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Applications of Quantitative Gait Analysis in the Assessment of Disease Progression in Duchenne Muscular Dystrophy

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Applications of Quantitative Gait Analysis in the Assessment of Disease Progression in Duchenne Muscular Dystrophy

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Biomedical Engineering

by

Kent Robert Heberer

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ABSTRACT OF THE DISSERTATION

Applications of Quantitative Gait Analysis in the Assessment of

Disease Progression in Duchenne Muscular Dystrophy

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Doctor of Philosophy in Biomedical Engineering

University of California, Los Angeles 2016

Professor Eileen Greenan Fowler, Co-Chair

Professor Alan Garfinkel, Co-Chair

Duchenne muscular dystrophy (DMD) is a progressive X-linked genetic neuromuscular disorder that primarily affects males, is characterized by muscle atrophy, progressing proximally to distally, due to a lack of functional dystrophin protein, and currently has no cure. The focus of this work is gaining a biomechanical understanding of disease progression and compensatory strategies through quantitative gait analysis and musculoskeletal modeling. Gait deviations such as excessive trunk lean, excessive anterior pelvic tilt, reduced hip extensor moments, increased plantar flexion and plantar flexor moments have been observed for this population and are the result of progressive muscle weakness. Data obtained via quantitative gait analysis has the potential to be a sensitive outcome measure for clinical trials in young boys with DMD. This was explored by determining that joint moments about the hip were sensitive to improvement with a

corticosteroid intervention in a group of young boys with DMD, as compared to a steroid-naïve group. The mechanical hypothesis of disease progression was explored through musculoskeletal modeling by calculating eccentric and concentric work performed by individual muscles during gait. Muscles that performed more eccentric work were generally those with a greater degree of involvement. Muscles with more involvement decreased work with disease progression. And there was an increase in work from distal muscles as the work from proximal muscles decreased. This laid groundwork towards linking two biomarkers of disease progression: muscle function during gait and fatty tissue infiltration as measured by imaging methods. Finally, Induced Acceleration Analysis was used to assess the efficacy of typical compensatory strategies that develop in response to proximal muscle weakness. To maintain ambulation, muscles must provide support and propulsion for the center of mass. With disease progression, the ability of proximal muscle decreases and contributions from distal muscles must increase to compensate. This work is the first study that uses quantitative gait analysis as an outcome measure for an intervention, and is the first study to use musculoskeletal modeling to analyze the biomechanics of gait in this population.

The dissertation of Kent Robert Heberer is approved.

Melissa Spencer

Jacob Schmidt

Alan Garfinkel, Committee Co-Chair

Eileen Greenan Fowler, Committee Co-Chair

University of California, Los Angeles

2016

This dissertation is dedicated to the children with DMD and their families.

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Figure 3-1: “Results from quantitative MRI of muscles of the thigh and shank.” was

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Chapter 1. Introduction

1.1. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a progressive X-linked genetic neuromuscular disorder that primarily affects males with a prevalence of 1 in 3500 live births.[1] Diagnosis is initially made through physician observation and is confirmed by blood DNA tests or muscle biopsy.[2–4] The disorder is caused by a mutation in the gene that codes for the dystrophin protein, which mechanically links the intercellular actin-myosin skeleton of muscle cells to the extracellular matrix.[5] Overall disease progression is denoted by decreased muscle strength and increased time on motor performance tasks.[4,6] Proximal muscle groups are predominately affected first, followed by distal groups, and a loss of ambulation occurs usually within the second decade of life.[4,7]

Due to the lack of the dystrophin protein, the muscle sarcolemma is more prone to damage in response to stresses placed on the muscle tissue during contractions required to perform activities of daily life.[8,9] Animal models have shown that eccentric contractions (when the muscle produces force while lengthening) create higher stresses and are more damaging to dystrophic muscle as compared to concentric contractions (when the muscle produces force while shortening).[10–13] Over time, damage to muscle cells becomes irreparable and general muscle weakness develops as functional muscle mass is replaced by fatty tissue.[3] Recent imaging studies have shown that fatty tissue infiltration affects proximal muscles first and to a greater extent than more distal muscles.[14–17] Furthermore, muscle groups with a greater degree of fatty tissue infiltration produce less force during strength testing,[14] and individuals with higher overall fatty infiltration took longer to complete timed functional tests.[18,19]

Corticosteroid treatment is part of the current standard of care for boys with DMD and is

generally initiated between the ages of 4-8.[20–22] While the mechanism of action is currently poorly understood,[23] recent studies have shown that a corticosteroid regimen can decrease the rate of strength loss, improve general functional abilities, and prolong ambulation.[24,25] Optimization studies have been performed to maintain the functional benefit while minimizing detrimental side effects, such as weight gain, behavioral changes, and pathological bone fractures.[26–28] The decision to initiate a corticosteroid intervention is usually made on an individual basis based on the functional state while considering age and pre-existing risk factors to mitigate side-effects.[20] Unfortunately, corticosteroid treatments slow but do not stop disease progression.

1.2. Randomized Clinical Trials

Currently, novel therapeutics, with the goal to delay or prevent disease progression through a number of cellular pathways, are being developed and a number of clinical trials are underway.[29] The most promising involve exon skipping drugs that allow dystrophin protein to be expressed in a semi-functional state. [5,30] These therapeutic drugs have a curative potential, but have been met with difficulties in randomized clinical trials.[21,31] GlaxoSmithKline (GSK) and Prosensa announced in September 2013 that the Phase III clinical trial of their exon-skipping drug Drisapersen failed to meet the primary endpoint, and Sarepta therapeutics announced in November 2013 that the FDA concluded that results for their exon-skipping drug Eteplirsen to be "premature".[31] Even though both drugs were able to improve dystrophin production as measured by muscle biopsy, this did not translate to functional improvement on a clinical measure.

Of paramount importance to the success of a randomized clinical trial (RCT) is the use of outcome measurements that are reliable, sensitive to change, and clinically meaningful. In contrast to the sophisticated and expensive methodologies (e.g. biomarkers) used to develop

novel medications, clinical trials in neuromuscular disease typically utilize timed and/or graded motor skills, manual muscle testing, and the 6 minute walk test (6MWT).[32] Recently, studies resulting from clinical trials have shown an inability of traditional outcome measures to adequately show significant change over the course of an intervention.[21,31,33] As previously mentioned, Eteplirsen from Sarepta Pharmeceuaticals and Drisapersen from Prosensa and GSK, failed to show efficacy in their primary endpoint measure of the 6-minute walk test.[31] The lack of FDA approval greatly threatened future drug development as concerns developed in pharmaceutical research groups regarding the financial viability of developing similar therapeutics. Questions regarding the clinical efficacy of exon-skipping therapeutics are certainly warranted, but after adequate success in initial and open-label testing, perhaps the questions should be directed at the primary endpoint measures. With the introduction of novel therapeutics targeted for this younger age group, the importance of sensitive identifiers of change is paramount.

1.3. Multi-site Natural History Study

The Kameron Gait and Motion Analysis Laboratory was one of three sites that participated in a 9-year natural history study investigating the functional changes associated with disease progression in Duchenne muscular dystrophy (supported by Shriners Hospitals for Children, Grant 79115). One of the goals of the study was to identify sensitive measures that are responsive to change over time that could be used as outcome measures for RCTs. Ambulatory children at a minimum age of 4 years were enrolled and were seen for clinical assessments and quantitative gait analysis at 6 or 12 month intervals until ambulation ceased. One child was removed from the analysis due to a change in diagnosis from DMD to Becker's muscular dystrophy. A total of 85 ambulatory boys were enrolled in the study. For the present study, data

from 21 boys were identified to assess changes in gait due to a corticosteroid intervention (12 as the steroid intervention group, and 9 as the steroid-naïve control group) and data from two boys spanning four annual visits were used to assess muscle work and compensatory strategies.

Current outcome measures may lack sensitivity, and so would be unable to detect more subtle changes in function and performance. Adequate participant motivation is a requirement of most of the utilized outcome measurements. It takes substantial cooperation and concentration to obtain maximum effort during pulmonary function, muscle strength testing and walking speed assessments, which may be difficult for younger children.[4] While functional assessments, such as the North Star Ambulatory Assessment,[32] do not require maximal effort, they require the child to perform tasks that may be difficult and, therefore, discouraging. Furthermore, maturation occurs in children between 4-7 years, including boys with DMD. During this age range, functional performance in an individual may improve, but may remain below normative benchmarks.[34] Thus, especially in younger children, identifying sensitive measures that reflect functional improvements are of paramount importance.

The purpose of the natural history study was to add to the current knowledge by demonstrating the changes in gait mechanics with disease progression in boys with DMD. Joint kinematics and kinetics were compared with normative data to determine the gait deviations that occurred in younger and older groups of boys and were susceptible to change over time. As will be discussed further in the following sections, data obtained through gait analysis are precise, quantitative measures of muscle function for a clinically meaningful assessment of natural movement. Therefore, data obtained via quantitative gait analysis should be explored as a primary outcome measure for RCTs. In addition, previous longitudinal studies involving gait analysis have not been performed for this population. Consequently, changes in gait kinematics

and kinetics that can be observed in individuals over short and long periods of time have not been assessed. The contributions of this study improve the current understanding of gait mechanics in boys with DMD.

1.4.Quantitative Gait Analysis and Normative Gait

Gait analysis and the techniques by which to quantify and analyze the gait patterns of individuals have become increasingly sophisticated over the past few decades. Observational gait analysis allows for the assessment of gross abnormalities, but may overlook subtle deviations from normal gait.[35] As with many fields, the advent of the computer greatly reduced the time required to collect, calculate, process, and analyze data obtained through these instrumented gait analyses.[36] The contributions of Drs. Perry,[35] Sutherland,[37] and Winter[38] laid the groundwork for clinical gait analyses as it is known today. Among other things, they established the importance and clinical usefulness of gait analysis in the treatment of individuals with movement disorders.

Gait dynamics are described by the combination of two concepts from mechanical dynamics: kinematics and kinetics. Kinematics describes the movement of (or between) body segments in the sagittal, coronal, and transverse planes. The joint angle is defined as the rotation of the reference frame of the distal segments about the joint center with respect to the proximal segment reference frame.[39] For example, the knee joint angle is the rotation of the shank with respect to the thigh. The trunk and pelvis, however, are defined by the rotation of their coordinate axes with respect to the lab coordinate system. Data are presented for each joint/segment (i.e. trunk, pelvis, hip, knee, and ankle) as the time series of the joint angle normalized to one gait cycle (from initial contact of the foot to the following initial contact of the same foot). Joint angle calculations are dependent on the accurate observations of body segment positions in space. Retroreflective markers are placed on bony landmarks, which are used by

commercially-available software to scale an anthropometric model and track joint center location and body segment orientation. Modern gait analysis systems use an array of 6 or more infrared cameras that track the position of these markers with high precision. The position of a marker in three dimensions can be calculated through direct linear transformations if the marker is recorded by at least two cameras during a frame. Joint velocity and acceleration can be calculated from joint angles through inverse kinematics.

Kinetics is the study of forces (and moments) that cause movement. Ground reaction forces are collected simultaneously with marker position data during each walking trial. The magnitude and direction of the force measured by the force plate (the normal force in a free-body diagram) is the reflection of the sum of all external forces (i.e. gravity) and internal forces (i.e. muscles) applied to each body segment resolved at the point of floor contact. Through a process called inverse dynamics, the net internal joint moments and forces acting at each joint are calculated. Essentially, the joint moment is a measure of the net force from muscles spanning the joint required to cause the observed motion.[35,38,40] Joint power is the scalar product of the joint moment and joint angular velocity. Positive power is defined as power generation, and occurs when the moment acts in the same direction as the angular velocity. Conversely, negative power is defined as power absorption and occurs when the joint moment acts in the opposite direction as angular velocity. In general, power generation and absorption can roughly be interpreted as the influence of a moment to add energy into the system or control the flow of energy within the system.[41]

In short, quantitative gait analysis is a tool by which the kinematic and kinetic properties of gait can be measured and assessed. Kinematics describe the motion of limb segments with respect to one another in the physiological planes, and kinetics describe the forces and moments

required to cause the observed motions. Together, they can accurately describe and indicate pathological and compensatory gait patterns through comparison with normative data.

1.5. Normative Gait

Sagittal plane kinematics from five participants without disability are shown in Figure 1-1, with the participant data shown as the colored lines and the normative range (mean +/- one standard deviation) shown by the grey band. For normal gait, the trunk is leaning slightly forward and the pelvis has an anterior tilt. The hip is flexed at initial contact, extends through stance, and flexes prior to toe off to reach peak flexion towards the end of swing. The knee is extended at initial contact, undergoes a flexion curve during early stance in response to loading, and undergoes a larger flexion curve through swing. The ankle is neutral at initial contact of the heel, rapidly plantar flexes as the foot drops to the floor, dorsiflexes as the tibia rotates over the foot, plantar flexes towards the end of stance during push-off, and then dorsiflexes during swing to assist with foot clearance.

Sagittal plane joint moments from five participants without disability are shown in Figure 1-2, with the participant data shown as the colored lines and the normative range (mean +/- one standard deviation) shown by the grey band. For normal gait, a hip extensor moment is present at initial contact and peaks during early stance. The hip moment then shifts to a flexor moment during mid stance, peaks during late stance and pulls the hip through swing. The knee initially has a flexor moment at initial contact, which rapidly changes to an extensor moment during loading response of early stance. This is followed by a flexor moment throughout the remainder of stance. The ankle has a dorsiflexor moment at initial contact, which shifts to a plantar flexor moment to control the progression of the tibia, and peaks during push off during late stance. The total support moment is the sum of the hip, knee, and ankle extensor moments,[42] and peaks

during early stance during single limb support while the contralateral limb is lifted into swing.

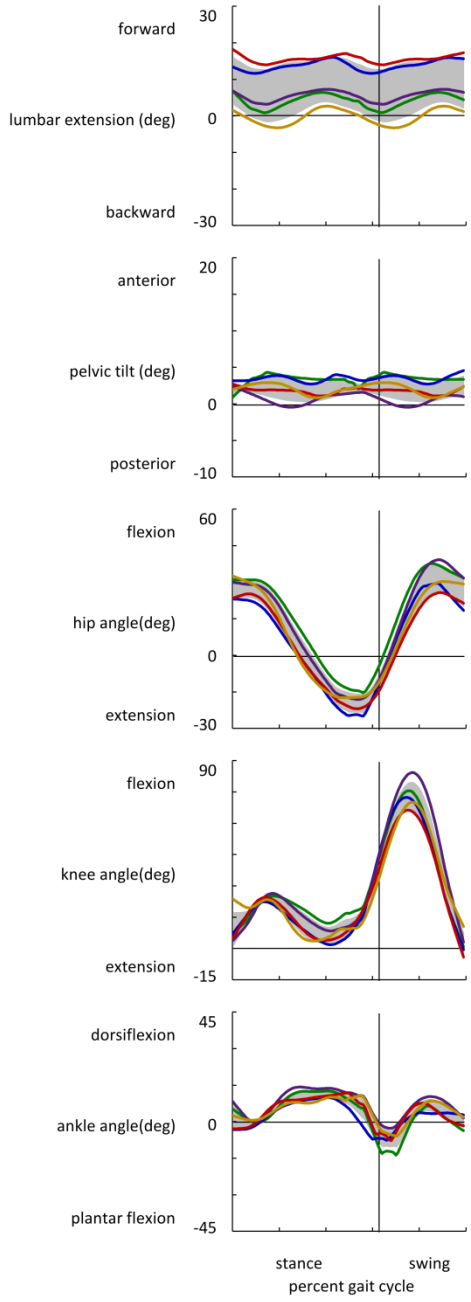

Figure 1-1: Normative sagittal plane kinematics over one complete gait cycle. Data from participants with typical development are shown by colored lines. Normative ranges (mean +/- SD) are shown by the grey bands. Toe off is designated by the vertical line.

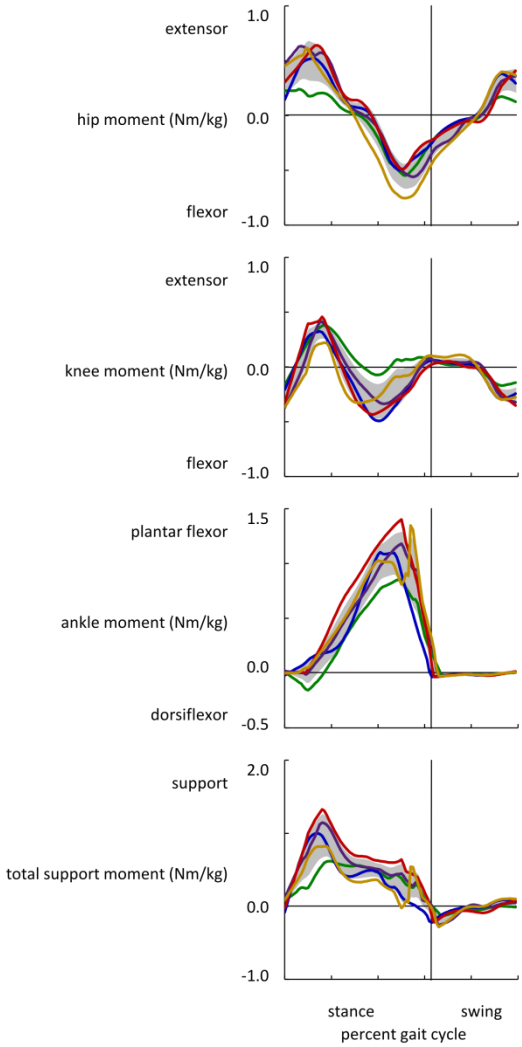

Figure 1-2: Normative sagittal plane joint moments over one complete gait cycle. Data from participant with typical development are shown by the colored lines. Normative ranges (mean +/- SD) are shown by the grey bands. Toe off is designated by the vertical line.

1.6. Stance Phase of Gait

The gait cycle is most generally split into two phases: stance, when the foot is in contact with the ground and the limb is providing support; and swing, when the foot is not in contact with the ground and the limb is moving forward through space. This study will focus on the stance phase of gait, as during this period the muscles of the leg are being utilized to maintain support of the trunk and to propel the body and contralateral swing limb forward. It is divided most generally into three phases: initial double support, single limb support, and terminal double limb support. Initial double support is approximately the first 10% of the gait cycle and consists of initial contact and loading response. The main function is to prepare the stance leg for single limb support and propel the contralateral leg into swing (this phase is concurrent with terminal double support for the contralateral limb). Single limb support starts with contralateral toe off and ends with contralateral initial contact, and accounts for approximately 40% of the gait cycle. During this phase, the stance leg supports the carrier segments of the head, arms, and trunk and controls progression of the stance limb over the foot. Towards the end of single limb support, the heel rises to advance the stance limb over the forefoot rocker and the knee and hip both extend. This action elongates time in swing for the contralateral limb to extend through terminal swing and functions to increase step length. Once the contralateral foot makes contact with the ground, the stance limb enters pre-swing, over which the hip and knee flex to begin to move the trailing limb forward and off the ground into swing. During each phase, different muscles are responsible for providing support and propulsion of the center of mass.

In normative gait, the hip extensors are active during the first half of the stance phase, from initial contact until the line of gravity passes posterior to the hip joint. The hip extensor moments and ankle plantar flexor moments during early stance have been attributed to the

muscles stabilizing, instead of driving, the joints in order to maintain balance, provide support, and supply propulsive forces.[43,44] Kinetically, this results in an extensor moment about the hip that begins in terminal swing, peaks during loading response and declines until midway through stance, as shown in Figure 1-2. This corresponds to concentric contraction of the hip extensor muscles, which are acting as power generators since the hip is extending over this time frame.[45] While the magnitude of the extensor moment is dependent on walking speed,[46] studies on normative gait in children have found that the average peak hip extensor moment during typical self-selected walking speeds ranges from .80 to 1.0 Nm/kg.[47] The knee extensors are active during early stance to eccentrically control the flexion of the knee during the flexion curve of loading response when the stance limb accepts full body weight and then to concentrically extend the knee through the middle of stance. Concurrently, the ankle dorsiflexors eccentrically control the rapid dorsiflexion following initial contact of the heel until the foot is flat on the floor, after which the plantar flexors eccentrically control the forward progression of the tibia over the foot.[45] This action results in a plantar flexor moment that increases to a maximum during the push off phase, which occurs in the second half of stance, as shown in Figure 1-2. Overall, the coordination of the hip, knee, and ankle extensor moments are integral to stance limb and gait stability. Impairments of one or more of these muscle groups requires alteration of kinematic or kinetic as a compensatory strategy.

1.7. Gait Analysis and Duchenne Muscular Dystrophy

Gait analysis techniques have been used extensively in the diagnosis and assessment of other neuromuscular disorders,[48–50] but have been underutilized in examining change in function following a therapeutic intervention program for boys with DMD. The pathomechanics of gait in individuals with DMD were first described by Sutherland.[37] They studied a group of boys with

DMD including a subset that had at least one follow-up session, which allowed a longitudinal examination of disease progression. Based on kinematic and ground reaction force data, they theorized that postural compensations of lumbar lordosis, increased anterior pelvic tilt, reduced hip extension, and increased ankle plantar flexion would move the center of gravity behind the hip joint and in front of the knee. While this compensatory gait pattern minimizes the extensor demand at the hip and knee, plantar flexion occurs over a greater percentage of the gait cycle, which is likely to place greater stress on the muscle membrane of these muscle fibers. Walking in a plantar flexed position is also associated with contractures, which further compromises function in boys with DMD. This begs the question of whether excessive plantar flexion (i.e. toe walking) is an undesired consequence of contracture formation or an advantageous compensatory mechanism to maintain ambulation.

Since that time, more sophisticated gait studies that included joint moments and powers have been performed in boys with DMD.[51–56] Findings included reduced peak and duration of hip extensor moments[53,56] and hip power gneeration.[52,53,56] These findings are consistent with reduced proximal strength in boys with DMD. Reduced peak knee extensor moments,[51,53,55] plantar flexor moments[53,55] and ankle power generation were also described.[52,53,55,56] While toe walking has been observed as a possible compensatory action, toe walking alone does not explain these results. Davids et al[57] examined the effect of voluntary toe walking on gait kinetics in children without disability as compared to children with cerebral palsy. During voluntary toe walking, reduced hip extensor moments and decreased hip power generation during stance were not present in children without disability.[57] These studies emphasize the importance of examining hip kinetics in boys with DMD as an early marker of gait pathology. Changes in peak hip extensor moments and powers during gait are markers of proximal muscle strength in this

patient population. In contrast to walking speed and other timed tests, joint kinetics, which are normalized to body weight, do not change appreciably after three years of age in typically developing children.[47]

Few studies have examined the effects of treatment in boys with DMD using gait analysis as an outcome measurement. The differences in gait patterns of boys with DMD who had undergone corticosteroid treatment as compared to a steroid naïve group have been reported.[52,54] Preliminary findings from a cross-sectional analysis of data from a natural history study did not show differences in kinematics between groups of boys with and without a history of corticosteroid use.[54] D'Angelo et al found in a cross-sectional study that for a group of 21 boys with DMD (11 steroid naïve, 10 treatment; average age 7 years) the boys with steroid treatment had stronger iliopsoas during manual muscle testing and greater ankle power generation during gait as compared to the steroid naïve group.[52] Few longitudinal studies incorporating gait analysis have been performed.[37,56,58] Khodadadeh[58] found that initial double support time increased with disease progression. Patte[56] found that stride length decreased, lumbar hyperlordosis and excessive anterior pelvic tilt increased, hip extension angle during stance became inadequate, and plantar flexion increased excessively. No studies to my knowledge have had the goal of analyzing changes in gait kinetics as the result of a therapeutic or pharmacological intervention.

1.8. Compensatory Gait Patterns in Duchenne Muscular Dystrophy

The vast majority of prior research has characterized the gait pattern of muscular dystrophy. From these observations, researchers have generated hypotheses as to the compensatory mechanisms that occur as a result of muscle weakness. Most of these inferences come from orthopaedic surgeons[35,59,60], or from studies that have analyzed the ground reaction

force overlayed with video and kinematics.[51,56] While these inferences are important, they are incomplete and more work should be done to validate these hypotheses.

In general, the compensations that occur in the child with DMD aim to minimize joint torques through changes in body alignment, and with disease progression these compensatory mechanisms become more unstable. The hip extensor, knee extensor, and ankle plantar flexor muscles act in a stabilizing manner to maintain balance, provide antigravity support, and supply propulsive energy during stance.[44] As the force generating capacity of the muscles decreases, the body uses postural adaptations to minimize the muscle force required to maintain balance and provide support. Sutherland et al.[37] concluded that the first compensatory mechanism is hyper lordosis of the trunk to move the line of force posterior to the hip joint, which would reduce the demand on the hip extensor muscles, and that the second is increased anterior pelvic tilt combined with increased plantar flexion to move the line of force in front of the knee to compensate for weak knee extensor muscles. Interestingly, they note that these compensatory mechanisms are in competition (leaning backward via lordosis improves hip stability, and leaning forward via anterior pelvic tilt and plantar flexion improves knee stability), and that the child must preserve an increasingly precarious balance between the two demands.[37] Patte and colleagues concluded that the observed changes in the gait pattern were due to insufficiency in the gluteus maximus and could be compensated for adequately enough with active toe-walking as long as the plantar flexor muscles were of sufficient strength.[56]

These compensatory strategies are interesting because of the energetic demands. For adequate support and propulsion of the center of mass, a minimum amount of energy is required to be input into the system. In normative gait, this is provided by the hip extensors in early stance, the knee extensors during mid stance, and the ankle plantar flexors during late stance.[61]

Proximal weakness in the hip and knee extensors for a child with DMD means that these muscles cannot supply adequate energy, and distal muscles are required to compensate through means of a toe-walking gait pattern. During this gait pattern, the ground reaction force moves anterior to the ankle and the knee. This forces the knee into excessive extension as the knee is stabilized by a static flexor moment from the non-contractile ligaments of the posterior capsule. This does not require muscular support and the knee is effectively "locked". The advantage to this gait pattern is that energy created by the plantar flexors should be transmitted more efficiently past the knee and up the kinetic chain to the pelvis and center of mass. This compensatory pattern will be explored in greater detail in Chapter 4.

In this population, a lack of compensatory patterns could be considered an indicator of adequate muscle strength. This relies on the assumption that compensatory strategies only occur in this pathological gait pattern as a means to decrease the demand torques about a joint. If a gait pattern that was closer to normative gait can be attained after a therapeutic intervention (which requires that joint torques/moments be closer to normal as well) then the patient would have improved. The advances in musculoskeletal modeling techniques offer a way to simulate pathological gait and determine the compensatory actions required to generate the observed gait pattern.

1.9. Musculoskeletal Modeling

OpenSim is an open-source platform for modeling, simulating, and analyzing the musculoskeletal system.[62] The current study has utilized a previously-published scalable model with 20 rigid bodies, 92 force actuators, and 23 degrees of freedom.[63] The rigid segments represent the skeleton and the excitable force actuators represent the muscles, tendons, and neuromuscular junctions, the properties of which were developed by Delp et al.[64] The generic

model is scaled to each person based on anthropometric and marker position data obtained via a standing calibration trial. Walking trials with marker position data and ground reaction forces, obtained via quantitative gait analysis can be used as inputs into the simulation. Standard techniques have been developed to calculate and simulate inverse kinematics, inverse dynamics, muscle excitations and forces, and the accelerations of the rigid segments induced by muscle forces. Inverse kinematics are calculated by measuring the joint angles as the markers on the scaled model track against those measured during the experimental trials. The residual reduction algorithm (RRA) refines model mass properties to minimize non-physiological forces applied to the pelvis, which balance dynamic errors resulting from modeling assumptions and marker data processing.[62,64] It does so by slightly adjusting the center of mass of larger body segments (i.e. the trunk) and permits the kinematics to vary to be more dynamically consistent with ground reaction forces and moments. Ultimately, the goal is to reduce the residual forces to the absolute minimum so that the motions of the rigid segments will match the observed kinematics and the forces would be supplied entirely by internal joint moments. The computed muscle control (CMC) module replaces internal joint moments with forces produced by the excitable force actuators.[65–67] At each time step, the excitation states for each of the 92 force actuators required to adequately accelerate body segments are calculated. It accounts for physiological constraints, such as Hill-type activation-contraction dynamics, the delay between muscle activation and force production, and force-length-velocity relationships of muscle fibers.[67] This module has been optimized by a cost function that minimizes the metabolic demand at each instant. The calculations involved are further described by Thelen et al.[66] This module outputs a set of controls for the model that describe the activations, forces, and speeds of each muscle to adequately generate enough force to recreate the internal joint moments (as calculated by the

RRA) and match segmental accelerations (as calculated by inverse kinematics). The controls can be analyzed further to determine the amount of eccentric and concentric power produced by individual muscles.[68] This previous study used a model of normative gait[69] to derive muscle work to compare to fatty tissue infiltration data.[14] However, as previously discussed, gait kinematics and kinetics of boys with DMD differ from normative gait. With respect to DMD-specific gait, there may be relationships between selective muscle weakness from fatty tissue infiltration and muscle function while walking in a compensatory pattern.

Muscle activations, forces, contractile velocities, and powers from normative participants overlayed on the normative average are shown in Figure 1-3. Activation patterns for the 10 muscles shown are, for the most part, similar to previously published studies using OpenSim modeling with EMG data. Activation timings in OpenSim as compared to observed EMG may differ due to assumptions in the numerical computations of the model.[70,71] Muscle activation patterns from normative gait data were compared to other studies incorporating OpenSim with a similar model[69,72,73] and with published EMG activation patterns.[35,38,74] The gluteus maximus was activated in early stance and late swing, which matched published OpenSim and EMG patterns, except for John et al, which did not show gluteus maximus activation during late swing.[69] The gluteus medius was activated throughout stance, which matched OpenSim and EMG patterns, except for Cappellini et al, which only showed activity during early stance.[74] The adductor magnus activation during early stance matches other OpenSim simulations, but does not match reported EMG data, which show activity during mid to late stance and throughout swing.[35,38,74] The vastus lateralis activations during early stance peak matches published OpenSim and EMG activity; however, the activation during late swing was only also found by the OpenSim simulation of Liu et al.[72] The activation of the rectus femoris during early stance

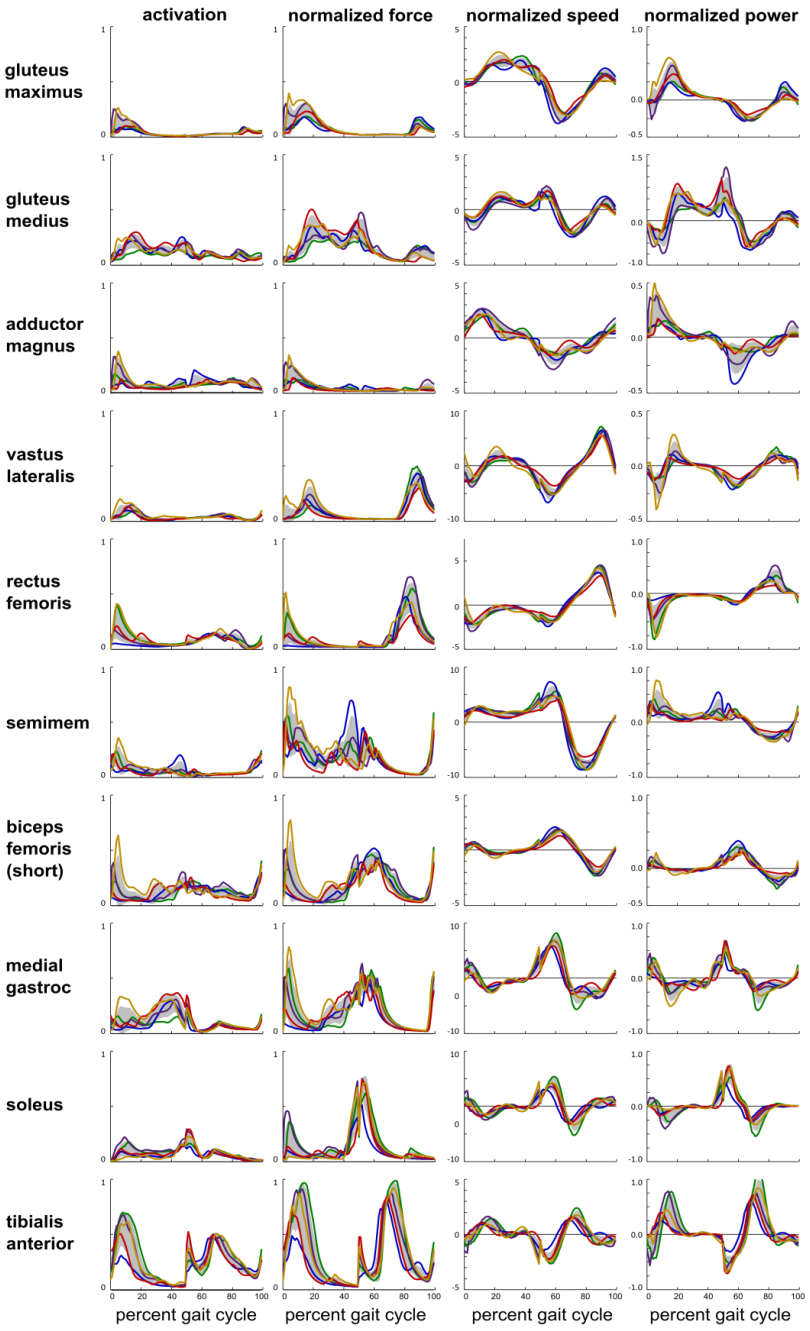

Figure 1-3: Muscle activations and normalized forces, speeds, and powers for normative participants.
Participant data are shown by the colored lines. The normal ranges (mean +/- SD) are shown by the grey bands. Activations range from 0 to 1, with 1 being fully activated. Normalized force is shown from 0 to 1, with 1 being equal to the maximum isometric force as defined by the model. Normalized speed has the convention of positive as shortening. Normalized power has the convention of positive as concentric power and negative as eccentric power.

and swing matched the simulations of Liu et al.[72] and van der Krogt et al,[73] and the EMG patterns from Winter[38] and Cappellini et al.,[74] although the timing during swing was premature compared to EMG. However, the activation pattern does not agree with John et al, which showed activity throughout stance.[69] The semimembranosus was activated from early stance through mid stance and again during late swing, which matched the published OpenSim simulations.[69,72,73] The prolonged activation during mid stance does not match published EMG data (except for Cappellini et al at walking speeds of 9 km/hr); which only report activity during swing. The uniarticulate hamstring muscle, the short head of the biceps femoris, was activated similar to the semimembranosus, except for an additional peak during late stance and early swing. The activity during late stance through toe off matched John et al. but not reported EMG activity. The medial gastrocnemius was activated during mid stance through late swing, which matched all published data. Activation during late swing through early stance matched Liu et al[72] and van der Krogt et al,[73] but not other EMG data. The soleus was activated similarly to the gastrocnemius, but had a steeper activation curve, which matched all published data. Activation during early stance was only present in one normative participant and may be erroneous. The tibialis anterior was activated during early stance and throughout swing, which matched all published data.

1.10. Induced Acceleration Analysis

A primary goal of the musculoskeletal system is to provide support and create locomotion. During the stance phase of gait, muscles of the stance limb share this responsibility. As muscles become weak, such as with disease progression in DMD, changes in kinematics and kinetics occur. This may create a demand on less affected muscles to compensate for weaker muscles by contributing more to support the body against gravity and to move through space. The effectiveness of these compensatory mechanisms can be determined by how individual

muscles can induce the acceleration of rigid body segments.

During different periods in the gait cycle, the center of mass can be accelerated forward (propelled), accelerated upwards against gravity (supported), and accelerated backward (decelerated or braked). In a rigid body, the sum of all the forces and moments acting on the body can be summed at the center of mass, which results in net linear and angular accelerations. For a human body during walking, the force to accelerate limb segments is supplied by muscle contractions, e.g. the quadriceps can accelerate the shank with respect to the thigh by contracting and applying force to both the tibia and the femur, resulting in knee extension acceleration. The net result of all forces and segment accelerations is measured by the ground reaction force, and the difference between the measured ground reaction forces and the sum of all muscular contributions can be attributed to acceleration due to skeletal alignment.[72] From the dynamic musculoskeletal modeling, as previously described, we can calculate the muscle forces required to generate the observed kinematics and kinetics. By looking at the application and magnitude of the force produced by each individual muscle, we can determine how the muscle contributes to the ground reaction force, and thus, the acceleration of the center of mass. For example, during mid stance contractions of the soleus and gastrocnemius increase the force between the forefoot and the ground. This resultant force is transferred up the stance limb and causes the center of mass to accelerate upwards.

Induced Acceleration Analysis (IAA) is a computational method that quantifies the contribution of joint moments, muscle forces, and gravity to segment center of mass (CoM) acceleration and joint angular acceleration.[75] OpenSim uses the controls output from the CMC module to drive a forward simulation. This simulation solves the model's system of equations of motion for each time point in the gait cycle, and includes foot-floor constraint forces, which were

defined to be non-penetrating and rolling without slipping.[63,76] Prior versions of the IAA module for OpenSim relied on a perturbation method, for which each force-producing element was sequentially stimulated to instantaneously apply 1N of force, and the resulting accelerations of body segments over a relatively short period of time were measured.[61,72,77,78] The advantages to the current analysis are speed of calculation and the removal of a stiff spring assumption to approximate contact points.[61,72,77]

These methods may also be used to analyze mechanical energy flow and power transfer within and from the lower extremities.[79] Recent studies have focused on determining the contributions of individual muscles to the support and propulsion of the trunk CoM or to stance limb stability (via hip and knee extension acceleration) during stance. With respect to the support and propulsion of the CoM, studies have found that the hip and ankle extensor mechanics coordinate to support and accelerate the trunk during normative gait patterns. During the early phase of stance, hip extensor moments were found to be the primary means of support for the trunk,[80–82] which were supplied mainly by the gluteus maximus.[61,77,83] Later during stance, it was found that the ankle plantar flexor moment became the primary source of support and propulsion,[80–82,84] which was primarily supplied by the triceps surae muscles.[61,77,85] With faster walking speeds or during running, the demand on the muscles to support and accelerate the CoM increases.[63,72] Conversely, Liu et al.[72] found that in slower walking speeds, skeletal alignment contributed more to the ground reaction force and that muscles contributed less, as compared to higher contributions from muscles at faster walking speeds. This has implications for the posture stabilization hypotheses for gait in DMD, especially at later disease states when walking speed begins to decrease drastically.

IAA has been applied to pathological gait patterns as a method to identify potential

compensatory gait patters. For example, weakness or impairments at the hip and/or ankle can cause a stiff-knee gait pattern as a compensatory mechanism.[86] Siegel et al used IAA in a pair of papers to identify compensatory patterns for individuals with weakness about the hip[87] and knee[88] and concluded that increased contributions from other extensor groups, such as the ankle plantar flexors, can compensate for weaknesses about proximal joints. Goldberg and Neptune[89] reported that increased plantar flexor moments could compensate for simulated hip extensor weakness and stiffness, which was in opposition to the findings of Jonkers et al,[90] which concluded that no one extensor group could adequately compensate for weaknesses or impairments in another. In patients with DMD, muscle weakness progresses proximally to distally, and must be compensated for in order to maintain ambulation. However, no study has applied IAA concepts to identify compensatory patterns in patients with DMD and how compensatory strategies change with disease progression.

Exemplar individual muscle contributions from a participant with typical development are shown in Figure 1-4. The normative average are shown as grey rays. Each ray shows the contribution to fore-aft (propulsive-braking) acceleration by the x-component of the vector, and the contribution to vertical (support) acceleration by the height of the vector. The larger extensor groups of the hip and knee (gluteus maximus, gluteus medius, vasti) are contributing to braking the center of mass during early stance and providing support into single limb support. Once single limb support has been established, these contributions diminish as the ground reaction force crosses anterior to the hip and the knee is fully extended. During mid to late stance, the ankle plantar flexors contribute in controlling the progression of the tibia over the foot. And during late stance, these muscles are the dominant contributors to providing support and propulsion through heel rise and push-off.

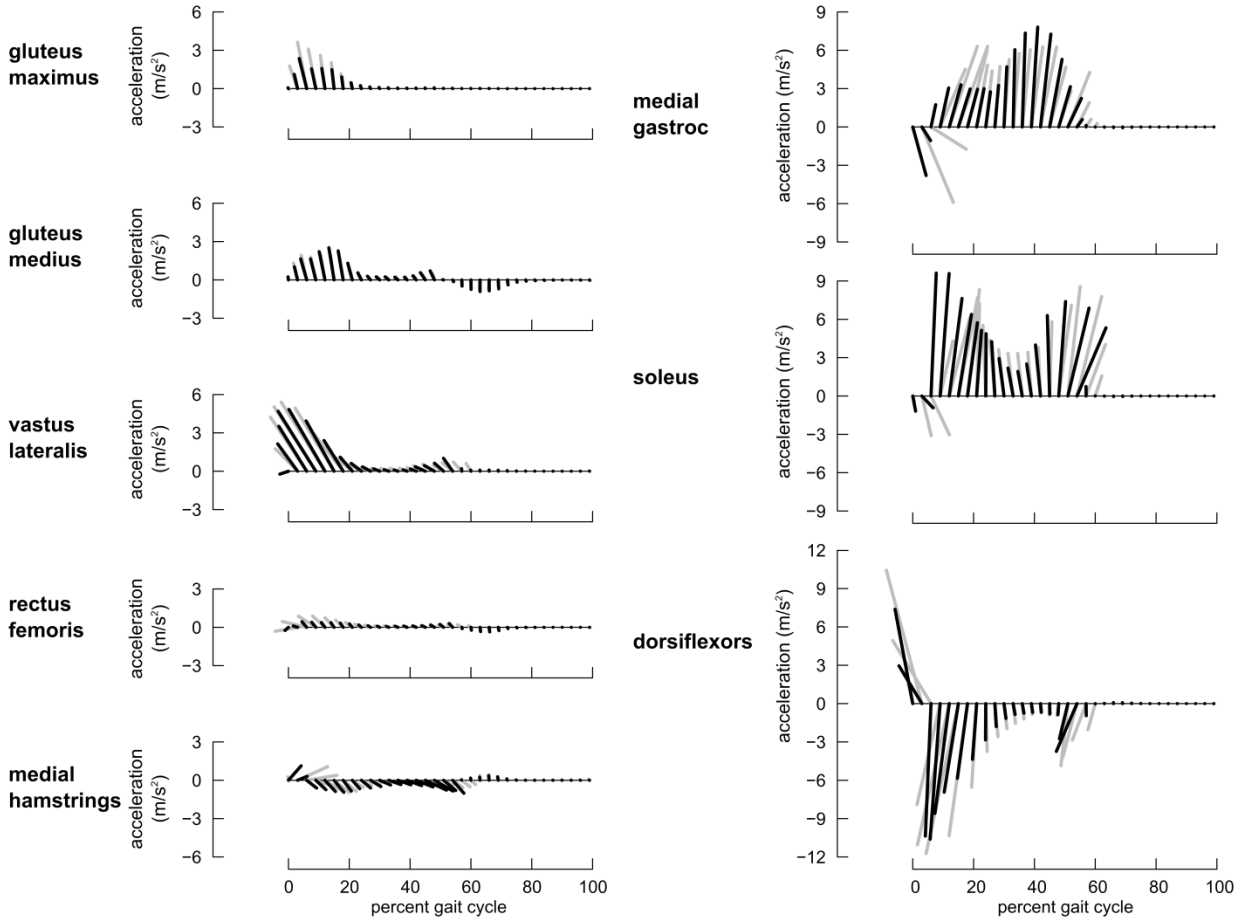

Figure 1-4: Exemplar normative individual muscle contributions to support and propulsion. Exemplar data from a participant with typical development is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

1.11.Significance of Study

This work aims to gain a better understanding of the biomechanical disease progression of DMD. First, quantitative gait analysis is a sensitive measure of gait pathology and could be used as an outcome measure in randomized clinical trials. The development of reliable, sensitive, and objective outcome measures for use in randomized clinical trials is of paramount importance for the next generation of novel therapeutics in the treatment of Duchenne muscular dystrophy.

The analysis of muscle function during pathological gait patterns with compensatory strategies will provide a greater understanding of selective muscle involvement and can lead to directed interventions and therapeutic programs. Specific outcome measures for individual muscles can be created for the assessment of interventions.

The purpose of the natural history study is to track changes in function with disease progression in boys with DMD. From this data, we aim to determine early identifiers of change in DMD for use in randomized clinical trials. As previously mentioned, Drisapersen from Prosensa and Eteplirsen from Sarepta Pharmeceuaticals both failed to show efficacy in their primary endpoint measure of the 6-minute walk test in September and November of 2013, respectively. Consequently, the stock value of both companies dropped substantially once news of the lack of FDA approval became public. This news was even more disheartening to the families of the boys with DMD, whose investments in the pharmaceutical companies go much deeper than financial. Questions regarding the efficacy of exon-skipping therapeutics are certainly warranted, but after adequate success in initial and open-label testing, perhaps the questions should be directed at the primary endpoints. While the standard of care, corticosteroids do not cure the disease, but they have been shown to slow the rate of disease progression and extend functional abilities. Determining the effect of a steroid intervention over short time periods will identify sensitive indicators of change that may be useful for determining the efficacy of novel therapeutics.

The mechanical hypothesis of disease progression may lead to a better understanding of selective muscle involvement, and can directly develop relationships between different measures of disease progression, such as muscle imaging, with clinical biomechanics. Finally, the assessment of compensatory strategies through induced acceleration analysis will aid in better

understanding the importance of muscle function to gait. Analyzing the gait biomechanics in this population will enhance our understanding of the effect of disease progression on function and compensatory strategies. Sophisticated musculoskeletal modeling techniques can provide insight as to how individual muscles function in pathological gait, which has implications for directed therapeutics, interventions, and outcome measures.

Chapter 2. Hip Kinetics During Gait as an Outcome Measure for Clinical Trials

The following chapter contains work from a manuscript submitted to *Gait and Posture* in February 2016 and an abstract accepted as a podium presentation at the 2015 Annual Conference of the Gait and Clinical Movement Analysis Society in Portland, Oregon

2.1.Introduction

Duchenne muscular dystrophy (DMD) is a progressive X-linked genetic neuromuscular disorder that primarily affects males. Progressive proximal to distal muscle weakness due to disruption in the manufacturing of the dystrophin protein is a hallmark of this disease.[4–6] Young children with DMD develop subtle compensatory strategies to minimize demand on weak muscles during gait, which become substantially more pronounced and unstable with greater involvement.[37,59] Ambulatory ability progressively deteriorates until walking ceases in the second decade of life.

Corticosteroid treatment, a standard of care for boys with DMD, is generally initiated between 4-8 years of age.[20,21,29] A corticosteroid regimen can preserve strength, improve general functional abilities, and prolong ambulation.[24,91–93] More recently, novel therapeutics have been developed to target genetic pathways (e.g. exon skipping, stop-codon read-through, dystrophin surrogates) and have curative potential.[30,94] Unfortunately, phase II and III trials have been met with difficulties in establishing efficacy.[21,29,95,96]

The success of a randomized clinical trial (RCT) is dependent on a number of factors. Of paramount importance is the use of outcome measurements that are reliable, sensitive to change and clinically meaningful. In contrast to the sophisticated and expensive methodologies (e.g. biomarkers) used to develop novel medications, clinical trials in neuromuscular disease typically utilize clinical measures including timed and graded motor skills, manual muscle testing and the

6 minute walk test (6MWT) to establish therapeutic efficacy.[26,28,32] Recent clinical trials suggest that these outcome measures may lack the sensitivity and specificity to detect significant improvements within the first 6-12 months of an intervention.[31,33] Outcomes that can detect more subtle changes in function and performance are needed.

Three-dimensional gait analysis offers a method of objectively quantifying changes in lower extremity function due to muscle weakness. The pathomechanics of gait in individuals with DMD, first described by Sutherland et al,[37] include postural compensations of lumbar lordosis, increased anterior pelvic tilt, reduced hip extension, and increased ankle plantar flexion. These strategies position the ground reaction force vector posterior to the hip joint and anterior to the knee, which reduces the demand on weaker hip and knee extensors. More recent studies have compared joint moments and powers in boys with DMD to typically developing children.[51–53,55,56] Joint moments reflect functional strength requirements during walking to maintain an upright posture, move the limbs, and support body mass. In contrast to traditional strength assessments, joint moments during gait do not require conscious voluntary effort and cooperation, and only requires the boy to walk. Reduced peak and duration of hip extensor moments[53,56] and powers[52,53,56] have been found using gait analysis, which are consistent with reduced proximal strength in boys with DMD. Additionally, reduced peak knee extensor moments,[51,53,55] plantar flexor moments,[53,55] and ankle power generation have also been noted.[52,53,55,56] These studies suggest that reduced joint moments and powers may be an important marker of gait pathology in boys with DMD. As DMD affects proximal muscles first,[4] hip kinetics are likely to be most affected in the early stages of DMD.

Gait analysis has been used extensively in the planning and assessment of treatments for neuromuscular disorders,[48,97] neurological disorders,[98] orthopaedic disabilities[99,100] and other gait

pathologies,[49,50] but to our knowledge, no longitudinal studies have utilized gait analysis to evaluate intervention efficacy in boys with DMD. Studies using gait analysis have been limited to cross-sectional comparisons of boys with DMD with and without a history of corticosteroid regimen.[52,54] Significant differences in joint kinematics were not found between these two groups,[54] but D'Angelo et al. found that boys with a history of corticosteroid use exhibited greater ankle power generation during gait as compared to boys who were steroid-naïve.[52]

The purpose of this study was to determine the sensitivity of joint kinetics as indicators of early changes in muscle strength for young boys with DMD. As corticosteroids are generally prescribed between 4-8 years of age, when functional ability may be improving,[32,101,102] we were particularly interested in determining the sensitivity of joint kinetics to intervention efficacy in this age group. During this age range, walking speeds improve for both typically developing children and boys with DMD.[103,104] In contrast to walking speed, joint kinetics do not appreciably change after three years of age for typically developing children.[47] In this study we quantified kinematic and kinetics at the hip, knee and ankle joints as well as temporal-spatial data using three-dimensional gait analysis. Because weakness progresses from proximal to distal muscles, hip kinetics are most likely to be below normal values in this age group and, therefore, may prove sensitive as primary outcome measures. We hypothesized that hip kinetics would improve in boys with DMD following initiation of corticosteroid intervention, as compared to a steroid-naïve group of boys who had not yet begun treatment. Commonly used timed tests of motor function for DMD clinical trials were included as comparative outcome measurements.

2.2.Methods

Our laboratory is one of three sites participating in a 9-year natural history study of gait biomechanics in boys with DMD supported by Shriners Hospitals. Ambulatory children at a

minimum age of 4 years were enrolled and underwent gait assessments at 6 or 12 month intervals until they stopped walking. While interventions were not the focus of the study, treatment was documented via parental report at each assessment, which allowed us to assess the effect of corticosteroid treatment in a subset of participants. The decision to initiate corticosteroids was made as part of their separate clinical treatment.

2.2.1.Study Population

The data used in this analysis was collected from participants that were enrolled in a larger multicenter natural history study of gait and function beginning in 2006 that did not include a treatment arm. Inclusion criteria for the natural history study were a diagnosis of DMD as determined by clinical evaluation and either a blood DNA study or muscle biopsy, ability to walk independently for 10 minutes, and ability to cognitively understand directions for testing procedures. Once all data had been collected, a cohort was identified to test the effects of corticosteroids in the present analysis. These participants had two visits with gait kinematics and kinetics performed one year apart, were between the ages of 4 and 8 at the baseline visit, and had no history of corticosteroid use at the baseline visit. To be included in the Naïve group, a continuation of no history of corticosteroid at the post visit was required. To be included in the Steroid group, a minimum of 3 months of a corticosteroid treatment prior to the post visit was required. Exclusion criteria for both groups consisted of less than 3 months of corticosteroid treatment prior to the post visit, or medical events such as surgery, fractures, major illness, or casting one year prior to baseline or during the study period. Twenty-one boys were identified and included in the present analysis. Of these, 12 began a corticosteroid regimen (Steroid group) and 9 remained steroid-naïve (Naïve group). The decision to initiate corticosteroid treatment was made as part of their separate individual clinical treatment plans. Corticosteroid treatment, if

applicable, was reported via medical history form by the parents or guardians at each visit.

2.2.2.Gait Analysis

Reflective marker position data and ground reaction force data were collected at self-selected, preferred walking speeds along a 15m walkway using an 8-camera motion capture system (Vicon, Oxford, UK or Motion Analysis, Santa Rosa, CA, USA) and at least 2 forceplates (AMTI, Advanced Medical Technology, Watertown, Massachusetts, USA or Kistler, Kistler Instruments, Switzerland). The clinical gait assessment was performed by trained evaluators and each assessment took approximately 45 minutes to one hour to complete. Spatial-temporal parameters, and kinematics and kinetics of the hip, knee, and ankle for all participants were calculated using Orthotrak (Motion Analysis, Santa Rosa, CA, USA). Kinematics and kinetics were time-normalized to percent of gait cycle. Joint moments and powers were normalized to body weight. Total support moment was calculated as the sum of hip, knee, and ankle moments at each percent in the gait cycle, with the convention of extensor moments as positive.[42] The stride with the maximum peak hip extensor moment for each limb was identified and analyzed.

2.2.3.Timed Functional Tests

The time to perform standardized functional tasks[32,105] was assessed using a stop watch. The times to walk or run 10m (10m Walk/Run), climb 4 stairs (4-Step Stair), and rise from a supine position to standing (Supine to Stand) were recorded.

2.2.4. Statistical Analysis

The peak hip extensor moment during stance, the duration of the hip extensor moment through stance, and peak hip power generation during hip extension were primary outcome measures. Peak values for the left and right limbs were averaged for each participant. Changes in spatial-temporal parameters, key kinematic and kinetic variables, and timed functional tests were

quantified within each group and between the two groups. Within-group changes were assessed using paired t-tests. Differences in the change scores between groups were assessed using independent t-tests. Statistics were calculated using JMP Statistical Software Package (SAS Institute Inc, Cary, NC) with significance set at $p = 0.05$.

Traditional statistical were confirmed with bootstrap resampling methods. Within-group changes were assessed by comparing the average observed change with the 95% confidence interval of the null hypothesis. The null hypothesis was determined for each group by generating 1000 samples for which the order of measurement of each participant was randomly determined. The average change of each sample was calculated, and the 95% confidence interval calculated as the 2.5^{th} percentile and 97.5^{th} percentile of the 1000 samples. Between-group changes were assessed by comparing the observed difference in the change scores between the two groups with the 95% confidence intervals of the null hypothesis. The null hypothesis was determined for the population by randomly assigning each participant to a group of 9 or a group of 12, to match the original Naïve and Steroid groups, respectively. The average change of each group was calculated, and the difference between the group of 12 and the group of 9 was calculated. This process was repeated 1000 times to generate the 95% confidence interval.

2.3.Results

Participant demographics are shown in Table 2-1. The two groups appear similar for age, height, weight, body mass index (BMI), and time to follow-up. The average duration of corticosteroid use in the Steroid group prior to post testing was 10.8 +/- 2.4 months (range 4-13 months). A significant increase in BMI for the Steroid group as compared to the Naïve group was found. This is consistent with weight gain as a side effect of the corticosteroid intervention.[20]

Table 2-1: Participant demographics for corticosteroid intervention

Measure (units)	Steroid Group		Naive Group		p^b
Number of participants (n)	12		9		
Age (years)	5.7	(1.3)	5.1	(1.1)	0.3
Time between visits (months)	12.4	(0.7)	11.6	(2.5)	0.3
Height (cm)					
Baseline	109.6	(8.8)	105.6	(5.3)	0.2
Post-Treatment	114.0	(9.9)	111.5	(5.6)	0.5
Change	4.4	(2.3)	6.0	(1.4)	0.06
Weight (kg)					
Baseline	19.6	(4.5)	18.4	(2.3)	0.4
Post-Treatment	23.9	(7.2)	20.4	(2.6)	0.1
Change	4.3	(3.8)	2.0	(0.9)	0.06
BMI (kg/m^2)					
Baseline	16.1	(1.5)	16.5	(1.5)	0.5
Post-Treatment	18.0	(2.8)	16.4	(1.6)	0.1
Change	1.9	(2.0)	-0.1	(0.8)	0.006*
Treatment					
Duration (months)	10.8	(2.4)			
Prednisone (n)	6				
Deflazacort (n)	6				

Mean (SD)

[b] *p* value from independent t-test

* = statistically significant difference ($p < .05$)

Average joint angles, moments, and powers at baseline and at follow-up for the Steroid and Naïve groups are shown in Figure 2-1. Relative to published normative kinematics and kinetics for children,[47] excessive hip flexion during swing was observed for both groups, excessive knee flexion during swing was observed for the Naïve group, and excessive plantar flexion during swing was observed for the Steroid group. Kinematics of the hip and knee were relatively consistent from the baseline to the post visit. The Steroid group increased peak ankle plantar flexion during stance (p = .0026) and swing (p = .006), and decreased peak dorsiflexion during swing (p = .041). The Naïve group decreased peak knee flexion during swing (p = .027).Significant between-group differences were not found for the kinematic parameters.

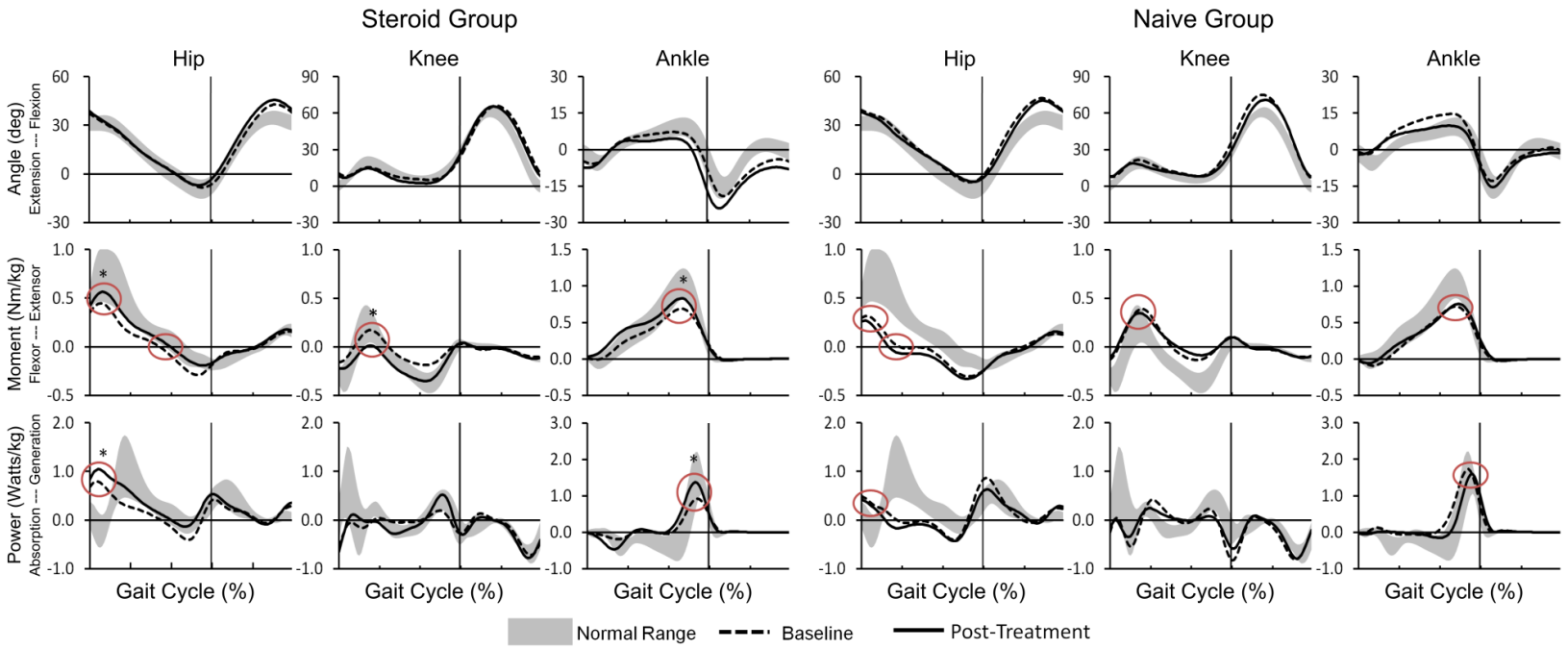

Figure 2-1: Sagittal plane kinematics and kinetics for the Steroid Group and the Naive Group.
Kinematics and kinetics for the hip, knee, and ankle for the Steroid group are shown on the left, and for the Naïve group on the right. Statistical analysis for kinetics performed for the circled regions. Normative data (mean +/- 1 SD) are presented as grey regions as a reference. Average baseline data are shown as the dashed lines, and post-treatment data are shown as the solid lines. Asterisks indicate significant differences between baseline and follow-up using paired t-test with significance at $p < .05$.

Peak hip extensor and ankle plantar flexor moments during stance were reduced relative to the age-matched normative range (mean+/-1 SD) reported by Chester et al. (.83+/-.28 and 1.10+/-.14) at baseline for both groups, but knee extensor moments were within or above the normal range (.24+/-.11).[47] The timing of peak hip power generation at less than 10% of the gait cycle at baseline was premature for both groups, compared to approximately 10-15% of the gait cycle for normative gait.[47] Statistical differences in key kinetic variables are shown in Table 2-2. The Steroid group significantly improved peak hip extensor moments and peak hip power generation at the post visit. Also, peak knee extensor moments declined, while peak ankle plantar flexor moments and power generation improved. While not statistically significant, the Naïve group showed a decline in all kinetic variables, except for peak ankle plantar flexor moment. Significant between-group differences favoring the Steroid group were found for peak hip extensor moment, duration of the hip extensor moment, peak hip power generation, and peak ankle power generation.

Spatial-temporal changes are reported in Table 2-3. A significant between-group difference was found for self-selected walking speed, reflected by a significant increase in stride length for the Steroid group and the significant decrease in cadence for the Naïve group. Results from the timed functional tests are reported in Table 2-4. A significant between-group difference was found for the 10m Walk/Run. The Steroid group significantly reduced the time to complete the 10m Walk/Run but a change was not found for the Naïve group. A significant within group improvement was observed for the Steroid group for the 4-Step Stair test. Significant within- or between-group differences were not found for the Supine to Stand timed test.

Table 2-2: Key kinetic variables

Measure (units)	Steroid Group	Naïve Group	p^b
Peak Hip Extensor Moment (Nm/kg)			
Baseline	0.49 (0.19)	0.33 (0.08)	
Post-Treatment	0.61 (0.19)	0.29 (0.13)	
Change	0.13 (0.13)	-0.04 (0.11)	0.007*
p^a	0.007*	0.3	
Duration Hip Extensor Moment (% GC)			
Baseline	33 (12)	28 (12)	
Post-Treatment	38 (15)	20 (8)	
Change	5 (10)	-9 (12)	0.007*
p^a	0.08	0.054	
Peak Knee Extensor Moment (Nm/kg)			
Baseline	0.21 (0.20)	0.40 (0.16)	
Post-Treatment	0.04 (0.22)	0.38 (0.13)	
Change	-0.17 (0.20)	-0.02 (0.10)	0.051
p^a	0.012*	0.6	
Peak Plantar Flexor Moment (Nm/kg)			
Baseline	0.74 (0.22)	0.74 (0.13)	
Post-Treatment	0.87 (0.21)	0.78 (0.06)	
Change	0.14 (0.14)	0.04 (0.14)	0.1
p^a	0.007*	0.4	
Peak Total Support Moment (Nm/kg)			
Baseline	0.66 (0.28)	0.55 (0.16)	
Post-Treatment	0.78 (0.36)	0.50 (0.18)	
Change	0.12 (0.26)	-0.04 (0.07)	0.09
p^a	0.1	0.1	
Peak Hip Power Generation (Watts/kg)			
Baseline	0.95 (0.58)	0.62 (0.17)	
Post-Treatment	1.36 (0.56)	0.49 (0.24)	
Change	0.41 (0.65)	-0.13 (0.27)	0.028*
p^a	0.049*	0.2	
Peak Ankle Power Generation (Watts/kg)			
Baseline	1.10 (0.32)	1.91 (0.64)	
Post-Treatment	1.55 (0.49)	1.71 (0.46)	
Change	0.45 (0.50)	-0.20 (0.35)	0.003*
p^a	0.009*	0.1	

Mean (SD), % GC = percent of gait cycle

[a] *p* value from paired t-tests, [b] *p* value from independent t-test

* = statistically significant difference ($p < .05$)

Table 2-3: Spatial-temporal parameters from gait analysis

Measure (units)	Steroid Group	Naïve Group	p^b
Walking Speed (m/s)			
Baseline	1.03 (0.17)	1.09 (0.19)	
Post-Treatment	1.12 (0.12)	1.01 (0.13)	
Change	0.10 (0.16)	-0.09 (0.15)	0.016*
p^a	0.057	0.1	
Cadence (steps/min)			
Baseline	144.1 (23.1)	157.8 (19.3)	
Post-Treatment	147.6 (15.8)	143.3 (8.9)	
Change	3.4 (16.3)	-14.5 (15.8)	0.021*
p^a	0.5	0.025*	
Stride Length (cm)			
Baseline	84.9 (7.2)	83.2 (9.8)	
Post-Treatment	92.4 (7.1)	84.7 (9.5)	
Change	7.5 (8.9)	1.4 (6.9)	0.1
p^a	0.014*	0.5	

Mean (SD)

[a] p value from paired t-tests, [b] p value from independent t-test

* = statistically significant difference ($p < .05$)

Table 2-4: Results from timed functional tests

Measure (units)	Steroid Group	Naïve Group	p^b
10m Walk/Run Time (s)			
Baseline	5.9 (0.8)	5.2 (1.2)	
Post-Treatment	4.9 (1.4)	5.5 (2.0)	
Change	-1.0 (1.0)	0.3 (1.3)	0.03*
p^a	0.005*	0.6	
4-Step Stair Climb Time (s)			
Baseline	4.3 (1.9)	5.0 (2.4)	
Post-Treatment	3.5 (2.2)	5.6 (5.1)	
Change	-0.8 (1.1)	0.6 (3.2)	0.2
p^a	0.04*	0.56	
Supine to Stand Time (s)	(n = 11)		
Baseline	5.3 (2.3)	4.6 (0.9)	
Post-Treatment	4.0 (1.6)	6.7 (4.1)	
Change	-1.3 (2.7)	2.2 (4.3)	0.053
p^a	0.13	0.17	

Mean (SD)

[a] p value from paired t-tests, [b] p value from independent t-test

* = statistically significant difference ($p < .05$)

Results from bootstrap methods are shown in Table 2-5. All statistically significant findings from traditional statistics were also found to be significant with bootstrap methods. In addition, bootstrap methods found a within-group improvement for walking speed for the Steroid group, a within-group decline in the Duration of Hip Extensor Moment for the Naïve group, and a between-group difference for Supine-to-Stand time, which favored the Steroid group.

Table 2-5: Results from Bootstrap Methods

Measure (units)	Within-Group Comparison (Post – Baseline)				Between-Group Comparison (Steroid – Naïve)		
	Ster. Chg.	Null 95% CI	Naïve Chg.	Null 95% CI	Obs. Diff.	Null 2.5th	Null 97.5th
Changes in Key Kinetic Variables (see Table 2-2)							
Peak Hip Extensor Moment (Nm/kg)	**0.13***	(-0.10 : 0.10)	-0.04	(-0.07 : 0.08)	**0.17***	(-0.12 : 0.13)	
Duration Hip Extensor Moment (% GC)	5.29	(-5.71 - 5.79)	*-8.72**	(-8.06 : 8.72)	**14.0***	(-10.0 : 9.83)	
Peak Knee Extensor Moment (Nm/kg)	**-0.17***	(-0.14 : 0.15)	-0.02	(-0.06 : 0.06)	-0.15	(-0.15 : 0.15)	
Peak Plantar Flexor Moment (Nm/kg)	**0.14***	(-0.11 : 0.10)	0.04	(-0.08 : 0.07)	0.09	(-0.12 : 0.12)	
Peak Total Support Moment (Nm/kg)	0.12	(-0.14 : 0.15)	-0.04	(-0.05 : 0.05)	0.16	(-0.19 : 0.19)	
Peak Hip Power Generation (Watts/kg)	**0.41***	(-0.41 : 0.39)	-0.13	(-0.18 : 0.19)	**0.55***	(-0.47 : 0.51)	
Peak Ankle Power Generation (Watts/kg)	**0.45***	(-0.36 : 0.37)	-0.20	(-0.26 : 0.26)	**0.66***	(-0.47 : 0.45)	
Changes in Spatial-Temporal Parameters (see Table 2-3)							
Walking Speed (cm/s)	*9.79**	(-10.2 : 9.51)	-8.52	(-10.6 : 10.1)	**18.3***	(-16.4 : 15.9)	
Cadence (steps/min)	3.43	(-8.99 : 9.41)	**-14.5***	(-13.6 : 13.1)	**17.9***	(-14.4 : 15.2)	
Stride Length (cm)	**7.46***	(-6.40 : 6.18)	1.45	(-4.33 : 4.26)	6.01	(-6.97 : 6.94)	
Changes in Timed Functional Tests (see Table 2-4)							
10m Walk/Run Time (s)	**-0.98***	(-0.76 : 0.75)	0.27	(-0.71 : 0.70)	**-1.26***	(-1.04 : 1.06)	
4-Step Stair Climb Time (s)	**-0.78***	(-0.71 : 0.74)	0.64	(-1.65 : 1.58)	-1.42	(-1.78 : 1.53)	
Supine-to-Stand Time (s)	-1.23	(-1.39 : 1.51)	2.19	(-2.71 : 2.75)	*-3.42**	(-3.20 : 3.21)	

% GC = percent of gait cycle, Ster. = Steroid, Chg. = Change, Obs. = Observed, Diff. = Difference
* = statistically significant difference (compared to null hypothesis)
Bolded values indicate significant results also found by traditional statistics
Italicized values indicate significant results not found by traditional statistics

2.4.Discussion

To our knowledge, this is the first longitudinal study of gait analysis before and after the initiation of corticosteroid treatment in boys with DMD. These results demonstrate the ability to detect a subtle, yet statistically significant, improvement in walking ability using kinetics that was not apparent when evaluating kinematic or timed test data.

The data at the baseline visit are consistent with the findings of previous cross-sectional studies. All participants in the present study match the "Early" group as identified by Sutherland et al.[37] At this stage, common kinematic compensations associated with DMD, such as excessive anterior pelvic tilt, were not yet apparent.[37] In the present study, peak hip extensor moments, the duration of the hip extensor moment, and peak hip power generation were reduced relative to normative data.[47,52,53,55,56] While peak ankle plantar flexor moments and peak ankle power generation were also reduced, peak knee extensor moments were within normal limits.[47] These findings are consistent with previous reports of early stage DMD.[52,53,55,56] and likely reflect a compensatory strategy to minimize the demand on weaker hip extensor muscles. Therefore, hip kinetics may have the potential to be indicators of change in younger boys before kinematic compensations are present.

Hip kinetics were sensitive to intervention, as the Steroid group showed improvements as compared to the Naïve group. Furthermore, peak hip extensor moments for the Steroid group improved to within the normal limits for this age range (mean +/- 1 standard deviation) of 0.55-1.11 Nm/kg.[47] While peak hip power generation for both groups was within normal limits for this age of 0.22-1.22 Watts/kg, the Steroid group remained above average whereas the Naïve group declined to below average.[47] As joint moments are provided by muscle forces, we can infer from these findings that the Steroid group had improved proximal muscle strength. In other

words, the Steroid group was observed to use a walking pattern that placed a greater demand on the hip extensors, thereby requiring greater strength in the hip extensor muscles. This was also observed for peak ankle plantar flexor moment and power generation within the Steroid group, which agrees with the findings of the cross-sectional study by D'Angelo et al.[52] In all, these findings show that with the increase in muscle strength due to the corticosteroid intervention, the Steroid group was able to walk in a more mechanically demanding pattern, which was observed and measured by joint kinetics.

Joint motion alone does not appear to be a sensitive indicator of early disease progression or corticosteroid initiation for this younger age group during this short intervention period. Inadequate kinetics at baseline revealed compensatory mechanisms related to weakness during stance. In contrast, kinematic differences appear to be compensatory strategies for limb clearance during swing. The lack of significance in the change scores between groups for key kinematic variables concurs with previous cross-sectional studies that demonstrated no differences in kinematics based on corticosteroid history.[52,54] While the Steroid group exhibited greater plantar flexion than the Naïve group at baseline, both groups showed an increase in plantar flexion at the post visit.

While hip joint kinetics are stable, improvement in the timed functional tests could be attributed to typical development for the age range included in this study. The only timed functional test that showed a significant between-group difference was the 10m Walk/Run time. The improvement for the Steroid group in 10m Walk/Run time is consistent with prior studies evaluating the efficacy of corticosteroids.[92,93] However, it has been shown that children without disability will improve 10m Walk/Run times over this age range.[103] In contrast, joint kinetics do not appreciably change after three years of age for typically developing children.[47] While the

between-group difference for Supine to Stand time was close to reaching significance, the 4-Step Stair test was not, indicating that these measures were not sensitive to changes in strength with the number of participants in this study. Unfortunately, comparisons to the NorthStar Ambulatory Assessment or 6-minute walk test are unable to be made as the present study was designed prior to the publication of these measures in 2009 and 2010, respectively.[106,107]

Spatial-temporal parameters reflect changes in gait during self-selected walking speeds. The between group difference found for the 10m Walk/Run results favoring the Steroid group is consistent with self-selected walking speed during gait analysis. However, gait analysis provides more detailed information. The decrease in cadence within the Naïve group and increase in stride length within the Steroid group appear to be factors that influenced the observed difference in walking speeds. As such, gait analysis provides additional insight about the relative contributions of stride length and cadence to the increased walking speed for the Steroid group. The significant between group difference in cadence was primarily due to a significant decrease within the Naïve group. In addition, stride length increased significantly within the Steroid group, which may reflect improved hip extensor strength in the stance limb hip extensors.

Following the steroid intervention, the Steroid group improved significantly to within normal limits for peak hip and ankle moments, but declined to below normal values for peak knee extensor moments. Despite this decline, which approached statistical significance, the Steroid group showed an overall improvement towards normal for total support moment throughout the gait cycle, which was not seen in the Naive group. It appears that increased hip extensor strength allowed the Streroid group to adopt a compensatory gait pattern that relied on increased kinetic contributions from the hip and ankle. Overall, the ground reaction force vector (GRF) moved to a more normal location anterior to the hip joint in the Steroid group. As weight

bearing is under the midfoot in boys with DMD, this shift caused the GRF to move anterior to the knee reducing the knee extensor moment required. It appears that the more distal and stronger ankle and knee joint musculature can vary their contributions in response to changes in proximal strength and biomechanical demands. A report by Hsu and Furumasu presented an illustration of natural disease progression that showed a shift of the GRF in a posterior direction relative to the knee with a concurrent increase in lumbar lordosis and backward trunk lean.[59] This compensation also increased the extensor moment at the knee. Thus, the strategy to decrease the demand on the hip extensors resulted in an increased demand on the knee extensors.

The results of this study demonstrate the ability of kinetic data obtained through motion analysis to detect a clinically meaningful improvement in walking ability following a short duration of steroid treatment that was not apparent through the use of kinematic data. These data support the increased strength following steroids initiation reported for this population [24]. Hip extensor moments during gait can be a proxy for traditional strength assessments since the orientation of the body during gait put a physiologic demand on the muscles to maintain that orientation and move the limbs and support body mass. As has been previously shown, the muscular demand, as seen by the moments produced at the hip joint, can be calculated via kinematic data and the resultant normal force, as measured by a force plate. When an individual moves in a way that results in a larger moment about a joint, the more muscular force is required to generate that moment. Hence, the increase in hip extensor moment can be attributed to a larger required muscular force to counter the kinematic orientation and corresponding normal force vector.

Hip extensor moments were chosen as proximal muscles are affected first, and followed progressively by distal muscle groups. Because of this, we expect to see kinetic changes (loss of

moment and power) at the hip before these changes occur at the knee or ankle. Related to this, muscle weakness about the hip and the resulting kinematic and kinetic changes would have a cascade effect and cause compensations to occur at more distal joints. Increased, or maintenance of, strength for muscles spanning the hip would delay the onset of these compensatory actions. Delaying compensatory action (which could cause further damage to muscles that span the knee and ankle due to increased demand) would prolong ambulation. Therefore, preventing decline in hip extensor moments would be clinically relevant as an outcome measure.

The joint moments are normalized to body mass, which is the standard for clinical gait analyses [108,109]. This is done to account for segment moments of inertia and to compare participants with differing body masses, since a person with more mass would take a larger moment to move (larger moment of inertia). This method also assumes that participants have similar strength to mass ratio, and that a difference in mass between two participants is due to a proportional increase in muscle mass. For this population, however, this assumption is not necessarily accurate. Weight gain is a side effect of the steroid intervention [22], but the weight that is gained is not entirely muscle mass. This results in a fat-heavy BMI, which would artificially decrease the normalized joint moments. Hence, non-normalized PHEM may be an appropriate measure for this population, especially when comparing the same participant after an intervention that can be associated with non-muscle mass weight gain.

Joint kinetics obtained through clinical gait analysis are sensitive, objective, and descriptive of walking as a functional task. However, outcome measures currently used by clinical trials, including timed functional tests, may not be sufficient to detect and quantify subtle changes in function and performance in early stages of DMD. Most current outcome measurements used for DMD clinical trials, require maximal effort, which is dependent on

participant familiarity with the task, cooperation, concentration, and motivation. Therefore, it may not be realistic for younger children to obtain maximum effort during tests such as pulmonary function tests, muscle strength testing, and walking speed assessments.[4] While functional assessments, such as the NorthStar Ambulatory Assessment,[106] do not require maximal effort, they require the child to perform tasks that may be challenging and, perhaps, discouraging. In contrast, gait analysis requires that participants walk using their typical pattern and follow basic instructions. While specialized equipment and trained staff are required, gait laboratories are becoming increasingly prevalent in major pediatric and orthopaedic hospitals. Quantitative gait analysis is a common tool for the assessment of gait pathology, and standard practice protocols for data collection, processing, and analysis are defined.[49,50] Further study is required to determine the reliability of gait analysis for this population, especially compared to currently used outcome measures. However, the results of the present analysis suggest that quantitative gait analysis is a reliable, sensitive tool to detect improvements after a relatively short period of time in younger subjects and therefore gait analysis could be employed in randomized clinical trials.

Study limitations include a lack of randomization and a relatively small sample size. The inclusion of the Naïve group was important to contrast changes in the Steroid group with the natural history of disease progression. We believe that the difference in kinetics at baseline is a spurious finding due to the non-randomized small sample size. The mean age, height, weight, and BMI of the two groups at baseline was similar, which would suggest similar levels of initial disability.

2.5. Conclusions and Future Study

Hip joint kinetics are early markers of proximal weakness that are responsive to change

with corticosteroid intervention and should be studied further for their reliability, feasibility, and applicability as outcome measures for novel therapeutics in DMD. In contrast, gait kinematics were unresponsive and between-group differences were not found for most timed functional tests. The improvement in hip kinetics found in this study is consistent with increased proximal strength from the corticosteroid intervention, whereas improvement in 10 m Walk/Run time could be attributed to typical development during early stages of DMD. These results provide detailed insights of disease progression and treatment response that would otherwise go undetected. While this was a small and non-randomized study, the results are promising and show that quantitative gait analysis could play a larger role in the assessment of the efficacy of novel therapeutics.

The limitations of this study can be addressed by future randomized, double-blind studies with an increased number of participants that also incorporate currently-used outcome measures. Further study would be benefitted by evaluating the relationships between changes in traditional outcome measures, changes in spatial-temporal parameters and changes in the proposed primary outcome measures. This would determine if the current methods are more sensitive than traditional methods. Also, the relationship between baseline and follow-up values should be explored. This would be beneficial in two ways. First, it would provide clinically meaningful values to the change that should be expected from another intervention, as a function of the baseline value. Secondly, it could be used to indicate a treatment threshold for steroid intervention, and manage expectations for improvement depending on the level of disease progression when steroids are initiated.

Chapter 3. Influence of Muscle Work on Disease Progression

The following chapter contains work from an abstract presented as a poster at the 2015 Conference of the American Society of Biomechanics in Columbus, Ohio

3.1. Introduction

The purpose of this chapter is to calculate the amount of eccentric and concentric work produced by individual muscles during pathological gait in boys with DMD. As a result, we can explore how muscle use during a functional task relates to the expected pattern of disease progression. The basis of this exploration is the "mechanical hypothesis" described by Deconinck and Dan, in that the variations in disease progression among muscles may be related to their functional roles during daily activities.[9] Therefore, by determining the demands placed on muscles during an activity of daily living, e.g. walking, would elucidate a potential mechanism for disease progression and the disparity by which muscles groups are preferentially affected.[9,68] We aim to show that muscle weakness is related to muscle use during a functional task, and that compensatory patterns are required adaptations that minimize the demand on weaker muscles. First, we hypothesized that muscles that perform more eccentric work would be those with greater fatty tissue infiltration. Second, we hypothesized that muscles with greater fatty tissue infiltration would produce less overall work during pathological gait. Finally, we hypothesized that in pathological gait the overall work production would decrease in the proximal thigh muscles and increase in the distal shank muscles.

Due to a lack of functional dystrophin protein, the muscle sarcolemma is more prone to damage in response to stresses placed on the muscle tissue during contractions required to perform activities of daily life.[8,9] Over time, this damage accumulates and becomes irreparable as functional muscle mass is replaced by fatty tissue.[3] Recent magnetic resonance imaging studies

have shown through that the resulting fatty tissue infiltration affects proximal muscles first and to a greater extent than more distal muscles.[14–17] Wokke et al used quantitative MRI techniques to calculate the percentage of the muscle cross sectional area that had been replaced by non-contractile tissue (dubbed the "fat fraction") and showed that proximal muscles of the thigh were, for the most part, affected to a greater extent than distal muscle of the shank, as shown in Figure 3-1.[14] Furthermore, it has been shown that muscle groups with a greater degree of fatty tissue infiltration produce less force during strength testing,[14] and individuals with higher overall fatty tissue infiltration took longer to complete timed functional tests.[18,19] While MRI and other imaging techniques offer a non-invasive and quantitative method of characterizing disease progression, there is still a gap concerning why individual muscles are affected at different rates. As such, we aim to relate the characterization of disease progression through MRI with the function of individual muscles during pathological gait. In particular, that the amount and type of muscle force may be related to the fat fraction as measured by Wokke et al.[14]

To determine the type of contraction and magnitude of contractile force during walking, sophisticated musculoskeletal modeling techniques are available to analyze data collected during quantitative gait analysis. OpenSim is an open-source platform for modeling, simulating, and analyzing the neuromusculoskeletal system.[62] It utilizes scalable models with 20 rigid bodies, 92 force actuators, and 23 degrees of freedom. The rigid segments represent the skeleton and the excitable force actuators represent the muscles, tendons, and neuromuscular junctions, the properties of which were previously reported by Delp et al.[64] Inverse kinematics are calculated by measuring the joint angles as the markers on the scaled model track against those measured during the experimental trials. Internal joint moments are calculated through inverse dynamics. Individual muscular forces required to reproduce internal joint moments are calculated by the

computed muscle control (CMC) module.[65–67] At each time step during the simulation, the excitation states for each of the 92 force actuators required to adequately accelerate body segments are calculated. It accounts for physiological constraints, including Hill-type activation-contraction dynamics, the delay between muscle activation and force production, and force-length-velocity relationships of muscle fibers.[67] The calculations involved are further described by Thelen et al.[66] The result is a set of controls that describe the activations, forces, and speeds of each muscle to adequately generate enough force to recreate the internal joint moments. These controls can be analyzed to determine the eccentric and concentric work produced by individual muscles.[68] Hu and Blemker used a model of normative gait[69] to determine that a relationship between eccentric muscle work and fatty tissue infiltration data[14] exists for the typical gait pattern of a unimpaired man.[68,69] However, gait kinematics and kinetics of boys with DMD differ from normative gait, especially with disease progression.[37,51–53,55,56] As such, it is important that the pathological gait patterns are explored with these methods. For example, there may be different relationships between muscle work and fatty tissue infiltration at younger ages, when gait pathologies are minimal, as compared to older ages, when compensatory patterns are present. At younger ages, muscle function may determine the development of fatty tissue infiltration; whereas, at older ages, compensatory gait patterns may be determined by the contractile ability of muscles (or lack thereof). This chapter will use quantitative data from two boys with DMD to explore the relationships between muscle work in pathological gait and fatty tissue infiltration.

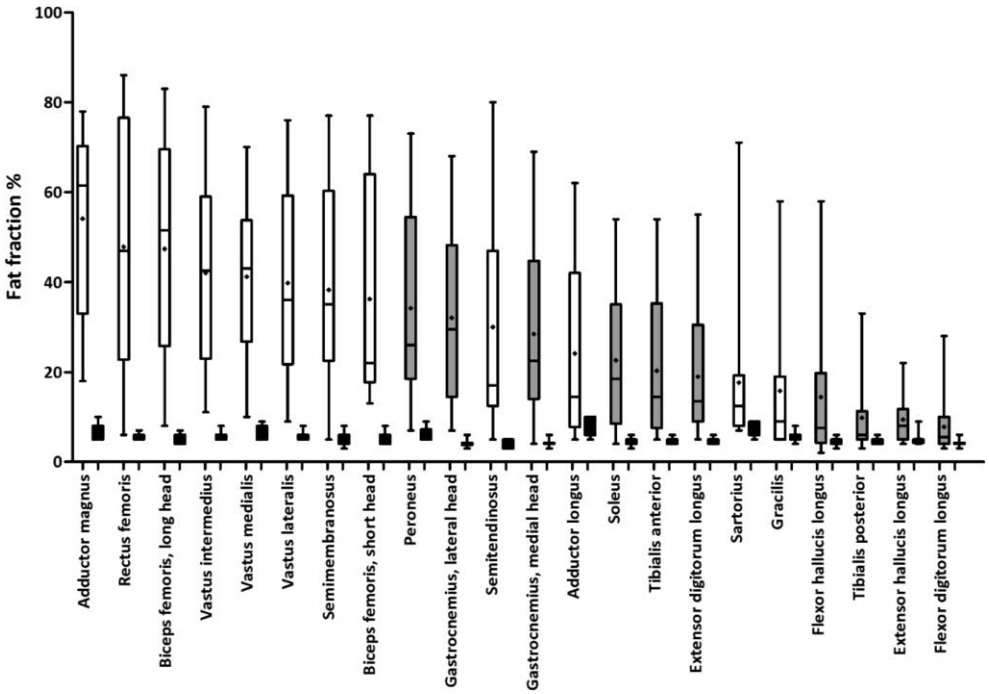

Figure 3-1: Results from quantitative MRI of muscles of the thigh and shank.
Box and whisker plots of average fat fractions per muscle in upper and lower leg of DMD patients and healthy controls. Fat fractions shown for all patients in all muscles of the upper leg (white) and lower leg (grey) and for all healthy controls in black. The upper leg is more affected compared to the lower leg muscles. Values shown as median ± maximum and minimum and are ordered by the mean fat fraction. Reproduced with permission from Elsevier.[14]

3.2.Methods

3.2.1. Study Population

The population for the present study is two boys over four visits at yearly intervals. At baseline, the boys were 5.1 and 9.3 years old. Data from five participants without disability between 4-10 years old were used for comparison. Demographics for all participants are shown in Table 3-1. The younger participant began a corticosteroid regimen 6 months prior to the first visit, and the older participant began a corticosteroid regimen 6 years prior to the first visit.

Table 3-1: Participant demographics for musculoskeletal modeling.

Younger Participant				
Visit	1	2	3	4
Age (years)	5.1	6.2	7.2	8.1
Height (cm)	109.0	113.0	115.0	116.0
Weight (kg)	17.5	18.3	20.9	22.8
BMI (kg/m^2)	14.7	14.3	15.8	16.9

Older Participant				
Visit	1	2	3	4
Age (years)	9.3	10.4	11.3	12.3
Height (cm)	122.0	126.5	130.5	135.5
Weight (kg)	28.2	30.0	27.4	29.3
BMI (kg/m^2)	18.9	18.7	16.1	16.0

Normative Participants						
						Avg
Age (years)	4.0	6.7	7.7	8.1	10.2	7.3
Height (cm)	103.5	118.0	125.5	130.5	145.0	124.5
Weight (kg)	16.4	19.3	25.3	23.0	29.8	22.7
BMI (kg/m^2)	15.2	13.9	16.1	13.5	14.1	14.6

3.2.2.Gait Assessment

Reflective marker position data and force data were collected at self-selected walking speeds using an 8-camera motion capture system (Motion Analysis, Santa Rosa, CA, USA) and 2 forceplates (Kistler, Kistler Instruments, Switzerland). Spatial-temporal parameters, and kinematics and kinetics of the hip, knee, and ankle were calculated using Orthotrak (Motion Analysis Corp). One representative trial that had 2 consecutive force plate strikes (right foot

followed by the left foot) was identified for each participant.

3.2.3. Musculoskeletal Modeling

Musculoskeletal modeling was performed for each representative trial using OpenSim.[62] Anthropometric and marker position data from a standing calibration were used to scale a musculoskeletal model with 23 degrees of freedom and 92 force actuators.[63,72] Inverse kinematics of the trunk, pelvis, hip, knee, and ankle were calculated through tracking the markers on the musculoskeletal model with the marker position data from the representative trial. The RRA was used to adjust joint kinematics and model mass to minimize residual forces. The model was then re-scaled with the recommended mass and the process repeated. Muscle forces, lengths, and activations to drive the Hill-type force actuators were calculated through CMC.[66,67]

3.2.4. Muscle Work Calculation

Muscle force and contraction velocity, outputs of the CMC module in OpenSim, were used to calculate eccentric and concentric muscle work. Muscle power was calculated as the scalar product of force and contractile velocity, with the convention of positive power the result of concentric contraction (positive contractile velocity as the force applied as the muscle shortens) and negative power the result of eccentric contractions (negative contractile velocity as the force is applied as the muscle lengthens). Muscle work was calculated as the numerical integral of muscle power, with concentric work the integral of positive muscle power and eccentric work the integral of negative muscle power. Muscle power and work were also normalized as described by Hu and Blemker.[68] Prior to the power calculation, muscle force was normalized to the maximum isometric force determined by the model[66] and muscle contractile velocity was normalized to the instantaneous muscle length.

Smaller actuator compartments that performed similar functions were combined. For

example, the gluteus maximus is defined by three force actuators corresponding to the anterior-lateral, midsection, and posterior-medial compartments. Muscle properties were then combined into a single gluteus maximus muscle. The 22 muscles for which fatty tissue infiltration data have been reported by Wokke et al were used for analysis.[14] The gluteus maximus and gluteus medius were added as other publications have reported fatty tissue infiltration values greater than or equal to the adductor magnus.[15,16]

3.2.5. Quantification of Fat Fraction Rank

Fatty tissue infiltration had been previously quantified as muscle fat fraction, which was modeled as the signal intensity of fat divided by the sum of the signal intensity of fat and the signal intensity of water.[14] As the data were unavailable, the muscles used in the analysis have been ordered by their relative fat fractions, dubbed the "fat fraction rank." Muscles with a higher fat fraction rank are defined to have a higher fat fraction (greater % fatty tissue) as compared to other muscles.

3.3.Results

3.3.1.Spatial Temporal Parameters, Joint Kinematics, and Joint Kinetics

While spatial-temporal parameters, joint kinematics, and joint kinetics are not the focus of this chapter, it is important to describe the differences between the participants across the four visits as these data are used as inputs for the model. Spatial temporal parameters for all participants are shown in Table 3-2. The younger participant walked at a similar speed to normative data, but had a shorter stride length and higher cadence. The older participant was below average for walking speed, stride length, and cadence. Joint kinematics for the specified trials as calculated by the RRA module of OpenSim are shown in Figure 3-2. Gait deviations identified were an increase in lumbar extension, anterior pelvic tilt, hip flexion, and ankle plantar

flexion. Both participants lacked a knee flexion loading response during early stance. The increase in lumbar extension was mirrored by an increase in anterior pelvic tilt. Overall, these gait deviations increased with age. Joint moments for the specified trials as calculated by the RRA module of OpenSim are shown in Figure 3-3. While both participants had hip extensor moments below average at the first visit, the younger participant improved and the older participant declined with age. Both participants had inappropriate knee flexor moments during stance, except for the third visit from the younger participant, which showed extensor moments, albeit inadequate as compared to normative data. Both participants had excessive plantar flexor moments during early stance, and the younger participant had inadequate plantar flexor moments during late stance. The younger participant remained relatively unchanged over time, but the older participant showed an increase in plantar flexor moments during early stance. Total support moments (the sum of hip, knee, and ankle moments) were greater than normal for both participants during early stance.

Table 3-2: Spatial-temporal data for musculoskeletal modeling trials

Younger Participant				
Visit	1	2	3	4
Walking speed (cm/s)	104.8	116.4	105.6	121.4
Stride length (cm)	78.6	91.7	91.7	90.6
Cadence (steps/min)	160.1	150.1	142.6	158.3
Toe-off (%GC)	60	57	59	57

Older Participant				
Visit	1	2	3	4
Walking speed (cm/s)	103.5	76.7	77.7	77.0
Stride length (cm)	94.5	82.5	87.0	84.6
Cadence (steps/min)	131.0	108.3	105.9	110.8
Toe-off (%GC)	58	59	60	61

Normative Participants						
Age	4.0	6.7	7.7	8.1	10.2	Avg
Walking speed (cm/s)	105.0	131.4	135.3	117.2	119.4	121.7
Stride length (cm)	85.7	100.0	115.2	106.6	123.7	106.2
Cadence (steps/min)	145.6	158.3	142.6	132.1	113.4	138.4
Toe-off (%GC)	62	59	59	59	61	60

%GC = percent gait cycle

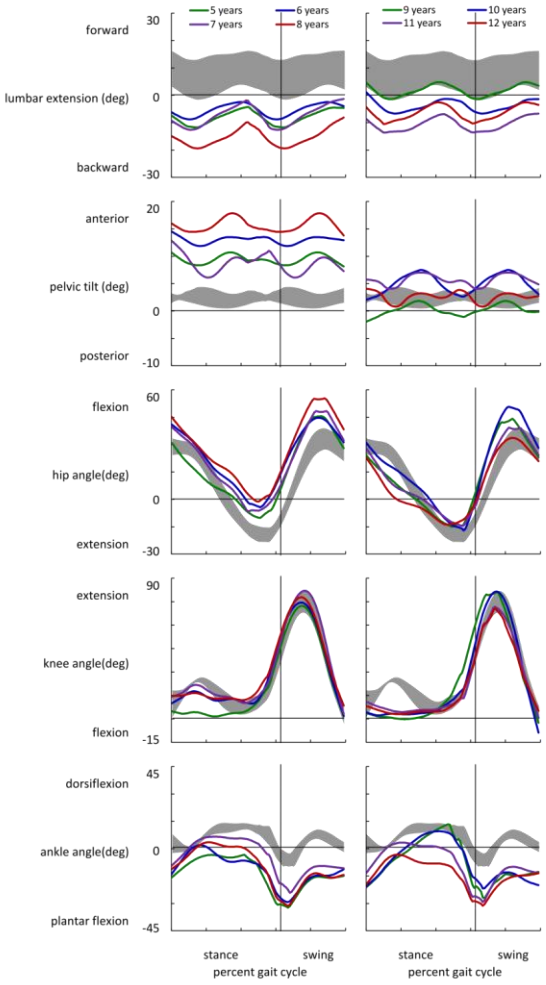

Figure 3-2: Sagittal plane kinematics for two boys with DMD over four visits.
The younger participant is shown on the left, the older participant on the right. Each visit is shown by green, blue, purple, and red lines. The normative range (mean +/- SD) is shown as the grey band.

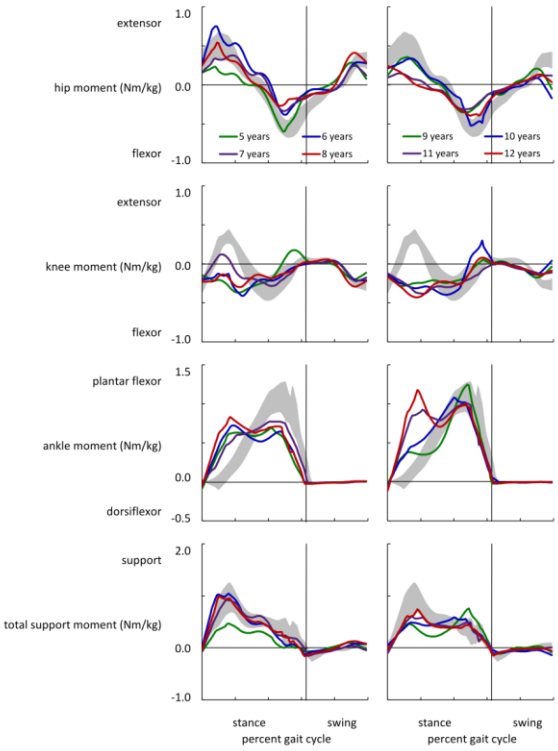

Figure 3-3: Sagittal plane joint moments for two boys with DMD over four visits.
The younger participant is shown on the left, the older participant on the right. Each visit is shown by green, blue, purple, and red lines. The normative range (mean +/- SD) is shown as the grey band.

3.3.2. Simulation Residual and Reserve Actuators

The computed muscle control algorithm successfully found solutions for all simulations for all participants. Residual values, shown in Table 3-3, are all under the threshold values of 10N for residual forces (FX, FY, and FZ) and 30Nm for RMS and 50Nm for maximum residual moments (MX, MY, and MZ). Reserve actuators for the hip, knee, and ankle motion are shown in Table 3-4, and all values are below the threshold limits of 10Nm for RMS and 25Nm for maximum reserve moments.

Table 3-3: Root-mean-square and maximum residual forces.

Younger Participant

Visit	5.1y		6.2y		7.2y		8.1y	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max
FX (N)	1.53	4.02	2.31	11.93	1.31	3.77	1.68	5.43
FY (N)	1.38	5.43	2.08	6.25	1.55	3.56	2.30	6.16
FZ (N)	1.02	2.58	0.68	1.25	1.27	2.54	1.77	4.36
MX (Nm)	2.98	7.87	3.20	9.39	3.45	8.48	3.70	6.46
MY (Nm)	0.62	1.10	1.81	4.54	2.15	4.10	1.17	2.38
MZ (Nm)	3.77	7.67	5.41	12.71	5.30	17.03	3.24	10.55

Older Participant

Visit	9.3y		10.4y		11.3y		12.3y	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max
FX (N)	0.80	2.13	1.46	2.19	0.99	2.34	0.73	1.69
FY (N)	1.88	3.97	1.97	3.12	0.88	2.93	1.39	2.71
FZ (N)	0.98	1.82	0.61	1.72	0.31	0.51	0.57	1.23
MX (Nm)	4.30	11.61	2.78	6.03	2.70	5.12	4.57	8.13
MY (Nm)	1.62	4.70	2.92	10.21	0.79	2.00	1.39	4.08
MZ (Nm)	4.17	10.12	5.41	12.59	3.15	9.27	4.13	8.52

Normative Participants

Age	4.0y		6.7y		7.7y		8.1y		10.2y	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max	RMS	Max
FX (N)	0.70	2.31	1.79	1.84	1.56	6.53	0.73	6.40	1.16	2.99
FY (N)	2.74	4.66	0.83	1.99	1.72	3.76	0.65	2.31	2.27	8.17
FZ (N)	1.11	2.62	1.06	1.23	0.82	1.76	0.57	2.02	0.78	1.54
MX (Nm)	1.84	4.01	2.78	5.36	4.03	8.08	3.02	6.61	3.45	7.09
MY (Nm)	0.66	1.97	1.60	4.02	2.59	7.89	1.50	3.29	1.18	4.15
MZ (Nm)	3.34	14.8	2.87	14.9	6.50	26.4	4.38	6.11	5.83	19.6

Residual forces in N; Residual moments in Nm; RMS = root-mean-square

FX = force in fore-aft direction; FY = force in vertical direction; FZ = force in medial-lateral direction

MX = moment about X-axis (direction of travel); MY = moment about Y-axis (vertical from floor);

MZ = moment about Z-axis (perpendicular to sagittal plane)

Table 3-4: Root-mean-square and maximum reserve actuator moments.

Younger Participant

Visit	5.1y		6.2y		7.2y		8.1y	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max
H F/E	0.013	0.029	0.013	0.028	0.014	0.032	0.016	0.038
H Ab/Ad	0.011	0.027	0.014	0.032	0.013	0.035	0.020	0.057
H I/E Rot	0.029	0.085	0.032	0.061	0.037	0.093	0.030	0.085
K F/E	0.017	0.035	0.017	0.041	0.085	0.594	0.018	0.039
A P/D	0.016	0.050	0.016	0.048	2.016	13.212	0.022	0.091

Older Participant

Visit	9.3y		10.4y		11.3y		12.3y	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max
H F/E	0.016	0.041	0.012	0.030	0.010	0.026	0.008	0.021
H Ab/Ad	0.026	0.067	0.017	0.034	0.015	0.042	0.013	0.030
H I/E Rot	0.044	0.120	0.025	0.104	0.011	0.034	0.013	0.039
K F/E	0.023	0.050	0.020	0.052	0.015	0.036	0.013	0.032
A P/D	0.305	2.575	0.010	0.033	0.021	0.157	0.008	0.025

Normative Participants

Age	4.0		6.7		7.7		8.1		10.2	
	RMS	Max	RMS	Max	RMS	Max	RMS	Max	RMS	Max
H F/E	0.013	0.029	0.019	0.010	0.013	0.028	0.005	0.073	0.012	0.020
H Ab/Ad	0.021	0.079	0.021	0.041	0.018	0.056	0.015	0.093	0.012	0.025
H I/E Rot	0.131	0.537	0.223	0.081	0.026	0.064	0.015	1.046	0.021	0.087
K F/E	0.019	0.052	0.016	0.023	0.355	2.959	0.010	0.038	0.660	5.167
A P/D	0.126	0.812	0.013	3.671	0.644	4.055	0.440	0.041	0.301	2.352

Reserves in Nm; RMS = root-mean-square

H F/E = hip flexor/extensor; H Ab/Ad = hip abductor/adductor; H I/E Rot = hip internal/external rotator; K F/E = knee flexor extensor moments; A P/D = ankle plantar/dorsiflexor moments

3.3.3. Muscle Forces, Contraction Velocity, and Power

Normalized muscle forces, velocity, and powers for nine representative muscle groups for the younger participant are shown in Figure 3-4, and for the older participant in Figure 3-5. For the younger participant, normalized force and power from the gluteus maximus, gluteus medius, adductor magnus, vastus lateralis, rectus femoris, and tibialis anterior during early stance were inadequate at baseline. Improvements with age were seen in the adductor magnus and tibialis anterior. The vastus lateralis,rectus femoris, and tibialis anterior showed a large improvement at the third visit, but all returned to baseline levels at the fourth visit. The medial gastrocnemius showed increased force production throughout stance and increased speed during late stance across the four visits, which resulted in increased eccentric power during early stance and increased concentric power during mid stance.

Normalized force, speed, and power for the older participant at baseline were similar to the younger participant; however, no improvement was shown over the four visits. The gluteus medius was initially producing excessive force during early stance, but this did not generate excessive power and ultimately declined with subsequent visits. The adductor magnus and rectus femoris were within the normal range for normalized force and power (concentric for the adductor magnus, eccentric for the rectus femoris) at baseline, but also declined with subsequent visits. Improvements in force occurred in the medial gastrocnemius, which provided excessive force throughout stance and a corresponding increase in eccentric power during early stance and concentric power during mid stance.

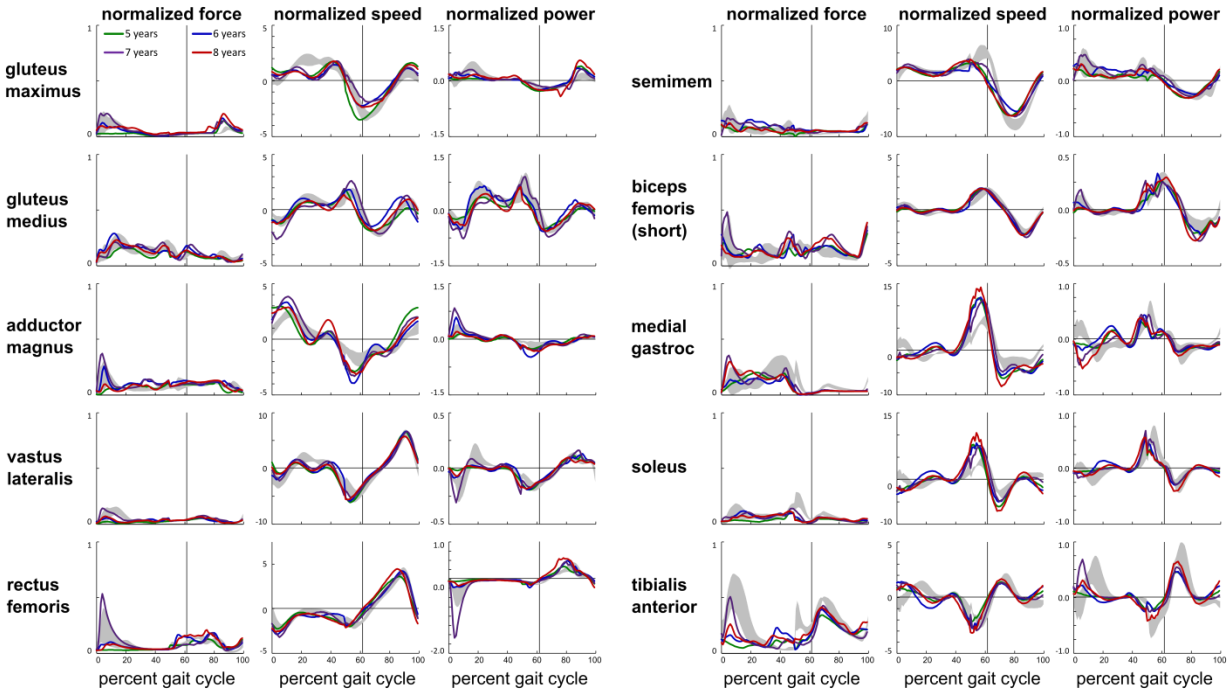

Figure 3-4: Normalized muscle forces, speeds, and powers for the younger particpant.
Each visit is shown by green, blue, purple, and red lines. The normative range (mean +/- SD) is shown as the grey band. Normalized speed is shown with positive as shortening and negative as lengthening. Normalized power is shown with positive as concentric and negative as eccentric.

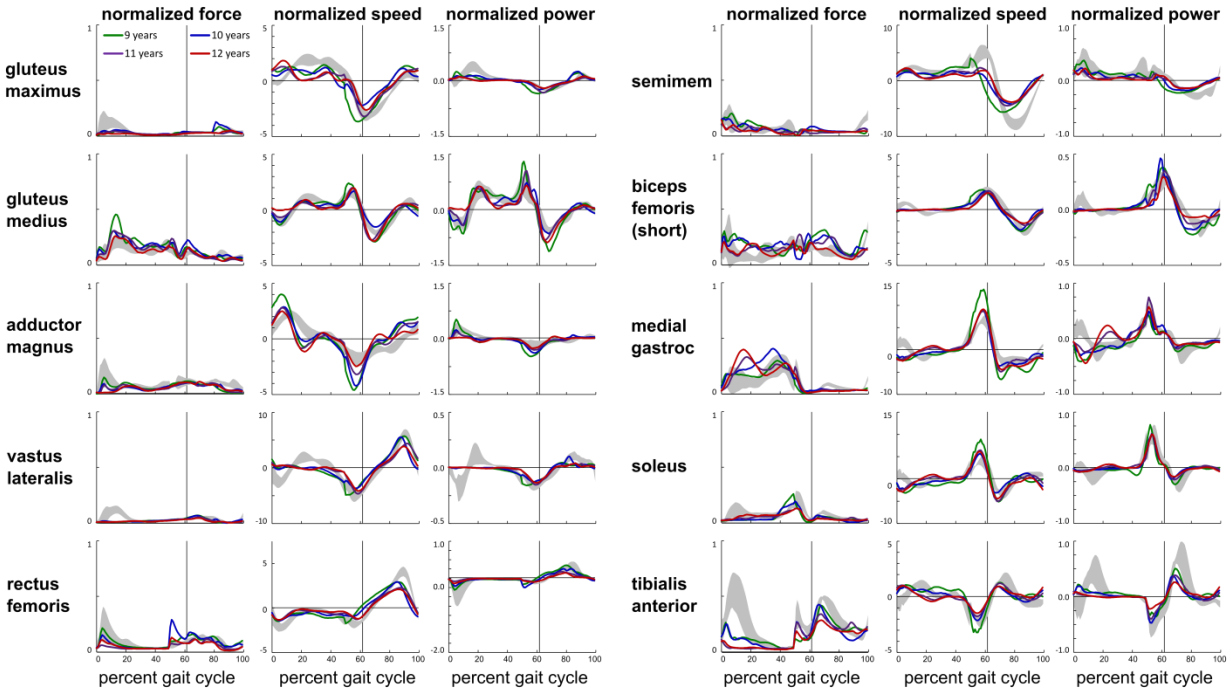

Figure 3-5: Normalized muscle forces, speeds, and powers for the older participant.
Each visit is shown by green, blue, purple, and red lines. The normative range (mean +/- SD) is shown as the grey band. Normalized speed is shown with positive as shortening and negative as lengthening. Normalized power is shown with positive as concentric and negative as eccentric.

3.3.4. Muscle Work

Normalized eccentric and concentric work generated by individual muscles are shown in Figure 3-6. The 22 muscles have been ordered by their fat fraction rank as per Wokke et al.[14,68] increasing in fat fraction from left to right. In addition, the gluteus maximus and gluteus medius were included with the highest and second-highest fat fraction ranks, respectively, for a total of 24 muscles.[15,16] Overall, there appear to be some general trends in the data regarding eccentric work and fat fraction rank. For normative gait, muscle eccentric work tended to increase as the fat fraction rank of the muscle increased, albeit with some exceptions, particularly with the high eccentric work from the tibialis anterior, soleus, medial gastrocnemius, and lateral gastronemius and relatively low fat fraction ranks. Grouping muscles by location (designated by the dark grey for proximal and light grey for distal muscles) and considering them separately strengthens the general trend. Exceptions occur for the proximal muscles with the gluteus maximus and for the distal muscles with the peroneals, each of which has the highest fat fraction rank for their group, but neither generates the most eccentric work for their group.

Both of the participants with DMD produced less eccentric and concentric work as compared to the normal range, as shown in Table 3-5, except for the 3rd visit from the younger participants and the 1st visit from the older participant. Over the first three visits, from age 5 through 7, the younger participant showed an increase in both eccentric and concentric work, which came through increases from the proximal and distal muscles. From the 3rd to the 4th visit, there was a decrease in both eccentric and concentric work; however, the distal muscles increased eccentric work and increased the proportion of concentric work over this period. For the older participant, there was a decline in both eccentric and concentric work over all four visits, from age 9 through 12. For eccentric work, both the proximal and distal muscles also

showed a decline, but the distal muscles showed a slight increase in percent of the total work, from 37% to 40%. For concentric work, the proximal muscles showed a decline over all four visits; whereas the distal muscles improved over the first three, and maintained their percent of the total work even though they showed a decline between the 3rd and 4th visits.

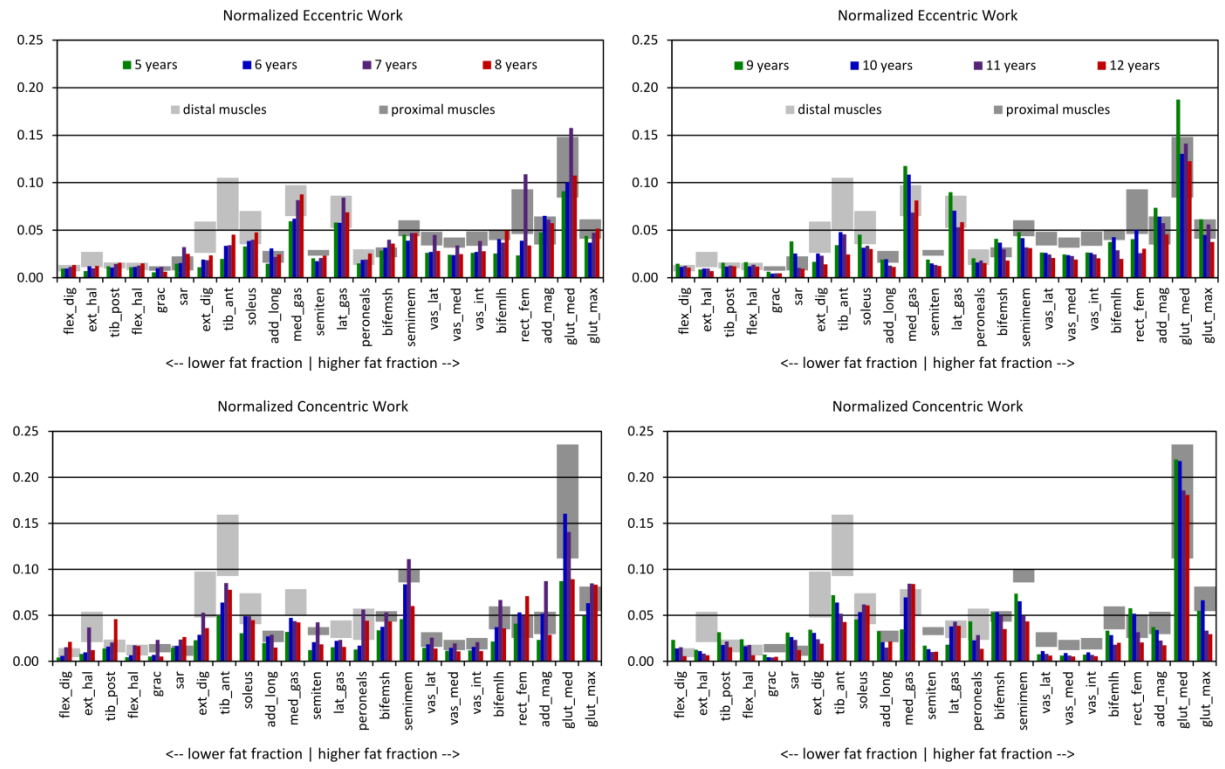

Figure 3-6: Normalized eccentric and concentric muscle work for both the younger and older participants with DMD.
The younger participant is shown on the left and the older participant is shown on the right. Each visit is shown by the green, blue, purple, and red bars. Normative ranges (mean +/- SD) are shown by the light grey (distal muscles) and dark grey (proximal muscles) bands. Muscles are ordered in increasing fat fraction rank from right to left. Muscle abbreviations from left to right: flex_dig = flexor digitorum; ext_hal = extensor hallucis; tib_post = tibialis posterior; flex_hal = flexor hallucis; grac = gracilis; sar = Sartorius; ext_dig = extensor digitorum; tib_ant = tibialis anterior; soleus; add_long = adductor longus; med_gas = medial gastrocnemius; semiten = semitendinosus; lat_gas = lateral gastrocnemius; peroneals; bifemsh = biceps femoris, short head; semimem = semimembranosus; vas_lat = vastus lateralis; vas_med = vastus medialis; vas_int = vastus intermedius; bifemlh = biceps femoris, long head; rect_fem = rectus femoris; add_mag = adductor magnus; glut_med = gluteus medius; glut_max = gluteus maximus.

The work performed by individual muscles, as shown in Figure 3-6, provides a more detailed picture than the overall eccentric and concentric work for each participant. The younger participant showed an increase in eccentric work across time regardless of fat fraction rank or muscle location. In contrast, the older participant shows a decline in eccentric work across time regardless of fat fraction or muscle location. For concentric work, the younger participant showed improvements in most muscles across the first three visits; however, proximal muscles with higher fat fractions, such as the gluteus medius, adductor magnus, and the long head of the biceps femoris, showed a decline from the third to the fourth visits. The older participant showed what appears to be a continuation of this trend, as concentric work from all proximal muscles declined over the four visits, with some of the largest decreases from the muscles with the highest fat fraction ranks. Conversely, distal muscles, such as the medial gastrocnemius and soleus, improved concentric work over the four visits.

Table 3-5: Overall average normalized eccentric and concentric work

	Younger Participant				Normative	
Visit	5.1y	6.2y	7.2y	8.1y	Mean (SD)	
Total Eccentric Work	0.67	0.78	1.03	0.90	0.99	(0.12)
Proximal Muscles	0.44	0.51	0.70	0.54	0.60	(0.07)
Distal Muscles	0.24	0.27	0.33	0.36	0.40	(0.11)
Total Concentric Work	0.59	0.88	1.18	0.87	1.12	(0.18)
Proximal Muscles	0.39	0.61	0.78	0.51	0.65	(0.07)
Distal Muscles	0.20	0.27	0.40	0.36	0.47	(0.14)
	Older Participant				Normative	
Visit	9.3y	10.4y	11.3y	12.3y	Mean (SD)	
Total Eccentric Work	1.03	0.90	0.75	0.67	0.99	(0.12)
Proximal Muscles	0.65	0.55	0.46	0.40	0.60	(0.07)
Distal Muscles	0.38	0.34	0.29	0.27	0.40	(0.11)
Total Concentric Work	0.98	0.95	0.81	0.71	1.12	(0.18)
Proximal Muscles	0.64	0.61	0.46	0.41	0.65	(0.07)
Distal Muscles	0.34	0.34	0.36	0.29	0.47	(0.14)

3.4.Discussion

The purpose of this chapter was to explore the mechanical hypothesis of disease progression in DMD by calculating eccentric and concentric work during pathological gait and comparing to a published measure of fatty tissue infiltration. To explore this further, three hypotheses were developed: 1) that muscles that perform more eccentric work would be those that rank higher with regard to fatty tissue infiltration, 2) that muscles with higher fat fractions would show decreased overall work, and 3) that work from proximal muscles would decrease over time, and work from distal muscles would increase to compensate. The results of our analysis, in general, agree with each of these hypotheses.

3.4.1. Eccentric Muscle Work Relates to Fat Fraction Rank

The results from normative gait data agree with Hu and Blemker, who found a strong relationship between fat fraction and eccentric work during normative gait.[68] There is a general trend towards higher eccentric work from muscles that have a higher fat fraction rank, which is strengthened when the muscles are grouped by location. This is further illustrated by comparing muscles with similar functions. For the quadriceps, the rectus femoris has a higher fat fraction than the rest of the vasti, and also performs more eccentric work. A similar trend arises for the hamstrings and the triceps surae. The exception is that the semimembranosus performs more eccentric work than the long head of the biceps femoris despite a lower fat fraction rank.

Another exception to the general trend is that some of the distal muscles generated more eccentric work than most of the proximal muscles, despite having a lower fat fraction rank. In particular, the lateral and medial gastrocnemius produced more eccentric work than the quadriceps and hamstrings, despite a lower fat fraction rank. This could be due to differences in the magnitude of eccentric force or rate of force production during gait. During normative gait,

the gastrocnemius generates eccentric work by means of relatively low power sustained over the first half of stance, as shown in Figure 1-3. Conversely, the quadriceps and the hamstrings generate eccentric work by means of a more rapid onset and higher magnitude sustained over a shorter period during early stance and late swing, respectively. Perhaps the slower loading rate of the gastrocnemius, as compared to the rapid braking action of the quadriceps and hamstrings, prevents muscle damage and could account for the lower fat fraction rank.

3.4.2.Compensatory Strategies Minimize Muscle Work

A normative walking pattern requires that muscles perform a certain amount of work to stabilize and drive skeletal segments about joints. Some of this work must be supplied eccentrically through lengthening contractions. Advancing through the gait cycle, examples of eccentric contractions include the tibialis anterior controlling lowering the foot to the ground following heel strike, the quadriceps controlling the knee during the knee flexion loading response in early stance, the gastrocnemius and soleus controlling the forward progression of the tibia over the foot during mid stance, the hip flexors (e.g. the rectus femoris) limiting hip extension during late stance, and the hamstrings slowing knee extension during late swing.[35,110] These eccentric contractions produce relatively large amounts of eccentric work. The participants with DMD had lower eccentric work at each baseline visits, and also showed compensatory gait patterns. The younger participant showed improvements in gait kinematics and kinetics, shown in Figure 3-2 and Figure 3-3, over the subsequent two visits, and also showed an increase in eccentric and concentric work. However, the older participant showed a decline in gait kinematics and kinetics, which corresponded to a decline in eccentric and concentric work over the four visits. Therefore, it is clear that changes in gait kinematics influence how muscles perform during gait. This is a limitation of the previous paper, in that boys with DMD do not

walk with a normative gait pattern, especially with later stages of involvement.

This begs the question of how the pathological gait patterns reduced the amount of eccentric and concentric work. The two participants discussed in this chapter adopted similar gait patterns that were missing typical features of normative gait. Both participants lacked heel strike at initial contact with the ground, but instead made contact with a relatively flat foot. This occurred for the younger participant at all visits (except the third) and at all visits for the older participant. In doing so, the eccentric demand on the tibialis anterior during early stance was reduced. This strategy was accompanied by the absence of a knee flexion loading response, which reduced the eccentric demand on the quadriceps, and was indicated by the lack of a knee flexion wave and inappropriate knee flexor moments during early stance. At his third visit, the younger participant exhibited a knee flexion loading response. Also at this visit there was increased eccentric work from the rectus femoris, the gluteus medius, and to a lesser extent, the quadriceps. This increase in eccentric work from the younger participant could indicate that the recent corticosteroid regimen is causing muscle growth and improved strength. The lack of such an improvement from the older participant over the four visits highlights the compensatory strategy that may help explain the reduction in eccentric work.

With respect to concentric work in proximal muscles, the older participant showed a progressive decline over all visits and the younger participant showed an increase over the first three visits and a decline between the third and fourth visits. At the baseline visit, each participant showed similar gait patterns that minimized concentric work for proximal muscles with higher fat fraction rankings. The first compensation was first discussed with respect to reducing eccentric work of the quadriceps by limiting the knee flexion loading response. This has the direct effect of eliminating concentric work from the quadriceps to extend the knee into

single limb stance. It also reduces the demand on the hip extensors to stabilize and extend the hip in coordination with knee extension. In particular, by reducing hip extension motion, the muscle applies force, if any, isometrically. This was shown in Figure 3-4 and Figure 3-5. Essentially, the hip has to work harder during the knee flexion loading respose, but if the knee is extended and the ankle is able to compensate, this reduces the demand on the hip extensor muscles by allowing them to provide force isometrically. This was evident from the decrease in the hip extensor moment in the older participant between the second and third visit, which corresponded to a decrease in concentric work from the gluteus maximus and gluteus medius. Conversely, there was an increase in concentric work from the gluteus maximums and gluteus medius in the younger participant, which coincided with an increase in hip extensor moment from the first through the third visit (which saw a knee flexion loading response pattern). This increase could be related to muscle growth from the recent corticosteroid intervention. If so, then the improved strength allowed the participant to use a gait pattern that placed a larger demand on the hip extensors. This also provides evidence that the increase in hip extensor moment seen in Chapter 2 could have been related to increased strength and force from proximal muscles. Overall, changes in gait kinematics and kinetics are related both to the ability of muscles to generate work and how muscles are used during gait.

The absence of a knee flexion loading response required additional concentric work from distal muscles to compensate. This was evident by the increase in plantar flexor moments during early stance, shown in Figure 3-3, and the increase in concentric work produced by the medial gastrocnemius despite the higher fat fraction rank of the distal muscles. By initiating contact on a near fully extended knee, the ankle plantar flexors were required to generate force to resist gravity and raise the center of mass to allow for swing limb clearance. This pattern, as previously

discussed, eliminates the eccentric requirement of the triceps surae to control the forward progression of the tibia over the foot. Instead, the ankle plantar flexes into single limb support, during which the associated plantar flexor moment would be supplied via concentric contraction. This action adds energy and work to the stance limb to support and propel the center of mass and would compensate for the decreased work production of the proximal muscles. As shown by fat fraction rank, the proximal muscles are relatively spared in comparison to the proximal muscles, and therefore could potentially be relied on for a compensatory strategy. Thus, the gastrocnemius and soleus add energy to the system to maintain ambulation and compensate for more involved proximal muscles. This compensatory pattern, and the ability to provide support and propulsion, will be discussed in further detail in Chapter 4.

3.4.3.Normalization Methods and Modeling Considerations

Muscle work has been shown normalized to muscle properties. Muscle forces have been normalized to the maximum isometric force defined by the model[66] and are dependent on activation and the force-length-velocity curve.[69] Muscle contraction velocity has been normalized to instantaneous muscle length, and is therefore dependent on joint angle and angular velocity. Muscle power generation is the product of muscle force and contractile velocity, and shows with concentric power the effect of muscle force towards generating movement, and with eccentric power, the ability of a muscle to modulate or restrain movement. This method has the distinct advantage to account for variation in muscle size and inherent strength introduced by the model equations.[68] By using this method, we are able to compare performance among muscles within the same subject by determining how muscles are preferentially activated to generate motion with respect to their maximum force ability. In a way, the normalized work can be considered a capacitive measure, showing the operating range of the muscle in comparison to the

maximum force of the muscle.

Most model parameters, such as optimal fiber length and resting tendon length, are scaled to each subject. This allows muscles of different length to be appropriately compared, as longer muscles would be expected to have faster contraction velocities (as compared to shorter muscles across the same joint). Also, this maintains appropriate parameters to be used with the Hill-type muscle model.[66,111] However, maximum isometric force does not scale with each subject, but remains consistent. This may unintentionally cause the model to preferentially activate muscles with greater maximum isometric force values, because they would require a lower activation cost for the same amount of force. Previous studies have examined the dependence of model results on maximum isometric force,[73] and a similar analysis would be appropriate for this population. On a related note, perhaps scaling maximum isometric force values to body weight or BMI, and then normalizing this "raw" work to body weight would produce a measure similar to joint moments. This would also allow direct comparisons for similar muscles across multiple participants with varying body mass.

Muscle force production is determined by how the body needs to move and the ability of the muscle to generate force. As the maximum isometric force of each muscle remained the same across all participants and time points, then we can effectively test how the demand placed on the muscle changes force production. Muscle force for a given activation level is subsequently based on the length of the muscle, and the contraction velocity. The ability of the muscle to utilize that force for movement is limited by the muscle-tendon moment arm. The moment arm in particular is determined by joint angles, exemplified by the moment arm of the quadriceps changing nearly two-fold as the knee flexion angle shifts from 90 degrees of flexion to 20 degrees of flexion. Compensatory gait patterns alter joint kinematics, which alters muscle length, contraction

velocity, and moment arm. These compensations may inherently reduce the demand on weaker muscles and increase the demand on unaffected muscles without changes in activation patterns.

3.5.Conclusions and Future Work

Overall, this study has the potential to identify the effect that stresses from muscular contractions during activities of daily life have on individual muscles and the effect that has on functional performance. The mechanical hypothesis of disease progression was explored through musculoskeletal modeling by calculating eccentric and concentric work performed by individual muscles during gait. Muscles that performed more eccentric work were generally those with a greater degree of involvement. Muscles with more involvement decreased work with disease progression. And there was an increase in work from distal muscles as the work from proximal muscles decreased. This laid groundwork towards linking two biomarkers of disease progression: muscle function during gait and fatty tissue infiltration as measured by imaging methods. Furthermore, if individual muscle involvement can be predicted, then directed therapeutics and outcome measures would be more specific, sensitive, and potentially effective.

Chapter 4. Individual Muscle Contributions to Support and Propulsion

The following chapter contains work from an abstract presented as a poster at the 2014 World Congress of Biomechanics in Boston, Massachusetts

4.1. Introduction

The purpose of this chapter is to analyze some of the compensatory gait biomechanics that develop with disease progression. To do so, Induced Acceleration Analysis (IAA) will be used to determine muscle contributions to the support and propulsion of the center of mass in pathological gait for boys with DMD and how these contributions change with disease progression. In doing so, we aim to elucidate the roles individual muscles play in the development of compensatory strategies to maintain ambulation in response to progressive proximal weakness. As discussed in the previous chapter, pathological gait patterns are the result of progressive weakness in proximal muscles. This was shown by a decrease in work from proximal muscles, especially those with higher fat fraction ranks. To maintain ambulation, a compensatory strategy arising from less involved distal muscles would be required, and the contributions towards the center of mass support and propulsion from individual muscles should reflect the strategy. The results of this study would be used to identify compensatory patterns and correlate these efforts with general disease progression. We hypothesized that in DMD, decreased proximal muscle contributions will necessitate increased distal compensatory contributions to the support and propulsion of the body center of mass.

Musculoskeletal modeling and simulation provides a framework for identifying the contributions of joint moments, muscle forces, and gravity to segment CoM acceleration and joint angular accelerations. Compensatory mechanisms from less affected distal muscles may show an increased contribution to center of mass support and propulsion because muscles are

capable of accelerating segments they are not connected to via dynamic coupling.[75] IAA is a computational method that determines how the resulting action of a force-producing element can induce the acceleration of other body segments and joints. Recent studies have focused on determining the contributions of individual muscles to the support and propulsion of the trunk CoM or to stance limb stability (via hip and knee extension acceleration) during stance.[61,63,72,77,83,85] With respect to the support and propulsion of the CoM, studies have found that the hip and ankle extensor mechanics coordinate to support and accelerate the trunk during normative gait patterns.

IAA has been applied to various pathological gait patterns as a method to identify potential compensatory gait patters. Liu et al described the changes associated with changes in walking speed during normative gait, and found that muscles are less required to contribute towards body center support and propulsion.[72] Pathological gait is generally associated with a reduction in walking speed, however, the biomechanical changes associated with the reduced walking speed do not adequately describe commonly adopted compensatory mechanisms in DMD. In other movement disorders, weakness or impairments at the hip and/or ankle can cause a stiff-knee gait pattern as a compensatory mechanism.[86] Siegel et al used IAA in a pair of papers to identify compensatory patterns for individuals with weakness about the hip[87] and knee[88] and concluded that increased contributions from other extensor groups, such as the ankle plantar flexors, can compensate for weaknesses about proximal joints. Goldberg and Neptune[89] reported that increased plantar flexor moments could compensate for simulated hip extensor weakness and stiffness, which was in opposition to the findings of Jonkers et al,[90] which concluded that no one extensor group could adequately compensate for weaknesses or impairments in another. In patients with DMD, muscle weakness progresses proximally to distally, and must be

compensated for in order to maintain ambulation. However, no study has applied IAA concepts to identify compensatory patterns in patients with DMD and how compensatory strategies change with disease progression. The muscles that contribute less than expected could be those that are more affected by disease progression or are those that are in a biomechanically unfavorable position. Conversely, muscles that contribute greater than expected towards the overall gait pattern could be acting in a compensatory manner.

4.2.Methods

4.2.1. Study Population

Data from two boys with DMD who were previously enrolled ina natural history study were used for analysis. At baseline, the boys were 5.1 and 9.3 years old. Data from 5 participants without disability ranging from 4-10 years old were used for comparison. Demographics for all participants are shown in the previous chapter in Table 3-1. The younger participant began a corticosteroid regimen 6 months prior to the first visit, and the older participant began a corticosteroid regimen 6 years prior to the first visit.

4.2.2. Gait Assessment

Reflective marker position data and force data were collected at self-selected walking speeds using an 8-camera motion capture system (Motion Analysis, Santa Rosa, CA, USA) and 2 forceplates (Kistler, Kistler Instruments, Switzerland). Spatial-temporal parameters, and kinematics and kinetics of the hip, knee, and ankle were calculated using Orthotrak (Motion Analysis Corp). One representative trial with 2 consecutive force plate strikes (right foot followed by the left foot) was identified for each participant.

4.2.3. Musculoskeletal Modeling

Musculoskeletal modeling was performed for each representative trial using OpenSim.[62]

Anthropometric and marker position data from a standing calibration were used to scale a musculoskeletal model with 23 degrees of freedom and 92 force actuators.[63,72] Inverse kinematics of the trunk, pelvis, hip, knee, and ankle were calculated through tracking the markers on the musculoskeletal model with the marker position data from the representative trial. Residual forces applied to the model, which compensate for dynamic inconsistencies between measured kinematics and ground reaction forces, were minimized by slightly adjusting the model mass and kinematics. Muscle forces, lengths, and activations to drive the Hill-type force actuators were calculated through CMC.[66,67]

4.2.4. Induced Acceleration Analysis

An induced acceleration analysis was used to compute the contributions of individual muscles to the vertical and fore-aft acceleration of the mass center. Induced acceleration analysis calculates the contributions from muscular actuators to the vertical and lateral acceleration of the center of mass of the body. Muscle activations, or controls, output from the CMC module are used by OpenSim to drive a forward simulation. The simulation solves the model's system of equations of motion for each time point in the gait cycle, and includes foot-floor constraint forces that were defined to be non-penetrating and rolling without slipping, using a constraint threshold of 1% of the subjects mass.[63,76] This methodology is different than has been previously reported, which used a perturbation analysis with spring-damper elements to approximate contact forces.[72,77]

Contributions to the center of mass acceleration will be assessed for the sagittal plane and will cover acceleration in the vertical and the fore-aft axes. These correspond to "support" and "propulsion-braking" accelerations, respectively. To simplify analysis, we summed across smaller actuator compartments that performed a similar function, or were used to define a single

muscle, e.g. the three compartments of the gluteus maximus is defined by three actuators. We also limited the analysis to the major muscle groups of the hip, knee, and ankle, and to movement in the sagittal plane, such that a representative muscle for flexion and extension about each joint. Furthermore, to obtain a full gait cycle, data from the left and right muscles were merged. This reduced the number of muscles to 8: the gluteus maximus, gluteus medius, vastus lateralis, rectus femoris, semimembranosus, medial gastrocnemius, soleus, and tibialis anterior. The total contribution of each muscle was calculated as the numerical integral of body center acceleration in each direction.

4.3. Results

Spatial-temporal parameters, kinematics, kinetics, and muscle forces were previously reported in Chapter 3. To better understand the role that induced accelerations have in gait, the results will cover three parts. First, the acceleration due to ground reaction forces, the sum of all muscles, and the skeletal resistance to gravity (calculated as 9.81 m/s^2 minus the contribution from 'Gravity') will be addressed. This will provide a baseline to frame the joint-specific and individual muscle contributions. Second, joint-specific contributions were assessed by summing the contributions from individual muscles that span the same joint. For biarticular muscles, the muscle was included with the joint on which they primarily acted, for example, as the primary role of the medial and lateral gastrocnemius is ankle plantar flexion, they were included with the ankle muscles as opposed to the knee muscles. This will show how the muscles that cause joint moments provide support and propulsion, from which we can determine joint-level compensatory patterns. Then contributions from individual muscles were assessed to determine how disease progression affects the ability for muscles to provide support and propulsion and the effectiveness of compensatory strategies.

4.3.1. Overall Contributions

Total acceleration from ground reaction forces, all muscles, and the skeletal resistance to gravity by skeletal alignment over 4 visits are shown in Figure 4-1 for the younger participant and Figure 4-2 for the older participant. Compared to normative data, the younger participant had excessive ground reaction forces and muscular contributions during early stance and inadequate ground reaction forces and muscular contributions during late stance. Contributions from skeletal alignment show a supportive peak at initial contact but are lower than normal and relatively

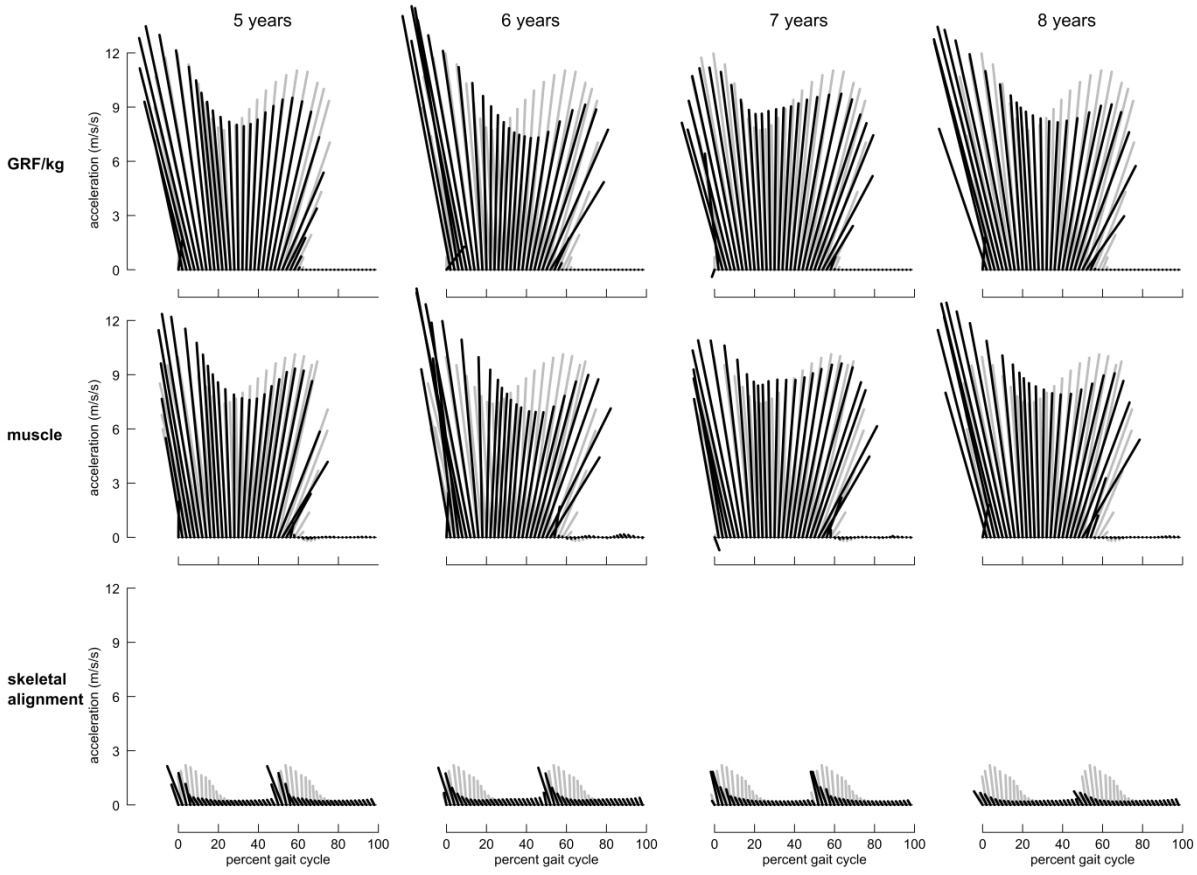

Figure 4-1: Ground reaction force, total muscle, and skeletal alignment contributions for the younger participant.
Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

constant throughout the gait cycle otherwise. The peak during early stance decreased over the four visits. The older participant had ground reaction forces similar to normative data with moderate peaks during early and late stance. Total muscular contributions were also similar, but showed a gradual increase in the peaks during early and late stance over the four visits. Skeletal alignment was reduced compared to normative data and showed a gradual decline over the four visits.

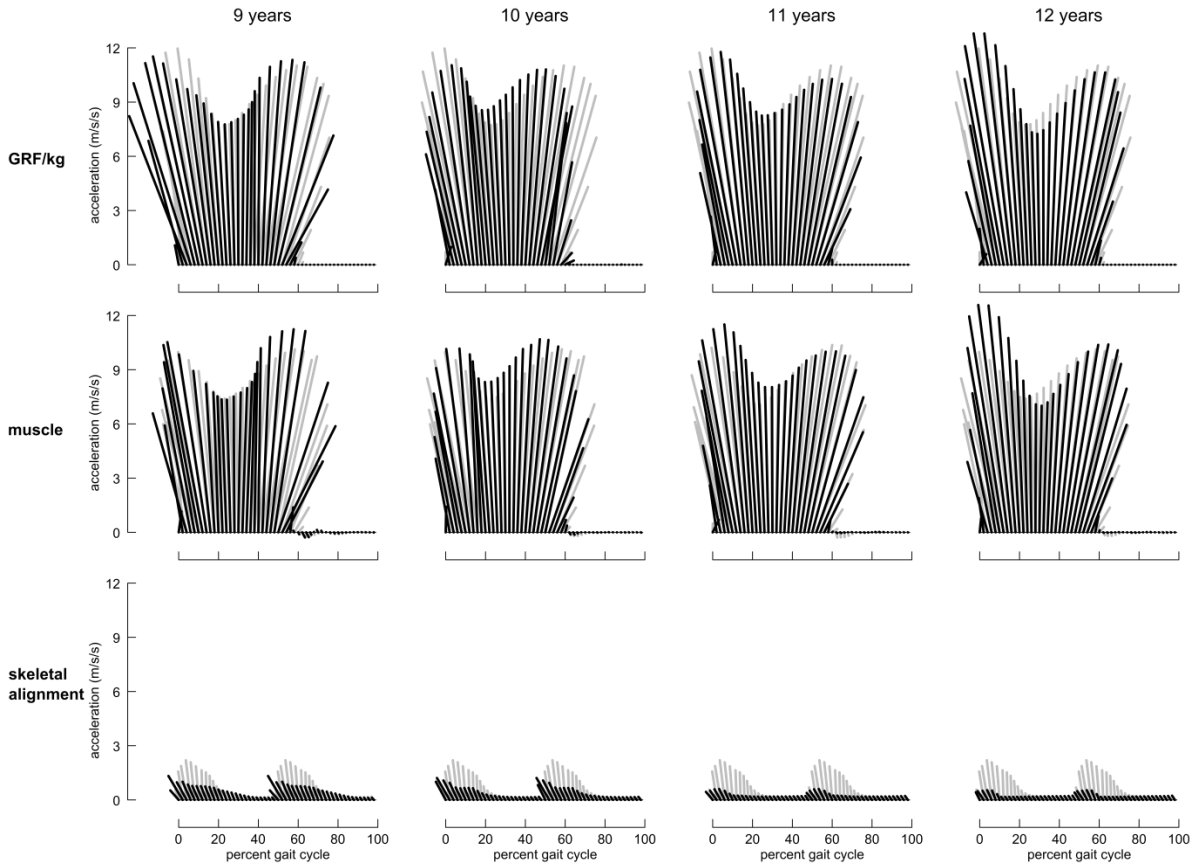

Figure 4-2: Ground reaction force, total muscle, and skeletal alignment contributions for the older participant.
Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

4.3.2.Joint-Specific Contributions

The muscular contributions were separated into joint-specific groups. Contributions from muscles whose primary role involves the hip, knee, and ankle have been respectively summed for each participant and are shown in Figure 4-3 and Figure 4-4 for the younger and older participants, respectively. Biarticular muscles were grouped by their primary function, e.g. hamstrings were considered as hip extensors and the gastrocnemius were considered as ankle plantar flexors. Normative data are shown as the grey rays in figures with participant data. There is a clear flow to control braking, support, and propulsion that transitions sequentially from the

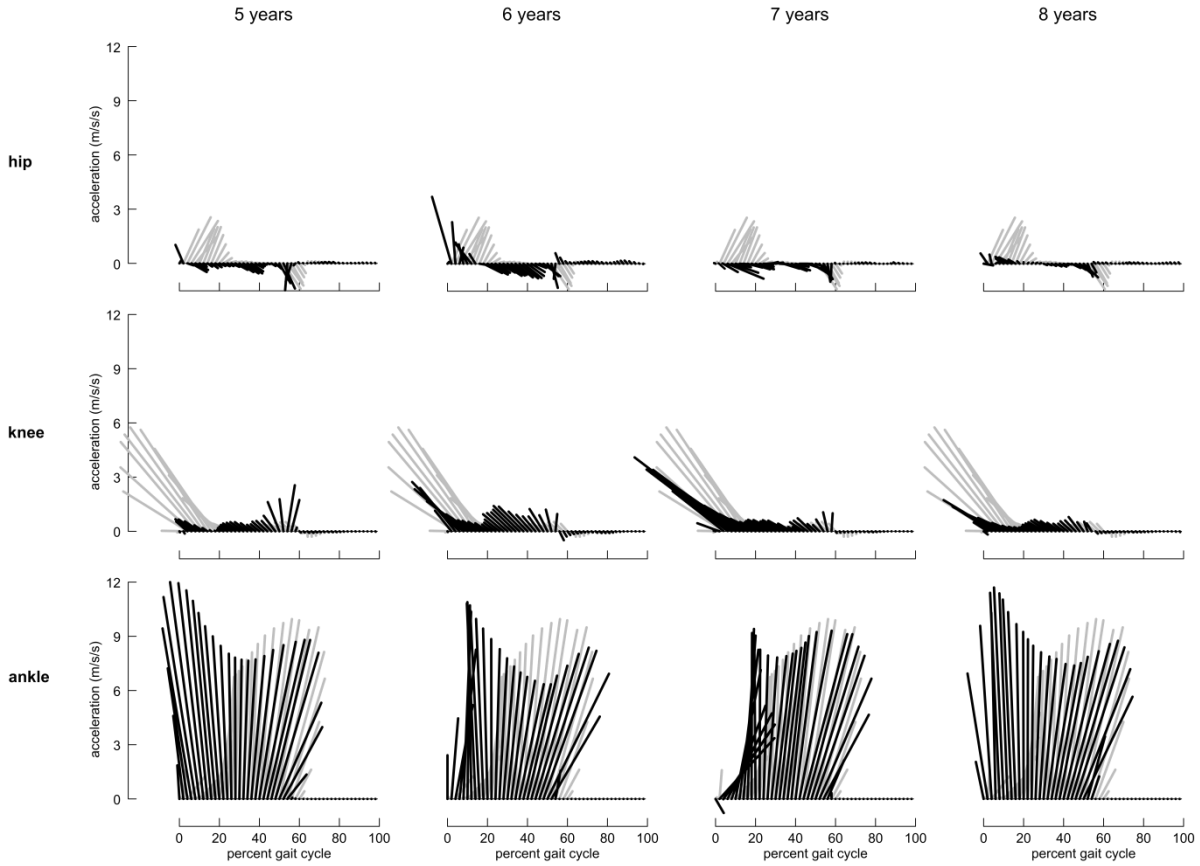

Figure 4-3: Joint-specific contributions at the hip, knee, and ankle for the younger participant. Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

muscles about the knee, the hip, and the ankle. Initially, muscles about the knee brake the center of mass while providing support into initial double support through the knee flexion loading response. The hip muscles counter the braking acceleration by contributing to propulsion while also contributing to the support of the center of mass during initial double limb support through the transition to single limb support, ultimately covering the first 20% of the gait cycle. Following this, the ankle muscles provided support through the remainder of stance. Also, the hip muscles (predominately the hip flexors) pulled the center of mass downwards during terminal double limb support to begin accelerating the limb into swing.

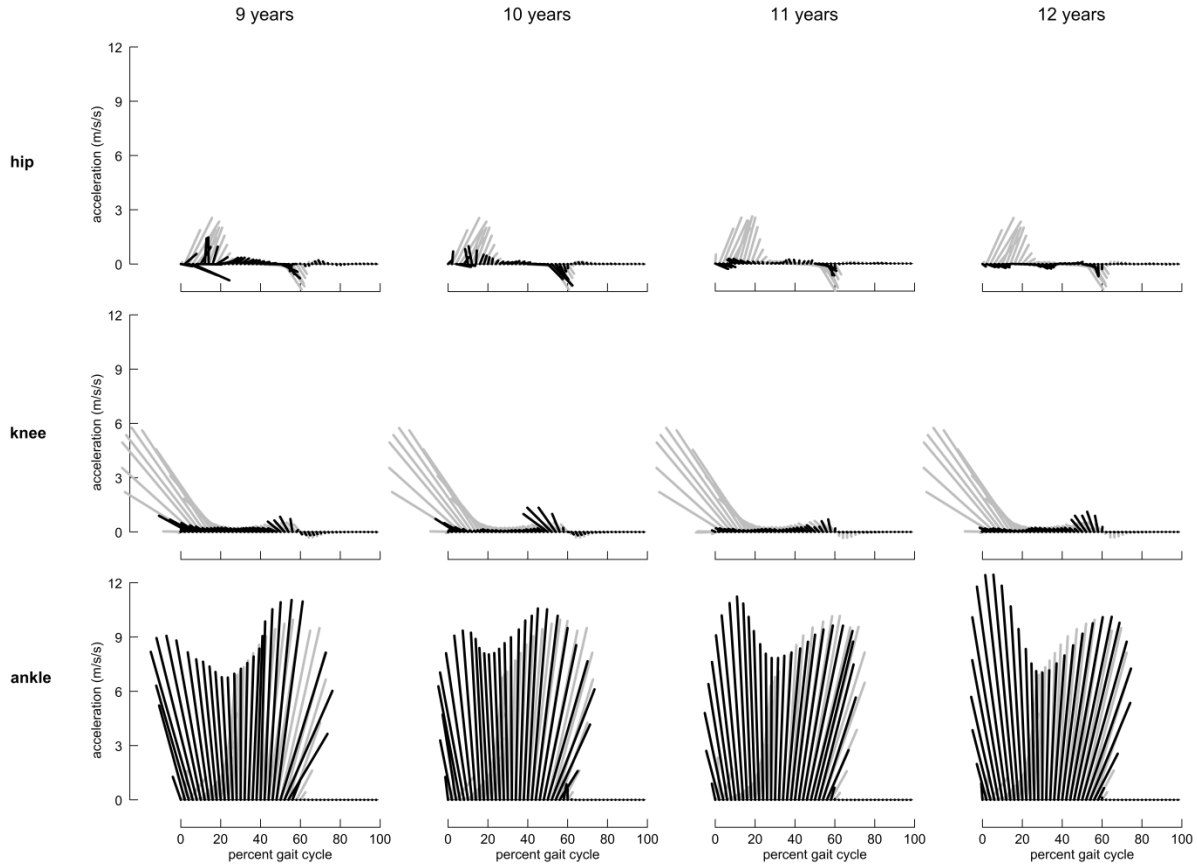

Figure 4-4: Joint-specific contributions at the hip, knee, and ankle for the older participant. Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

The two participants exhibited different distributions of contributions among the muscles about the hip, knee, and ankle as compared to normative data. The younger participant, shown in Figure 4-3, showed little contribution from the hip muscles to support, although contributions to forward progression remained. Knee muscles showed contributions to braking and support, especially during the third visit, at which the participant exhibited a knee loading response, but were all relatively low compared to normative data. Ankle muscles contributed to support throughout stance, except for initial contact of the third visit. For the older participant, shown in Figure 4-4, a similar distribution was present. The hip and knee muscles contributed little to support, and the ankle muscles exclusively provided support and propulsion during stance.

4.3.3. Individual Muscle Contributions

The joint-specific contributions were then separated into individual muscles. The contributions to center of mass support and propulsion from 8 representative muscle groups (gluteus maximus, gluteus medius, vasti, rectus femoris, hamstrings, gastrocnemius, soleus, and dorsiflexors) are shown in Figure 4-5 and Figure 4-6 for the younger and older participants, respectively. Exemplar normative muscle contributions can be seen in Figure 1-4, and normative averages are shown as the grey rays in the figures for each participant. During normative gait, the larger extensor groups of the hip and knee (gluteus maximus, gluteus medius, vasti) are contributing to braking the center of mass during early stance and providing support into single limb support. Once single limb support has been established, these contributions diminish as the ground reaction force crosses anterior to the hip and the knee is fully extended. During mid to late stance, the ankle plantar flexors contribute in controlling the progression of the tibia over the foot. And during late stance, these muscles are the dominant contributors to providing support and propulsion through heel rise and push-off.

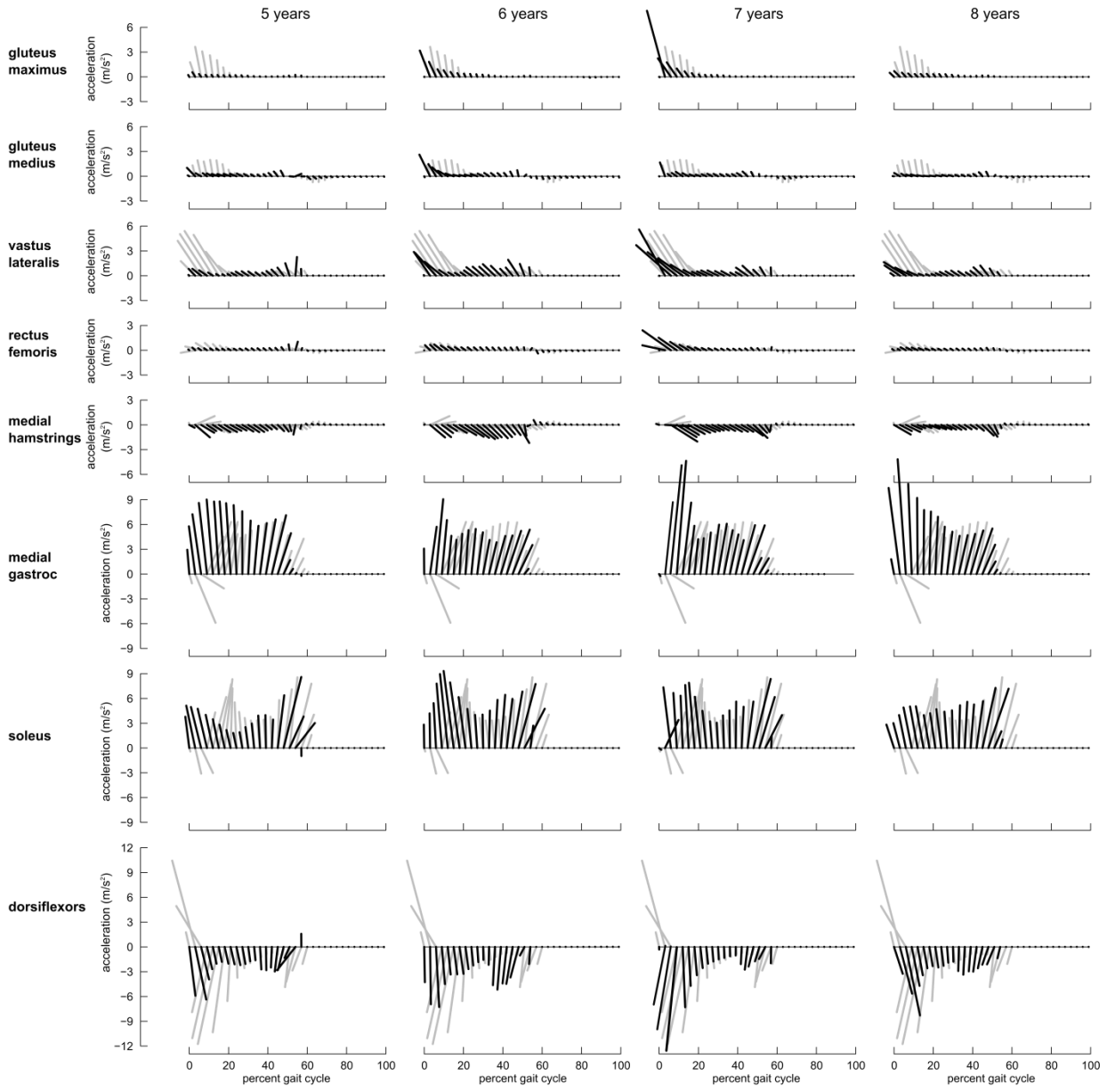

Figure 4-5: Individual muscle contributions for the younger participant.
Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

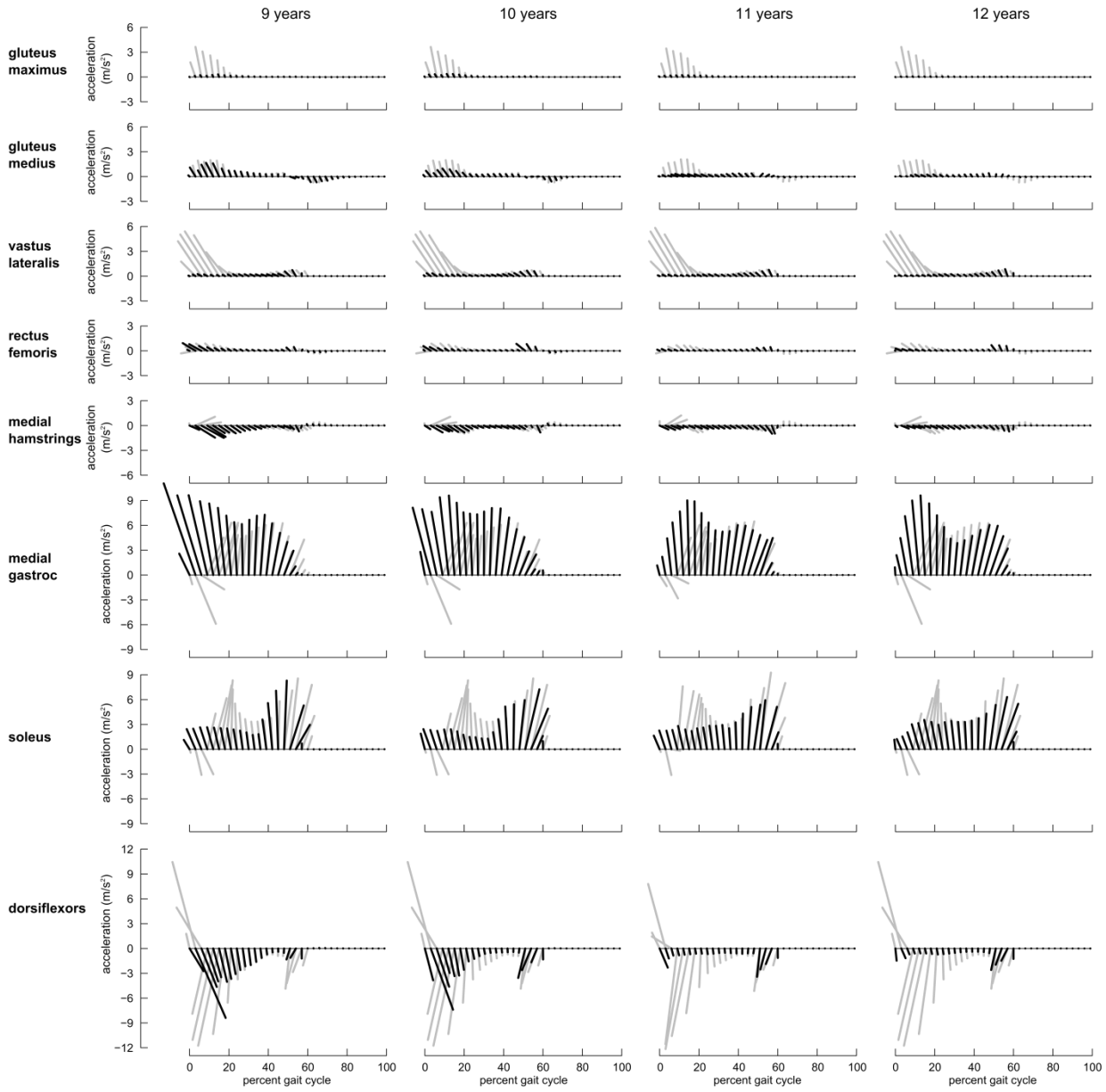

Figure 4-6: Individual muscle contributions for the older participant.
Participant data is shown in black; normative average is shown in grey. Rays are the vector of vertical and fore/aft contributions, equally scaled. Vectors in the upward or forward direction show positive contributions to support and propulsion, and vectors in the downward or backward direction show negative contributions to support and propulsion (i.e. braking). Toe off occurred at approximately 60% of the gait cycle at all visits.

The individual muscle contributions of the two participants reflect the joint-specific contributions with reduced support and propulsion from hip and knee muscles and increased contributions from ankle muscles. The younger participant, shown in Figure 4-5, showed low contributions to support from the gluteus maximus, gluteus medius, vasti, the rectus femoris, and dorsiflexors. Contributions from the gastrocnemius and soleus were increased, especially during early stance. The older participant, shown in Figure 4-6, exhibited almost a continuation of the trends from the younger participant. Contributions toward support were practically nonexistent from the gluteus maximus, gluteus medius, vasti, the rectus femoris, the hamstrings, and the dorsiflexors. Increased contributions were seen for the hamstrings and the soleus; however, a reduction during mid stance was found for the soleus, possibly due to the reduced negative contributions of the dorsiflexors.

These trends are clarified by the average contributions of each muscle towards acceleration in each direction, as shown in Figure 4-7. For the younger participant, braking contributions were initially reduced compared to normative data, but increased over the first three visits from the vasti and rectus femoris. Propulsive contributions from the hamstrings and gastrocnemius followed the same trend. Contributions to support from proximal muscles were reduced compared to normal; whereas, most support came from the gastrocnemious and soleus. For the older participant, braking contributions were reduced from all proximal muscles; however, braking contributions were provided from the gastrocnemius and the soleus. Over the four visits, a decrease in propulsive contributions occurred for the hamstrings, and an increase occurred for the gastrocnemius. Vertical support, while initially within the normal range for the gluteus medius, declined for all proximal muscles. However, most contributions to support were provided by the gastrocnemius and soleus, although the soleus was below the normal range.

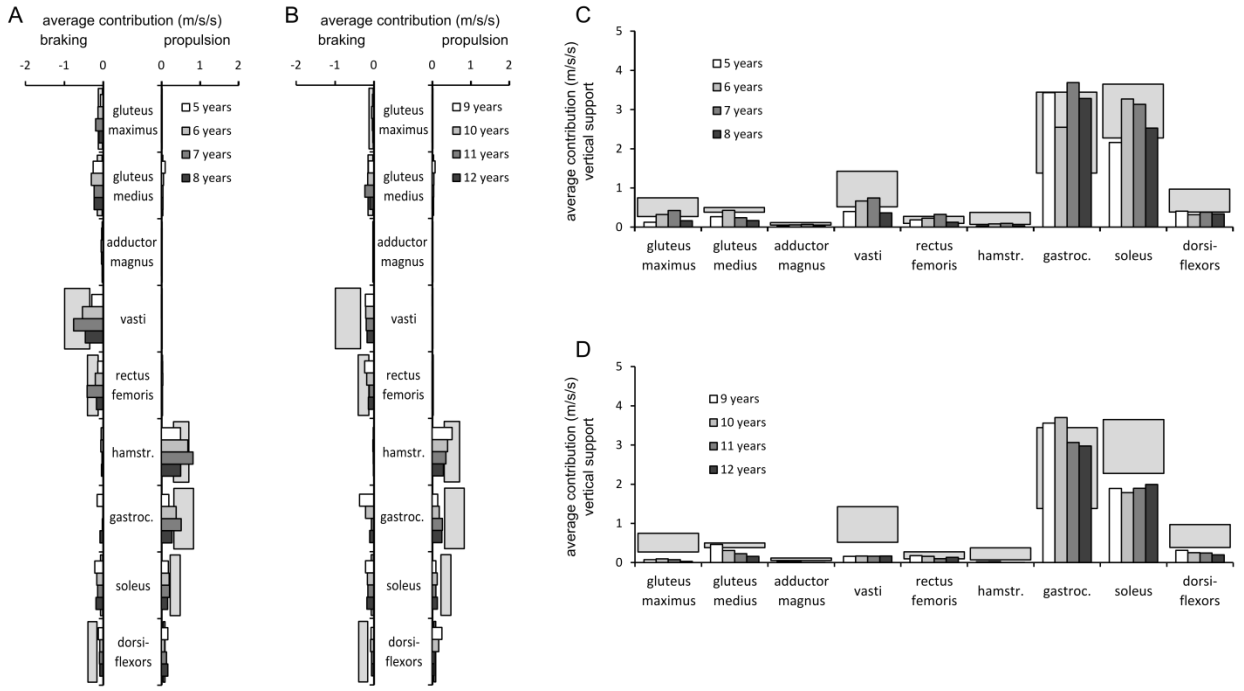

Figure 4-7: Average contributions to fore-aft and vertical acceleration over the gait cycle. Contributions towards each direction (braking, propulsion, and support) were summed for each muscle over the gait cycle, and divided by stride time. Data for participant visits are shown by white, light grey, dark grey, and black bars, subsequently. Normative ranges (average +/- 1SD) are shown as the light grey boxes. Contributions to braking and propulsion for the younger participant are shown in A, and for the older participant in B. Contributions toward vertical support are shown for the younger participant in C, and for the older participant in D.

4.4.Discussion

Induced acceleration analysis is a powerful technique to identify causal relationships between muscle action and motion. In normal gait, contributions to braking, support, and propulsion are modulated and shared among muscles about the knee, hip, and ankle. For pathological gait, for which muscles may be impaired or weakened, IAA can determine the effectiveness of compensatory strategies to provide these important biomechanical functions to maintain ambulation.

In general, the inadequate contributions to support and propulsion from the proximal muscles for both participants over the four visits required increased contributions from the

plantar flexors (gastrocnemius and soleus). The reduced contributions from the proximal muscles are consistent with the inadequate hip and knee extensor moments during early stance. The increased contributions from distal muscles are consistent with the observed increased plantar flexor moments, which are the result of a toe walking compensatory strategy. This compensatory mechanism generated adequate support and propulsion of the CoM to maintain ambulation. With disease progression, increased contributions from distal muscles to support and progression compensate for proximal muscle weakness. Our data confirm the important compensatory role of ankle plantar flexion to maintain ambulation in DMD.

The two participants showed unique changes with disease progression. The younger participant showed an increase in contributions from the proximal muscles over the first three visits. This increase came from the gluteus maximus and vasti, which are major hip and knee extensors, respectively. Over this same time period, hip and knee extensor moments increased to reach a maximum at the third visit. Thus, we see that muscle contributions may be related to joint moments, or vice versa. Also, since the younger participant had recently begun a corticosteroid treatment, these increased contributions from proximal muscles may have been due to increased strength from the intervention. On the other hand, the older participant showed progressive declines over all four visits from all proximal muscles. At the first visit, it appeared that the gluteus medius exhibited increased contributions and may have been compensating for the weaker gluteus maximus. The decrease in dorsiflexor contributions over time may have been related to the increase in plantar flexion and plantar flexor moments throughout stance. The increased contributions from the medial gastrocnemius and soleus show the importance of distal contributions during later stages of disease progression.

Normative data for ground reaction force acceleration is comparable to the “free”

walking speed group of Liu et al.[72], but muscular contributions are higher (especially during early and mid stance) and correspond to reduced skeletal contributions. Muscular contributions were higher for both participants with DMD, as well. This increased contribution may be due to the difference in calculation methods, in that Liu et al used perturbation methods to calculate the induced accelerations, whereas induced accelerations for the current participants were calculated by solving the equations of motion with a kinematic constraint, as per Hamner et al.[63] Albeit larger in magnitude, the normative contributions of individual muscles to support and propulsion are similar to the results published by Liu et al.[72] Differences arose mainly the dorsiflexors and soleus, which both had larger contributions than were published by Liu et al.[72]

The ground reaction and total muscle contributions for the participants with DMD matched, to varying degrees, the patterns from our normative data and the speed groups from Liu et al.[72] The younger of the two, had ground reaction force patterns comparable to the "fast" walking speed group,[72] but the vertical peak during late stance was reduced. The ground reaction force of the younger participant suggests a type of "falling" gait with the high impact during early stance with late propulsion driving the ipsilateral limb into swing and the contralateral limb into single limb support. The older participant is most similar to the "free" walking speed group,[72] with moderate peaks during early and late stance. Muscular contributions, however, were more similar to the "slow" walking speed group.[72]

The compensatory strategies previously identified in Chapter 3 are highlighted with the results of IAA. Normal gait patterns include a knee loading response, which requires the hip muscle to opposing the braking contributions of the knee extensors, but also to contribute to center of mass support through the action of hip extension. Reductions in strength at the knee or the hip would then lead to the loss of knee flexion loading response. The primary source of

support and propulsion then shifts to the ankle muscles, in particular, the gastrocnemius and soleus. This was present for all the visits of the two participants with DMD. The role of the hip extensors changes from active hip extension (which would be consistent with contributions to support and propulsion) to stabilizing the pelvis and trunk. For the participants with DMD, the lack of a knee flexion loading response meant that initial contact is made with a relatively straight leg with a fully extended knee. This restricts the vertical distance for the hip joint to travel and thus the body mass center cannot be accelerated upwards via hip motion alone. Maintaining trunk stability during gait requires muscle strength, which was seen in the increase in gluteus maximus force for the younger participant over the first three visits (corresponding to the increase in hip extensor moment).

Previous studies have examined the impact of pathological and simulated weakness on compensatory patterns in gait through IAA. Siegel et al examined at hip weakness during late single limb support in idiopathic inflammatory myopathy and discovered a variety of compensations, including the one found in the present study of ankle plantar flexors contributing towards hip extension through stance.[87] In simulated muscle weakness, a study by Jonkers et al and Goldberg and Neptune both found that a reduction in gluteus maximus strength would result in increased contributions from the soleus and hamstrings.[89] We found that the primary compensation arises from the soleus and gastrocnemius with respect to support. The hamstrings did show an increased contribution to propulsion, but at the expense of contributing to downward acceleration, which had to be countered elsewhere. Overall, given adequate muscle strength and no limitation in the range of motion, the participants with DMD were able to compensate with increased contributions from ankle plantar flexors to maintain the support and propulsion of the center of mass.

4.5.Conclusions and Future Work

Our data show that as the proximal extensor muscles lose strength, increased contributions from distal extensor groups are required to compensate, and are able to do so through changes in kinematics and ground reaction forces. In particular, the development of excessive plantar flexion through a toe-walking gait pattern is a necessary compensatory pattern that helps maintain ambulation in the presence of weakened proximal hip or knee extensors. Consequently, the onset of toe walking, as measured by increased and premature contributions from the plantar flexors during stance, could be a negative indicator that proximal strength is being lost. This can be confirmed by determining the contributions from proximal groups, such as the gluteus maximus, to determine if this analysis is sensitive to an intervention.

This analysis also shows the muscles that are required to contribute the most towards center of mass acceleration during this particular pathological gait pattern. As such, maintaining strength and function in these muscles is of paramount important to preserve ambulatory ability and would be optimal targets for therapeutic interventions, powered orthoses or other accessibility devices.

Chapter 5. Validation of OpenSim for Analyzing Duchenne Muscular Dystrophy

5.1. Introduction

The modeling community has adopted the concepts of Verification, Validation, and Uncertainty Quantification (VVUQ) to rigorously assess the credibility of computational models. *Verification* is the process of determining that the computational model accurately solves the mathematical model, *validation* is the process of using experimental data to ensure that computational model accurately represents real-world process it simulates, and *uncertainty quantification* (UQ) is the process to determine the extent to which uncertainty in inputs to the computational model may affect the results of the model.[112,113] Many fields in the scientific community have adopted principles of VVUQ in the development and evaluation of computational models, such as cardiac modeling.[113] In particular, the American Society of Mechanical Engineers (ASME) has developed sets of standards for VVUQ for solid mechanics, fluid mechanics, and heat transfer models. These methods rigorously evaluate computational models, thereby providing strong support for their adoption in their respective fields.

The concepts of VVUQ have also been recently adopted by the general musculoskeletal modeling community and OpenSim in particular.[70] The modeling tools and algorithms of OpenSim have been previously verified.[62,66,67,111] Validation parameters and best practices for OpenSim have also been established, and include the comparison of simulation outputs, such as muscle activations, to experimental observations, such as electromyography.[70] With respect to the present study, Chapter 3 shows how the outputs of the model compare these recommended best practices. Results from the RRA module towards reducing residual forces were shown in Table 3-3, and results from the CMC module to find a solution without excessive use of reserve actuators were shown in Table 3-4. Quantification has been performed for OpenSim models by

determining that uncertainties in simulation inputs, such as marker placement, movement artifact, segment mass, and muscle model parameters, propagate through the workflow and can significantly alter the output of the model.[114]

This focus of this chapter will be to assess the results from the musculoskeletal simulations of pathological gait in boys with DMD. For verification, the residual reduction module will be assessed by showing that the recommended change in mass reduces the residuals calculated during the computed muscle control module. For validation, the muscle activations calculated by the computed muscle control module, which were discussed in Chapter 1.9, will be revisited. And for uncertainty quantification, a sensitivity analysis of OpenSim to possible sources of error from marker placement and ground reaction forces will be performed.

5.2. Methods

Two subjects that have been included in the previous chapters will be used for this analysis, one with DMD and one with typical development. Both participants were between 9 and 10 years old.

5.2.1. Uncertainty Quantification for Placement of Foot Markers

Increased plantar flexion was seen in both participants with DMD and may have been a compensatory mechanism. Errors in foot marker placement may affect joint angle, joint moment, and muscle force calculations. To test the downstream effects of possible marker placement error, the placement of the calcaneal and metatarsal markers was adjusted in Cortex. Myers et al 2015 found that the calcaneus and second metatarsal heads have placement errors with variability (+/- 2 SD) of 4.9mm and 6.3mm, respectively.[114] The Helen Hayes marker set is defined such that the heel and toe markers have the same vertical position when the foot is flat on the floor, i.e. at 0 degrees of plantar flexion during standing (assuming the tibia is vertical).

Based on the range of variability, the maximum theoretical vertical displacement would be 10mm between the heel and toe. As an exploration of the impact of this error, this range was increased to a possible different of 20mm. Thus, the five conditions were the original position of the heel and toe, a difference of +/-10mm and a difference of +/-20mm. The markers were adjusted such that the average vertical position between the two markers remained the same as the original trial. Joint kinematics and kinetics were calculated using Orthotrak. The resultant changes in joint angles were applied to the kinematic inputs for the CMC module in OpenSim. Changes in muscle length, force, and work as compared to foot marker position were determined.

5.2.2. Uncertainty Quantification for Ground Reaction Force Center of Pressure

Accurate ground reaction forces are required to accurately calculate joint moments and muscle forces. Discrepancies between marker position and ground reaction force data would cause kinetics to be calculated incorrectly. To determine the resulting changes to joint moments and muscle kinetics, the ground reaction force center of pressure was shifted with respect to the model. While technical improvements in force plate design have occurred over the past few decades, error in center of pressure measures may have been as large as 30mm.[115] Errors this large should occur with low probability, but this provides a good indication of the outermost bounds that one could expect. Thus, the center of pressure was shifted 10mm, 20mm, and 30mm in both the anterior and posterior directions. Joint moments were calculated in Orthotrak, and muscle forces, etc were calculated with OpenSim for each change in the ground reaction force.

5.3.Results

5.3.1. Effect on Sagittal Plane Angles and Moments

Adjustment of the calcaneal and metatarsal markers resulted in large systematic changes

to ankle angles and relatively no change to ankle moments over the gait cycle for both participants, which are shown in Figure 5-1. A 10mm discrepancy between heel and toe marker position resulted in a 3deg change in ankle angle over the gait cycle, and a 20mm discrepancy resulted in a 6deg change in ankle angle. A higher heel position (denoted by "heel +10mm"and "heel +20mm") resulted in increased plantar flexion, and a higher toe position (denoted by "toe +10mm" and "toe +20mm") resulted in increased dorsiflexion (or reduced plantar flexion). There was no change in ankle moment with foot marker adjustments. This was consistent for both participants.

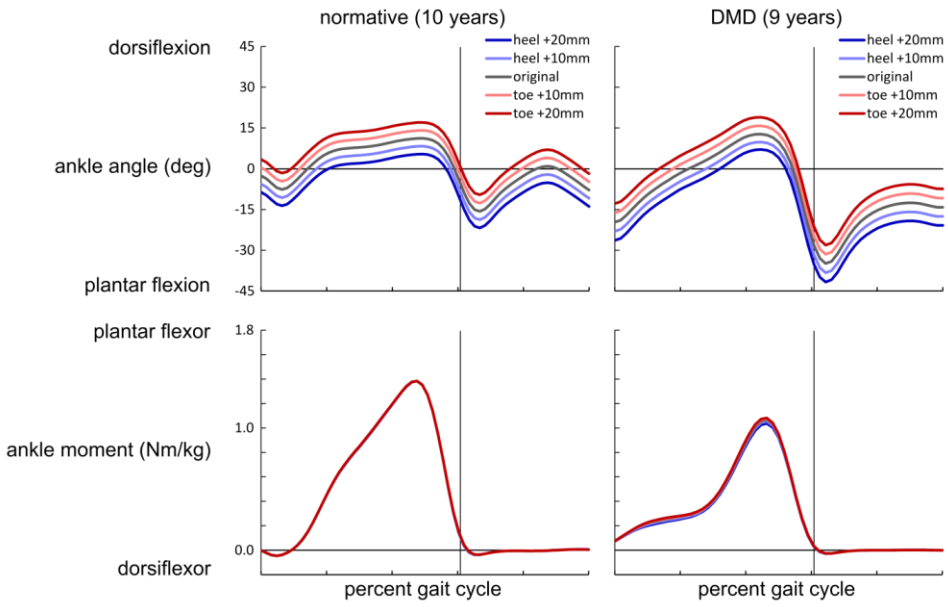

Figure 5-1: Effects of heel and toe marker position on sagittal plane ankle angles and moments. Sagittal plane ankle angles are shown in the top row, moments are shown in the bottom row. The normative participant is shown on the left, and the participant with DMD is shown on the right. Toe-off is indicated by the vertical line. Results from the original trial are shown in grey. Results from increasing the vertical position of the heel marker with respect to the toe marker are shown in shades of blue (light blue = +10mm, dark blue = +20mm). Results from increasing the vertical position of the toe marker with respect to the heel are shown in shades of red (light red = +10mm, dark red = +20mm).

Adjustments to the ground reaction force center of pressure resulted in systematic changes to hip, knee, and ankle moments for both participants, and are shown in Figure 5-2. The anterior shifts progressively increased hip extensor and ankle plantar flexor moments and progressively decreased knee extensor moments for each participant. The posterior shifts progressively increased knee extensor moments and decreased hip extensor and ankle plantar flexor moments for each participant.

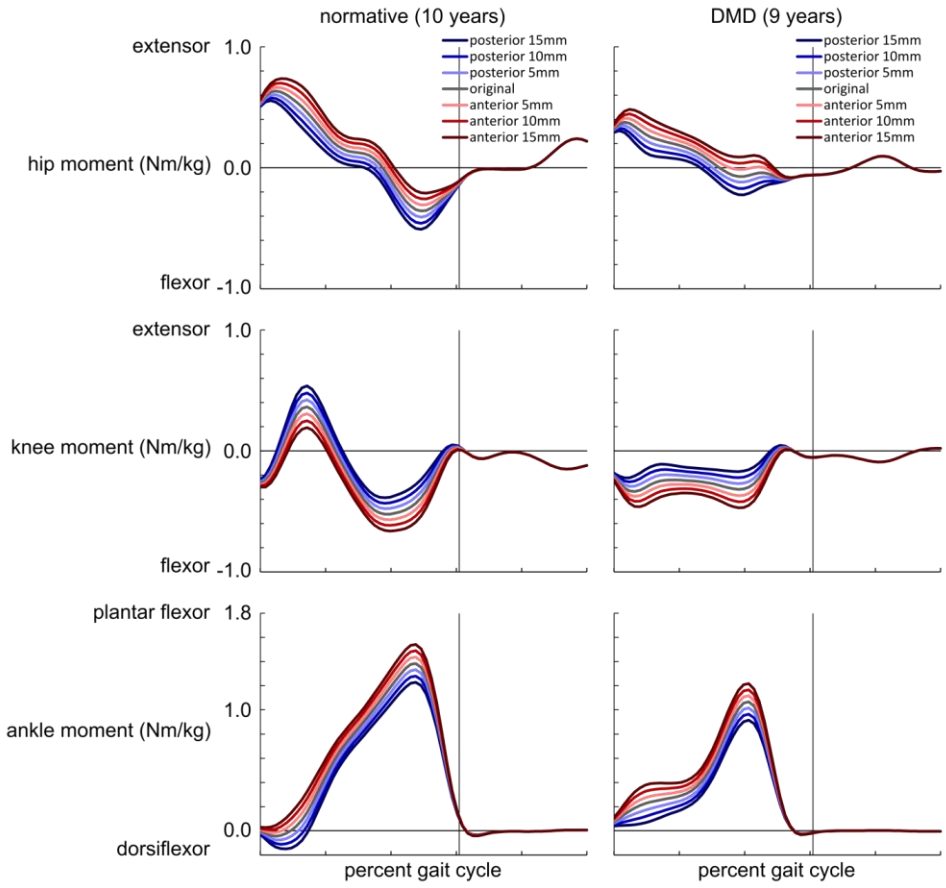

Figure 5-2: Effect of ground reaction force center of pressure on sagittal plane joint moments. Sagittal plane hip moments are shown in the top row, knee moments are shown in the middle row, and ankle moments are shown in the bottom row. The normative participant is shown on the left, and the participant with DMD is shown on the right. Toe-off is indicated by the vertical line. Results from the original trial are shown in grey. Results from altering the ground reaction force center of pressure in the posterior direction are shown in shades of blue (light blue = +5mm, blue = +10mm, dark blue = +15mm). Results from altering the ground reaction force center of pressure in the anterior direction are shown in shades of red (light red = +5mm, red = +10mm, dark red = +15mm).

5.3.2. Effect on Muscle Simulation

Changing the foot marker placement caused a change in ankle angle, which caused a change in fiber length for both participants, shown in Figure 5-3. The length of the plantar flexors decreased with increased plantar flexion and increased with increased dorsiflexion. The dorsiflexors showed the opposite response. Muscle activation and force generation were largely unchanged, shown in Figure 5-3. Normalized muscle work for each condition is shown in Figure 5-4. Increased plantar flexion showed increased work from gluteus medius and the triceps surae, and decreased work from the dorsiflexors and hamstrings. Increased dorsiflexion showed the reverse. The change in instantaneous length would alter normalized speed, which then would alter normalized work - acting at a longer length would decrease normalized speed, which would decrease normalized work, and is consistent with observations. The resultant average absolute percent change in muscle work for each condition is shown in Table 5-1. Given that the expected discrepancy of heel and toe marker placement should not exceed 10mm, we can conclude that the estimate in muscle work has approximately a 3% margin of error.

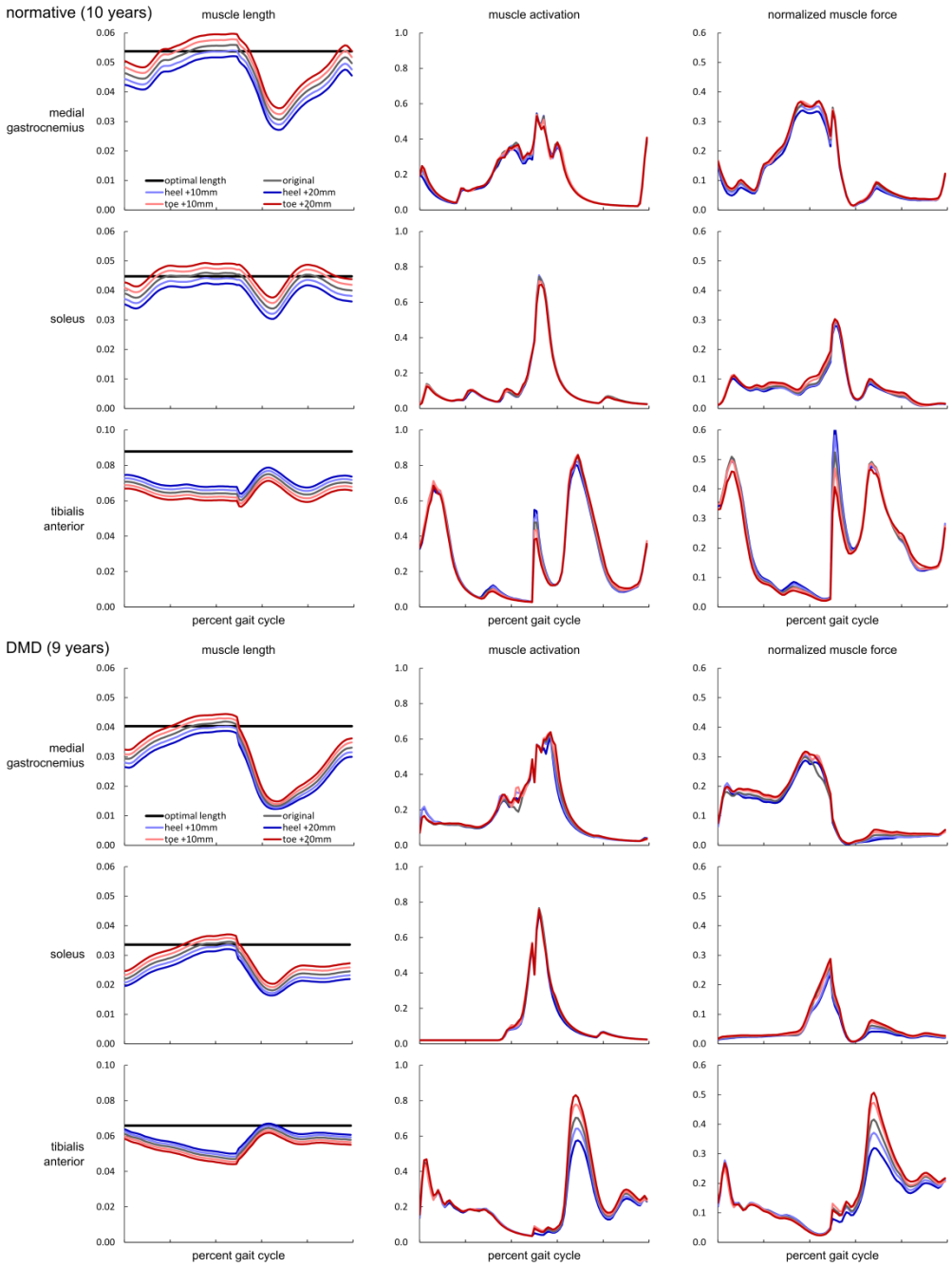

Figure 5-3: Effect of foot marker placement on ankle muscle simulation.
Muscle length is shown in the left column, activation is shown in the middle column, and normalized force is shown in the right column. Data from the normative participant is shown as the top three rows, and data from the participant with DMD is shown as the bottom three rows. Results from the original trial are shown in grey. For muscle length, the optimal fiber length is shown as the thick black line. Results from increasing the vertical position of the heel marker with respect to the toe marker are shown in shades of blue (light blue = +10mm, dark blue = +20mm). Results from increasing the vertical position of the toe marker with respect to the heel are shown in shades of red (light red = +10mm, dark red = +20mm).

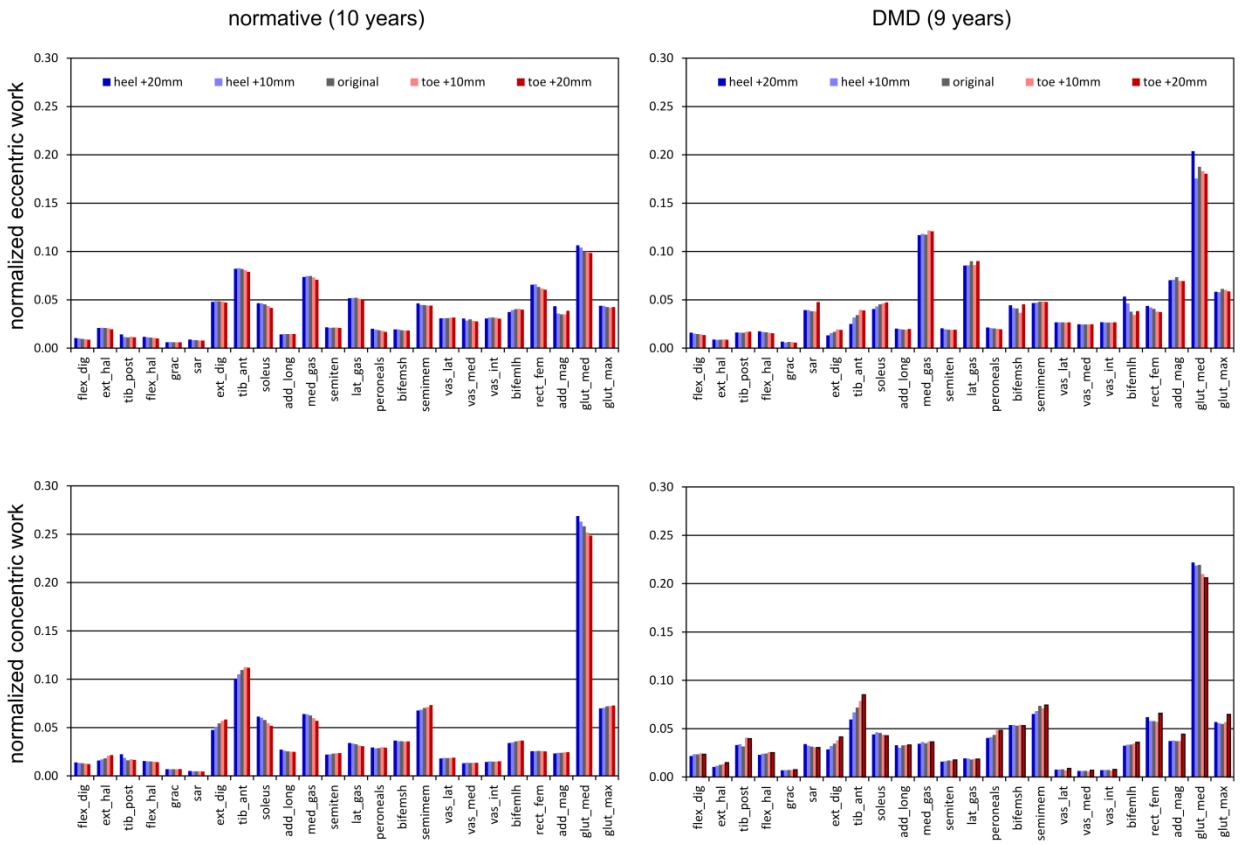

Figure 5-4: Effect of foot marker placement on eccentric and concentric muscle work. Normalized eccentric work is shown in the top row, and normalized concentric work is shown in the bottom row. Data from the normative participant is shown on the left, and data from the participant with DMD is shown on the right. Results from the original trial are shown in grey. Results from increasing the vertical position of the heel marker with respect to the toe marker are shown in shades of blue (light blue = +10mm, dark blue = +20mm). Results from increasing the vertical position of the toe marker with respect to the heel are shown in shades of red (light red = +10mm, dark red = +20mm).

Table 5-1: Average absolute percent change in muscle work due to foot marker placement.

Participant	Normalized Work	Heel +20mm (+6 deg PF)	Heel +10mm (+3 deg PF)	Toe +10mm (+3 deg DF)	Toe +20mm (+6 deg DF)
Normative	Eccentric	5.49%	2.27%	2.00%	4.03%
	Concentric	6.06%	3.00%	2.81%	4.26%
DMD	Eccentric	7.73%	4.12%	4.15%	5.48%
	Concentric	5.98%	3.45%	6.29%	8.64%

PF = plantar flexion; DF = dorsiflexion

Alterations to the ground reaction force center of pressure changed joint moments, and altered muscle forces. As shown in Figure 5-5, the posterior shift in the ground reaction force was associated with increased force generation from the rectus femoris, and reduced force generation from the gluteals, hamstrings, medial gastrocnemius, and tibialis anterior. Conversely, the anterior shift showed increased force generation from the gluteals, hamstrings, and triceps surae, and decreased force generation from the rectus femoris. Changes in normalized muscle work, shown in Figure 5-6, also followed this trend, with the posterior shift showing increased eccentric work in the rectus femoris, and to a lesser extent, the vasti, from both participants, and increased concentric work in the tibialis anterior, but only in the normative participant. The anterior shift showed increased eccentric and concentric work for nearly all muscles for both participants, in particular, the gluteals, hamstrings, and triceps surae. The resultant average absolute percent change in muscle work for each condition is shown in Table 5-2. The normative participant was much more resistant to changes in the ground reaction force center of pressure, with the extreme shifts resulting in average margins of error of 5-8%. The participant with DMD was more sensitive to shifts in the ground reaction force center of pressure, with the posterior shift causing a 7-12% change in work and anterior shift causing a 12-22% change in work.

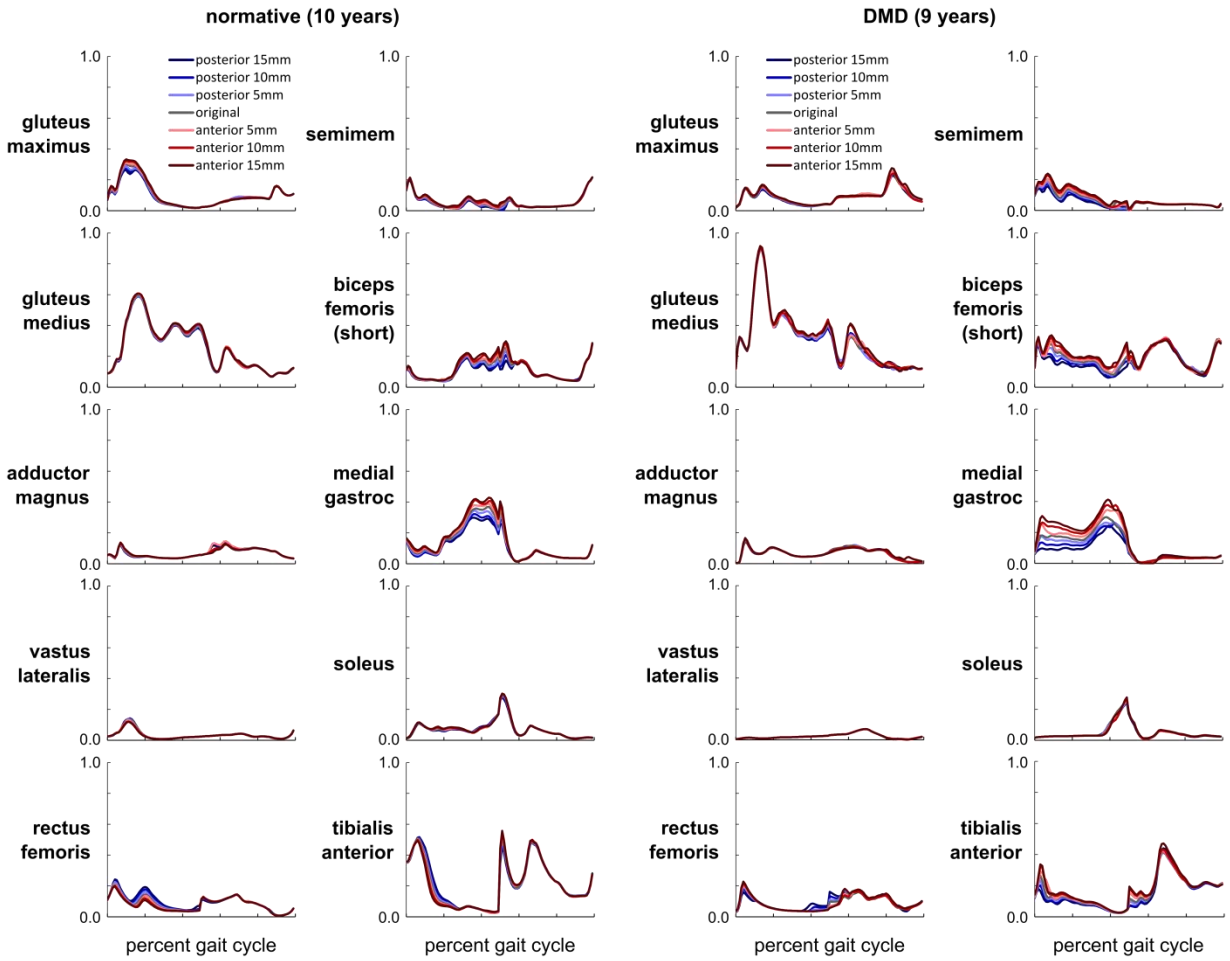

Figure 5-5: Effect of ground reaction force center of pressure on simulated muscle force generation.

Data from the normative participant are shown in the two columns on the left, and data from the participant with DMD are shown in the two columns on the right. Results from the original trial are shown in grey. Results from altering the ground reaction force center of pressure in the posterior direction are shown in shades of blue (light blue = +5mm, blue = +10mm, dark blue = +15mm). Results from altering the ground reaction force center of pressure in the anterior direction are shown in shades of red (light red = +5mm, red = +10mm, dark red = +15mm).

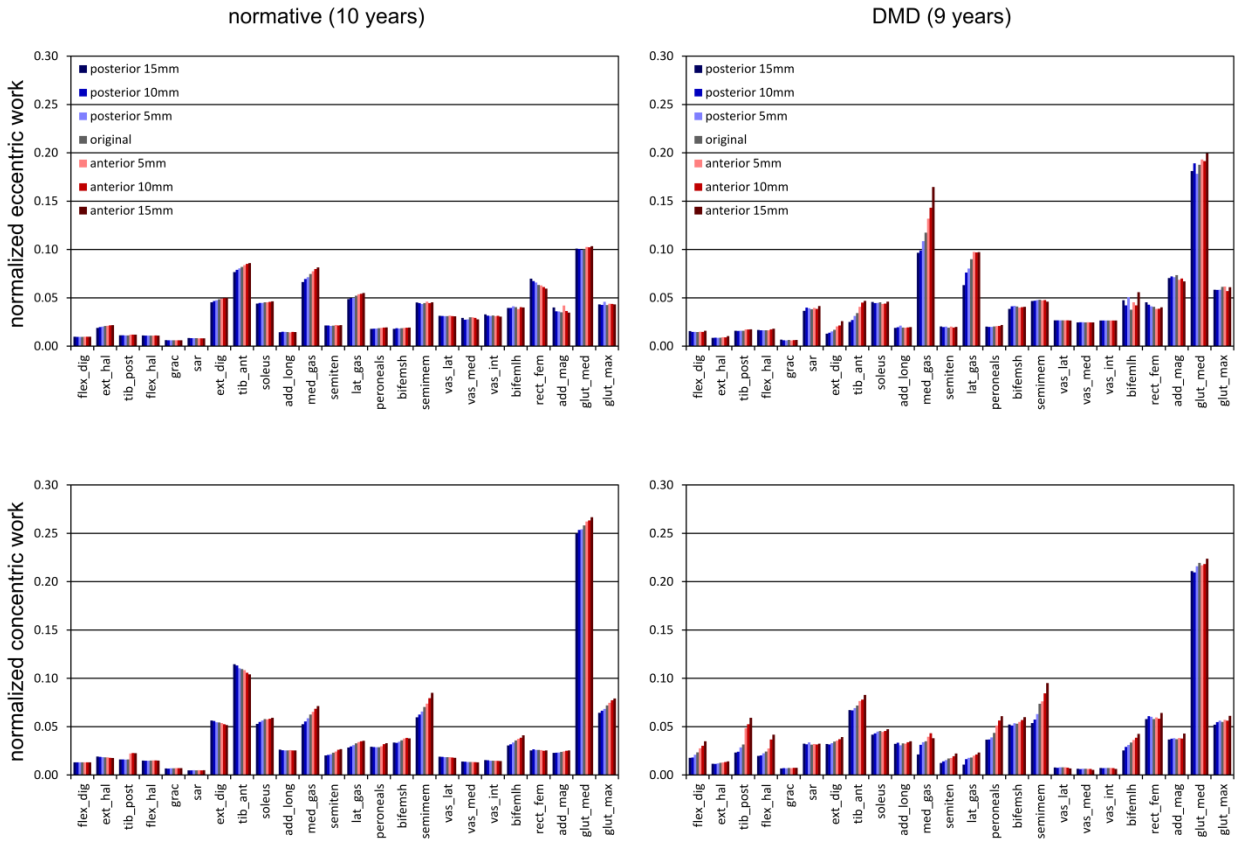

Figure 5-6: Effect of ground reaction force center of pressure on eccentric and concentric muscle work.

Normalized eccentric work is shown in the top row, and normalized concentric work is shown in the bottom row. Data from the normative participant is shown on the left, and data from the participant with DMD is shown on the right. Results from the original trial are shown in grey. Results from altering the ground reaction force center of pressure in the posterior direction are shown in shades of blue (light blue = +5mm, blue = +10mm, dark blue = +15mm). Results from altering the ground reaction force center of pressure in the anterior direction are shown in shades of red (light red = +5mm, red = +10mm, dark red = +15mm).

Table 5-2: Average absolute percent change in muscle work due to center of pressure shift.

		Posterior Shift			Anterior Shift		
Participant	Normalized Work	15mm	10mm	5mm	5mm	10mm	15mm
Normative	Eccentric	4.15%	2.30%	2.21%	2.87%	2.51%	3.27%
	Concentric	5.82%	4.39%	2.33%	3.90%	6.15%	7.86%
DMD	Eccentric	7.76%	4.88%	5.14%	5.88%	6.43%	11.74%
	Concentric	12.34%	8.92%	4.99%	7.37%	13.04%	22.12%

5.4. Discussion and Conclusion

The basic UQ analysis performed in this chapter has shown possible downstream effects of two potential sources of error that may arise during quantitative gait analysis. Discrepancies in foot marker placement were shown to primarily affect ankle kinematics, which, at a reasonable level of error, may cause approximately a 3% error in normalized work output. Alterations to the location of the center of pressure from ground reaction forces with respect to the model, were shown to affect the joint moments, muscle forces, and muscle work to a larger extent: for the normative model, a large discrepancy (15mm in either direction) may have caused up to 8% error in normalized work output, and for the DMD model, a large discrepancy may have caused up to a 22% error in normalized work output. At the very least, this shows the importance of accurate ground reaction forces and model position when performing these simulations.

The DMD model may have been more sensitive to shifts in the ground reaction force center of pressure due to the elevated demands of the compensatory gait pattern exhibited by the participant. As previously discussed, this strategy involves a shifting of the ground reaction force so that the vector is anterior to the ankle joint through increased plantar flexion and toe-walking. While this position is able to reduce the extensor demand about the knee and the hip, there is an increased plantar flexor demand on the ankle. Moving the vector further forward increases the lever arm for the ankle and hip, which increases the muscular demand for the ankle plantar flexors and hip extensors. However, since the knee is statically stabilized, there is no subsequent decrease in muscular demand. Thus, there is an unbalanced increase in work (as compared to the normative gait pattern, which showed decreased work from knee extensors with the anterior shift of the ground reaction force), which causes the increased error. The posterior shift has the opposite effect. However, since the knee is fully extended and the ground reaction force vector is

still anterior to the hip, knee, and ankle, there is no increase in knee extensor demand (a static flexor moment is still present). Thus, there is a direct reduction in hip and ankle extensor/plantar flexor work, but no increase in knee extensor work. Overall, since the adopted compensatory strategy effectively removes the necessity for knee extensor muscle force and work, the only changes that arise when the ground reaction force is altered are for hip extensors and ankle plantar flexors. The increased baseline (from the mechanically-demanding toe walking pattern) combined with unbalanced changes in muscular demand (minimized knee extensor forces) results high sensitivity of the simulation outputs to ground reaction force and model position data.

Chapter 6. Future Directions

6.1.Summary of Findings

Duchenne muscular dystrophy (DMD) is a fatally progressive X-linked genetic neuromuscular disorder that primarily affects males with a prevalence of 1 in 3500 live births and currently has no cure.[1] Clinical measures of disease progression have traditionally been qualitative grades of functional tests and quantitative measures of the time to complete these functional tests, for example, the NorthStar Ambulatory Assessment[32] or the 6-minute Walk Test.[107] In addition to traditional laboratory tests, such as creatine kinase, dystrophin staining, and genetic testing,[20] non-invasive measures through MRI and ultrasound have been able to qualify and quantify rates of muscle involvement.[14–18]

The purpose of this work has been to explore the use of quantitative gait analysis as a measure of disease progression in DMD. Gait analysis techniques have been used extensively in the diagnosis and assessment of other neuromuscular disorders,[48–50] but have been underutilized in examining improvements in function due to a therapeutic intervention program for boys with DMD. Therefore, the first area of exploration was in determining the clinical relevance of gait analysis for this population. This was addressed in Chapter 2, in which hip kinetics were shown to be sensitive to change after a corticosteroid intervention for a small non-randomized sample. A joint moment is a measure of the net force provided by muscles that span the joint; for the hip, the peak hip extensor moment is the peak demand placed on the hip extensor muscles. An inadequate peak hip extensor moment implies that a compensatory strategy has been adopted to reduce the demand on weakened hip extensor muscles. Since muscle involvement in DMD progresses from proximal to distal, even younger children should show deficits in hip kinetics and would therefore have the potential to improve with a therapeutic intervention. Even with the

relatively small sample, significant between-group differences were found, which provides evidence for the clinical relevance of quantitative gait analysis as an outcome measure for therapeutic trials. At the very least, this work has showed that quantitative gait analysis offers a more detailed method of measuring changes in function for this population that may otherwise go unnoticed.

Musculoskeletal modeling and simulation provides a framework for identifying the roles of individual muscles during human motion. Chapter 3 explored disparities in muscle involvement by calculating the eccentric and concentric work produced by individual muscles during pathological gait. The purpose of this exploration was twofold, the first to better understand the mechanical hypothesis of disease progression,[9] which may help to explain the mechanisms behind the proximal to distal pattern of involvement. Second, this work aimed to begin to establish links between gait analysis as a clinical measure and muscle imaging as a non-invasive laboratory measure. By using previously published fatty infiltration data[14–16] as the basis on which to rank the muscles of the lower extremities in terms of their rates of involvement, some general trends emerged from the data, although there were some exceptions. For normative gait, muscles that performed more eccentric work were those that had higher fat fraction ranks, especially in the larger extensor muscles. For DMD, increased involvement as determined by compensatory gait patterns, showed an overall decrease in both eccentric and concentric work. Furthermore, increased involvement was related to increased contributions of distal muscles, in terms of the percent of total work, as compared to proximal muscles. Exceptions to the general findings were present, which may indicative of the small sample size of two participants over four visits. Or, it may be indicative of additional factors that have not been taken into account, such as the rate of eccentric loading, other functional movements, and assumptions in modeling

parameters. Overall, however, this work has laid groundwork in establishing a relationship between muscle use during a functional task and eventual involvement during later stages of disease progression.

A powerful application of musculoskeletal modeling is the ability to go beyond the standard kinematics and kinetics from quantitative gait analysis to determine the effectiveness of individual muscles towards creating motion, especially during pathological gait with compensatory strategies. Chapter 4 explored the contributions of joint moments, muscle forces, and gravity to body mass center acceleration during pathological gait patterns through the use of Induced Acceleration Analysis (IAA). During the stance phase of gait, muscles of the stance limb share the responsibility to stabilize the stance limb, support the body center of mass, and provide forward propulsion. With DMD, as muscles weaken due to increased involvement, changes in kinematics and kinetics occur. For the participants shown in this work, this included reductions of hip extensor moments, a loss of the knee loading response, and an increase in ankle plantar flexor moments. These compensations increased the demand on less affected distal muscles about the ankle to compensate for weaker proximal muscles about the hip and knee by contributing more to the body center of mass support and propulsion. The increased demand on the triceps surae through increased plantar flexion during stance is a necessary compensation to maintain ambulation with weakness in the hip and knee extensors.

As with any mathematic model, the assumptions, limitations, and uncertainties of the model must be taken into account when interpreting the results. In Chapter 5, two possible sources of systematic error were explored to quantify the uncertainty for the modeling results. Alterations to foot marker placement caused changes to ankle kinematics and muscle lengths during gait, which resulted in an estimated error for muscle work of approximately 5%.

Alterations to the ground reaction force vector origin with respect to marker positions caused changes to hip, knee, and ankle moments, and resulted in estimated error for muscle work of approximately 3% for normal gait, and up to 12% for pathological gait. This exploration shows the ability for systematic errors in data collection to propagate and generate uncertainty in musculoskeletal simulations. While the magnitude of the applied alterations were quite large compared to the accepted estimates of these errors in practice,[114,115] this analysis shows that pathological gait may be more sensitive to these errors as compared to normative data. Therefore, great care must be taken to collect accurate data and in interpreting the results of musculoskeletal simulations.

6.2. Further Directions for Gait Analysis as an Outcome Measure

The results of Chapter 2 show that gait analysis may be useful as an outcome measure for randomized clinical trials based on the sensitivity to improvement from a corticosteroid intervention in the small sample. The 6-minute walk test, which was originally a measure for cardiopulmonary health and fitness in adults,[116] became standardized and adopted for DMD,[105,107] quantitative gait analysis can become standardized measure for randomized clinical trials. The current work was limited by the small, non-randomized sample size. This can be addressed by future randomized, double-blind studies with an increased number of participants that also incorporate currently-used outcome measures. Further study would be benefitted by evaluating the relationships between changes in traditional outcome measures, changes in spatial-temporal parameters and changes in the proposed primary outcome measures. This would determine if the current methods are more sensitive than traditional methods. Also, the relationship between baseline and follow-up values should be explored. This would be beneficial in two ways. First, it would provide clinically meaningful values to the change that should be

expected from another intervention as a function of the baseline value. Secondly, it could be used to indicate a treatment threshold for steroid intervention, and manage expectations for improvement depending on the level of disease progression when steroids are initiated.

6.3. Further Directions for Musculoskeletal Modeling and Duchenne Muscular Dystrophy

6.3.1. Relationship to Muscle Imaging

In the present work, relationships between muscle work during gait and fatty tissue infiltration had to be inferred from previously published data.[14–16] Therefore, the next steps would be to assess imaging and muscle work for the same participants. This would allow the direct comparison of two measures of disease progression and would limit the variability and uncertainty from using different populations with potentially different degrees of involvement.

6.3.2. Modeling Parameters

Previous studies have examined the impact of changing the maximum isometric force properties of the Hill-type muscle models in simulating weakness, and found that changing the maximum isometric force would either a) cause the muscle to be activated at a higher level or b) cause another muscle with a similar function to be activated more.[73,89,90] The "failure analysis" by van der Krogt et al shows the dependence of the model solutions on the maximum isometric strength parameter.[73] By systematically reducing this parameter in various muscle groups, such as the gluteus maximus, they were able to show how other muscles groups, such as the hamstrings, could increase activation and force production to compensate and maintain the same gait pattern. However, even though boys with DMD have muscle weakness that preferentially affects proximal muscles before distal muscles, changing muscle parameters could inadvertently change the solutions from the model. Therefore, to determine the impact of gait kinematics and ground reaction forces on muscle work and contribution to the center of mass acceleration, it

seemed appropriate to leave the maximum isometric force of individual muscles consistent among participants and visits. However, future study could perform a similar "failure analysis" to van der Krogt et al.[73] to determine if the compensatory gait patterns of boys with DMD are as susceptible to simulated weakness as normative gait patterns. This would also be able to test the hypothesis that the compensatory patterns become more mechanically passive in trying to find a balance between competing compensations for the hip and the knee.[37]

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