed related contractile properties, despite large differences in isometric muscle strength and a ~55 year age difference between groups.[25] It is possible that changes could be occurring at the muscle fibre level, but do not manifest at the whole muscle level. Fink et al. performed histochemical analysis on muscle fibres biopsied from the vastus medialis in knee OA patients at the time of surgery and reported selective type II fibre atrophy in 68% patients and type I (15% of patients) and type II (37% of patients) fibre type grouping, as evidence of a collateral reinnervation process.[15] Selective type II fibre atrophy is more indicative of age-associated changes (i.e. sarcopenia)[13] although it could be that type II fibres appear more affected in the quadriceps due its relative large complement of Type II muscle fibres.[19] Further investigation is necessary to determine if fibre types are different in the quadriceps of knee OA patients.

Second, we did not obtain information about MU recruited at higher contraction intensities. Pilot testing revealed that many participants could not maintain a contraction intensity ≥ 30% MVC for 30 s. However, due to the proposed reliance of the vastus medialis on recruitment to grade force,[25] it could be argued that a step transition in contractile intensity from 10% to 20% MVC provided meaningful information about different MUs at each contraction intensity. Unfortunately, it is difficult both technically and physically (i.e. from the perspective

of the patient) to contract and sample MUs at higher contractile intensities in this muscle.

The results of this study serve to further understanding of the mechanisms of quadriceps muscle weakness in knee OA. Our observation of increases in N-MUP size parameters and reductions in firing rates, suggest that deficits in muscle strength in knee OA are accompanied by early pathological changes at the level of the MU. However, these changes were not accompanied by a difference in whole muscle evoked contractile properties indicating that even in severe OA, chronic disuse alterations have not taken place (e.g. speeding of muscle fibre contractile properties due to increased proportion of fast twitch, type II muscle fibres). Overall, our results support a model of early disuse. The clinical significance of these findings is unclear, but pathological changes to the MU may impact on function and disease prognosis.

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CHAPTER 7

GENERAL DISCUSSION AND SUMMARY

7.0 GENERAL DISCUSSION

The results of this thesis have implications for: 1) defining disease severity and measuring clinically related outcomes in knee OA, 2) understanding the mechanisms of muscle weakness and 3) improving rehabilitation of neuromuscular dysfunction in knee OA. In Chapter 2, it was observed that defining knee OA using radiographic criteria in isolation may lead to inaccurate outcome measurement, particular if the outcome of interest is a clinically relevant measure (e.g. quadriceps muscle strength). The results from Chapter 4 suggest the measurement of whole muscle volume derived from high contrast and resolution MRI is a valid outcome measure as it predicted a significant proportion of the variance in muscle strength. In this study we also established the reliability of different manual segmentation methods for the first time.

The observations in chapter 2 provided justification for the use of WOMAC (i.e. clinical disease severity) as the independent variable in Chapters 3, 5 and 6. Participants were stratified into tertiles of disease severity according to raw WOMAC scores. In Chapter 3, it was observed that not only is strength reduced across a clinical spectrum of knee OA, but also muscle isotonic power (the product of knee extensor torque and velocity of contraction). Furthermore, the deficits in muscle power, particular at lower contraction intensities were larger than those

observed for strength and predicted a larger proportion of the variance in self-reported function. The implication of this finding is that reducing deficits in quadriceps velocity and power may better attenuate the decline in function seen in this patient population.

Chapter 3, 4, 5 and 6 provided information about the mechanism of quadriceps neuromuscular dysfunction in those with knee OA. Traditionally, quadriceps muscle weakness has been attributed to disuse atrophy as a result of knee pain.[2] The results of our study lend support to the disuse model but show some deviation from experimental studies of disuse. The reductions in strength and power in those with severe knee OA were not accompanied by changes in specific torque or power (i.e. muscle quality). It can be inferred from this result that quadriceps muscle deficits are due predominantly to reduced muscle fibre size. This finding was supported in Chapter 3 and 5 where muscle mass was shown to be the greatest predictor of the variance in isometric strength (Chapter 3) and VA deficits were small and even those with severe knee OA achieved VA = 90% (Chapter 5). The finding that of high levels of VA in OA patients is contrary to the findings of similar studies[7, 9, 12] and is not consistent with experimental models of immobilization.[3] However, knee OA is not an experimental model of disuse and we did not control for patient activity levels in this study (see section 7.1), therefore it's possible that the effects of disuse in this population are restricted to the muscle fibre size, such that type II fibres are selectively affected by disuse. In Chapter 3 we observed that deficits in power were significant only at the higher contractile intensities and velocity was similarly affected at only the highest velocities. As type

II, fast twitch muscle fibres are recruited only during high intensity, high velocity contractions, the deficits observed are consistent with a selective type II fibre atrophy model. Subsequently in Chapter 6, we did not observe alterations in evoked contractile properties to suggest any long-term alterations in muscle fibre phenotype.

One of the most novel findings in this study was increased MU size and slightly reduced MU firing rates in those with severe knee OA compared to healthy controls. As the contractions used in this study were of relatively low intensity (10% and 20% MVC) it is likely that we undersampled larger, faster MUs to get a representative sample. However, the vastus medialis is known to be a muscle that grades torque predominantly through MU recruitment (as opposed to rate coding) and thus we likely sampled a different population of MUs at each contraction intensity. The significance of the MU remodeling and reductions in firing rate is unclear and could represent either a pathological or compensatory process.

7.1 LIMITATIONS

There were several limitations to the interpretation of the results of these studies:

1) A central limitation mentioned in Chapters 2, 3, and 5 was the use of an ordinal measure (i.e. WOMAC) as a disease stratification tool. As there are currently no universally accepted criteria to define disease severity in knee OA,[6] there is significant variation in disease definition between studies. A simple method for defining mild, moderate and severe knee OA is using KLG, where KLG<2 is mild, KLG = 2 is moderate and KLG>2 is severe.[13] However, we observed a discrepancy in

outcome measurement when using clinical versus radiographic disease definitions, which provided the justification for using WOMAC as a predictor variable. Although WOMAC has been well validated, it is usually used as an outcome measure and is a subjective, ordinal measure with inherent limitations. In spite of using WOMAC to create clinically homogeneous subgroups, some patients with scores near a cutoff were likely dissimilar clinically from those with less extreme scores. It is unknown if our groups would have been more homogenous had we employed a disease definition encompassing both clinical and radiographic criteria, however we were not able to obtain X-rays for all study participants.

2) As participants were community dwelling and recruited from outpatient clinics, control over some participant characteristics was not feasible. Accordingly we could not control for factors that may have influenced the study results. For example, some participants in all groups had previously undergone injection therapy for knee pain. Galban et al. reported that knee joint intrusion with saline alters quadriceps muscle metabolism with accelerated depletion of energy stores and fatigue during stimulation in rats.[5] It's possible that cortisone or hyaluronan injections alter muscle outcomes independent of the effects of disease severity. Other potential study confounders that were not subject to control included physical activity levels, medications, compartmental distribution of knee OA, degree of knee laxity, degree of antagonist co-contraction and etiology of OA (i.e. primary versus secondary/traumatic). In spite of the influence of potential confounders on our results, the findings of this study do have external validity and extend to community dwelling men and women.

3) The measure of disability used in these studies (i.e. WOMAC function subscale) was self-reported and therefore subjective. The literature supporting the notion that deficits in muscle power are stronger predictors of disability than strength are based on objective performance measures.[1, 10] It is unclear if the associations observed between strength, power and disability would have persisted or been stronger if more objectives measures were used (Chapter 3). Similarly, the degree of VA was not associated with self-reported function (Chapter 5) and it is unclear if VA deficits have any impact on functional performance.

4) As mentioned above, the MUs analyzed in Chapter 6 were only sampled during low intensity contractions. Participants were either unable to sustain an isometric knee extension contraction at higher contractile intensities, or the interference pattern generated at higher intensities was too complex to decompose in a reasonable period of time for the participants. Thus, it is unknown if remodeling (i.e. increases in size) and reduced firing rates would also be evident in MUs recruited at higher contractile intensities.

5) There are limitations inherent in the cross-sectional design employed herein. Primarily, temporality of associations cannot be established. For example in Chapter 4, participants in the severe group had reduced muscle volume compared to those with mild OA. However, it is unclear whether reduced muscle mass precedes or follows changes in clinical disease severity and thus inferences made about the natural history of quadriceps muscle weakness in knee OA are speculative.

7.2 FUTURE DIRECTIONS

There is still much to understand about quadriceps neuromuscular function in knee OA. First, further information about the natural history of quadriceps muscle function, particularly with respect to changes in muscle volume and intrinsic muscle properties is required. This can be accomplished by assessing patients longitudinally, however such a study would be difficult as the clinical course of knee OA from first visit to primary care, through to joint replacement can be quite variable. Additionally, as mentioned above, our results would be supported by studies employing more objective measures of functional performance. Another feature of study design that would build on these findings would be to correlate our data on MU properties with information about muscle fibre histology. Fink et al showed changes consistent with selective type II fibre atrophy in patients with knee OA at the time of arthroplasty[4] and it would be interesting to determine whether these changes are accompanied by alterations to the MU.

As mentioned throughout, our findings having implications for rehabilitation and prognosis, although these results are preliminary in that they provide only the foundation for further testing. Treatment of knee OA targets symptoms only and is not currently disease modifying.[8] Furthermore, muscle function preceding arthroplasty predicts success on functional performance tests post-arthroplasty.[11] Muscle deficits have also been observed post-arthroplasty[12] and it is unknown if muscle power and intrinsic muscle fibre and motor unit properties are affected after knee arthroplasty. Studies are required to determine 1) the effect of current and new interventions on MRI-derived measures of muscle mass, 2) the efficacy of treatments that specifically affect deficits in muscle power on strength and quality of

life measures, 3) the impact of strength, power and intrinsic muscle deficits post-knee arthroplasty and 4) whether quadriceps neuromuscular deficits persist post-arthroplasty.

7.3 SUMMARY

Quadriceps neuromuscular dysfunction in those with severe knee OA encompasses much more than reductions in isometric muscle strength. The results of this thesis revealed deficits in muscle volume, isotonic power and alterations to MUs in those with severe compared to mild knee OA or healthy control. Our results also suggest that knee OA is accompanied by reductions in muscle fibre size (particularly of the type II fibres), although this result needs to be substantiated. Perhaps most importantly, the results of this study likely have direct implications for patient care. As clinical findings are often discrepant from radiographic findings, the use of X-rays to make treatment and referral decisions may not result in appropriate patient care. Furthermore, targeting the mechanisms of muscle weakness with specific interventions (e.g. deficits in power) may result in greater attenuation of disability experienced by this disease population.

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APPENDIX A

INSTRUCTIONS TO PATIENTS

In Sections A, B and C, questions will be asked in the following format. You should give your answers by putting an " ✗ " in one of the boxes.

EXAMPLES:

1. If you put your " ✗ " in the left-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☒	☐	☐	☐	☐

Then you are indicating that you have **no** pain.

2. If you put your " ✗ " in the right-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☒

Then you are indicating that your pain is **extreme.**

3. Please note:
   a) that the further to the right you place your " ✗ " the **more** pain you are experiencing.
   b) that the further to the left you place your " ✗ " the **less** pain you are experiencing.
   c) **please do not** place your " ✗ " **outside the box**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

V3 - English for Canada

PAIN

Think about the pain you felt in your _____ (study joint) due to your arthritis during the last 48 hours.

(Please mark your answers with an " ✗ ".)

QUESTION: **How much pain do you have?**	Study Coordinator Use Only
1. Walking on a flat surface. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PAIN1 _____
2. Going up or down stairs. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PAIN2 _____
3. At night while in bed, i.e., pain that disturbs your sleep. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PAIN3 _____
4. Sitting or lying. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PAIN4 _____
5. Standing upright. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PAIN5 _____

V3 - English for Canada

STIFFNESS

Think about the stiffness (not pain) you felt in your_____ (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an " ✗ ".)

6. How **severe** is your stiffness **after first awakening** in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. How **severe** is your stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Study Coordinator Use Only

STIFF6 _____

STIFF7 _____

V3 - English for Canada

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.**

(Please mark your answers with an " ✗ ".)

QUESTION: **What degree of difficulty do you have?**					Study Coordinator Use Only
8. Descending stairs.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN8 _____
9. Ascending stairs.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN9 _____
10. Rising from sitting.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN10 _____
11. Standing.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN11 _____
12. Bending to the floor.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN12 _____
13. Walking on a flat surface.					
None ☐	Mild ☐	Moderate ☐	Severe ☐	Extreme ☐	PFTN13 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.**

(Please mark your answers with an " ✗ ".)

QUESTION: **What degree of difficulty do you have?**	Study Coordinator Use Only
14. Getting in or out of a car, or getting on or off a bus. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN14 _____
15. Going shopping. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN15 _____
16. Putting on your socks or stockings. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN16 _____
17. Rising from bed. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN17 _____
18. Taking off your socks or stockings. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN18 _____
19. Lying in bed. None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐	PFTN19 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.**

(Please mark your answers with an " ✗ ".)

QUESTION: **What degree of difficulty do you have?**

	None	Mild	Moderate	Severe	Extreme	Study Coordinator Use Only
20. Getting in or out of the bath.	☐	☐	☐	☐	☐	PFTN20 _____
21. Sitting.	☐	☐	☐	☐	☐	PFTN21 _____
22. Getting on or off the toilet.	☐	☐	☐	☐	☐	PFTN22 _____
23. Performing heavy domestic duties.	☐	☐	☐	☐	☐	PFTN23 _____
24. Performing light domestic duties.	☐	☐	☐	☐	☐	PFTN24 _____

V3 - English for Canada

APPENDIX B

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
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OCT 29 2009

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. T.J. Doherty

Review Number: 15634 **Revision Number:** 2

Review Date: October 20, 2009 **Review Level:** Expedited

Protocol Title: Mechanisms of quadriceps muscle weakness in knee osteoarthritis

Department and Institution: Neurology, London Health Sciences Centre

Sponsor:

Ethics Approval Date: October 27, 2009 **Expiry Date:** August 31, 2010

Documents Reviewed and Approved: Revised co- investigators (add Dr. A. Goela & C. Harper-Little) , revised privacy and confidentiality and revised Letters of Information and Consent Forms - Control and Patient. Addition of MRI screening questionnaire Version 1: Feb 2009

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 `he Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

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 HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

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.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. T.J. Doherty
Review Level: Full Board
Review Number: 16495
Revision Number: 1
Review Date: January 22, 2010
Approved Local # of Participants: 20
Protocol Title: The effect of osteoarthritic knee pain on motor unit properties in the quadriceps muscle
Department and Institution: Clinical Neurological Sciences, London Health Sciences Centre
Sponsor:
Ethics Approval Date: January 26, 2010
Expiry Date: October 31, 2010
Documents Reviewed and Approved: Revised inclusion criteria and revised Letter of Information and Consent Form.
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

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Investigators must promptly also report to the HSREB:

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.

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Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information

☐ Janice Sutherland (jsuther@uwo.ca)	☑ Elizabeth Wambolt (ewambolt@uwo.ca)	☐ Grace Kelly (grace.kelly@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

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APPENDIX C

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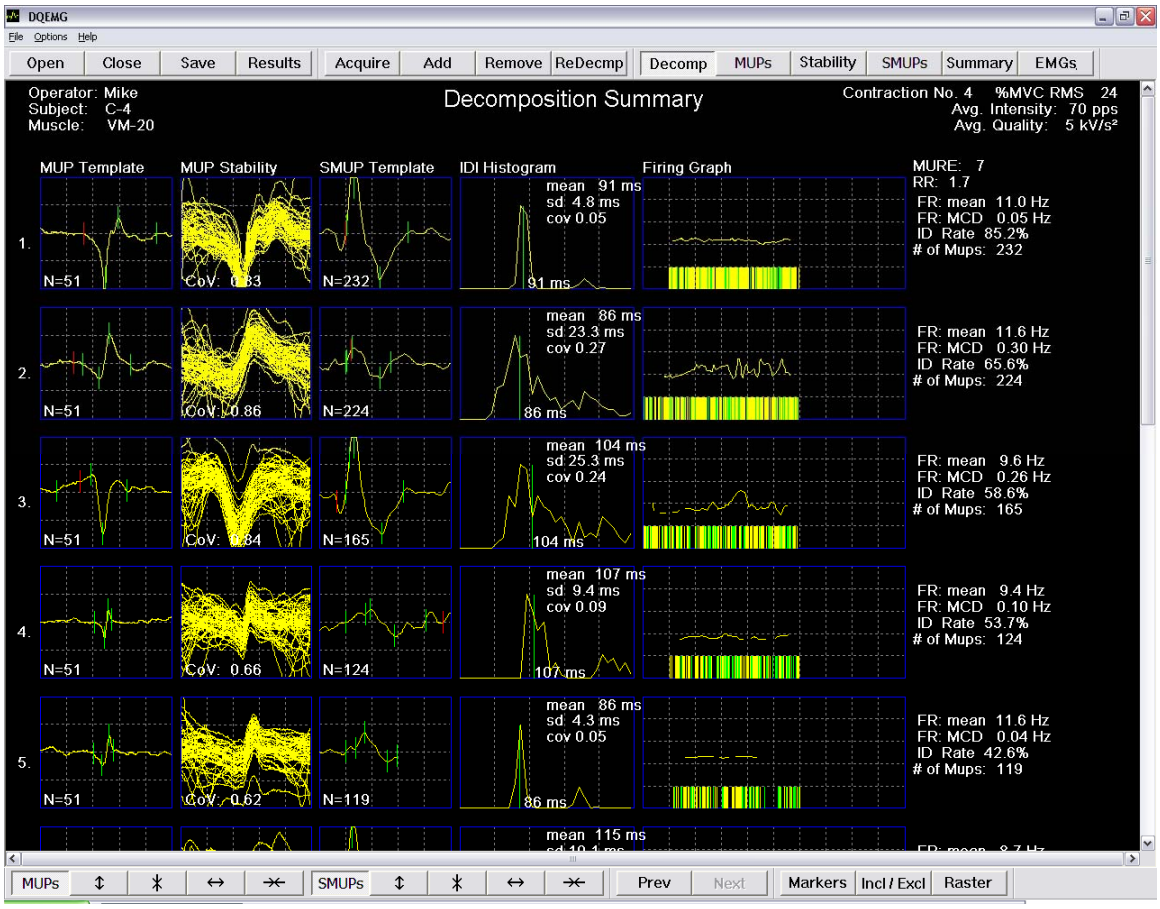
APPENDIX D



Output screen for decomposition of the needle EMG interference pattern during a 30 s contraction of the vastus medialis in a healthy control subject. Five individual motor unit potential trains were identified (labeled 1-5 on the far left). Panel descriptions from left-to-right: MUP Template: individual needle motor unit potential trains representing the median of 51 N-MUPs assigned to the template; MUP Stability: Shimmer plot of the 51 N-MUPs; SMUP Template: SMUP derived from spike-triggered averaging of the needle signal; IDI Histogram: Distribution of the IDIs for the N-MUPs comprising the motor unit potential train; Firing Graph: plot of the firing rate characteristics (inverse of the IDI) over the 30 s interval. EMG:

electromyography; N-MUP: needle motor unit potential; SMUP: surface motor unit potential; IDI: interdischarge interval.

CURRICULUM VITAE
Mike Berger

EDUCATION

09/2006 – present	MD/PhD Candidate Schulich School of Medicine & Dentistry, The University of Western Ontario *Expected graduation date-05/2013*
09/2006-06/2008	Completion of pre-clerkship requirements for undergraduate medicine
06/2008 – present	PhD Candidate, School of Kinesiology, Faculty of Health Sciences, University of Western Ontario Thesis: Neuromuscular Factors in Knee Osteoarthritis Supervisor: Dr. Tim Doherty, MD, PhD, *Completion of Candidacy Examinations (03/2009)*
09/2001 – 04/2005	B.Sc. (Hon) Kinesiology (Scholar's Electives Program) with distinction, The University of Western Ontario Thesis: The effect of prior heavy-intensity exercise on oxygen uptake kinetics in the upper regions of the moderate-intensity exercise domain Supervisor: Dr. John Kowalchuk, PhD

ACADEMIC HONOURS AND SCHOLARSHIPS

2011	CIHR MD/PhD Graduate Fellow in Musculoskeletal Health Research-Joint Motion Program (JuMP).
10/2010 – 05/2011	Ontario Research Coalition Early Researcher Award
09/2010	Canadian Society for Clinical Investigation Abstract Prize
09/2010-05/2011	Ontario Graduate Scholarship in Science and Technology (Doctoral)

05/2009 – 04/2010	Ontario Graduate Scholarship (Doctoral)
05/2008 – 04/2009	Ontario Graduate Scholarship in Science and Technology (Doctoral)
06/2008	Canadian Association of Physical Medicine and Rehabilitation Medical Student Essay Contest Winner ("Considering the Role of Quadriceps Muscle Weakness in Knee Osteoarthritis")
06/2005	Queen Elizabeth II Graduate Scholarship (University of Calgary)-*declined*
06/2005	British Columbia Rhodes Scholarship Finalist (nomination received from The University of Western Ontario)
05/2005	Dr. Michael S. Yuhasz Gold Medal in Kinesiology (UWO)
05/2004	Canadian Society for Exercise Physiology Award (UWO)
04/2003	UWO Faculty Association Scholarship
04/2003	Faculty of Health Sciences In-course Scholarship

RESEARCH

2010-2011	Research assistantship in the Autonomic Assessment Laboratory, London Health Sciences Centre, University Hospital, London, ON
Summer 2007-11	Research assistantship in the Neuromuscular Assessment Laboratory, London Health Sciences Centre, University Hospital, London, ON
01/2009-04/2009	Member of the American Association for Neuromuscular and Electrodiagnostic Medicine; Motor Unit Number Estimation Practice Issues Review Panel
01/2009-present	Research assistant for single centre non-randomized trial of the effect of Vitamin D on muscle function in frail elderly
Summer 2005	NSERC Undergraduate Student Research Award

PUBLICATIONS

Berger MJ and TJ Doherty, Sarcopenia: Prevalence, Mechanisms, and Functional Consequences. Interdiscip Top Gerontol. (2010) 37: p.94-114.

Berger MJ, Watson BV and Doherty TJ. Effect of maximal voluntary contraction on the amplitude of the compound muscle action potential: implications for the interpolated twitch technique. *Muscle and Nerve*. (2010). 42(4): 498-503.

Ritsma, BR, **Berger MJ,** Charland DA, Khoury MA, Phillips JT, Quon, MJ, Strong MJ and Schulz VM. Non-invasive positive pressure ventilation in amyotrophic lateral sclerosis (ALS): prevalence, approach and barriers to use in Canadian ALS centres. *The Canadian Journal of Neurological Sciences*. 37(1), 2010 pp. 54-60.

Berger, MJ and TJ, Doherty. The role of the neuromuscular system in the development, progression and rehabilitation of osteoarthritis of the knee. *Critical Reviews in Physical Rehabilitation Medicine.* 19(3), 2007 pp. 227-249.

CONFERENCE ABSTRACTS

Berger MJ, Chess DG and Doherty TJ. Evoked contractile properties of the quadriceps muscle across a clinical spectrum of knee osteoarthritis. American College of Sports Medicine. May 31-June 4. Denver, CO.

Derry KD, **Berger MJ**, McKenzie CA, Harper-Little C, Venance SL, & Doherty TJ. Cross Sectional Area as an Estimate of Quadriceps Muscle Volume Assessed by MRI in Knee Osteoarthritis and Muscular Dystrophy. Radiological Society of North America. Nov. 29-Dec 4, 2010. Chicago, IL

Berger MJ, Chess DG and Doherty TJ. Reductions in strength and power across a clinical spectrum of knee osteoarthritis. Young Investigators Forum, Canadian Society For Clinical Investigation. Sept 20-22, 2010. Ottawa, ON.

Ritsma, BR, **Berger MJ**, Charland DA, Khoury MA, Phillips JT, Quon, MJ, Strong MJ and Schulz VM. Non-invasive positive pressure ventilation in amyotrophic lateral sclerosis (ALS): prevalence, approach and barriers to use in Canadian ALS centres. International Symposium on ALS/MND (Berlin, Germany), Dec. 2009.

Berger MJ, Watson BV and Doherty TJ. M-wave amplitude during maximal voluntary contraction: Implications to the interpolated Twitch Technique. *Muscle and Nerve (2009).* 40(4): 721.

Gurd, BJ, **Berger, MJ**, duManoir, GR, Paterson, DH, and Kowalchuk, JM (2005) Regional Differences in the Deoxyhemoglobin Response Suggests Heterogeneity in

Oxygen Delivery to the Vastus Lateralis. Presented at the Workshop on Investigation of Human Muscle Function In Vivo, in Nashville, October 20-23

Gurd, BJ, duManoir, GR, **Berger, MJ**, Paterson, DH, and Kowalchuk, JM (2006) Slower pulmonary VO_2 and muscle deoxygenation kinetics in knee-extension compared to cycle ergometer exercise. Med. Sci. Sports Exerc. 38:S224.

duManoir, GR, Gurd, BJ, **Berger, MJ**, Kowalchuk, JM, and Paterson, DH (2006) Kinetics of Pulmonary O_2 Uptake and Muscle Deoxygenation During Active and Passive Recovery. Med. Sci. Sports Exerc. 38:S223.

INVITED PRESENTATIONS

"Quadriceps neuromuscular function before and after total knee arthroplasty" Division of Orthopaedics Research Rounds. London, ON Jan. 10, 2011

Berger, MJ, McKenzie, CA, Chess, DG, Harper-Little, C, Doherty TJ. Quadriceps muscle atrophy across a clinical spectrum of knee OA" 4th International Workshop on Imaging Based Measures of Osteoarthritis. Vancouver, BC; June 5, 2010

"Report on CITAC Activites, 2009-10". Business meeting of the American Physician-Scientist Association. Chicago, IL, April 22, 2010.

"M_{MAX} amplitude during maximal voluntary contractions: Implications to the interpolated twitch technique." Meeting of the Exercise Neuroscience Group, London, ON; June 19, 2009.

"Mechanisms of muscle weakness in knee osteoarthritis." Fowler-Kennedy Sports Medicine Clinic Research Rounds. London, ON. June 18, 2009

"A 20th Century Pediatrician and The Emergence of Modern Pediatrics." History of Medicine Days. University of Calgary. March 31, 2007.

PROFESSIONAL AFFILIATIONS

2010-2011	President, Clinician-Investigator Trainee Association of Canada
2009-2010	President-Elect, Clinician-Investigator Trainee Association of Canada
2008-2010	Mentorship Committee Chair, Clinician-Investigator Trainee Association of Canada

2007-2008	UWO Student Representative for the Clinician-Investigator Trainee Association of Canada

TEACHING

2011	Teaching Assistantship, Kinesiology Undergraduate Cadaver Anatomy Lab
2009-10	Teaching Assistantship, Kinesiology Undergraduate Cadaver Anatomy Lab
2008-09	Teaching Assistantship, Kinesiology Undergraduate Anatorium (nomination for UWO TA Award)