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DEFINING SAGITTAL PLANE GAIT MECHANICS AND JOINT LOADING IN PEOPLE WITH MARFAN SYNDROME

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DEFINING SAGITTAL PLANE GAIT MECHANICS AND JOINT LOADING IN PEOPLE WITH MARFAN SYNDROME

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Engineering
at the University of Kentucky

By

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2023

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ABSTRACT OF DISSERTATION

DEFINING SAGITTAL PLANE GAIT MECHANICS AND JOINT LOADING IN PEOPLE WITH MARFAN SYNDROME

Marfan syndrome (MFS) is a genetic condition that is associated with altered muscle composition, which leads to muscle dysfunction. People with MFS exhibit high instances of lower extremity (LE) joint pain that inhibits their ability to perform activities of daily living, such as walking. Despite these detrimental impacts of MFS, there have been no attempts to characterize the effects of MFS on LE joint loading and health during walking that are associated with LE pain and dysfunction. As people with MFS exhibit a high incidence rate of osteoarthritis (OA), the need to understand the potential alterations in LE extremity mechanics during gait that are associated with poor joint health in the MFS population is warranted. Therefore, the objective of this study was to investigate LE joint mechanics during walking in people with MFS.

We performed a cross-sectional assessment in people with MFS and healthy, asymptomatic controls, where sagittal plane LE joint mechanics were assessed during a fixed velocity gait task. Participants with MFS were required to have a confirmed case of MFS via genetic testing or qualification via the Ghent criterion and were cleared for exercise by our study physician. Following an extensive literature review, a sagittal plane traditional gait analysis and musculoskeletal (MSK) modeling were performed on people with MFS to assess lower extremity gait mechanics. For our traditional gait analysis, an assessment of peak lower extremity joint angles, peak joint moments, joint moment impulses, and joint moment durations was performed. In terms of MSK modeling, peak hip, knee and ankle muscle force production, muscle force impulse, joint contact force (JCF), JCF impulse, total LE joint loading (summation of the average LE JCF for each joint) and each joints contribution to total LE joint loading was assessed.

The results showed that people with MFS ambulated with more hip flexion, knee and ankle dorsiflexion, which places the LE in a more flexed position while walking. In turn, the more flexed LE places a larger demand on the hip and knee extensor and ankle plantarflexor musculature (i.e., higher joint moments) during the stance phase of gait in order to maintain LE stability and support. Participants with MFS also exhibited altered muscle force production and JCF loading patterns compared to healthy controls. Both traditional gait analysis and musculoskeletal modeling, demonstrate that people with MFS

ambulate with altered LE kinematics and moments, muscle force production and JCF patterns. The gait mechanics, muscle force production, and joint contact loading patterns described in this dissertation provides clinicians with preliminary information that may be used to develop gait-related interventions to improve LE joint function and health in people with MFS.

In conclusion, people with MFS exhibit similar gait mechanics as other populations that are predisposed to OA. These findings may be responsible for the high instances of early onset OA seen in the MFS community but will need to be investigated further in order to better understand the association between gait mechanics and joint health in the MFS population.

KEYWORDS: Marfan Syndrome, Gait Mechanics, Lower Extremity, OpenSim, Osteoarthritis, Joint Pain

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04/19/2023

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DEDICATION

To my dear wife, Krystal,
for supporting me with love, hard work, and dedication during my academic journey

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Although the following dissertation is an individual work, it benefited from, and most likely would not exist without the insights, direction, and support of several people. Firstly, my advisor, Dr. Michael Samaan, for granting me the opportunity to conduct this research and for his efforts to help me better understand my work. His dedication to not only high levels of research but mentoring his students is an inspiration. In addition, I would like to thank Walter Menke and Mariana Jacobs for assisting me in transitioning from an engineer into a biomechanist. Finally, I would like to thank my family and friends for believing in me, despite tough times, even when I was ready to give up.

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CHAPTER 1. BACKGROUND

1.1 MARFAN SYNDROME

Marfan Syndrome (MFS) is a connective tissue disorder caused by mutations in the fibrillin-1 (FBN-1) gene, which reduces FBN-1 production in the body. (Giske et al., 2003; Loeys et al., 2010; Nelson et al., 2015; Ramirez et al., 2018) This genetic abnormality is present in approximately 1-2:5000 people worldwide and impacts the structural integrity of muscle tissue. (Hasan et al., 2007; Nelson et al., 2015) FBN-1 is a major component in microfibrils, which ensures optimal structure of the extracellular matrix of connective tissue. (Aalders et al., 2020) This lack of structural integrity caused by decreased FBN-1 production on cardiac muscle tissue leads to aortic dilation and rupture in many people with MFS. (Aalders et al., 2020; Cavinato et al., 2021) Modern medicine and refined surgical techniques have led to improved treatment of aortic dilation and rupture in people with MFS and have extended the life expectancy of these individuals by over a decade. (Hasan et al., 2007) The improvements in treatments related to cardiac health in people with MFS has led to a growing interest of the impact MFS on the musculoskeletal (MSK) system. (Silverman et al., 1995)

Common effects of MFS on the MSK system are joint pain, muscle weakness, and early-onset osteoarthritis (OA). Previous literature has shown that 32 – 48% of people with MFS self-report lower extremity (LE) pain and exhibit decreased quadriceps and hamstring muscle strength. (Giske et al., 2003; Nelson et al., 2015; Percheron et al., 2007; Speed et al., 2017) This lower extremity pain is related to mechanical stress experienced during walking or exercise, and when combined with muscle weakness has been linked to decreased physical activity and higher levels of fatigue. (Speed et al., 2017; Voermans et al., 2009) Muscle weakness in people with MFS may be due to smaller and highly variable muscle fiber size as well as fatty infiltration of the muscle. (von Kodolitsch et al., 2019) Since the knee joint musculature is highly important for stabilization during the stance phase of gait, weakness in this musculature has been shown to cause compensatory activation from the trunk and other LE musculature. (Hewett & Myer, 2011) Muscle weakness and the potentially corresponding altered gait mechanics may lead to a higher

rate of joint degeneration in people with MFS. A study on the effects of aging on people with MFS showed a 4% higher incidence rate of OA (~9 years earlier on average) when compared to people without MFS. (Hasan et al., 2007) The combination of joint pain, muscle weakness, ease of fatigue, and early-onset OA plays a significant role in the quality of life (QOL) of people with MFS.

This longer life span allowed by modern medicine has left many people with MFS with increased time spent with joint pain and discomfort and has led to a higher awareness of the MSK-related effects of MFS on joint health and function. Despite 67% of people with MFS presenting with OA (Nelson et al., 2015), high instances of self-reported lower extremity joint pain, ease of fatigue, and decreased knee joint muscular strength, the effects of MFS on the MSK system during activities of daily living such as walking have yet to be studied. Assessing the potential differences between gait mechanics, muscle strength and patient reported outcomes of the MFS population and healthy individuals can lead to a better insight of the link between gait mechanics, muscle weakness and joint pain in the MFS population.

1.2 STUDYING PEOPLE WITH MARFAN SYNDROME USING BIOMECHANICAL METHODS

Understanding how people move during activities of daily living (ADL), such as walking, is a common method of quantifying the impacts of abnormal pathology on the human body due to the typical frequency of the task being performed. These in-vivo methodologies consist of both kinematic and kinetic measurements and allow for a assessment of the effects of abnormal pathology on joint mechanics. (Perry & Burnfield, 2010) Although these methods have been used to investigate similar pathologies, no studies have investigated gait mechanics in people with MFS.

MFS shares similarities with other connective tissue disorders such as Ehler's Danlos syndrome (EDS) and other pre-arthritic conditions such as femoroacetabular impingement syndrome (FAIS). The effects of FAIS and EDS on the MSK system during gait have been studied using kinematic and kinetic methods. (Robbins et al., 2020; Samaan et al., 2017; Spiker et al., 2021; Vermeulen et al., 2022) Although musculoskeletal

modeling is used in various pathologies to estimate physiological-based parameters (e.g. muscle and contact forces) that are difficult to measure in-vivo, musculoskeletal modeling has not been used to study the effects of connective tissue disorders (i.e. EDS or MFS) on the MSK system.

1.3 KINEMTAIC-BASED METHODS

Studies in patients with EDS and FAIS have used kinematic-based methods to analyze magnitudes of peak lower extremity joint angles (e.g., hip flexion/extension, knee flexion/extension, ankle plantar-/dorsiflexion) and range of motion (ROM). Prior work has shown that patients with EDS ambulate with higher ankle dorsiflexion and ankle eversion angles during the stance phase of gait compared to healthy individuals. (Vermeulen et al., 2022) Previous studies have also shown that patients with FAIS walk with higher ankle dorsiflexion, knee flexion, hip flexion, and knee valgus angles during the stance phase compared to asymptomatic controls. (Freemyer et al., 2021; Spiker et al., 2021) Overall, people exhibiting high instances of joint pain and early onset OA show significant differences in hip, knee, and ankle kinematics during the stance phase of gait when compared to healthy controls.

1.4 KINETIC-BASED METHODS

Kinetic measures utilize vertical ground reaction forces (vGRF) in conjunction with kinematic-based measures to perform inverse dynamics to better understand the loading applied to each joint (e.g., moments, impulse, and loading rates) during dynamic activity such as walking. Although no studies have analyzed any kinetic measures within EDS, this process has been thoroughly studied within the FAIS population. These studies have shown increased peak ankle dorsiflexor moment, increased hip flexor and ankle dorsiflexor impulse, and increased hip flexor and knee extensor moment durations in people with FAIS. (Samaan et al., 2017) Gait analysis studies within people with EDS have shown increased ankle eversion angle and decreased peak plantar flexor moment. (Galli et al., 2011; Vermeulen et al., 2022)This indicates that pre-arthritic populations exhibit altered lower extremity loading and duration of loading during gait.

1.5 EQUATIONS OF MOTION

In physics there are three classical mechanics methods of defining segment position in space: Newtonian equations of motion (EOM), Lagrangian EOM, and Hamiltonian EOM. All three methodologies will result in the same solution,

$$\ddot{\theta} = -\frac{g}{l}\sin\theta$$

when analyzing curvilinear motion in a system. Where θ and $\ddot{\theta}$ are angular position and angular acceleration, respectively, g is gravitational acceleration, and l is distance from the rotational point. However, each methodology has a different pathway of achieving this solution, presenting each with its' own set of benefits and drawbacks. Understanding each of these benefits and drawbacks can help give insight into an appropriate methodology to be used.

1.5.1 Newtonian

Newtonian EOM are derived from the application of Newton's laws of motion,

$$\sum \vec{F} = m\vec{\boldsymbol{a}}$$

and

$$\sum \vec{F} = \frac{\overrightarrow{dp}}{dt}.$$

Where $\vec{F}$ is the force vector, m is mass, $\vec{\boldsymbol{a}}$ is segment acceleration, and p is momentum. This method is computationally cheap as it utilizes vectors that programs such as MATLAB are designed to handle. Segment motion is described by force application and is constrained by these forces which makes it especially powerful for segment tracking in biomechanics where vGRF can be measured directly. The main disadvantage of utilizing Newtonian EOM are they cannot easily generalize to describe motion at high velocities or very small segment sizes.

1.5.2 Lagrangian

The Lagrangian method utilizes the Lagrangian (L) defined by the following equation,

$$L = K - U,$$

where K is the amount of kinetic energy in the system and U is the amount of potential energy in the system. This method describes motion in reference to energies in the system compared to the applied forces in the Newtonian method. The following Euler-Langrange equation ensures that this method still conserves momentum as seen in the Newtonian method:

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L}{\partial \dot{\theta}}\right) = \frac{\partial L}{\partial \theta}.$$

This methodology is preferred by some physicists due to its' straightforward method of deriving EOM without vectors and the ability to pick any starting coordinates without any constraining forces to describe the system. Another benefit of this methodology also works for smaller particles such as atoms in a system but does not work at high velocities. Though the Lagrangian method is a powerful tool for describing motion. However, it is ideally suited for analysis of relativistic theories and is computationally expensive as multiple derivatives need to be taken. Therefore, it may not be optimal for use in biomechanics.

1.5.3 Hamiltonian

The Hamiltonian method analyzes motion utilizing the total energy (H) in the system (sum of kinetic and potential energy),

$$H = K + U.$$

This method utilizes a pair of first-order differential equations, compared to the second-order seen in the Lagrangian method, to maintain conservation of momentum.

$$\dot{\theta} = \dot{p} = \frac{\partial H}{\partial p}, \dot{p} = -\frac{\partial H}{\partial \theta}$$

This difference allows for the assessment motion in a system described by angular position (θ) and momentum. This methodology works well for quantum assessments but doesn't work for high-speed analysis. The main limitation of this method is that all motion has to be first written in terms of momentum before an analysis can be performed.

1.5.4 Methodology Chosen

When accounting for each methodology and its' strengths and weaknesses, Newtonian EOM were chosen for this analysis. These EOM account for the GRF recorded in a biodynamics laboratory, while being mathematically simple enough to minimize calculation time. The downsides of Newtonian EOM also do not affect biomechanical calculations as we are analyzing body segments at a low angular velocity.

1.6 MUSCULOSKELETAL SIMULATION

Musculoskeletal simulations allow for the estimation of physiological parameters, such as muscle and joint contact forces, that are difficult to measure *in-vivo* during gait analysis. These MSK simulations use three-dimensional gait data and can be performed using open-source software such as OpenSim. (Delp et al., 2007) The OpenSim software has been used to study both normal and pathological gait patterns, (Delp et al., 2007; Samaan et al., 2019; Seth et al., 2018) squatting, (Imani Nejad et al., 2020; Lu et al., 2020) sidestep cutting, (Maniar et al., 2020; M. A. Samaan et al., 2016) etc. The OpenSim user network has grown tremendously over the past 15 years and includes a network of validated MSK models, algorithms and tools that are open-source to the OpenSim community. (Seth et al., 2018) Figure 1.1 shows the workflow that was utilized via OpenSim for MSK modeling.

Subject-specific models can be created by scaling default MSK models to match segment lengths and inertial properties. Inverse kinematic data can then be estimated to describe segment and joint positions during dynamic activity. In order to ensure dynamic consistency in these MSK simulations, errors caused by subtle inaccuracies during the calibration of the motion capture system, many users employ the residual reduction algorithm (RRA) (Kuo, 1998) within the OpenSim software. RRA minimizes the residual

external forces and moments applied during the MSK simulation when estimating the joint moments needed to accurately track segment and joint position during dynamic movement. In order to minimize the residual forces and moments applied to the MSK model, RRA applies weighting factors to each degree of freedom (DOF) of the MSK model. These weighting factors can be determined manually but there are open-source tools (Michael A. Samaan et al., 2016; Weinhandl et al., 2013) specifically developed for OpenSim that can be used to computationally determine the optimal weighting factors used by RRA to minimize the residual forces and moments on the MSK model. Upon completion of RRA, the user must determine whether or not the model's kinematic trajectory was tracked accurately (residual error). There are established guidelines and values for assessing whether or not the residual kinematic errors, forces and moments produced by RRA are within an acceptable range. (Hicks et al., 2015)

The RRA-adjusted joint kinematics and kinetics can then be used to predict the muscle activations and muscle forces needed to produce the joint kinematics and moments for each degree of freedom (DOF) of the MSK model through the motion being studied. Computed muscle control (CMC) uses a forward dynamics algorithm to estimate the corresponding muscle activations needed to generate the specific kinematic pattern being analyzed. (Thelen & Anderson, 2006) One benefit of CMC is that it includes the principles of co-contraction between agonist and antagonist muscles to predict muscle force activation and production during a task. (Thelen & Anderson, 2006) To ensure the accuracy of these muscle forces, surface electromyography (sEMG) is typically used to perform a qualitative comparison to the estimated muscle activations from CMC. (Hicks et al., 2015) CMC-estimated joint kinematics and muscle forces can then be used to determine the magnitude and direction of lower extremity joint contact forces (JCF) through the joint reaction analysis (JRA). (Steele et al., 2012) Musculoskeletal simulations are a computationally-based method to analyze gait-related data and can provide clinically relevant muscle- and joint-related information that can be used as targets in future interventions to improve gait patterns and joint pain exhibited by people with MFS.

1.7 RESEARCH GAP

Despite some prior work demonstrating lower extremity muscle weakness in people with MFS (Giske et al., 2003; Percheron et al., 2007), the impact of MFS on lower extremity joint mechanics, gait patterns, muscle force production, and joint loading is not well understood and has yet to be assessed in the MFS community. People with MFS self-report joint pain and fatigue during walking, (Nelson et al., 2015) yet the clinical community is not fully informed of the potential biomechanical and muscle-based factors that can be targeted in MFS-based interventions. (Peters et al., 2001) Therefore, investigating joint mechanics using the a combination of proven methodologies of classical biomechanics (kinematics and kinetics) and MSK modeling during gait in people with MFS would provide preliminary information needed by clinicians to begin to understand the potential targets for these future interventions that will reduce pain and improve overall function during walking in people with MFS.

1.8 DISSERTATION OBJECTIVES AND AIMS

The objective of this project was to understand how MFS affects LE joint function and mechanics during walking. The main hypothesis is that decreased peak knee joint musculature strength will significantly impact knee joint kinematics, kinetics, and loading which will lead to more systemic compensations to perform a self-optimized walking task. The aims of this study as the first step towards future prospective studies, were:

1) Investigate the effects of MFS on lower extremity gait. We hypothesized that due to weaker knee joint musculature, people with MFS will ambulate with altered lower extremity joint mechanics compared to asymptomatic controls.
2) Assess dynamic lower extremity muscle force production of people with MFS during walking. We hypothesized that during the stance phase there will be lower peak knee quadriceps and hamstring muscle force production that will be compensated by increased hip extensor and ankle plantarflexor muscle force production.
3) Examine the magnitude and distribution of joint contact forces across the entire lower extremity in people with MFS. We hypothesized that due to knee joint muscle

weakness, the MFS cohort will exhibit higher knee joint contact forces and in turn, lead to a larger contribution of the knee joint to the overall lower extremity joint loading.

1.9 ORGANIZATION OF THE DISSERTATION

The following chapters are outlined to address each of this dissertation's aims. Chapter 2 will focus on aim 1, investigating changes in sagittal plane hip, knee and ankle joint kinematics and kinetics during the stance phase of gait. Similarly, chapter 3 will focus on aim 2, assessing muscle force production in people with MFS compared to healthy controls. Chapter 4 will specifically speak to aim 3, which will assess lower extremity joint contact forces in people with MFS during walking. Chapter 5 will present a comprehensive discussion of this dissertation and discuss limitations and future work.

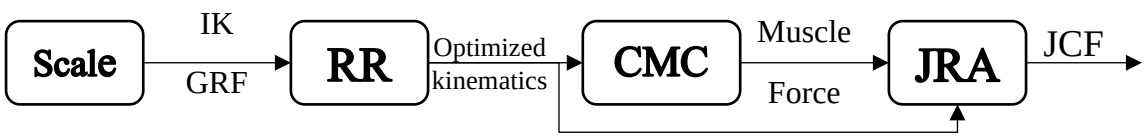

Figure 1.1:Visualization of workflow used in OpenSim to accurately predict muscle force production and joint contact forces.

CHAPTER 2. SAGITTAL PLANE LOWER EXTREMITY GAIT MECHANICS OF PEOPLE WITH MFS

2.1 INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder arising from mutations in the fibrillin-1 gene. (Giske et al., 2003; Loeys et al., 2010) Mutations in the FBN-1 gene reduce FBN-1 production, which has profound effects on muscle tissue composition and causes muscle dysfunction. (Hasan et al., 2007; Nelson et al., 2015) Previous research has focused on the potentially lethal impact of MFS on the cardiovascular system (Aalders et al., 2020; Cavinato et al., 2021; von Kodolitsch et al., 2019) but improved surgical techniques and modern medicine have significantly reduced adverse cardiovascular outcomes and has increased life expectancy in people with MFS (Hasan et al., 2007; Silverman et al., 1995). With this increase in life expectancy, the negative impact of MFS on the musculoskeletal system has become more apparent to the medical community.

Previous research has shown that people with MFS exhibit decreased knee joint muscular strength, high instances of lower extremity joint pain, and also exhibit signs of early onset OA at higher-than-normal incidence rates. (Giske et al., 2003; Hasan et al., 2007; Nelson et al., 2015; Percheron et al., 2007) Despite these findings, there have been no attempts to understand how MFS affects gait mechanics and the corresponding impact of gait mechanics on joint function and clinical outcomes in the MFS population.

Walking is among the most common activities of daily living, with the average person walking between 4-5 km daily. (Bassett et al., 2000) Prior work has used three-dimensional (3D) gait analysis to describe the effects of other connective tissue disorders on joint mechanics during walking. (Galli et al., 2011) More specifically, people with hypermobile Ehlers-Danlos Syndrome (EDS) walk with lower ankle dorsiflexion and a lower plantarflexor moment during terminal stance. (Galli et al., 2011) Prior work has shown that people with MFS exhibit weaker knee musculature compared to those without MFS yet the impact of muscle weakness on gait mechanics in the MFS population has yet to be investigated. The presence of altered gait mechanics may help to explain the high

incidence rate (67%) of early onset OA in people with MFS (Hasan et al., 2007; Nelson et al., 2015) and would provide clinicians with clinically relevant information that is needed to establish interventions that would mitigate joint disease in the MFS population. Therefore, the purpose of this study was to assess the effects of MFS on lower extremity joint kinematics and kinetics during walking. H_0: There is no relationship between lower extremity kinematics and kinetics in people with MFS compared to healthy controls. H_A: There will be a relationship between lower extremity kinematics and kinetics in people with MFS compared to healthy controls.

2.2 METHODS

2.2.1 Participants

This cross-sectional study tested 11 people with MFS (9 female; age = 39.7±11.7 yrs.; body mass index [BMI] = 27.2±5.15 kg/m^2) and 11 sex and BMI-matched heathy controls (9 female; age = 30.3±7.06 yrs.; BMI = 24.5±3.84 kg/m^2). All control data were part of a database built by our laboratory consisting of healthy, asymptomatic individuals from the local community. All participants with MFS referred to this study were diagnosed using either the Ghent Criteria (Loeys et al., 2010) or genetic testing and cleared for participation by our study physician. Study participants were excluded from this study if they exhibited: 1) prior lower extremity injury in the past 6 weeks; 2) prior surgery on the test limb; 3) prior diagnosis of rheumatoid arthritis or high blood pressure; 4) neurological or other lower extremity conditions that may affect movement; or 5) BMI > 35 kg/m^2. Subjects' test limbs were defined as the most symptomatic/painful limb for the MFS group (McLean et al., 2007) and the dominant limb for the control group. Our University's Institutional Review Board approved this study and all study participants provided written informed consent prior to any testing.

2.2.2 Gait Analysis

Three-dimensional segment position and ground reaction force (GRF) data were collected simultaneously at 250Hz and 1000Hz using a 14-camera motion capture system (Motion Analysis, Santa Rosa, CA), and 2 in-ground force plates (Bertec, Columbus, OH),

respectively (Figure 2.1). Forty-two (34 tracking markers, 8 calibration markers) passive retroreflective markers were used to obtain 3-D segment position data. Retroreflective markers were placed on the sternal notch, C7 vertebrae, and bilateral acromion processes to track position of the torso. Pelvic tracking was performed using markers placed on the anterior superior iliac spines, iliac crests, and posterior superior iliac spines. Retroreflective markers were placed bilaterally on the medial and lateral femoral epicondyles and malleoli and were used to determine knee and ankle joint centers, respectively. Rigid body clusters, consisting of 4 markers each, were also placed bilaterally on the lateral thighs and shanks. The foot segments were tracked using markers placed bilaterally on the heel shoe counter, first, second and fifth metatarsal heads. A 1-second static calibration trial was obtained, and then all calibration markers were removed. Each participant was then asked to perform 5 successful walking trials at a fixed speed of 1.35 $m \cdot s^{-1}$, the average level ground walking speed for males and females. (Perry & Burnfield, 2010) A trial was considered successful if the participant's entire foot of the test limb made a clean strike on one of the two force plates and their speed was within ±5% (0.7 $m \cdot s^{-1}$) of the target walking speed. Walking speed was measured using two sets of electronic timing gates (Brower Timing Systems, Draper, UT, USA). To minimize the effects of footwear, all participants performed their gait analysis with standardized sneakers (New Balance model MR662WSB, Boston, MA).

Raw marker position and GRF data were filtered using a fourth-order, low-pass Butterworth filter, with cut-off frequencies of 6Hz and 50Hz, respectively. The static calibration trial was used to create an 8-segment musculoskeletal model consisting of the trunk, pelvis, bilateral thighs, shanks, and feet in Visual3D (C-Motion, Germantown, MD). Local joint coordinate systems were created to describe segment position and orientation. (Spoor & Veldpaus, 1980) Joint angles were described using a Cardan sequence of X-Y'-Z'' and were normalized to the static calibration trial. Initial contact was defined as the time point where the vertical GRF exceeded 20 Newtons and toe-off was defined as the time point where vertical GRF dropped below 20 Newtons. Data were analyzed during the stance phase consisting of initial contact to toe-off and normalized to 101 points (0 – 100% stance). A custom MATLAB script was used to perform a sagittal plane gait analysis for the hip, knee, and ankle joints. The outcome measures included peak joint angles, joint ROM, peak internal joint moments, joint moment impulse, and joint moment impulse

duration during the stance phase. All joint moments were normalized by body mass ($Nm \cdot kg^{-1}$). Peak knee extensor and flexor moments were assessed during the first and second halves of the stance phase. In addition, we assessed the knee joint excursion, which was computed as the change in sagittal plane position of the knee joint from initial contact to peak knee flexion during the first half of stance (loading response). Joint moment impulses were calculated as the integral of a specific joint moment with respect to time ($Nm \cdot s \cdot kg^{-1}$). In our study, hip flexion, knee extension and ankle dorsiflexion angles and moments were considered positive.

2.2.3 Statistical Analysis

All demographic data were analyzed using independent t-tests. All data were tested for normality and homoscedasticity via Shapiro-Wilk and Levene's test, respectively. Group differences were assessed via an ANCOVA adjusting for age or Mann-Whitney U-test where applicable. All statistical analysis was performed in SPSS v29 (IBM, Armonk, NY). Statistical significance was defined as $\alpha=0.05$.

2.3 RESULTS

The MFS cohort was significantly older than the control cohort ($p=0.04$) (Table 2.1). People with MFS ambulated with a higher peak hip flexion angle ($p=0.02$), peak knee flexion angle during the first half of stance ($p=0.01$), and knee excursion during the first half of stance ($p=0.02$), as well as a higher peak ankle dorsiflexion angle ($p<0.001$) (Figure 2.2). No group differences were observed in the hip, knee, or ankle ROM ($p>0.05$) (Table 2.1).

The MFS cohort exhibited higher peak knee extensor moments during the first ($p=0.02$) and second halves ($p=0.03$) of stance, a lower peak knee flexor ($p=0.04$) moment during the first half of stance and a lower peak ankle dorsiflexor moment ($p<0.001$) compared to healthy controls (Figure 2.3). When compared to controls, people with MFS ambulate with a higher hip extensor moment impulse ($p=0.05$) and hip extensor impulse duration ($p=0.03$), a higher knee extensor moment impulse ($p=0.01$) and knee extensor

impulse duration (p=0.001), as well as a lower ankle dorsiflexor moment impulse (p=0.01) (Table 2.1).

2.4 DISCUSSION

Our study compared lower extremity joint mechanics during gait between people with MFS and asymptomatic, healthy individuals. Higher peak hip and knee flexion angles, larger knee excursion during loading response, as well as higher peak ankle dorsiflexion angles were observed in people with MFS during walking. Higher peak knee extension, lower peak knee flexion, and lower peak ankle dorsiflexion moments were exhibited by the MFS cohort during walking. In addition, the MFS cohort ambulated with higher hip and knee extensor joint moment impulses as well as lower ankle dorsiflexor joint moment impulses compared to the control cohort. These results suggest that people with MFS exhibit altered hip, knee and ankle joint kinematics and kinetics during walking. More specifically, our results indicate that people with MFS ambulate with a more flexed lower extremity, which places a higher demand on the hip and knee extensors to maintain an upright position during walking. These altered lower extremity joint mechanics during walking may help to explain the higher incidence rate of OA and joint pain in the MFS population yet further evaluation to understand the link between joint mechanics and joint degeneration in the MFS population is needed.

Our MFS cohort ambulated with higher peak hip flexion angles compared to the control group as well as a higher hip internal extensor moment impulse, which was driven by a significantly higher duration of the hip internal extensor moment despite a similar peak hip extensor moment as the control group. The higher internal hip extensor moment impulse suggests a larger demand on the hip extensor musculature to stabilize the more flexed hip joint present during walking in the MFS cohort. Prior work has shown that people with femoroacetabular impingement syndrome (FAIS), a pre-arthritic hip disease, ambulate with similar peak internal hip extensor moments yet a higher internal hip extensor moment impulse compared to asymptomatic controls and that a higher internal hip extensor moment impulse was associated with higher severity of hip joint cartilage damage and hip pain in patients with FAIS (Samaan et al., 2017). Prior work also demonstrated that patients

with hip OA ambulate with higher peak hip flexion angles compared to those without hip OA and that higher peak hip flexion angles were associated with higher severity of hip joint cartilage damage in those with hip OA. (Kumar et al., 2015) When considering our results and these prior studies (Kumar et al., 2015; Samaan et al., 2017), it can be suggested that the MFS cohort in our study may be exhibiting hip joint mechanics that are similar to patients with FAIS and hip OA and suggests that potentially detrimental hip joint mechanics may be placing people with MFS at a higher risk of hip joint degeneration and hip pain.

Compared to healthy individuals without MFS, people with MFS exhibit quadriceps and hamstrings muscle weakness. (Giske et al., 2003; Percheron et al., 2007) Similar to people who have underwent an anterior cruciate ligament reconstruction (ACLR) (Blackburn et al., 2016; Hart et al., 2016; Zeng et al., 2022), the MFS cohort in our study ambulated with a higher peak knee flexion angle and knee joint excursion during loading response, which may indicate quadriceps muscular dysfunction. This more flexed knee joint position observed in our MFS cohort may increase the muscular demand of the knee extensors in order to stabilize the knee joint during loading response. More specifically, the higher peak knee extensor moment and knee extensor moment impulse exhibited by the MFS cohort suggests a larger demand upon the quadriceps musculature to stabilize the knee joint during the stance phase of gait compared to asymptomatic controls. Prior work has demonstrated that a higher internal knee extensor moment and knee flexion angle during loading response was associated with worsening knee joint cartilage health in the ACLR population. (Teng et al., 2017) Similar to the ACLR population, our MFS cohort ambulate with higher knee flexion and a higher internal knee extensor moment impulse and suggests that these altered knee joint mechanics may be associated with a higher risk of knee joint cartilage degeneration in individuals with MFS.

The MFS cohort in our study demonstrated altered ankle joint mechanics during walking compared to the asymptomatic control group. More specifically, the MFS cohort walked with more ankle dorsiflexion, which may be due to the more flexed hip and knee joints observed in the MFS cohort during walking. Although MFS is a form of connective tissue disorder, our study results differ from those in the hypermobile EDS population

(another form of connective tissue disorder) which demonstrate that people with hypermobile EDS ambulate with significantly lower peak ankle dorsiflexion angles (i.e. more plantarflexion) compared to asymptomatic controls (Galli et al., 2011). This flexed lower extremity position during the first half of the stance phase exhibited by the MFS cohort, may be decreasing the overall demand on the ankle dorsiflexor musculature needed to stabilize the lower extremity and may help to explain the lower peak dorsiflexor moment and moment impulse observed in the MFS cohort. These abnormal ankle joint mechanics observed in people with MFS may be a compensatory mechanism to account for proximal joint muscle weakness and gait alterations yet the overall relationship of these altered ankle joint mechanics with potential joint degeneration in the MFS population is not well understood and requires further investigation.

There are a few limitations that should be considered when interpreting the results of our study. Firstly, over 80% of our subjects with MFS are female, which is not an accurate representation of the MFS population as prevalence of MFS is similar between males and females (Jimenez-Altayo et al., 2017). Our study did not assess muscle activations during walking and future gait assessments in the MFS population should incorporate electromyography to determine the impact of MFS on muscle activations during dynamic activity. Due to the cross-sectional nature of our study, we are unable to determine whether these altered joint mechanics observed in the MFS cohort are causative or compensatory in nature. Future work should incorporate both gait analysis and imaging in a prospective study approach to determine the impact of MFS on lower extremity joint function and health.

2.5 CONCLUSION

In conclusion, people with MFS ambulate with altered hip, knee, and ankle joint mechanics when compared to asymptomatic controls. These altered lower extremity joint mechanics in our MFS cohort are similar to the gait mechanics observed in people with hip and knee joint disease, suggesting that people with MFS exhibit gait mechanics that may be associated with joint degeneration. More specifically, our study indicates that altered gait mechanics may be associated with the prior notion that people with MFS are at a higher

risk of developing OA. In addition, our study provides the clinically relevant information needed to guide clinicians in developing gait-related interventions to optimize joint function and to mitigate joint degeneration in the MFS population.

Table 2.1: Results are reported as mean ± standard deviation for the control and Marfan Syndrome (MFS) groups. Positive joint angles and moments represent hip flexion, knee extension, and ankle dorsiflexion. * indicates statistical significance ($p<0.05$)

	Control	**MFS**	**p**
Demographics			
N	11 (9 F : 2 M)	11 (9 F : 2 M)	-
Age (years)	30.3 ± 7.06	39.7 ± 11.7	0.04*
BMI (kg·m-2)	24.5 ± 3.8	27.2 ± 5.15	0.21
Joint Angles (°) and Range of Motion (ROM; °)			
Peak Hip Extension	-10.3 ± 4.21	-7.91 ± 6.02	0.55
Peak Hip Flexion	26.7 ± 3.98	32.4 ± 4.92	0.02*
Peak Knee Extensor (1st half of stance)	0.75 ± 6.19	-4.75 ± 5.41	0.12
Peak Knee Extension (2nd half of stance)	-3.02 ± 3.54	-5.39 ± 6.11	0.40
Knee Flexion (Initial Contact)	0.37 ± 6.58	-5.50 ± 5.72	0.12
Peak Knee Flexion (1st half of stance)	-7.56 ± 6.40	-19.7 ± 8.42	0.01*
Knee Excursion	7.81 ± 4.82	14.2 ± 5.17	0.02*
Peak Ankle Dorsiflexion	10.24 ± 2.06	15.4 ± 3.13	0.001*
Peak Ankle Plantarflexion	-6.89 ± 3.16	-5.99 ± 3.74	0.84
Hip ROM	36.9 ± 4.86	40.3 ± 6.29	0.21
Knee ROM	42.4 ± 5.62	44.4 ± 5.96	0.71
Ankle ROM	23.4 ± 3.48	25.9 ± 4.86	0.35
Internal Net Joint Moment *(Nm·kg^{-1})*			
Peak Hip Extensor	-0.78 ± 0.23	-0.77 ± 0.24	0.22
Peak Hip Flexor	0.83 ± 0.18	0.71 ± 0.18	0.08
Peak Knee Extensor (1st half of stance)	0.39 ± 0.20	0.68 ± 0.26	0.02*
Peak Knee Flexor (1st half of stance)	-0.40 ± 0.13	-0.34 ±0.11	0.04*
Peak Knee Extensor (2nd half of stance)	0.16 ± 0.08	0.25 ± 0.11	0.03*
Peak Knee Flexor (2nd half of stance)	-0.24 ± 0.10	-0.14 ± 0.16	0.24
Peak Ankle Plantarflexor	-1.47 ± 0.11	-1.33 ± 0.28	0.11
Peak Ankle Dorsiflexor	0.28 ± 0.05	0.23 ± 0.07	< 0.001*
Joint Moment Impulses *(Nm·s·kg^{-1})*			
Hip Extensor	0.04 ± 0.01	0.08 ± 0.05	0.05*
Hip Flexor	0.23 ± 0.07	0.20 ± 0.09	0.19
Knee Extensor	0.08 ± 0.05	0.17 ± 0.08	0.01*
Knee Flexor	0.05 ± 0.03	0.04 ± 0.02	0.26
Ankle Plantarflexor	0.37 ± 0.05	0.36 ± 0.11	0.38
Ankle Dorsiflexor	0.04 ± 0.01	0.03 ± 0.02	0.01*
Joint Moment Durations (s)			
Hip Extensor	0.15 ± 0.06	0.26 ± 0.14	0.03*
Hip Flexor	0.53 ± 0.04	0.50 ± 0.11	0.65

Table 2.1 (Continued)

Knee Extensor	0.36 ± 0.12	0.54 ± 0.11	0.001*
Knee Flexor	0.32 ± 0.11	0.23 ± 0.10	0.11
Ankle Plantarflexor	0.49 ± 0.04	0.54 ± 0.07	0.06
Ankle Dorsiflexor	0.20 ± 0.03	0.23 ± 0.08	0.32

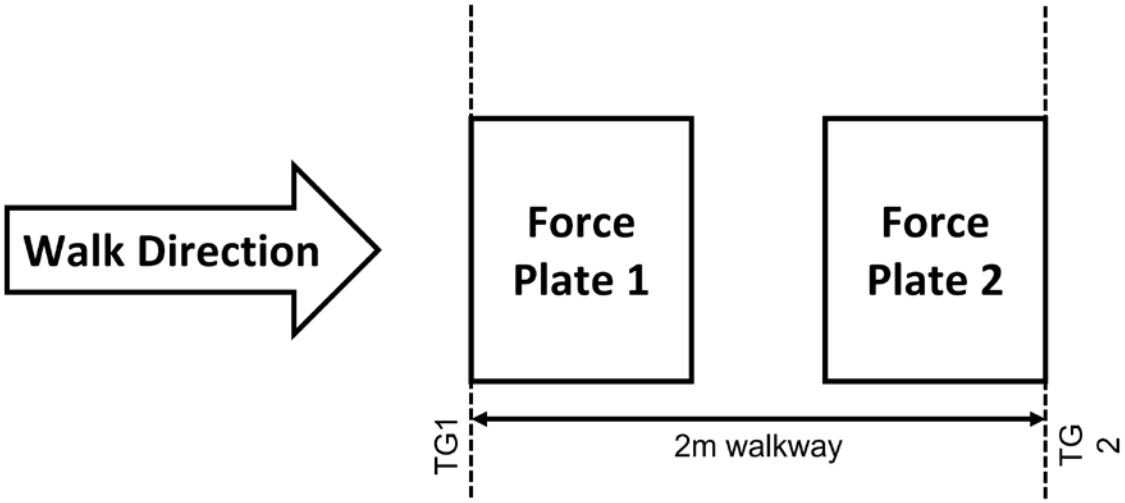

Figure 2.1:Schematic of 2m walkway for gait trials. Where TG1 and TG2 are timing gates 1 and 2, respectively.

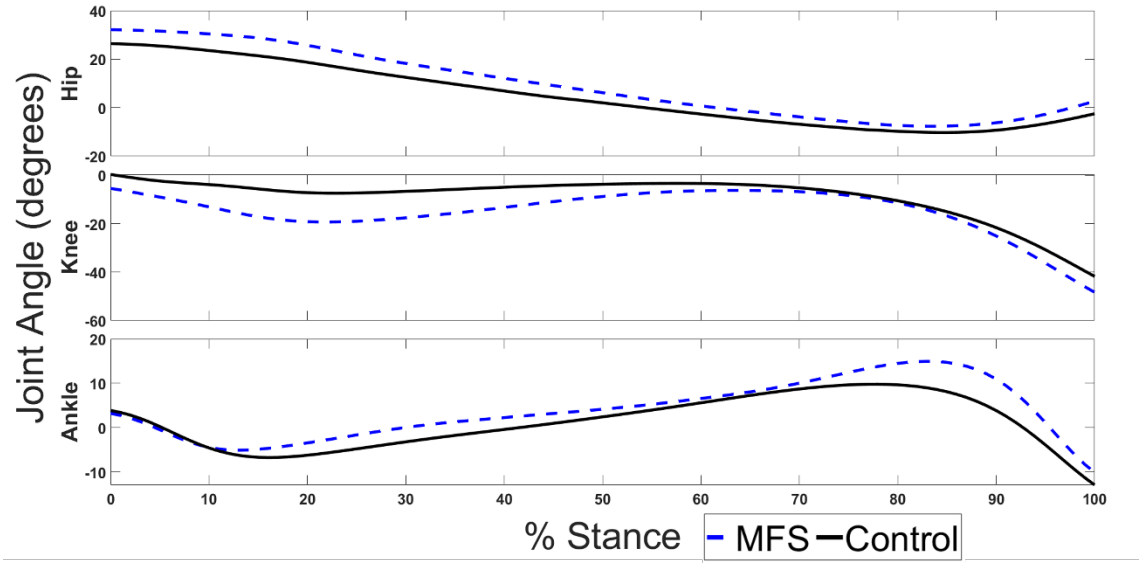

Figure 2.2: Joint angles in the sagittal plane during the stance phase of gait for the Marfan Syndrome (MFS), dashed line, and control cohort, solid line. Positive joint angles represent hip flexion, knee extension, and ankle dorsiflexion.

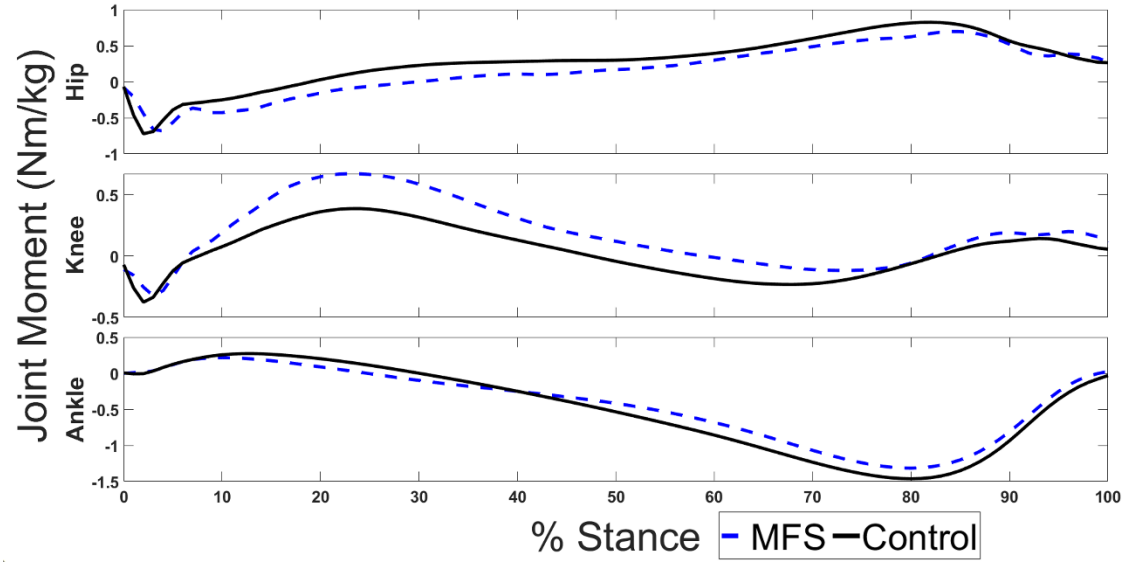

Figure 2.3: Joint moments in the sagittal plane during the stance phase of gait for the Marfan Syndrome (MFS), dashed line and control cohort, solid line. Positive internal moments represent hip flexion, knee extension, and ankle dorsiflexion moments.

CHAPTER 3. MUSCLE FORCE PRODUCTION DURING GAIT IN PEOPLE WITH MFS

3.1 INTRODUCTION

Marfan Syndrome (MFS) is an autosomal dominant connective tissue disorder characterized by mutations in the FBN-1 gene. (Peters et al., 2001) This gene mutation is linked to decreased FBN-1 production leading to decreased structural integrity of the muscle tissue. (Aalders et al., 2020) Previously, researchers focused on developing new surgical techniques and medication to prevent early-onset heart failure in people with MFS. (Aalders et al., 2020; Hasan et al., 2007; Silverman et al., 1995) Due to the implementation of these new techniques and medication, the life expectancy of people with MFS has increased by over 25% between 1972 and 1993. (Hasan et al., 2007) The increased life expectancy in people with MFS, has led to increased awareness of the impact of MFS on the musculoskeletal system. Compared to healthy individuals without MFS, people with MFS exhibit signs of early onset osteoarthritis (OA) at higher-than-normal incidence rates (Hasan et al., 2007), decreased knee joint muscular strength (Giske et al., 2003; Percheron et al., 2007), and high instances of joint pain (Nelson et al., 2015; Peters et al., 2001; Speed et al., 2017). Although these prior findings indicate detrimental clinical outcomes and significantly impact the quality of life in the MFS population, there have been no attempts to understand specific musculoskeletal impairments during dynamic tasks, such as walking, in people with MFS.

The average person walks approximately 4-5km daily (Bassett et al., 2000), making it one of the most common activities of daily living (ADL). Traditional gait analysis allows for the measurement of joint kinematics and moments during walking but is not able to directly assess physiological parameters, such as muscle force production during walking. Musculoskeletal (MSK) modeling allows for the estimation of muscle force production during dynamic activity and has been used to describe the effects of various degenerative joint diseases on lower extremity muscle force production during gait. (Boggess et al., 2018; Richards & Higginson, 2010; Samaan et al., 2019; Schroeder et al., 2022) Patients with femoroacetabular impingement syndrome (FAIS), a pre-arthritic hip disease, exhibit

lower vasti and higher sartorius muscle force production during walking compared to healthy, asymptomatic individuals (Samaan et al., 2019). Patients with prior anterior cruciate ligament reconstruction (ACLR) exhibit lower quadriceps and higher hamstring muscle forces during walking. (Boggess et al., 2018; Schroeder et al., 2022) Both the FAIS and ACLR populations are prone to early hip and knee joint degeneration, respectively, and the use of MSK modeling to understand muscle force production during gait helps to provide clinically relevant information as to the underlying musculoskeletal abnormalities that may be associated with poor joint health in these populations. Prior work in people with MFS, indicates approximately 40-50% weaker knee musculature than those without MFS. (Giske et al., 2003; Percheron et al., 2007) This knee joint muscle weakness would suggest that people with MFS would exhibit altered lower extremity knee joint muscle forces during walking. As people with MFS are at a higher-than-normal risk of developing OA (Hasan et al., 2007), there is a need to investigate the impact of MFS on lower extremity joint muscle function during walking. This information will help clinicians develop targeted muscle- and gait-related interventions to optimize joint function and mitigate joint disease in the MFS population.

To our knowledge, investigation of lower extremity muscle force production during walking in people with MFS has yet to be performed. Using MSK modeling in people with MFS will allow for an understanding of muscle force patterns during gait and will provide clinicians with the information needed to prescribe appropriate interventions to restore normal joint mechanics, reduce joint pain and preserve joint health. Therefore, the purpose of this study was to assess muscle force production in people with MFS during walking compared to healthy, asymptomatic individuals. H_0: There is no relationship between lower extremity muscle force production in people with MFS compared to healthy controls. H_A: There will be a relationship between lower extremity muscle force production in people with MFS compared to healthy controls

3.2 METHODS

3.2.1 Participants

This cross-sectional study consisted of 11 people with MFS (9 female; age = 39.7±11.7 yrs.; body mass index [BMI] = 27.2±5.15 kg/m^2) and 11 healthy, sex- and BMI-matched asymptomatic controls (9 female; age = 30.27±7.06 yrs.; body mass index [BMI] = 24.5±3.84 kg/m^2). Inclusionary criteria for this study were: 1) No lower extremity injury in the past 6 weeks; 2) No prior surgery on the test limb; 3) No prior diagnosis of rheumatoid arthritis or high blood pressure; 4) No neurological or other lower extremity conditions that may affect movement; or 5) BMI < 35 kg/m^2. The test limb was selected as the dominant limb (Borotikar et al., 2008) for the control cohort and the more symptomatic or painful limb for people with MFS.

3.2.2 Experimental data collection and processing

Three-dimensional segment position data were collected at 250Hz using a 14-camera motion capture system (Motion Analysis, Santa Rosa, CA) while ground reaction force (GRF) data were collected simultaneously at 1000Hz using two in-ground force plates (Bertec, Columbus, OH). A modified Cleveland Clinic marker set consisting of 42 retroreflective markers was used to collect segment position data. Calibration markers were placed bilaterally on the medial and lateral femoral epicondyles, medial and lateral malleoli, as well as the first metatarsal heads. Pelvic tracking was performed using markers placed on the anterior superior iliac spines, iliac crests, and posterior superior iliac spines. The thighs and shanks were tracked using rigid body clusters, consisting of 4 markers each, placed on the lateral aspect of each segment. A rigid foot model was used to track the position of both feet by placing markers on the heel shoe counters, second- and fifth-metatarsal heads. Trunk position was tracked using markers placed on the sternal notch, C7 vertebrae, and bilateral acromion processes. A one-second static calibration trial was obtained to determine the participant's neutral body position before all calibration markers were removed.

All participants were asked to perform 5 successful walking trials at a fixed speed of 1.35 $m \cdot s^{-1}$, the average level ground walking speed for males and females. (Perry & Burnfield, 2010) A trial was considered successful if the participant's entire foot made a clean strike on one of the force plates and their speed was within 5% of the expected fixed walking speed. Walking speed was measured using two sets of electronic timing gates (Brower Timing Systems, Draper, UT, USA). To minimize the effects of footwear, all participants performed their gait trials using standardized sneakers (New Balance model MR662WSB, Boston, MA). All raw marker and ground-reaction force data were filtered using a fourth-order Butterworth filter at 6Hz and 50Hz, respectively. (Samaan et al., 2019) An 8-segment kinematic model, consisting of a trunk, pelvis, bilateral thighs, shanks, and feet, was created using the participants' static calibration trial in Visual3D (C-Motion Inc., Germantown, MD). The joint centers for the hip, knee, and ankle were defined using the CODA pelvis (Bell et al., 1989; Bell et al., 1990), the midpoint between the medial and lateral femoral epicondyles, and the midpoint between the medial and lateral malleoli (Samaan et al., 2019), respectively.

Surface electromyography (sEMG) data were collected simultaneously at 1000Hz with the marker and GRF data using a wireless EMG system (Delsys Trigno, Natick, MA). For this study, electrodes were placed on the vastus medialis (VMED), vastus lateralis (VLAT), rectus femoris (RFEM), and gluteus medius (GMED) according to the Surface Electromyography for the Non-Invasive assessment of Muscles (SENIAM) guidelines (Hermens et al., 1999)

Each participant's skin around those specific muscles was shaved and cleaned with an isopropyl alcohol pad prior to electrode placement. After placing each electrode, a 5-second maximum voluntary isometric contraction (MVIC) was performed for the quadriceps and gluteus medius musculature. The quadriceps MVIC was conducted by placing the participant in a seated position and asking the participant to maximally extend their knee joint, while having the knee joint fixed at 90° of flexion and stabilizing the pelvis, using adjustable straps at the ankle and pelvis, respectively (Figure 1). The GMED MVIC was performed by asking the participant to perform maximal leg abduction while standing upright with the test limb fixed at a neutral position using an adjustable strap

attached to the ankle (Figure 1). The participant was provided with a walking pole to help maintain balance and was instructed to not apply any force through the pole. All dynamic and MVIC EMG data were processed by initially removing the DC bias from the signal, then applying a fourth order Butterworth, bandpass filter (20-500Hz), EMG data were then full-wave rectified, a fourth order low-pass filter (6Hz) was applied, and EMG data were full-wave rectified for a second time. All dynamic EMG data were then normalized by the respective peak MVIC values for that specific muscle.

3.2.3 Musculoskeletal modeling

The generic OpenSim Gait 2392 MSK model (Delp et al., 2007) consisting of eight segments, 19 degrees of freedom (DOF) and 92 musculotendon actuators was scaled using the anthropometric data obtained from the standing calibration trial, to create a subject specific MSK model for each study participant. This MSK model utilizes a 3 degree of freedom (DOF) ball and socket joint for the torso and hips, a 6-DOF (3 translational, 3 rotational) joint for the pelvis, and a 1-DOF hinge joint for the knees and ankles. The residual reduction algorithm (RRA) tool in OpenSim was utilized via an in-house custom MATLAB script that implements a numerical optimization algorithm to determine optimal task weights for each DOF and corresponding segment masses of the MSK model that reduce the residual forces and moments applied to the MSK simulation. (M. A. Samaan et al., 2016; Weinhandl et al., 2013) These residual forces and moments were normalized by body weight (%BW) and body weight multiplied by height (%BW·Ht), respectively, when assessing model validation. Computed muscle control (CMC) was used to estimate muscle forces needed to replicate model kinematics, while accounting for muscle activation dynamics. Evaluation of RRA performance was accomplished by utilizing previously published guidelines. (Hicks et al., 2015) In addition, qualitative comparison of experimental EMG data and estimated muscle activations from CMC (Figure 3.2) was performed to assess validation of the simulations. Peak muscle force magnitudes (normalized to BW) and muscle force impulses (BW·s) of the gluteus maximus (GMAX), gluteus medius (GMED), gluteus minimus (GMIN), adductors (ADD: summation of adductor magnus, brevis, and longus), piriformis, rectus femoris (RF), sartorius (SART), iliopsoas (summation of iliacus and psoas), vasti (VASTI: summation of vastus lateralis,

medialis and intermedius), tibialis anterior (TA), and hamstrings (HAM: summation of biceps femoris short and long heads, semitendinosus and semimembranosus) during the stance phase of gait were assessed. The stance phase was defined as initial contact (vertical GRF > 20 N) to toe-off.

3.2.4 Statistical analysis

Group differences in demographics were assessed using independent t-tests. All muscle force data were assessed for normality and homoscedasticity using the Shapiro-Wilks and Levene's test, respectively. Group differences in peak muscle forces were assessed using an ANCOVA (adjusting for age) or a Mann-Whitney U-test, where applicable. All statistical analysis was performed in SPSS v29 (IBM, Armonk, NY). Statistical significance was defined as $\alpha=0.05$.

3.3 RESULTS

There were no differences in sex or BMI ($p > 0.05$) (Table 3.1) between our co yet the MFS group was significantly older ($p=0.04$) than the control group. All MSK simulations closely followed our kinematic experimental data with root mean square (RMS) errors of less than 0.15 cm in pelvic medial/lateral translation, less than 0.4 cm in anterior/posterior translation, and less than 0.05 cm in superior/inferior translation, less than 0.11° of pelvic rotation, and less than 0.37° for the lower extremity joint angular positions. The RMS errors for the residual forces and moments were less than 0.02 BW and 0.02 BW*Ht, respectively. These RMS errors were within the published guidelines (Hicks et al., 2015), indicating that are simulations were reliable. Additionally, a good qualitative match was found between experimental EMG data and CMC estimated muscle activations (Figure 3.2).

People with MFS ambulate with higher GMIN ($p=0.05$), GMED ($p = 0.02$) and VASTI ($p = 0.002$) peak forces as well as lower TA ($p = 0.004$), HAM ($p = 0.02$), and Iliopsoas ($p = 0.03$) peak forces compared to controls (Figure 3.3). In addition, people with MFS ambulated with higher GMIN ($p = 0.004$), GMED ($p < 0.001$), VASTI ($p = 0.002$),

and GASTROC ($p = 0.006$) muscle force impulses, but lower iliopsoas ($p = 0.01$) and RFEM ($p = 0.004$) muscle force impulses compared to controls (Table 3.1).

3.4 DISCUSSION

This study compared muscle function during gait between people with MFS and asymptomatic controls. To the authors' knowledge, this is the first attempt to quantify muscle force production in people with MFS during dynamic activity. The MFS cohort exhibited higher GMIN, GMED, and VASTI peak forces yet lower TA, HAM, and Iliopsoas peak forces during gait compared to healthy controls. People with MFS also ambulated with higher GMIN, GMED, VASTI and GASTROC muscle force impulses yet lower iliopsoas and RFEM muscle force impulses. Although we are unable to determine whether these altered muscle force production patterns are compensatory in nature, our study results provide novel information and indicate that people with MFS ambulate with altered muscle function compared to asymptomatic, healthy controls. These altered muscle force patterns provide clinically relevant information that will help guide clinicians in developing muscle- and gait-related interventions to improve lower extremity joint function during walking in the MFS population.

During loading response, people with MFS utilize a higher GMED peak force to stabilize the hip joint compared to controls. Similarly, during terminal stance a higher GMIN peak force is observed while a lower peak iliopsoas force is observed in the MFS group. Similar patterns are observed in muscle force impulse, whereby the MFS group exhibited higher GMIN and GMED muscle force impulse yet lower iliopsoas and rectus femoris muscle force impulse compared to the control group. These alterations in iliopsoas and rectus femoris muscle force impulse may be attributable to an overall lower amount of muscle force production during the stance phase. These results suggest that there is a higher demand on the hip abductor musculature (GMIN and GMED) to support the hip joint and to compensate for lower overall force production by the iliopsoas and rectus femoris. In addition, these data may suggest that people with MFS utilize a more glute-dominant strategy for hip joint stabilization during the stance phase of gait yet the long-term impact

of higher gluteal muscle force production on hip joint health is not well understood and requires further investigation.

Previous literature on people with MFS demonstrated decreased knee joint muscle strength when compared to healthy controls (Giske et al., 2003; Percheron et al., 2007) yet these prior studies have not investigated the impact of MFS on muscle function during walking. Our study results demonstrate that people with MFS ambulate with higher VASTI and lower HAM peak muscle forces compared to asymptomatic, healthy individuals and may suggest that the MFS group utilize a quadriceps dominant compensatory strategy to stabilize the knee joint during gait. Lower peak quadricep and higher peak hamstring muscle forces have been observed in the ACLR cohort (Boggess et al., 2018; Schroeder et al., 2022) yet the MFS group in our study exhibits the opposite neuromuscular patterns during walking despite quadriceps weakness in both the ACLR (Patel et al., 2023) and MFS (Giske et al., 2003; Hasan et al., 2007)cohorts. These differences in quadriceps muscle function during walking between the ACLR and MFS populations may be attributed to the overall mechanism of quadriceps weakness in the ACLR (acute injury) and MFS (genetic connective tissue disorder) populations. People with MFS may develop this compensatory quadriceps force production mechanism in order to optimize function and maintain knee joint stability during walking. In addition, when compared to the control cohort, the MFS cohort exhibited higher VASTI impulses yet similar HAM impulses control groups in this study. The higher VASTI muscle force impulse may suggest that the MFS group employ a gait strategy that places a larger demand on the knee extensor musculature throughout the entire stance phase to further assist with lower extremity support. Both the peak VASTI and HAM muscle forces occur during loading response. The lower peak HAM force in the MFS cohort may be necessary in optimizing knee joint muscle co-contraction during loading response and to compensate for the higher peak VASTI force. Lower RFEM force impulse, but no difference in peak RFEM force suggests that people with MFS are utilizing the RFEM musculature for a shorter duration during the stance phase compared to controls. As the RFEM is a bi-articular muscle, the lower RFEM muscle force impulse in the MFS group may suggest an altered neuromuscular pattern to compensate for the higher VASTI muscle force impulse by lowering the overall demand on the RFEM muscle needed to provide knee joint support during the stance phase of

walking. In addition, as the MFS and control cohorts exhibited similar GMAX (primary hip extensor) muscle force production, these altered muscle force patterns exhibited by the knee joint musculature may be indicative of distal joint compensation to provide additional lower extremity support during walking.

Despite a lack of information on ankle joint muscle strength in the MFS population, the MFS group ambulated with lower TA peak muscle force during loading response as the control group and may suggest ankle dorsiflexor muscle dysfunction in the MFS group. In addition, the MFS group ambulated with similar peak GAST muscle force yet a higher GAST muscle force impulse as the control group. The higher GAST muscle force impulse may be due to an overall larger amount of GAST muscle force production during the entire stance phase and may be a compensatory strategy employed by the MFS group to counteract the lower TA muscle forces and to provide additional support at the ankle joint during walking. When considered in conjunction with the altered knee joint muscle force patterns, the MFS group may be utilizing a distal joint muscle-based gait strategy to compensate for potential hip joint muscle dysfunction or hip-related pain in order to maintain sufficient lower limb support to successfully accomplish the walking task.

There are some limitations that should be considered when interpreting the results of our study. Firstly, we utilized the default muscle properties within the Gait2392 musculoskeletal model and future work should utilize muscle properties that are more representative of the MFS population in order to provide a more accurate representation of the effects of MFS on muscle tissue composition and dynamic muscle function. The altered knee and ankle joint muscle force patterns exhibited by the MFS population may be due to a hip-related muscle dysfunction or hip-related pain avoidance mechanism, yet the walking task utilized in our study may not be demanding enough to fully elucidate this potential compensatory mechanism. Future work should utilize more demanding activities of daily living, such as a sit-to-stand task, to help elucidate and better understand the distal joint compensations exhibited by the MFS population during activities of daily living. Lastly, our MFS cohort consisted of 80% female participants which is not representative of the MFS population, as the prevalence of MFS is equal between sexes. (Jimenez-Altayo et al., 2017)

3.5 CONCLUSION

In conclusion, people with MFS walk with abnormal lower extremity muscle force production when compared to asymptomatic controls. The results of this study suggest that people with MFS potentially exhibit distal joint alterations in muscle force production in order to compensate for hip joint muscle dysfunction or hip-related pain. In addition, as people with MFS exhibit a higher incidence of OA compared to the healthy, asymptomatic population, these alterations in lower extremity muscle force production may be related to joint degeneration in MFS yet future work that combines gait analysis and imaging should be performed in order to assess the relationship between gait alterations and joint health in the MFS population. Our study highlights the alterations in lower extremity muscle force production during gait in the MFS population and provides clinicians with information to develop muscle- and gait-related interventions to optimize joint function and potentially mitigate joint disease within the MFS population.

Table 3.1: Participant demographics and muscle force measures for the control and Marfan syndrome cohorts are reported as mean ± standard deviation. * indicates statistical significance ($p<0.05$)

	Marfan	**Control**	**p**
Demographics			
N	11	11	-
Sex	9F | 2M	9F | 2M	-
Age (years)	39.7±11.7	30.3±7.06	0.04*
BMI (kg/m^2)	27.2±5.15	24.5±3.84	0.21
Peak Force (BW)			
GMIN	0.47 ± 0.09	0.32 ± 0.09	0.05*
GMED	1.56 ± 0.23	1.38 ± 0.23	0.02*
GMAX	0.87 ± 0.22	0.76 ± 0.22	0.17
Hamstrings	1.81 ± 0.44	1.98 ± 0.44	0.02*
Sartorius	0.12 ± 0.03	0.14 ± 0.03	0.51
Adductors	0.59 ± 0.15	0.54 ± 0.15	0.15
Iliopsoas	2.21 ± 0.35	2.53 ± 0.35	0.03*
Peri	0.41 ± 0.09	0.37 ± 0.09	0.52
Rectus Femoris	0.96 ± 0.30	1.15 ± 0.30	0.13
Vasti	1.05 ± 0.32	0.89 ± 0.32	0.001*
Gastrocnemius	3.61 ± 0.26	3.4 ± 0.26	0.18
TA	0.83 ± 0.16	1.06 ± 0.16	0.005*
Muscle Force Impulse (BW·s)			
GMIN	0.16 ± 0.02	0.11 ± 0.02	0.004*
GMED	0.71 ± 0.10	0.58 ± 0.10	< 0.001*
GMAX	0.22 ± 0.05	0.17 ± 0.05	0.26
Hamstrings	0.34 ± 0.03	0.32 ± 0.03	0.92
Sartorius	0.03 ± 0.01	0.042 ± 0.01	0.63
Adductors	0.09 ± 0.02	0.086 ± 0.021	0.10
Iliopsoas	0.55 ± 0.18	0.74 ± 0.18	0.01*
Peri	0.11 ± 0.03	0.11 ± 0.028	0.27
Rectus Femoris	0.28 ± 0.13	0.40 ± 0.13	0.004*
Vasti	0.20 ± 0.04	0.18 ± 0.04	0.002*
Gastrocnemius	1.05 ± 0.10	1.0 ± 0.26	0.006*
TA	0.17 ± 0.03	0.21 ± 0.03	0.43

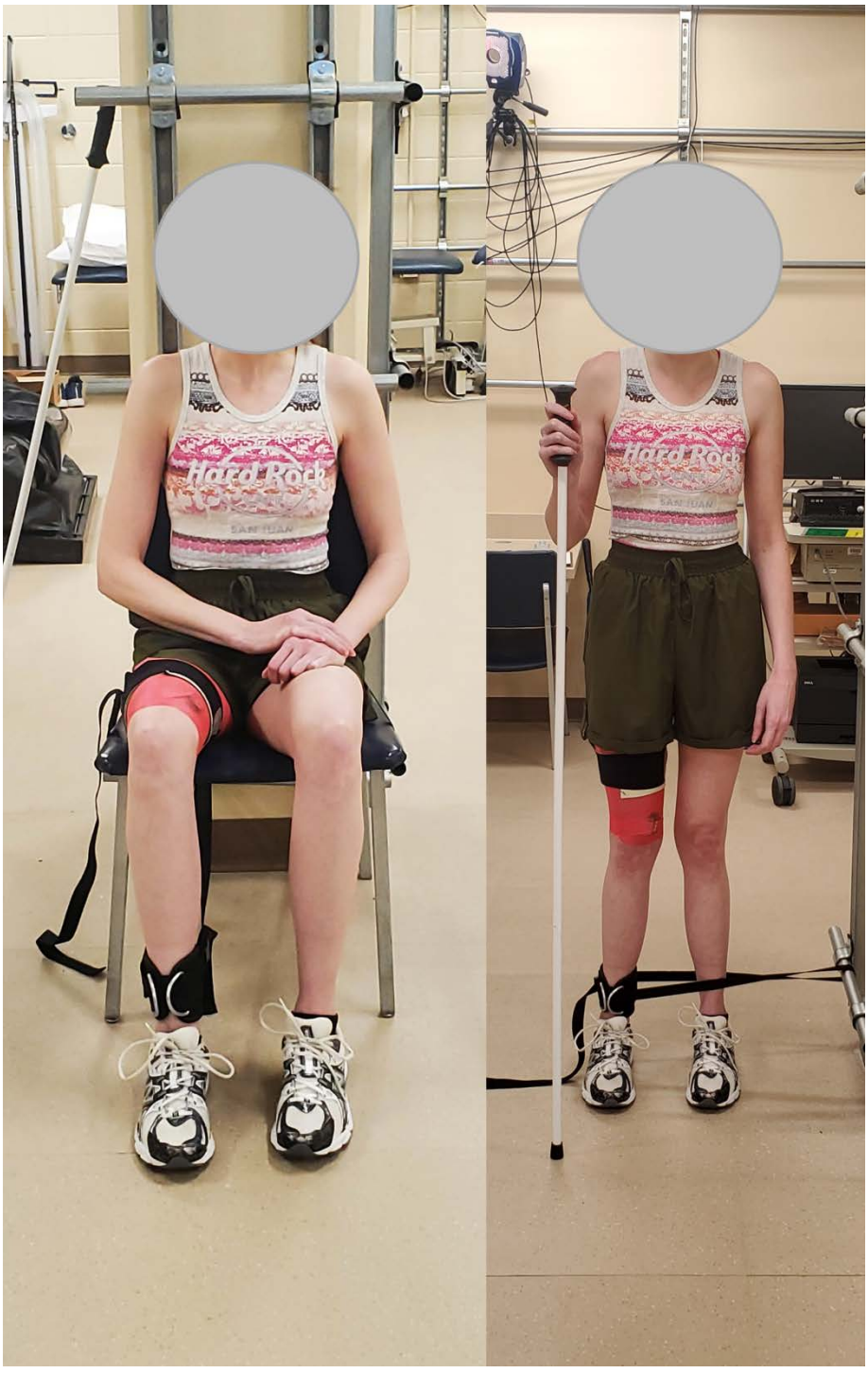

Figure 3.1: Testing procedure for collecting maximal voluntary isometric contractions (MVIC) for the quadriceps (left) and gluteus medius (right) musculature.

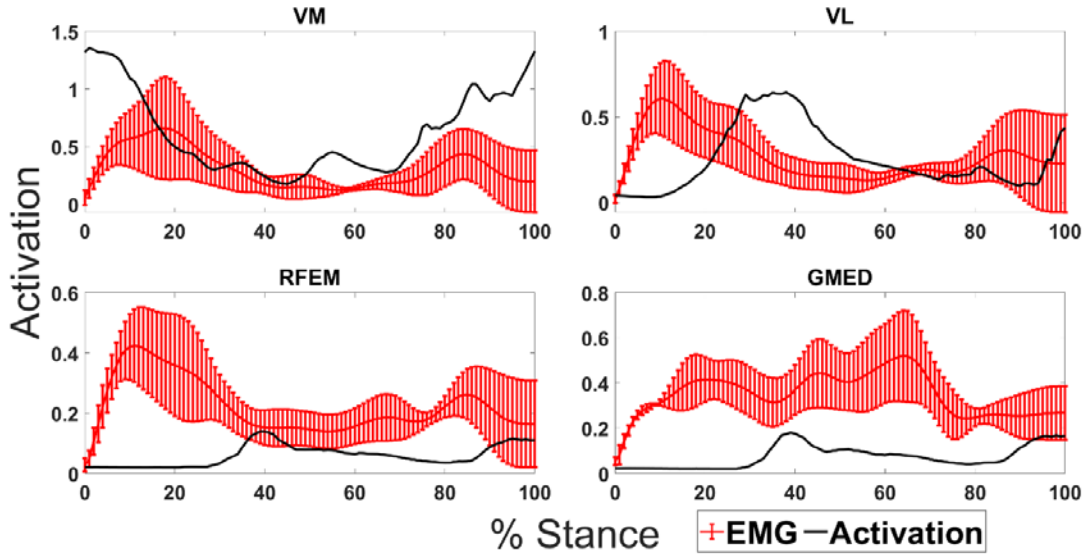

Figure 3.2: Average electromyography (EMG) signal and estimated muscle activation via computed muscle control (CMC) during walking for one participant with Marfan syndrome. EMG profiles represent ±1 standard deviation of the average for only one participant.

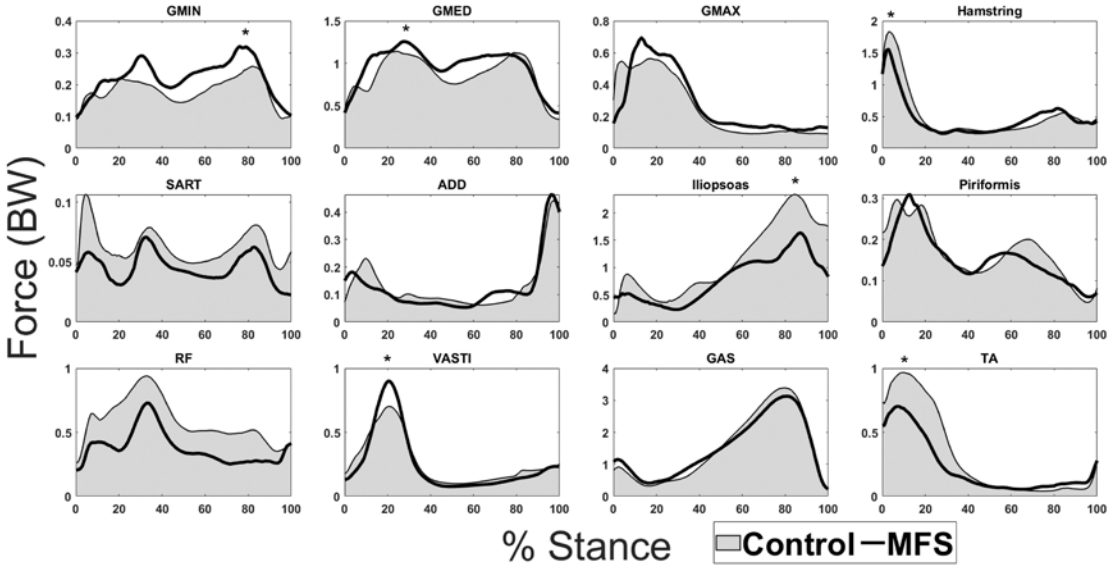

Figure 3.3: Muscle force production, normalized to body weight (BW), during the stance phase of gait for the control and Marfan syndrome (MFS) cohorts. Abbreviations: Gluteus Minimus (GMIN), Gluteus Medius (GMED), Gluteus Maximus (GMAX), Sartorius (SART), Adductors

CHAPTER 4. LOWER EXTREMITY JOINT REACTION ANALYSIS

4.1 INTRODUCTION

Marfan syndrome (MFS) is a heritable connective tissue disorder that affects the production of fibrillin-1 (FBN1) via alterations in the FBN1 gene (Peters et al., 2001). The decreased FBN-1 production in people with MFS drastically impacts muscle composition and correspondingly results in muscle dysfunction. (Aalders et al., 2020) Previously research on people with MFS has focused on the effects of MFS on cardiac muscle tissue due to the high instances of heart failure and aortic rupture. However, improvements in surgical techniques and modern medicine has provided people with MFS better cardiovascular-related outcomes, which has resulted in longer life expectancies but has made the negative impact of MFS on the musculoskeletal (MSK) more apparent. More specifically, people with MFS exhibit higher-than-normal instances of early onset osteoarthritis (OA) (Hasan et al., 2007), higher instances of lower extremity joint pain (Nelson et al., 2015; Peters et al., 2001; Speed et al., 2017), self-reported weakness (Voermans et al., 2009), and decreased knee joint muscular strength (Giske et al., 2003; Percheron et al., 2007). Despite these poor clinical outcomes, no prior work has been performed to understand the impact of MFS on lower extremity joint mechanics during activities of daily living (ADL) that may be associated with poor joint health and function.

One of the most common ADL is walking, with the average person walking 4-5km daily. (Bassett et al., 2000) Previous research on people with MFS has shown that people with MFS have approximately 50% weaker knee joint musculature compared to healthy controls. (Giske et al., 2003; Percheron et al., 2007) Previous work in hip OA and knee OA has utilized MSK modeling to determine abnormalities in the joint contact forces (JCF) produced during walking. Previous studies that assessed JCF in people with hip and knee OA demonstrated inconsistencies with the timing and magnitudes of differences in hip and knee JCF. Meireles et al. showed no differences in peak knee JCF during walking between healthy controls and established knee OA. (Meireles et al., 2016) However, another study demonstrated that when compared to healthy controls, people with hip or knee OA ambulate with lower ipsilateral hip JCF during loading response, midstance, and toe-off

yet these same hip and knee OA groups only demonstrated lower ipsilateral knee JCF during loading response. (Van Rossom et al., 2023) In addition, a prior study demonstrated that when compared to healthy controls, people with a recent anterior cruciate ligament (ACL) rupture ambulated with higher hip compressive JCF during loading response, higher knee compressive JCF during terminal stance as well as higher ankle compressive JCF at both loading response and terminal stance. (Aghdam et al., 2022) These previously defined alterations in hip, knee and ankle JCF during walking suggest that musculoskeletal injury and orthopedic disease impacts joint loading patterns in a diverse manner. This prior work in JCF-related alterations across these various populations may help us to understand the impact of MFS on lower extremity JCF.

To our knowledge assessment of lower extremity JCF patterns has yet to be performed in the MFS population. The use of MSK modeling in the MFS population will allow for a greater understanding of the impact of this connective tissue disorder on lower extremity JCF patterns during walking and the correspondingly high incidence rate of lower extremity joint pain (32 – 46%) and early onset OA (67%) within the MFS population. The findings from this study may provide clinicians with the necessary tools to prescribe appropriate interventions to restore normal joint loading, reduce joint pain and to mitigate cartilage tissue degradation in the MFS population. Therefore, the purpose of this study was to assess lower extremity JCF patterns in people with MFS during walking. We hypothesized that people with MFS would exhibit altered lower extremity JCF patterns during walking compared to healthy, asymptomatic controls. H_0: There is no relationship between lower extremity joint contact force production in people with MFS compared to healthy controls. H_A: There will be a relationship between lower extremity joint contact force production in people with MFS compared to healthy controls.

4.2 METHODS

4.2.1 Participants

This cross-sectional study tested 11 people with MFS (9 female; age = 39.7±11.7 yrs.; body mass index [BMI] = 27.2±5.15 kg/m^2) and 11 sex- and BMI-matched healthy, asymptomatic controls (9 female; age = 30.27±7.06 yrs.; BMI = 24.5±3.84 kg/m^2). The

healthy control data utilized in this study originated from our laboratory's healthy control database. All participants with MFS referred to this study were diagnosed using either the Ghent Criteria or genetic testing and were cleared for participation by our study physician. Inclusionary criteria for participants in this study were: 1) No lower extremity injury in the past 6 weeks; 2) No prior surgery on the test limb; 3) No prior diagnosis of rheumatoid arthritis or high blood pressure; 4) No neurological, spine, or other lower extremity conditions that may affect movement; and 5) BMI < 35 kg/m^2. The dominant limb [13] was selected as the test limb for the healthy control cohort while the more painful/symptomatic limb was tested for people with MFS.

4.2.2 3D Motion Capture

Three-dimensional segment position and ground reaction force (GRF) data were collected simultaneously at 250Hz and 1000Hz using a 14-camera motion capture system (Motion Analysis, Santa Rosa, CA), and 2 in-ground force plates (Bertec, Columbus, OH), respectively. Forty-two (34 tracking markers, 8 calibration makers) retroreflective markers were used to obtain the 3D position of each segment. The torso position was tracked using markers placed on the acromion processes, sternal notch, and C7 vertebrae. Pelvis segment tracking was performed using markers that were placed bilaterally on the iliac crests, anterior and posterior superior iliac spines. Calibration markers were placed bilaterally on the medial and lateral femoral epicondyles as well as the medial and lateral malleoli. Three-dimensional thigh and shank positions were tracked using rigid body clusters, consisting of 4 markers each and were placed bilaterally on the lateral aspect of the thighs and shanks. The feet were tracked using markers placed bilaterally on the heel shoe counter, first, second, and fifth metatarsal heads. A 1-second static calibration trial was obtained and then the calibration markers were removed.

Participants were asked to perform 5 successful overground walking trials at a fixed speed of 1.35 $m \cdot s^{-1}$, the average level ground walking speed for males and females. (Perry & Burnfield, 2010) A trial was considered successful if the participant's entire foot of the test limb made a clean strike on one of the two force plates and their speed was within ±5% (±0.7 $m \cdot s^{-1}$) of the target walking speed. Walking speed was measured using two sets of electronic timing gates (Brower Timing Systems, Draper, UT). To minimize the effects of

footwear, all participants performed their gait analysis with standardized sneakers (New Balance model MR662WSB, Boston, MA). Raw marker position and GRF data were filtered using a fourth-order low-pass Butterworth filter, with cut-off frequencies of 6Hz and 50Hz, respectively. The static calibration trial was used to create scaled MSK models for each participant and consisted of the trunk, pelvis, bilateral thighs, shanks, and feet in Visual3D (C-Motion, Germantown, MD). Lower extremity joint centers for the hip, knee, and ankle are defined from the CODA pelvis, the midpoint between the medial and lateral femoral epicondyles, and the midpoint between the medial and lateral malleoli, respectively.

Surface electromyography (sEMG) was collected simultaneously with the marker and GRF data using a wireless EMG system (Delsys Trigno, Natick, MA) at 1000Hz. To prepare the participants' skin for electrode placement, the skin was shaved and then cleaned with an isopropyl alcohol pad. Electrodes were placed on the vastus lateralis (VLAT), vastus medialis (VMED), rectus femoris (RFEM), and gluteus medius (GMED) according to the Surface Electromyography for the Non-Invasive assessment of Muscles (SENIAM) guidelines. (Hermens et al., 1999) After placing each electrode, a 5-second maximum voluntary isometric contraction (MVIC) was performed for the quadriceps and gluteus medius musculature. The quadriceps MVIC was conducted by placing the participant in a seated position and fixing the knee joint angle to 90°, by using an adjustable strap that was attached to the ankle joint and wall and stabilizing the pelvis using adjustable straps. The subject was then asked to extend the knee as hard as they can and hold for 5 seconds. The GMED MVIC was performed by asking the participant to stand upright while the lower extremity was fixed in a neutral position using an adjustable strap that was attached to the ankle joint and wall. The subject was then asked to abduct the hip maximally and hold for 5 seconds while using a walking pole to help maintain balance. Verbal encouragement was provided during both the MVICs to ensure maximal effort. All EMG data were processed by removing DC noise from the signal, then applying a fourth-order, Butterworth bandpass filter (20-500Hz), data was then full-wave rectified, low-pass filtered using a fourth-order, Butterworth filter with a cut-off frequency of 6Hz and data were then full-wave rectified.

4.2.3 Musculoskeletal Modeling

The default Gait 2392 musculoskeletal model (Gait 2392) in OpenSim consisting of eight segments, 19 degrees of freedom (DOF), and 92 musculotendon actuators (Delp et al., 2007) was used to create a subject-specific scaled model for each participant, using the anthropometric data obtained from the standing calibration trial. This model utilizes a 3-DOF ball and socket joint for the torso and hips, a 6-DOF (3 translational, 3 rotational) for the pelvis, and a 1-DOF hinge joint for the knees and ankles. An in-house custom MATLAB script, which implemented a numerical optimization algorithm, was used to systematically determine optimal task weights for each DOF and adjusted segment masses from the residual reduction algorithm (RRA) within OpenSim. (Michael A. Samaan et al., 2016) These optimized task weights and segment masses minimized the residual forces needed to maintain dynamic equilibrium of the MSK simulation in order to closely replicate our experimental gait data. Reduced residual forces from RRA were then normalized by body weight (%BW) and then multiplied by subject height (%BW·Ht). Computed muscle control (CMC) was used to estimate muscle force production needed to replicate experimental kinematics. Validation of our MSK model was done by following previously published guidelines for RRA performance and qualitative comparison of collected EMG data and estimated muscle activation from CMC. (Thelen & Anderson, 2006) Joint reaction analysis (JRA) (Steele et al., 2012) was then used to estimate the hip, knee and ankle JCF for the test limb and were normalized by body weight (BW). JRA estimates the corresponding JCF between 2 segments (e.g., femur and tibia) by accounting for both the external loads (i.e. gravity) and internal loads (i.e. muscle force) to provide a representation of the overall internal joint load. The magnitudes of the hip, knee, and ankle JCF were calculated by taking the square root of the sum of the squares of the JCF in each of the three directions. The stance phase of gait (initial contact to toe-off) was divided into two halves, initial contact to midstance (FH) and midstance to toe-off (SH). Initial contact was defined as the time point where the vertical GRF (vGRF) exceeds 20 Newtons. Midstance was defined as the time point where the minimum vGRF occurs between the two peak vGRF during the stance phase (Figure 4.1). We assessed the peak magnitudes of the hip, knee and ankle JCF as well as the total joint loading (TJL, summation of the

average hip, knee and ankle JCF magnitude) to assess joint loading across the entire lower extremity, each joint's contribution to the TJL (%; peak magnitude divided by total joint load for a specific joint) and JCF impulse (BW·s) during the FH and SH of the stance phase.

4.2.4 Statistical Analysis

Group differences in demographics were assessed using independent t-tests. All JCF-related data were assessed for normality and homoscedasticity using Shapiro-Wilks and Levine's test, respectively. Group differences in JCF-related data were assessed using an ANCOVA (adjusting for age) or a Mann-Whitney U-test, as needed. All statistical analyses were performed in SPSS v29 (IBM, Armonk, NY). Statistical significance was defined as $\alpha=0.05$.

4.3 RESULTS

There were no between group differences in sex or BMI ($p > 0.05$) (Table 4.1). However, our MFS cohort was significantly older ($p=0.04$) than the control cohort. All MSK simulations closely followed our kinematic experimental data with root mean square (RMS) errors of less than 0.15 cm in pelvic medial/lateral translation, less than 0.4 cm in anterior/posterior translation, and less than 0.05 cm in superior/inferior translation, less than 0.11° of pelvic rotation, and less than 0.37° for the lower extremity joint angular positions. The RMS errors for the residual forces and moments were less than 0.02 BW and 0.02 BW*Ht, respectively. These RMS errors were within the published guidelines (Hicks et al., 2015), indicating that are simulations were reliable. Additionally, a good qualitative match was found between experimental EMG data and CMC estimated muscle activations (Figure 4.2).

No between group differences ($p>0.05$) were observed in peak hip, knee, or ankle JCF during the FH (Table 1). During the SH, people with MFS walked with a lower peak hip JCF ($p=0.003$) yet similar peak knee and ankle JCF as the controls (Figure 4.3). The TJL during the FH was similar between the MFS and control groups ($p>0.05$). However, the TJL was lower in people with MFS during the SH ($p=0.03$) with correspondingly higher

ankle joint contributions (p=0.03) to TJL (Figure 4.4). In addition, people with MFS ambulated with higher hip (p=0.01), knee (p=0.02), and ankle (p=0.01) JCF impulse during the FH, as well as lower hip (p=0.03) and knee (p=0.05) JCF impulse during the SH.

4.4 DISCUSSION

In this study, we compared lower extremity JCF patterns during walking between people with MFS and asymptomatic, healthy controls. People with MFS ambulated with a lower peak magnitude of the hip JCF during the SH. Although TJL during the FH was similar between the MFS and control groups, the MFS group ambulated with a lower TJL during the SH with a corresponding higher ankle joint contribution to the TJL during the SH. In addition, the MFS group walked with higher hip, knee, and ankle JCF impulses during the FH yet lower hip and knee JCF impulses during the SH when compared to the control group. These altered lower extremity JCF patterns during walking may provide insight into the biomechanical alterations that may be associated with muscular dysfunction during dynamic activity in the MFS population and the corresponding higher incidence rate of OA within the MFS population.

Multiple studies on people with existing hip and knee OA, compared to healthy controls, show lower hip and knee contact forces during loading response and midstance. (Meireles et al., 2016; Van Rossom et al., 2023) However, people with ACL rupture exhibit higher hip JCF but no differences in knee or ankle JCF when compared to controls during walking. (Aghdam et al., 2022) Our MFS cohort however, displayed lower peak hip JCF in the second half of stance. Although prior work in the hip and knee OA populations demonstrate lower ipsilateral hip JCF during walking, these prior studies did not indicate whether or not the lower hip JCF occurred in the first or second half of stance. Prior work has shown that anterior hip JCF increases with increasing hip extension during walking (Lewis et al., 2010) and therefore, people with MFS may offload their hip joints particularly during the SH, when the hip joint begins to extend, in order to reduce hip joint pain during walking. Our study results help to elucidate the potential time frame within the gait cycle where people with MFS exhibit hip-related gait alterations and provide clinicians with a preliminary understanding of the potential biomechanical implications of MFS on gait.

People with MFS exhibit lower TJL during the SH, but no differences in overall TJL or contributions to the TJL during the FH when compared to controls. Although hip and knee joint contributions to the TJL during the SH were similar, the MFS group ambulated with a higher ankle joint contribution to the TJL during the SH. This suggests that people with MFS utilize similar JCF patterns during the first half of stance to stabilize the lower extremity but shift to a more ankle joint contribution during the SH to stabilize the lower extremity in order to potentially compensate for the lower peak hip JCF that leads to the overall lower TJL during the SH. More specifically, the MFS group may have adopted a biomechanical strategy to produce larger overall ankle joint forces during the SH in order to maintain dynamic equilibrium and to maintain lower extremity joint stability during the SH. These TJL-related outcomes further support that alterations in JCF patterns within the MFS population exist during the SH of stance.

Analyzing the time application of these JCF highlight some significant differences between people with MFS and controls. Although no between-group differences were seen in peak hip, knee and ankle JCF during the FH, people with MFS exhibited higher hip, knee, and ankle impulses during the FH compared to asymptomatic controls. Lower hip and knee JCF impulses yet similar ankle JCF impulse were observed during the SH in the MFS group compared to the control group. These suggest that people with MFS exhibited an increased duration of the JCF throughout the entire lower extremity during the FH and demonstrate a similar pattern of higher JCF duration for the hip and knee joints during the SH. One study comparing controls to people with early OA and established OA show higher JCF impulse in people with established OA, but similar JCF impulse in people with early OA when compared to controls. Prior work demonstrated that people with established knee OA ambulate with higher compressive hip (Aghdam et al., 2022) JCF compared to healthy controls. Similar to this prior study, the MFS group in our study ambulated with higher hip, knee and ankle JCF impulses during the FH of stance, which may lead to increased joint degeneration and help to explain the higher incidence rates of OA in the MFS population (Hasan et al., 2007). On the other hand, our MFS cohort walked with lower hip and knee JCF impulses during the SH which suggests an offloading-based mechanism in order to potentially reduce hip- and knee-related pain during the SH of stance. These JCF-impulse related data help to provide unique information that helps to

potentially describe the biomechanical alterations present in the MFS population during walking yet further work is required in order to understand the potential link between these altered loading patterns with joint pain and cartilage degradation in the MFS population.

There are some limitations that should be considered when interpreting the results of our study. Firstly, our model utilized the default muscle properties within the Gait2392 musculoskeletal model, and future work should utilize disease specific muscle properties in order to provide a more accurate representation of the effects of MFS on muscle tissue composition and dynamic muscle function. The altered ankle and knee joint contact forces exhibited by people with MFS may be driven by a hip-related pain avoidance mechanism, but the walking task studied may not be demanding enough to highlight this potential compensatory mechanism. Future work should utilize more demanding activities of daily living, such as a sit-to-stand task, to help elucidate and better understand the distal joint compensations exhibited by the MFS population during activities of daily living. Lastly, our MFS cohort consisted of 80% female participants which is not representative of the MFS population, as the prevalence of MFS is equal between sexes. (Jimenez-Altayo et al., 2017)

4.5 CONCLUSION

In conclusion, people with MFS ambulate with altered lower extremity joint contact forces when compared to healthy, asymptomatic controls. These altered JCF patterns were primarily observed during the SH yet alterations in time dependent joint loading (i.e., JCF impulse) was evident during the FH. Our results suggest that people with MFS are potentially loading their entire lower extremity for a longer duration of time during the FH yet loading their hip and knee joints for a longer duration of time during the SH. In addition, people with MFS minimize their peak hip JCF, which leads to a lower TJL yet a larger ankle joint contribution to the TJL in order to maintain lower extremity stability during the SH. Future work that combines joint imaging with JCF analysis will provide further insight into the loading characteristics and potential corresponding mechanisms of joint disease in people with MFS. Our study findings may provide clinicians with a more comprehensive understanding of the impact of MFS on lower extremity joint loading patterns during

walking and will help clinicians develop muscle and gait related interventions to mitigate joint disease and optimize joint function.

Table 4.1: Results are reported as mean ± standard deviation for the control and Marfan Syndrome (MFS) groups during the first (FH) and second (SH) halves of the stance phase. * indicates statistical significance ($p<0.05$)

	Marfan	**Control**	**p**
Demographics			
N	11	11	-
Sex	9F | 2M	9F | 2M	-
Age (years)	39.7±11.7	30.3±7.06	0.04*
BMI (kg/m^2)	27.2±5.15	24.5±3.84	0.21
Peak Joint Contact Force (BW)			
Hip FH	4.8 ± 1.27	5.1 ± 1.2	0.18
Knee FH	3.4 ± 0.9	4.1 ± 0.7	0.07
Ankle FH	3.3 ± 1.3	3.0 ± 0.5	0.77
Hip SH	4.1 ± 0.8	5.1 ± 0.6	0.003*
Knee SH	4.0 ± 0.9	4.1 ± 0.6	0.30
Ankle SH	4.9 ± 1.2	4.8 ± 0.3	0.62
Joint Loading (BW)			
Total Joint Loading FH	8.1 ± 1.6	9.0 ± 1.2	0.14
Total Joint Loading SH	9.5 ± 1.5	10.2 ± 0.9	0.03*
Hip Contribution FH	41.0 ± 4.3	41.7 ± 3.5	0.79
Knee Contribution FH	30.7 ± 1.6	32.5 ± 2.8	0.18
Ankle Contribution FH	28.4 ± 5.3	25.8 ± 2.3	0.45
Hip Contribution SH	34.2 ± 4.5	36.9 ± 2.6	0.16
Knee Contribution SH	28.6 ± 2.1	29.6 ± 1.7	0.51
Ankle Contribution SH	37.2 ± 4.6	33.5 ± 2.4	0.03*
Joint Contact Impulse (BWs)			
Hip FH	1.1 ± 0.5	0.6 ± 0.4	0.009*
Knee FH	0.8 ± 0.4	0.5 ± 0.2	0.02*
Ankle FH	0.8 ± 0.4	0.4 ± 0.2	0.006*
Hip SH	1.4 ± 0.6	1.9 ± 0.4	0.03*
Knee SH	1.1 ± 0.5	1.5 ± 0.4	0.05*
Ankle SH	1.4 ± 0.5	1.5 ± 0.3	0.22

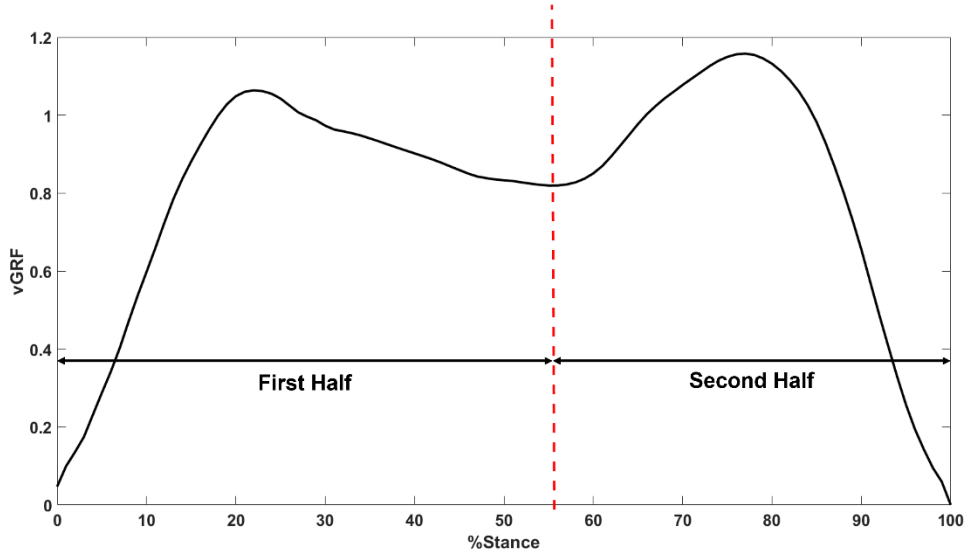

Figure 4.1: Schematic to describe how the first and second halves of the stance phase were determined using the vertical ground reaction force (vGRF) profile. Dashed line represents midstance.

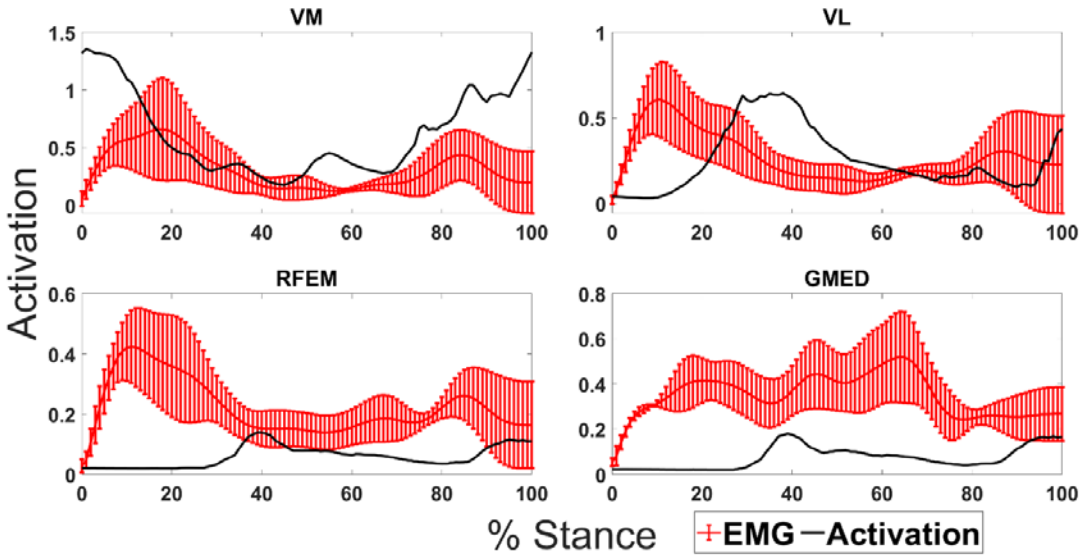

Figure 4.2: Estimated activation levels (black) of the vastus medialis (VM), vastus lateralis (VL), rectus femoris (RFEM), and gluteus medius (GMED) during the stance phase of gait compared to collected EMG data (red with error bars)

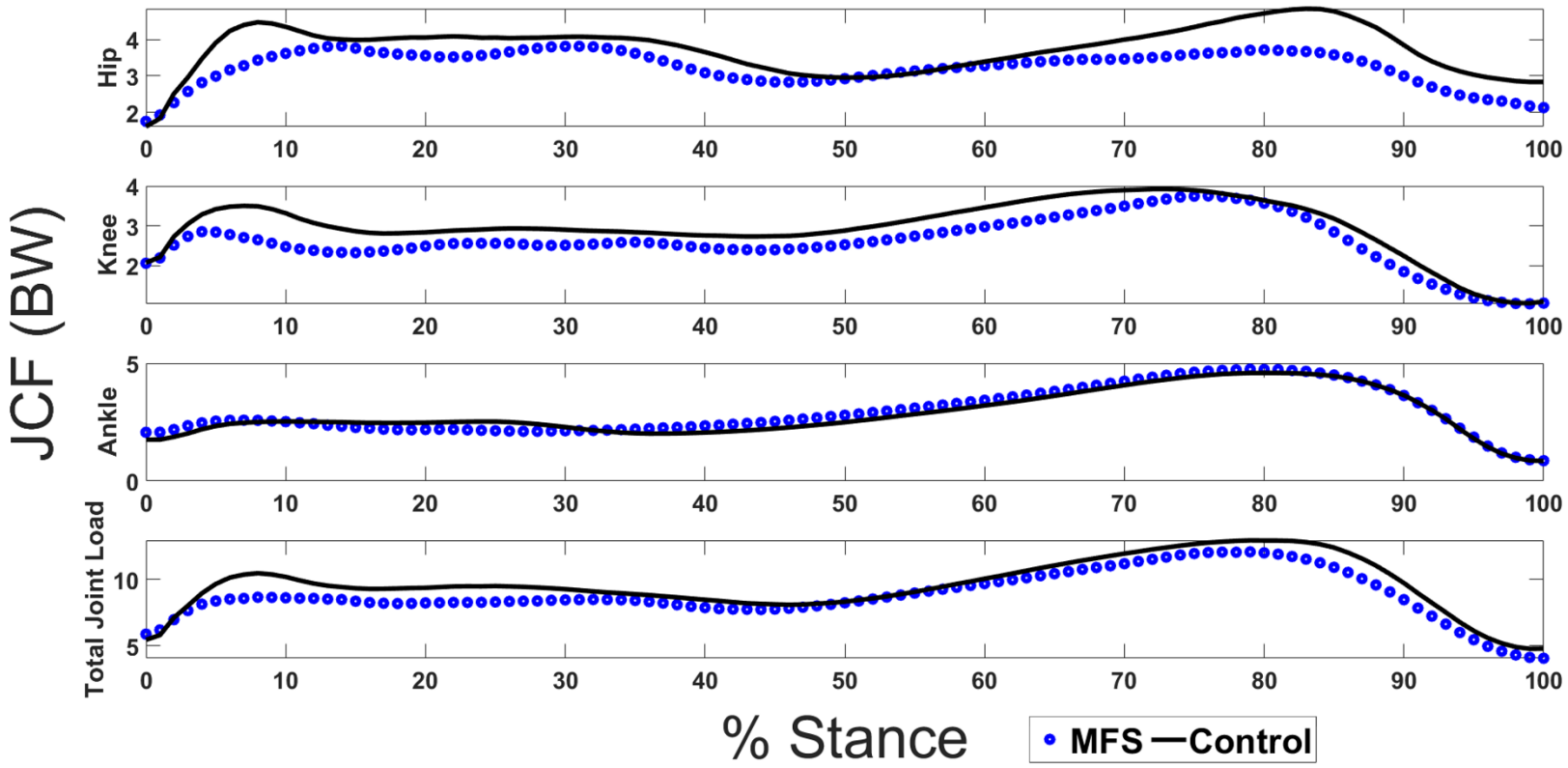

Figure 4.3: Hip, knee, and ankle joint contact forces (JCF) as well as total JCF (summation of hip, knee and ankle JCF) for healthy controls (black line) and people with Marfan syndrome (MFS) (blue circle line).

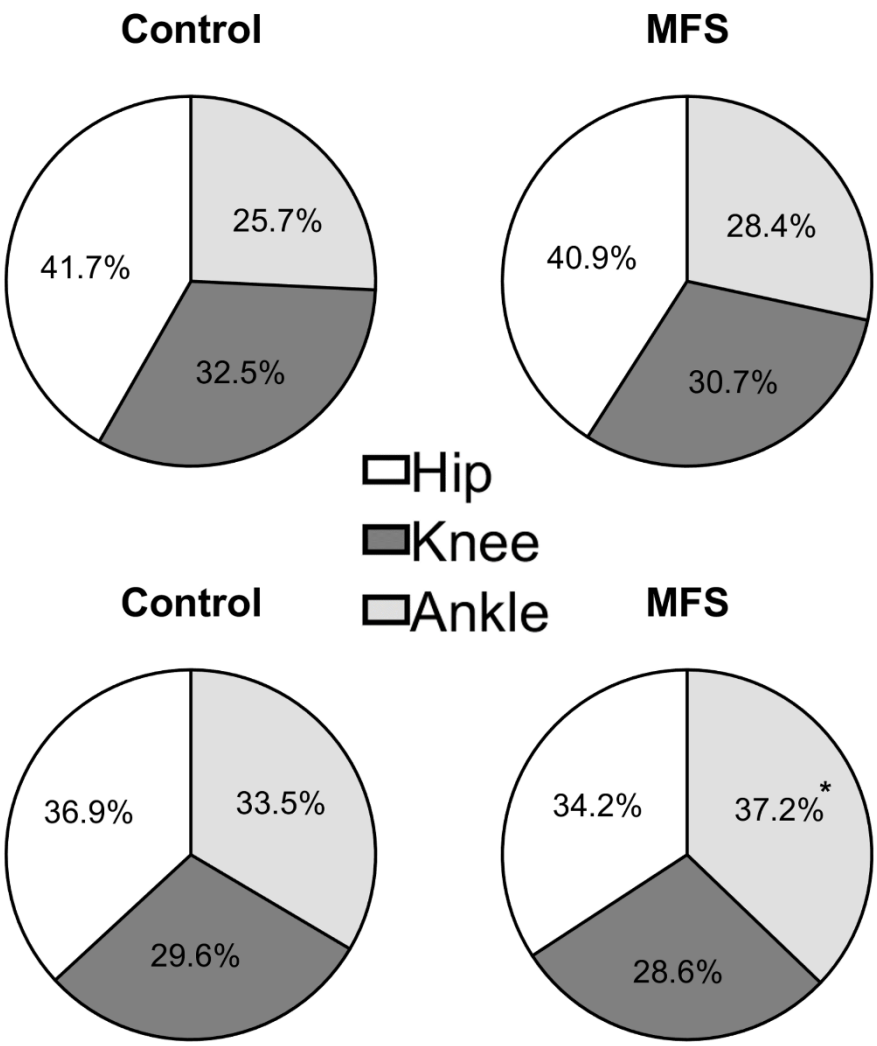

Figure 4.4: Contributions for the hip, knee, and ankle joints during the first half (top) and second half (bottom) of stance between the healthy control (left) group and people with Marfan syndrome (MFS) group (right). * indicates between group differences

CHAPTER 5. CONCLUSION

5.1 CONCLUSION

This dissertation assessed how MFS, a connective tissue disorder characterized by abnormal FBN-1 production, affects lower extremity joint kinematics and kinetics during the stance phase of gait. Although it has been shown that people with MFS exhibit high incidences of lower extremity joint pain and early-onset OA and poor quality of life, no study has attempted to understand the biomechanical characteristics of people with MFS during common activities of daily life, such as walking. Traditional gait analysis provided an understanding of the effects of MFS on hip, knee and ankle joint sagittal plane kinematics and moments. Also, MSK modeling was implemented to better understand how MFS affects muscle force production and joint contact forces. To our knowledge, this is the first study to quantify gait mechanics in the MFS community.

Sagittal plane gait kinematics and kinetics outcomes were selected based on a comprehensive review of sagittal plane gait mechanics in similar pre-arthritic and connective tissue disorders. These outcome measures have been used to characterize altered joint mechanics in other populations and may give insight into the root causes of joint pain and OA development in the MFS population. Specifically, the more flexed lower extremity and increased demand on the glute and quadriceps musculature, but a decreased demand on the ankle dorsiflexor musculature during the stance phase of gait may result in abnormal joint loading on the hip and knee joints and may be responsible for the high incidence of early onset OA in people with MFS. However, without a longitudinal study that assesses joint mechanics and their relationship to joint health, it becomes difficult to understand if these altered mechanics are causative or compensatory in nature. In terms of muscle force production abnormal hip, knee, and ankle peak forces and force impulses were observed in the MFS group. More specifically higher VASTI, glute, and GASTROC muscle force production was seen in people with MFS compared to controls during the stance phase of gait. It should be noted that our musculoskeletal simulations incorporated muscle-related properties of healthy individuals and do not account for MFS-specific muscle composition, which may impact the estimated muscle force production observed in

this work. In reference to lower extremity joint loading, higher joint loading impulse was seen across the lower extremity during the first half of stance, while lower impulse was observed in the second half of stance. Furthermore, people with MFS exhibit similar aberrant gait, muscle force production, and joint contact forces as those people with pre-arthritic conditions and OA.

In conclusion, people with MFS place a larger demand on the hip and knee extensor musculature during the stance phase of gait. The larger demand on the hip and knee extensor musculature during walking does not affect the peak magnitude of JCF during loading response, yet it may be associated with the higher total amount of joint contact loading observed during loading response. This higher amount of joint contact loading observed people with MFS may attribute to the increased incidence of early onset OA. All three individual aims of this dissertation aided in providing clinically relevant information to clinicians in terms of the development of gait-related treatments for people with MFS. Regardless of the methodology utilized in this study (i.e., gait analysis and musculoskeletal simulations), people with MFS exhibited gait characteristics that are similar to those demonstrated by people with joint disease and OA. However, since our MFS cohort was significantly older, some differences seen in gait mechanics, muscle force production and joint contact forces may be attributed to aging, and further studies should be performed to understand the effects of aging in people with MFS.

5.2 FUTURE WORK

The current study may serve as a basis for further investigation into the intricacies of the effects of MFS on the MSK system. As OA is a multi-factorial disease, more comprehensive assessments with MFS population should be performed to include evaluation of the impact of MFS on muscle function and clinical outcomes. More specifically, future work should focus on the relationship between altered gait mechanics and muscle function with joint-related structural and clinical outcomes in the MFS population. In addition, aging significantly impacts muscle function yet the additional impact of MFS in aging on gait mechanics, muscle function and joint health are not well

understood and requires further investigation to develop effective interventions to mitigate the impact of MFS on joint degeneration.

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